Advancing the Management of Plasma Cell Dyscrasias

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THE ANNUAL APSHO MEETING

Learning Objectives

- Interpret differential diagnoses of plasma cell dyscrasias
- Assess recent changes in clinical management of the spectrum of multiple myeloma (smoldering, monoclonal gammopathy of undetermined significance [MGUS])
- Evaluate the risks and benefits of early treatments for smoldering myeloma
- Plan management strategies for patients with solitary plasmacytomas and amyloidosis

Financial Disclosure

- Dr. Faiman has acted as a consultant and served on the speakers bureau for Amgen and Takeda; she has served on the speakers bureau for Celgene and Janssen.
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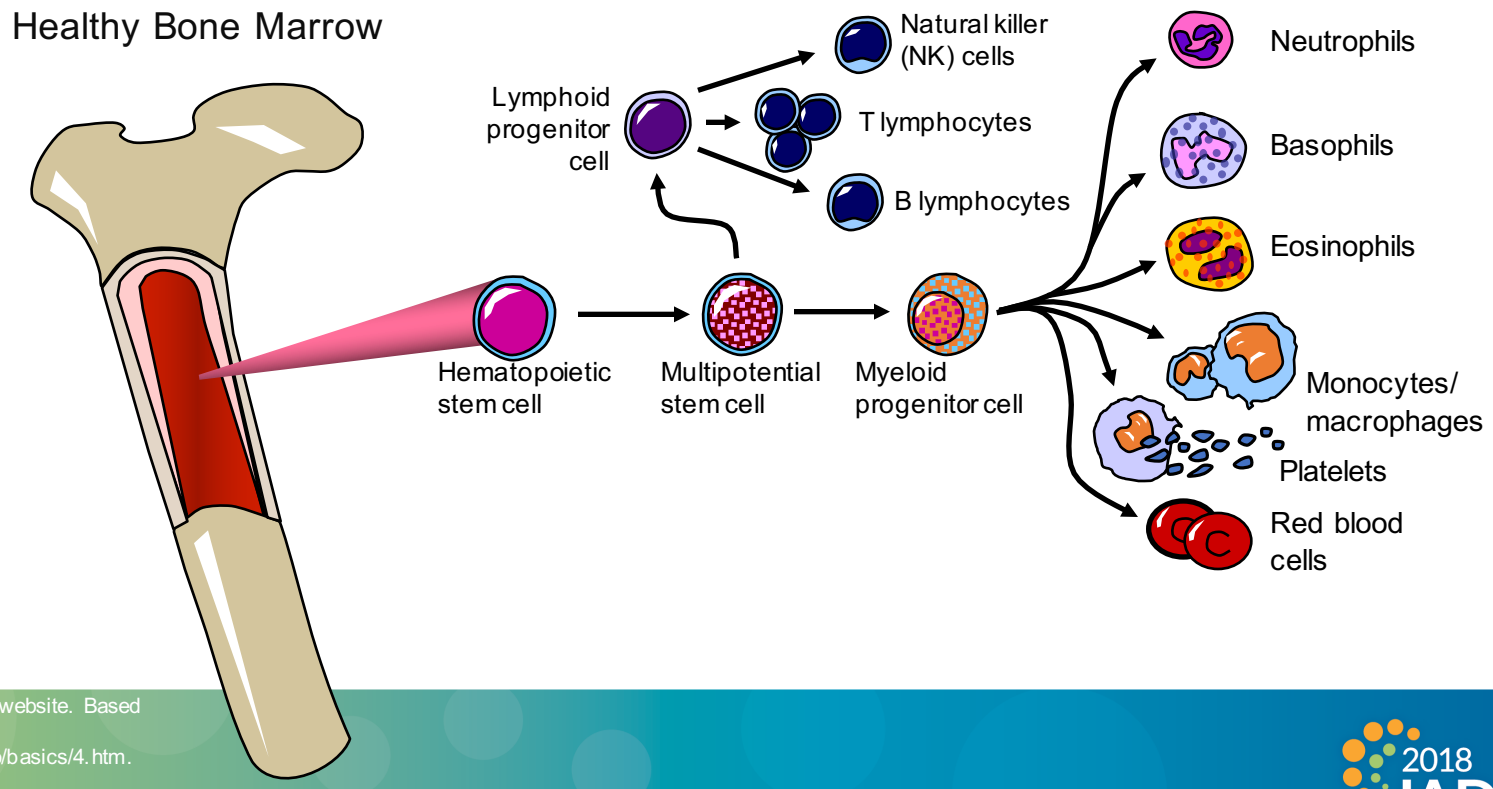
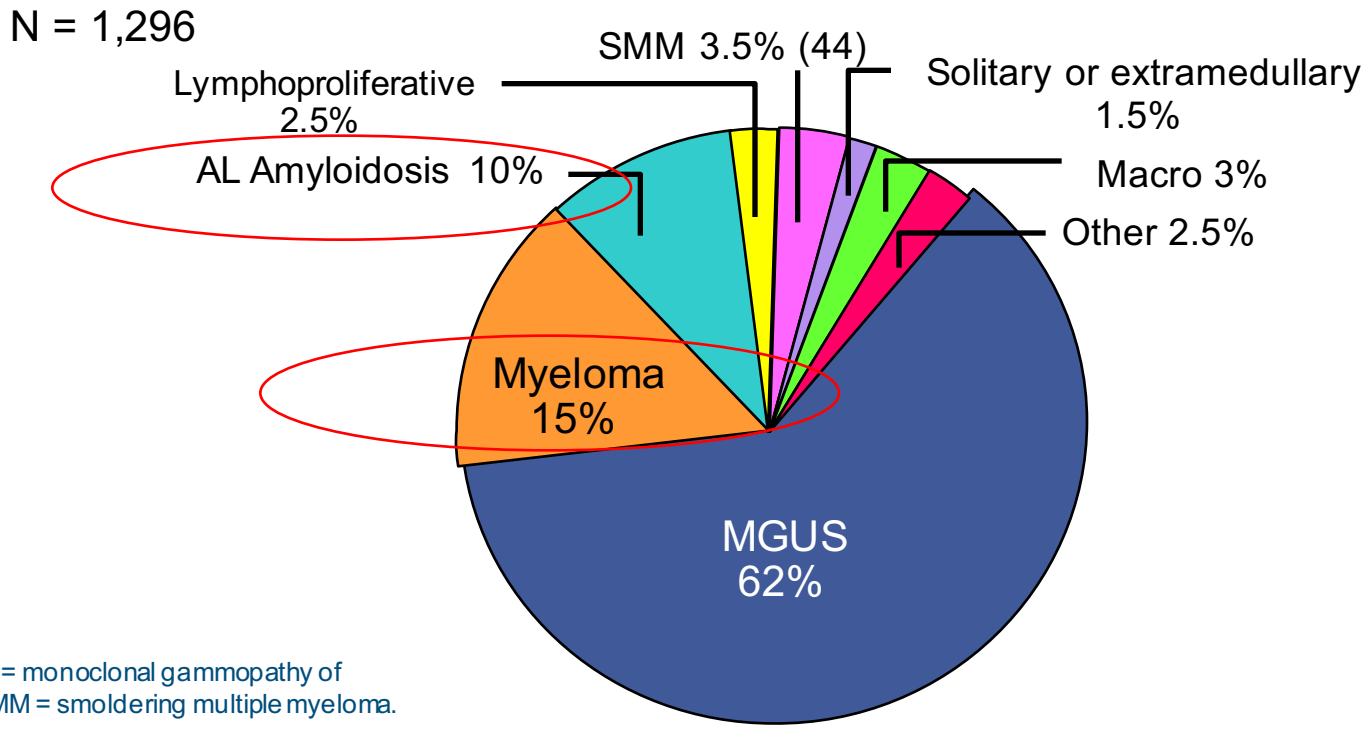
All Blood Cells Begin as Hematopoietic Stem Cells



NIH Stem Cell Information website. Based on: https://stemcells.nih.gov/info/basics/4.htm.

Plasma Cell Disorders: Distribution of Plasma Cell Dyscrasias

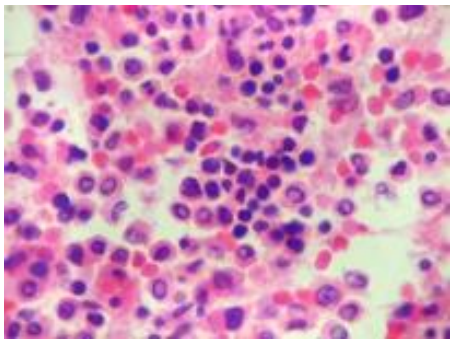


AL = amyloidosis; MGUS = monoclonal gammopathy of uncertain significance; SMM = smoldering multiple myeloma.

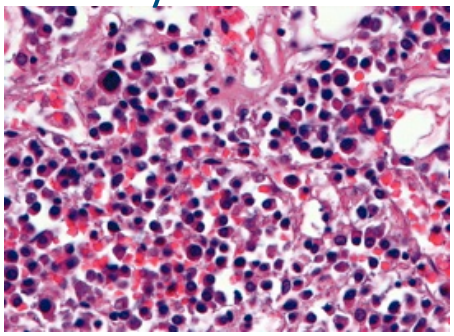
Kyle RA et al. Plasma cell disorders. In: Goldman L et al, eds. *Cecil Textbook of Medicine*. 22nd ed. Philadelphia, PA: WB Saunders Company; 2004.

Myeloma Is a Cancer of Plasma Cells

Normal BM



Myeloma BM



- Cancer of plasma cells
- Often preceded by nonmalignant state(s): MGUS or SMM
- Healthy plasma cells produce antibodies/immunoglobulins (Ig)
- Overproduction of a normal Ig "clone"
  - 65% IgG; 20% IgA, 20% light chain only
  - Baseline and ongoing monitoring of the disease is essential: CBC, CMP, SPEP, UPEP, serum free light chains

BM = bone marrow; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; CBC = complete blood count; CMP = complete metabolic panel.

Kyle RA, et al. Mayo Clin Proc. 2003;78:21-33; Cross TS, et al. Postgrad Med J. 2006;82:e13-e13.

Myeloma Disease Overview: Case Presentation

- Bob is a 51-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
- Routine labs

Complete Blood Count

- WBC count 3,300/µL
- Hemoglobin 10.3 g/dL
- Platelet count 138,000/µL

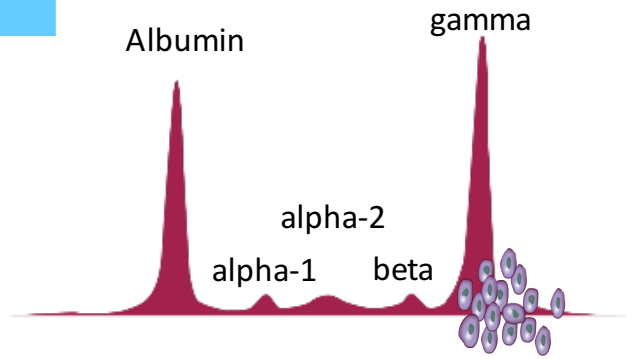
Complete Chemistry Panel

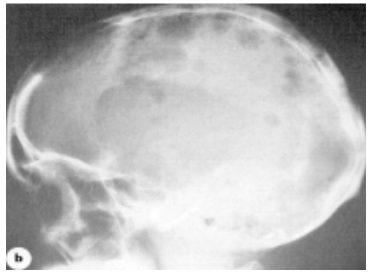
- Creatinine 1.7 g/dL
- Calcium 10.4 mg/dL
- Albumin 3.2 g/dL
- Total protein 10.9 g/dL

APP = advanced practice provider; WBC = white blood cell.

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





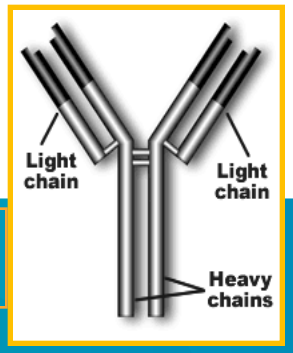
β2m = β2 microglobulin; CT = computed tomography; EM = extramedullary; FISH = fluorescence in situ hybridization; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PET = positron emission tomography; sFLV = serum free light chain.

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.

