New Drugs and Novel Mechanisms of Action in Treating Patients With Multiple Myeloma

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Learning Objectives

1. Differentiate between the various mechanisms of action of new and emerging agents used to treat MM
2. List monitoring parameters for toxicities associated with newer agents used to treat MM
3. Describe the signs of early and serious toxicity that providers and patients need to be aware of when initiating therapy with new agents for MM
4. Identify the optimal drug therapy regimen for individual patients with MM on patient-specific factors

MM = multiple myeloma.
Financial Disclosure

• Ms. Gleason has acted as a consultant for Karyopharm and Takeda.

• Dr. Kaufman has acted as a consultant for Bristol-Myers Squibb, Celgene, Incyte, and Pharmacyclics.
Overview of MM

**MGUS**
- Clonal protein in serum or urine

**Smoldering MM**
- Clonal protein in serum or urine
- AND
- Plasmocytosis (10%–60%) in BM
- OR
- M spike ≥ 3 g/dL in serum or ≥ 500 mg/24 hour in urine

**Symptomatic MM**
- Clonal protein in serum or urine
- Clonal plasmocytosis in BM or tissue
- Morbidity or imminent threat of morbidity
  - Hypercalcemia
  - Renal insufficiency
  - Anemia
  - Bone lesions
  - Clonal PC in marrow ≥60%
  - Involved:uninvolved SFLC >100
  - >1 focal lesions on MRI

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**No routine treatment**

**Treatment usually indicated**

BM = bone marrow; MGUS = monoclonal gammopathy of undetermined significance; MRI = magnetic resonance imaging; PC = plasma cells; SFLC = serum-free light chain.

Slide courtesy of Dr. Costa.
MM Epidemiology

- **Risk factors**
  - Unknown in the majority of cases
  - Increased with age, male sex, obesity, and black race

- **Survival**
  - In 2012, there were an estimated 89,568 people living with MM (survivors) in the United States
  - 5-year OS has increased from 24.7% (1975–1977) to 48.5% (2005–2011; \( P < .05 \))

- **Variable response to treatment and variation in survival**
  - From a few months to >10 years
  - High-risk attributes are thought to play a primary role
  - 20% of patients survive >10 years, regardless of therapy
  - Novel agents may neutralize the effects of some high-risk features
  - Achievement of MRD-negative status early in the course of disease is key

<table>
<thead>
<tr>
<th>New Cases (US, 2015)</th>
<th>Deaths (US, 2015)</th>
<th>Mean Age at Diagnosis, Years</th>
<th>5-Year OS 1975–2011 (( P &lt; .5 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>30,330</td>
<td>12,650</td>
<td>69</td>
<td>Increased by 23.8%</td>
</tr>
</tbody>
</table>

MRD = minimal residual disease; OS = overall survival.

History of MM

- 1844: First documented case
- 1845: Abnormal urine protein, later termed Bence Jones protein
- 1895: Description of plasma cells
- 1928: First large case series of MM
- 1939: Serum protein spike identified
- 1956: Light chains types (later termed kappa and lambda) recognized
- 1975: Durie-Salmon staging system
- 2005: International Staging System
- 2006: Cytogenetic classification
- 2012: Carfilzomib
- 2015: Panobinostat

Novel agents in development

- 1947: Urethane
- 1958: Melphalan
- 1962: Corticosteroids
- 1983: ASCT
- 1999: Thalidomide
- 2002: Bortezomib
- 2003: Lenalidomide
- 2013: Pomalidomide
- 2015: Elotuzumab
- 2015: Daratumumab
- 2015: Ixazomib

ASCT = autologous stem cell transplantation.

Smoldering Myeloma
Should Patients With High-Risk Smoldering Myeloma Be Treated?

- Previously, no benefit shown with alkylating agents, bisphosphonates, interleukin-1β antagonists, and thalidomide

- Lenalidomide vs. observation: Phase III randomized trials
  - PETHEMA (N = 119)
    - Lenalidomide/dexamethasone delayed time to progression
      - Median: Not reached (lenalidomide/dexamethasone) vs. 21 months (observation)
      - HR: 0.18; 95% CI: 0.09–0.32; P < .001
    - Lenalidomide/dexamethasone improved OS vs. observation
  - ECOG-E3A06 (planned N = 380)
    - Ongoing phase II/III trial of lenalidomide vs. observation in smoldering MM
    - Initial phase II data: 33% ORR; grade 3 neutropenia and fatigue

CI = confidence interval; HR = hazard ratio; ORR = overall response rate.
## Current Trials Exploring Interventions for Smoldering MM

