Cleveland Clinic

Multiple Myeloma

Co-Presenters

Chakra Chaulagain, MD, FACP

Staff, Cleveland Clinic, Weston, FL

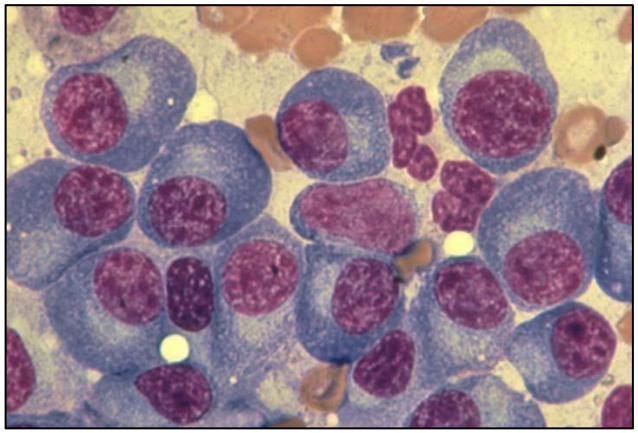
Beth Faiman PhD, RN, MSN, CNP, AOCN

Nurse Practitioner, Cleveland Clinic, Cleveland OH

May 17, 2019

Myeloma Is a Cancer of Plasma Cells

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



At a Glance

Estimated New Cases in 2019	32,110
% of All New Cancer Cases	1.8%

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

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

Image courtesy of American Society of Hematology
SEER data. Accessed on 4/21/2019 from https://seer.cancer.gov/statfacts/html/mulmy.html
Kyle et al. *Mayo Clin Proc.* 2003;78:21-33; ACS, 2018; NCCN Guidelines, 2018.

Immunoglobulin Structure

Immunoglobulins are made up of 2 heavy chains

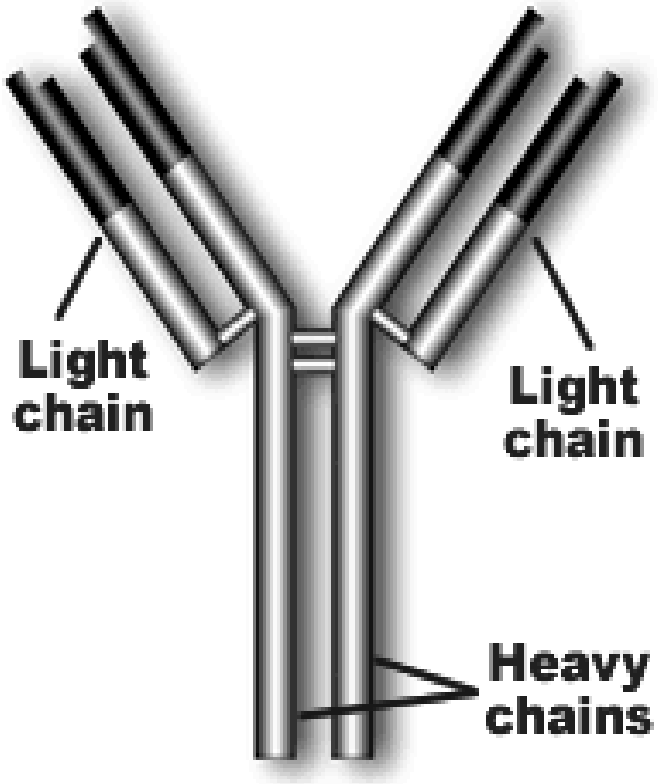
IgG, IgA and IgM

in myeloma or AL

2 light chains

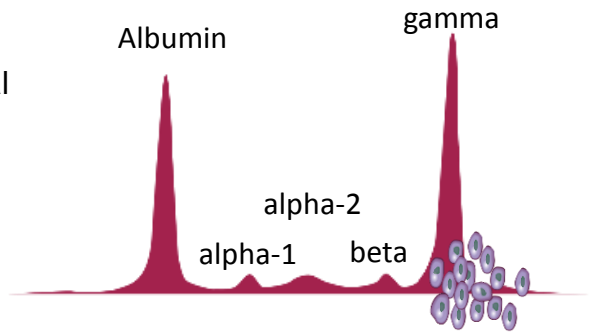
Kappa or Lambda

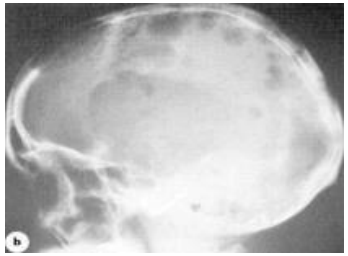
Abnormal, overproduction of one clone of a protein “monoclonal protein”, elevated free light chains



Initial Evaluation Investigative Workup

Test	Possible finding(s) with myeloma
CBC with differential counts	↓ Hgb, ↓ WBC, ↓ platelets
CMP and electrolytes	↑ Creat, ↑ Ca++, ↑ uric acid, ↓ Alb
Serum electrophoresis with quantitative immunoglobulins (SPEP)	↑ M protein in serum, may have ↓ levels of normal antibodies
Immunofixation of serum	Identifies light/heavy chain types M protein
β_2m and LDH	↑ Levels (measure of tumor burden)
24-hour urine protein electrophoresis with immunofixation (UPEP)	↑ Monoclonal protein (*Bence Jones*)
BM aspirate and biopsy, FISH and cytogenetics	≥ 10% clonal plasma cells, prognosis (FISH and cytogenetics) Congo red BM stain if amyloid suspected
Skeletal survey; low-dose whole-body CT or PET should be considered	Osteolytic lesions, osteoporosis, EM disease
MRI	Does not replace skeletal survey; consider w/SMM





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

Kumar et al. NCCN Guidelines. Multiple myeloma. V4.2018/ Ghobrial IM, et al. Blood. 2014;124:3380-3388. Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-3548. Faiman B. Clin Lymphoma Myeloma Leuk. 2014;14:436-440.

Multiple Myeloma Typically Preceded by Premalignant Conditions

Condition	MGUS[1-4] (Monoclonal Gammopathy of Undetermined Significance)	SMM[1-5,8] (Smoldering Multiple Myeloma)	Active Multiple Myeloma[6-8]
	Premalignant		Malignant
Clonal plasma cells in bone marrow	<10%	10%-60%	≥10%
Presence of Myeloma Defining Events	None	None	Yes
Likelihood of progression	~1% per year	~10% per year	Not Applicable
Treatment	No; observation	Yes for high risk*; No for others	Yes

1. Kyle RA, et al. *N Engl J Med.* 2007;356:2582-90.
2. International Myeloma Working Group. *Br J Haematol.* 2003;121:749-57.
3. Jagannath S, et al. *Clin Lymphoma Myeloma Leuk*. 2010;10(1):28-43.
4. Kyle RA, et al. *Curr Hematol Malig Rep*. 2010;5(2):62-69.
5. Mateos M-V, et al. *Blood.* 2009;114:Abstract 614.
6. Durie BG, Salmon SE. *Cancer*. 1975;36:842-854.
7. Durie BG, et al. *Leukemia*. 2006;20(9):1467-1473.
8. Rajkumar SV, et al. Lancet *Oncology* 2014; 15:e538-e548.

Myeloma Disease Overview: Case Presentation

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

Complete Blood Count

- WBC count 3,300/µL
- Hemoglobin 9.3 g/dL
- Platelet count 138,000/µL

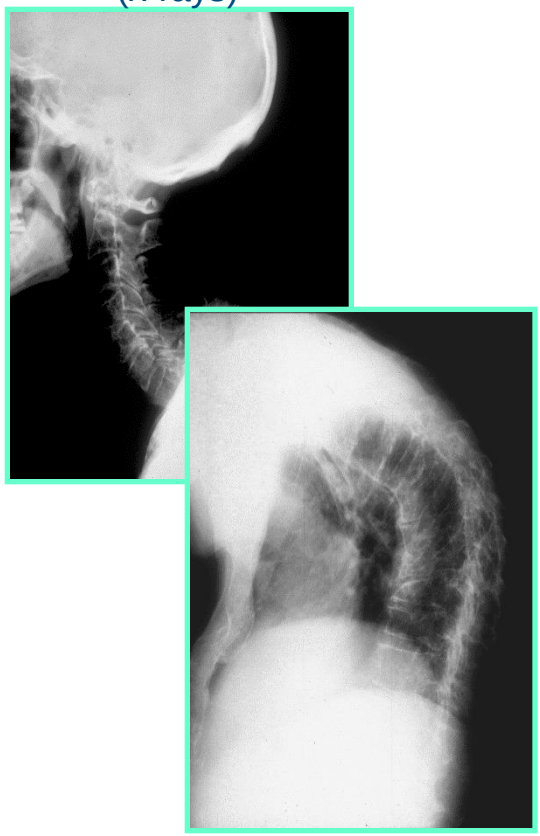
Complete Chemistry Panel

- Creatinine 2.1 g/dL
- Calcium 12.4 mg/dL
- Albumin 3.2 g/dL
- Total protein 10.9 g/dL

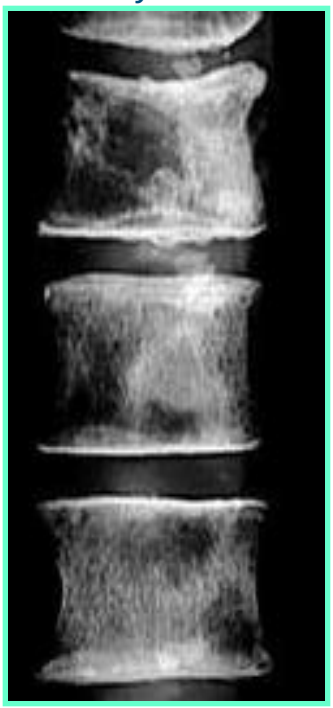
Skeletal Survey and MRI

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

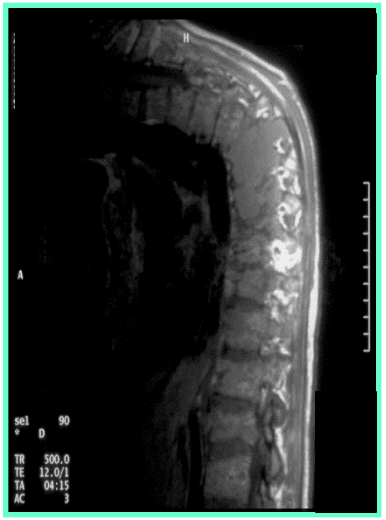
Skeletal survey (x-rays)