Myeloma Disease Overview

- 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?*

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

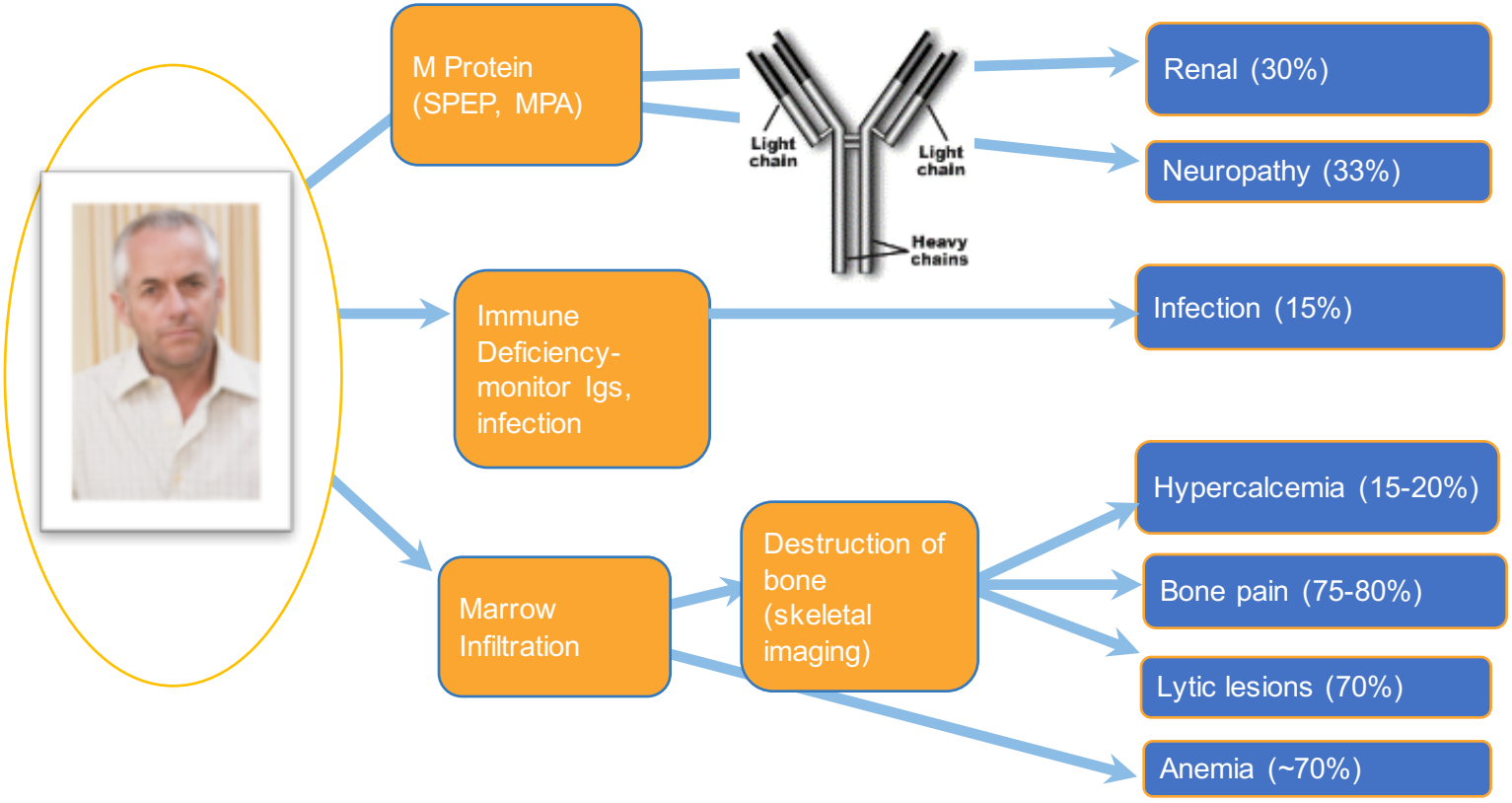


Immunoglobulin structure

MMA = methylmelonic acid

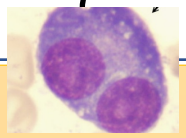
Baz et al; Cancer 101 (4):790-795, 2004

The Multiple Effects of Multiple Myeloma

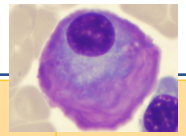


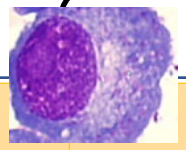
Faiman, B., et al., 2017, Clinical Journal of Oncology Nursing; Miceli, T. et al., 2017, Clinical Journal of Oncology Nursing; Kyle et al., 2003; Faiman and Bilotii, 2013.

Differential Diagnosis of MM



Premalignant





Malignant

Condition	MGUS[1-4] (Monoclonal Gammopathy of Undetermined Significance)	SMM[1-5,8] (Smoldering Multiple Myeloma)	Active Multiple Myeloma[6-8]
Clonal plasma cells in bone marrow	<10%	10%-60%	≥10%
Presence of myeloma-defining events (MDEs)	None	None	Yes
Likelihood of progression	~1% per year	~10% per year x 5 years then 1%/year	Not applicable
Treatment	No; observation	Yes for high risk*; No for others	Yes

*Clinical trial is preferred or offer treatment

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.

Diagnostic Criteria

Clonal bone marrow ≥ 10% or bony/extramedullary plasmacytoma

AND any one or more Myeloma Defining Events (MDE)

Based on Bob's high M protein, he agreed to enroll in a clinical trial for high-risk smoldering MM

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

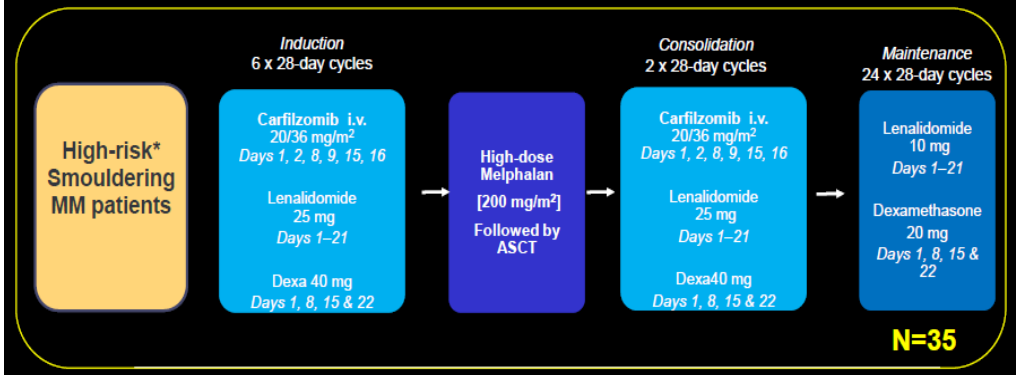
- **BM** Clonal bone marrow ≥ 60%
- **FLC** sFLC ratio >100
- **MRI** >1 focal lesion by MRI

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

Is an Aggressive Approach to Treat Smoldering MM Recommended?

GEM-CESAR: Study Design

- Multicenter, open-label, randomized phase II trial

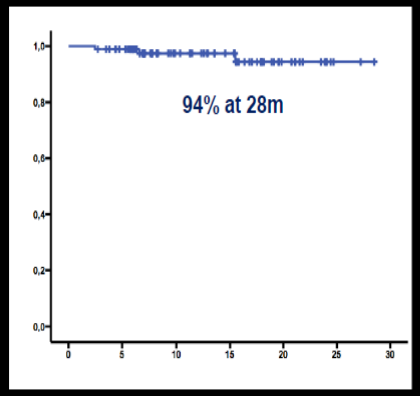


High-risk was defined according to the Mayo and/or Spanish models

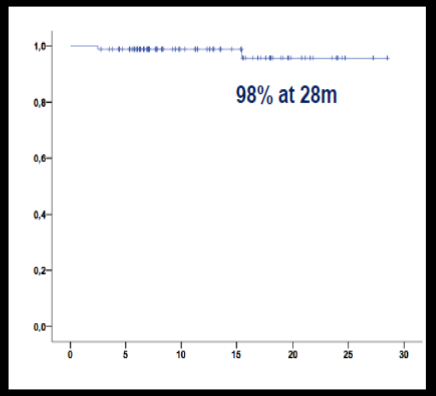
- Patients with any one or more of the biomarkers predicting imminent risk of progression to MM were allowed to be included but…
- New imaging assessments were mandatory at screening and if bone disease was detected in the CT or PET-CT, patients were excluded

GEM-CESAR Outcomes

PFS — Median follow-up: 10 (1-28) — OS



Two patients experienced relapse from CR before the end of induction and they proceeded to subsequent therapy



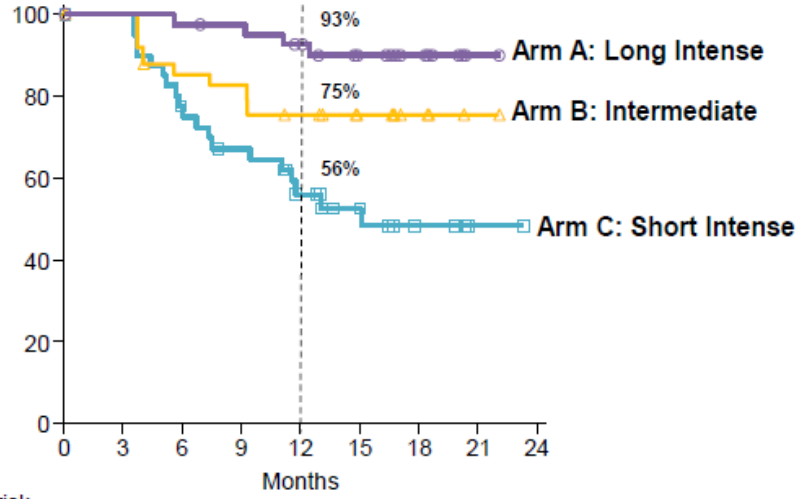
Two deaths: one patient who relapsed from CR and was refractory and died due to disease progression; other patient due to massive ischemic stroke during induction

75% had an excellent response but at what cost?

Mateos MV, et al. ASH 2017. Abstract 402.

Daratumumab Alone in Smoldering MM

CENTAURUS: PFS (Biochemical or Diagnostic)



No. at risk									
Long Intense	41	41	40	39	36	21	12	1	0
Intermediate	41	41	34	33	28	16	7	1	0
Short Intense	41	40	30	25	18	13	5	1	0

PFS = progression-free survival

Extended daratumumab dosing prolongs biochemical/diagnostic PFS

1. Rajkumar SV, et al. *Lancet Oncol.* 2014;15:e538-e548.

American Society of Hematology

Hofmeister CC, et al. ASH 2017. Abstract 510.

