Updates in the Management of Multiple Myeloma

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Faculty Disclosures

• Ms. Zitella has no relevant financial disclosures to report.
Planner Disclosures

• The planners involved in this educational activity have no financial disclosures to report.
Educational Objectives

• Describe the role of new medications in the treatment of MM

• Identify adverse events and related nursing management strategies with new medications and combinations used to treat MM

• Determine supportive care needs of MM patients considering their medication regimen and co-morbidities

• Outline strategies to reduce the risk of skeletal, thrombotic, and infectious complications in MM
Abbreviations (1)

- ADCC, antibody dependent cell mediated cytotoxicity
- AE, adverse event
- Alb, albumin
- ANC, absolute neutrophil count
- ASCT, autologous stem cell transplant
- B₂m, β2-microglobulin
- BCMA, B-cell maturation antigen
- BMPC, bone marrow plasma cells
- BSA, body surface area
- CA, calcium
- CBC, complete blood count
- Cr, creatinine
- CR, complete remission
- CrCl, creatinine clearance
- CT, computed tomography
- DVT, deep vein thrombosis
- FISH, fluorescence in situ hybridization
- FLC, free light chain
- G-CSF, granulocyte colony-stimulating factor
- GEP, gene expression profile
- GI, gastrointestinal
Abbreviations (2)

- H&P, history and physical
- Hb, hemoglobin
- HCT, hematopoietic cell transplantation
- HSV, herpes simplex virus
- IFE, immunofixation electrophoresis
- Ig, immunoglobulin
- IMiD, immunomodulatory agent
- INR, international normalized ratio
- IRR, infusion related reaction
- ISS, International Staging System
- IV, intravenous
- IVIG, intravenous immunoglobulin
- IMWG, International Myeloma Working Group
- κ, kappa
- KRD, carfilzomib/lenalidomide/dexamethasone
- λ, lambda
- LDH, lactate dehydrogenase
- LLN, lower limit of normal
- LMWH, low molecular-weight heparin
Abbreviations (3)

- M, monoclonal
- mAb, monoclonal antibody
- MDE, myeloma-defining events
- MGUS, monoclonal gammopathy of undetermined significance
- MM, multiple myeloma
- MRD, minimal residual disease
- MRI, magnetic resonance imaging
- NDMM, newly diagnosed multiple myeloma
- NGS, next-generation sequencing
- NGF, next-generation flow
- NS, normal saline
- NSAID, non-steroidal anti-inflammatory drug
- ONJ, osteonecrosis of the jaw
- OS, overall survival
- PCLI, plasma cell labeling index
- PCP, pneumocystis pneumonia
- PE, pulmonary embolism
- PET, positron emission tomography
- PFS, progression-free survival
- PI, proteasome inhibitor
Abbreviations (4)

- RBC, red blood cell
- RR, relapsed/refractory
- RT-PCR, reverse transcription polymerase chain reaction
- SC, subcutaneous
- SIFE, serum immunofixation electrophoresis
- SINE, selective inhibitor of nuclear export
- SMM, smoldering multiple myeloma
- SPEP, serum electrophoresis

- TSP, tumor suppressor proteins
- ULN, upper limit of normal
- UPEP, urine protein electrophoresis
- VGPR, very good partial response
- VRD, bortezomib/lenalidomide/dexamethasone
- VTE, venous thromboembolism
- WBC, white blood cells
Multiple Myeloma (MM)

- Malignancy of plasma cells
- Normal plasma cells produce antibodies: IgG, IgA, IgM, IgD, IgE
- MM cells are clonal and produce a monoclonal Ig, also called M protein
- Characterized by:
  - Accumulation of MM cells in the bone marrow
  - Monoclonal Ig in serum/urine
  - Bone destruction
- Incurable with current therapy

*Image: ASH Image Bank #63228 https://imagebank.hematology.org*
## MM Fast Facts

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimated New Cases in 2020</strong></td>
<td>32,270</td>
</tr>
<tr>
<td>% of All New Cancer Cases</td>
<td>1.8%</td>
</tr>
<tr>
<td><strong>Estimated Deaths in 2020</strong></td>
<td>12,830</td>
</tr>
<tr>
<td>% of All Cancer Deaths</td>
<td>2.1%</td>
</tr>
<tr>
<td><strong>Median Age at Diagnosis</strong></td>
<td>69 years</td>
</tr>
<tr>
<td>Median OS (2010-2016)</td>
<td>54%</td>
</tr>
<tr>
<td># people living with MM (2017)</td>
<td>140,779</td>
</tr>
</tbody>
</table>

MM Type Based on the Immunoglobulin (Ig) Produced by the MM Cell

- Each plasma cell produces only 1 type of heavy chain and 1 type of light chain
  - Heavy chain (77%)
    - 5 types of heavy chains: IgG, IgA, IgM, IgD, and IgE
  - Light chain (Bence-Jones protein) (20%)
    - 2 types of light chains: kappa [κ] and lambda [λ]
  - Nonsecretory (1-2%)
    - No detectable Ig in serum or urine
- IgG kappa is the most common type of MM

# Stages of Monoclonal Plasma Cell Disease

<table>
<thead>
<tr>
<th></th>
<th>MGUS</th>
<th>SMM</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>M protein</td>
<td>&lt;3 g/dL</td>
<td>&gt;3 g/dL</td>
<td>&gt;3 g/dL</td>
</tr>
<tr>
<td>Bone marrow plasma cells</td>
<td>&lt;10%</td>
<td>≥10% to ≤60%</td>
<td>≥10%</td>
</tr>
<tr>
<td>Myeloma-defining event</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Monoclonal Gammopathy of Undetermined Significance (MGUS)**