Osteolytic lesions



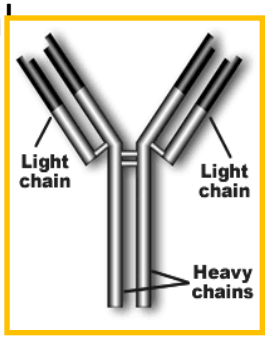
MRI of spine showing T6 wedge deformity



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

Case Presentation continued

- **Additional labs:**
  - Monoclonal protein analysis (MPA): IgG 4,300 mg/dL and kappa 5,900 mg/dL
  - Serum protein electrophoresis (SPEP): Monoclonal "spike" 4.2 g/dL
  - 24-hour urine: normal < 0.16 g/24 hours
  - $Beta_2$-microglobulin: elevated 2.6 mg/L
  - Anemia panel showed low B_{12}, high MMA, suggestive of vitamin B_{12} deficiency
  - Bone marrow biopsy showed 40% kappa restricted "clonal" plasma cells; normal cytogenetics, no IgH translocations.
  - *What is Bob' s diagnosis?*



Immunoglobulin structure

M proteins: Lab/Normal Reference Range	Value
MPA serum IgG 717–1,411 mg/dL	**4,300**
MPA serum IgA 78–391 mg/dL	29
MPA serum IgM 53–334 mg/dL	24
MPA serum kappa 534–1,267 mg/dL	**5,900**
MPA serum lambda 253–653 mg/dL	< 30

Diagnostic Criteria: SLiM CRAB

Clonal bone marrow ≥ 10% or bony/extramedullary plasmacytoma

AND any one or more Myeloma Defining Events (MDE)

- **C** alcium elevation
- **R** enal complications
- **A** nemia
- **B** one disease

- **BM** Clonal bone marrow ≥ 60%
- **FLC** sFLC ratio >100
- **MRI** >1 focal lesion by MRI

Rajkumar SV, et al. *Lancet Oncology*. 2014; 15:e538-e548. Kyle RA, et al. Leukemia. 2010; 24(6):1121–1127.

Staging MM: R-ISS

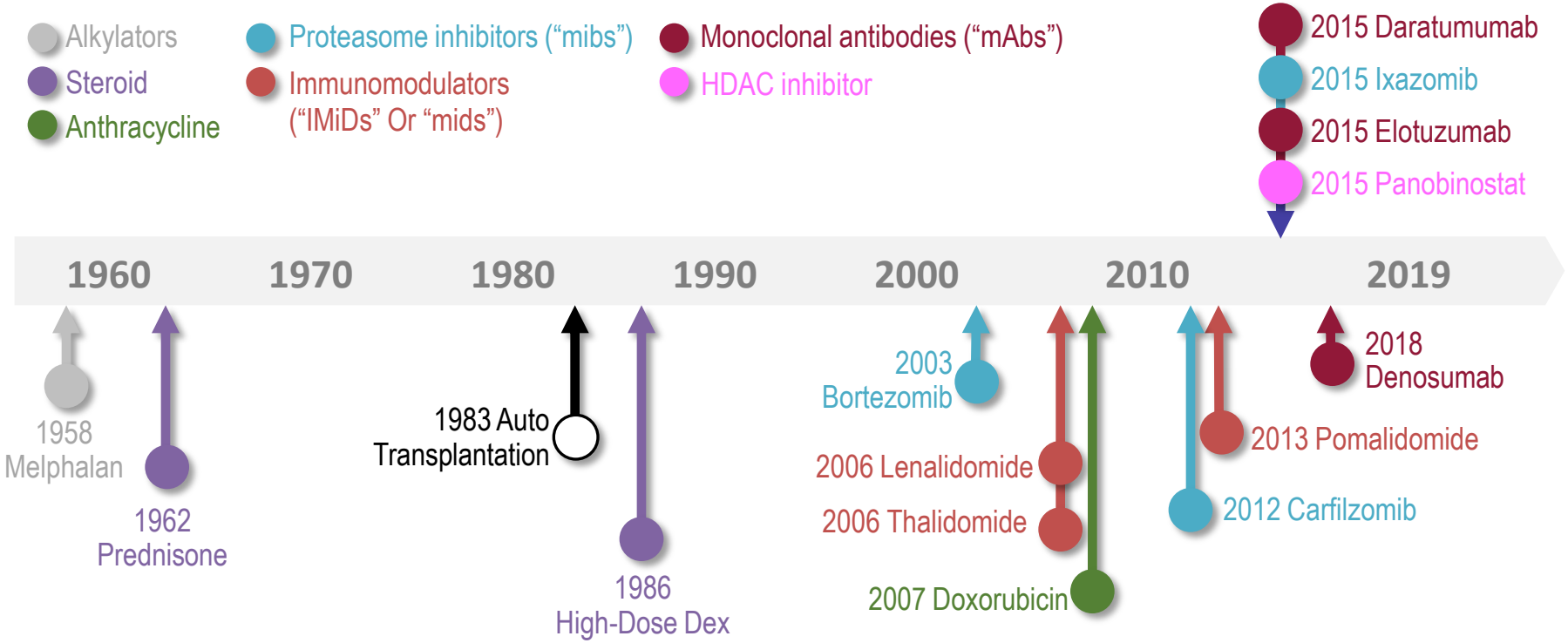
Serum LDH, β_2 microglobulin, albumin, and cytogenetics (FISH) are required to determine stage using the R-ISS System

Stage	ISS Criteria[1]	R-ISS Criteria[2,3]
I	Serum β_2 microglobulin <3.5 mg/L serum albumin ≥3.5 g/dL	ISS Stage I **AND** No del(17p), t(4;14), and/or t(14;16**)** **AND** normal LDH
II	Not stage I or III	Not stage I or III
III	Serum β_2 microglobulin ≥5.5 mg/L	ISS stage III **AND** del(17p), t(4;14), and/or t(14;16) **OR** LDH is greater than ULN

*Neither stage I nor stage III.
†Testing by FISH; standard risk = no chromosome abnormality;
high risk = del(17p) and/or t(4:14) and/or t(14:16).
del, deletion; FISH, fluorescence in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase;
MM, multiple myeloma; R-ISS, revised ISS; t, translocation; ULN, upper limit of normal.

1. Greipp et al. *J Clin Oncol*. 2005;23:3412-3420.
2. Palumbo et al. *J Clin Oncol*. 2015;33:2863-2869.
3. Chng et al. *Leukemia* 2014;28:269-277.

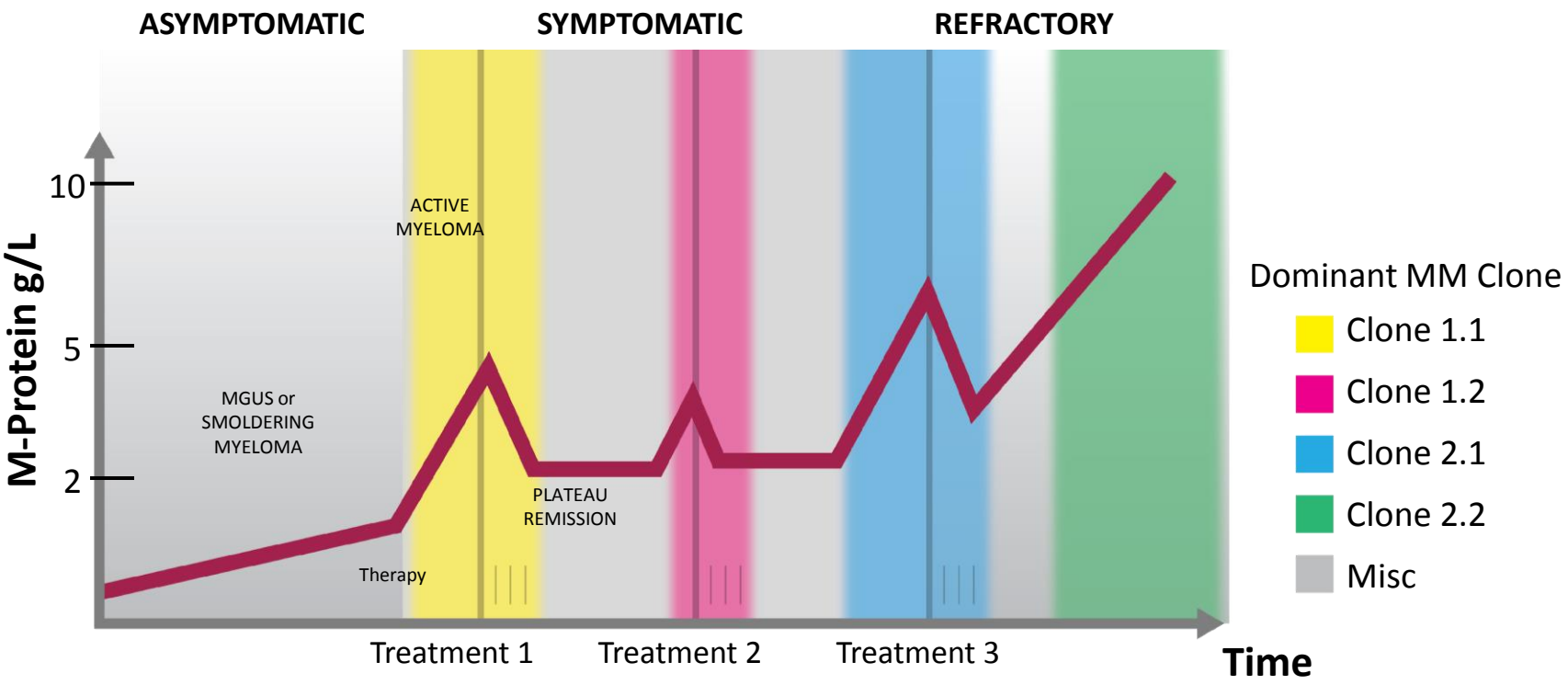
Expanding Treatment Options for Multiple Myeloma:Mibs, Mids, and mAbs



Auto = autologous; Dex= dexamethasone.

Tariman, J. *Nurs Clin North Am.* 2017;52(1):65-81. DRUGS@FDA.gov

Relapsing Nature of Multiple Myeloma: Clones Change Over Time



MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma.

