JADPRO Regional Lectures | An APSHO Educational Activity

JADPRO Regional Lectures
Hematologic Malignancies

Updates in Multiple Myeloma

Program Chair

Sandra E. Kurtin
PhDc, ANP-C, AOCN®
Arizona Cancer Center

Faculty

Beth Faiman
PhD, MSN, APRN-BC, AOCN®
Cleveland Clinic

Ann McNeill
RN, MSN, APN
John Theurer Cancer Center at Hackensack University Medical Center

Faculty Financial Disclosures

- Ms. Kurtin has acted as a consultant for AbbVie, Bristol-Myers Squibb, Celgene, Genentech, Incyte, Janssen, and Takeda.
- Dr. Faiman has acted as a consultant, received honoraria from, and has served on the speakers bureau for Amgen, Bristol-Myers Squibb, Celgene, and Takeda.
- Ms. McNeill has served on the speakers bureau for Celgene, Pharmacyclics, Seattle Genetics, and Takeda.

Planning Committee Financial Disclosures

- Moshe C. Ornstein, MD, MA, Cleveland Clinic Taussig Cancer Institute (Reviewer) has nothing to disclose.
- Dorothy Caputo, MA, BSN, RN (Lead Nurse Planner) has nothing to disclose.
- Alana Brody, Lynn Rubin, and Patti McLafferty (Harborside Medical Education) have nothing to disclose.
- Sandy Leatherman, Annamarie Luccarelli, and Jessica Tamasi (APSHO) have nothing to disclose.
- Claudine Kiffer and Annie Yueh (Harborside Press) have nothing to disclose.

The hematologic malignancies educational activity is supported by educational funding donation provided by Amgen, Celgene Corporation and Pharmacyclics LLC, an AbbVie Company and Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC.

Learning Objectives

- Identify the mechanism of action for novel agents used for the treatment of hematologic malignancies, including those used for multiple myeloma
- List monitoring parameters for toxicities associated with newer agents used to treat multiple myeloma
- Describe the signs of early and serious toxicity that providers and patients need to be aware of when initiating therapy with new agents for multiple myeloma
- Describe best practices for optimizing selection and sequencing of treatments in the upfront and relapsed/refractory settings
- Anticipate and identify potential adverse events that may be associated with newer targeted and immunotherapies and how such adverse events may be adequately addressed to optimize patient outcome
- Identify strategies for encouraging patient adherence to oral therapeutics
- Discuss the pivotal role and necessary expertise of the AP as a vital part of the interprofessional oncology/hematology team

Multiple Myeloma Epidemiology

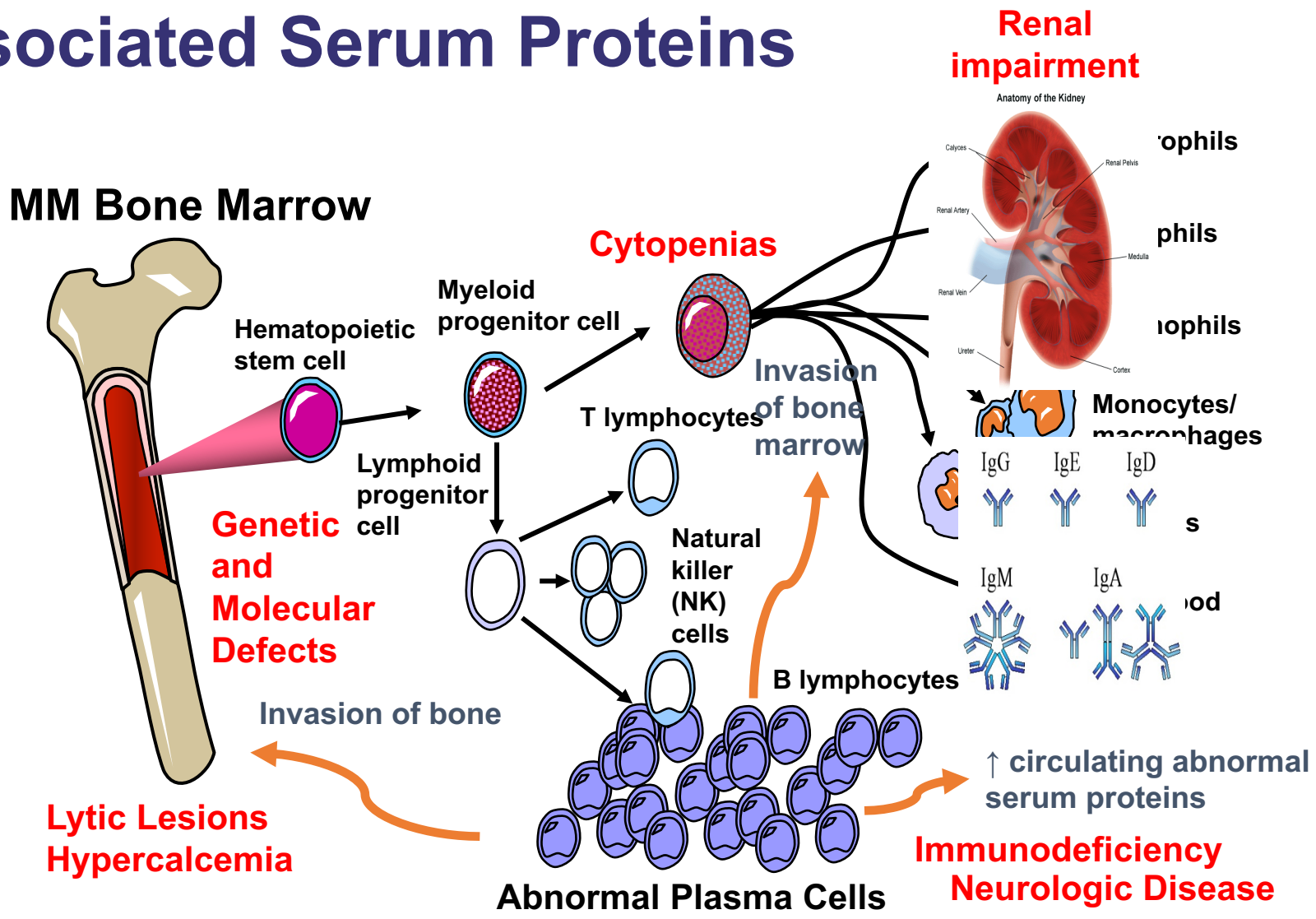
New Cases (US, 2017)	Deaths (US, 2017)	Mean Age at Diagnosis, yr	5-yr Overall Survival (US, 2017)
30,280	12,590	69	49.6%

- 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) ($p < .05$)

MM = multiple myeloma; OS = overall survival.

Badros AZ. *J Natl Compr Canc Netw* 2010;8(suppl 1):S28-S34; Siegel L, et al. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66(1):7-30; Kumar SK, et al. Presented at ASH. 2012. Abstract 3972; Kumar SK, et al. *Blood* 2008;111:2516-20; NCI, Cancer Stat Facts: Myeloma, http://seer.cancer.gov/statfacts/html/mulmy.html.

Overproduction of Abnormal Plasma Cells and Associated Serum Proteins

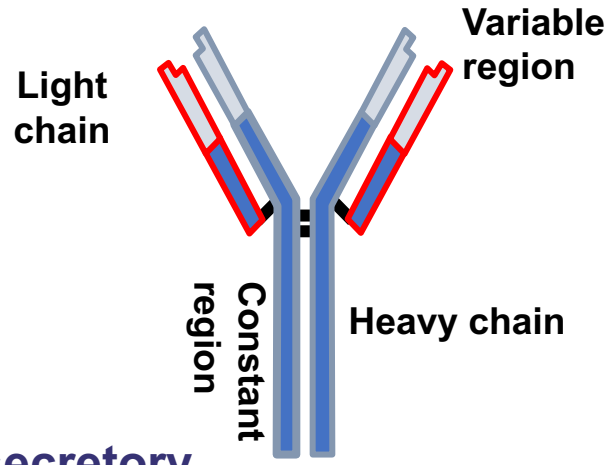


NIH, Stem Cell Basics, http://stemcells.nih.gov/info/.
Image created by Sandy Kurtin, The University of Arizona Cancer Center.

Classification of MM

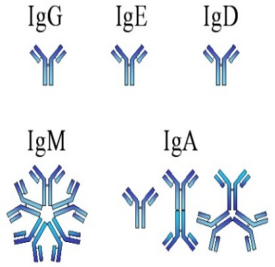
Heavy chain

- IgG, IgA, IgD, IgM, IgE
- 77% of myeloma cases
- IgG and IgA most common



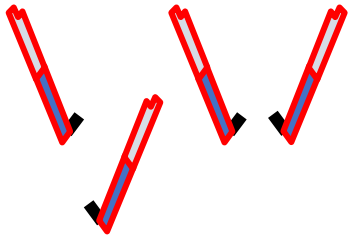
Nonsecretory

- No detectable immunoglobulin
- 1% to 2% of myeloma cases



Light chain (Bence-Jones protein)

- Kappa (κ) or lambda (λ)
- 20% of myeloma cases



Serum free light chain

Ig = immunoglobulin

Kumar SK, et al. *Mayo Clinic Proc* 2009;84:1095-10; Schmidt-Hieber M, et al. *Haematologica* 2013;98:279-87.

Newly Diagnosed Multiple Myeloma

Case Study: 63-year-old Female With Back Pain

- Presented to the ED with c/o progressive and severe back pain over a 3-day period. She first noticed this while hiking.
- PMH: Hypothyroid, borderline hypertension

Imaging

- Plain films
  - Multiple lytic lesions throughout the thoracolumbar spine
  - Acute pathologic fracture involving the T8 vertebral body; 25% height loss
- MRI total spine
  - Numerous osseous metastatic disease throughout all levels of the cervical, thoracic and lumbar spine; acute compression fracture of T8 with moderate resultant central canal stenosis
- CT thoracic spine
  - Large lytic lesion T8, extending into the left pedicle with bulging of the posterior vertebral wall
  - Large lytic lesion T12, occupying approximately 30% of the vertebral body

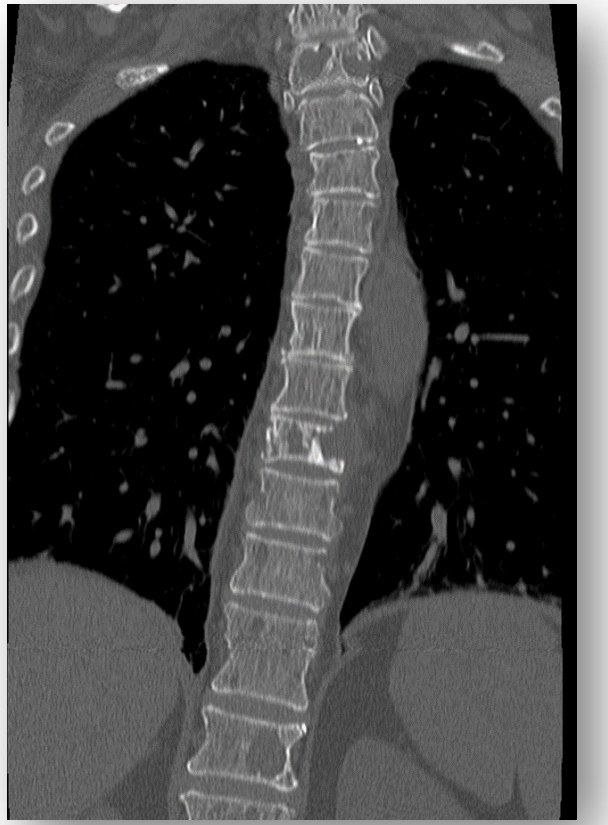


Image courtesy of Sandra Kurtin, PhDc, ANP-C, AOCN

Case Study: 63-year-old Female With Back Pain (cont.)

- Labs
  - SPEP and UPEP no monoclonal protein, M spike 0
  - Normal immunoglobulin levels, Hgb, calcium, albumin and β_2
  - Light chains
    - Kappa 105.00 (0.33–1.94 mg/dL)
    - Kappa/lambda ratio 187.50 (0.26–1.65)
- Bone marrow biopsy
  - 20% kappa light chain restricted plasma cells
  - Normal female karyotype, 46,XX[20]
  - FISH: NORMAL FISH result

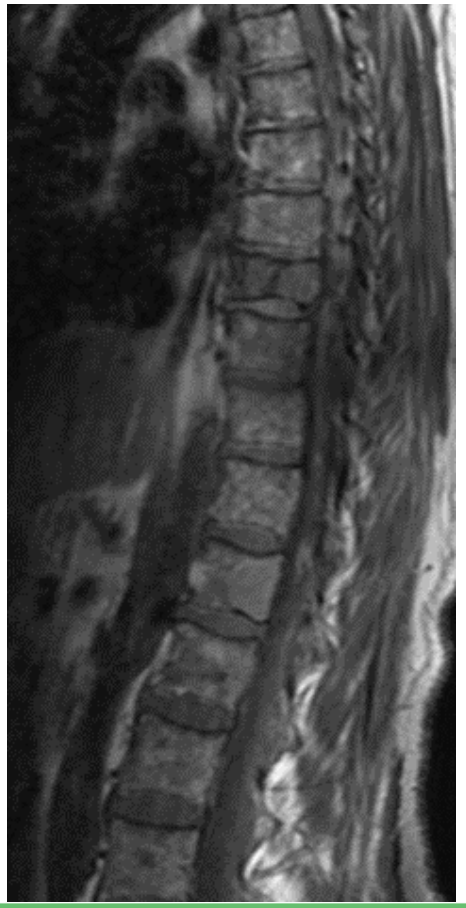


Image courtesy of Sandra Kurtin, PhDc, ANP-C, AOCN

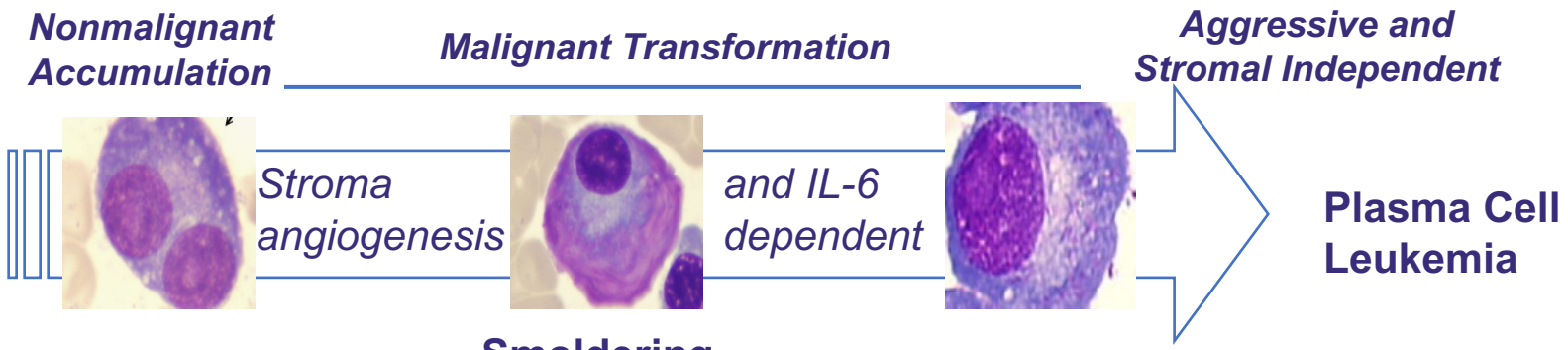
Audience Response Question

You are considering treatment for this 63-year-old female patient. Staging indicates ISS stage I. Past medical history includes hypothyroidism and hypertension. She was very active hiking and riding before presenting to the ED. Neurosurgery was consulted and did not feel surgery was needed. She is wearing a torso brace. Interventional Radiology feels the patient needs treatment before considering vertebroplasty.