Premalignant precursor condition present in 3-4% of general population >50 y
Risk of progression to MM: 1% per year

**Smoldering Multiple Multiple Myeloma (SMM)**

Risk of progression to MM: 10% per year
Clinical Manifestations

- Decreased normal Ig
  - Immunodeficiency
    - Infections
- Hyperviscosity
- Amyloidosis
- Renal failure
- MM cells
- Bone marrow infiltration
  - Cytokine release
  - Lytic lesions
  - Anemia
  - Hypercalcemia
  - Bone pain

<table>
<thead>
<tr>
<th>Test</th>
<th>Possible finding(s) with myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential</td>
<td>↓ Hb, ↓ WBC, ↓ platelets</td>
</tr>
<tr>
<td>Electrolytes, creatinine, LFTs, uric acid</td>
<td>↑ Cr, ↑ Ca, ↑ uric acid, ↓ Alb</td>
</tr>
<tr>
<td>Serum protein electrophoresis (SPEP)</td>
<td>↑ M protein in serum</td>
</tr>
<tr>
<td>Serum immunofixation (SIFE)</td>
<td>Presence of monoclonal protein and type</td>
</tr>
<tr>
<td>Serum quantitative immunoglobulins (IgG, IgM, IgA)</td>
<td>May have ↓ levels of normal antibodies or ↑ levels of involved antibodies</td>
</tr>
<tr>
<td>B&lt;sub&gt;2&lt;/sub&gt;m and LDH</td>
<td>↑ Levels (measure of tumor burden)</td>
</tr>
<tr>
<td>24-hour urine for UPEP and immunofixation (UIFE)</td>
<td>↑ Light chains (Bence-Jones protein)</td>
</tr>
<tr>
<td>Serum-free light chain assay</td>
<td>↑ Free-light chains in serum</td>
</tr>
</tbody>
</table>
| Bone marrow aspirate and biopsy, with IHC, flow cytometry, and myeloma FISH panel * | ≥10% plasma cells  
FISH: del13, del17p13, t(4;14), t(11;14), t(14;16), t(14;20), 1q21 gain/amplification, 1p deletion |
| Whole body low-dose CT or PET/CT                                    | Involvement with bone disease                                      |

**IMWG Diagnostic Criteria for MM: SLiM-CRAB**

**BMPC ≥10% or biopsy-proven bony or extramedullary plasmacytoma AND ≥1 MDE**

<table>
<thead>
<tr>
<th>Malignancy biomarker</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>Clonal bone marrow plasma cells ≥60%</td>
</tr>
<tr>
<td>Li</td>
<td>Uninvolved/involved serum FLC ratio ≥100 and involved FLC concentration ≥10 mg/dL</td>
</tr>
<tr>
<td>M</td>
<td>One or more focal lesions on MRI studies ≥5 mm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>End-organ damage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Calcium elevation: Serum calcium &gt;1 mg/dL higher than ULN or &gt;11 mg/dL</td>
</tr>
<tr>
<td>R</td>
<td>Renal dysfunction: CrCl &lt;40 mL/min or serum Cr &gt;2 mg/dL</td>
</tr>
<tr>
<td>A</td>
<td>Anemia: Hemoglobin &lt;10 g/dL or hemoglobin &gt;2 g/dL below the LLN</td>
</tr>
<tr>
<td>B</td>
<td>Bone disease: One or more osteolytic lesions on skeletal radiography, CT, or PET/CT</td>
</tr>
</tbody>
</table>

mSMART 2.0: Cytogenetic Classification of MM

**High Risk 20%**
- FISH
  - Del17p
  - t(14;16)
  - t(14;20)
- GEP
  - High-risk signature

**Intermediate Risk 20%**
- FISH
  - t(4;14)
- Cytogenetic deletion 13 or hypodiploidy
- PCLI ≥3%

**Standard Risk 60%**
- All others including:
  - Hyperdiploid
  - t(11;14)
  - t(6;14)

OS 3 Years
OS 4-5 Years
OS 8-10 Years

# Revised International Staging System (ISS)

<table>
<thead>
<tr>
<th>Stage</th>
<th>International Staging System (ISS)</th>
<th>Revised-ISS (R-ISS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Serum B$_2$m &lt;3.5 mg/dL&lt;br&gt;Serum albumin &gt;3.5 g/dL&lt;br&gt;Median survival: 62 months</td>
<td>ISS stage I and standard risk chromosomal abnormalities by FISH&lt;br&gt;<strong>AND</strong> Serum LDH ≤ULN&lt;br&gt;5 year OS rate: 82%; PFS at 46 months: 55%</td>
</tr>
<tr>
<td>II</td>
<td>Not ISS stage I or II&lt;br&gt;Median survival: 44 months</td>
<td>Not R-ISS stage I or III&lt;br&gt;5 year OS rate: 62%; PFS at 46 months: 36%</td>
</tr>
<tr>
<td>III</td>
<td>Serum B$_2$m ≥5.5 mg/L&lt;br&gt;Median survival: 29 months</td>
<td>ISS stage III and either high risk chromosomal abnormalities by FISH&lt;br&gt;<strong>OR</strong> Serum LDH &gt;ULN&lt;br&gt;5 year OS rate: 40%; PFS at 46 months: 24%</td>
</tr>
</tbody>
</table>

Minimal Residual Disease (MRD)