Eligibility criteria and definition of high-risk SMM vary among trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sponsor/Study Director</th>
<th>Intervention</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG-E3A06 NCT01169337</td>
<td>National Cancer Institute / S. Lonial</td>
<td>Lenalidomide vs. observation</td>
<td>Currently recruiting</td>
</tr>
<tr>
<td>NCT02697383</td>
<td>Memorial Sloan Kettering Cancer Center / C.O. Landgren</td>
<td>Ixazomib/dexamethasone x12 cycles followed by 24 cycles of maintenance for patients ≥ PR</td>
<td>Currently recruiting</td>
</tr>
<tr>
<td>NCT02415413</td>
<td>PETHEMA / San Miguel &amp; Mateos</td>
<td>KRd x6 cycles → stem cell collection → KRd 2 cycles → Rd maintenance 24 cycles</td>
<td>Currently recruiting</td>
</tr>
<tr>
<td>NCT02316106</td>
<td>Janssen Research &amp; Development</td>
<td>3 schedules of daratumumab (long intense, intermediate, short intense)</td>
<td>Currently recruiting</td>
</tr>
<tr>
<td>NCT02603887</td>
<td>MD Anderson / Manasanch</td>
<td>Pembrolizumab 200 mg IV Q21d 24 cycles</td>
<td>Not yet open</td>
</tr>
<tr>
<td>NCT02279394</td>
<td>Dana-Farber Cancer Institute / I. Ghobrial</td>
<td>Elotuzumab/lenalidomide +/- Dex</td>
<td>Currently recruiting</td>
</tr>
</tbody>
</table>

KRd = carfilzomib, lenalidomide, and dexamethasone; PR = partial response.
**Indications for Considering Treatment (IMWG Consensus Guidelines)**

- At least one of the **CRAB Criteria** (evidence of end organ damage)

<table>
<thead>
<tr>
<th>CRAB Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalcemia</td>
<td>Serum calcium &gt;2.75 mmol/L (&gt;11 mg/dL)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Serum creatinine ≥ 2 mg/dL or creatinine clearance &lt;40 mL per min</td>
</tr>
<tr>
<td>Anemia</td>
<td>Hemoglobin &gt;2.0 g/dL below the lower limit of normal, or a hemoglobin value &lt;10.0 g/dL</td>
</tr>
<tr>
<td>Bone</td>
<td>Lytic lesions, pathologic fractures, or severe osteopenia</td>
</tr>
</tbody>
</table>

**New Myeloma Defining Events: The Biomarkers**

- ≥60% clonal bone marrow plasma cells
- Serum involved/uninvolved free light chain ratio ≥100
- >1 Focal bone lesion (≥5 mm) on MRI

CRAB = calcium (elevated), renal failure, anemia, bone lesions; IMWG = International Myeloma Working Group.

Induction Therapy: Agents/Transplant/Maintenance
**R-ISS for MM**

- **R-ISS I (n = 871)**
  - Including ISS stage I (serum β2-microglobulin level < 3.5 mg/L and serum albumin level ≥3.5 g/dL)
  - No high-risk CA [del(17p) and/or t(4;14) and/or t(14;16)]
  - Normal LDH level (less than the upper limit of normal range)

- **R-ISS III (n = 295)**
  - Including ISS stage III (serum β2-microglobulin level >5.5 mg/L)
  - High-risk CA or high LDH level

- **R-ISS II (n = 1,894)**
  - Including all the other possible combinations

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-Year OS*</th>
<th>5-Year PFS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ISS I</td>
<td>82%</td>
<td>55%</td>
</tr>
<tr>
<td>R-ISS II</td>
<td>62%</td>
<td>36%</td>
</tr>
<tr>
<td>R-ISS III</td>
<td>40%</td>
<td>24%</td>
</tr>
</tbody>
</table>

*At a median follow-up of 46 months.
LDH = lactate dehydrogenase; PFS = progression-free survival; R-ISS = Revised International Staging System.
# MM Risk Categories

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Standard Risk (80%) (Expected OS: 6–7 Years)</th>
<th>High Risk (20%) (Expected OS: 2–3 Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISH</td>
<td>t(11;14), t(6;14)</td>
<td>del(17p), t(4;14)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t(14;16), +1q21</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Hyperdiploidy</td>
<td>Hypodiploidy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>del(13q)</td>
</tr>
<tr>
<td>β₂-microglobulin*</td>
<td>Low (&lt;3.5 mg/L)</td>
<td>High (≥5.5 mg/L)</td>
</tr>
<tr>
<td>PCLI</td>
<td>&lt;3%</td>
<td>High (≥3%)</td>
</tr>
<tr>
<td>Gene expression profile</td>
<td>Good risk</td>
<td>High risk</td>
</tr>
</tbody>
</table>

**Other high-risk features**
- Extramedullary disease
- Plasma cell leukemia
- Plasmablastic morphology

*Patients with t(4;14), β₂-microglobulin <4 mg/L, and Hb ≥10 g/dL may have intermediate-risk disease.