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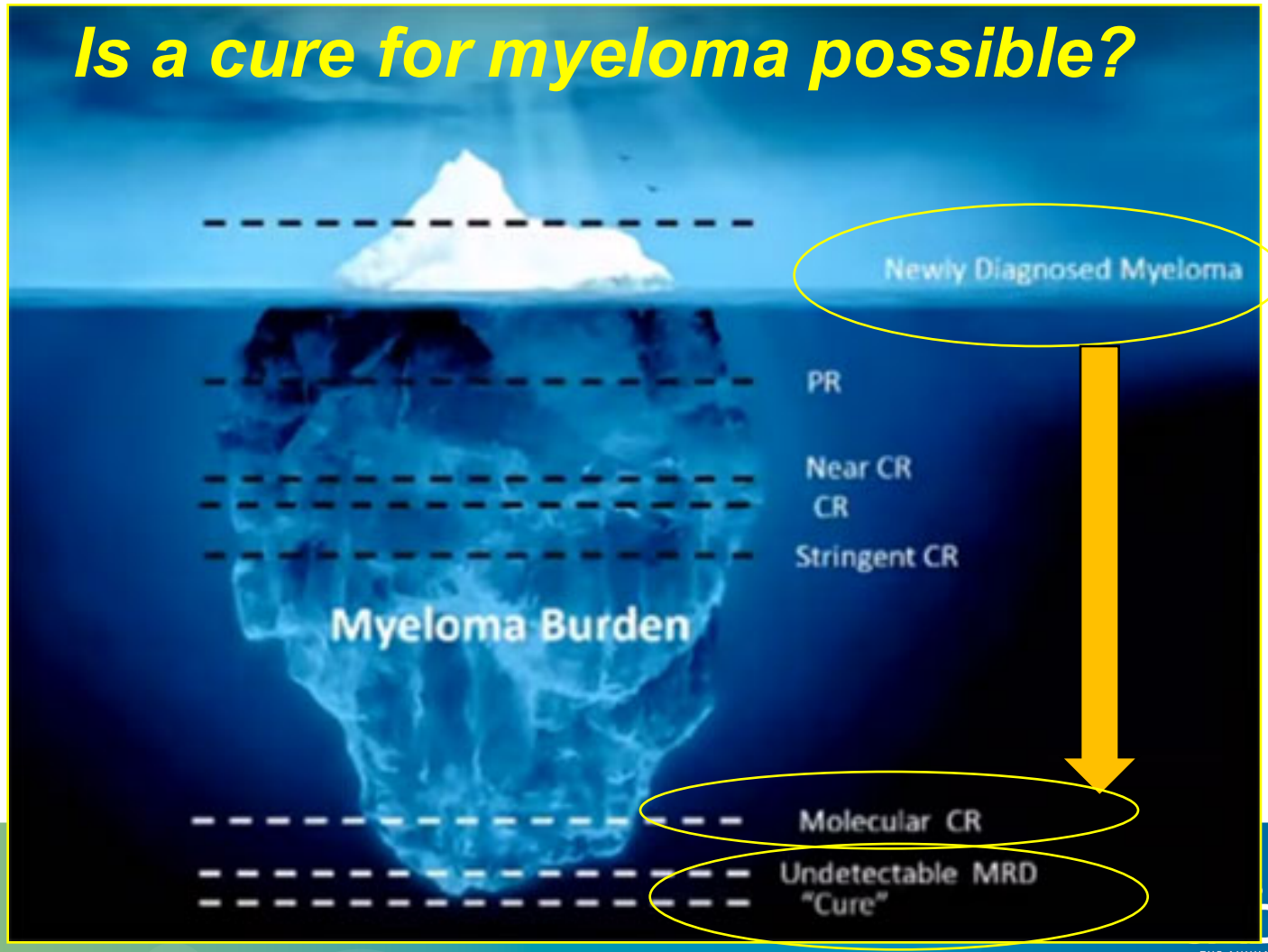
Pro and Cons of Early treatment for SMM

- Pros
  - Possible survival benefit in one study[1]
  - Delay/prevent potentially irreversible complications (fractures/renal failure)
  - Contemporary therapy is better tolerated
- Cons
  - Methodologic flaws in the one study with survival benefit
  - Concern for long term toxicity / second malignancy[2]
  - Not all patients require therapy and criteria to define risk are inconsistent
  - Financial impact? QOL?

QOL = quality of life

1. Mateos MV et al. *Lancet Oncol*. 2016;17(8):1127
2. Hjorth M et al. *Eur J Haematol*. 1993;50: 95-102

Is a cure for myeloma possible?

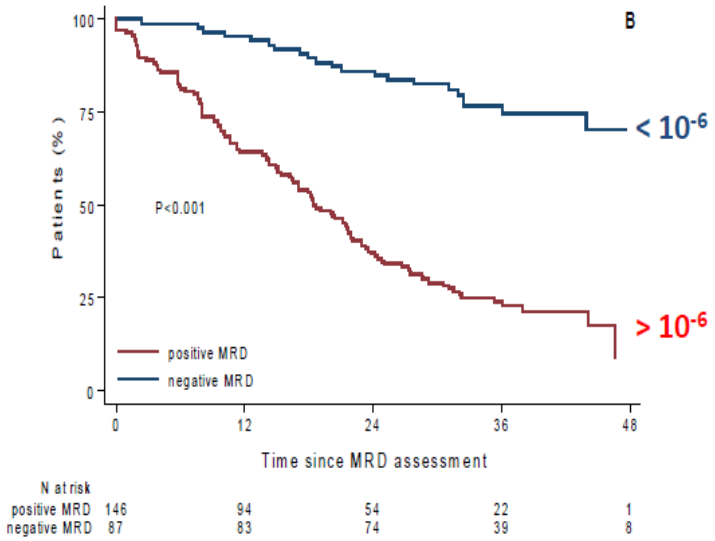


Minimal Residual Disease (MRD) and Transplant, Aiming for a "Cure"

The lower the level of myeloma cells, the longer the response

Importance of MRD sensitivity in IFM 2009 Trial

VRd ± ASCT

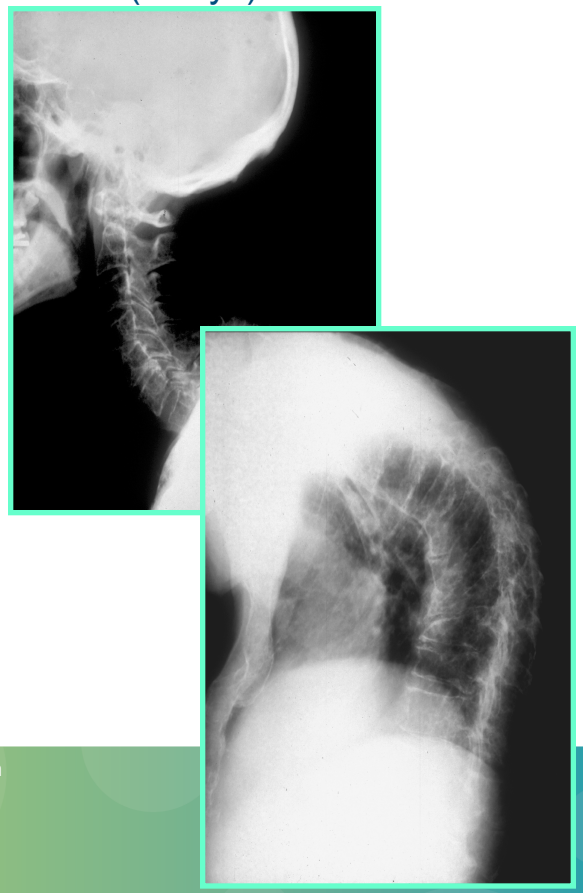


Skeletal Survey and MRI

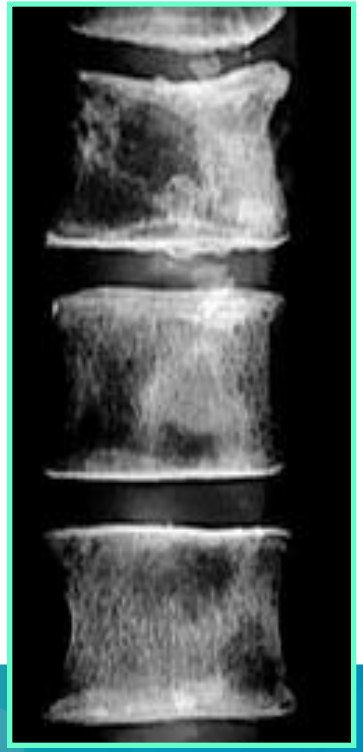
While undergoing screening for a clinical trial, Bob developed acute back pain when lifting furniture.

Based on the skeletal findings, Bob was admitted to the hospital for evaluation, management and pain control.

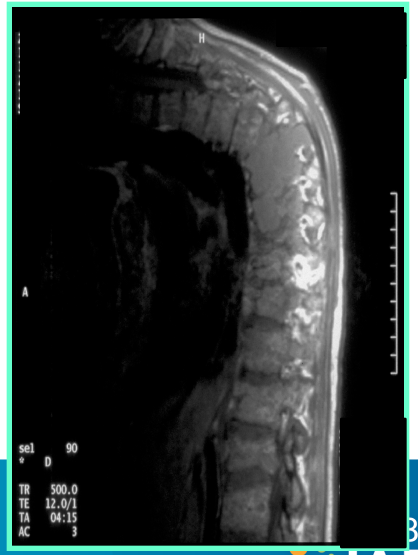
Skeletal survey
(x-rays)



Osteolytic lesions



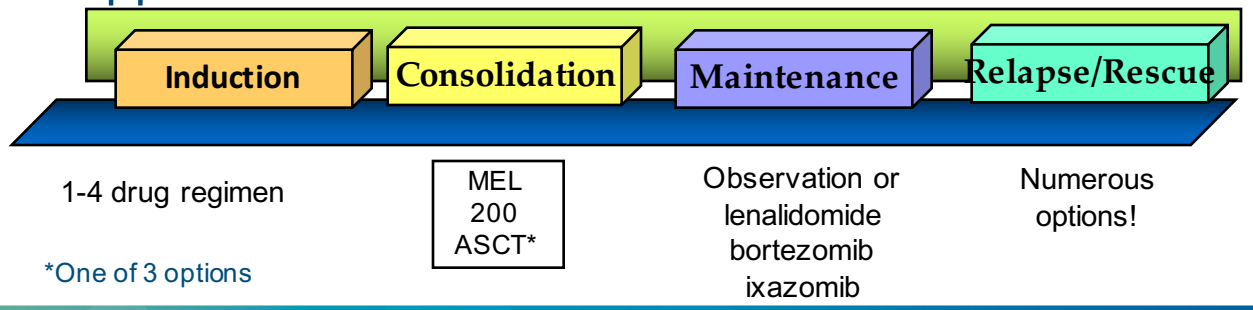
MRI of spine showing
T6 wedge deformity



Courtesy of Beth Faiman

What Is Bob's Diagnosis and Plan?

- Anemia, renal insufficiency, and osteopenia were not thought to be related to MM.
- With multiple lytic lesions 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 (bisphosphonates, antiviral antibiotics)
  - Financial and social support services



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

Drugs Used 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.

National Cancer Institute. Drugs approved for multiple myeloma and other plasma cell neoplasms.

Side Effects of Common Myeloma Drugs (1)

	Thalidomide	Lenalidomide	Pomalidomide	Bortezomib	Carfilzomib	Ixazomib
Neuropathy (PN)	✓			✓*		✓
Thrombosis (DVT, PE)	✓more with dex	✓more with dex	✓more with dex		✓	
Myelosuppression	✓ neutro	✓anemia, thrombo, neutro	✓ neutron, anemia, thrombo	✓ thrombo	✓ neutro, thrombo	✓ thrombo
Cardiopulmonary	✓slow heart rate	✓slow heart rate	✓shortness of breath	✓hypotension	✓shortness of breath, other	
Fatigue, weakness	✓	✓	✓	✓	✓	✓
Sedation	✓					
Rash	✓	✓	✓			✓
GI disturbance	✓ constipation	✓ diarrhea, constipation	✓ diarrhea, constipation	✓ nausea, vomiting, diarrhea	✓nausea, vomiting, diarrhea, constipation	✓nausea, vomiting, diarrhea
VZV				✓	✓	✓

*** Subcutaneous or weekly administration of bortezomib reduces risk of PN**

PN = peripheral neuropathy; DVT = deep vein thrombosis; PE = pulmonary embolism; dex = dexamethasone; Neutro = neutropenia (low white blood cell) count; Thrombo = thrombocytopenia (low platelets); GI = gastrointestinal

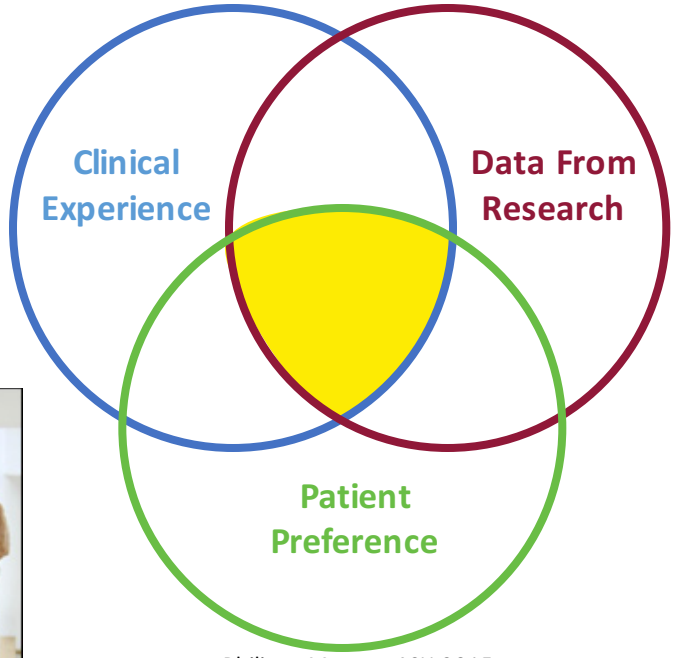
Side Effects of Common Myeloma Drugs (2)

	Panobinostat	Elotuzumab	Daratumumab
Peripheral neuropathy			
Infusion reaction		✓ ~ 10%	✓ ~ 40%
Myelosuppression	✓ neutro, thrombo		✓neutro, thrombo
Cardiopulmonary	✓QT↑, arrhythmias, ischemia		
Fatigue, weakness	✓	✓	✓
Rash			
GI disturbance	✓diarrhea, nausea, vomiting	✓diarrhea, nausea	✓ diarrhea

Prescribing information: panobinostat, elotuzumab, daratumumab, ixazomib.