MRD negative status is an important indicator of prolonged PFS and OS

Diagnosis

- **PR**
- **VGPR**
- **CR**
- **sCR**

**SERUM TOOLS**

- MRD x $10^{-3}$
- MRD x $10^{-4}$
- MRD x $10^{-4}$
- MRD x $10^{-6}$

**FLOW CYTOMETRY**

**RT-PCR**

**NEXT GENERATION FLOW CYTOMETRY**

**NEXT GENERATION SEQUENCING**

Less sensitive

More sensitive

<5% of BM plasma cells and immunofixation negative
Natural History of MM

**Diagnosis**
- MGUS or SMM
- Asymptomatic
- Symptomatic

**M Protein (g/L)**
- 20
- 50
- 100

**Induction followed by continuous therapy**
- Induction
- Consolidation
- Maintenance

**Relapse Phases**
- 1st RELAPSE
- 2nd RELAPSE
- 3rd RELAPSE
- Refractory Disease

**Tx**
- 2nd Line Tx
- 3rd Line Tx
- 4th Line Tx

**SCT Eligible**
- SCT ineligible

**MRD Assessment**

Case Study: Jerry

- Jerry, a 52-yr-old male, presented to ED with severe back pain
  - Plain films of spine and pelvis showed degenerative changes
  - CT of spine (bone protocol) with osseous demineralization and a moth-eaten appearance of bones
- Admitted with acute kidney injury and hypercalcemia
- Suspicion for multiple myeloma: consult hematology/oncology

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>1.8 g/dL</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>52 ml/min</td>
</tr>
<tr>
<td>Calcium</td>
<td>11.8 mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.4 g/dL</td>
</tr>
<tr>
<td>Total protein</td>
<td>9.2 g/dL</td>
</tr>
<tr>
<td>White blood cell</td>
<td>4,200/mcL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>8.6 g/dL</td>
</tr>
<tr>
<td>Platelet</td>
<td>144,000/mcL</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>2400/mcL</td>
</tr>
</tbody>
</table>
## Additional Tests for Jerry

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-2 microglobulin (&lt;2.51 mg/L)</td>
<td>3.8 mg/L</td>
</tr>
<tr>
<td>LDH (120-250 U/L)</td>
<td>146 U/L</td>
</tr>
<tr>
<td>IgG (672-1760 mg/dL)</td>
<td>3200 mg/dL</td>
</tr>
<tr>
<td>IgG-kappa M protein</td>
<td>3.4 g/dL</td>
</tr>
<tr>
<td>Serum free kappa (3.3-19.4 mg/L)</td>
<td>2700 mg/dL</td>
</tr>
<tr>
<td>Bone marrow biopsy: Kappa restricted, ~70% marrow cellular</td>
<td></td>
</tr>
<tr>
<td><strong>FISH</strong>: negative for t(4;14), t(11;14), or t(14;16)</td>
<td></td>
</tr>
</tbody>
</table>
Your Turn: What is the diagnosis?

A. Monoclonal gammopathy of unknown significance
B. Smoldering multiple myeloma
C. Multiple myeloma, IgG Kappa type
D. Systemic AL amyloidosis
Your Turn: What is the stage?

A. Stage I
B. Stage II
C. Stage III
Advances in Treatment Options Improving Survival

Source: Shah UA, Mailankody, S. BMJ. 2020;370:m3176. Used with permission.
Treatment Goals

• **Goals of therapy**: disease control, improved quality of life, and prolonged survival
  – Deep response with induction therapy leads to better OS

• **Treatment decisions based on**:  
  – Standard vs high risk cytogenetics  
  – Eligibility for autologous HCT

* If transplant-eligible

General Considerations for Selection of Therapy

- H&P with particular attention to bone health, fatigue, infections, neuropathy
- Co-morbidity evaluation
- Fit vs frail
- Lifestyle and personal wishes
- Financial considerations
- Availability of a caregiver

### Clinical Considerations in Induction Therapy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>High tumor burden</td>
<td>- Pulse dexamethasone</td>
</tr>
<tr>
<td></td>
<td>- Combination therapies with alkylators and immunomodulatory agents (IMiDS) and bortezomib</td>
</tr>
<tr>
<td>Renal failure</td>
<td>- Pulse dexamethasone</td>
</tr>
<tr>
<td></td>
<td>- Proteasome Inhibitor (PI) +/- alkylator</td>
</tr>
<tr>
<td></td>
<td>- Renal dosing required for selected agents - may benefit from graduated induction</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>- Pulse dexamethasone</td>
</tr>
<tr>
<td></td>
<td>- Bisphosphonates</td>
</tr>
<tr>
<td></td>
<td>- Risk-adapted induction</td>
</tr>
<tr>
<td>Frail</td>
<td>- Avoid high-dose dexamethasone</td>
</tr>
<tr>
<td></td>
<td>- Dose modifications may be indicated for selected agents</td>
</tr>
<tr>
<td>Clotting or bleeding history</td>
<td>- Assess risk of use of IMiDs</td>
</tr>
<tr>
<td></td>
<td>- Evaluate platelet function with concurrent use of anticoagulation/ anti-platelet agents</td>
</tr>
<tr>
<td>Preexisting neuropathy</td>
<td>- Assess use of bortezomib/thalidomide</td>
</tr>
</tbody>
</table>
Your Turn: What initial therapy would be appropriate for Jerry?

