Treatment of Multiple Myeloma in First Relapse

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Objectives

- Review initial treatment recommendations and considerations for multiple myeloma (MM)
- Compare recent literature on multi-agent treatment regimens for myeloma in first relapse
- Assess toxicity profile and important supportive considerations for novel agents
- Apply novel treatment strategies to patient cases based on literature supported outcomes as well as patient-specific comorbidities

Multiple Myeloma

- Accounts for ~15% of US hematologic malignancies
  - 1.8% of overall cancers
- ~30,330 new cases in US in 2016
  - ~12,650 associated deaths
  - Median age at diagnosis is 69 years old
- Rates of new diagnosis rising each year over past decade at the same rate as annual deaths over the same period
  - Remains an incurable disease

Multiple Myeloma

- Immortalized malignant plasma cells
  - Adhere and accumulate in bone marrow
  - Lead to bone destruction and marrow failure
  - Production of M protein
- Exact etiology not completely defined
  - Overexpression of apoptotic genes (ex. p53)
  - Molecules stimulate clonal growth (ex. IL-6)

Malignant Plasma Cells

- Monoclonal gammopathy of undetermined significance (MGUS)
- Asymptomatic multiple myeloma (smoldering)
- Multiple Myeloma

CRAB features of end-organ damage

0.5 – 1% Many people >50 years old have this

10% per year for the first 5 years

NO CRAB features or end-organ damage

**International Myeloma Working Group Diagnostic Criteria for Plasma Cell Dyscrasia**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>M-protein</th>
<th>Bone Marrow Plasma Cells</th>
<th>Myeloma-defining events</th>
<th>Biomarkers of malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGUS</td>
<td>&lt;3g/dL</td>
<td>&lt;10%</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Solitary Plasmacytoma of Bone</td>
<td>Not required</td>
<td>No normal PCs</td>
<td>No</td>
<td>Not defined</td>
</tr>
<tr>
<td>Solitary Plasmacytoma of Bone with Minimal Marrow Involvement</td>
<td>Not required</td>
<td>&lt;10%</td>
<td>No</td>
<td>Not defined</td>
</tr>
<tr>
<td>Smoldering myeloma</td>
<td>≥3g/dL in serum or &gt;500mg/24h in urine OR &gt;10–60% PCs</td>
<td>≥10%</td>
<td>(or &lt;10% if plasmacytoma+ CRAB or biomarker of malignancy or ≥1 plasmacytoma present)</td>
<td></td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>Not required</td>
<td>≥10%</td>
<td>(or &lt;10% if plasmacytoma+ CRAB or biomarker of malignancy or ≥1 plasmacytoma present)</td>
<td></td>
</tr>
</tbody>
</table>

**MGUS**
- Serum calcium: greater than 1 mg/dL
- Serum creatinine: greater than 1.5 mg/dL
- Serum creatinine: greater than 1 mg/dL
- Serum calcium: greater than 1 mg/dL

**Solitary Plasmacytoma of Bone**
- Not required
- No normal PCs
- No
- Not defined

**Solitary Plasmacytoma of Bone with Minimal Marrow Involvement**
- Not required
- <10%
- No
- Note defined

**Smoldering myeloma**
- ≥3g/dL in serum or >500mg/24h in urine or >10–60% PCs
- ≥10%
- (or <10% if plasmacytoma+ CRAB or biomarker of malignancy or ≥1 plasmacytoma present)

**Multiple Myeloma**
- Not required
- ≥10%
- (or <10% if plasmacytoma+ CRAB or biomarker of malignancy or ≥1 plasmacytoma present)

**CRAB criteria for myeloma-defining events**
1. HyperCalcemia: Serum calcium >1 mg/dL higher than the ULN or >11 mg/dL
2. Renal insufficiency: CrCl <40 ml/min or SCr >2 mg/dL
3. Anemia: Hgb <10 g/dL or >2 g/dL below the LLN
4. Bone lesions: ≥1 osteolytic lesion on skeletal radiography, CT, or PET-CT

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**Frontline Treatment Paradigm**
- Goal to achieve a deep response, complete remission, and optimize progression-free survival

**Induction:**
- RVd (R)-Vinblastine, Doxorubicin, Dexamethasone
- CyBorD (C)-Cyclophosphamide, Vincristine, Dexamethasone

