Multiple Myeloma

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Myeloma Is a Cancer of Plasma Cells

- Cancer of plasma cells
- Healthy plasma cells produce immunoglobulins G, A, M, D, and E
- Myeloma cells produce abnormal immunoglobulin “paraprotein

At a Glance

<table>
<thead>
<tr>
<th>Estimated New Cases in 2019</th>
<th>32,110</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of All New Cancer Cases</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

| Estimated Deaths in 2019    | 12,960 |
| % of All Cancer Deaths      | 2.1%   |

Most frequently diagnosed in ages 65 to 74 years (median, 69 years)

Image courtesy of American Society of Hematology
Immunoglobulin Structure

Immunoglobulins are made up of 2 heavy chains

- \textit{IgG, IgA and IgM}
- \textit{in myeloma or AL}

2 light chains

- \textit{Kappa or Lambda}

Abnormal, overproduction of one clone of a protein “monoclonal protein”, elevated free light chains
# Initial Evaluation Investigative Workup

<table>
<thead>
<tr>
<th>Test</th>
<th>Possible finding(s) with myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential counts</td>
<td>↓ Hgb, ↓ WBC, ↓ platelets</td>
</tr>
<tr>
<td>CMP and electrolytes</td>
<td>↑ Creat, ↑ Ca++, ↑ uric acid, ↓ Alb</td>
</tr>
<tr>
<td>Serum electrophoresis with quantitative immunoglobulins (SPEP)</td>
<td>↑ M protein in serum, may have ↓ levels of normal antibodies</td>
</tr>
<tr>
<td>Immunofixation of serum</td>
<td>Identifies light/heavy chain types M protein</td>
</tr>
<tr>
<td>β₂m and LDH</td>
<td>↑ Levels (measure of tumor burden)</td>
</tr>
<tr>
<td>24-hour urine protein electrophoresis with immunofixation (UPEP)</td>
<td>↑ Monoclonal protein (<em>Bence Jones</em>)</td>
</tr>
<tr>
<td>BM aspirate and biopsy, FISH and cytogenetics</td>
<td>≥ 10% clonal plasma cells, prognosis (FISH and cytogenetics) Congo red BM stain if amyloid suspected</td>
</tr>
<tr>
<td>Skeletal survey; low-dose whole-body CT or PET should be considered</td>
<td>Osteolytic lesions, osteoporosis, EM disease</td>
</tr>
<tr>
<td>MRI</td>
<td>Does not replace skeletal survey; consider w/SMM</td>
</tr>
</tbody>
</table>

β₂m = β2 microglobulin; CT = computed tomography; EM = extramedullary; FISH = fluorescence in situ hybridization; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PET = positron emission tomography; sFLV = serum free light chain.

# Multiple Myeloma Typically Preceded by Premalignant Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>MGUS(^{1-4}) (Monoclonal Gammopathy of Undetermined Significance)</th>
<th>SMM(^{1-5,8}) (Smoldering Multiple Myeloma)</th>
<th>Active Multiple Myeloma(^{6-8})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonal plasma cells in bone marrow</td>
<td>&lt;10%</td>
<td>10%-60%</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>Presence of Myeloma Defining Events</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Likelihood of progression</td>
<td>~1% per year</td>
<td>~10% per year</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Treatment</td>
<td>No; observation</td>
<td>Yes for high risk*; No for others</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* In clinical trial (preferred) or offer treatment for those likely to progress within 2 years

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Myeloma Disease Overview: Case Presentation

- Bob is a 55-year-old accountant and avid runner who presents to the APP with complaints of back pain that had progressed from mild over 3 weeks.
- No significant medical history except for controlled hypertension, hyperlipidemia
- Routine labs

**Complete Blood Count**
- WBC count 3,300/μL
- Hemoglobin 9.3 g/dL
- Platelet count 138,000/μL

**Complete Chemistry Panel**
- Creatinine 2.1 g/dL
- Calcium 12.4 mg/dL
- Albumin 3.2 g/dL
- Total protein 10.9 g/dL
Skeletal Survey and MRI

Skeletal survey (x-rays)

Osteolytic lesions

MRI of spine showing T6 wedge deformity

Bob developed acute back pain when lifting furniture that evening. Based on the skeletal findings, Bob was admitted to the hospital for evaluation, management and pain control.