A. Carfilzomib/lenalidomide/dexamethasone
B. Melphalan/prednisone/thalidomide
C. Bortezomib/lenalidomide/dexamethasone
### Treatment Approach to Newly Diagnosed MM

**NOTE:** Clinical trial participation should be encouraged.

#### Transplant-Eligible

<table>
<thead>
<tr>
<th>Standard Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRd x 4 cycles</td>
<td>Dara-VRd or KRd x 4 cycles</td>
</tr>
<tr>
<td>ASCT</td>
<td>ASCT</td>
</tr>
<tr>
<td>Lenalidomide maintenance</td>
<td>Bortezomib-lenalidomide maintenance</td>
</tr>
</tbody>
</table>

#### Transplant-Ineligible

<table>
<thead>
<tr>
<th>Standard Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRd x 12 cycles followed by lenalidomide maintenance -OR- DRd x 12 cycles followed by Dara-lenalidomide maintenance</td>
<td>VRd x 12 cycles</td>
</tr>
<tr>
<td>Bortezomib-lenalidomide maintenance</td>
<td>Bortezomib-lenalidomide maintenance</td>
</tr>
</tbody>
</table>

NCCN. Clinical Practice Guidelines in Oncology: Multiple Myeloma—v.3.2021.
Treatment Principles

• Combination therapies have demonstrated improved response rates, PFS, and/or OS compared to single agents

• A 3-drug regimen is recommended in most patients including a PI and an IMiD

• Supportive and palliative care should be provided concurrently with disease modifying treatment with bisphosphonates, antimicrobials, and reduced doses of steroids

• Improving quality of life and survival are primary goals of treatment
## Immunomodulatory Agents (IMiDs)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing and Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide¹</td>
<td>• 25 mg/day by mouth for induction&lt;br&gt;• Variable dosing in combination regimens&lt;br&gt;• Dose modification based on renal function, cytopenias</td>
</tr>
<tr>
<td>Pomalidomide²</td>
<td>• 4 mg/day on days 1-21 using a 28-day cycle&lt;br&gt;• Dose modifications for cytopenias</td>
</tr>
<tr>
<td>Thalidomide³</td>
<td>• 50-200 mg/day by mouth at bedtime&lt;br&gt;• Variable dosing in combination regimens&lt;br&gt;• Dose modification for neuropathy, cytopenias</td>
</tr>
</tbody>
</table>

All IMiDs are subject to REMS program for embryo-fetal toxicity

## Adverse Events (AEs) with IMiDs

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Thalidomide&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Lenalidomide&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Pomalidomide&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>√ More with dex</td>
<td>√ More with dex</td>
<td>√ More with dex</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>√ Neutropenia</td>
<td>√ Neutropenia, thrombocytopenia, anemia</td>
<td>√ Neutropenia, thrombocytopenia, anemia</td>
</tr>
<tr>
<td>Fatigue, weakness</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Sedation</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Gastrointestinal disturbance</td>
<td>√ Constipation</td>
<td>√ Constipation, diarrhea</td>
<td>√ Constipation, diarrhea</td>
</tr>
<tr>
<td>Renal/Hepatic</td>
<td></td>
<td>√ Reduce dose for decreased CrCL</td>
<td></td>
</tr>
</tbody>
</table>

*dex, dexamethasone; len, lenalidomide*

1. Thalidomide [prescribing information]; 2. Lenalidomide [prescribing information]; 3. Pomalidomide [prescribing information].
# Proteasome Inhibitors (PIs)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing and Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib¹</td>
<td>• 1.3 mg/m² IV or SC on D1, 4, 8, 11, every 21 days x 2 cycles, then weekly dosing 3 wks on/1 wk off</td>
</tr>
<tr>
<td></td>
<td>• Dose modification for neuropathy, cytopenias</td>
</tr>
<tr>
<td>Carfilzomib²</td>
<td>• 20 mg/m² IV (cycle 1), 27 mg/m² (cycles 2-12) on D1, 2, 8, 9, 15, 16, every 28 days</td>
</tr>
<tr>
<td></td>
<td>• Variable dosing as a single agent and in combination regimens</td>
</tr>
<tr>
<td></td>
<td>• Dose modifications for cytopenias, cardiopulmonary symptoms</td>
</tr>
<tr>
<td>Ixazomib³</td>
<td>• 4 mg orally on D1, 8, and 15 of a 28-day cycle</td>
</tr>
<tr>
<td></td>
<td>• Dose should be taken at least 1 hour before or at least 2 hours after food</td>
</tr>
<tr>
<td></td>
<td>• Dose modification for moderate or severe hepatic impairment, or renal impairment</td>
</tr>
</tbody>
</table>

1. Bortezomib (Velcade) [package insert]; 2. Carfilzomib (Kyprolis) [package insert]; 3. Ixazomib (Ninlaro) [package insert].
# AEs with PIs

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Bortezomib(^1)</th>
<th>Carfilzomib(^2)</th>
<th>Ixazomib(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td>(\checkmark)</td>
<td>(\checkmark)</td>
<td>(\checkmark)</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>Neutropenia,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>thrombocytopenia, anemia</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>(\checkmark)</td>
<td>(\checkmark)</td>
<td></td>
</tr>
<tr>
<td>Cardio/Pulmonary</td>
<td>(\checkmark)</td>
<td>(\checkmark)</td>
<td>(\checkmark)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ECG abnormalities</td>
<td></td>
</tr>
<tr>
<td>Fatigue, weakness</td>
<td>(\checkmark)</td>
<td>(\checkmark)</td>
<td></td>
</tr>
<tr>
<td>Viral reactivation of herpes zoster</td>
<td>(\checkmark)</td>
<td>(\checkmark)</td>
<td>(\checkmark)</td>
</tr>
<tr>
<td>Gastrointestinal disturbance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea and vomiting, diarrhea</td>
<td>Nausea and vomiting, diarrhea, constipation, mucositis/stomatitis</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Renal/Hepatic</td>
<td>(\checkmark)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Bortezomib (Velcade) [prescribing information]; 2. Carfilzomib (Kyprolis) [prescribing information]; 3. Ixazomib (Ninlaro) [prescribing information].
Your Turn: What other therapy should be ordered for Jerry?