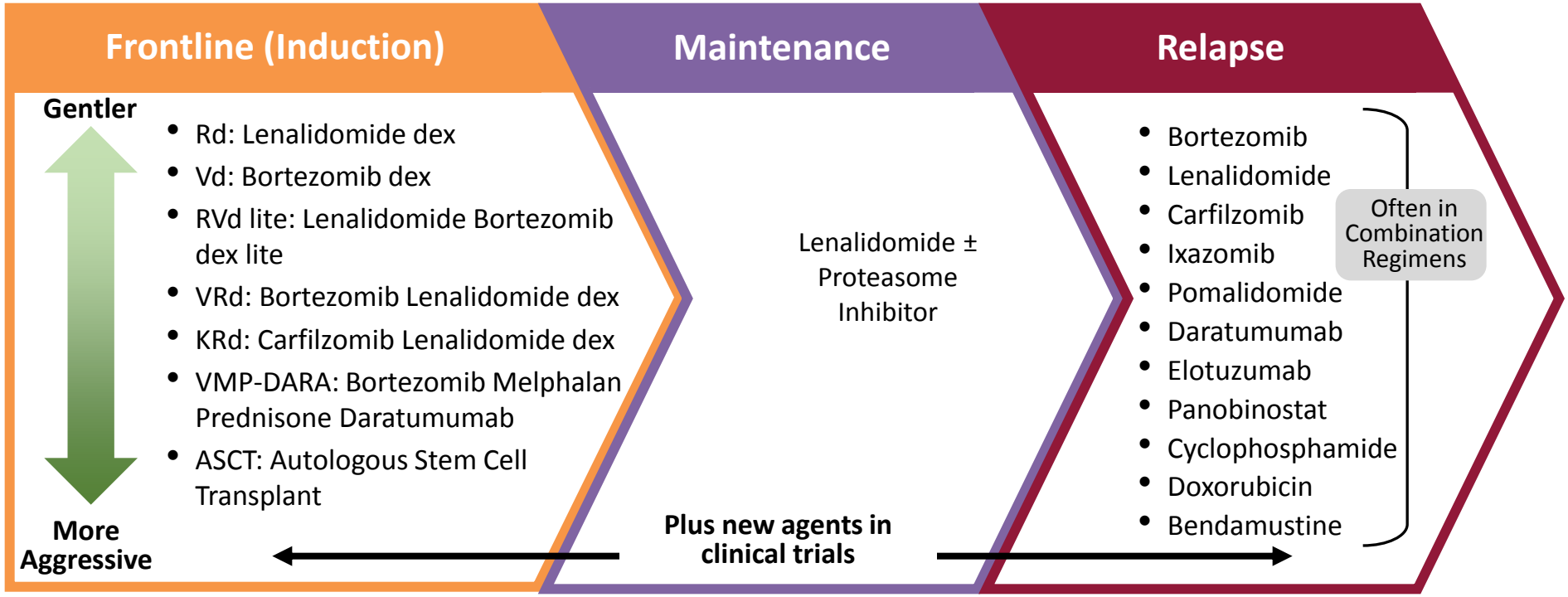
Adapted from Dr. Brian Durie and Keats JJ, et al. *Blood*. 2012;120:1067-1076.

Classes: Mides, Mibs, MABs and Others to Treat MM

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

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

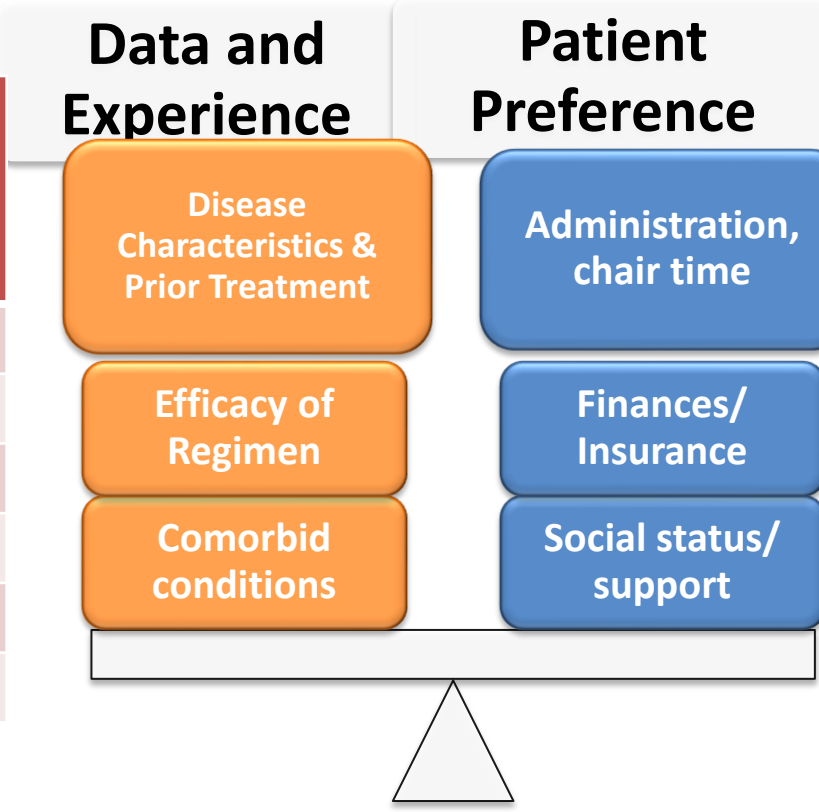
Common Treatments for Multiple Myeloma



Faiman B, et al. *J Adv Pract Oncol.* 2016:7(suppl 1):17-29. Joseph Mikhael, MD, Med https://www.medscape.com/viewarticle/882042. NCCN Guidelines. Multiple Myeloma. V2.2019.

Balancing the Many, Many Choices at Diagnosis and Relapse

FDA-approved after 1+ myeloma therapies*	Combinations*	Comments
Carfilzomib	KRd, Kd	IV
Pomalidomide	Pd	oral
Elotuzumab	ERd	IV
Daratumumab	DRd, DVd	IV
Ixozasomib	IRd	oral
Panobinostat	Pano-Vd	oral, diarrhea



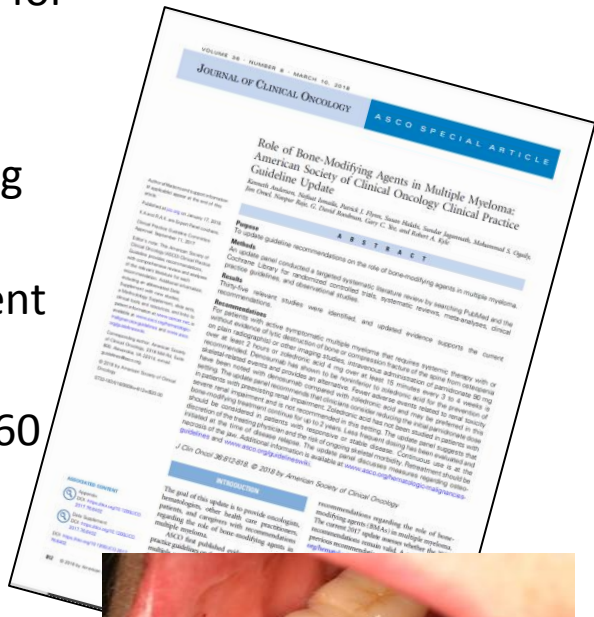
Faiman B, et al. *J Adv Pract Oncol* 2016; 2016: 7(suppl 1):17-29; Faiiman et al., 2017; Philippe Moreau, ASH 2015

ASCO Guideline Update: Bone-Modifying Agents

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

- **Pamidronate:** 90 mg over 2+ hrs every 3-4 weeks
  - In pts with severe renal impairment (CrCl <30 mL/min): 90 mg over 4-6 hrs
  - Consider dose adjustment for mild-moderate renal impairment
- **Zoledronic acid:** 4 mg over 15+ min every 3-4 weeks
  - Dose adjust for mild-moderate renal impairment (CrCl 30 to 60 mL/min) per PI
  - Not recommended (nor studied) in pts with sever renal impairment
- **Denosumab:** Demonstrated non-inferiority to zoledronic acid in SRE
  - Fewer renal AEs; may be preferred in pts with kidney disease; Hypocalcemia can be an issue

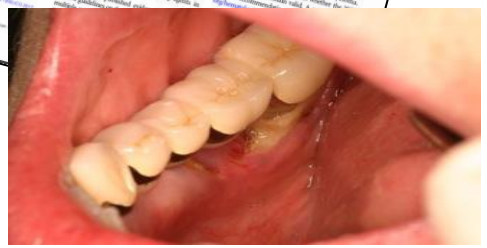
Continuous bone-modifying agent treatment by provider discretion. Retreatment with bone-modifying agent recommended at relapse.


JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Role of Bone-Modifying Agents in Multiple Myeloma: American Society of Clinical Oncology Clinical Practice Guideline Update

ABSTRACT

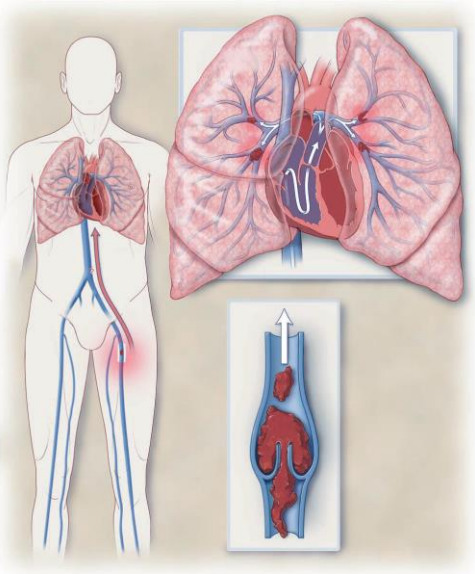

Osteonecrosis of the Jaw

CrCl = creatinine clearance; PI = prescribing information; SRE = skeletal related events.

Anderson K, et al. *J Clin Oncol.* 2018;36:812-818.