Images Courtesy of Beth Faiman PhD, MSN, APRN-BC, AOCN
Case Presentation continued

- **Additional labs:**
  - Monoclonal protein analysis (MPA): IgG 4,300 mg/dL and kappa 5,900 mg/dL
  - Serum protein electrophoresis (SPEP): Monoclonal “spike” 4.2 g/dL
  - 24-hour urine: normal < 0.16 g/24 hours
  - Beta₂-microglobulin: elevated 2.6 mg/L
  - Anemia panel showed low B₁₂, high MMA, suggestive of vitamin B₁₂ deficiency
  - Bone marrow biopsy showed 40% kappa restricted “clonal” plasma cells; normal cytogenetics, no IgH translocations.
  - *What is Bob’s diagnosis?*

<table>
<thead>
<tr>
<th>M proteins: Lab/Normal Reference Range</th>
<th>Value</th>
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<tbody>
<tr>
<td>MPA serum IgG 717–1,411 mg/dL</td>
<td>4,300</td>
</tr>
<tr>
<td>MPA serum IgA 78–391 mg/dL</td>
<td>29</td>
</tr>
<tr>
<td>MPA serum IgM 53–334 mg/dL</td>
<td>24</td>
</tr>
<tr>
<td>MPA serum kappa 534–1,267 mg/dL</td>
<td>5,900</td>
</tr>
<tr>
<td>MPA serum lambda 253–653 mg/dL</td>
<td>&lt; 30</td>
</tr>
</tbody>
</table>
Diagnostic Criteria: SLiM CRAB

Clonal bone marrow $\geq 10\%$ or bony/extramedullary plasmacytoma

AND any one or more Myeloma Defining Events (MDE)

- Calcium elevation
- Renal complications
- Anemia
- One disease

BM: Clonal bone marrow $\geq 60\%$

FLC: sFLC ratio $>100$

MRI: $>1$ focal lesion by MRI

**Staging MM: R-ISS**

Serum LDH, β\(_2\) microglobulin, albumin, and cytogenetics (FISH) are required to determine stage using the R-ISS System

<table>
<thead>
<tr>
<th>Stage</th>
<th>ISS Criteria(^1)</th>
<th>R-ISS Criteria(^2,3)</th>
</tr>
</thead>
</table>
| I     | Serum β\(_2\) microglobulin <3.5 mg/L serum albumin ≥3.5 g/dL | ISS Stage I  
AND  
No del(17p), t(4;14), and/or t(14;16)  
AND  
normal LDH |
| II    | Not stage I or III | Not stage I or III |
| III   | Serum β\(_2\) microglobulin ≥5.5 mg/L | ISS stage III  
AND  
del(17p), t(4;14), and/or t(14;16)  
OR  
LDH is greater than ULN |

*Neither stage I nor stage III.

†Testing by FISH; standard risk = no chromosome abnormality; high risk = del(17p) and/or t(4:14) and/or t(14:16).
del, deletion; FISH, fluorescence in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised ISS; t, translocation; ULN, upper limit of normal.

Expanding Treatment Options for Multiple Myeloma: Mibs, Mids, and mAbs

- Alkylators
- Steroid
- Anthracyclines
- Proteasome inhibitors ("mibs")
- Immunomodulators ("IMiDs" Or "mids")
- Monoclonal antibodies ("mAbs")
- HDAC inhibitor

1970: 1983 Auto Transplantation
1980: 1986 High-Dose Dex
2000: 2007 Doxorubicin
2019: 

Auto = autologous; Dex= dexamethasone.
Relapsing Nature of Multiple Myeloma: Clones Change Over Time

MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma.
# Classes: Mides, Mibs, MABs and Others to Treat MM

<table>
<thead>
<tr>
<th>Immuno-modulatory Drugs</th>
<th>Proteasome Inhibitors</th>
<th>Chemotherapy Anthracyclines</th>
<th>Chemotherapy Alkylators</th>
<th>Steroids</th>
<th>Histone Deacetylase Inhibitors</th>
<th>Monoclonal Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide (PO)</td>
<td>Bortezomib (IV/SC)</td>
<td>Doxorubicin (IV)</td>
<td>Cyclophosphamide (IV, PO)</td>
<td>Dexamethasone (IV, PO)</td>
<td>Panobinostat (PO)</td>
<td>Elotuzumab (IV)</td>
</tr>
<tr>
<td>Lenalidomide (PO)</td>
<td>Carfilzomib (IV)</td>
<td>Liposomal doxorubicin (IV)</td>
<td>Bendamustine (IV)</td>
<td>Prednisone (PO)</td>
<td></td>
<td>Daratumumab (IV)</td>
</tr>
<tr>
<td>Pomalidomide (PO)</td>
<td>Ixazomib (PO)</td>
<td></td>
<td>Melphalan (PO)</td>
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</table>