A. Zoledronic acid 4 mg IV q month
B. Aspirin 81 mg PO qd
C. Acyclovir 400 mg PO BID
D. All of the above
NCCN Recommendations for Adjunctive Treatment for MM

**Infection**
- IVIG for recurrent infections
- Pneumovax and influenza vaccine
- PCP, herpes and antifungal prophylaxis for high-dose or long-term steroids
- Herpes zoster prophylaxis with bortezomib

**Bone disease**
- Bisphosphonates
- Radiation therapy
- Orthopedic consultation
- Vertebroplasty or kyphoplasty

**Renal dysfunction**
- Avoid aggravating factors: contrast, NSAIDs, dehydration
- Not a contraindication to HCT
- Monitor bisphosphonates closely

**Coagulation/thrombosis**
- Prophylactic anticoagulation with IMiDs

**Hypercalcemia**
- Hydration, steroids, furosemide
- Zoledronic acid preferred

**Hyperviscosity**
- Plasmapheresis

**Anemia**
- Consider erythropoietin
- Transfusion
- Type and screen patients prior to daratumumab administration
Prevention and Treatment of Infections

- **Monitor blood counts in initial phase** of treatment where risk is greatest
- IVIG for serum IgG <500
- Immunizations
  - Poor response to pneumococcal and influenza vaccines (**STILL GIVE**)
  - **DO NOT GIVE** live herpes zoster vaccine
  - May give Shingrix herpes zoster vaccine
- Shingles prophylaxis
  - Acyclovir is recommended for all PI therapy
  - Acyclovir is recommended for 60 d following auto transplant
- Review signs and symptoms to report with patient and caregivers, including who to contact and how
- Prompt identification of symptoms and institution of treatment
- Subsequent treatment may require dose modification, dose delay, or administration of G-CSF for neutropenia
- PCP and antifungal prophylaxis if CD4 count <200
Bone Destruction

- Malignant cells produce osteoclast-activating factors that destroy bone cells
  - Leads to osteolysis, bone pain, pathological fractures, and/or hypercalcemia
  - Bisphosphonates inhibit bone destruction
  - Monitor patients for
    - Acute phase reactions
    - Renal dysfunction
    - Osteonecrosis of the jaw

Bone Lytic Lesions in MM

Femur

Image from http://www.e-radiography.net/ibase5/Femur/Femur_myeloma_solitary_lesion.jpg

Lytic lesions

Humerus

Management of Bone Disease

- **Treat the myeloma**
- Bisphosphonates
- Radiotherapy
  - Impending fracture
  - Cord compression
  - Plasmacytomas
- Orthopedic consultation
  - Impending or actual long-bone fractures
  - Bony compression of spinal cord
  - Vertebral column instability
- Kyphoplasty/vertebroplasty
- Home safety evaluation
- Pain management
- Use of spinal support (braces) may be indicated
- Ongoing evaluation of bone health

Percutaneous “Balloon Kyphoplasty” Surgical Management

Kyphoplasty uses a “balloon” to create a cavity for bone cement to reduce vertebral fracture and pain.

- Percutaneous
- Correct kyphosis
- Restore stability
- Restore height
- Relieve pain

Bisphosphonates

- Indicated for documented bone disease including osteopenia
  - Zoledronic acid 4 mg IV over 15 mins q month (first choice)
  - Pamidronate 90 mg IV over 4 hours q month
- Decrease bone pain and incidence of skeletal events in advanced disease
- Monitor renal function before each infusion
- Monitor serum calcium and vitamin D at regular intervals
- Recommend monthly bisphosphonates for 2 years
  - Can switch to q 3 month dosing when no active MM
  - After 2 years, further use is at the discretion of the treating physician
  - Resume treatment on relapse with new onset of skeletal events

Anderson K, Ismaila N, Kyle RA. *J Oncol Pract.* 2018;14(4), 266–269; Pamidronate (Aredia) [prescribing information]; Zolendric acid (Zometa) [prescribing information].
### Bisphosphonate Use in MM: Renal Dose Reductions

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Pamidronate</th>
<th>Dosing (mg) 90 mg/500 mL NS IV</th>
<th>Dosing (mg) 2-4 hours</th>
<th>Dosing (mg) 4-6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30</td>
<td>2-4 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>4-6 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Zoledronic Acid</th>
<th>Dosing (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>50-60</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>3.3</td>
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</tr>
<tr>
<td>30-39</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>Not recommended</td>
<td></td>
</tr>
</tbody>
</table>

Anderson K, Ismaila N, Kyle RA. *J Oncol Pract.* 2018;14(4), 266–269; Pamidronate (Aredia) [prescribing information]; Zolendric acid (Zometa) [prescribing information].
# Bisphosphonate Use in MM: AEs

| Flu-like symptoms | • Fever, myalgias, arthralgias  
|                   | • Occurs usually 12-48 hours following infusion; lasts 6-24 hours  
|                   | • Occurs in minority of patients (10%-20%)  
|                   | • Generally reduced with continued dosing  
|                   | • Slow rate of infusion and use of steroids and antihistamines may help reduce intensity |
| Hypocalcemia      | • Calcium 1000 mg/day and vitamin D 400 IU/day in 2 divided doses |
| Osteonecrosis of jaw (ONJ) | • Comprehensive dental exam prior to therapy  
|                      | • Excellent dental hygiene  
|                      | • Avoidance of invasive dental procedures  
|                      | • Use of bisphosphonates (>2.5 years) increases the risk for development of ONJ |

Venous Thromboembolism (VTE) in MM

- Patients with MM have higher risk of VTE
  - >10% will develop VTE during the course of their disease
- Multifactorial risk due to patient, disease, and treatment factors
- VTE prevention recommended based on risk factors