FISH = fluorescence in situ hybridization.

Framework for Newly Diagnosed MM: Patient Treatment Plan

Eligibility for Transplant: Comorbidities

PS = performance status.

Transplant Candidate

Induction therapy

Stem cell harvest

ASCT (early vs. delayed)

Consolidation and/or maintenance

Not Transplant Candidate

Induction therapy

Maintenance or extended therapy phase
### FDA-Approved Drugs to Treat MM

<table>
<thead>
<tr>
<th>Drug</th>
<th>Abbreviation</th>
<th>Drug Class</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>btz</td>
<td>Proteasome inhibitor</td>
<td>Velcade</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>car</td>
<td>Proteasome inhibitor</td>
<td>Kyprolis</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>dara</td>
<td>Monoclonal antibody</td>
<td>Darzalex</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>elo</td>
<td>Monoclonal antibody</td>
<td>Empliciti</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>len</td>
<td>Immunomodulatory agent</td>
<td>Revlimid</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>Ixa</td>
<td>Proteasome inhibitor</td>
<td>Ninlaro</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>thal</td>
<td>Immunomodulatory agent</td>
<td>Thalomid</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>pom</td>
<td>Immunomodulatory agent</td>
<td>Pomalyst</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>pan</td>
<td>Histone deacetylase inhibitor</td>
<td>Farydak</td>
</tr>
<tr>
<td>Melphalan</td>
<td>mel</td>
<td>Alkylating agent</td>
<td>Alkeran, Alphalan</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>CTX</td>
<td>Alkylating agent</td>
<td>Cytoxan</td>
</tr>
<tr>
<td>Prednisone</td>
<td>P, pred</td>
<td>Corticosteroid</td>
<td>Deltasone</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>D, d, dex, DXM</td>
<td>Corticosteroid</td>
<td>Decadron</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>pmd</td>
<td>Bisphosphonate</td>
<td>Aredia</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>zol</td>
<td>Bisphosphonate</td>
<td>Zometa</td>
</tr>
</tbody>
</table>

**FDA = US Food and Drug Administration.**
NCCN Preferred Regimens: Category 1

- Combination therapies have demonstrated improved response rates, PFS, and/or OS compared with single agents
- Supportive and palliative care should be provided concurrently with disease-modifying treatment bisphosphonates, antibiotics, and reduced doses of steroids
- Improving quality of life and survival has become an important goal of treatment

<table>
<thead>
<tr>
<th>Myeloma Preferred Induction Regimens*</th>
<th>Combination</th>
<th>Abbreviation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib/dexamethasone (dex)†</td>
<td>Bortezomib</td>
<td>VD or Vd</td>
</tr>
<tr>
<td>Bortezomib/cyclophosphamide/dex</td>
<td>Bortezomib</td>
<td>CyBoD</td>
</tr>
<tr>
<td>Bortezomib/doxorubicin/dex†</td>
<td>Bortezomib</td>
<td>VRD or VRd</td>
</tr>
<tr>
<td>Bortezomib/thalidomide/dex†</td>
<td>Bortezomib</td>
<td>VTD or VTd</td>
</tr>
<tr>
<td>Lenalidomide/dexamethasone†</td>
<td>Lenalidomide</td>
<td>RD or Rd</td>
</tr>
<tr>
<td>Bortezomib/dex</td>
<td>Lenalidomide</td>
<td>RD</td>
</tr>
<tr>
<td>Lenalidomide/low-dose dex†</td>
<td>Lenalidomide</td>
<td>Rd</td>
</tr>
<tr>
<td>Bortezomib/cyclophosphamide/dex</td>
<td>Bortezomib</td>
<td></td>
</tr>
<tr>
<td>Bortezomib/lenalidomide/dex</td>
<td>Bortezomib</td>
<td></td>
</tr>
<tr>
<td>Bortezomib/thalidomide/dex†</td>
<td>Bortezomib</td>
<td></td>
</tr>
<tr>
<td>Lenalidomide/dexamethasone†</td>
<td>Lenalidomide</td>
<td></td>
</tr>
<tr>
<td>Melphalan/prednisone/thalidomide†</td>
<td>Melphalan/prednisone/thalidomide</td>
<td>MPT</td>
</tr>
</tbody>
</table>

*NCCN Guidelines Multiple Myeloma Version 3.2016; †Category 1
Case

- 65-year-old male presents with anemia and bone pain
- Initial workup shows Hgb of 9.6, normal WBC and platelets
- Chemistries shows total protein of 9.9; creatinine and calcium are normal
- Skeletal survey shows diffuse lytic disease
- SPEP and UPEP shows 4.2 g/dL of IgG kappa protein, and 210 mg/24 hours of kappa light chains in the urine; free light ratio is 5:1
- Bone marrow 50% with no high-risk features