Bortezomib +/- lenalidomide and dexamethasone is a common standard of care for newly diagnosed MM patients in the US +/- transplant if eligible, and desire.
Common Treatments for Multiple Myeloma

Frontline (Induction)
- Rd: Lenalidomide dex
- Vd: Bortezomib dex
- RVd lite: Lenalidomide Bortezomib dex lite
- VRd: Bortezomib Lenalidomide dex
- KRd: Carfilzomib Lenalidomide dex
- VMP-DARA: Bortezomib Melphalan Prednisone Daratumumab
- ASCT: Autologous Stem Cell Transplant

Gentler

Maintenance
- Lenalidomide ± Proteasome Inhibitor
- Plus new agents in clinical trials

More Aggressive

Relapse
- Bortezomib
- Lenalidomide
- Carfilzomib
- Ixazomib
- Pomalidomide
- Daratumumab
- Elotuzumab
- Panobinostat
- Cyclophosphamide
- Doxorubicin
- Bendamustine

Often in Combination Regimens

Balancing the Many, Many Choices at Diagnosis and Relapse

<table>
<thead>
<tr>
<th>FDA-approved after 1+ myeloma therapies*</th>
<th>Combinations*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfilzomib</td>
<td>KRd, Kd</td>
<td>IV</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>Pd</td>
<td>oral</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>ERd</td>
<td>IV</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>DRd, DVd</td>
<td>IV</td>
</tr>
<tr>
<td>Ixozasomib</td>
<td>IRd</td>
<td>oral</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>Pano-Vd</td>
<td>oral, diarrhea</td>
</tr>
</tbody>
</table>

Data and Experience

- Disease Characteristics & Prior Treatment
- Efficacy of Regimen
- Comorbid conditions

Patient Preference

- Administration, chair time
- Finances/Insurance
- Social status/support

ASCO Guideline Update: Bone-Modifying Agents

A bone-modifying agent is recommended for ALL pts receiving anti-myeloma therapy regardless of bone disease status for up to 2 years. Three options:

• **Pamidronate**: 90 mg over 2+ hrs every 3-4 weeks
  – In pts with severe renal impairment (CrCl <30 mL/min): 90 mg over 4-6 hrs
  – Consider dose adjustment for mild-moderate renal impairment

• **Zoledronic acid**: 4 mg over 15+ min every 3-4 weeks
  – Dose adjust for mild-moderate renal impairment (CrCl 30 to 60 mL/min) per PI
  – Not recommended (nor studied) in pts with severe renal impairment

• **Denosumab**: Demonstrated non-inferiority to zoledronic acid in SRE
  – Fewer renal AEs; may be preferred in pts with kidney disease; Hypocalcemia can be an issue

Continuous bone-modifying agent treatment by provider discretion. Retreatment with bone-modifying agent recommended at relapse.

CrCl = creatinine clearance; PI = prescribing information; SRE = skeletal related events.
MM Patients are at risk for VTE, Infection

• VTE Comprises
  – Deep Vein Thrombosis (DVT): Proximal DVT (knee or higher) is a prognostic marker for recurrence and mortality
  – Pulmonary Embolism (PE): Severity depends on size and cardiopulmonary reserve

All patients w/ MM should be screened for DVT risk factors: Surgery, immobilization, hospitalization, renal disease, combination rx, obesity and consider prophylactic AC or ASA

• Infection risk
  – Gram+ encapsulated organisms
  – Hand washing, avoid others w/ known illness
  – Immunizations (influenza, pneumococcal, shingles)
  – Education re: Triggers to call, prompt treatment of sx
### Updated Response Results*