### IMPEDE VTE Score

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>POINT SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of VTE before multiple myeloma diagnosis</td>
<td>+5</td>
</tr>
<tr>
<td>IMiD therapy</td>
<td>+4</td>
</tr>
<tr>
<td>Pelvic, hip, or femur fracture</td>
<td>+4</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
</tr>
<tr>
<td>High Dose (&gt;160 mg/month)</td>
<td>+4</td>
</tr>
<tr>
<td>Low Dose (≤160 mg/month)</td>
<td>+2</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>+3</td>
</tr>
<tr>
<td>Tunneled line or central venous catheter</td>
<td>+2</td>
</tr>
<tr>
<td>Erythropoiesis-stimulating agent</td>
<td>+1</td>
</tr>
<tr>
<td>Body mass index ≥25 kg/m²</td>
<td>+1</td>
</tr>
<tr>
<td>Existing thromboprophylaxis:</td>
<td></td>
</tr>
<tr>
<td>Therapeutic anticoagulation</td>
<td>-4</td>
</tr>
<tr>
<td>Prophylactic anticoagulation</td>
<td>-3</td>
</tr>
<tr>
<td>Ethnicity/Race = Asian/Pacific Islander</td>
<td>-3</td>
</tr>
</tbody>
</table>

NCCN Clinical Practice Guidelines in Oncology: Cancer-Associated Venous Thromboembolic Disease—v.1.2020
Recommendations for Thrombosis Prophylaxis

**Low risk:** ≤3 points
- None
- Aspirin 81-325 mg/d

**High risk:** >3 points
- LMWH
- Warfarin with therapeutic dosing (INR 2-3)
- Direct oral anticoagulants

NCCN Clinical Practice Guidelines in Oncology: Cancer-Associated Venous Thromboembolic Disease—v.1.2020
Peripheral Neuropathy

- Associated with MM (found in 3%–13% of patients)
- Present in ~80% of previously treated patients
- Characterized by numbness, tingling, burning in feet or hands, and may start as discomfort and progress to severe shooting pain and cramps
- Baseline assessment and symptom assessment at each visit
- No effective preventive strategies
- Caution with supplements:
  - Avoid green tea or vitamin C with bortezomib administration
  - Daily doses of B6 should not exceed 100 mg
- Symptomatic treatment:
  - Duloxetine, gabapentin, amitriptyline, sertraline
- Dose reduction, delay, or omission of drug
  - Agent-specific guidelines
  - Administer bortezomib SC

# Management of Common Lenalidomide Toxicities

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
<th>Interventions</th>
</tr>
</thead>
</table>
| Myelosuppression (neutropenia, thrombocytopenia) | • Predominant toxicity  
• Occurs most often with higher doses  
• More common in combination with dex | • Monitor CBCs **bi-weekly** for first 12 wk and then q month  
• Hold for ANC <1000/mcL  
• Hold for platelets <30,000/mcL  
• Transfusions, growth factors |
| Thromboembolic events (DVT, PE)              | • More common in combination with dex                                        | • Anticoagulation recommended based on risk                                    |
| Rash                                         | • Mild to moderate patchy, raised, macular skin lesions, sometimes with localized urticarial or pruritus | • Antihistamines  
• Example: Cetirizine 10 mg/d, famotidine 20 mg BID and L-lysine 500 mg PO BID  
• Topical corticosteroids |
| Diarrhea                                     | • Usually mild/intermittent  
• Cramping and/or diarrhea                                                               | • Dietary modification  
• Antidiarrheals (eg, loperamide)  
• Dose reduction                                                               |
# Management of Common Bortezomib Toxicities

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
<th>Intervention</th>
</tr>
</thead>
</table>
| Fatigue, malaise | Most often reported during cycles 1-2 | • Energy conservation  
• Alternate rest and activity |
| GI events (nausea, diarrhea, vomiting, constipation) | Mild to moderate | • Antiemetics and antidiarrheals  
• Fluid and electrolyte replacement  
• Hold bortezomib treatment for Grade 3 AEs; therapy may be reinitiated at 25% reduced dose when symptoms resolve |
| Hypotension | Mild to moderate; may occur throughout therapy | • Adjustment of antihypertensive medications  
• Hydration |
| Thrombocytopenia | Transient thrombocytopenia generally occurs during dosing period (days 1–11), with return to baseline days 12–21 | • Monitor platelet count prior to each dose  
• Platelet transfusions prn  
• Hold bortezomib treatment at onset if platelet count <25,000/mL; therapy may be reinitiated at 25% reduced dose with acceptable platelet recovery |
| Peripheral neuropathy | Numbness, tingling, burning in feet or hands; worsens with additional dosing | • Dose/schedule modification may improve symptoms  
• Instruct patients to call if new or worsening symptoms occur  
• Symptom control with medication ( duloxetine, sertraline, gabapentin) |

Bortezomib [prescribing Information]. Available at: https://www.velcade.com/files/pdfs/VELCADE_PRESCRIBING_INFORMATION.pdf
Jerry receives 4 cycles of bortezomib, lenalidomide, dexamethasone (VRd) followed by autologous hematopoietic cell transplant and achieves CR.
Your Turn: What do you recommend next?

A. Stop therapy, check myeloma labs every month and treat at relapse
B. Complete 4 more cycles of VRd
C. Maintenance therapy with lenalidomide
D. Proceed to 2nd autologous hematopoietic cell transplant
Your Turn: What therapy would you consider for Jerry?

After 14 months on lenalidomide maintenance therapy, he has a relapse. What therapy would you consider?