Hgb = hemoglobin; IgG = immunoglobulin G; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; WBC = white blood cell
Myeloma Drug Development

Backbone

IMID, immunomodulatory drug; HDAC, histone deacetylase; KSP, kinesin spindle protein; SINE, selective inhibitor of nuclear export
*Not yet FDA-approved for MM; only available in clinical trials
†Treatments studied in MMRC trials

Image courtesy of Multiple Myeloma Research Foundation
SWOG S0777: Newly Diagnosed MM

**Study Design**
Randomized phase III trial of VRd vs. Rd in previously untreated active MM

- VRd x eight 21-day cycles
  - Len 25 mg/d; dex 40 mg weekly
  - n = 230

- Rd x six 28-day cycles
  - Len 25 mg, dex 20 mg 2 consecutive days each week
  - n = 243

- Followed by Rd maintenance until PD, unacceptable toxicity, or withdrawal of consent

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

**Timeline**
- Median follow-up: 55 months; median time on maintenance: 385 days

**Prophylaxis**
- All patients received aspirin 325 mg/day; bortezomib patients received HSV prophylaxis

HSV = herpes simplex virus; PD = partial disease.
**SWOG S0777: Key Takeaways**

<table>
<thead>
<tr>
<th>Survival (mo)</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>0.0018*</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>0.025†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.516–0.973)</td>
<td></td>
</tr>
</tbody>
</table>

<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>

AE = adverse event.

**VRd induction followed by continuous Rd maintenance represents potential new standard of care for newly diagnosed MM**
IFM/DFCI 2009: Phase III, Randomized Symptomatic, Newly Diagnosed MM Patients (N = 700)

**Study design**
- Patients 65 years of age or younger with symptomatic, measurable NDMM
- RVd x 8 followed by Rd maintenance
  - RVd: Bortezomib 1.3 mg/m² IV on days 1, 4, 8, 11 + lenalidomide 25 mg on days 1–14 + dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11, 12
  - VS.
  - RVd x 3 -> cyclophosphamide mobilization -> MEL200 + HSCT -> R maintenance

**Outcomes**
- Primary objective: PFS
- Secondary objectives: ORR, MRD, TTP, OS, safety

HSCT = hematopoietic stem cell transplantation; NDMM = newly diagnosed multiple myeloma; TTP = time to progression.
IFM/DCF1 2009: Overall Conclusions

• ASCT vs. RVD in patients 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

• Longer follow-up required to make any conclusions about OS

• ASCT should remain a standard of care for eligible patients with myeloma

• Similar, confirmatory trial ongoing in United States

Case

• Diagnosed with ISS stage 1 MM, and started on RVD x 4 cycles followed by stem cell collection and lenalidomide maintenance; he was in CR at day +100

• He does well for 4 years, and then develops asymptomatic biochemical relapse over 12 months with a protein of 1.2, mild anemia, and questionable new bone lesion

• Treatment recommendation?

CR = complete remission.
Relapse
Definitions

Relapsed Myeloma

- Previously treated myeloma patients who, after a period of being off therapy, require salvage therapy

Refractory Myeloma

- Disease that is nonresponsive while on therapy, or progresses within 60 days of the last therapy

Relapsed and Refractory Myeloma

- Refractory disease in patients who have never achieved a minor response or better, and then either become nonresponsive while on salvage therapy or progress within 60 days of last therapy

MM Is Characterized by a Pattern of Remission and Relapse

- Asymptomatic
- Symptomatic
- Relapsing
- Refractory

Remission duration decreases with each line of therapy

- MGUS or indolent myeloma
- Active myeloma
- Relapse
- Remission

Front-line therapy 2nd or 3rd-line therapy

Treatment Selection for Relapsed/Refractory Myeloma

**Disease Characteristics**
- How deep was the patient's response to their prior therapy?
- How long was the duration of their response to their previous therapy?
- How aggressive is their disease?
- Are they eligible for a clinical trial?

**Patient Characteristics**
- What is the patient's performance status?
- Does the patient have pre-existing toxicities from either their myeloma or previous treatment regimens?
- What are the patient's comorbidities?
- Are they transplant eligible?
- Are they eligible for a clinical trial?
Common Approach to Treatment of Relapsed/Progressive MM

Patients with Relapsed or Progressive MM

- **Transplant-eligible patient**
  - Previous SCT >12–18 months ago
    - Consider re-induction and autologous SCT
  - Previous SCT <12–18 months ago
    - Novel drug +/- steroid and +/- alkylator or anthracycline

- **Transplant-ineligible patient**
  - Previous treatment without novel drugs
    - <6–9 months ago
      - Change regimen
    - >6–9 months ago
      - Consider repeating previous regimen
  - Previous treatment with novel drugs
    - <6–9 months ago
      - Change regimen
    - >6–9 months ago
      - Consider repeating previous regimen