<table>
<thead>
<tr>
<th></th>
<th>VRd (n=215)</th>
<th>Rd (n=207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>24.2% (52)</td>
<td>12.1% (25)</td>
</tr>
<tr>
<td>Very good partial response (VGPR)</td>
<td>50.7% (109)</td>
<td>41.1% (85)</td>
</tr>
<tr>
<td><strong>VGPR or better</strong></td>
<td><strong>74.9%</strong></td>
<td><strong>53.2%</strong></td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>15.3% (33)</td>
<td>25.6% (53)</td>
</tr>
<tr>
<td><strong>Overall Response Rate (ORR)</strong></td>
<td><strong>90.2% (194)</strong></td>
<td><strong>78.8% (163)</strong></td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>7.0% (15)</td>
<td>16.4% (34)</td>
</tr>
<tr>
<td>PD or death</td>
<td>2.8% (6)</td>
<td>4.8% (10)</td>
</tr>
</tbody>
</table>

*Both SWOG and IRC stratified Cochran-Mantel-Haenszel analyses indicated improved responses with VRd (odds ratio = 0.528: P=0.006 [ITT] odds ratio= 0.38: P=0.001 [sensitivity analysis])
3-Drug Combination Better Than 2 in Newly Diagnosed Multiple Myeloma With Delayed ASCT SWOG 0777 UPDATE

PFS

Using Forest plot technique other correlates of improved outcomes (PFS and OS) with VRd are S8,M (<4); BMPC (60%); hemoglobin (>10 GMS/dl); serum creatinine (<2 mg/dl) i.e. predominantly good risk (early disease) risk features

*For all analyses, both SWOG and IRC assessments have been conducted using the fully updated datasets with current datalock in May 2018

ASCT = autologous stem cell transplant; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; Rd = lenalidomide-dexamethasone; VRd = bortezomib-lenalidomide-dexamethasone.

Meta-Analysis: Lenalidomide Maintenance After ASCT Demonstrates Improved PFS and OS vs Placebo/Observation

PFS and OS benefit observed across subgroups:
- Older or younger than 60
- Male or female
- ISS stage I/II, III
- Response after ASCT (prior to maintenance)
- Different induction regimens

Multiple clinical studies have confirmed the benefits of lenalidomide maintenance in MM pts after ASCT

ASCT = autologous stem cell transplant; CI = confidence interval; HR = hazard ratio; ISS = International Staging System; NDMM = newly diagnosed multiple myeloma; OS = overall survival; PFS = progression-free survival.

Tourmaline-3 Ixazomib Post-ASCT Data

What Is Bob’s Diagnosis and Plan?

Discussion

- Anemia, renal insufficiency, hypercalcemia and osteopenia were thought to be related to MM.
- With multiple lytic lesions, hyperca++ and vertebral compression fractures, treatment for active MM is necessary.
- What are the next steps?
  - Treatment decision-making: clinical trial vs. standard care options
  - Supportive care (bone modifying agent, antiviral antibiotics, thromboprophylaxis)
  - Financial and social support services

*One of 3 options

Rajkumar et al., 2014, IMWG working group guidelines for MM diagnosis
What if Bob was not a candidate for ASCT?

Discussion

• Clinical Trials are always preferred!
• Continue VRd as in SWOG0777 (8 cycles then stop bortezomib?)
• VRd light (Weekly SC bortezomib)
• FIRST trial: Rd vs Rd fixed dosing vs MPT: PFS and OS advantage with Rd
• **Key point:** Some form of rx should be ongoing in MM until disease progression, unacceptable toxicity

## Is Treatment Working: IMWG Myeloma Response Criteria

### Flow MRD negative*

Negative by NGF (next-generation flow) (minimum sensitivity 1 in $10^5$ nucleated cells or higher)*

### sCR
- mCR **AND** normal FLC ratio, BM negative by flow, 2 measures

### Molecular CR
- CR **AND** negative PCR

### CR
- Negative immunofixation; no more than 5% plasma cells in BM; 2 measures

### VGPR
- 90% reduction in myeloma protein

### PR
- At least 50% reduction in myeloma protein

### MR

### SD

### PD

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BM = bone marrow; CR = complete response; FLC = free light chain; mCR = molecular CR; MR = minimal response (only in relapsed); NGS = next-generation sequencing; PD = progressive disease; PR = partial response; sCR= stringent complete response; SD = stable disease; VGPR = very good partial response.
Getting to Minimal Residual Disease (MRD): New Definitions Deeper than CR

Key concept: Deeper responses (less residual disease) generally means better patient outcomes

MANY ways to get to deeper responses:
- Multi-drug regimens
- ASCT
- Longer therapy duration (e.g., continuous regimens or maintenance)

ASCT = autologous stem cell transplant; CR = complete response.