A. Daratumumab, bortezomib, dexamethasone (DVd)
B. Selinexor
C. Pomalidomide and dexamethasone (Pd)
D. Bendamustine
Relapsed Disease – Diagnostic Criteria

- Direct indicators of increasing disease or end organ damage
- Development of new soft tissue plasmacytomas or bone lesions
- Definite increase in size of existing plasmacytomas or bone lesions
- Hypercalcemia (>11 mg/dL)
- Decrease in Hb ≥2 g/dL not related to therapy
- Increase creatinine 2 mg/dL or more
- Hyperviscosity related to serum paraprotein
Relapsed Disease: Considerations for Treatment

**PATIENT RELATED FACTORS**
- Age/frailty
- Performance status
- Patient preference
  - QOL
  - Social support
  - Mode of administration (IV/PO)
  - Convenience
- Comorbidities
  - Renal function
  - Neuropathy
  - Thrombosis
  - Cardiac
  - Diabetes
  - Other
- Bone marrow reserve

**DISEASE/TREATMENT RELATED FACTORS**
- Tumor burden
- Cytogenetics
- Relapsed vs refractory
- Duration of response to initial therapy
- Regimen efficacy
- Toxicity/tolerability of previous regimen
- Prior HDT/ASCT
- Potential toxicity
  - Myelosuppression
  - Neuropathy
  - VTE
  - Secondary cancers
- Cost and copays

Relapsed Disease: Treatment Options

Myeloma Therapies
• Bortezomib (V)
• Lenalidomide (R)
• Carfilzomib (K)
• Daratumumab (D)
• Elotuzumab (E)
• Pomalidomide (P)
• Ixazomib (I)
• Panobinostat
• Cyclophosphamide (C)
• Doxorubicin
• Bendamustine
• Selinexor (S)
• Isatuximab (Isa)
• Venetoclax

Common Combinations
VRd, Vd
VRd, Rd
KRd, Kd (twice weekly or weekly), KCd
DRd, DVd, DPd, D-VMP
ERd, EPd, Evd
Pd, DPd, EPd, PCd
IRd, IPd, Id
Panobinostat+ Vd, panobinostat+ K
PCd, VTD-PACE
Liposomal doxorubicin + bortezomib
Sd, SPd
Isa-Pd
Venetoclax+ Vd

If relapse is >6 months after primary induction, regimen may be used again

NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma—v.3.2021.
Carfilzomib

• Second generation PI
  – Irreversibly binds to 20S proteasome
• FDA indications:
  – In combination with dexamethasone or lenalidamide plus dexamethasone in patients with R/R MM who have received 1-3 lines of therapy
  – Single agent in patients with R/R MM who have received 1-3 lines of therapy
• Dose:
  – Monotherapy: 20/56 mg/m² on days 1, 2, 8, 9, 15, 16 q 3 weeks
  – With dexamethasone: 20/70 mg/m² on days 1, 8, 15 q 3 weeks
  – With lenalidomide and dexamethasone: 20/27 mg/m² IV on days 1, 2, 8, 9, 15, 16 q 3 weeks

Carfilzomib: Clinical Management

- **AEs:**
  - Anemia, fatigue, thrombocytopenia, nausea, pyrexia, dyspnea, diarrhea, headache, peripheral edema, renal failure, hypertension, new onset or worsening of pre-existing cardiac failure, cardiomyopathy, myocardial ischemia, and myocardial infarction

- HSV prophylaxis recommended

- Cap BSA at 2.2 $m^2$

- Hydration recommended to prevent tumor lysis syndrome (especially for cycle 1)

- Hydrate with caution in patients with pre-existing cardiac abnormality

- Pre-medicate with dexamethasone to prevent infusion related reactions

- Monitor renal function

- Monitor blood pressure

Ixazomib

- Oral PI
- FDA indication:
  - In combination with lenalidomide and dexamethasone for treatment of patients with MM who have received ≥1 prior therapy
- Common AEs:
  - Diarrhea, constipation, peripheral neuropathy, peripheral edema, back pain, cyclic thrombocytopenia
- Discuss with patient importance of adherence to schedule
- HSV prophylaxis recommended
- Rapid response (1.1 months)
- Fast absorption (do NOT repeat dose after vomiting)
Daratumumab

- First in class monoclonal antibody (mAb) targeting CD38
- CD38 is a glycoprotein overexpressed on MM cells
- FDA indications:
  - In combination with lenalidomide and dexamethasone in NDMM patients ineligible for ASCT or R/R MM who received ≥1 prior therapy
  - In combination with bortezomib, melphalan, and prednisone in NDMM ineligible for ASCT
  - In combination with bortezomib, thalidomide, and dexamethasone in NDMM who are eligible for ASCT
  - In combination with bortezomib and dexamethasone in patients who have received at ≥1 prior therapy
  - In combination with carfilzomib and dexamethasone in patients who have received 1-3 prior lines of therapy
  - In combination with pomalidomide and dexamethasone, in patients who have received ≥2 prior therapies
  - As monotherapy in patients who have received ≥3 lines of prior therapy

Dratumumab (Darzalex) [prescribing information], Janssen Biotech, Inc., Horsham PA. 2020
Daratumumab: Clinical Considerations

• Infusion related reactions
  – Pre-medication with steroid, acetaminophen and antihistamine
  – Infusion rate titration
  – Post-daratumumab steroid recommended after first 4 infusions

• Rapid infusion daratumumab may be considered over 90 min from day 15 onward if no IRR

• AEs:
  – Neutropenia, thrombocytopenia, fatigue, diarrhea, vomiting, arthralgias, dyspnea, peripheral edema, peripheral neuropathy, upper respiratory tract infections
Daratumumab/Hyaluronidase SC Injection