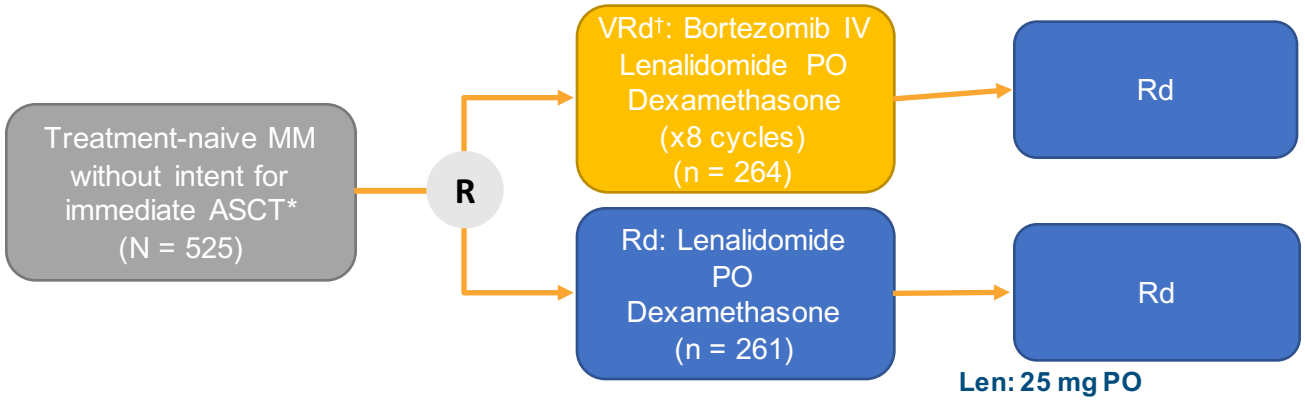
How old is too old? What determines "correct" treatment?

- Many studies define elderly as >65
- Age is just a number
- Geriatric Assessment and Frailty
  - http://www.myelomafrailtyscorecalculator.net/
- The correct treatment balances:
  - Performance status
  - Comorbid conditions
  - Discuss treatment goals
  - Desire for aggressive treatment
- Mutual agreement between patient, treatment team is recommended



Philippe Moreau. ASH 2015.

VRd vs Rd: SWOG S0777 Data
3 vs 2-Drug Regimen as Initial Induction



	VRd	Rd	HR; *P*
Median PFS, mo	43	30	0.712; .0018 (1-sided)
Median OS, mo	75	64	0.709; .025 (2-sided)

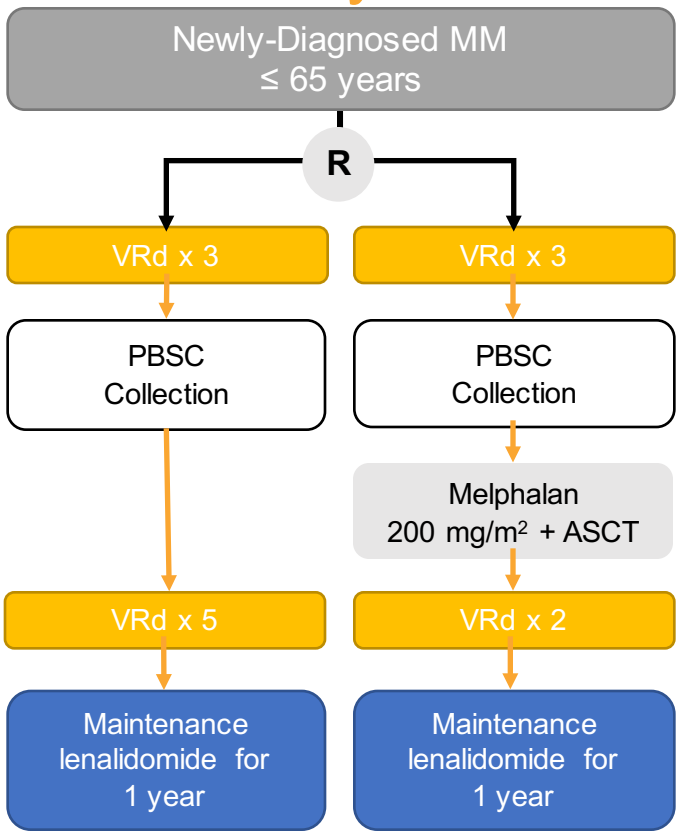
VRd showed better PFS in patients with high- or standard-risk disease vs Rd‡

*All patients received aspirin (325 mg/d).
†Patients received VZ prophylaxis.
‡High-risk cytogenetics included: t(4;14), t(14;16), or del(17p); preliminary data from 316 patients.

ASCT = autologous stem cell transplantation; CR = complete response; ISS = International Staging System; OS = overall survival; R = randomized; Rd = lenalidomide, dexamethasone; SWOG = Southwest Oncology Group; VRd = bortezomib, lenalidomide, dexamethasone.

Durie BG, et al. *Lancet.* 2017;389:519-527.

IFM 2009 Study: ASCT vs. No ASCT



	VRd	ASCT
N	350	350
CR,* %	48	59
Median PFS,† mo	**36**	**50**
4-year OS, %	82	81

*P = .03. †P < .001.

Primary endpoint: PFS; OS data not yet mature.

- Transplant-related mortality: 1.7%
- Regardless of MRD status, PFS was prolonged in the ASCT arm vs the VRd arm
- More MRD-negative patients in the ASCT arm

IFM = Intergroupe Francophone du Myélome; PBSC = peripheral blood stem cell; R = randomized.

Attal et al. *N Engl J Med.* 2017;376:1311-1320.

Maintenance Therapy w/wo Transplant, Relapsed Treatment

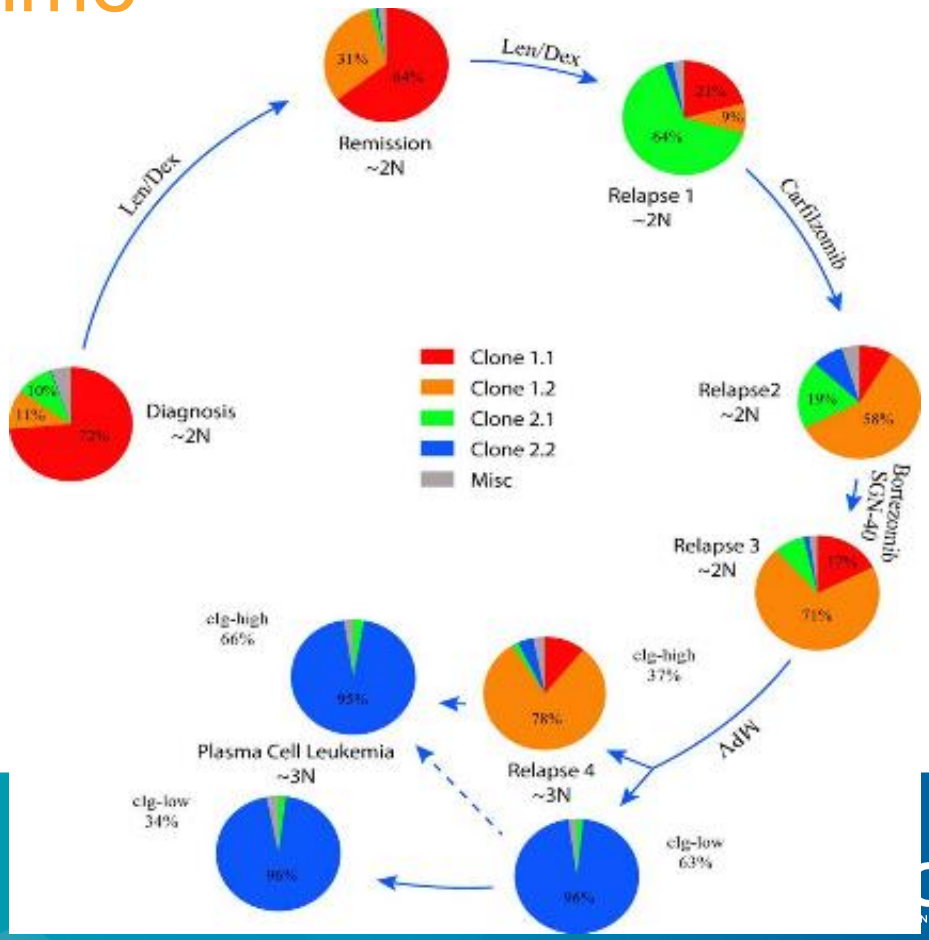
- Updated lenalidomide maintenance
- Elotuzumab + len/dex after transplant[1]
- Ixazomib-based induction followed by long-term ixazomib maintenance (overall response rate of 94%, including a complete response of 35%)[2]
- KRd (carfilzomib/lenalidomide/dexamethasone) vs Rd~ the ASPIRE trial[3]
  - Pts stayed in remission longer with 3 vs 2 drugs
- Pom/cyclophosphamide/dex in relapsed myeloma w/wo transplant (IFM 2013)[4]

1. Thomas SK, et al. ASH 2017. Abstract 840
2. Dimopoulos MA, et al. ASH 2017. Abstract 902
3. Stewart et al., 2017
4. Gardaret L, et al. ASH 2017. Abstract 837

Multiple Myeloma Is a Clonal Disease; Clones Change Over Time

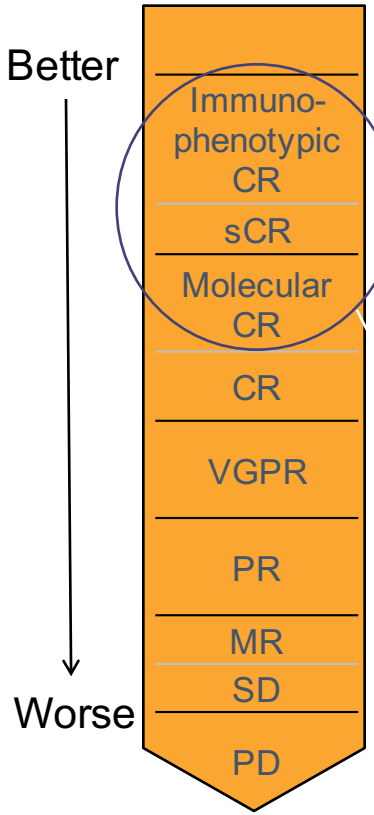
- Effective MM treatment reduces or eliminates the dominant clone
- Other clones can still exist.
- Ongoing treatment to suppress clones

Update on Bob:
After 5 years of remission, M spike rises from undetectable (0) to 1.36g/dL



Keats J J et al. *Blood* 2012;120:1067-1076.