Which of these options would you choose?

A. Radiation to the spine → observation
B. Lenalidomide, bortezomib, dexamethasone induction → autologous stem cell transplant → maintenance lenalidomide
C. Radiation to the spine → lenalidomide and dexamethasone
D. Radiation to the spine → lenalidomide, bortezomib, dexamethasone induction → autologous stem cell transplant → maintenance lenalidomide
E. Unsure

Disease Trajectory



MGUS

- < 10% BMPC
- < 30 g/L M-protein
- No MDE
- 1%/year risk of progression to MM

Smoldering Myeloma

- 10%-60% BMPC
- ≥ 30g/L M-protein (IgG or IgA)

OR

- ≥ 500 mg/24 hr urinary protein
- No MDE or amyloidosis
- 10%/yr risk of progression to MM in the first 5 yr

Multiple Myeloma

≥ 10% clonal BMPC or biopsy proven bony or extramedullary plasmacytoma AND 1 or more MDE including CRAB features

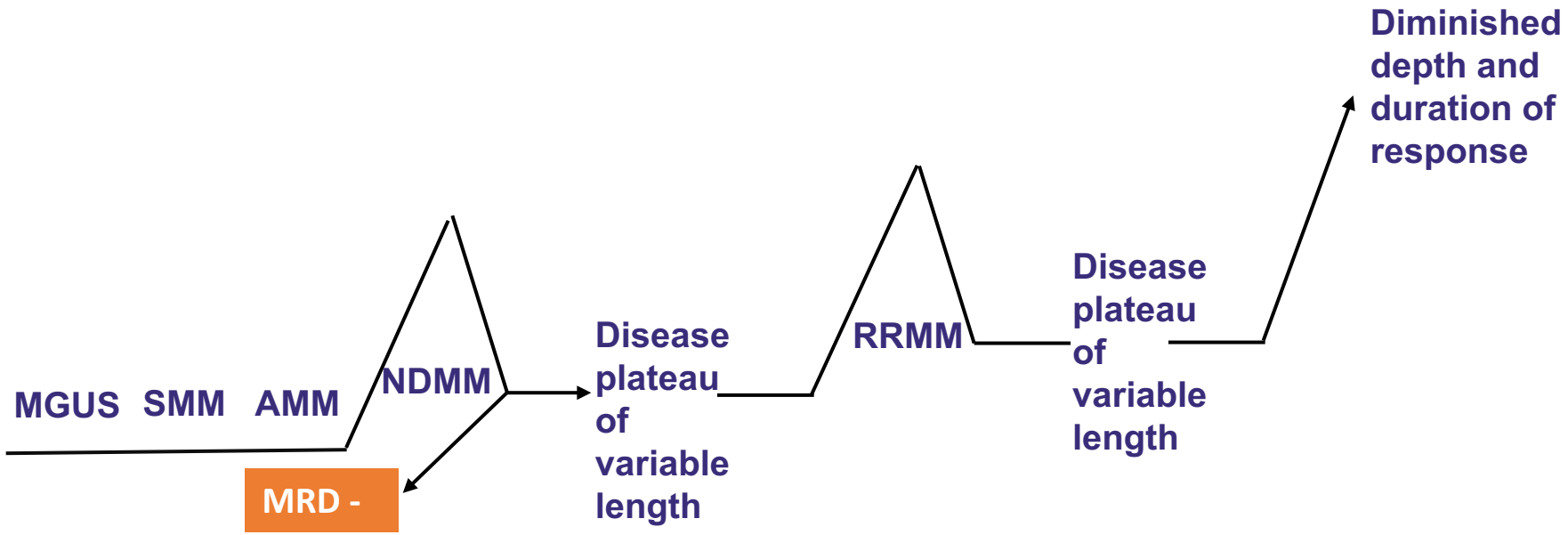
Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder specifically.

Myeloma Defining Events (MDE)

IL = interleukin; MGUS = monoclonal gammopathy of undetermined significance; BMPC = bone marrow plasma cell; MDE = myeloma-defining event; CRAB = hypercalcemia, renal dysfunction, anemia, and lytic bone lesions.

Rajkumar SV, et al. *Lancet Oncol* 2014;15(12):e538-48; Kuehl WM, et al. *Nat Rev Cancer* 2002;2:175-87; Agarwal A, et al. *Clin Cancer Res* 2013;19:985-94; Durie BG, et al. *Hematol J* 2003;4:379-98; Kurtin SE. *J Adv Pract Oncol* 2010;1:19-29.

Natural History of Multiple Myeloma



SMM = asymptomatic MM; NDMM = newly diagnosed MM; MRD = minimal residual disease negative; RRMM = relapsed and/or refractory MM.

Rajkumar S, et al. *Am J Hematol* 2014;89(10):999-1009; Ludwig H, et al. *Leukemia* 2014;28(5):981-92; Mikael JR, et al. *Mayo Clin Proc* 2013;88:360-76; Palumbo A, et al. *J Clin Oncol* 2015;32(6):587-600; Palumbo A, et al. *J Clin Oncol* 2014;33(26):2863-9; Reprinted with permisson, Kurtin 2017.

MDEs: CRAB Criteria Revised

- Calcium elevation
  - Serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than ULN or > 2.75 mmol/L (> 11 mg/dL)
- Renal dysfunction
  - Creatinine clearance < 40 mL/min or serum creatinine > 177 µmol/L (> 2 mg/dL)
- Anemia
  - Hemoglobin > 20 g/L below LLN or < 100 g/L
- Bone disease
  - One or more osteolytic lesions on skeletal radiography, CT, or PET/CT

Any one or more biomarkers of malignancy

- BMPC > 60%
- Involved/uninvolved serum free light chain ratio ≥ 100
- > 1 focal lesion > 5 mm on MRI studies

ULN = upper limit of normal; LLN = lower limit of normal; CT = computed tomography; PET = positron emission tomography; MRI = magnetic resonance imaging.

Kurtin SE, et al. *J Adv Pract Oncol* 2016;7:59-70; Rajkumar SV, et al. *Lancet Oncol* 2014;15(2):e538-48.

Diagnostic Workup for Myeloma

Source	Tests	Significance
Blood	CBC, diff, platelets	Marrow involvement: anemia is part of CRAB criteria
	CMPNL	Renal function: creatinine is a part of the CRAB criteria
	SPEP with IFE	Identification of monoclonal protein (IgG, IgA, IgD, IgE, IgM)
	Serum free light chains	Identification of predominant light chain (κ or λ)
	Albumin	Necessary to determine ISS stage, these measures have prognostic value
	β_2 microglobulin	
	LDH	
Urine	UPEP	Identification of urine monoclonal proteins

CBC = complete blood count; diff = differential; CMPNL = comprehensive metabolic panel; SPEP = serum protein electrophoresis; IFE = immunofixation; ISS = International Staging System; LDH = lactate dehydrogenase; UPEP = urine protein electrophoresis.

Kurtin et al. *J Adv Pract Oncol.* 2016;7(S1):S59-S70. Adapted from Kurtin, 2010. Data from: NCCN, 2015; Ludwig H, et al. *Leukemia* 2014;28(5):981-92; Rajkumar et al, 2014; Mikael JR, et al. *Mayo Clin Proc* 2013;88:360-76.

Diagnostic Workup for Myeloma (cont.)

Source	Tests	Significance
Bone Marrow	Hematopathology	Characterization of the bone marrow including cellularity, hematopoiesis, and percentage of plasma cells
	Flow cytometry	Used to detect molecular defects that hold prognostic significance
	Metaphase cytogenetics	Identification of chromosomal abnormalities; may not reflect full scope of abnormalities – plasma cells are fully matured
	FISH	More sensitive measure of chromosomal aberrations; now part of revised ISS staging

FISH = fluorescence in situ hybridization.

Kurtin SE, et al. (2016) *J Adv Pract Oncol*, 7(S1), S59-S70. Adapted from Kurtin, 2010. Data from: NCCN, 2015; Ludwig H, et al. *Leukemia* 2014;28(5):981-92; Rajkumar et al, 2014; Mikael JR, et al. *Mayo Clin Proc* 2013;88:360-76.

Diagnostic Workup for Myeloma: Imaging

Technique	How It Works	When to Use	Limitations to Use
WBXR/bone survey	Series of x-rays of axial and appendicular skeleton	Baseline and relapse	• Bone lesions only seen if > 30% bone loss occurs • More accurate for lesions in the ribs and skull than newer techniques
MRI	• Three-sequence approach (T1, T2, STIR, post-gadolinium) detects MM activity in bone marrow • Highly sensitive	• Procedure of choice to evaluate a painful lesions • Verify solitary plasmacytomas, non-secretory disease • Assess spinal cord compression	• Lack of specificity reflects marrow infiltration not specifically bone deterioration • Expense and time • Excludes patients with implanted metal

WBXR = whole-body x-ray; STIR = short time inversion recovery.

Dimopoulos M, et al. *J Clin Oncol* 2015;33(6):657-64; Regelink JC, et al. *Br J Haematol* 2013;162(1):50-61; Dimopoulos M, et al. *Blood* 2011;117(18):4701-5; NCCN, Clinical Practice Guidelines: Multiple Myeloma V3, 2016.

Diagnostic Workup for Myeloma: Imaging (cont.)

Technique	How It Works	When to Use	Limitations to Use
CT	• Multiple computerized x-ray images from different angles • Highly sensitive	• Early detection of bone lesions not detected by WBXR • More sensitive to detect small osteolytic lesions	• Does not differentiate between active and inactive lesions • Higher levels of radiation exposure
PET	• FDG tracer illuminates metabolically active cells • Highly sensitive	Assess extra-medullary disease; response; MRD	Lack of specificity of findings may result in false-positive results; expense
DEXA (bone densitometry)	Measurement of osteopenia or osteoporosis	If comorbid conditions exist for osteoporosis	Does not measure osteolytic disease

FDG = 18-fluorine-fluoro-deoxyglucose; DEXA = dual-energy X-ray absorptiometry.

Dimopoulos M, et al. *J Clin Oncol* 2015;33(6):657-64; Regelink JC, et al. *Br J Haematol* 2013;162(1):50-61; Dimopoulos M, et al. *Blood* 2011;117(18):4701-5; NCCN, Clinical Practice Guidelines: Multiple Myeloma V3, 2016.