- Daratumumab co-formulated with human hyaluronidase administered SC
- Hyaluronidase increases the permeability of the SC tissue
- FDA Indications
  - In combination with bortezomib, melphalan and prednisone in NDMM patients ineligible for ASCT
  - In combination with lenalidomide and dexamethasone in NDMM patients ineligible for ASCT and in patients with R/R MM who have received ≥1 prior therapy
  - In combination with bortezomib and dexamethasone in patients who have received ≥1 prior therapy
  - As monotherapy, in patients who have received ≥3 prior lines of therapy including a PI and an IMiD or who are double-refractory to a PI and an IMiD
- Dose: Daratumumab 1800 mg/hyaluronidase 30,000 units/15 ml
- Administration: Inject SC into the abdomen over 3-5 min
- Significantly reduced incidence of infusion reactions compared with IV
  - Pre-medications: Corticosteroid, acetaminophen, antihistamine
  - Post-medications recommended (methylprednisolone 20 mg x 2 days)
- HSV prophylaxis recommended
- Greater patient convenience and decreased chair time

Dartumumab Hylaluronidase (Darzalex Fastpro) [prescribing information], Janssen Biotech, Inc., Horsham PA. 2020.
Elotuzumab

• mAb targeting SLAMF-7
  – SLAMF-7 is a marker of normal and malignant plasma cells
• FDA indication:
  – In combination with lenalidomide and dexamethasone after 1-3 therapies
  – In combination with pomalidomide and dexamethasone after ≥2 therapies including lenalidomide and a PI
• Not active as single agent, must be used in combination
• Risk of IRR (~10%)
  – Rate titration and premedication required
• Monitor patients for cytopenias
Isatuximab

• mAb targeting CD38
  – CD38 is a glycoprotein overexpressed on MM cells

• FDA indication:
  – In combination with pomalidomide and dexamethasone after ≥2 therapies including lenalidomide and a PI

• AEs: infusion reactions, infections, neutropenia
Laboratory Considerations: Interference with SPEP and IFE Testing

- Anti-CD38 mAbs (daratumumb, elotuzumab, isatuximab) may interfere with SPEP and IFE tests
- mAbs are IgG antibodies; can appear as another M spike
  - Over-estimation of M protein and reduced CR rates

Laboratory Considerations: Blood Bank

- Anti-CD38 mAbs (daratumumab, elotuzumab, and isatuximab) may interfere with blood bank tests
- Binds to RBCs which interferes with blood bank compatibility tests (including antibody screening and cross matching)
- Type and screen patients prior to mAb therapy and inform blood bank
- Provide patient with card stating they are on anti-CD38 mAbs with contact numbers for oncologist and blood bank

Selinexor

- First in class oral selective inhibitor of nuclear export (SINE) compound
  - Inhibits XPO1, which is major exporter of tumor suppressor proteins (TSP)
  - Reactivates TSPs relevant to multiple myeloma, inhibits NK-kB signaling, and reduces c-myc levels
- FDA indication:
  - In combination with dexamethasone for R/R MM after ≥4 lines of therapy and refractory to ≥2 PIs, ≥2 IMiDs, and an anti-CD38 mAb
- Dose: 80 mg with dexamethasone PO on days 1 and 3 weekly

Selinexor: Clinical Management

- **Thrombocytopenia (74%)**
  - Onset 28 days
  - Dose reduction or interruption of therapy may be required
- **Neutropenia (34%)**
  - Onset 25 days
  - Consider addition of anti-microbials and growth factors
- **Nausea/vomiting (72%)**
  - Onset 3 days
  - Administer 5HT3 receptor antagonist or olanzapine
- **Diarrhea (44%)**
  - Onset 15 days
  - Anti-diarrheal agents (after ruling out infection)
- **Anorexia/ weight loss (53%)**
  - Onset 8 -15 days
  - Monitor weight, nutritional status and volume status
- **Hyponatremia (39%)**
  - Onset 8 days
  - IV saline or salt tablets may be required
B-cell Maturation Antigen (BCMA)-Targeted Immunotherapy

Several strategies for immunotherapy in MM with anti-BCMA target
• Chimeric antigen receptor T cell (CAR-T)
• Bispecific T cell engager (BiTE)
• Antibody drug conjugate (ADC)

Belantamab Mafadotin

- First anti-BCMA immunotherapy approved (8/5/2020)
- FDA indication:
  - R/R MM after ≥4 prior therapies including an anti-CD38 mAb, a PI, and an IMiD
- Binds to BCMA expressing cells and causes antibody dependent cell mediated cytotoxicity (ADCC) as well as inhibits microtubule network
- AEs: keratopathy
  - REMS program: Ophthalmic exams required at baseline, prior to each dose, and promptly for worsening symptoms
Daratumumab/bortezomib/dexamethasone started for 1st relapse following VRd + auto HCT and lenalidomide maintenance. In order to start therapy:

- Blood bank alerted to type and screen
- HSV prophylaxis with acyclovir 400 mg PO BID
- Check myeloma labs q month, including IgG
- IVIG for IgG <500
COVID-19: Minimizing Risk in Patients with MM (Patients and Caregivers)

- Avoid close contact with people who are sick
- Stay at least 6 feet away from other people
- Avoid touching eyes, nose and mouth
- For objects and surfaces that are touched often, clean and disinfect frequently using a regular household cleaner
- Wash hands often with soap and water for a minimum of 20 seconds or use a hand sanitizer with ≥60% alcohol
- In areas with a high incidence of COVID-19, frequency of patient visits may be reduced by adjusting treatment schedules or switching to an all-oral therapy if appropriate
- SCT and CAR-T cell therapies may be held due to the high risk of infection rates and immunosuppressive nature of these therapies

Summary

• Although currently not curable, the median OS for MM has improved dramatically over the last decade due to advances in therapy

• Long-term survival with good quality of life is the goal
  – MRD improves survival

• Care of the patient with MM requires intensive monitoring and intervention for symptoms of disease and treatment side effects

• Patients with MM are immunocompromised and it’s important to reduce the risk of COVID-19 exposure and infection
Thank you!