Monitoring MM is Essential: The IMWG Myeloma Response Criteria



Category	Response Criteria
sCR, stringent complete response	Normal free light chain (FLC); no clonal BM plasma cells
CR, complete response	Negative IFX and < 5% BM plasma cells
VGPR, very good partial response	Positive IFX and negative SPEP; ≥ 90% urine protein decrease; urine M-protein level < 100 mg per 24 h
PR, partial response	≥ 50% decrease serum M-protein and ≥ 90% decrease in 24 h urinary M-protein
SD, stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease

- sCR AND BM negative by next gen flow (10^6)
- CR AND normal FLC ratio, BM negative by flow, 2 measures
- CR AND negative PCR (10^5)
- CR: Negative immunofix; <5% PC in BM; 2 measures

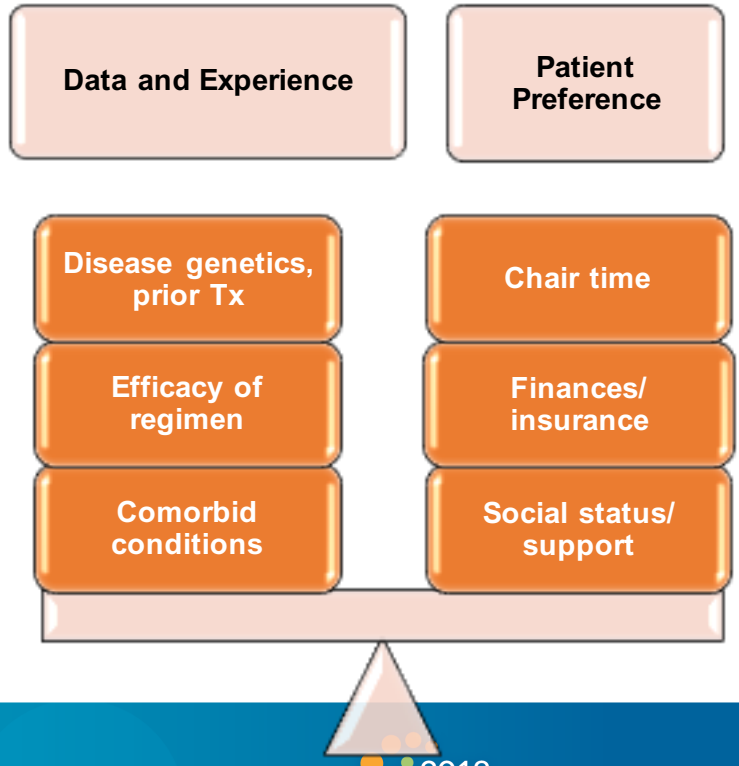
sCR = stringent complete response; VGPR = very good partial response; PR = partial response; SD = stable disease; MR = minimal response (only in relapsed); PD = progressive disease.

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.

Choices at Relapse/After 1+ Prior Myeloma Therapies

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

*Lenalidomide (R) and/or bortezomib (V) are used in 2nd line combinations



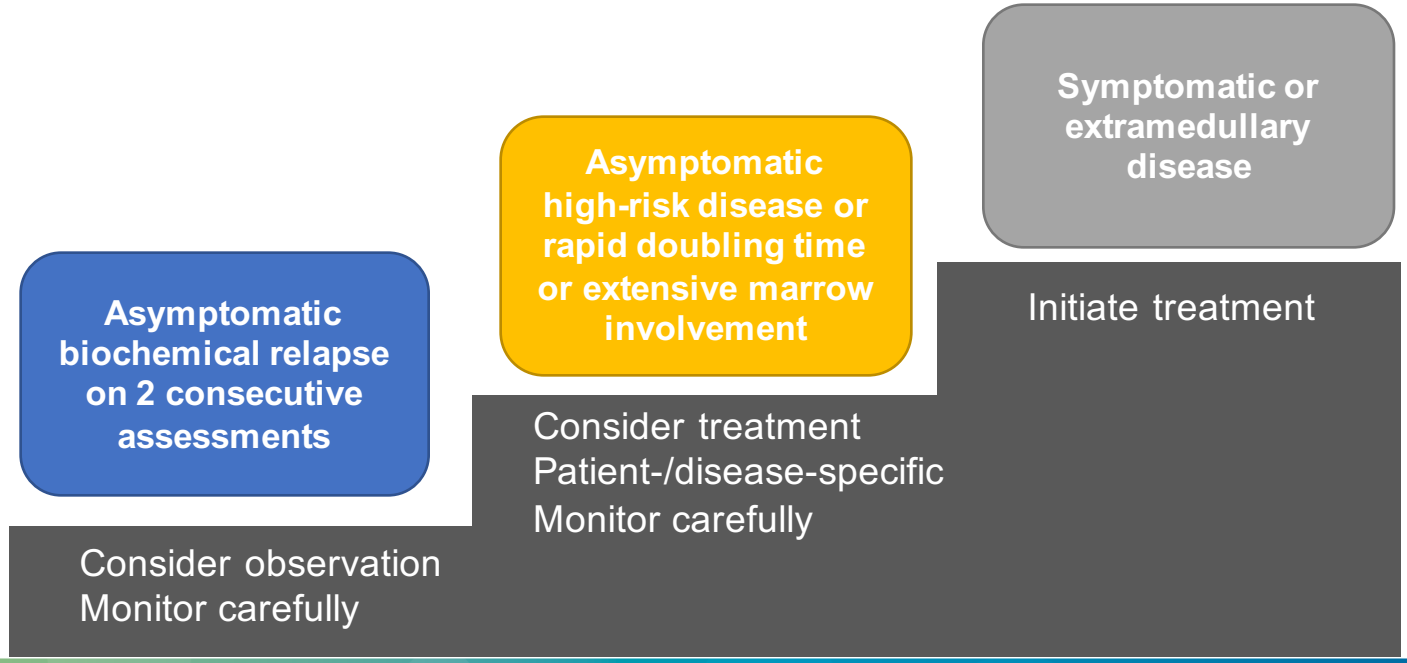
Faiman B, et al. *J Adv Pract Oncol* 2016; 2016: 7(suppl 1):17-29; Philippe Moreau, ASH 2015

Factors in Selecting Treatment for Relapsed/Refractory Myeloma

- Disease-related factors
  - Duration of response to initial therapy
  - High/low risk status
  - Biochemical disease progression, or symptomatic?
  - Other comorbid conditions
- Treatment-related factors
  - Previous therapy exposure (relapsed or refractory)
  - Toxicity of regimen (combination vs single agent)
  - Mode of administration (e.g., oral or IV)
  - Cost and convenience (out of pocket copays for IV/oral)

When to Initiate Therapy at Relapse

Not every relapse requires immediate therapy



Kumar et al. NCCN Guidelines. Multiple myeloma. V4.2018.

Strategies at Relapse: Start low, go slow…or "Go for it"?

Slow-Growing Myeloma in First Relapse

- If initial treatment with bortezomib, lenalidomide repeat or change therapy
- Ixazomib, carfilzomib, daratumumab, and elotuzumab are all considerations with len/dex or *pom/dex?*
- Consider if high/low risk disease at diagnosis

Treating Relapsed-Refractory Myeloma

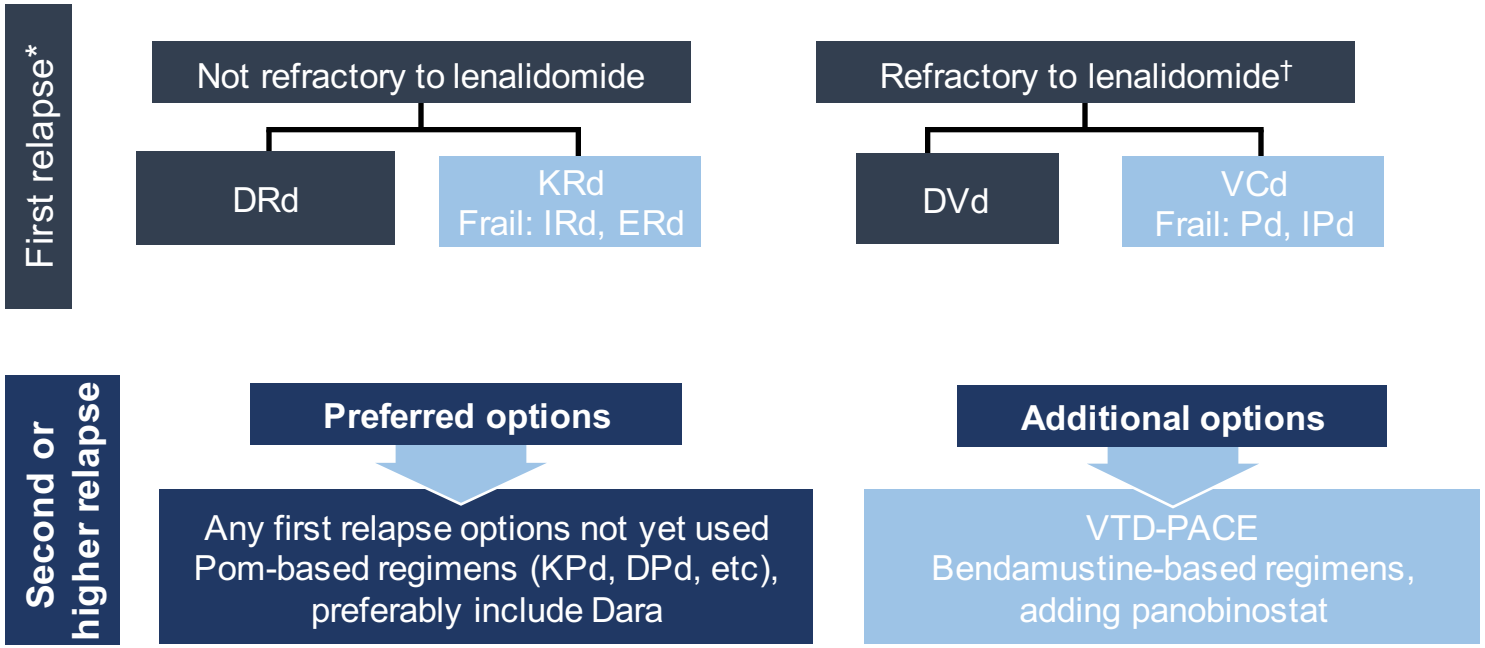
- Any peripheral neuropathy or renal dysfunction?
- What has been tried (protease inhibitor-based, immunomodulatory imide drug (IMiD)-based)
- Are clinical trials available?

Aggressive Myeloma With Rapid, Multiple Relapses

- Transplant if not done (allo, auto)
- Chemotherapy-based salvage with aggressive clones is often necessary
- Monoclonal antibodies (MoAb) candidates

Remember to discuss goals and costs of therapy
Encourage health maintenance to maintain "fitness" for next therapy

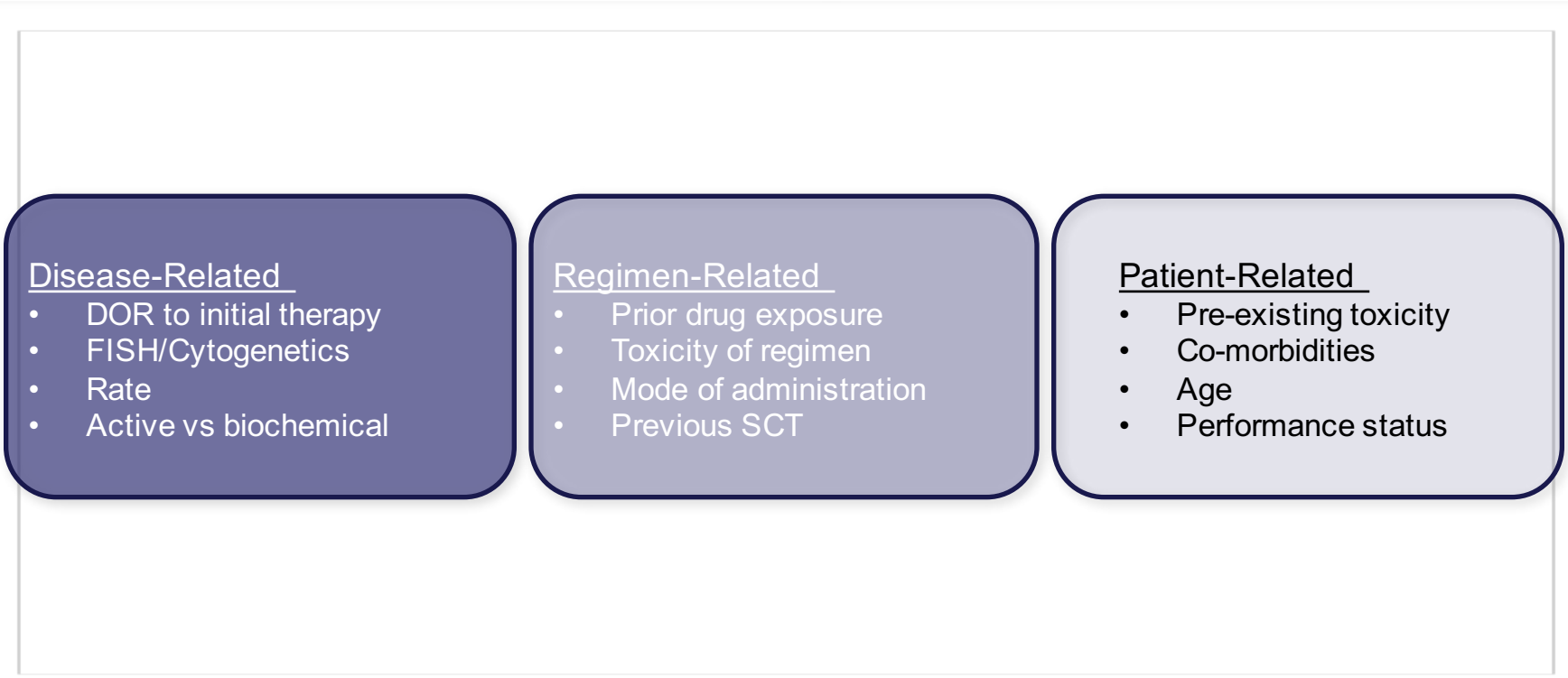
Suggested Preferred Treatment Options for RR Myeloma: An Example Decision Tree