*Available clinical trial applicable to all patients

Approved Agents for the Relapsed/Refractory Setting

- **Proteasome Inhibitors**
  - Carfilzomib
  - Ixazomib

- **Immunomodulator**
  - Pomalidomide

- **HDAC Inhibitor**
  - Panobinostat

*HDAC = histone deacetylase.*
Pomalidomide

- **FDA approval:** February 8, 2013
- **Class:** IMiD
- **Administration:** oral
- **REMS program**
  - Discuss administration with patient: 4 mg once daily on days 1–21 of 28-day cycle
  - Take without food
    - At least 2 hours before/after meals

- **Do not break, chew, or open the capsules**
- **Adherence:** consistent schedule (AM or PM)
- **Educate patients on:**
  - DVT prophylaxis
  - Infection risk/blood counts
  - Fatigue
  - Should not cause peripheral neuropathy

### Pomalidomide Common AE (in > 30%)

<table>
<thead>
<tr>
<th>AE</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue and asthenia</td>
<td>55</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>52</td>
</tr>
<tr>
<td>Constipation</td>
<td>38</td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>34</td>
</tr>
<tr>
<td>Upper resp. tract infection</td>
<td>32</td>
</tr>
<tr>
<td>Back pain</td>
<td>32</td>
</tr>
<tr>
<td>Pyrexia (pom + dex)</td>
<td>30</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis; IMiD = immunomodulatory drug.

Carfilzomib

• FDA approval: July 20, 2012
• Class: proteasome inhibitor
• Administration:
  • Premedicate: 4 mg dexamethasone before carfilzomib
    • All doses cycle 1; 1st dose cycle 2
    • Additional doses/cycles if infusion reactions
  • Hydrate: 250 to 500 mL IV saline
    • Before carfilzomib; after (optional)
  • Monitor for overhydration
• Administer carfilzomib IV
  • Over ~ 10 min (longer if needed)
  • Rinse IV with saline before and after
• Monitor AEs, which may include cardiopulmonary
• The drug may require dose adjustment for toxicities; diuretics, inhalers; minimal peripheral neuropathy

<table>
<thead>
<tr>
<th>Carfilzomib AEs (All Grades) &gt;30%</th>
<th>AE</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Carfilzomib: ASPIRE Trial

- The international, randomized, phase III superiority trial evaluating carfilzomib with lenalidomide and low-dose dexamethasone (KRd) vs. lenalidomide and low-dose dexamethasone (Rd) in patients with relapsed or refractory MM who had received 1 to 3 lines of therapy

- Primary endpoint: Progression-free survival

**KRD (n = 396)**
- PFS = 26.3 months
- ORR = 87%
- ≥CR = 32%
- PFS increased by 9 months with KRD; higher ORR, deeper response and longer median duration of response with KRD

**RD (n = 396)**
- PFS = 17.6 months
- ORR = 67%
- ≥CR = 9%

Carfilzomib: ENDEAVOR Trial

- The phase III, randomized, multicenter, superiority study comparing carfilzomib and dexamethasone (Kd) to bortezomib and dexamethasone (Vd) in patients with relapsed or refractory MM

- Primary endpoint: Progression-free survival

- **KD** (n = 464)
  - PFS = 18.7 months
  - ORR = 77%
  - ≥CR = 13%

- **VD** (n = 465)
  - PFS = 9.4 months
  - ORR = 63%
  - ≥CR = 6%

Doubled the PFS with KD; higher ORR, deeper response, and longer median duration of response with KD; PFS benefit was extended whether you had prior treatment with a PI or not

Ixazomib

<table>
<thead>
<tr>
<th>Approval Date</th>
<th>• 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Class</td>
<td>• Second generation oral proteasome inhibitor</td>
</tr>
</tbody>
</table>
| Mechanism of Action | • Reversibly and preferentially binds and inhibits the 20S proteasome  
                      • Induces apoptosis of MM cell lines  
                      • The combination of ixazomib and lenalidomide demonstrates synergistic cytotoxic effects |
| FDA-Approved Indication | • In combination with dexamethasone and lenalidomide for the treatment of patients with MM who have received at least one prior therapy |

Ixazomib: TOURMALINE-MM1 Trial

• An international, randomized, double-blind, placebo-controlled clinical trial evaluating IRD compared with placebo with lenalidomide and dexamethasone in patients with relapsed and/or refractory MM who received 1–3 prior lines of therapy

• Primary endpoint: Progression-free survival

IRD (n = 360) → PFS = 20.6 months, ORR = 78%, ≥CR = 12%

Placebo RD (n = 362) → PFS = 14.7 months, ORR = 72%, ≥CR = 7%

N = 722

40% decrease in risk of progression; PFS extended to patients with high risk cytogenetics (overcomes high risk)