MM Patients are at risk for VTE, Infection

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



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

- **Infection risk**
  - Gram+ encapsulated organisms
  - Hand washing, avoid others w/ known illness
  - Immunizations (influenza, pneumococcal, shingles)
  - Education re: Triggers to call, prompt treatment of sxs

SWOG 0777: No upfront ASCT; PFS benefit

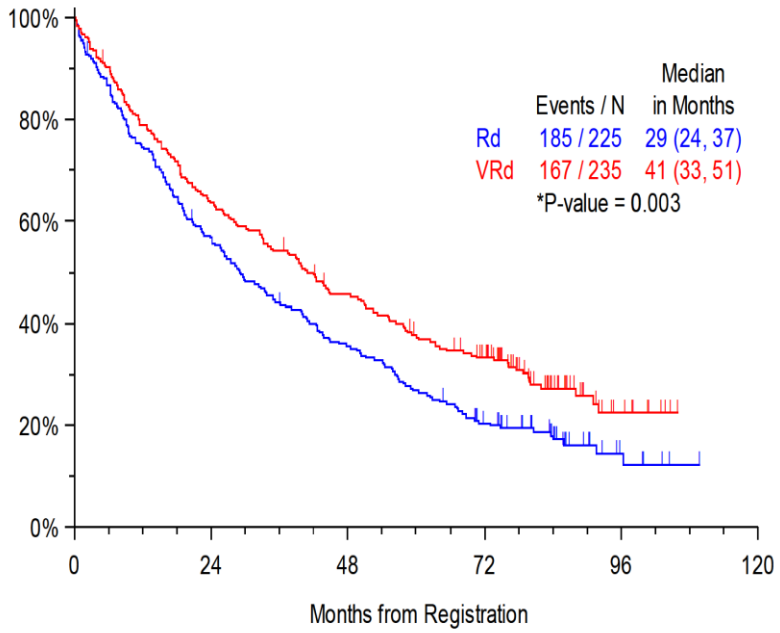
Updated Response Results*

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

*Both SWOG and IRC stratified Cochran-Mantel-Haenszel analyses indicated improved responses with VRd (odds ratio = 0.528: P=0.006 [ITT] odds ratio= 0.38: P=0.001 [sensitivity analysis])

3-Drug Combination Better Than 2 in Newly Diagnosed Multiple Myeloma With Delayed ASCT SWOG 0777 UPDATE

PFS

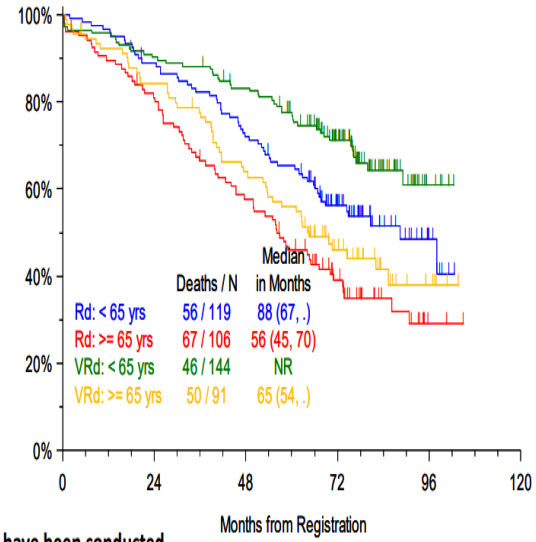


Median PFS (months)

Age (years)	VRd	Rd
<65	48	34
≥65	34	24
>75	34	17

Using Forest plot technique other correlates of improved outcomes (PFS and OS) with VRd are $S\beta_2M$ (<4); BMPC (60%); hemoglobin (>10 GMS/dl); serum creatinine (<2 mg/dl) i.e. predominantly good risk (early disease) risk features

Overall Survival by Age

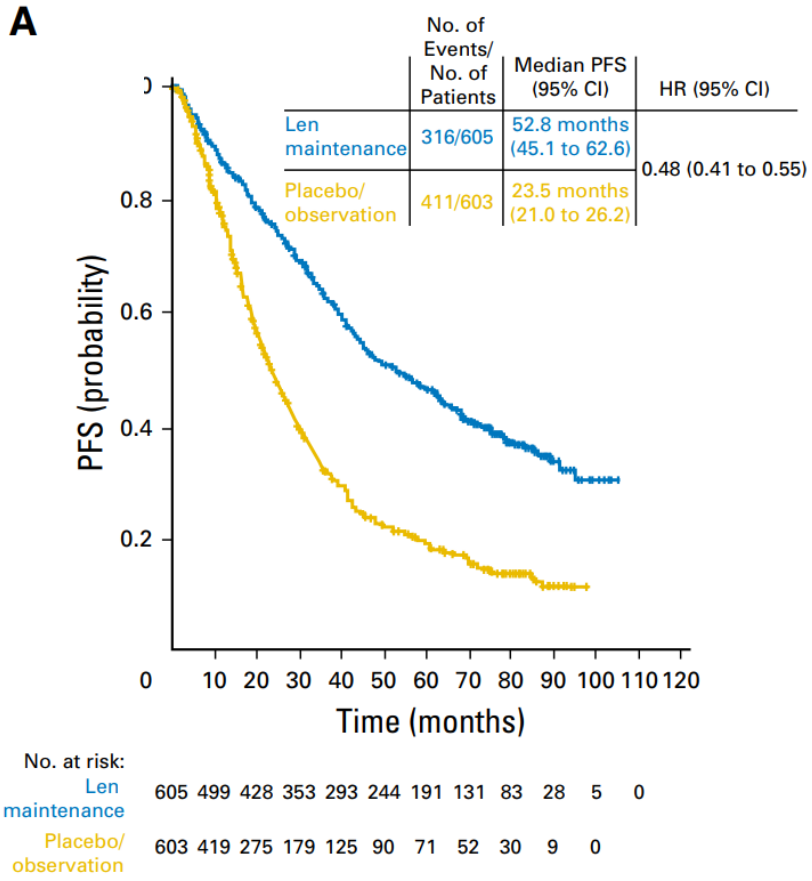


*For all analyses, both SWOG and IRC assessments have been conducted using the fully updated datasets with current datalock in May 2018

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

Durie B, et al. ASH 2018. Abstract 1992.

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



PFS and OS benefit observed across subgroups:

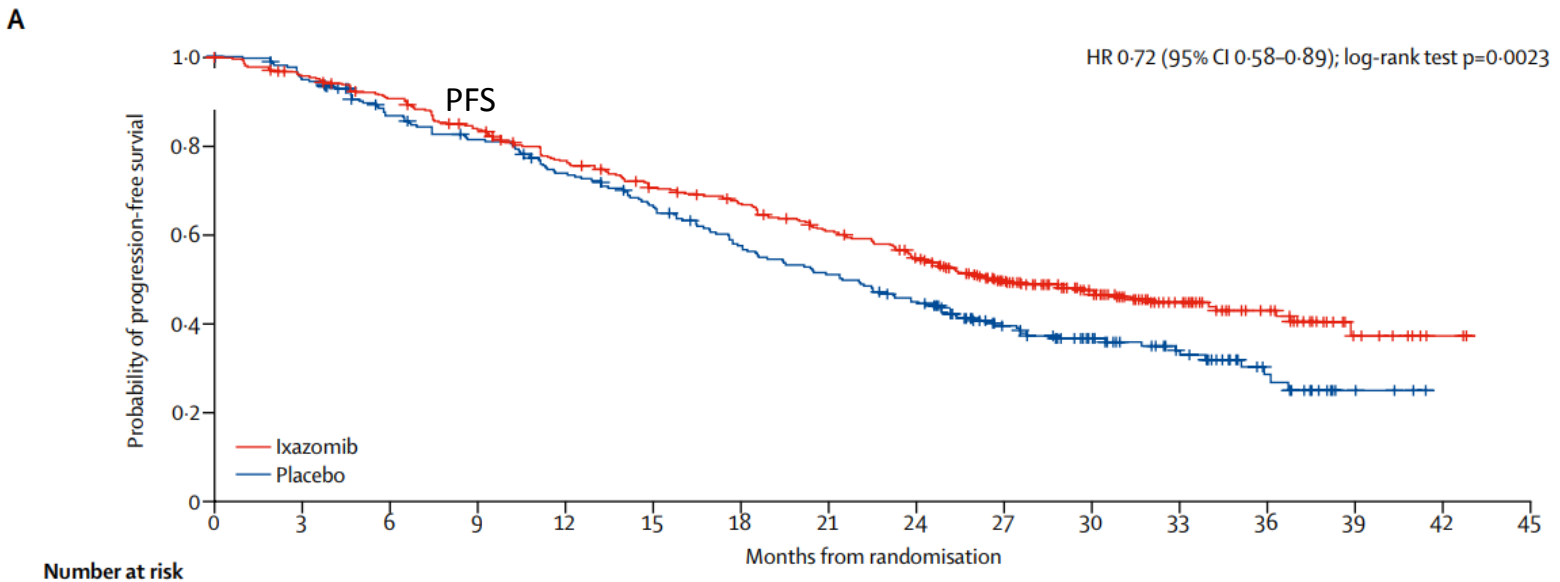
- Older or younger than 60
- Male or female
- ISS stage I/II, III
- Response after ASCT (prior to maintenance)
- Different induction regimens

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

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

McCarthy PL, et al. *J Clin Oncol.* 2017;35(29):3279-3289.

Tourmaline-3 Ixazomib Post- ASCT Data



Number at risk (number censored)

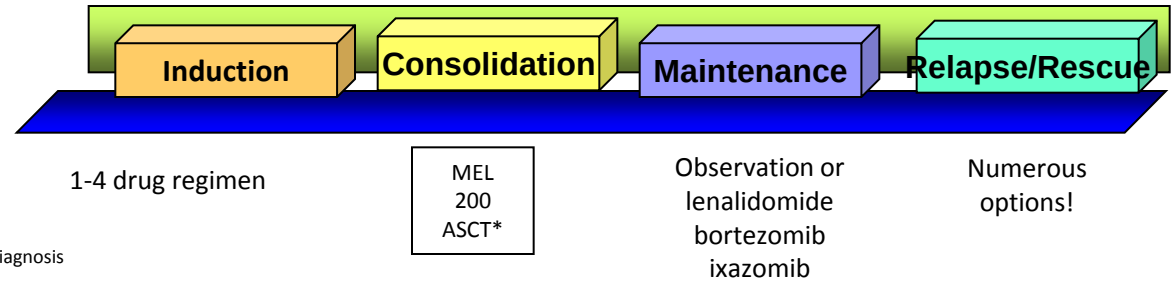
Ixazomib	395	363	340	311	279	255	238	213	187	135	93	56	35	9	3	0
	(0)	(15)	(19)	(22)	(26)	(30)	(33)	(37)	(41)	(76)	(112)	(146)	(165)	(188)	(194)	(197)
Placebo	261	238	210	195	174	153	130	117	100	69	46	32	15	3	0	0
	(0)	(10)	(18)	(20)	(22)	(25)	(27)	(27)	(29)	(50)	(68)	(78)	(91)	(102)	(105)	(105)

Dimopoulous MA, et al. *Lancet*. 2019;393(10168):253-264. Dimopoulos MA, ASH 2018. Abstract 301.