**Consolidation:**
- Autologous Hematopoietic Stem Cell Transplant
  - (if eligible)
  - OR Doublet/Triplet regimens

**Maintenance:**
- IMID
- PI

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**Prognosis**
- Survival improved notably in recent years
  - Introduction of immunomodulatory drugs (IMIDs) and proteasome-inhibitors (PIs) initially in relapsed disease
  - With transplant PFS >5 years and OS >10 years is a reality
- 5 year survival rate in 2003 estimated as 34%
- More recent statistics (2016) estimate 49%
- Considered a chronic condition

**MM as a Chronic Disease**
- Despite improving prognosis remains incurable
  - Majority of patients relapse at which point disease is difficult to manage
- Finding effective treatment at each consecutive relapse is CRITICAL for prolonging overall survival
  - Difficult with increasing drug resistance and decreasing remission duration with each successive regimen

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**An Evolving Paradigm**

**Corticosteroids**
- Prednisone
- Dexamethasone

**PIs**
- Bortezomib
- Carfilzomib

**IMIDs**
- Thalidomide
- Lenalidomide
- Pomalidomide

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**An Evolving Paradigm**

**Corticosteroids**
- Prednisone
- Dexamethasone

**PIs**
- Bortezomib
- Carfilzomib

**IMIDs**
- Thalidomide
- Lenalidomide
- Pomalidomide
**An Evolving Paradigm**

**Corticosteroids**
- Dexamethasone
- Prednisone

**IMIDs**
- Thalidomide
- Lenalidomide
- Pomalidomide

**Histone Deacetylase Inhibitor**
- Panobinostat

**Clinical Trial**
- Vnda, PDAC, PBL, LBL

**Monoclonal Antibodies**
- Daratumumab (CD38)
- Elotuzumab (SLAMF7)

**Immunotherapy**
- Pembrolizumab
- CAR-T

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**The New Novel Agents for MM**

Options in relapse disease

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**Ixazomib**
- 20S reversible proteasome inhibitor, oral
- Approved after at least 1 prior line of therapy

**Pearls**
- Adherence – oral regimens increasingly complicated
- Taken on empty stomach, 1 hour before or 2 hours after meals
- Peripheral neuropathy – generally not expected to worsen
- Diarrhea
- Thrombocytopenia
- Back pain

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**Elotuzumab**
- Monoclonal antibody targets CS-1 (or SLAMF7)
- Approved for after at least 1 prior therapy

**Pearls:**
- Infusion reactions primary concern
- Premedication regimens (30-90 minutes prior): diphenhydramine (25-50mg), ranitidine (50mg), acetaminophen (650-1000mg)
- Split PO and IV dex dosing
- Lymphopenia, leukopenia, thrombocytopenia
- Electrolyte changes

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**TOURMALINE-MM1**
- Lenalidomide-dexamethasone triplet
  - Phase 3 RD ± ixazomib for relapsed and relapsed/refractory MM patients having received 1-3 prior lines of therapy
  -IRD, 28-day cycle: ixazomib 4mg PO days 1, 8, and 15; lenalidomide 25mg days 1-21, dexamethasone 40mg days 1, 8, 15, 22
  - PFS significantly longer with ixazomib (IRD) arm – study reported at 1st pre-specified analysis
  - Serious adverse events similar in both groups
  - Patient reported quality of life similar in both groups

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**ELOQUENT-2**
- Lenalidomide-dexamethasone triplet
  - RD ± elotuzumab for relapsed and relapsed/refractory MM patients having received 1-3 prior lines of therapy
  - ERD, 28-day cycle: elo 10mg/kg weekly cycles 1 & 2 then days 1 & 15; len 25mg daily days 1-21; dex 40mg on weeks without elo and 8mg + 28mg on elo days
  - PFS and ORR significantly improved in ERD group at the interim analysis
  - Fewer complete responses seen in ERD group
  - Similar safety profiles, ERD with increased risk of herpes zoster and risk of infusion reactions
  - Patient reported quality of life similar in both groups

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Carfilzomib
- 20S irreversible proteasome inhibitor
- Approved after at least 1 prior line of therapy
- Pearls:
  - Dosing escalation, various dosing schemes (often multiday; 20mg/m² followed by doses 27-70mg/m²)
  - IV, PO dex with each dose (myeloma dosing)
  - Pre- and post-hydration considerations
  - Cardiotoxicity