IRD = ixazomib, lenalidomide, and dexamethasone.
Ixazomib/Lenalidomide/Dexamethasone

Starting dose is 4 mg oral capsule

Dosing Schedule for ixazomib taken with lenalidomide and dexamethasone

<table>
<thead>
<tr>
<th>28-Day Cycle (a 4-week cycle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
</tr>
<tr>
<td>Day 1</td>
</tr>
<tr>
<td>Ixazomib</td>
</tr>
<tr>
<td>Lenalidomide</td>
</tr>
<tr>
<td>Dexamethasone</td>
</tr>
</tbody>
</table>

For moderate hepatic impairment or severe renal impairment, reduce starting dose to 3 mg.

Ixazomib: Administration Precautions

- Take ixazomib approximately at the same day each week
- Take 1 hour before food or 2 hours after food
- Ixazomib and dexamethasone should not be taken at the same time
- Antiviral prophylaxis is required
- Thromboprophylaxis in combination with lenalidomide
- Avoid concomitant administration with strong CYP3A inducers

Ixazomib: Adverse Reactions Occurring ≥20%

- Diarrhea
- Constipation
- Thrombocytopenia
- Peripheral neuropathy
- Nausea/vomiting
- Back pain
- Peripheral edema

Panobinostat

**Approval Date**
- 2015, accelerated approval based on PFS

**Drug Class**
- Nonselective histone deacetylase inhibitor (oral)

**Mechanism of Action**
- Inhibition of histone deacetylase activity results in cell cycle arrest and apoptosis of some transformed cells and cytotoxicity
- Helps to turn on tumor suppressor genes

**FDA-Approved Indication**
- In combination with bortezomib and dexamethasone for the treatment of patients with MM who have received at least two prior regimens, including bortezomib and an immunomodulatory agent

Panobinostat: PANORAMA-1 Trial

- A multicenter, randomized, placebo-controlled, double-blind phase III trial of FVD vs. placebo, bortezomib, and dexamethasone in patients with relapsed or relapsed and refractory MM who have received between one and three previous treatment regimens
- Primary endpoint: Progression-free survival

FVD = panobinostat, bortezomib and dexamethasone.
Panobinostat/Bortezomib/Dexamethasone

- For mild hepatic impairment, reduce starting dose to 15 mg
- For moderate hepatic impairment, reduce starting dose to 10 mg

Starting dosage is panobinostat 20 mg

<table>
<thead>
<tr>
<th>Medication Key</th>
<th>Panobinostat 20 mg oral</th>
<th>Bortezomib 1.3 mg/m² by injection</th>
<th>Dexamethasone 20 mg oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYCLES 1–8</td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 3</td>
</tr>
<tr>
<td>Week 1</td>
<td>F V D</td>
<td>D</td>
<td>F</td>
</tr>
<tr>
<td>Week 2</td>
<td>F V D</td>
<td>D</td>
<td>F</td>
</tr>
<tr>
<td>Week 3</td>
<td>F V D</td>
<td>D</td>
<td>F</td>
</tr>
</tbody>
</table>

Consider continuing treatment for an additional 8 cycles for patients with clinical benefit, unless they have unresolved severe or medically significant toxicity. The total duration of treatment may be up to 16 cycles (48 weeks)

<table>
<thead>
<tr>
<th>CYCLES 9–16</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>F V D</td>
<td>D</td>
<td>F</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>F V D</td>
<td>D</td>
<td>F</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>REST</td>
<td></td>
</tr>
</tbody>
</table>

Panobinostat: Administration Precautions

- Avoid star fruit, pomegranates, and grapefruit
- If dose is missed, can take up to 12 hours after the specified dose time
- **Ensure antidiarrheals are at home**
- Obtain baseline ECG and monitor throughout therapy
  - Do not initiate panobinostat if QTcF > 450 msec or clinically significant baseline ST-segment or T-wave abnormalities
- Obtain serum electrolytes prior to therapy and weekly or more often if needed
- Monitor liver function tests and complete blood counts

ECG = electrocardiogram.
Panobinostat: Adverse Reactions ≥20%

- Diarrhea (68%), severe in 25%
- Fatigue
- Nausea/vomiting
- Peripheral edema
- Low appetite
- Pyrexia
- Myelosuppression
  - Thrombocytopenia 67%
  - Severe neutropenia 34%
- Electrolyte abnormalities
Case

- Challenge in choosing is that all the salvage regimens are based on lenalidomide-sensitive patients
- Many patients in the United States will have been on lenalidomide maintenance post transplant
- Patient elected to go on IRD as he wanted an all oral regimen
- Does well for 24 months, and then has progression with anemia and bone pain
- What treatment would be considered next?
Continuing Evolution of MM Treatment: New Classes and Targets