DPd = daratumumab-pomalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; DVd, daratumumab-bortezomib-dexamethasone; ERd = elotuzumab-lenalidomide-dexamethasone; IPd = ixazomib-pomalidomide-dexamethasone; IRd= ixazomib-lenalidomide-dexamethasone; KPd = carfilzomib-pomalidomide-dexamethasone; KRd = carfilzomib-lenalidomide-dexamethasone; Pd = pomalidomide-dexamethasone; RR = relapsed/refractory; VCd = bortezomib-cyclophosphamide-dexamethasone; VTD-PACE = bortezomib-thalidomide-dexamethasone-cisplatin-doxorubicin-cyclophosphamide-etoposide.

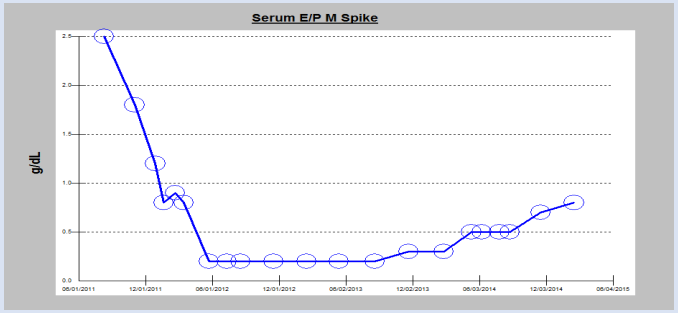
Rajkumar SV, et al. N Engl J Med. 2016;375:1390-1392.

Relapsed/Refractory MM: General Considerations



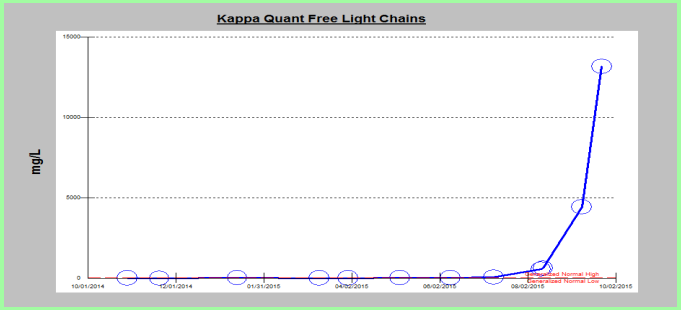
Traditional Approach to Relapsed Disease

- **Indolent**
  - First
  - Slow and asymptomatic
  - Low /standard risk



Treatment implications
Single agent / doublet
Sequential vs combination therapies
Emphasis on patient preference and convenience

- **Aggressive**
  - Multiple
  - Fast or symptomatic
  - High risk



Treatment implications
Triplet or combination therapies
Emphasis on efficacy

Possible Change in Paradigm for RRMM

- Combination therapy (triplets) shown to outperform (doublets) in relapsed setting in terms of response and PFS: e.g., ASPIRE[1], IFM 2005-04[2]
- QOL data favors triplets in some situations (ASPIRE)[1]
- CR rates high with novel agent triplets (ASPIRE)[1] and MRD- noted (POLLUX)[4]
- The “new triplets” combinations with monoclonal antibodies don’t have overlapping toxicities (ELOQUENT2 and POLLUX)[3,4]

- Not many trials have examined sequential vs combination therapy (CRD vs RD + CD)
- Limited QOL data
- Limited data on OS

1. Stewart et al. *N Engl J Med.* 2015;372(2):142-52
2. Garderet et al. *J Clin Oncol*. 2012; 30(20):2475-82
3. Lonial et al. *N Engl J Med.* 2015 Aug 13;373(7):621-31
4. Dimopoulos MA, et al. *N Engl J Med* 2016 375:1319-1331

Regimens Studied in RRMM

Pomalidomide	Carfilzomib	Daratumumab	Elotuzumab	Ixazomib	Panobinostat
Dara Pom D	KD	Dara	Elo RD	Ixa	Pano V D
Car Pom D	KRD	Dara Pom	Elo Pom D	Ixa Dex	Car Pano Dex
Ixa Pom Dex	K Cy Dex	Dara Len	Elo Bort D	IRD	Len Pano
Bort Pom Dex	K Dara Dex	Dara Bort		Ixa Pom Dex	
Elo Pom Dex	Car Pano	Dara Carfil			
Pom Cy Dex					

Carfilzomib: Proteasome Inhibitor

Carfilzomib+Rd
FDA approved
July 2015

Carfilzomib+d
56 mg/m^2
FDA approved
January 2016

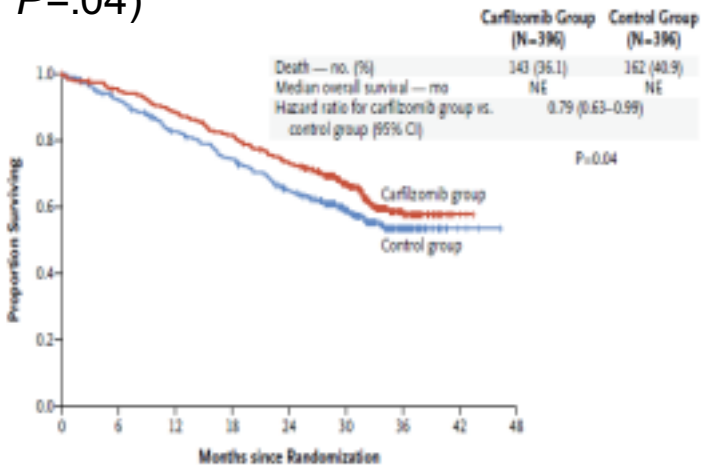
KRd mg/m^2
FDA approved
January 2016

Clinical pearls

- Avoid starting first cycle at the end of the week – dyspnea
- Hydration but not over hydration
- Premedication (dex)
- Aspirin prophylaxis
- Monitor blood counts, response
- Monitor for infection
- Herpes virus prophylaxis
- Know cardiac and pulmonary status
- Diuretics

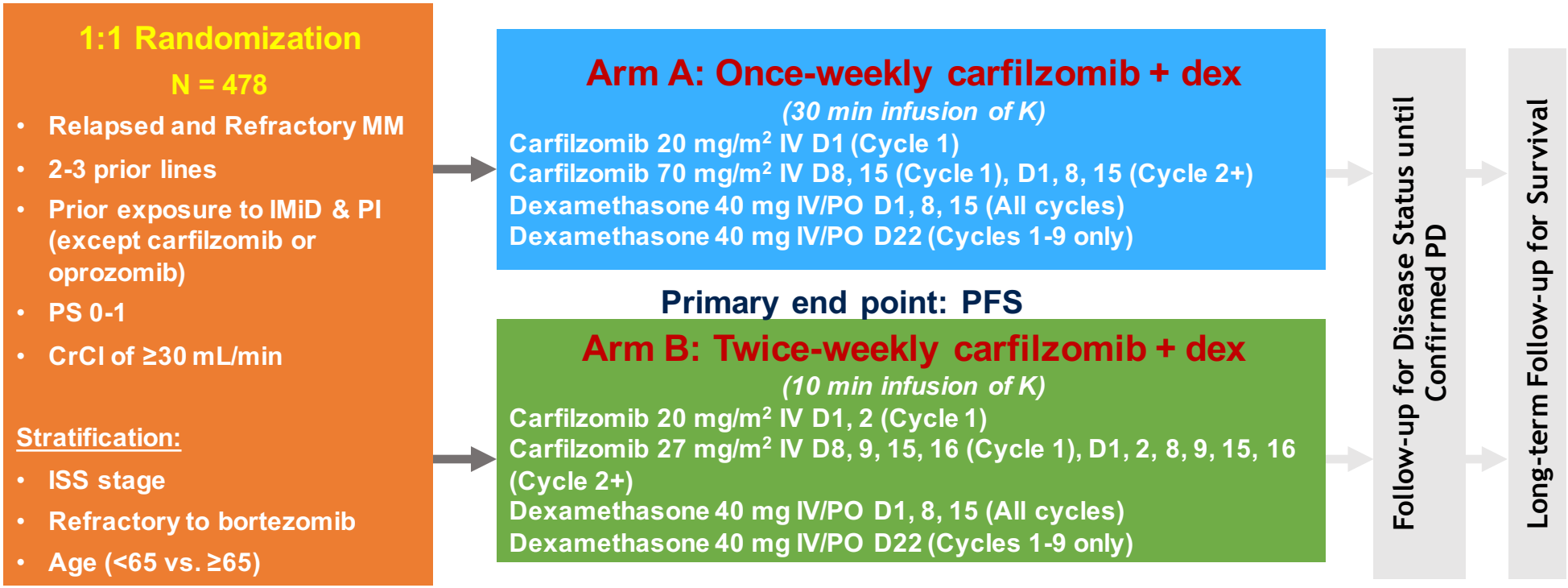
Overall Survival (OS)

24-month OS favored KRd
(24-mo OS 73.3% KRd vs 65.0% Rd; *P*=.04)



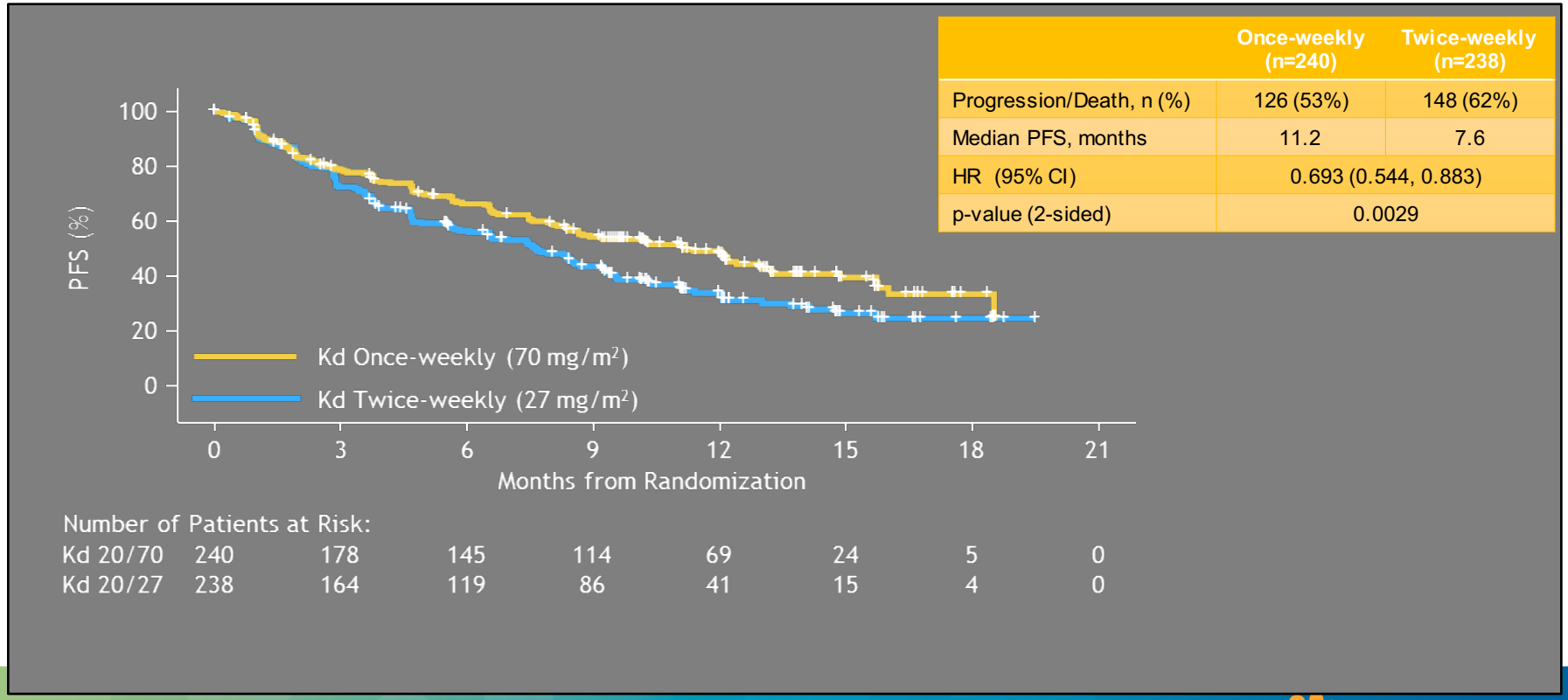
Stewart K, et al. N Engl J Med. 2015; 372:142-152.