ENDEAVOR
- Bortezomib combination
  - Phase III study of bortezomib-dex vs carfilzomib-dex for relapsed and relapsed/refractory MM patients having received 1-3 prior lines of therapy
  - KD, 28-day cycle: carfilzomib twice weekly for 3 weeks with 20-56 dosing scheme; dex 20mg twice weekly
  - VD, 21-day cycle: bortezomib 1.3mg/m² days 1, 4, 8, 11; dex 20mg days 1, 2, 4, 5, 8, 9, 11, 12
- PFS significantly improved in KD group at interim analysis
- PFS improvement in subgroups with previous bortezomib
- Higher ORR with KD, no difference at this time in OS

ASPIRE
- Lenalidomide-dexamethasone triplet
  - RD ± carfilzomib for relapsed and relapsed/refractory MM patients having received 1-3 prior lines of therapy
  - KRD, 28-day cycle: carfilzomib twice weekly for 3 weeks (cycles 1-12) and every other week after (cycles 13-18) then stopped with 20-27 dosing scheme; len 25mg daily days 1-21; dex 40mg once weekly
- PFS significantly improved in KRD group at interim analysis
  - Higher ORR with KRD
  - Median OS not reached in either group at interim
  - Similar safety profiles between groups
  - Patient reported higher quality of life similar in KRD group

Daratumumab
- Monoclonal antibody targets CD38
- Indicated in combination with IMiD or PI after at least 1 prior line of therapy
  - Monotherapy after at least 3 prior lines of therapy (original approval)
- Pearls:
  - Disrupts Coombs test, interferes with antibody screening and cross matching – important to screen prior to administration
  - High rate of infusion reactions (specifically 1st dose)
  - Infusion duration, volume, premedications (post-steroid?)
  - Not on package insert; premedicate with montelukast
  - Neutropenia
  - Diarrhea

CASTOR
- Bortezomib combination
  - Phase III study of bortezomib-dex ± daratumumab for relapsed and relapsed/refractory MM patients having received 21 prior line of therapy
  - DVD, 21-day cycles: dara 16mg/kg weekly for 3 weeks in cycles 1-3, once every 3 weeks cycles 4-8, monthly thereafter; bor 1.3mg/m² cycles 1-8, 11 cycles 1-8; dex 20mg days 1, 2, 4, 5, 8, 9, 11, 12
- Median PFS was not reached in DVD group, significantly improved
  - ORR improved in DVD, OS comparison ongoing

POLLUX
- Lenalidomide-dexamethasone triplet
  - RD ± daratumumab for relapsed and relapsed/refractory MM patients having received 21 prior line of therapy
  - DRD, 28-day cycles: dara 16mg/kg weekly for 2 cycles, every other week cycles 3-6, week 1 only thereafter; len 25mg daily days 1-21; dex 40mg weekly
- Median PFS was not reached in DRD group, significantly improved
  - ORR improved in DRD, OS comparison ongoing
  - Daratumumab with a notable side effect profile but manageable with less DRD discontinuation

EQUULEUS

- Pomalidomide triplet combination
  - Phase 1b study, open-label study of daratumumab combined with multiple therapies, results of dara + pomalidomide-dex reported in 103 cases of relapsed/refractory MM ≥1 line of therapy
  - DPd, 28-day cycle: dara 16mg/kg weekly for 3 weeks in cycles 1-2, once every 3 weeks cycles 3-6, monthly thereafter; pom 4mg days 1-21; dex 40mg weekly

- Median PFS 8.8 months, 12-month PFS 42%
  - ORR 60% (42% VGPR, CR, sCR)

Panobinostat

- Histone deacetylase (HDAC) inhibitor
  - Promotes immune function and decreases malignant proliferation
  - Approved in combination with PI and dex after at least 2 prior regimens
  - Pearls:
    - Diarrhea (BBW)
      - Managed with recommended dosing and aggressive antidiarrheals
    - Thrombocytopenia, neutropenia, lymphopenia
    - Fatigue
    - Peripheral neuropathy
    - ECG changes (QTc prolongation; BBW)