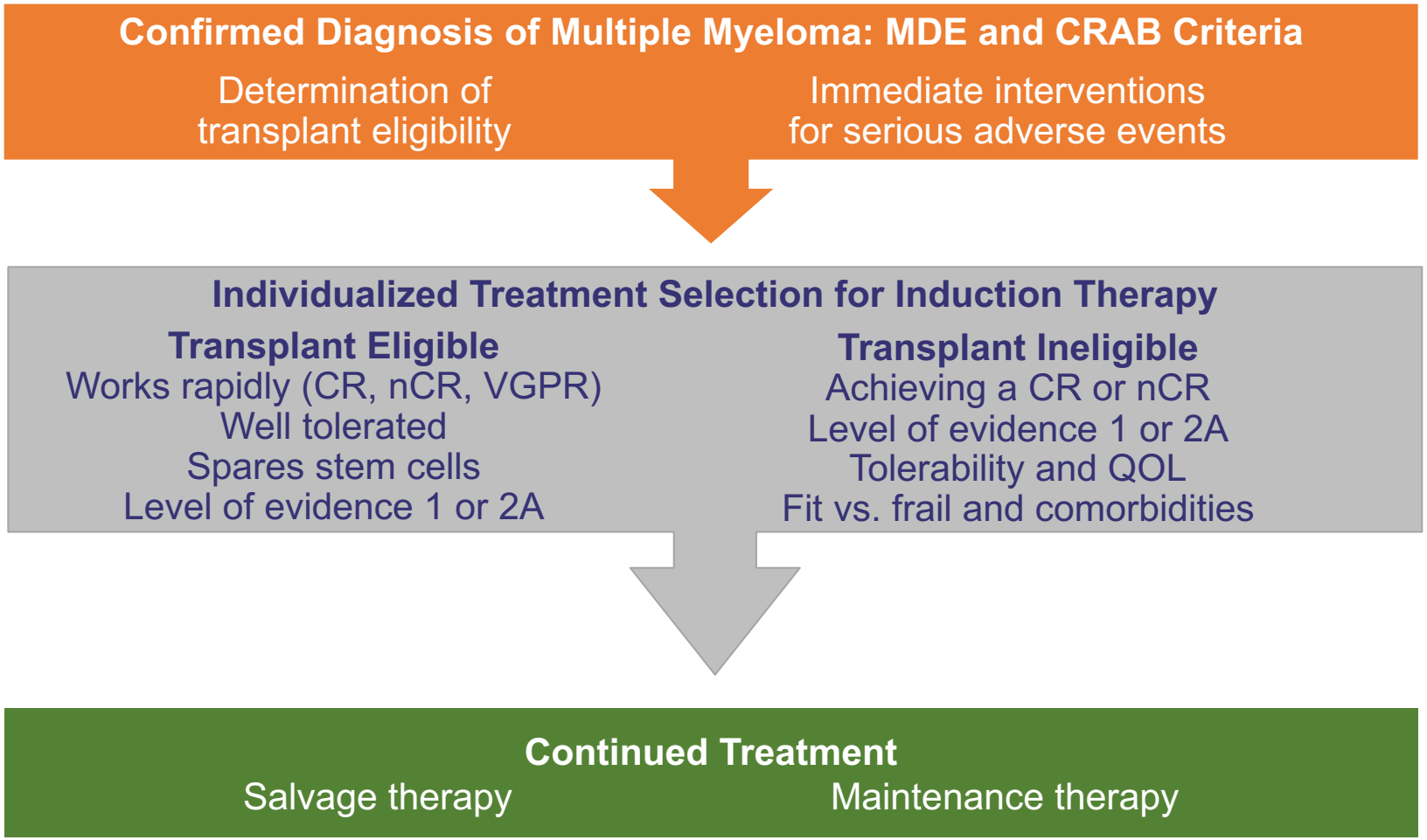
Updated MM Staging

Stage	ISS	Revised-ISS (R-ISS)
I	Serum beta 2 microglobulin < 3.5 mg/dL Serum albumin ≥ 3.5 g/dL Median survival: 62 mo	ISS stage I and standard risk chromosomal abnormalities by iFISH AND Serum LDH < ULN (varied by institution) 5-year OS rate: 82%; PFS at 46 mo 55%
II	Not ISS stage I or II Median survival: 44 mo	Not R-ISS stage I or III 5-year OS rate: 62%; PFS at 46 mo 36%
III	Serum beta-2 microglobulin ≥ 5.5 mg/L Median survival: 29 mo	ISS stage III and either high-risk chromosomal abnormalities by iFISH OR Serum LDH > ULN (varied by institution) 5-year OS rate: 40%; PFS at 46 mo 24%

iFISH = interphase FISH; OFS = progression-free survival.

Greipp PR, et al. *J Clin Oncol* 2005;23:3412-20; Palumbo A, et al. *J Clin Oncol* 2015;33:2863-9.

General Approach to Treatment of NDMM

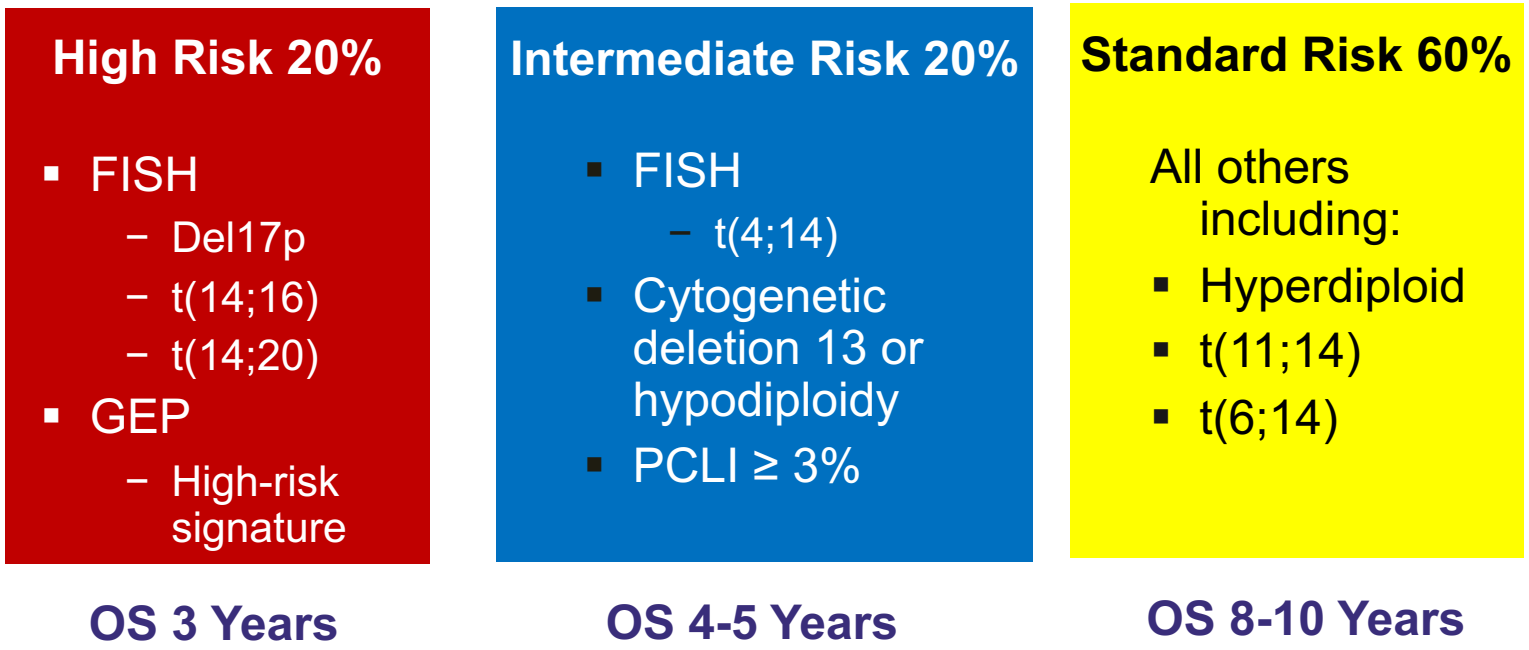


CR = complete response; nCR = near complete response; VGPR = very good partial response; QOL = quality of life.

NCCN Clinical Practice Guidelines: Multiple Myeloma V3, 2016

Cytogenetic Classification

- mSMART 2.0: classification of active MM



GEP = gene expression profiling; PCLI = plasma cell labeling index.

Mikhael JR, et al. *Mayo Clinic Proc* 2013;88:360-76.

General Principles of Treatment

- Achieving an early and deep response is key to obtaining and maintaining MRD-negative status
- HSCT remains a standard of care in eligible patients
- Maintenance therapy should be considered post-HSCT
- Treatment until disease progression or unacceptable toxicity is a core principle in the treatment of RRMM
- Improving or maintaining quality of life is a primary goal
- Combination therapies have demonstrated improved OR, PFS, and OS compared with single agents
- Supportive and palliative care should be provided concurrently with disease-modifying treatment

HSCT = hematopoietic stem cell transplantation; OR = overall response.

Factors Affecting Transplant Eligibility

- Age
  - Older patients are more sensitive to toxicity; less physical reserve
- Fit vs. frail
- Comorbidities: heart disease, lung disease
  - Increased risk of infection
  - Decreased tolerability for high-dose therapy
- Renal and hepatic function
- Personal preference
- Insurance coverage
- Eligibility of a caregiver

NCCN, Clinical Practice Guidelines: Multiple Myeloma V3, 2016; Miceli T, et al. *Clin J Oncol Nurs* 2013;17 Suppl:13-24.

Functional Status, Comorbidities, Frailty, and Vulnerability

- Functional status: Measures by ECOG and KPS
  - ADLs: Ability to bathe, dress, toilet and maintain continence, transfer, and eat independently
  - IADLs: Finances, shopping, housekeeping, transportation, and self-medication
- Comorbidities
  - Cardiovascular, renal, hepatic, pulmonary, endocrine, rheumatologic disease, and other cancers
  - Number, severity, controlled, or uncontrolled
- Frailty
  - Weight loss, weakness, poor nutritional intake, cognitive impairment, and poor endurance
  - Cardiovascular Health Study (5,317 patients): Frailty associated with hospitalization, falls, declining ADLs including diminished mobility, and death (p <.001)
- Vulnerability
  - A complex of comorbidity (presence of chronic diseases or conditions), disability (physical or mental impairment), and frailty (fatigue, low activity) that could prevent adequate therapy

ECOG = Eastern Cooperative Oncology Group; KPS = Karnofsky Performance Status; ADLs = activities of adult living; IADLs = instrumental activities of adult living.

Palumbo A, et al. *Blood* 2011;118:4519-29; Pal SK, et al. *CA Cancer J Clin* 2010;60:120-32; Balducci L, et al. *Oncologist*. 2000;5:224-37.

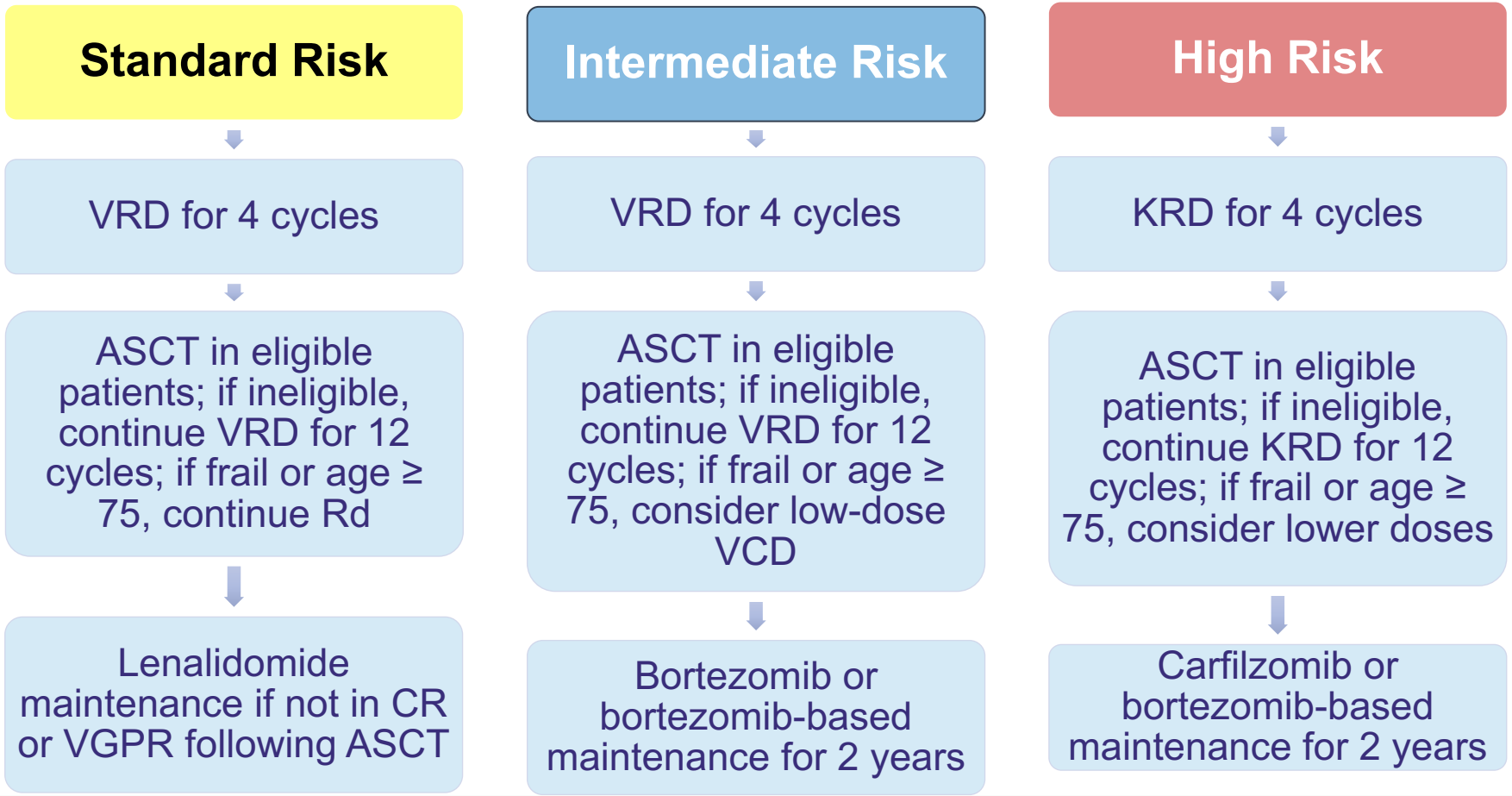
FDA-Approved Drugs to Treat MM

Drug	Drug Class	Brand
Bortezomib	Proteasome inhibitor	Velcade
Carfilzomib	Proteasome inhibitor	Kyprolis
Daratumumab	Monoclonal antibody	Darzalex
Elotuzumab	Monoclonal antibody	Empliciti
Lenalidomide	Immunomodulatory agent	Revlimid
Ixazomib	Proteasome inhibitor	Ninlaro
Thalidomide	Immunomodulatory agent	Thalomid
Pomalidomide	Immunomodulatory agent	Pomalyst
Panobinostat	Histone deacetylase inhibitor	Farydak
Melphalan	Alkylating agent	Alkeran, Alphalan
Cyclophosphamide	Alkylating agent	Cytoxan
Prednisone	Corticosteroid	Deltasone
Dexamethasone	Corticosteroid	Decadron
Pamidronate	Bisphosphonate	Aredia
Zoledronic acid	Bisphosphonate	Zometa

FDA = US Food and Drug Administration.