Some MM Pts (~17%) Experience Long-Term Remissions

Mayo Clinic follow-up of 2,125 pts with MM at ≥ 10 years

Case study continued

• Bob continues on maintenance with lenalidomide.
• Starts showing signs of slow, biochemical disease progression after 48 months but feels great.
• Labs: M spike
  From 0.00g/dL to 0.96g/dL.
Many Treatment Options at Relapse

Treatment Options

- Bortezomib
- Lenalidomide
- Carfilzomib
- Ixazomib
- Pomalidomide
- Daratumumab
- Elotuzumab
- Panobinostat
- Cyclophosphamide
- Doxorubicin
- Bendamustine

New agents in clinical trials

<table>
<thead>
<tr>
<th>FDA-approved myeloma therapies</th>
<th>Common Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib (SQ admin)</td>
<td>VRD, Vd</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>VRD, Rd</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>KRd, Kd</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>Pd, DPd, EPd, PCd</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>DRd, DVd, DPd, D-VMP</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>ERd, EPd</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>IRd</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>Panobinostat + Vd</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Liposomal doxorubicin + V</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>PCd, VTD-PACE</td>
</tr>
</tbody>
</table>

C = cyclophosphamide; D = daratumumab; d = dexamethasone; E = elotuzumab; I = ixazomib; K = carfilzomib; P = pomalidomide; PACE = cisplatin, doxorubicin, cyclophosphamide, etoposide; R = lenalidomide; SQ = subcutaneous; T = thalidomide; V = bortezomib.

Practical Approach to Treatment of Patients With Relapsed Myeloma

• **Disease-related factors**
  – Duration of response to initial therapy
  – High-risk vs low-risk status
  – Molecular relapse vs symptomatic relapse
  – Other comorbid conditions, patient frailty

• **Treatment-related factors**
  – Previous/current therapy exposure (relapsed or refractory)
  – Toxicity/tolerability of previous regimen (combination vs single agent)
  – Mode of administration (ie, PO or IV)
  – Cost and convenience (out-of-pocket copays for IV vs PO)
  – Patient preference

IV = intravenous; PO = orally.
Pomalidomide Clinical Pearls

• Oral immunomodulatory agent active in R-refractory pts
• Monitor
  – Blood counts—neutropenia most frequent GR 3/4 AE
  – Liver function
  – Response
• Proactive AE management
• Patient education
  – Adherence and REMS
  – Infection prevention
  – Refrain from smoking (reduces pom exposure)
  – Protect renal health (renal excretion of pom)
    • Hydration
    • Avoid NSAIDS, IV contrast, other drugs with renal interactions


AE = adverse event; IV = intravenous; EPd = elotuzumab pomalidomide dexamethasone; GR = grade; NSAID = non-steroidal anti-inflammatory drug; P = pomalidomide; pom = pomalidomide; R = lenalidomide; REMS = Risk Evaluation and Mitigation Strategies.
Ixazomib: Oral Proteasome Inhibitor

• Oral proteasome inhibitor
  – Indication: Patients with multiple myeloma who have received at least 1 prior therapy
  – In combination with Rd
• Administration
  – Oral capsule 1X per week; do not crush, chew or open
  – Empty stomach: 1 hr before/2h after food
• Clinical pearls
  – Adherence, schedule, viral prophylaxis
  – Rapid response (1.1 months)
  – Fast absorption (if vomit, do NOT repeat dose)
  – Cyclic thrombocytopenia
  – Peripheral neuropathy, peripheral edema

CI = confidence interval; HR = hazard ratio; IRd = ixazomib-lenalidomide-dexamethasone; PFS = progression-free survival; Rd = lenalidomide-dexamethasone.

Rd = lenalidomide-dexamethasone; hr = hour.