Comparing treatment options

Assessing studied combination therapies

LENALIDOMIDE-DEX TRIPLETS

TOURMALINE-MM1 ELOQUENT-2 ASPIRE POLLUX

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>ORR</th>
<th>≥VGPR</th>
<th>Median PFS, mos</th>
<th>PFS HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM1 RD RD RD RD</td>
<td>71%</td>
<td>39%</td>
<td>14.7</td>
<td>0.74</td>
</tr>
<tr>
<td>MM1 RD RD RD KD</td>
<td>78.3*</td>
<td>48%</td>
<td>20.6*</td>
<td>0.70</td>
</tr>
<tr>
<td>MM1 RD RD RD KRD</td>
<td>66%</td>
<td>28%</td>
<td>14.9</td>
<td>0.69</td>
</tr>
<tr>
<td>MM1 RD RD RD DRD</td>
<td>79%</td>
<td>33%</td>
<td>17.6</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Median OS, mos:
- NR
- 16.1
- 16.5
- 17.2

Enfamilmary, Pusaarino, Kurniawan, A-1+1, MM1-randomized, RCT, NR=not reported, OR=overall response rate, ≥VGPR=very good partial response, PFS=progression-free survival, VGPR=very good partial response, p=0.05


ENDEAVOR CASTOR

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Overall Response Rate</th>
<th>Median Progression-Free Survival, mos</th>
<th>PFS HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>VD KD VD DVD</td>
<td>63% 77% 63.2% 82.9%</td>
<td>9.4 18.7 7.2 Not yet reached*</td>
<td>0.53 0.39</td>
</tr>
</tbody>
</table>

DVD=daratumumab-bortezomib-dexamethasone, KD=carfilzomib-dexamethasone, NR=not reported, pt=patient, VD=bortezomib-dexamethasone

*Statistically significant

## Len- vs Bor-based Combinations

<table>
<thead>
<tr>
<th>MM1</th>
<th>ELO-2</th>
<th>ASPIRE</th>
<th>POLLUX</th>
<th>ENDEAVOR</th>
<th>CASTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arm</td>
<td>RD</td>
<td>RD</td>
<td>RD</td>
<td>RD</td>
<td>VD</td>
</tr>
<tr>
<td>ORR</td>
<td>71.5%</td>
<td>66%</td>
<td>66.7%</td>
<td>76.4%</td>
<td>63%</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>39%</td>
<td>28%</td>
<td>40.4%</td>
<td>44.2%</td>
<td>29%</td>
</tr>
<tr>
<td>Med PFS, mos</td>
<td>14.7</td>
<td>14.9</td>
<td>17.6</td>
<td>1-yr 60.1%</td>
<td>9.4</td>
</tr>
<tr>
<td>Med PFS, mos</td>
<td>NR</td>
<td>NR</td>
<td>2-yr 65.1%</td>
<td>1-yr 86.6%</td>
<td>NR</td>
</tr>
</tbody>
</table>

- The lenalidomide-dexamethasone doublet has outperformed the bortezomib-dexamethasone doublet across phase III studies
- No head-to-head comparisons


### Prior Treatment Exposure

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>PI naïve</th>
<th>PI exposed</th>
<th>IMID naïve</th>
<th>IMID exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRD</td>
<td>0.75</td>
<td>0.74</td>
<td>0.70</td>
<td>0.74</td>
</tr>
<tr>
<td>KRD</td>
<td>0.73</td>
<td>0.70</td>
<td>0.69</td>
<td>0.80</td>
</tr>
<tr>
<td>KD</td>
<td>0.48</td>
<td>0.56</td>
<td>0.38</td>
<td>0.60</td>
</tr>
<tr>
<td>DVD</td>
<td>0.25</td>
<td>0.46</td>
<td>0.50</td>
<td>0.38</td>
</tr>
<tr>
<td>ERD</td>
<td>0.72</td>
<td>0.68</td>
<td>0.78</td>
<td>0.64</td>
</tr>
<tr>
<td>VD</td>
<td>0.35</td>
<td>0.37</td>
<td>0.36</td>
<td>0.42</td>
</tr>
</tbody>
</table>


### Resistance Profile

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Lenalidomide Refractory</th>
<th>Bortezomib Refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRD</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>KRD</td>
<td>0.64 (IMID Refractory)</td>
<td>0.80</td>
</tr>
<tr>
<td>KD</td>
<td>0.80</td>
<td>0.37</td>
</tr>
<tr>
<td>DVD</td>
<td>0.50 (IMID Refractory)</td>
<td>N/A</td>
</tr>
<tr>
<td>ERD</td>
<td>N/A</td>
<td>NR</td>
</tr>
<tr>
<td>VD</td>
<td>N/A</td>
<td>0.50</td>
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</tbody>
</table>