ARROW Study Design



CrCl = creatinine clearance; K = carfilzomib; PI = proteasome inhibitor.

ARROW: PFS



	Once-weekly (n=240)	Twice-weekly (n=238)
Progression/Death, n (%)	126 (53%)	148 (62%)
Median PFS, months	11.2	7.6
HR (95% CI)	0.693 (0.544, 0.883)	
p-value (2-sided)	0.0029	

Mateos MV et al. ASCO 2018 abstract 8000

Pomalidomide

Pomalidomide ± dex
FDA approved
February 2013

Carfilzomib +
Pomalidomide ± dex
FDA approved
2017

DARA +
Pomalidomide + dex
FDA approved
2018

- Oral immunomodulatory agent (IMiD)
- Administration
  - Oral; Recommended with low-dose dex, take without food
- Monitor
  - Blood counts: neutropenia most frequent GR 3/4 AE, liver function, response
- Patient education
  - Adherence and REMS, Infection prevention, protect renal health
    - Hydration
    - Avoid NSAIDs, IV contrast, other drugs with renal interactions

AE = adverse event; GR = grade; pom = pomalidomide; REMS = Risk Evaluation and Mitigation Strategies; NSAID = non-steroidal anti-inflammatory drug.

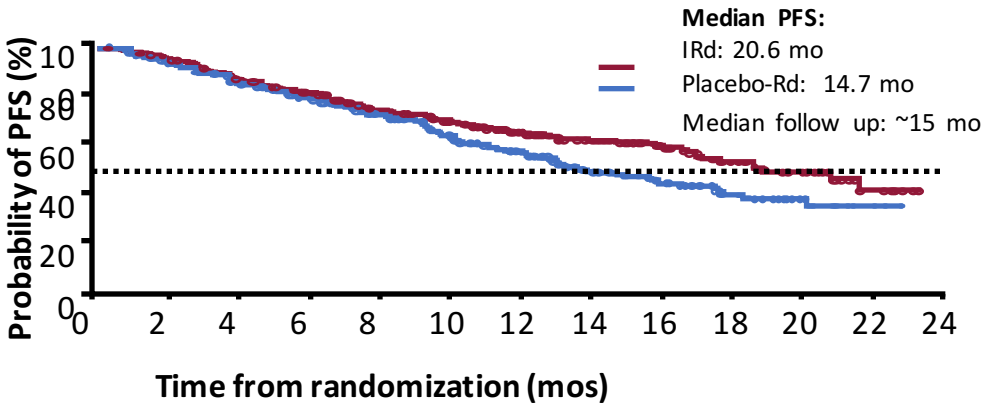
POMALYST® (pomalidomide) prescribing information ; Faiman B, et al. *J Adv Pract Oncol* 2016;7:45–52

Ixazomib: Oral Proteasome Inhibitor

Ixazomib+Rd
FDA approved
November 2015

- Administration
  - Oral capsule 1x per week; do not crush or chew capsules or open capsule
  - Empty stomach: 1 hr before or 2 hr after food
  - Adherence, schedule, viral prophylaxis; Rapid response (1.1 months); fast absorption (if vomit, do NOT repeat dose)
  - Cyclic thrombocytopenia, peripheral neuropathy, peripheral edema

Ixazomib: PFS improvement added to Rd



Log-rank P = .012
HR (95% CI): 0.742 (0.587-0.939)
Number of events:
IRD 129; placebo-Rd 157

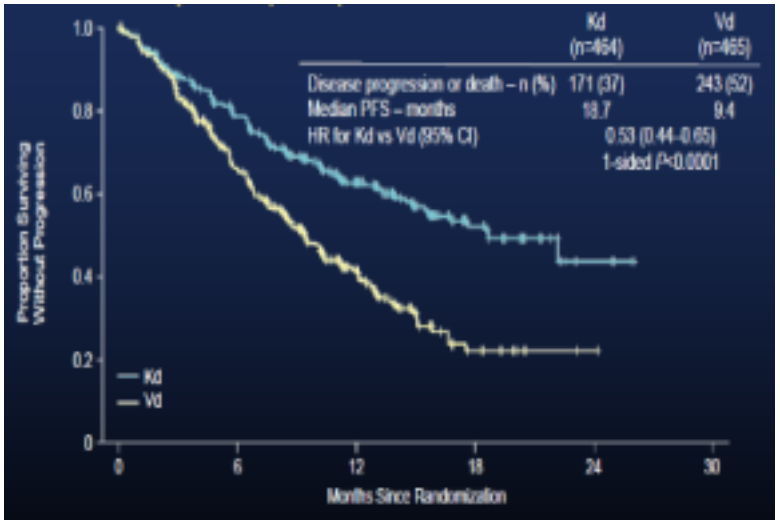
35% improvement in PFS for IRd vs. Rd

NINLARO® (ixazomib) prescribing information; Faiman B, et al. J Adv Pract Oncol 2016;7:45–52.

Clinical Pearls for Elotuzumab

Elo+ Rd FDA approved 2015

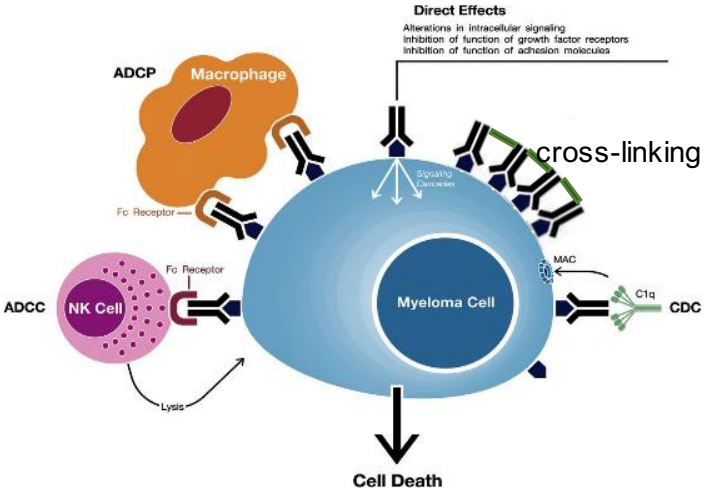
- Antibody administration: Risk of infusion reaction: 10%
  - 3-24 hr before = Dex 28 mg;
    45-90 min before = Dex 8 mg IV, H1, H2 and acetaminophen
  - Infuse at rate of 0.5 mL/min and escalate to 5 mL/min
  - Give weekly for 8 weeks then twice monthly until PD
- Prescribed w/ len-dex
  - DVT prophylaxis (for len), steroid side effects & schedule (am vs. pm), shingles prevention
- Monitoring
  - Blood counts (hold/adjust dose if needed)
  - Response assessment (monthly)
  - Glucose (dex can affect), renal, hepatic function



Double median PFS in Kd arm compared to Vd (18.7 vs 9.4 months)

Dimopoulos MA et al. EHA meeting 2015. Abstract LB2071.
Empliciti™ (elotuzumab) Prescribing Information; Gleason C, et al. J Adv Pract Oncol 2016; 7 (suppl 1): 53-57.

Daratumumab Mechanism



Daratumumab FDA approved November 2015

Daratumumab combinations DRd DVd and DPd FDA approved 2016, 2018

Premeds: corticosteroids, antipyretics, and antihistamine

montelukast and loratadine?

Post med: oral corticosteroid for 2 days after infusion

- Educate patients/caregivers about infusion expectations (schedule, reactions, etc)
- Infection risk
- Herpes prophylaxis (acyclovir)
- INTERFERENCE WITH CR and type, cross-match

Schedule:

Weeks 1-9 weekly

Weeks 9-24 every 2 weeks

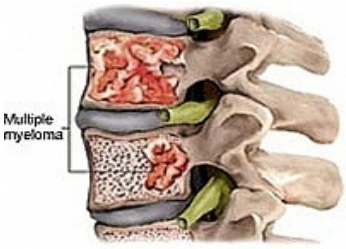
Weeks 25 on every 4 weeks

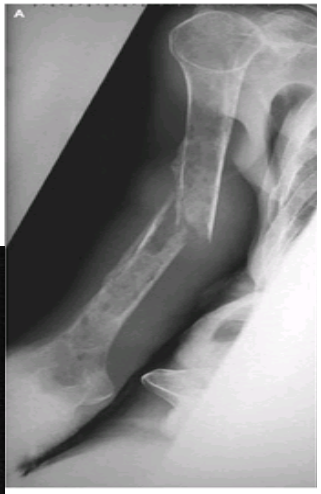
ADCC = antibody-dependent cell-mediated cytotoxicity
ADCP = antibody-dependent cellular phagocytosis
CDC = complement-dependent cytotoxicity
MAC = membrane attack complex

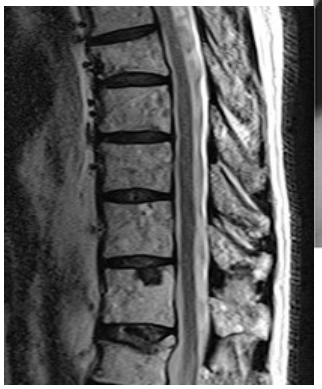
Image adapted from Van de Donk N, et al. Blood 2016; 127(6):681-695; Gleason C, et al. J Adv Pract Oncol 2016; 7 (suppl 1): 53-57.

Bone and Bone-modifying Agents (BMAs)

- ASCO Guidelines recommend BMAs for all MM patients to decrease SREs
  - IV: pamidronate or zoledronic acid, give every 3-4 wk for up to 2 yr
  - SC: Denosumab non-inferior to ZA, safe in kidney disease
  - Consider a 3-mo interval during maintenance or inactive disease periods
  - Resume treatment with relapse if stopped
  - Monitor calcium and replete calcium and vitamin D - especially w/ denosumab
- BMAs are not recommended in patients with solitary plasmacytoma, SMM, or indolent MM unless evidence of osteoporosis, osteopenia
- Good dental hygiene and routine monitoring to minimize risk of ONJ
  - Dental exam prior to starting (if possible)
  - Withhold BMAs for major dental procedures
- Renal disease
  - Pamidronate and zoledronic acid are not recommended if severe renal insufficiency (GFR <30 mL/min). Consider denosumab.
- Supportive care: surgical intervention, radiation, pain control if SRE







SRE = skeletal-related events; ONJ = osteonecrosis of the jaw; ZA = zoledronic acid.