What Is Bob's Diagnosis and Plan? Discussion

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

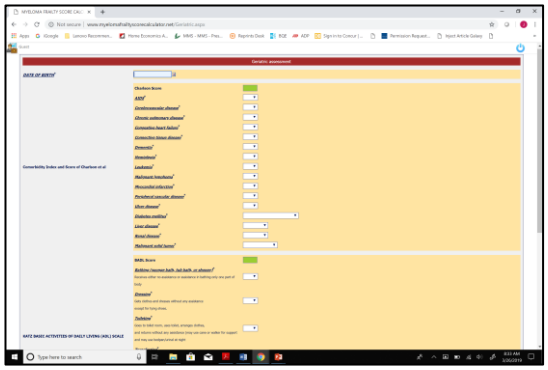
*One of 3 options



Rajkumar et al., 2014, IMWG working group guidelines for MM diagnosis

What if Bob was not a candidate for ASCT? Discussion

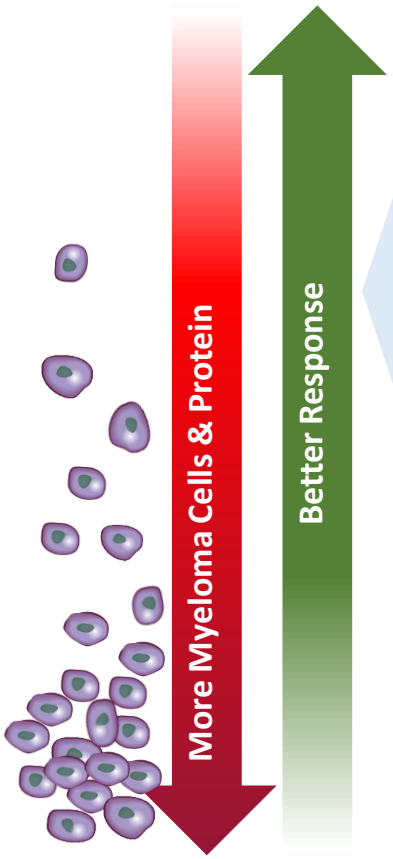
- Clinical Trials are always preferred!
- Continue VRd as in SWOG0777 (8 cycles then stop bortezomib?)
- VRd light (Weekly SC bortezomib)
- FIRST trial: Rd vs Rd fixed dosing vs MPT: PFS and OS advantage with Rd
- **Key point:** Some form of rx should be ongoing in MM until disease progression, unacceptable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



Online myeloma frailty score calculator at **http:/www.myelomafrailtyscorecalculator.net/**

Palumbo A, et al. *Blood.* 2015;125(13):2068-2074.
http:/www.myelomafrailtyscorecalculator.net/ accessed April 9, 2019.

Is Treatment Working: IMWG Myeloma Response Criteria



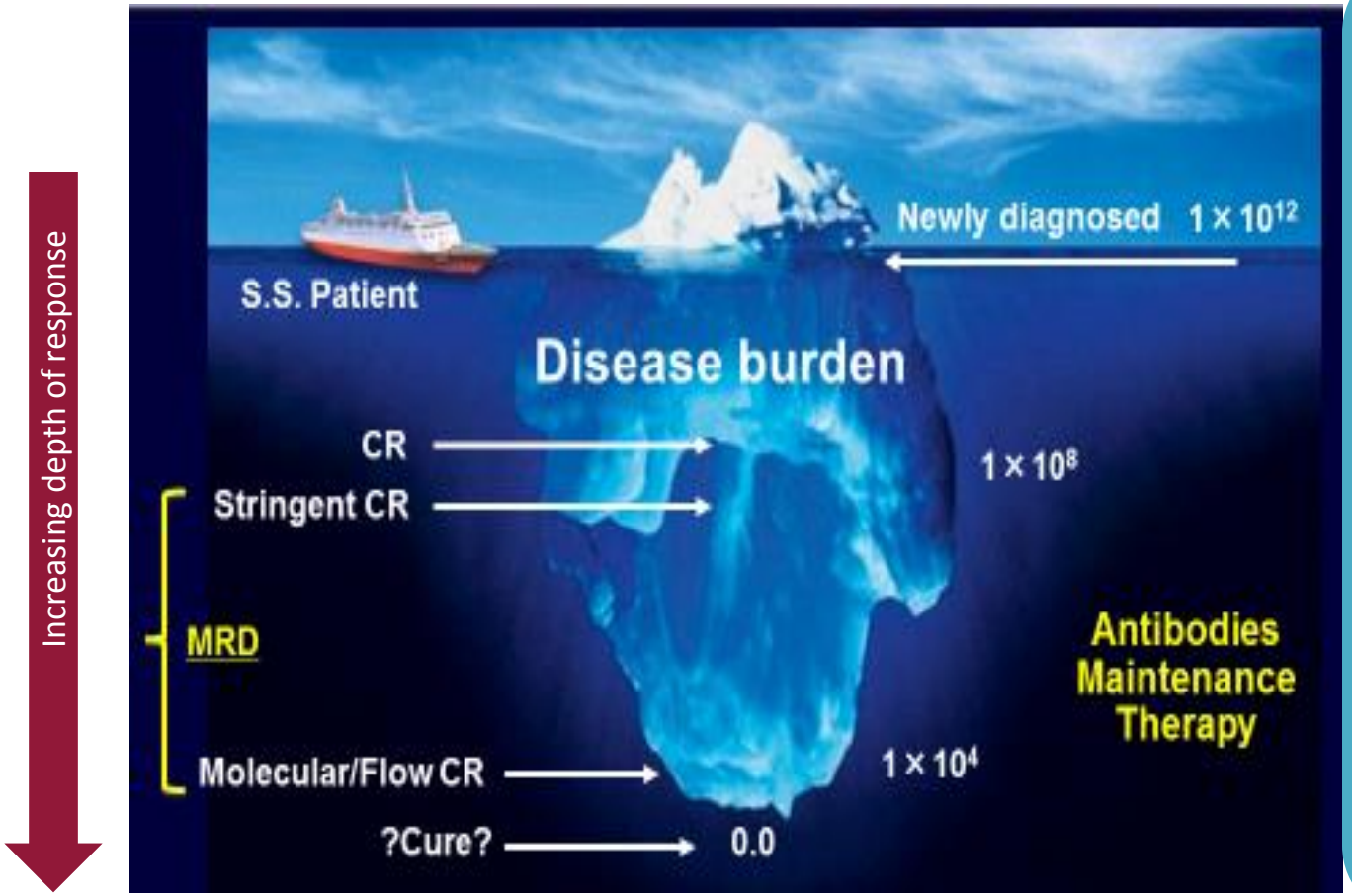
Flow MRD negative*	**Negative by NGF (next-generation flow)** (minimum sensitivity 1 in 10^5 nucleated cells or higher)*
sCR	mCR **AND** normal FLC ratio, BM negative by flow, 2 measures
Molecular CR	CR **AND** negative PCR
CR	Negative immunofixation; no more than 5% plasma cells in BM; 2 measures
VGPR	90% reduction in myeloma protein
PR	At least 50% reduction in myeloma protein
MR	
SD	
PD	

BM = bone marrow; CR = complete response; FLC = free light chain; mCR = molecular CR; MR = minimal response (only in relapsed); NGS = next-generation sequencing; PD = progressive disease; PR = partial response; sCR= stringent complete response; SD = stable disease; VGPR = very good partial response.

*IMWG minimal residual disease consensus criteria published August 2016.

Palumbo A, et al. International Myeloma Working Group. *J Clin Oncol.* 2014;32:587-600. Durie BM, et al; International Myeloma Working Group. *Leukemia.* 2006;20(9):14671473. Kumar S, et al. *Lancet Oncol.* 2016;17(8):e328-e346.

Getting to Minimal Residual Disease (MRD): New Definitions Deeper than CR



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

MANY ways to get to deeper responses:

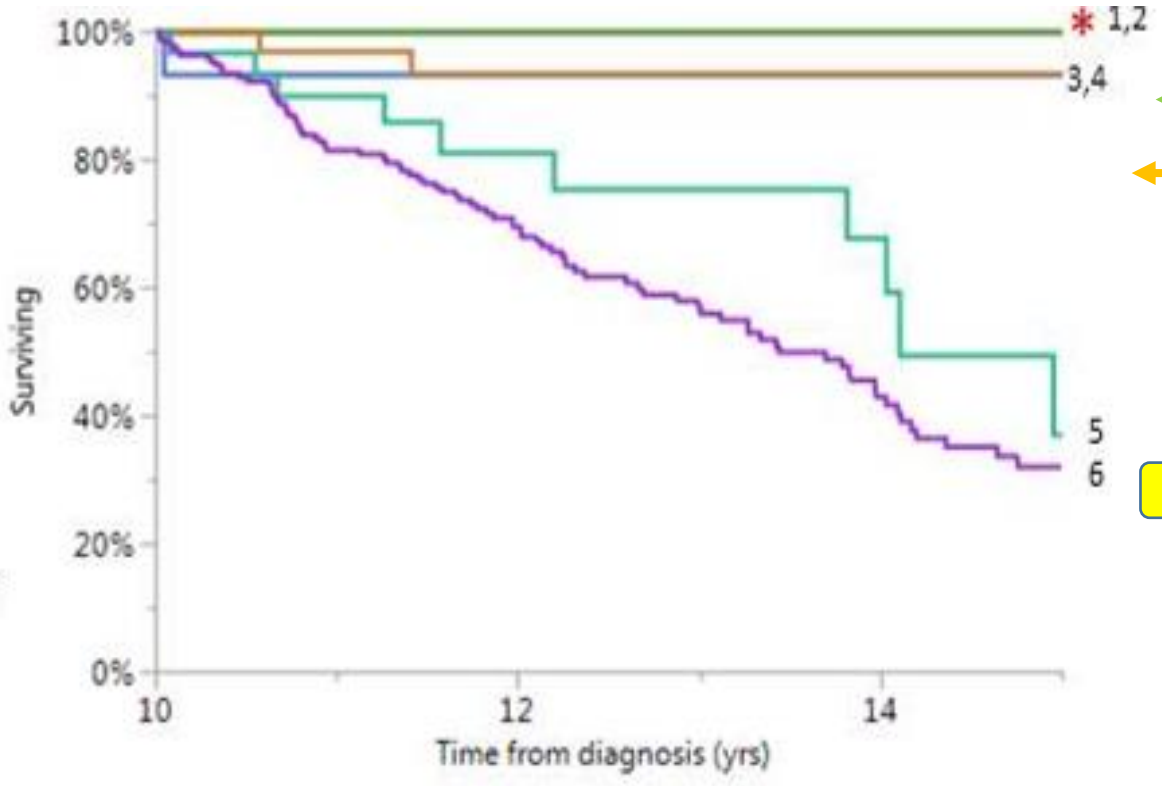
- Multi-drug regimens
- ASCT
- Longer therapy duration (eg, continuous regimens or maintenance)

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

From S. Lonial; Kumar S, et al. *Lancet Oncol.* 2016; 17(8):e328-e346.