Novel Therapies and Immunotherapy

- Chemotherapy
  - Carfilzomib
  - Bortezomib
  - Thalidomide
  - Lenalidomide
  - Thalidomide

- Monoclonal antibody
  - Isatuximab

- Proteasome inhibitor
  - Pomalidomide
  - Panobinostat

- HDAC inhibitor
  - Bortezomib

- IMiD
  - Lenalidomide

- Adoptive T cell therapy
  - CAR-T

- Vaccines
  - Atezolizumab
  - Nivolumab
  - Isatuximab

- Checkpoint inhibitors
  - Ixazomib
  - Elotuzumab
  - Vemurafenib

KSP = kinesin spindle protein; PLD = pegylated liposomal doxorubicin; SINE = selective inhibitor of nuclear export.
Newer Agents for Refractory Disease
MAb-Based Targeting of Myeloma

ADCC = antibody-dependent cellular cytotoxicity; CDC = complement-dependent cytotoxicity.

## Excitement of Monoclonal Antibodies

### Advantages
- Novel mechanism of action
  - Additive or synergistic effects with current anti-MM drugs
- Generally well tolerated
  - Toxicity profile nonoverlapping with approved anti-MM drugs
- Can be combined with other immune therapies
- May be ideally suited to eliminate MRD
- May be beneficial in all patient groups (SMM, ND, RR, MRD)
- Many targets possible
  - MM cell
  - Microenvironment
  - Immune signals

### Disadvantages
- Infusion reactions can limit therapy in some
- No biomarkers for response to predict who may most benefit
- Few long-term survivors
- Cost: Very expensive to produce
Elotuzumab

Elotuzumab is an anti-SLAMF7 monoclonal antibody (mAb). SLAMF7 is expressed on both multiple myeloma (MM) cells and natural killer (NK) cells. It tags MM cells for antibody-dependent cell-mediated cytotoxicity (ADCC) via NK cells and activates NK cells via EAT-2 for MM cell destruction independent of ADCC. Activity in combination with lenalidomide led to the ELOQUENT trial.

NK = natural killer.
## Phase I/II Elotuzumab + Len/Dex: Efficacy

<table>
<thead>
<tr>
<th>Best Confirmed Response, n (%)</th>
<th>All Patients n = 28</th>
<th>Patients w/o Prior Lenalidomide n = 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (≥ PR)</td>
<td>23 (82)</td>
<td>21 (95)</td>
</tr>
<tr>
<td>VGPR</td>
<td>8 (29)</td>
<td>7 (32)</td>
</tr>
<tr>
<td>PR</td>
<td>14 (50)</td>
<td>13 (59)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (11)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (7)</td>
<td>0</td>
</tr>
</tbody>
</table>

†Assessments were performed once per cycle; †Progression defined by IMWG Criteria; Stratification in phase II: prior therapies (1 vs. 2 or 3 lines), prior thalidomide or thalidomide analogs

Len/dex: lenalidomide plus low dose dexamethasone.

Most Common Treatment Emerging Grade 3/4 AEs Before and After 18 Months of Treatment

- Across dosages, 51 patients received therapy for over 18 months.
- Most treatment-emergent AEs occurred within 18 months of therapy.

<table>
<thead>
<tr>
<th>Grade 3/4 AEs,* n (%)</th>
<th>Onset</th>
<th>Elotuzumab + len/dex 10 mg/kg</th>
<th>Elotuzumab + len/dex 20 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤18 months n = 39</td>
<td>&gt;18 months n = 20</td>
<td>≤18 months n = 59</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8 (21)</td>
<td>1 (5)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8 (21)</td>
<td>1 (5)</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>10 (26)</td>
<td>1 (5)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (13)</td>
<td>1 (5)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2 (5)</td>
<td>0</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (8)</td>
<td>1 (5)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (10)</td>
<td>2 (10)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3 (8)</td>
<td>1 (5)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3 (8)</td>
<td>1 (5)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (8)</td>
<td>0</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

*In ≥5% of patients across elotuzumab 10 and 20 mg/kg.

## Best Response From the Phase II Cohort

<table>
<thead>
<tr>
<th></th>
<th>Phase II Elotuzumab 10 mg/kg</th>
<th>Phase II Elotuzumab 20 mg/kg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>36</td>
<td>37</td>
<td>73</td>
</tr>
<tr>
<td>ORR (≥PR), n (%) (95% CI)*</td>
<td>33 (92) (78–98)</td>
<td>28 (76) (59–88)</td>
<td>61 (84) (73–91)</td>
</tr>
<tr>
<td>CR/stringent CR, n (%)</td>
<td>5 (14)</td>
<td>4 (11)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>VGPR, n (%)</td>
<td>18 (50)</td>
<td>14 (38)</td>
<td>32 (44)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>10 (28)</td>
<td>10 (27)</td>
<td>20 (27)</td>
</tr>
<tr>
<td>&lt;PR, n (%)</td>
<td>3 (8)</td>
<td>9 (24)</td>
<td>12 (16)</td>
</tr>
</tbody>
</table>