Clinical Pearls for Elotuzumab, Antibody Targeting SLAMF-7

• Antibody administration
  – Risk of infusion reaction: 10%
    • 3-24 hrs before= Dex 28 mg; 45-90 mins before= Dex 8 mg IV, H1, H2, and acetaminophen
    – Infuse at rate of 0.5ml/min and escalate to 5 ml/min over time
  – Give weekly for 8 weeks then twice monthly until PD
• Prescribed len-dex
  – DVT prophylaxis (for len)
  – Steroid side effects and schedule (AM vs PM)
• Monitoring
  – Blood counts (hold/adjust dose if needed)
  – Response assessment (monthly); interference
  – Glucose (dex can affect)
  – Renal, hepatic function

dex = dexamethasone; len = lenalidomide; DVT = deep vein thrombosis; PD = progressive disease.

**Daratumumab (DARA, D)**

- Human CD38-directed monoclonal antibody
- **Indications**
  - In combination with VMP in newly diagnosed MM patients who are not eligible for transplant
  - In combination with Rd or Vd in MM patients with at least 1 prior therapy
  - In combination with pomalidomide and dex in pts with at least 2 prior therapies including lenalidomide and a proteasome inhibitor
  - As a monotherapy in MM patients who have received at least 3 prior lines of therapy includin a PI and an IMiD OR are double-refractory to a P and an IMiD
- **Current clinical trials**
  - Many underway: watch for new combinations, indications

**DRd = daratumumab-lenalidomide-dexamethasone; DVd = daratumumab-lenalidomide-dexamethasone; IMiD = immunomodulatory agent; PI = proteasome inhibitor; Rd = lenalidomide-dexamethasone; Vd = bortezomib-dexamethasone; VMP = bortezomib-melphalan-prednisone.**

**CASTOR Clinical Trial: MM Pts With 1 Prior Therapy**

**PFS**

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at risk</th>
<th>Vd</th>
<th>Dvd</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>247</td>
<td>251</td>
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</tr>
<tr>
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**Pollux Clinical Trial: MM Pts With 1 Prior Therapy**

**PFS**

- **DVd (n=251)**
  - mPFS, mos: 16.7
  - HR (95% CI): 0.32 (0.25–0.40)
  - p value: <0.0001

- **Vd (n=247)**
  - mPFS, mos: 7.1
  - HR (95% CI): 0.41 (0.31–0.53; P < 0.0001)

CI = confidence interval; dex = dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone; HR = hazard ratio; Mos = months; NR = not reached; PFS = progression-free survival; Rd = lenalidomide-dexamethasone; Vd = bortezomib-dexamethasone.

Special Considerations With Antibody Therapy

- Potential interference with laboratory tests
  - Co-migration of therapeutic antibody with M protein: Overestimation of M protein and reduced CR rates
- Solutions
  - Laboratory assays to minimize effects (eg, high resolution mass spectrometry)
  - Awareness
- Elotuzumab, daratumumab, isatuximab (in development) are all IgG antibodies

Dara = daratumumab.
Carfilzomib: Proteasome Inhibitor

• IV proteasome inhibitor, indications:
  – In combination with dex or len-dex in patients with relapsed or refractory MM who have received 1-3 lines of therapy
  – As a single agent in patients with relapsed or refractory multiple myeloma who have received 1 or more lines of therapy

• Clinical pearls
  – Escalate dose
  – Dose-dependent 10- or 30-min infusion
  – Hydration but not over hydration
  – Premedication (dex)
  – Aspirin prophylaxis
  – Monitor blood counts, response
  – Monitor for infection
  – Herpes virus prophylaxis
  – Know cardiac and pulmonary status and optimize heart failure and blood pressure management
  – Diuretic (furosemide or torsemide) or inhalers if needed

Overall Response Rate:
Once Weekly
Car/dex 20/27mg/m2 vs Car/dex 20/70mg/m2 RRMM

ORR: 62.9%
ORR: 40.8%

Kd 20/56 mg/m² once weekly FDA approved
KRd 20/27 mg/m²
Kd 20/70 mg/m²
K monotherapy 20/27 mg/m²

dex = dexamethasone; IV = intravenous; K = carfilzomib; Kd = carfilzomib, dexamethasone; KRd = carfilzomib, lenalidomide, dexamethasone; len = lenalidomide; MM = multiple myeloma.
Case study Follow up

- Bob opted for treatment with daratumumab, pomalidomide and dexamethasone.
- Type and screen
- Shingles prevention
- Aspirin for VTE prophylaxis
- Other thoughts regarding treatment options?
Selinexor: First-in-class, Oral Selective Inhibitor of Nuclear Export (SINE) Compound: STORM Trial