### High Risk Disease Considerations

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>RD</th>
<th>KRD</th>
<th>RD</th>
<th>KRD</th>
<th>RD</th>
<th>DRD</th>
<th>RD</th>
<th>DRD</th>
<th>VD</th>
<th>KD</th>
<th>VD</th>
<th>KD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>73.5</td>
<td>91.2</td>
<td>56.0</td>
<td>79.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥VGPR (%)</td>
<td>45.3</td>
<td>75.1</td>
<td>27</td>
<td>65.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>19.5</td>
<td>35.1</td>
<td>13.0</td>
<td>17.3</td>
<td>12.0</td>
<td>10.0</td>
<td>10.0</td>
<td>6.0</td>
<td>6.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category / Risk</th>
<th>ASPIRE</th>
<th>POLLUX</th>
<th>ENDEAVOR</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>HR</td>
<td>HR</td>
</tr>
<tr>
<td>IRD</td>
<td>0.66</td>
<td>0.70</td>
<td>0.57</td>
</tr>
<tr>
<td>KRD</td>
<td>0.70</td>
<td>0.70</td>
<td>0.58</td>
</tr>
<tr>
<td>≥VGPR (%)</td>
<td>0.65</td>
<td>0.44</td>
<td>0.63</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>0.66</td>
<td>0.66</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**High risk:** del(17p) (in ≥60% of PCs for ASPIRE), t(4;14), t(14;16)

*Statistically significant


### Toxicities to individualize therapy selection

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>All AEs</th>
<th>≥Gr 3 or 4 AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRD</td>
<td>82</td>
<td>34</td>
</tr>
<tr>
<td>KRD</td>
<td>89</td>
<td>2</td>
</tr>
<tr>
<td>≥Gr 3 or 4 AEs</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td>≤Gr 3 or 4 AEs</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>≥Gr 3 or 4 AEs</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td>≥Gr 3 or 4 AEs</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>≤Gr 3 or 4 AEs</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>≥Gr 3 or 4 AEs</td>
<td>32</td>
<td>2</td>
</tr>
</tbody>
</table>

**Statistically significant


## Considering Safety Profiles

Toxicities to individualize therapy selection
# ELOQUENT-2 Safety

<table>
<thead>
<tr>
<th>AE (%)</th>
<th>All AEs</th>
<th>≥Gr 3 or 4</th>
<th>≥Gr 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>82</td>
<td>34</td>
<td>89</td>
</tr>
<tr>
<td>Anemia</td>
<td>96</td>
<td>19</td>
<td>95</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>84</td>
<td>19</td>
<td>78</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>95</td>
<td>77</td>
<td>98</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47</td>
<td>5</td>
<td>36</td>
</tr>
<tr>
<td>Cough</td>
<td>31</td>
<td>-1</td>
<td>16</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>25</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Fatigue</td>
<td>47</td>
<td>8</td>
<td>39</td>
</tr>
<tr>
<td>Fever</td>
<td>37</td>
<td>3</td>
<td>25</td>
</tr>
</tbody>
</table>

# ASPIRE Safety

<table>
<thead>
<tr>
<th>AE (%)</th>
<th>All AEs</th>
<th>≥Gr 3 or 4</th>
<th>≥Gr 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>17.8</td>
<td>26.5</td>
<td>36.3</td>
</tr>
<tr>
<td>Anemia</td>
<td>42.6</td>
<td>39.8</td>
<td>39.8</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>29.1</td>
<td>31.1</td>
<td>22.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20.4</td>
<td>17.2</td>
<td>17.2</td>
</tr>
<tr>
<td>Cough</td>
<td>22.4</td>
<td>13.3</td>
<td>13.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16.8</td>
<td>7.7</td>
<td>11.9</td>
</tr>
<tr>
<td>Fever</td>
<td>26.6</td>
<td>1.6</td>
<td>12.8</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>21.5</td>
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# POLLUX Safety

<table>
<thead>
<tr>
<th>AE (%)</th>
<th>All AEs</th>
<th>≥Gr 3 or 4</th>
<th>≥Gr 3 or 4</th>
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<tr>
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<tr>
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<tr>
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<td>Cough</td>
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# CASTOR Safety