Mayo Clinic Approach to Newly Diagnosed MM

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



VRD = bortezomib, lenalidomide, and dexamethasone; KRD = carfilzomib, lenalidomide, and dexamethasone; ACST = autologous stem cell transplantation; Rd = lenalidomide, and dexamethasone; VCD = bortezomib, cyclophosphamide, and dexamethasone.

Mikhael JR, et al. *Mayo Clinic Proc* 2013;88:360-76.

Audience Response Question

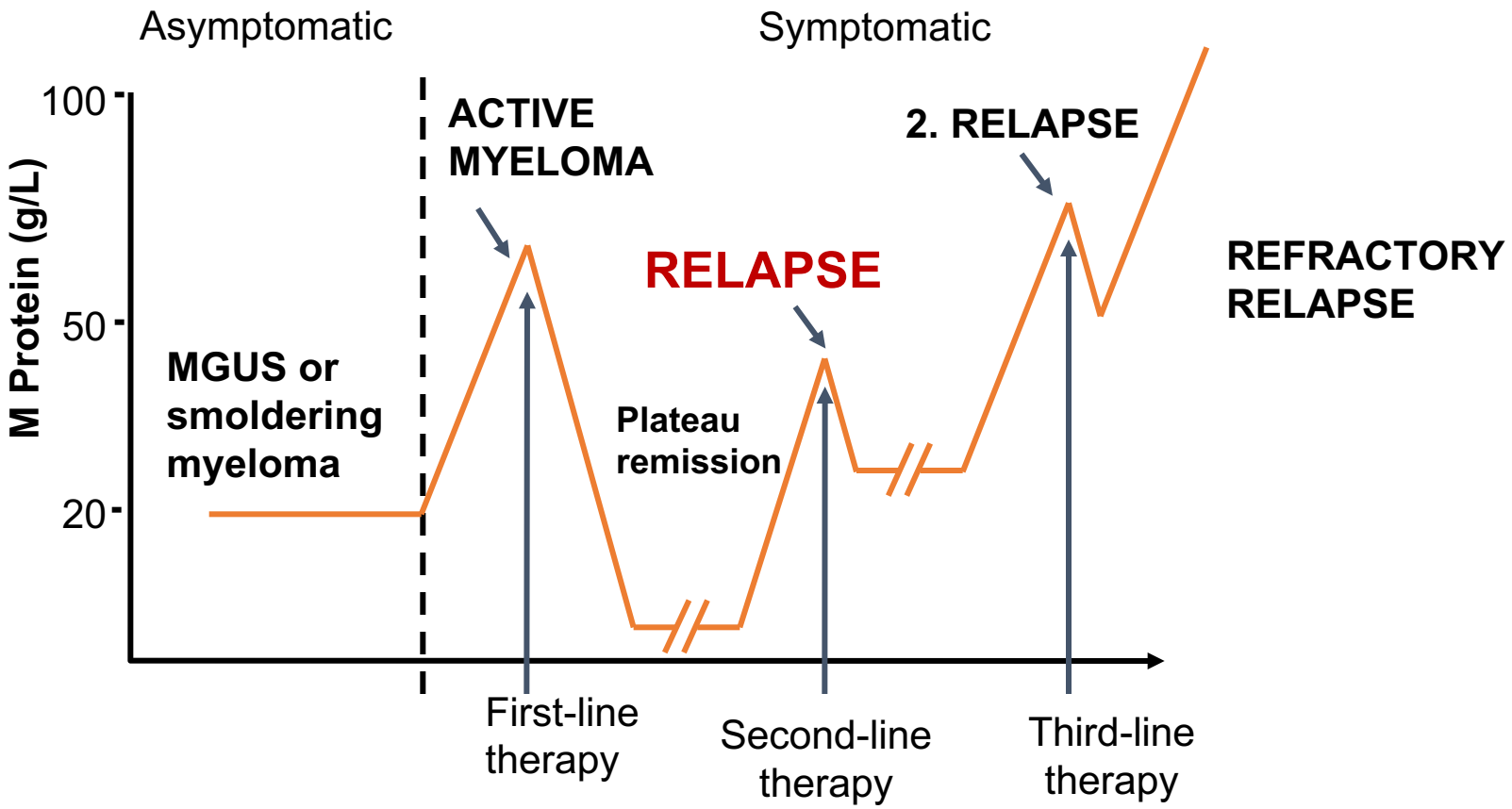
You are considering treatment for this 63-year-old female patient. Staging indicates ISS stage I. Past medical history includes hypothyroidism and hypertension. She was very active hiking and riding before presenting to the ED. Neurosurgery was consulted and did not feel surgery was needed. She is wearing a torso brace. Interventional Radiology feels the patient needs treatment before considering vertebroplasty.

Which of these options would you choose?

A. Radiation to the spine → observation
B. Lenalidomide, bortezomib, dexamethasone induction → autologous stem cell transplant → maintenance lenalidomide
C. Radiation to the spine → lenalidomide and dexamethasone
D. Radiation to the spine → lenalidomide, bortezomib, dexamethasone induction → autologous stem cell transplant → maintenance lenalidomide
E. Unsure

Relapsed and Relapsed-Refractory Multiple Myeloma

Natural History of Multiple Myeloma



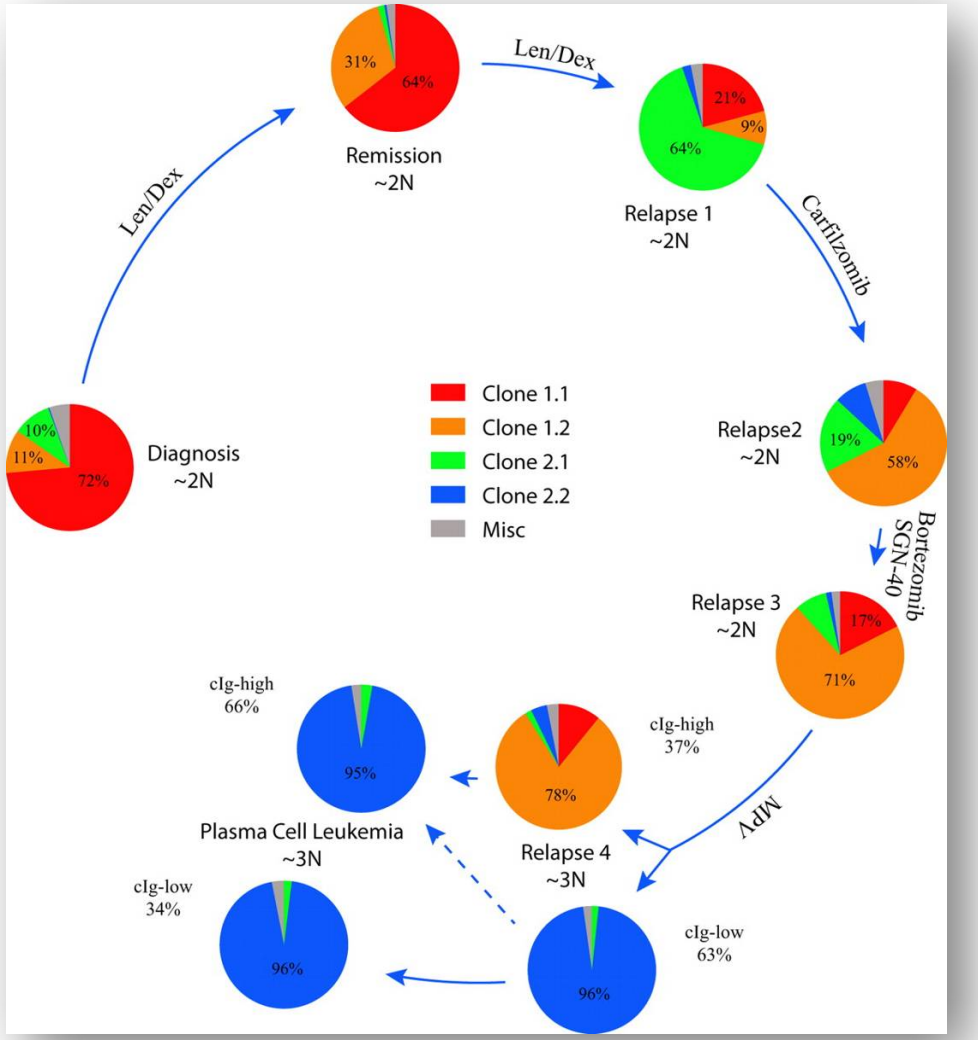
Adapted with permission from Durie B at www.myeloma.org.

Relapsed and Relapsed Refractory MM

- **Primary refractory:** Failure to achieve any response to specific MM treatments, often 2 or 3 novel agent combination regimens
- **Relapse:** Development of clinically measurable disease or secondary organ effects after achieving a CR
- **Progression:** Development of clinically measurable signs of increase disease activity after achieving PR or disease plateau
  - Progression of disease is implied in the term “relapsed”
- **Relapsed and refractory:** Defined as a lack of response or disease progression on or within 60 days of the last therapy
  - The therapy in use at the time of progression is what the patient is refractory to

PR = partial response.

Clonal Evolution in MM



- MM clones detected by FISH and cytogenetics can evolve
- At each relapse, there is a change in the dominant clone
- It is critical to reevaluate the patient at each point of relapse to characterize the disease and select the best treatment

Keats JJ, et al. *Blood* 2012;120:1067-76.

Monitoring for Response and Surveillance

Evaluation of treatment response until best response

- Heavy/light chain monthly with initiation of therapy, until best response
- CMPNL, CBC, diff, platelets, and other labs as indicated based on treatment plan and individual profile

Surveillance

- Myeloma panel every 3 months
- Skeletal survey yearly
- Other laboratory or diagnostic testing as indicated by individual disease and personal attributes

Kurtin S, et al. *J Adv Pract Oncol* 2016;7(S1):S59-70.

Monitoring for Response and Surveillance

Suspected relapse or progression

- Increase frequency of myeloma panel
- Repeat imaging as clinically indicated
- Repeat bone marrow biopsy to detect changes/clonal evolution with progression
- Continued monitoring for organ damage
- Evaluation of any residual adverse events
- Reassess comorbidities and fit vs. frail
- Infectious disease workup based on transplant history, infectious history, and treatment plan

Kurtin S, et al. *J Adv Pract Oncol* 2016;7(S1):S59-70.

Selecting Treatment for Relapsed/Refractory MM

Treatment selection depends on many factors

- Clinical trial data
- Previous therapy and response
- Length of time since last therapy
- Performance status and comorbidities
- Adverse event profile
- Patient preference

NCCN, Clinical Practice Guidelines: Multiple Myeloma V3, 2016

Key FDA Approvals 2012–2017

- **2012:** 7/20/12: Carfilzomib/dex (ASPIRE trial) – RRMM after 2 prior therapies
- **2013:** 2/8/13: Pomalidomide/dex – RRMM after 2 prior therapies
- **2014:** 8/14: Bortezomib/dex retreatment (RETRIEVE Trial) in patients who received bortezomib > 6 months prior to RRMM
- **2015**
  - 2/25/15: Panobinostat/bortezomib/dex (Panorama I trial) – RRMM after at least 2 prior therapies
  - 11/11/15: Ixazomib/dex (TOURMALINE-MM1) – RRMM after at least 1 prior treatment
  - 11/16/15: Daratumumab/dex (MMY2002 [SIRIUS] study) – RRMM after at least 3 prior therapies
  - 11/30/15: Elotuzumab/lenalidomide/dex (ELOQUENT-2 trial) – RRMM after 1-3 prior therapies
- **2016:** 7/26/16: Updated indication for daratumumab: dara/len/dex (POLLUX) or dara/bor/dex (CASTOR)
- **2017:** Updated dosing recommendation for KRD and KD

dex = dexamethasone; dara = daratumumab; len = lenalidomide; bor = bortezomib; KD = carfilzomib and dexamethasone.

https://www.accessdata.fda.gov/scripts/cder/daf/

Clinical Management of the Patient With MM: Maximizing Therapies by Mitigating Adverse Events

Adverse Events for Immunomodulatory Agents

Side effect	Thalidomide	Lenalidomide	Pomalidomide
Peripheral neuropathy	√		
Thromboembolism	More with dex	More with dex	More with dex
Myelosuppression	Neutropenia	Neutropenia, thrombocytopenia, anemia	Neutropenia, thrombocytopenia, anemia
Fatigue, weakness	√	√	√
Somnolence	√		
Rash	√	√	√
Gastrointestinal disturbance	√Constipation	Constipation, diarrhea	Constipation, diarrhea
Renal/Hepatic		Reduce dose for decreased CrCL	

CrCL = creatinine clearance.

Colson K. *Support Care Cancer* 2015;23(5):1431-45.

Adverse Events for Proteasome Inhibitors

Side effect	Bortezomib	Carfilzomib	Ixazomib
Peripheral neuropathy	√		Majority grade 1/2
Myelosuppression	Thrombocytopenia	Neutropenia, thrombocytopenia, anemia	Neutropenia, thrombocytopenia, anemia
Cardio/pulmonary	Hypotension		ECG changes
Fatigue, weakness	√	√	
Herpes zoster	√	√	√
Gastrointestinal disturbance	N/V, diarrhea	N/V, diarrhea, constipation, mucositis	Diarrhea
Renal/hepatic	Hepatic		
Rash			√

ECG = electrocardiography; N/V = nausea/vomiting.

Colson K. *Support Care Cancer* 2015;23(5):1431-45.