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

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



≥ 5 year remission off Rx

≥ 5 year remission on maintenance

~17% of long-term MM survivors may represent patients "operationally cured"

Watch for

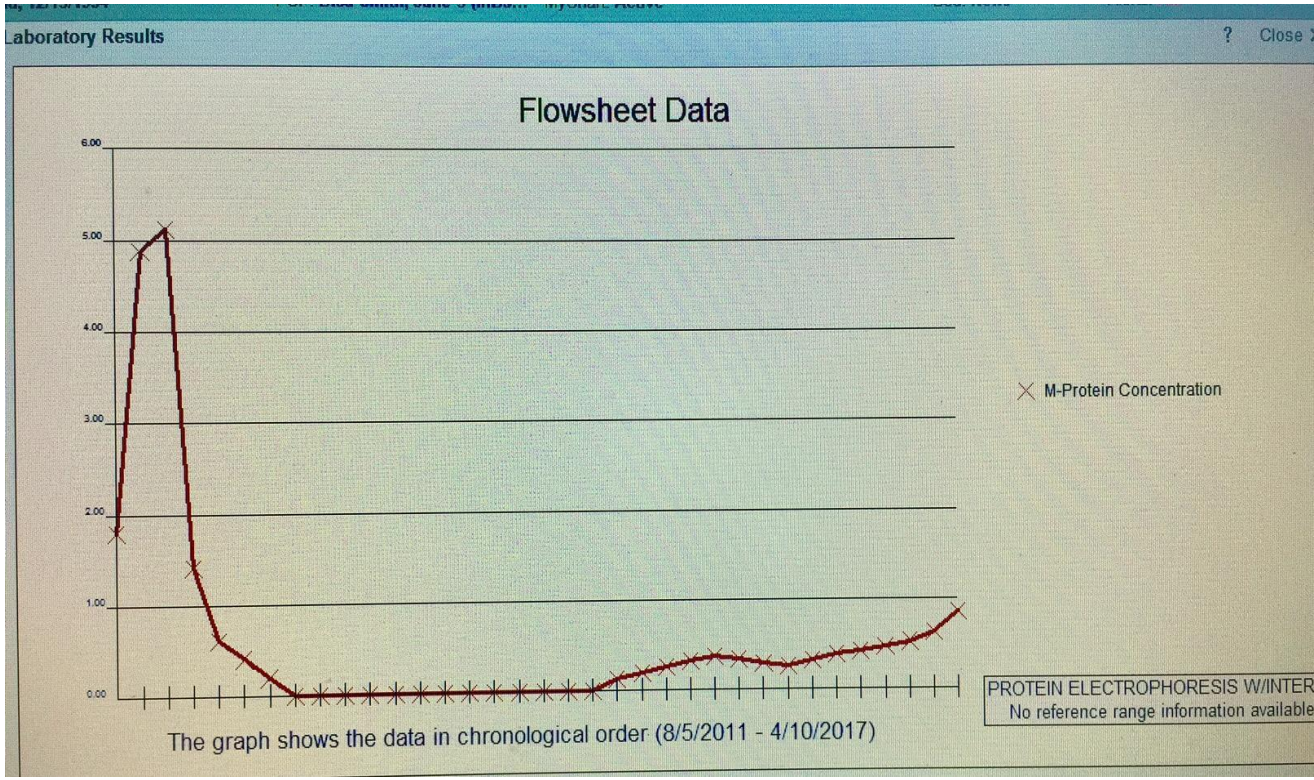
Updates since research is ongoing to characterize which pts achieve long-term remissions

Grieb B, et al. ASH 2018. Abstract #1912.

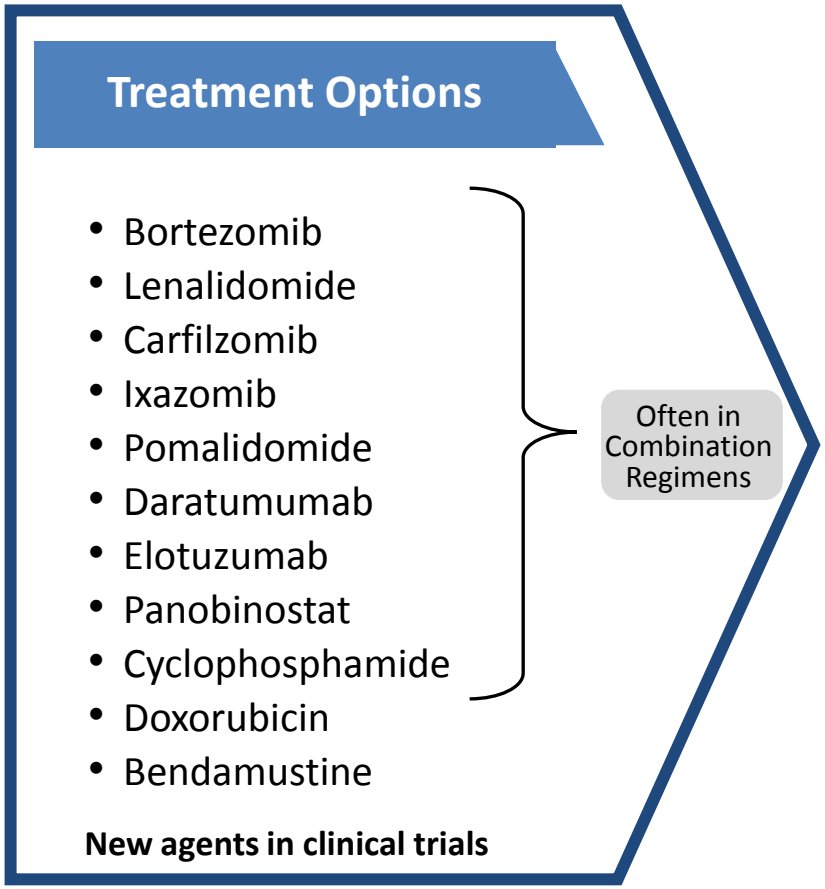
Case study continued

- Bob continues on maintenance with lenalidomide.
- Starts showing signs of slow, biochemical disease progression after 48 months but feels great.
- Labs: M spike

From 0.00g/dL to 0.96g/dL.



Many Treatment Options at Relapse



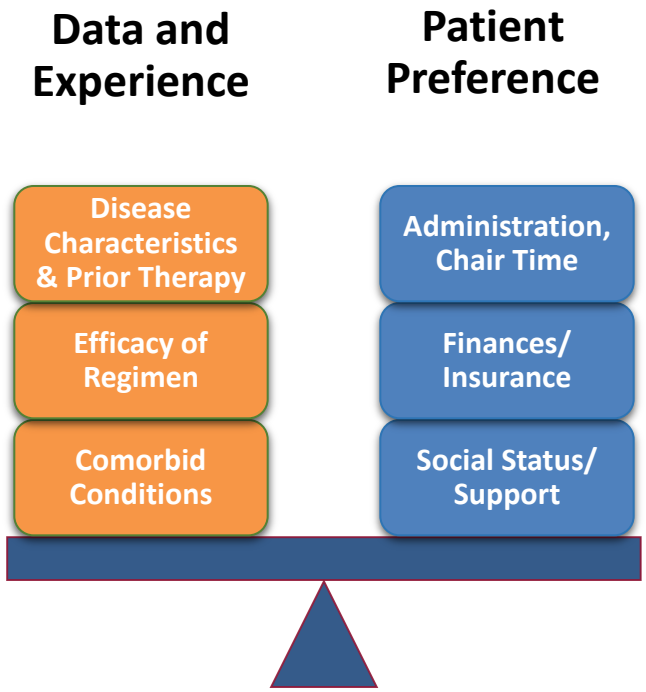
FDA-approved myeloma therapies	Common Combinations
Bortezomib (SQ admin)	VRD, Vd
Lenalidomide	VRD, Rd
Carfilzomib	KRd, Kd
Pomalidomide	Pd, DPd, EPd, PCd
Daratumumab	DRd, DVd, DPd, D-VMP
Elotuzumab	ERd, EPd
Ixazomib	IRd
Panobinostat	Panobinostat + Vd
Doxorubicin	Liposomal doxorubicin + V
Cyclophosphamide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

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

Faiman B, et al. *J Adv Pract Oncol.* 2016;2016:7(suppl 1):17-29.

Practical Approach to Treatment of Patients With Relapsed Myeloma

- **Disease-related factors**
  - Duration of response to initial therapy
  - High-risk vs low-risk status
  - Molecular relapse vs symptomatic relapse
  - Other comorbid conditions, patient frailty
- **Treatment-related factors**
  - Previous/current therapy exposure (relapsed or refractory)
  - Toxicity/tolerability of previous regimen (combination vs single agent)
  - Mode of administration (ie, PO or IV)
  - Cost and convenience (out-of-pocket copays for IV vs PO)
  - Patient preference



IV = intravenous; PO = orally.

Faiman B, et al. *J Adv Pract Oncol.* 2016;2016:7(suppl 1):17-29.

Pomalidomide Clinical Pearls

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

New
EPd
FDA approved
November 2018

Dara-Pd
FDA approved
June 2017

P ± dex
FDA approved
February 2013

POMALYST® (pomalidomide) Prescribing Information. Faiman B, et al. *J Adv Pract Oncol.* 2016;7:45-52.

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

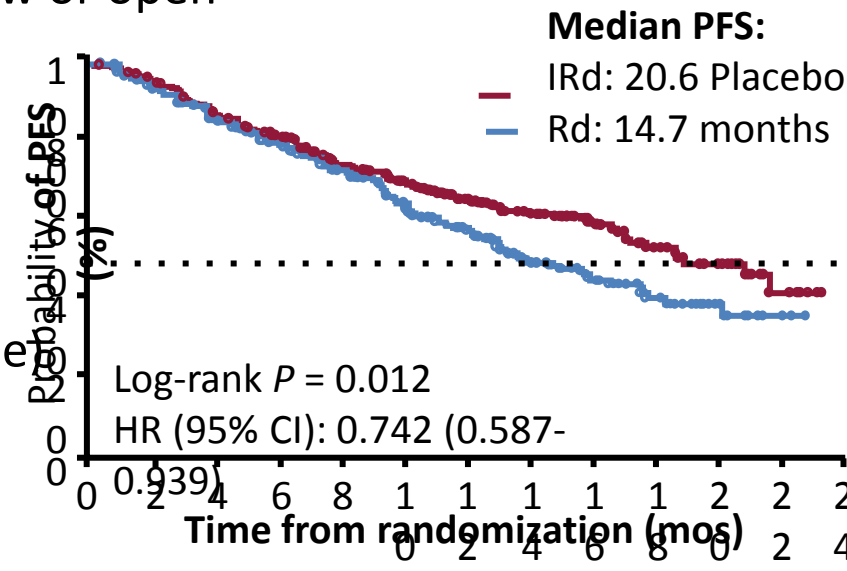
Ixazomib: Oral Proteasome Inhibitor

Ixazomib+Rd
FDA approved
November 2015

35% improvement in PFS for IRd v Rd

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

Median follow-up: ≈15 months



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

Rd = lenalidomide-dexamethasone; hr = hour.

NINLARO® (ixazomib) Prescribing Information. Faiman B, et al. *J Adv Pract Oncol.* 2016;7:45-52.

Moreau P, et al. ASH 2015. Abstract 727.