<table>
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<tr>
<th>AE (%)</th>
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<th>≥Gr 3 or 4</th>
</tr>
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<tbody>
<tr>
<td>Neutropenia</td>
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<td>9.3</td>
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<tr>
<td>Thrombocytopenia</td>
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<tr>
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<tr>
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# ENDEAVOR Safety

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<td>Fatigue</td>
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<tr>
<td>Fever</td>
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# POLLUX Safety

<table>
<thead>
<tr>
<th>AE (%)</th>
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<td>Neutropenia</td>
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<tr>
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<td>31.7</td>
<td>3.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Cough</td>
<td>23.9</td>
<td>0.0</td>
<td>12.7</td>
</tr>
<tr>
<td>Fever</td>
<td>15.6</td>
<td>1.2</td>
<td>11.4</td>
</tr>
</tbody>
</table>

# Selecting therapy

Tailoring therapy based on literature and patient factors
How to Choose?

• Is the patient better suited for a lenalidomide- or non-lenalidomide-based therapy?
• Does the patient have symptomatic progression?
• Does the patient have high risk disease biology?
• Toxicity?

Miscellaneous Factors

• Patient’s preference
• Logistical/socio-economic considerations to choice of regimen
  ▫ i.e. all-oral regimen for patients limited by travel and distance
• Options for later lines of therapy

Candidates for Len-based Therapy

• Disease progression on proteasome inhibitor-based regimen
• Disease progression on bortezomib maintenance therapy
• Disease progression on no treatment after a prior course of therapy of defined duration
• Intolerant to bortezomib
• Lenalidomide-sensitive or naive disease

Len-based therapy selection

• Clinical progression:
  ▫ len-dex-carfilzomib or len-dex-daratumumab
• Bridge to salvage first or second autologous stem cell transplant:
  ▫ len-dex-carfilzomib or len-dex-daratumumab
  ▫ Limited data on feasibility of stem cell collection after dara-RD
• High-risk disease (clinical or biochemical progression):
  ▫ len-dex-carfilzomib or len-dex-daratumumab
  ▫ Biochemical progression, standard risk disease:
    ▫ may consider len-dex-elotuzumab
    ▫ May consider saving carfilzomib and daratumumab for later lines

Candidates for non-Len-based Therapy

• Disease progression on lenalidomide-based regimen
• Clinical disease progression on lenalidomide maintenance therapy
• Intolerance to lenalidomide
**Non-Len-based therapy selection**

- Bortezomib-dexamethasone no longer an appropriate standard of care
  - Select situations when not a good candidate for alternatives
- Car-dex or bor-dex-dara appropriate for clinical or biochemical progression
  - Consider off-label cyclophosphamide/Pi-based triplet for clinical progression (CyBorD, Car-Cy-dex)
  - Consider off-label pom-based triplets for clinical progression especially in high risk disease (PVD, KPD, Pom-Dara-dex)
- Co-morbidities
  - Pre-existing neuropathy: consider alternative to bortezomib
  - Significant cardiopulmonary disease: consider alternative to carfilzomib
  - Severe COPD/asthma: consider alternative to dara or monitor

**Symptomatic Progression**

- Myeloma Urgencies/Emergencies
  - Hypercalcemia
  - New or worsening lytic bone lesions
  - Progressive renal dysfunction
- Urgent/emergent, symptomatic relapse requires therapy that has a high likelihood of producing a deep response
  - First consideration: KRD and DRD (≥VGPR in 70-75%)
  - Second consideration: DVD and KD (≥VGPR in 55-60%)
  - Third consideration: IRD and ERD (≥VGPR in 35-50%)
  - Consider for biochemical or clinical relapse with isolated anemia

**Future of MM therapy**

- Optimizing frontline therapy
- Cost and availability
- Treatment duration
  - Particularly in first relapse where long remission seen
- More novel therapies and approaches in the pipeline
- Pharmacists involvement

**Conclusions**

- First-generation novel agents dramatically improved OS in MM
- Finding effective treatment at each consecutive relapse critical for prolonging OS
- Triplet therapy preferred in a patient-specific, risk-adapted approach to therapy selection at relapse
- Treatment paradigms in MM continuing to evolve
- Pharmacy team can play a huge role in optimizing outcomes

**Treatment of Multiple Myeloma in First Relapse**

Justin Arnall, PharmD, BCOP
Pharmacist Clinical Coordinator, Hematologic Malignancies
Levine Cancer Institute, Carolinas HealthCare System