Adverse Events for Monoclonal Antibodies

Side effect	Elotuzumab*	Daratumumab
Infusion reactions	√	√
Interference with type and screen and red blood cell antibody testing	-	√
Interference with detecting IgG kappa	√	-
Fatigue	√	√
Infection	√	√
SPM	√	-
Hepatotoxicity	√	-
Nausea	√	-

SPM = second primary malignancy. *In combination with lenalidomide and dexamethasone.

Colson K. *Support Care Cancer* 2015;23(5):1431-45.

Adverse Events for Other Approved Agents

Side effect	Panobinostat	Cyclophosphamide	Melphalan
Diarrhea	√	-	√
Nausea	-	√	√
Myelosuppression	-	√	√
Transaminitis	√	-	-
Fatigue	√	√	√
Pneumonia	√	-	-
SPM	-	√	√

Colson K. *Support Care Cancer* 2015;23(5):1431-45.

Newer Agents and Updated Approvals for the Treatment of Myeloma

Lenalidomide Maintenance After HSCT

- FDA expanded the indication for lenalidomide on 2/22/17 as maintenance therapy for patients with MM following HSCT
- Lenalidomide maintenance therapy extended PFS vs. placebo in two pivotal studies
- US study (CALGB 100104, 460 patients; 47 locations; ClinicalTrials.gov Identifier: NCT00114101:
  - Median PFS at unblinding (median follow-up of 34 months, planned interim analysis) was 2.8 years for REVLIMID vs. 1.6 years for placebo (HR 0.38; 95% CI: 0.27-0.54; *p* <.001)
- EU study (IFM 2005-02, 614 patients; 77 locations):
  - Median PFS at unblinding (median follow-up of 45 months, planned interim analysis) was 3.4 years for REVLIMID vs. 1.9 years for placebo (HR 0.50; 95% CI: 0.39-0.64; *p* <.001)
  - Updated analysis shows no difference in OS, but a significant difference in PFS 50 months vs. 36 months (HR, 0.65; P<0.001)
- Dosing
  - 10 mg once daily, dosed continuously on days 1-28 of repeated
  - 28-day cycles; if tolerated, dose can be increased to 15 mg after 3 cycles
  - Continue until disease progression or unacceptable toxicity

HR = hazard ratio; CI = confidence interval; EU = European Union.

Attal et al. *Blood*. 2013;122:406; Attal et al. *N Engl J Med*. 2017;376(14):1311-1320; McCarthy PL, et al. *N Engl J Med*. 2012;366(19):1770-178.

Lenalidomide Maintenance After HSCT (cont.)

- Phase III BMT CTN 0702 StaMINA trial
  - No difference at 38 months of follow-up in PFS or OS in NDMM following RVD induction
    - Single ASCT (PFS 52.2%; OS 83.4%)
    - Tandem ASCT (PFS 56.5%; OS 82%)
    - ASCT followed by additional consolidation (PFS 56.7%; OS 85.7%)
- Each treatment approach was followed by lenalidomide maintenance therapy
- Patients who receive optimal induction therapy (e.g., triplet-based therapy with both an IMiD and a proteasome inhibitor), the benefit of a tandem transplantation and/or additional consolidation prior to maintenance therapy is negligible and likely not needed

IMiD = immunomodulatory drug.

Carfilzomib in RRMM

Kd

Randomized phase III **ENDEAVOR** trial: Kd (n = 464) vs. Vd (n = 465)

- 9.3-mo increase in median PFS
  - Kd (18.7 mo) vs. Vd (9.4 mo) HR 0.53 (95% CI: 0.44-0.65); one-sided *p* <.00011

Dosing

- Days 1 and 2 of cycle 1: 20 mg/m^2
- All subsequent doses **56 mg/m^2**

KRd

Randomized phase III **ASPIRE** trial: KRd (n = 396) vs. Rd (n = 396)

- Improved CR rates with KRd (32%) vs. Rd (9%)
- Improved PFS
  - KRd (26.3 mo) vs. Rd (17.6 mo) HR 0.69 (95% CI: 0.57-0.83); two-sided *p* =.00011

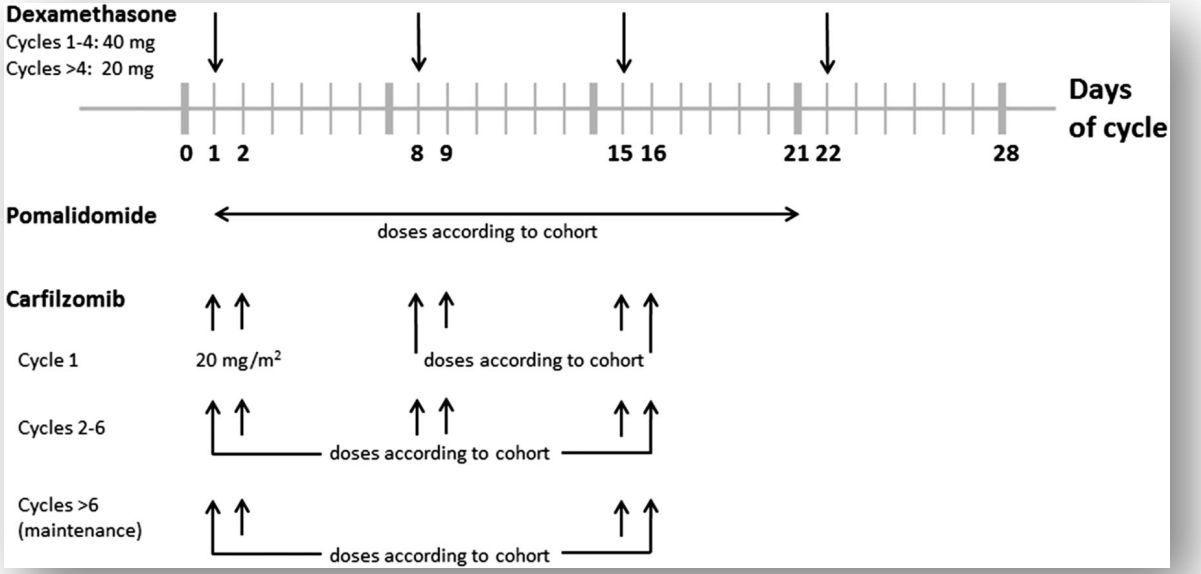
Dosing

- Day 1 and 2 of cycle 1: 20 mg/m^2
- All subsequent doses **27 mg/m^2**

Carfilzomib prescribing information, Onyx Pharmaceuticals Inc., 2012, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202714lbl.pdf; Dimopoulos MA, et al. *Lancet Oncol* 2016;17(1):27-38; Stewart AK, et al. *N Engl J Med* 2015;372:142-52.

Carfilzomib/Pomalidomide/Dexamethasone

- Open-label, multicenter, phase I, dose-escalation study
- Patients with RRMM, including lenalidomide (n = 32)
  - Heavily pretreated patient population (median of 6 lines of prior therapy)
- Primary objective: Evaluate safety, determine MTD



Safety

- Hematologic AEs occurred in ≥ 60% of all patients, including 11 patients with grade ≥ 3 anemia
- Dyspnea was limited to grade 1/2 in 10 patients
- Peripheral neuropathy was uncommon and limited to grade 1/2
- Eight patients had dose reductions during therapy, and 7 patients discontinued treatment due to AEs
- Two deaths were noted on study due to pneumonia and pulmonary embolism (n = 1 each)

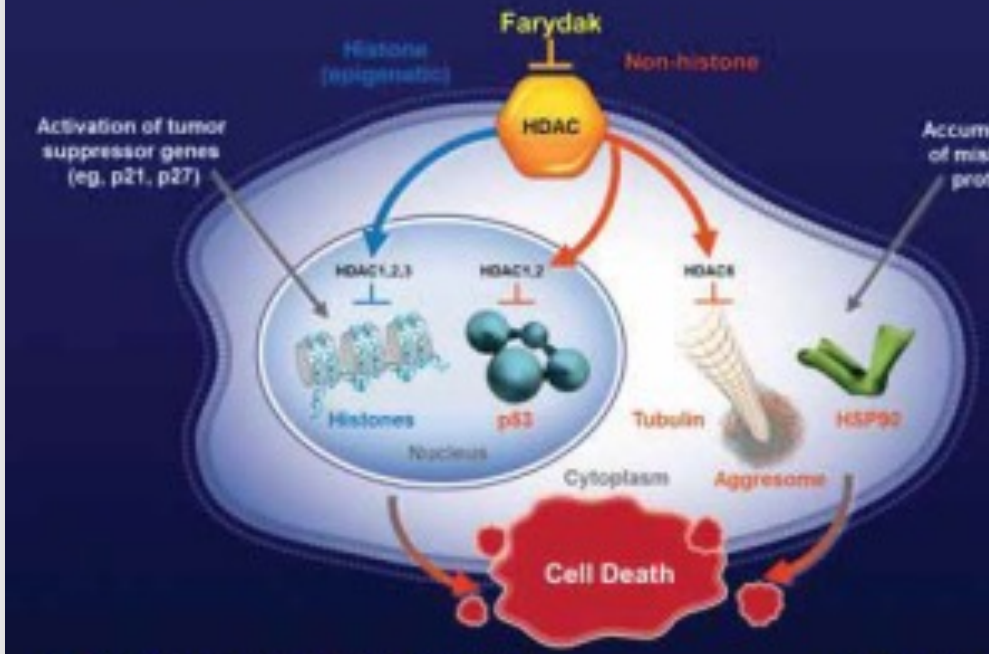
MTD of CPD (28-day cycle)
Carfilzomib 20/27 mg/m^2
Pomalidomide 4 mg
Dexamethasone 40 mg

MTD = maximum tolerated dose; AEs = adverse events; CPD = carfilzomib, pomalidomide, and dexamethasone

Shah JJ, et al. *Blood*. 2015;126(20):2284-2290; ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT01464034.

Panobinostat

- Panobinostat is a pan-deacetylase inhibitor that inhibits a broad range of deacetylase enzymes, which target both histone and non-histone proteins involved in oncogenesis[1]



Panobinostat inhibits growth and promotes death of myeloma cells through inhibition of HDAC enzymes:

- **Histone proteins**, which are implicated in epigenetic dysregulation, resulting in activation of tumor suppressor genes[1-5]
- **Non-histone proteins**, which promote toxic accumulation of misfolded proteins, leading to cell stress[1,6-8]

1. Atadja P. *Cancer Lett.* 2009; 280:233-241
2. Bolden JE, et al. *Nat Rev Drug Discov.* 2006; 5:769-784
3. De Bruyne E, et al. *Blood.* 2010; 115:2430-2440
4. Mannava S, et al. *Blood.* 2012;119:1450-1458
5. Kalushkova A et al. *PloS One.* 2010;5:e11483
6. Catley L, et al. *Blood.* 2006 ;108:3441-3449
7. Hideshima T, et al. *Mol Cancer Ther.* 2011; 10:2034-2034
8. Hipp MS, et al. *Trends Cell Biol.* 2014;24:506-514

Panobinostat in Combination With Bortezomib and Dexamethasone

Registration trial: Phase III PANORAMA1 trial

Primary objective: PFS with PAN-BTZ-Dex vs. Pbo-BTZ-Dex in RMM or RRMM

Efficacy

- PFS benefit of 7.8 months with PAN-BTZ-Dex among patients who received ≥ 2 prior regimens including bortezomib and an IMiD
- Prior IMiD (12.3 vs. 7.4 mo; HR 0.54; 95% CI: 0.43-0.68)
- Prior bortezomib plus IMiD (10.6 vs. 5.8 mo; HR 0.52; 95% CI: 0.36-0.76)
- ≥ 2 prior regimens including bortezomib and an IMiD (12.5 vs. 4.7 mo; HR 0.47; 95% CI: 0.31-0.72)

PAN = panobinostat; BTZ = bortezomib; Pbo = placebo.

Safety

Common grade 3/4 adverse events:

- Thrombocytopenia, lymphopenia, neutropenia, diarrhea, and asthenia/fatigue
- Minimal peripheral neuropathy
- Incidence of on-treatment deaths among patients who received prior bortezomib and an IMiD (regardless of number of prior regimens) was similar between treatment arms

Class: Histone deacetylase inhibitor

FDA-approved indication (2/25/2015):

In combination with bortezomib and dexamethasone for the treatment of MM in patients who have received at least 2 prior chemotherapy regimens

Richardson PG, et al. *Blood* 2016;127(6):713-21.

PAN-BTZ-Dex: Clinical Management

Patient management

- Severe diarrhea in 25% of patients
  - At first sign of abdominal cramping, loose stools, or onset of diarrhea, patients should be treated with antidiarrheal medication (e.g., loperamide)
  - Consider and administer prophylactic antiemetics as clinically indicated
  - May require dose modification
- Cardiac toxicities, including ischemic events and severe arrhythmias
- Hematologic toxicities: Thrombocytopenia and myelosuppression may require dose modification
- Hepatotoxicity
- Embryo-fetal toxicity

Dosing considerations

- Hepatic impairment
  - Mild: Starting dose 15 mg
  - Moderate: Starting dose 10 mg
  - Severe: Avoid panobinostat use
- Renal impairment
  - No dose modification
  - Not studied in patients on dialysis
- Coadministration with CYP3A inhibitors: starting dose 10 mg

Richardson PG, et al. *Blood* 2016;127(6):713-21.