Number of events: IRd 129; placebo-Rd 157

Clinical Pearls for Elotuzumab, Antibody Targeting SLAMF-7

- Antibody administration
  - Risk of infusion reaction: 10%
    - 3-24 hrs before= Dex 28 mg; 45-90 mins before= Dex 8 mg IV, H1, H2, and acetaminophen
  - Infuse at rate of 0. 5ml/min and escalate to 5 ml/min over time
  - Give weekly for 8 weeks then twice monthly until PD
- Prescribed len-dex
  - DVT prophylaxis (for len)
  - Steroid side effects and schedule (AM vs PM)
- Monitoring
  - Blood counts (hold/adjust dose if needed)
  - Response assessment (monthly); interference
  - Glucose (dex can affect)
  - Renal, hepatic function

New

EPd
FDA approved
November 2018

Elotuzumab+Rd
FDA approved
November 2015

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

Empliciti™ (elotuzumab) Prescribing Information. Gleason C, et al. *J Adv Pract Oncol.* 2016;7(suppl 1):53-57.

Daratumumab (DARA, D)

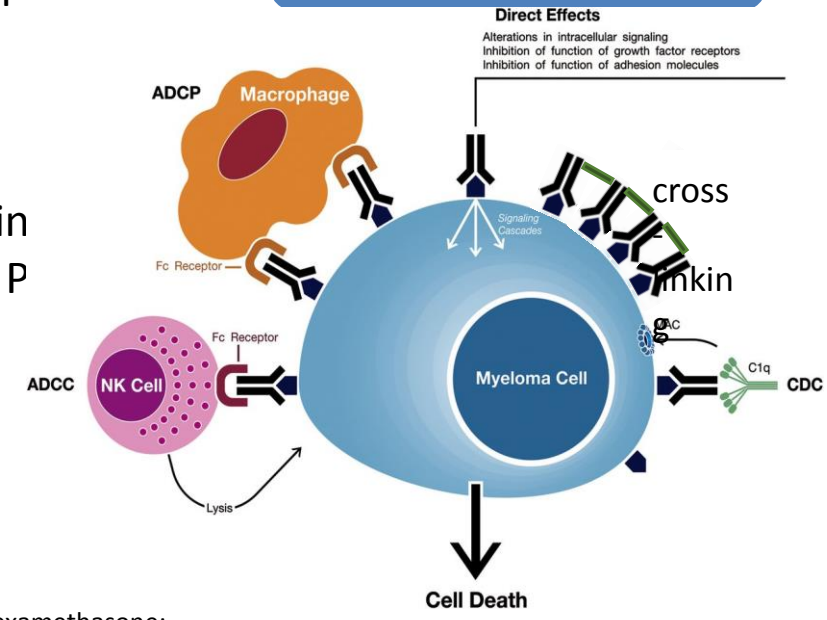
- Human CD38-directed monoclonal antibody
- Indications
  - In combination with VMP in newly diagnosed MM patients who are not eligible for transplant
  - In combination with Rd or Vd in MM patients with at least 1 prior therapy
  - In combination with pomalidomide and dex in pts with at least 2 prior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

VMP + DARA
1st line non-transplant
FDA approved May 2018

DRd, DVd
1 prior therapy
FDA approved Nov. 2016

DPd
2 prior therapies
FDA approved June 2017

DARA monotherapy
3 prior therapies
FDA approved Nov. 2015



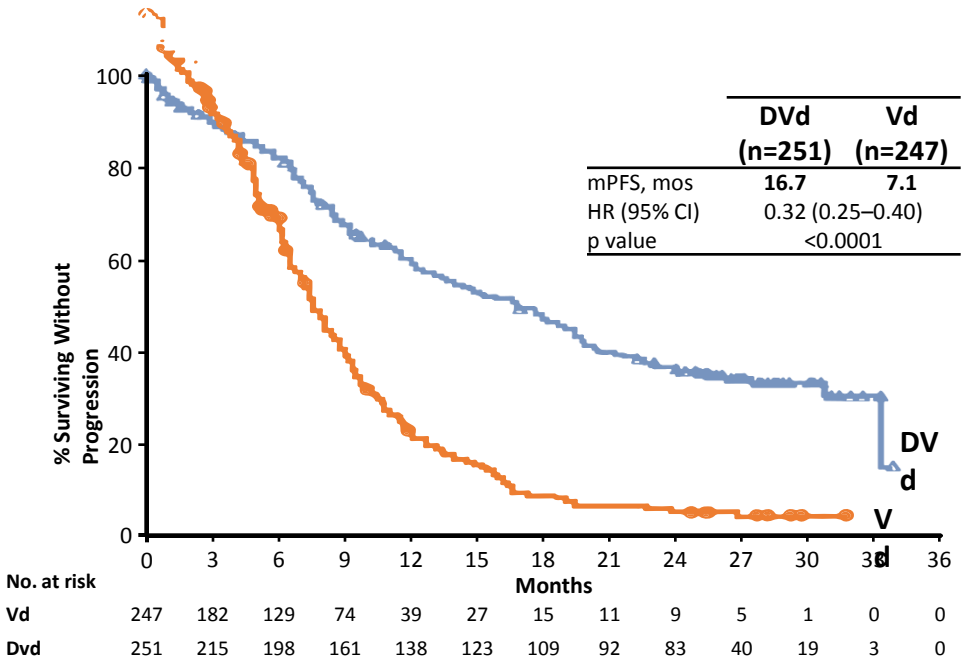
DRd = daratumumab-lenalidomide-dexamethasone; DVd = daratumumab-lenalidomide-dexamethasone; IMiD = immunomodulatory agent; PI = proteasome inhibitor; Rd = lenalidomide-dexamethasone; Vd = bortezomib-dexamethasone; VMP = bortezomib-melphalan-prednisone.

Darzalex® (daratumumab) Prescribing Information. Gleason C, et al. *J Adv Pract Oncol.* 2016;7(suppl 1):53-57.

DVd and DRd

CASTOR Clinical Trial: MM Pts With 1 Prior Therapy

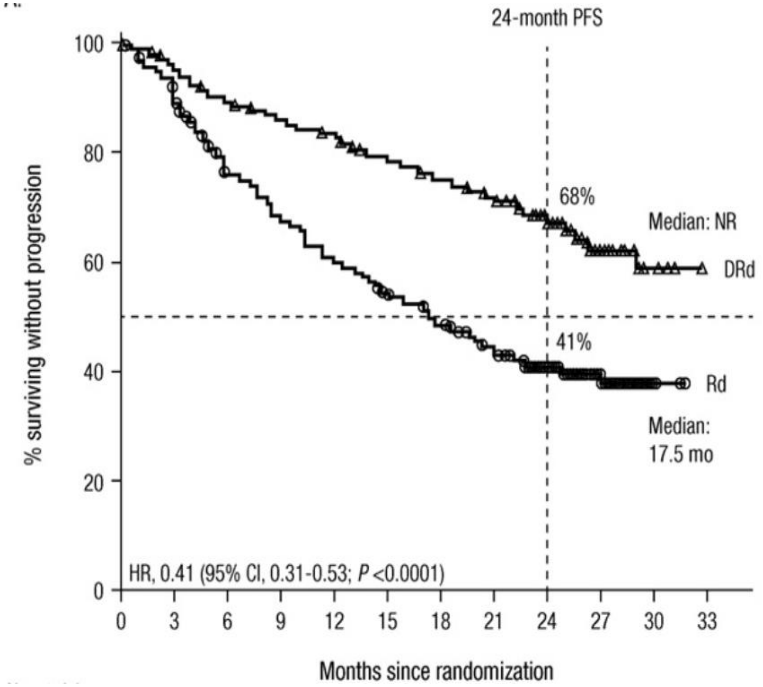
PFS



	DVd (n=251)	Vd (n=247)
mPFS, mos	**16.7**	**7.1**
HR (95% CI)	0.32 (0.25–0.40)	
p value	<0.0001	

Pollux Clinical Trial: MM Pts With 1 Prior Therapy

PFS

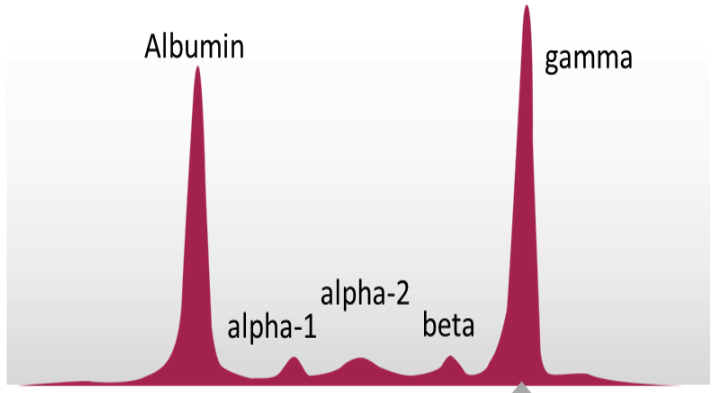


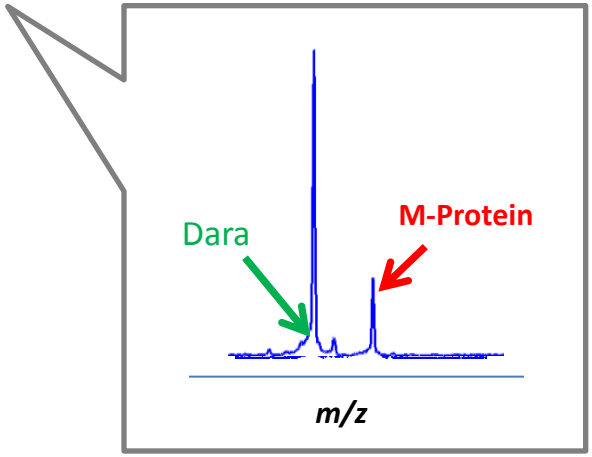
CI = confidence interval; dex = dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone; HR = hazard ratio; Mos = months; NR = not reached; PFS = progression-free survival; Rd = lenalidomide-dexamethasone; Vd = bortezomib-dexamethasone.

Spencer A, et al. *Blood* 2017;130:3145. Dimopoulous MA, et al. ASH 2017. Abstract 739.

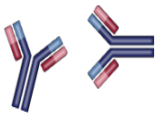
Special Considerations With Antibody Therapy

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





IgG antibody therapy and IgG myeloma



Dara = daratumumab.

Mills JR, Murray DL. *J Appl Lab Med.* 2017;1(4):421-431.