MM patients with a median of 7 prior regimens
- **ORR of 26.2%**, including 2 stringent CRs
  - 2 pts with stringent CR (sCRs were MRD negative at $10^{-6}$ and $10^{-4}$)
  - 2 pts with previous PD after CAR T-cell: PR
    - Median time to response: 1mo (range 1 to 14 wks)
- Median OS: 8.6 mos
  - 15.6 mos in patients with ≥ MR vs 1.7 mos in pts with PD/NE
- Most commonly occurring grade ≥ 3 AEs were heme, GI, constitutional symptoms, and hyponatremia
- Investigators concluded that selinexor is a potential novel, oral treatment option for patients with MM who have exhausted all approved therapies

Selinexor (KPT-330) inhibits XPO1. By blocking tumor suppressor proteins (TSP) from being exported from the nucleus, selinexor forces nuclear restoration and reactivation of TSPs leading to selective induction of apoptosis of cancer cells

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CAR = chimeric antigen receptor; CR = complete response; MM = multiple myeloma; MR = minimum response; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; sCR = stringent complete response.

New Ways to Target and Kill Myeloma Cells in Development

**CAR-T Cell Therapy**
- Patient T cells
- Chimeric antigen receptor DNA
- Grown in lab
- Reinfused in pt
- Myeloma Cell
- T Cell mediated death
- CD269 (BCMA) or other antigen

**BiTE Antibody**
- Bi-specific T cell Engager
- CD3
- BiTE binds CD3 on T cell and CD269 on myeloma cell
- CD269 (BCMA)
- Myeloma Cell
- T Cell mediated death

**Drug-Antibody Conjugate**
- Cytotoxic drug
- Antibody targeted to myeloma
- CD269 (BCMA)
- Myeloma Cell
- Infusion
- Effector cell mediated death
- Multiple ways to kill myeloma cells

Examples:
- **bb2121, LCAR-B38M, MCARH171**
- **AMG 420**
- **GSK2857916**

BCMA = B-cell maturation antigen.
Future Directions, Final Thoughts

- Advanced practice providers are critical to the management of MM
- Explosion of new therapies has led to an interest in diagnosis, management of MM
- CAR-T and BiTE technology moving forward for myeloma
- Selinexor likely to be approved by FDA soon
- Daratumumab combinations are expanding for myeloma
- Never underestimate your role in patient care
Multiple Choice Questions

Chakra Chaulagain, MD, FACP
Treatment with which one of the following agents can be associated with the rash shown?

a. Lenalidomide  
b. Bortezomib  
c. Rituximab  
d. Vincristine
A 65 y/o man with MM started bortezomib, dexamethasone and lenalidomide (VRD) therapy. All of the following supportive care (s) is/are appropriate except,

a. acyclovir for varicella zoster prophylaxis
b. Aspirin 81mg daily for thromboprophylaxis
c. Zoledronic acid for prevention of skeletal related events
d. Vaccination against varicella zoster (Zostavax, live zoster vaccine)
Case Presentation

- 75 y/o M presented to ER with weakness & weight loss of 20 pounds. He was being evaluated by ortho for revision of hip arthroplasty, during preop assessment, he was found to have hypercalcemia, 17.9, creatinine 5.05. Hb 12.5 at presentation and corrected to 6.9 after normalization of calcium with treatment. Bone survey reveled lytic lesion in the right femur. He has constipation for the last 5 days and was not able to walk due to low back pain. MRI reveled no cord compression. Surprisingly mental status okay.

- SPEP, showed M spike of 0.13 g/dL, serum free kappa light chain 7584 mg/L, lambda 5.1 and K/L >100. IgA, IgM, IgG were all low. Bone marrow biopsy reveled 90% bone marrow involvement by kappa restricted plasma cells.

- Patient met all CRAB criteria (Ca=>11, R=creatinine >2, A=Hb <10, B= lytic bone lesion/s). A diagnosis of multiple myeloma was made.
What is the **first step** in the management of this patient’s hypercalcemia?

a. isotonic saline infusion  
b. Isotonic saline along with furosemide  
c. Dexamethasone  
d. Intravenous bisphosphonates
THANK YOU!!