Panobinostat Dosing

Table 1. Panobinostat Recommended Schedule

21-day cycle

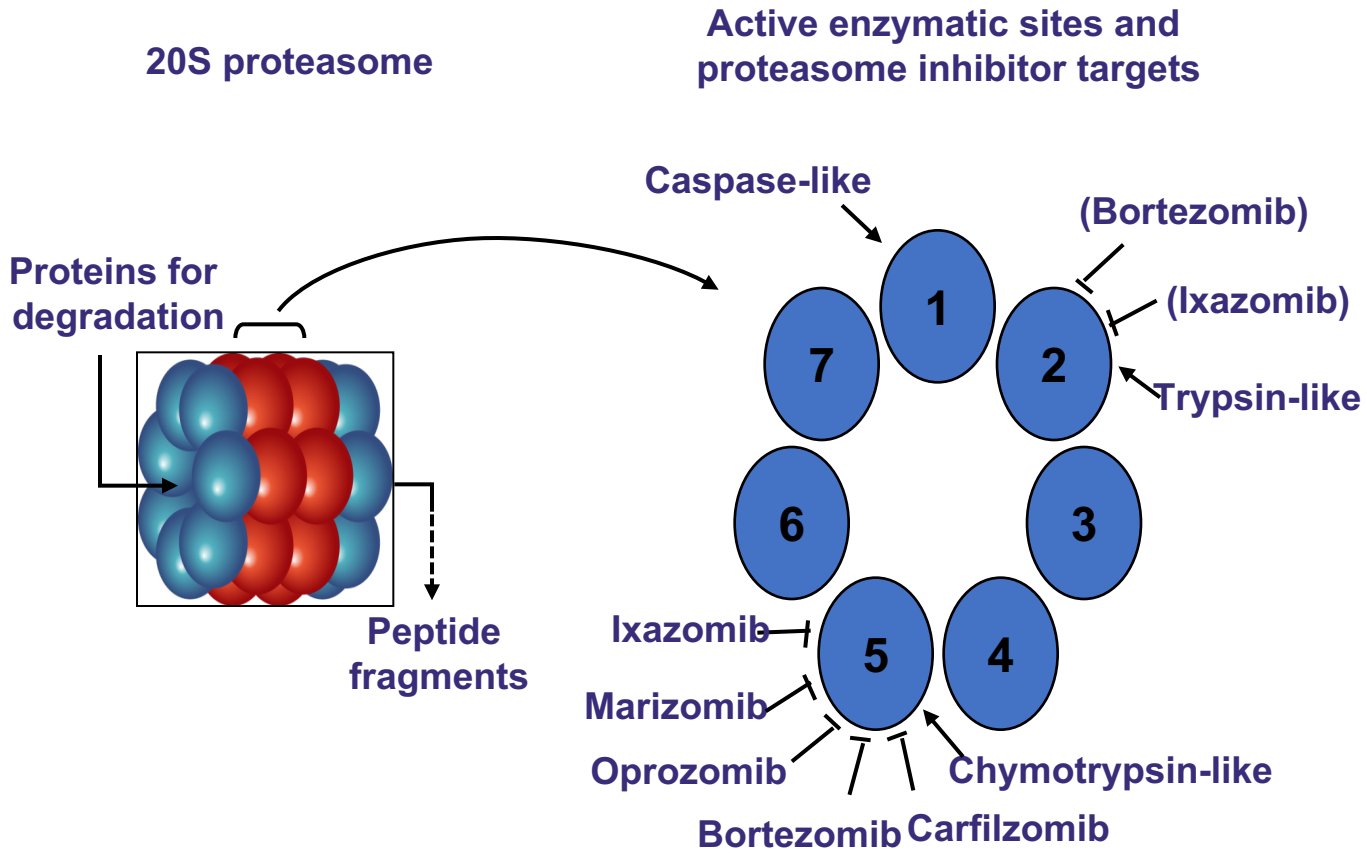
Cycles 1 to 8	Week 1 Days					Week 2 Days					Week 3
Panobinostat	1		3		5	8		10		12	Rest period
Bortezomib	1			4		8			11		Rest period
Dexamethasone	1	2		4	5	8	9		11	12	Rest period

Note. Recommended dosing schedule for panobinostat in combination with bortezomib and dexamethasone during cycles 1 to 8. Panobinostat is dosed orally at 20 mg, bortezomib is dosed at 1.3 mg/m^2, and dexamethasone is recommended at a dose of 20 mg. Information from Novartis Pharmaceuticals (2015).

- Capsules should not be opened, broken, or chewed
- Continue up to 8 cycles for patients with clinical benefit who do not experience unacceptable toxicity
- Advise patients to avoid star fruit, pomegranate, grapefruit, or their juices because they can affect panobinostat pharmacology
- If dose reduction is required, dose of panobinostat should be reduced in increments of 5 mg (i.e., from 20 to 15 mg, or from 15 to 10 mg)

Novartis Pharmaceuticals, 2015; Noonan et al. *J Adv Pract Oncol*. 2016;7(Suppl).

Molecular Targets of Proteasome Inhibitors



Adapted from McBride A, et al. *Expert Rev Anticancer Ther* 2013;13:339-58.

Ixazomib Citrate

Class: Proteasome inhibitor

Registration trial: TOURMALINE-MM1

ClinicalTrials.gov identifier: NCT01850524

- International, randomized, double-blind, placebo-controlled clinical trial of 722 patients
  - Ixazomib, lenalidomide, and dexamethasone compared with placebo, lenalidomide, and dexamethasone in RRMM
- Approval based on a 6-mo improvement in median PFS: 20.6 mo vs. 14.7 mo (placebo regimen) HR 0.74; 95% CI: 0.587-0.939); *p* =.012.
- Median time to response 1.1 mo in the ixazomib arm and 1.9 mo in the placebo arm

FDA-approved indication (11/20/2015): In combination with lenalidomide and dexamethasone in patients who have received at least 1 prior therapy

AEs

- No grade 4 non-hematologic toxicity
- Grade 3 occurring in > 5% of patients with a > 5% difference in the two arms:
  - Thrombocytopenia: 3% of patients on ixazomib and 1% on the placebo arm had a platelet count of < 10,000 during treatment
  - Diarrhea (42% vs. 36%), constipation (34% vs. 25%)

Other AEs

- Neutropenia, peripheral edema, backache
- Disorder of the eye
- Rash: Generally self-limiting
- Neuropathy: Majority were grade 1/2 with incidence similar in both arms

Ixazomib prescribing information, Millennium Pharmaceuticals, 2016, https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208462lbl.pdf.

Ixazomib Citrate: Clinical Management

Patient management

- Baseline CBC
  - ANC > 1,000/mm^3
  - Platelet count > 75,000/mm^3
- Monitor CBC at least monthly or more frequently if indicated
  - Platelet nadir, days 14-21 of each cycle
- All patients should receive shingles prophylaxis (Acyclovir)
- Treatment should be continued until disease progression or unacceptable toxicity
- Oral adherence

Dosing considerations

- Avoid concomitant use with strong CYP3A inducers
- Hepatic impairment
  - Reduce the starting dose to 3 mg in patients with moderate or severe hepatic impairment
- Renal impairment
  - Reduce the starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis
- Dose modification must be balanced for all drugs in the regimen

ANC = absolute neutrophil count.

Ixazomib prescribing information, Millennium Pharmaceuticals, 2016, https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208462lbl.pdf.

Ixazomib Citrate: Dosing

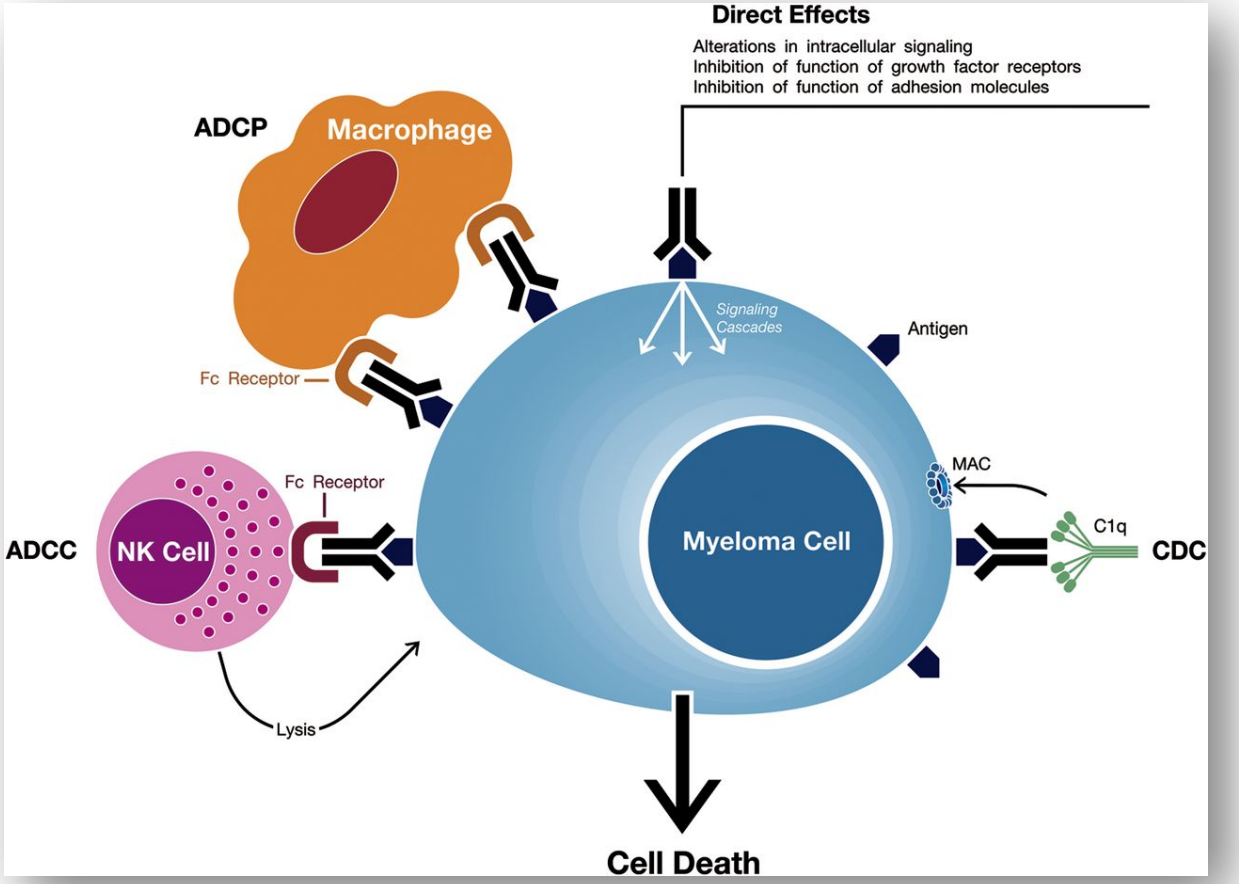
Dosing Schedule for Ixazomib

	Week 1		Week 2		Week 3		Week 4	
	Day 1	Days 2-7	Day 8	Days 9-14	Day 15	Days 16-21	Day 22	Days 23-28
Ixazomib	√		√		√			
Lenalidomide	√	√ daily	√	√ daily	√	√ daily	√	
Dexamethasone	√		√		√		√	

- Swallow pill whole, do not crush or chew
- Should be taken at least 1 hour before or at least 2 hours after food
- After oral administration median time to peak plasma concentration = 1 hour
- Missed doses or emesis:
  - Missed dose should not be taken with 72 hours of the next scheduled dose
  - Do not repeat the dose if vomiting occurs

Ixazomib prescribing information, Millennium Pharmaceuticals, 2016, https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208462lbl.pdf.

Mechanisms of Action of Monoclonal Antibodies Targeting Surface Antigens on MM Cells

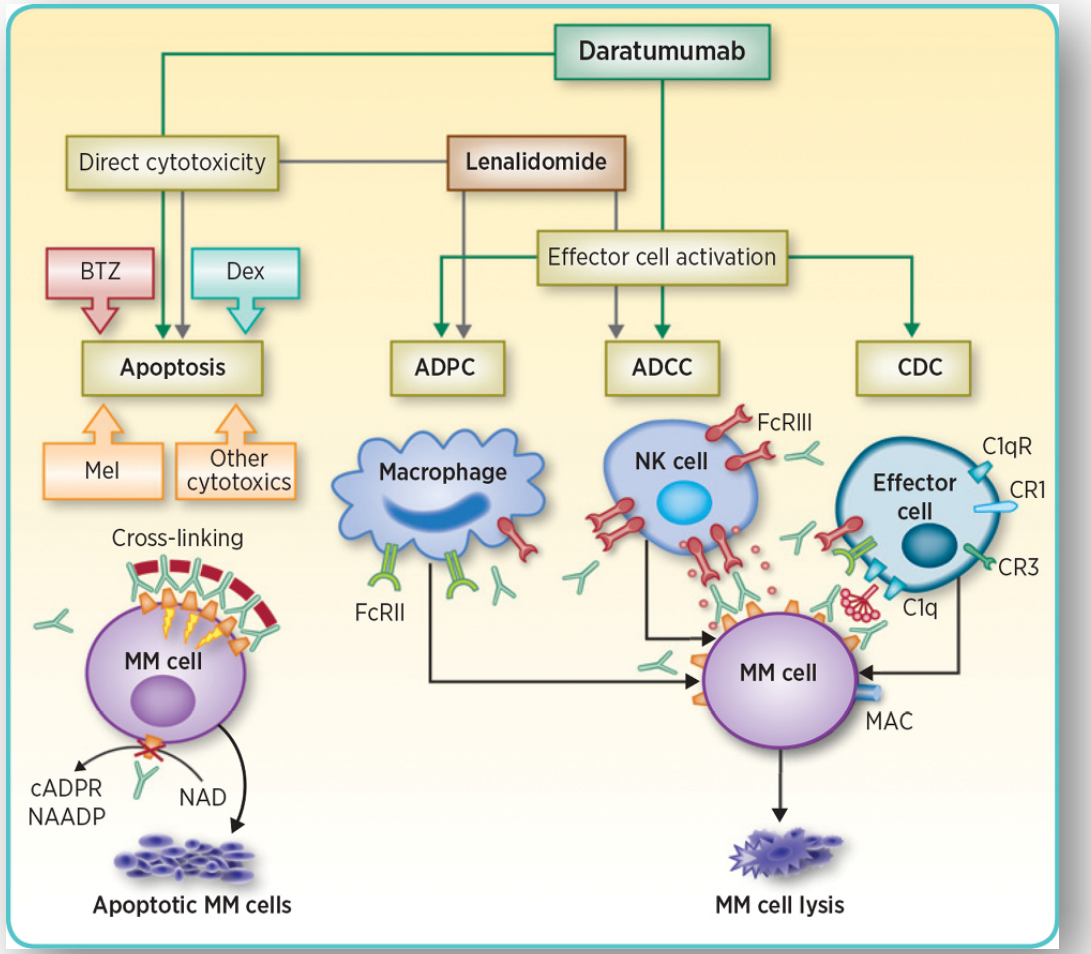


ADCP = antibody-dependent cellular phagocytosis; ADCC = antibody-dependent cellular cytotoxicity.