Carfilzomib: Proteasome Inhibitor

New

Kd
20/70 mg/m²
once weekly
FDA approved

KRd
20/27 mg/m²

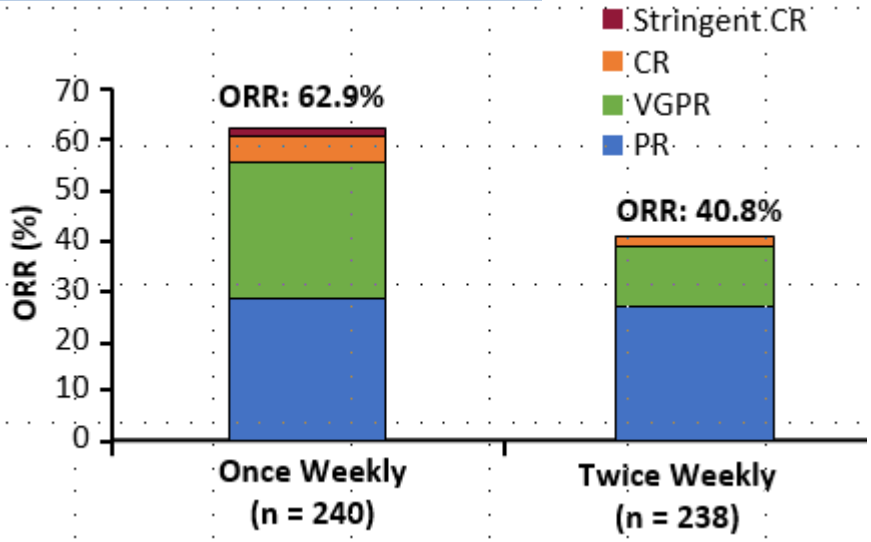
Kd
20/56 mg/m²

K monotherapy
20/27 mg/m²

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

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

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



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

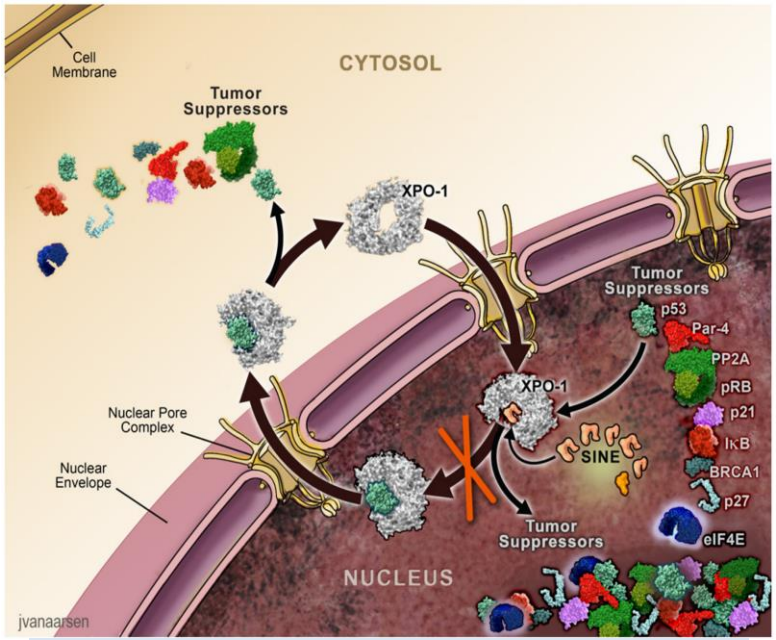
Stewart K, et al. *N Engl J Med.* 2015;372:142-152.

Case study Follow up

- Bob opted for treatment with daratumumab, pomalidomide and dexamethasone.
- Type and screen
- Shingles prevention
- Aspirin for VTE prophylaxis
- Other thoughts regarding treatment options?

Selinexor: First-in-class, Oral Selective Inhibitor of Nuclear Export (SINE) Compound: STORM Trial

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



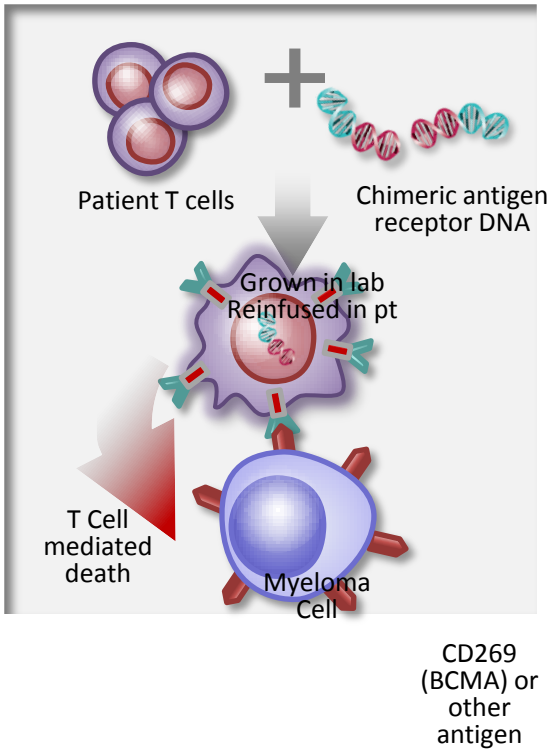
Selinexor (KPT-330) inhibits XPO1. By blocking tumor suppressor proteins (TSP) from being exported from the nucleus, selinexor forces nuclear restoration and reactivation of TSPs leading to selective induction of apoptosis of cancer cells

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

Chari A, et al. ASH Abstract 598. Karyopharm Press Release December 3, 2018. https://investors.karyopharm.com/node/11626/pdf accessed March 13, 2019.

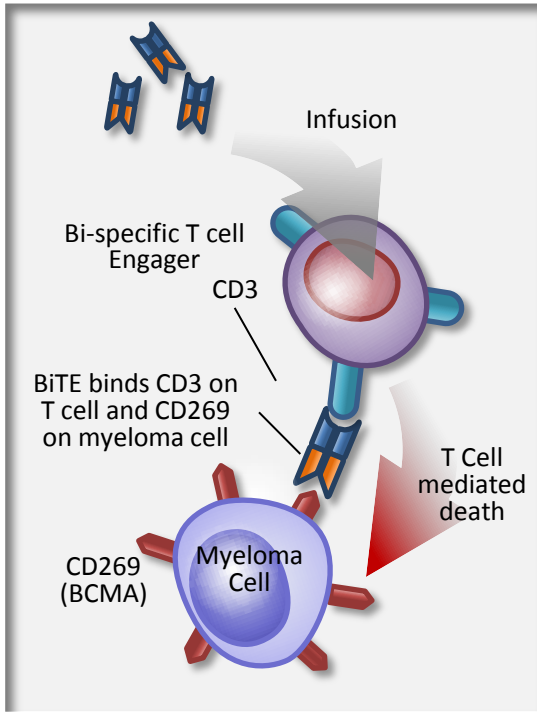
New Ways to Target and Kill Myeloma Cells in Development

CAR-T Cell Therapy



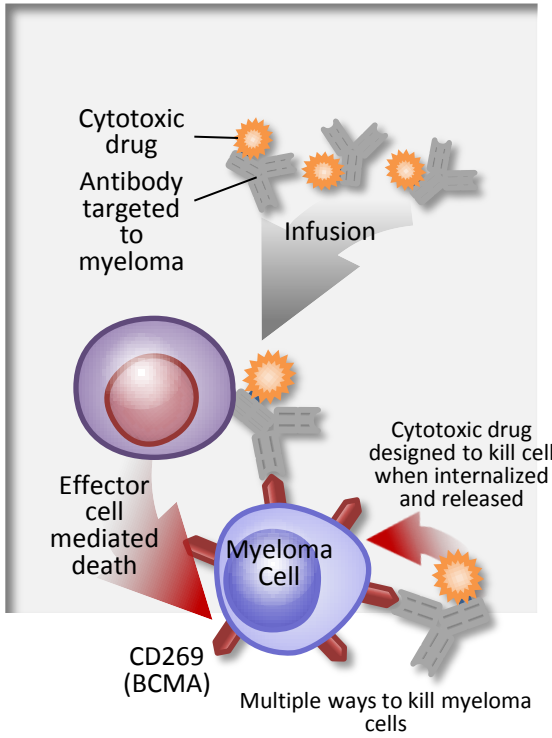
Examples: **bb2121, LCAR-B38M, MCARH171**
Raje NS, et al. ASH 2018. Abs #8007; Zhao W-H, et al. ASH 2018. Abs #955; Mailankody S, et al ASH 2018. Abs #959.

BiTE Antibody



Example: **AMG 420**
Topp MS, et al ASH 2018. Abstract #1010.

Drug-Antibody Conjugate



Example: **GSK2857916**
Trudel S, et al. *Lancet Oncol*. 2018;19(12):1641-1653.

BCMA = B-cell maturation antigen.

Future Directions, Final Thoughts

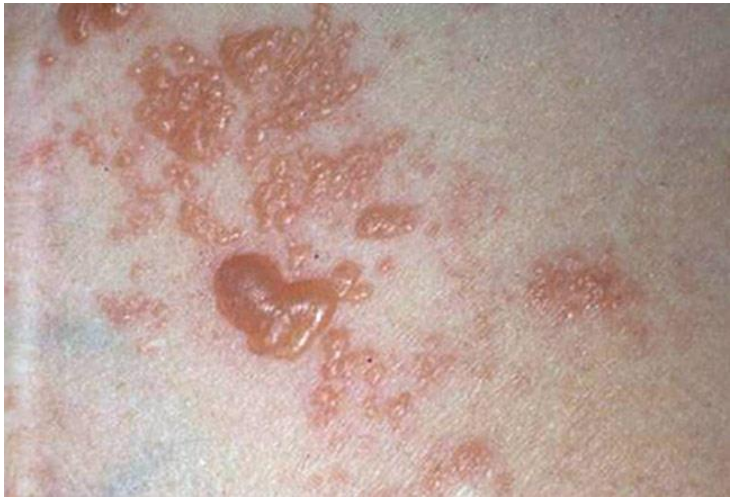
- Advanced practice providers are critical to the management of MM
- Explosion of new therapies has led to an interest in diagnosis, management of MM
- CAR-T and BiTE technology moving forward for myeloma
- Selinexor likely to be approved by FDA soon
- Daratumumab combinations are expanding for myeloma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

Multiple Choice Questions

Chakra Chaulagain, MD, FACP

Treatment with which one of the following agents can be associated with the rash shown?

a. Lenalidomide
b. Bortezomib
c. Rituximab
d. Vincristine



A 65 y/o man with MM started bortezomib, dexamethasone and lenalidomide (VRD) therapy. All of the following supportive care (s) is/are appropriate except,

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

Case Presentation

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

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

- **Patient met all CRAB criteria (Ca=>11, R=creatinine >2, A=Hb <10, B= lytic bone lesion/s). A diagnosis of multiple myeloma was made.**

MCQ

- What is the **first step** in the management of this patient's hypercalcemia ?

  a. isotonic saline infusion

  b. Isotonic saline along with furosemide

  c. Dexamethasone

  d. Intravenous bisphosphonates

THANK YOU!!