*By Clopper-Pearson method

ELOQUENT-2 Study Design

- Open-label, international, randomized, multicenter phase III trial (168 global sites)
- Endpoints
  - Co-primary: PFS and ORR
  - Other: OS (data not yet mature); duration of response, quality of life, safety
- All patients received premedication to mitigate infusion reactions prior to Elo administration

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

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

ELOQUENT-2: Key Adverse Events Reported in ≥30% of Patients

- Exposure-adjusted infection rate was 197 (incidence rate per 100 person–years of exposure) in both arms
- There was no detriment to overall health-related quality of life with the addition of Elo to Ld

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>E-Ld (n = 318)</th>
<th>Ld (n = 317)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Common nonhematologic adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>149 (47)</td>
<td>27 (8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>119 (37)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>149 (47)</td>
<td>16 (5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>113 (36)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>95 (30)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Cough</td>
<td>100 (31)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Common hematologic toxicities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>316 (99)</td>
<td>244 (77)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>260 (82)</td>
<td>107 (34)</td>
</tr>
<tr>
<td>Infections</td>
<td>259 (81)</td>
<td>89 (28)</td>
</tr>
</tbody>
</table>
ELOQUENT-2: Infusion Reactions

- Infusion reactions occurred in 10% of patients
- 70% of infusion reactions occurred with the first dose
- No grade 4 or 5 infusion reactions
- Elotuzumab infusion was interrupted in 15 (5%) patients due to an infusion reaction (median interruption duration 25 minutes)
- 2 (1%) patients discontinued the study due to an infusion reaction

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>E-Ld (n = 318)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1/2</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>29 (9)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Chills</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Daratumumab

- Anti-CD38 mAb
- Active as single agent and in combination with lenalidomide
- First mAb approved for the treatment of MM patients who have received at least 3 prior lines of therapy, including a PI and an IMiD or who are double refractory to a PI and an IMiD
- Infusion reactions main side effect
- Potential impact on both standard- and high-risk disease

Daratumumab (cont)

• The most clinically advanced of the anti-CD38 monoclonal antibodies

A phase II study in patients who had already received multiple lines of therapy showed:

• The majority of patients had reduction in their paraprotein levels compared to their baseline levels

• Between 21% and 29% overall response rates were observed even in patients who were refractory to:
  – Carfilzomib
  – Pomalidomide
  – Bortezomib + lenalidomide
  – Or all four agents

Overall Response Rate: DARA + LEN/DEX

- Clinical benefit rate (ORR + minimal response) = 88%

Overall Response Rate: DARA + POM-D

- ORR in double-refractory patients = 67%
- Clinical benefit rate (ORR + minimal response) = 74%

The Practical Part: Infusion Reactions

### Common Symptoms

- **Anti-CD38 mAb**
  - Sinus/nasal congestion
  - Throat irritation
  - Cough, dyspnea, wheezing
  - Rare: Anaphylaxis, severe HTN, CP, arrhythmias

- **Elotuzumab**
  - Fever, chills
  - Hypertension
  - Less: bradycardia, hypoTN

### Treatment

- Recognize early and stop infusion (37% Dara, 5% Elo)
- Give additional premedications
- Restart at half the rate (discontinue if grade 4 or recurs)

---

**Be prepared:**

- Start infusions early
- Pre-med everyone → additional meds likely to be needed

The Practical Part: Response and Blood Typing

Assessing Response
- mAb may be detectable on SPEP/IFE
- Can obscure CR assessment

Infection
- VZV prophylaxis

Blood Banking
- Anti-CD38 may interfere with blood bank tests
  - CD38 on reagent RBCs
    - Positive DAT
    - Positive antibody screen
    - Approaches to resolve anti-CD38 interference
  - *Send type and screen BEFORE first dose-DARA
  - Genotype/phenotype recipient’s RBCs
  - DTT-treating reagent RBCs (+/- available, give Kell-cells)
  - Neutralize anti-CD38 in plasma (anti-idiotype, sCD38)

Case

- Patient started on pomalidomide/daratumumab/dexamethasone
- Thromboprophylaxis due to pomalidomide
- T&S sent to blood bank prior to daratumumab infusion
- Tolerating well and currently responding to therapy
Summary

• While myeloma is currently not curable, the median overall survival has improved dramatically over the past decade
• The goal of therapy is to improve the depth and duration of response
• There are many therapeutic options, with more agents on the way
• Toxicities are manageable with close monitoring and dose modifications
• Clinical trials are available and should be considered