Niels WC, et al. *Blood* 2016;127:681-95.

Daratumumab

- Humanized monoclonal antibody
- Target: CD38
  - Responsible for receptor mediated adhesion, signal transduction, and regulation of intracellular calcium
- Dara eliminates tumor cells expressing the CD38 antigen
- Mechanism: ADCC
  - Major mechanism of cell death
  - CDC
  - Apoptosis
- Results in decline in M protein and bone marrow plasma cells



CDC = complement-dependent cytotoxicity.

Laubach, J. P., & Richardson, P. G. (2015). *Clin Cancer Res, 21*(12), 2660-2662.

Daratumumab

FDA approval: November 16, 2015

Registration trial: MMY2002 (SIRIUS) study

ClinicalTrials.gov identifier: NCT01985126

- Approval was based on a multicenter, open-label study evaluating response rates in 106 patients with RRMM treated with daratumumab monotherapy
- Median of 5 prior lines of therapy
- The objective response rate was 29% (95% CI: 21%-39%) with a median response duration of 7.4 months (range: 1.2 to 13.1+ months)

FDA-approved indication (11/16/15)

- Treatment of patients with MM who have received at least 3 lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent
- Updated approval 7/26/16: The FDA granted daratumumab a breakthrough therapy designation for use in combination with len/dex or bor/dex as a treatment for patients with MM following at least 1 prior therapy
- Most recent study is exploring SC infusion of dara over 30 minutes using same schedule (PAVO study)

Adverse events

- The most frequently reported adverse reactions (incidence ≥ 20%) were infusion reactions, fatigue, nausea, back pain, pyrexia, cough, and upper respiratory tract infection
- Interference with cross-matching and red blood cell antibody screening

US FDA, Daratumumab injection, 2015, http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm472904.htm; Daratumumab prescribing information, Janssen Biotech, Inc., 2015, http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761036s000lbl.pdf.

Daratumumab

Administration: IV
Recommended dosing: 16 mg/kg
Premedicate with corticosteroids, antipyretics, and antihistamines, montelukast

Schedule	Weeks
Weekly	Weeks 1-8
Every 2 weeks	Weeks 9-24
Every 4 weeks	Weeks 25 until disease progression

Infusion rates for daratumumab administration

	Dilution volume	Initial rate (first hour)	Rate increment	Maximum rate
First infusion	1000 mL	50 mL/hr	50 mL/hr every hour	200 mL/hr
Second infusion	500 mL	50 mL/hr	50 mL/hr every hour	200 mL/hr
Subsequent infusions	500 mL	100 mL/hr	50 mL/hr every hour	200 mL/hr

U.S. FDA, Daratumumab injection, 2015, http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm472904.htm; Daratumumab prescribing information, Janssen Biotech, Inc., 2015, http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761036s000lbl.pdf.

Special Considerations for Daratumumab

Prophylactic treatment

- Montelukast 10 mg the day before and again on the morning of infusion, may consider the day after dosing
- Most patients will not need this after the first 2-3 cycles

Post-infusion

- Consider antihistamines, b-2 adrenergic receptor agonist by inhalation, or control medication for patients with asthma and COPD such as inhalation corticosteroids

Note: Patients with FEV1, 50% or with moderate to severe asthma within the past 2 years, or with uncontrolled asthma, were excluded from trials with daratumumab

Recommendations

- FEV1 testing for patients with suspicion of having COPD, and it should be considered to exclude patients from daratumumab treatment if FEV1, 50% of predicted

COPD = chronic obstructive pulmonary disease.

van de Donk NW, et al. *Blood* 2016;127(6):681-95.

Daratumumab Emerging Data

- Daratumumab in combination with frontline treatment in NDMM
  - POLLUX TRIAL: dara/Rd vs. Rd (n = 286)
  - CASTOR TRIAL: dara/Vd vs. Vd (n = 251)
- In both CASTOR and POLLUX
  - MRD-negative patients had PFS > 90% at 12 months regardless of treatment arm
  - PFS was longer with the triplet regimens vs. the doublet regimens for patients with MRD negativity
  - MRD negativity correlates with prolonged PFS

Dimopoulos MA, et al. *N Engl J Med* 2016;375:1319-31; Palumbo A, et al. *N Engl J Med* 2016;375:754-66.

Daratumumab Emerging Data (cont.)

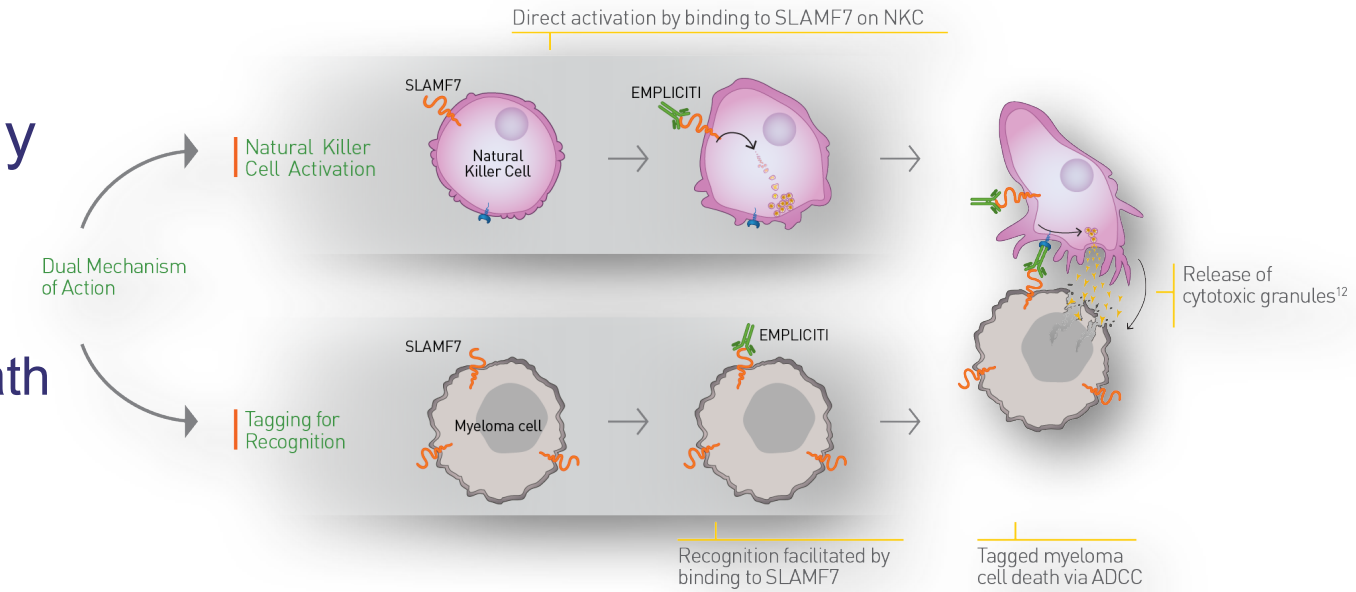
- Phase Ib PAVO trial
- Evaluation of subcutaneous infusion of dara (n = 53)
- Randomized to:
- Dara 1,200 mg plus 30,000 U rHuPH20 via SC infusion (n = 8)
- Dara 1,800 mg plus 45,000 U rHuPH20 via SC infusion (n = 45)
- Efficacy
  - ORR: 25% with 1,200 mg and 38% with 1,800 mg
  - Comparable to the initial studies of IV daratumumab as a single agent
- Safety
  - 24% with dara 1,800 mg SC compared with ~ 50% when given IV
  - Other AEs similar to IV administration

rHuPH20 = recombinant hyaluronidase; ORR = overall response rate.

Usmani SZ, et al. 2016. ASH Abstract 1149.

Elotuzumab

- Humanized monoclonal antibody
- Target: myeloma cells expressing signaling lymphocyte activation family 7 (SLAMF-7, also called CS1)
- Elotuzumab exerts a dual effect:
  - Induces NK-mediated myeloma cell death with minimal effect on normal cells
  - Mediating antibody-dependent cell-mediated cytotoxicity through the CD16 pathway



ORR = overall response rate; PFS = progression-free survival.

Lonial S, et al. *J Clin Oncol* 2013;31 (suppl; abstr 8542); Facon T, et al. *Haematologica* 2013;98(s1):319.

Elotuzumab (cont.)

Registration trial: Phase III ELOQUENT-2 trial combining ELO, lenalidomide, and low-dose dexamethasone

ClinicalTrials.gov identifier: NCT01239797

- Randomized patients with RRMM (1-3 prior therapies) who were *not* refractory to lenalidomide to receive ERd or standard lenalidomide-dexamethasone in 28-day cycles
- Treatment was continued until disease progression or unacceptable toxicity
- The primary endpoints were PFS and ORR
- At interim analysis, 646 patients had been enrolled (321 ERd, 325 Rd)
- A number of patients in this trial had adverse disease attributes, including del(17p) in 32% and t(4;14) in 9%
- At 24 months of follow-up, patients in the ERd arm demonstrated a 30% reduction in the risk of disease progression or death compared to the Rd alone arm (HR 0.70; 95% CI: 0.57-0.85); p =.0004
- PFS favored ERd over Rd, with a median of 19.4 (16.6-22.2) months vs. 14.9 (12.1-17.2) months and HR 0.70 (95% CI: 0.57-0.85; p =.0004)
- At 2 years of follow-up, 35% (ERd) and 21% (Rd) of patients remained on therapy; discontinuation was mainly for disease progression (42% ERd, 47% Rd)

FDA-approved indication (11/30/2015)

- Indicated in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received one to three prior therapies

ELO = elotuzumab; ERd = elotuzumab, lenalidomide, and low-dose dexamethasone; Rd = lenalidomide and dexamethasone.

Elotuzumab package insert, Bristol-Myers Squibb Company, 2015, https://packageinserts.bms.com/pi/pi_empliciti.pdf.

Elotuzumab: Clinical Management FDA Approval November 30, 2015

- Interference with determination of CR
- Elotuzumab is a humanized IgG kappa monoclonal antibody that can be detected on both SPEP and immunofixation
- May interfere with testing for response or relapse
- Testing is recommended immediately prior to dosing
- Correlation with clinical findings is recommended

Infections

- Grade 3/4 infections were 28% (ERd) and 24.3% (Rd)
- Monitor patients for development of infections and treat promptly
- Implement infection prophylaxis as indicated

SPM

- 9.1% (ERd) and 5.7% (Rd)
- No difference in hematologic SPM
- Slightly higher incidence for solid tumors (3.5% vs. 2.2%) and skin cancers (4.4% vs. 2.8%) in the ELO arm
- Monitor patients for SPM

Hepatotoxicity

- Monitor liver enzymes periodically
- Stop elotuzumab upon grade 3 or higher elevation of liver enzymes
- After return to baseline values, continuation of treatment may be considered

Elotuzumab package insert, Bristol-Myers Squibb Company, 2015, https://packageinserts.bms.com/pi/pi_empliciti.pdf; Lonial S, et al. *N Engl J Med* 2015;373(7):1-11; Cheng M, et al. *Cell Mol Immunol* 2013;10(3):230-52; Lonial S, et al. *N Engl J Med* 2015;373(suppl):1-18.

Elotuzumab: Administration and Dosing

Premedication

- Dexamethasone 28 mg orally 3-24 hours prior to infusion
- H1 and H2 blocker, dexamethasone 8 mg IV and acetaminophen 45-90 minutes prior to infusion

Dosing: 10 mg/kg intravenously

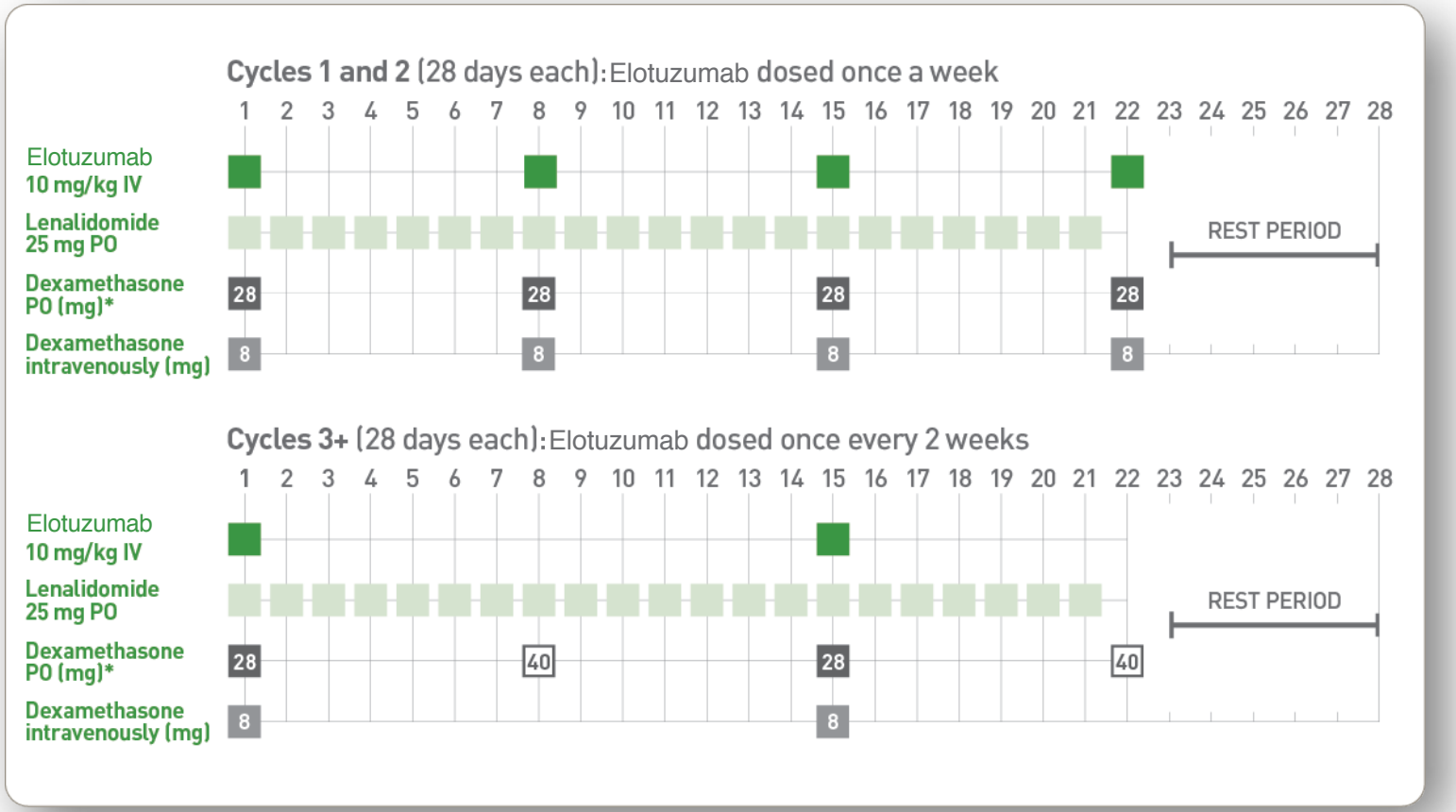
	Start of infusion	30 min	60 min or more
Cycle 1 dose 1	0.5 mL/min	1 mL/min	2 mL/min
Cycle 1 dose 2	1 mL/min	2 mL/min	
Cycle 1 dose 3 and 4 and all subsequent cycles	2 mL/min		

Infusion reactions

- 70% of infusion reactions occurred during the first dose
- The most common symptoms of an infusion reaction included fever, chills, and hypertension
- Bradycardia and hypotension also developed during infusions
- 5% of patients required interruption of the administration of elotuzumab for a median of 25 minutes due to infusion reaction

Elotuzumab package insert, Bristol-Myers Squibb Company, 2015, https://packageinserts.bms.com/pi/pi_empliciti.pdf; Lonial S, et al. *N Engl J Med* 2015;373(7):1-11; Cheng M, et al. *Cell Mol Immunol* 2013;10(3):230-52; Lonial S, et al. *N Engl J Med* 2015;373(suppl):1-18.

Elotuzumab: Dosing



The recommended dosage of elotuzumab is 10 mg/kg administered IV

Patients must be premedicated prior to each dose of elotuzumab

Treatment should continue until disease progression or unacceptable toxicity

Elotuzumab package insert, Bristol-Myers Squibb Company, 2015, https://packageinserts.bms.com/pi/pi_empliciti.pdf; Lonial S, et al. *N Engl J Med* 2015;373(7):1-11; Cheng M, et al. *Cell Mol Immunol* 2013;10(3):230-52; Lonial S, et al. *N Engl J Med* 2015;373(suppl):1-18.

Prevention and Treatment of Infusion Reactions in Multiple Myeloma

Prevention

- Premedication, consisting of steroids, antihistamines, and acetaminophen, 30-60 minutes prior to infusion
- Both daratumumab and elotuzumab have specific recommendations for premedication, administration, and post-infusion management

Treatment

- Interrupt infusion
- Activate rapid response team if available
- Activate standing orders/protocol
  - Administer antihistamines, corticosteroids, IV fluid, b-2 adrenergic receptor agonist by inhalation, oxygen if needed
- After infusion reaction is resolved, restart infusion at lower rate as described in the administration guidelines for the specific drug

van de Donk NW, et al. *Blood* 2016;127(6):681-95.

Novel Targets for MM

Drug/Class	Study	Phase
Venetoclax BCL-2 inhibitor	A Study Evaluating Venetoclax in MM Subjects Who Are Receiving Bortezomib and Dexamethasone as Standard Therapy (NCT02755597)	III
Nivolumab PD-1 inhibitor MAb	Study of Combinations of Nivolumab, Elotuzumab, Pomalidomide and Dexamethasone in MM (NCT02726581)	III
Isatuximab (SAR650984) Anti-CD38 MoAb	SAR650984 in combination with pomalidomide and dexamethasone as well (NCT02283775)	III

Novel Targets for MM (cont.)

Drug/Class	Study	Phase
Pembrolizumab PD-1 inhibitor MAb	Study of Lenalidomide and Dexamethasone With or Without Pembrolizumab in Participants With ND Treatment Naive MM (NCT02579863) Study of Pomalidomide and Low Dose Dexamethasone With or Without Pembrolizumab in Refractory or RRMM (NCT02579863)	III
	Phase 2 Multi-center Study of Anti-PD-1 During Lymphopenic State After HDT/ASCT for MM (NCT02331368) Pembrolizumab in MM Patients With Residual Disease (NCT02636010)	II

Novel Targets for MM (cont.)

Drug/Class	Study	Phase
Encorafenib Binimetinib BRAF/MEK inhibitors	BRAF/MEK Inhibition in RRMM (NCT02834364)	II
Ibrutinib BTK inhibitor	Study of Ibrutinib in Combination With Bortezomib and Dexamethasone in Subjects With RRMM	II
CART-19 CAR-T	CART-19 Post-ASCT for MM (NCT02794246)	II
Selinixor XPO1 inhibitor (SINE)	Selinexor Treatment of Refractory Myeloma (NCT02336815)	II
Dendritic cell vaccine	Dendritic Cell/Myeloma Fusion Vaccine for Multiple Myeloma (NCT02728102; NHLBI)	II

Adjunctive and Supportive Care in MM

Prevention and Treatment of Infections

- Establish a plan for close monitoring of blood counts in initial phase of treatment where risk is greatest
- Review reportable signs and symptoms with patient and caregivers, including who to contact and how
- Prompt identification of symptoms and institution of treatment
- Low threshold for imaging for pneumonia
- Consider atypical infections including regional microbes
- IVIG for serum IgG < 500
- Immunizations
  - GIVE pneumococcal and influenza vaccines
  - DO NOT GIVE herpes zoster vaccine
- Shingles prophylaxis
  - Acyclovir is recommend for all proteasome inhibitor therapy
- G-CSF agents as secondary prophylaxis as appropriate
- Treatment for fungal infections using azoles as indicated

IVIG = intravenous immunoglobulin; G-CSF = granulocyte colony-stimulating factor.

NCCN, Clinical Practice Guidelines: Multiple Myeloma V3, 2016; Anderson KC, et al. *J Natl Compr Canc Netw* 2015;13:1398-435; Colson K, et al. *Support Care Cancer* 2015:23(5):1431-45.

IMWG Recommendations for Use of Bisphosphonates in MM

Factor	2013 Recommendation
Patient population	Newly diagnosed patients with MM who require antimyeloma treatment (regardless of bone status)
Administration	IV
Duration/frequency	Monthly during initial therapy and ongoing in patients who are not in remission New data suggest an interval of every 12 weeks does not change the incidence of SREs After 2 years, discontinue if CR/VGPR; continue if ≤ PR
Monitoring	Monthly creatinine clearance
Choice	Zoledronic acid (first option) Pamidronate (second option)

IMWG = International Myeloma Working Group.

Terpos E, et al. *J Clin Oncol* 2013;31(18):2347-57; Himelsteing AL, et al. *JAMA* 2017;317(1):48-58.

Bisphosphonate Use in MM: Adverse Events

- 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

NS = normal saline.

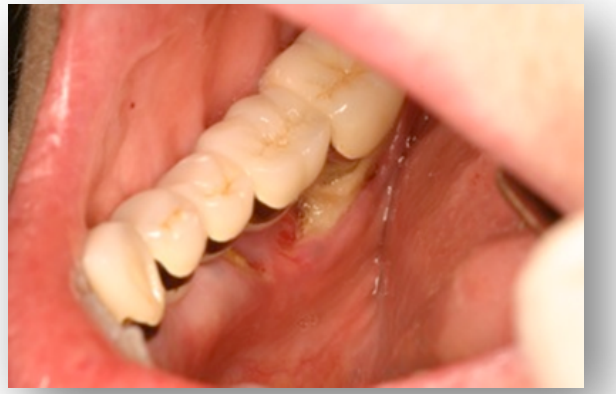
Pamidronate: Use in Renal Patients	
Creatinine clearance (mL/min)	**Dosing (mg) 90 mg/500 mL NS IV**
>30	2-4 hours
<30	Not recommended

Zoledronic Acid: Use in Renal Patients	
Creatinine clearance (mL/min)	**Dosing (mg)**
>60	4.0
50-60	3.5
40-49	3.3
30-39	3.0
<30	Not recommended

NCCN, Clinical Practice Guidelines: Multiple Myeloma V3, 2016; Terpos E, et al. *Blood* 2013;121(17): 3325-8; Pamidronate prescribing information, Novartis Pharmaceuticals, 2012, https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20927lbl.pdf; Zoledronic acid prescribing information, Novartis Pharmaceuticals, 2014, https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/Zometa.pdf.

Osteonecrosis of the Jaw

- Baseline dental exam prior to starting bisphosphonate treatment
  - Dental procedures (below the gum line/extensive) should be done prior to starting IV bisphosphonates if possible
  - If below the gum line procedures are necessary, hold bisphosphonates 2 months prior to and after procedures
- Avoid unnecessary dental procedures once IV bisphosphonate start
- There is no standard treatment: prevention is key
  - Excellent oral hygiene is best prophylaxis
  - Limit alcohol and tobacco use
  - Consider supplementation with calcium 1,000 mg/day and vitamin D 400 IU/day
- Long-term use of bisphosphonates (> 2.5 years) increases the risk for development of ONJ

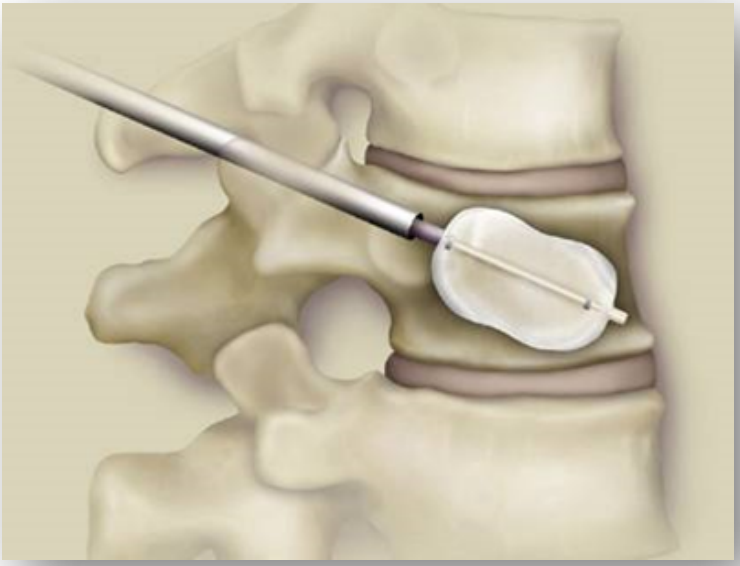


ONJ = osteonecrosis of the jaw.

Boonyapakorn T, et al. *Oral Oncol* 2008;44(9):857-69; Jackson GH, et al. *Br J Haematol* 2014;166(1):109-17.

Treatment of Bone Disease

- Bisphosphonates
- Kyphoplasty/vertebroplasty
- Home safety evaluation
- Pain management
- Use of spinal support (braces) may be indicated
- Ongoing evaluation of bone health
- A phase III trial of denosumab (monoclonal antibody against RANK-L , that is used to treat bone disease) in patients with newly diagnosed MM showed an increase of 10 months in PFS (time before the myeloma comes back) compared with zoledronic acid



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

Image: Medtronic, Kyphon Products Division

NCCN, Clinical Practice Guidelines: Multiple Myeloma V3, 2016; Terpos E, et al. *J Clin Oncol* 2013;31(18):2347-57.

Venous Thromboembolism Prophylaxis

- All patients with cancer are at risk for VTE
- IL-6 plays a role in VTE risk for patients with MM
- Consider cumulative risk
  - Personal factors: lifestyle, comorbidities
  - Medications: IMiDs, high-dose dex, doxorubicin regimens
- Prevention
  - < 1 risk factor for VTE: aspirin 81 mg
  - > 2 risk factors for VTE
    - LMWH (equivalent to enoxaparin 40 mg per day)
    - Warfarin: target INR 2-3
    - Newer agents are being investigated

VTE = venous thromboembolism; LMWH = low molecular weight heparin; INR = international normalized ratio.

Palumbo A, et al. *Leukemia* 2008;22(2):414-23; Khorona AA, et al. *J Thromb Thrombolysis* 2016;41(1):81-91; Leebeek, F. W. G. (2016). Thrombosis Research, 140, S76-S80..

Summary

- Although currently not curable, the median OS for MM has improved dramatically over the past decade
  - Understanding of the pathobiology of the disease will improve the rationale of supportive care requirements
- Improved long-term survival is the goal
  - Early depth of response → sustained response with an acceptable level of toxicity
- Myeloma is not a single disease
  - Risk-adapted treatment is key
- Many new agents are on the way; many will be oral
- Collaborative clinical management together with patient and caregiver empowerment will promote the best outcomes and preserve future treatment options