Niesvizky and Badros. *J Natl Compr Canc Netw*. 2010;8(suppl 1):S13-S20.
Drake. *Oncology*. 2009;23(14 suppl 5):28-32;
Anderson et al. *J Clin Oncol*. 2018;36:812-818.

Amyloidosis

Amyloidosis: Overview

- Amyloidosis: extracellular tissue deposition of fibrils
- Composed of low-molecular-weight subunits (most of which are in the molecular weight range of 5 to 25 kD) of a variety of proteins
- These proteins often circulate as constituents of plasma.
- Hereditary and nonhereditary types
- GOAL: Improve speed with which diagnosis is made

Amyloidosis: Types AL and AA

AL amyloid: Deposition of protein derived from Ig light chain fragments

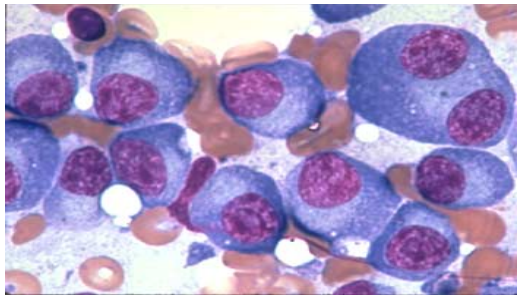
- Detectable M protein in serum or urine or sFLC in 98% of patients
- Accounts for approximately 80% in developed countries

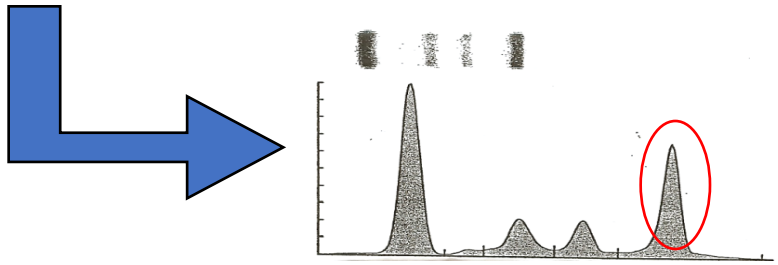
AA amyloid: Chronic diseases in which there is ongoing or recurring inflammation (i.e., RA or spondyloarthropathy)

Fibrils are composed of fragments of the acute phase reactant serum amyloid A

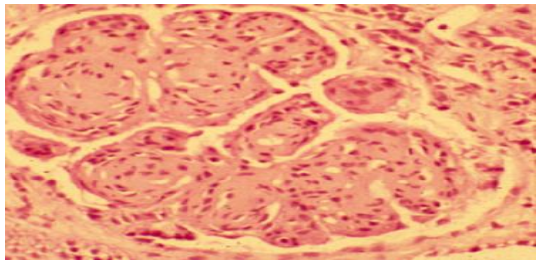
Other types: Dialysis related, senile (WT transthyretin), hereditary (mutant transthyretin or fibrinogen)

Amyloid and LCDD: Therapy

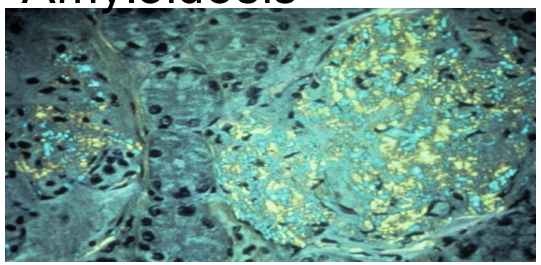




LCDD



Amyloidosis



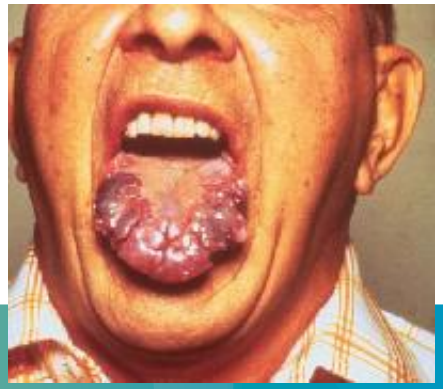
Current Treatment Paradigm: Target the Plasma Cell Clone to Reduce Light Chain Production

Primary (AL) Amyloidosis and Light and Heavy Chain Deposition Diseases

- Amyloid fibrils misfolding of a number of different proteins that form beta-sheet fibrils which are deposited extracellularly in various organs
  - These proteins range from immunoglobulin (Ig) light chains in primary systemic amyloidosis (AL can be identified on biopsy specimens both by their characteristic appearance on electron microscopy,
  - Congo red (leading to green birefringence under polarized light)
  - Thioflavine T (producing an intense yellow-green fluorescence)

Symptoms of Amyloidosis

- Heart
  - Congestive heart failure
  - Palpitations / arrhythmia
- Nerve
  - Numbness / tingling or pain in fingers and toes
  - Weakness
  - Autonomic



- Kidney
  - Swelling
  - “Foamy” urine
- Skin
  - Easy bruising or bleeding or tongue enlargement, “geographic tongue”

Index of Suspicion

- Non DM nephrotic syndrome
- Non ischemic restrictive cardiomyopathy
- Non DM neuropathy
- Atypical myeloma presentation
- Macroglossia and raccoon eyes are often late presentations

AL Amyloidosis Diagnosis

- Consider screening patients with plasma cell dyscrasia
  - 24-hour UPEP – high % albuminuria
  - NT pro BNP, Troponin T
  - – possible cardiac involvement
  - Echocardiogram if NT pro BNP is abnormal
    - Look for decreased % global strain

AL Amyloidosis Diagnosis

- Bone marrow biopsy
  - Stain for kappa or lambda in blood vessels, Congo red stain not always +
- Fat biopsy: usually + late in the disease, some early
- Laser microdissection and tandem mass spectrometry of amyloid affected tissue

Tests Suggested for Primary (AL) Amyloidosis: Cardiac

Cardiac manifestations may be absent, minor

- In 1/3 of patients, disease manifested by cardiac events
- Most common ECG abnormality in cardiac amyloidosis is low voltage in the limb leads (50%)

  ECHO may show LV wall thickening with evidence of diastolic dysfunction, granular, “sparkling” appearance of the myocardium, IVS thickness in more advanced disease

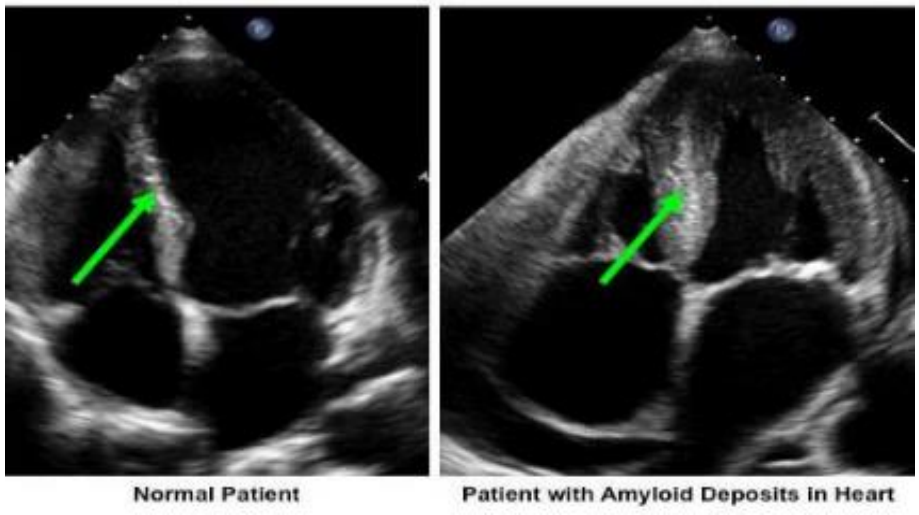
  Global strain

  Cardiac MRI - global and subendocardial late enhancement of the myocardium
- Endomyocardial biopsy definitive diagnosis
- OS 6-9 mo if heart failure > years with treatment

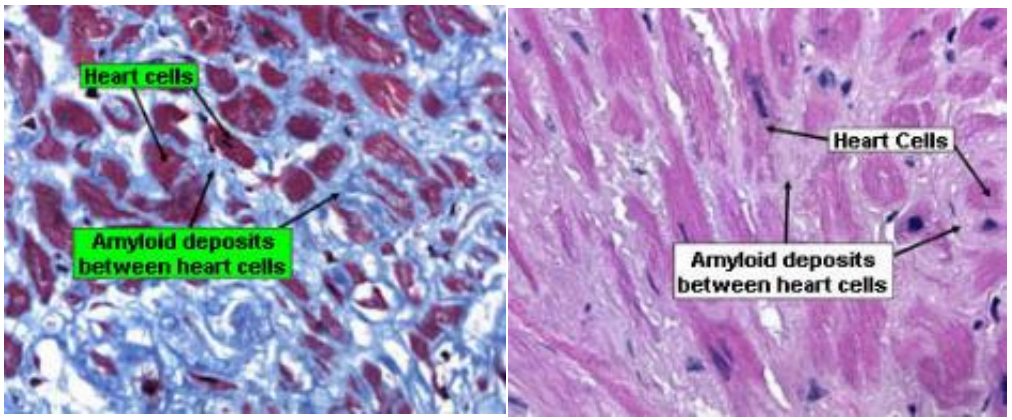
ECG = electrocardiogram; ECHO = echocardiogram; LV = left ventricular; IVS = interventricular septum.

Diagnosis Clues: Heart and Nerve

- Longitudinal strain pattern shows “apical sparing” Phelan Heart 2012
- LVH (thickening) on echocardiogram without LVH on EKG, low voltage EKG



LVH = left ventricular hypertrophy



Amyloid fibrils stain blue, light pink and encircle each heart cell

Images used with permission from Dr. Elizabeth Sagatys, Moffitt Cancer Center.

Tests Suggested for the Diagnosis and Monitoring of Primary (AL) Amyloidosis

- Some have systemic MM as well as AL amyloid
- SPEP, UPEP
- B_2M, CBC diff, CMP, ALB
- Monoclonal protein, blood and urine
- 24-hr urine for protein
- Skeletal survey to r/o lesions
- High sensitivity TNT assay – improves detection of cardiac involvement and powerful diagnostic determinant
- Serum free light chain assay – more sensitive for organ response
- Echocardiography, fat-pad aspirate “congo red stain”
- Thioflavin if endomyocardial bx

Treatment of Amyloidosis: AL and AA

Treat to prevent complications and further organ damage

No drugs FDA approved to treat AL amyloid but lots of good options for many

- Corticosteroids such as dexamethasone, melphalan, cyclophosphamide or lenalidomide or bortezomib
- Clinical trials with transplant, daratumumab, carfilzomib

Secondary AA can lead to renal failure d/t high circulating levels of Serum Amyloid A

- Treatment aim is to control primary disease, such as RA, Crohn's disease; colchicine in familial Mediterranean fever (FMF)

Venner Blood 2012 and Mikhael Blood 2012

Amyloidosis Case Presentation

- 58-year-old schoolteacher with acute on chronic renal insufficiency
- Past history of hypertension x 5 years, type 2 diabetes (DM2), and hyperlipidemia
- Presents to PCP with progressive shortness of breath and bilateral LE edema

Physical Examination

- General: in no acute distress but visibly dyspneic after ambulating to exam room from lobby
- CV: diastolic murmur but heart rate regular at 118 BPM
- Lungs: Clear
- Abdominal: No HSM, soft
- Ext: 2+ pitting edema

Labs

- CBC: WBC 9.5, Hgb 11.4, platelets 152K
- Chemistry: Albumin 2.7, creatinine 1.9, calcium 9.2
- Troponin: <0.01; NT-pro-BNP: 3600 (normal <150)
- Serum free light chains: lambda 3250 mg/L (normal 3.0-19.4)
- 24-hr urine: 86% albumin, 11.2 g/24 hr (NORMAL <.16) lambda light chain protein on immunofixation
- Bone marrow: 10% clonal lambda plasma cells; Congo red stain positive

Cardiac and Renal

- Echocardiogram shows diastolic dysfunction, thickened IVS (2.1); enlarged wall motion abnormality, global strain 9.2%
- Baseline creatinine less than 1.6 mg/dL; currently 2.2 mg/dL
- Renal insufficiency previously attributed to 5-year history of hypertension, but kidney biopsy showed amyloid deposits

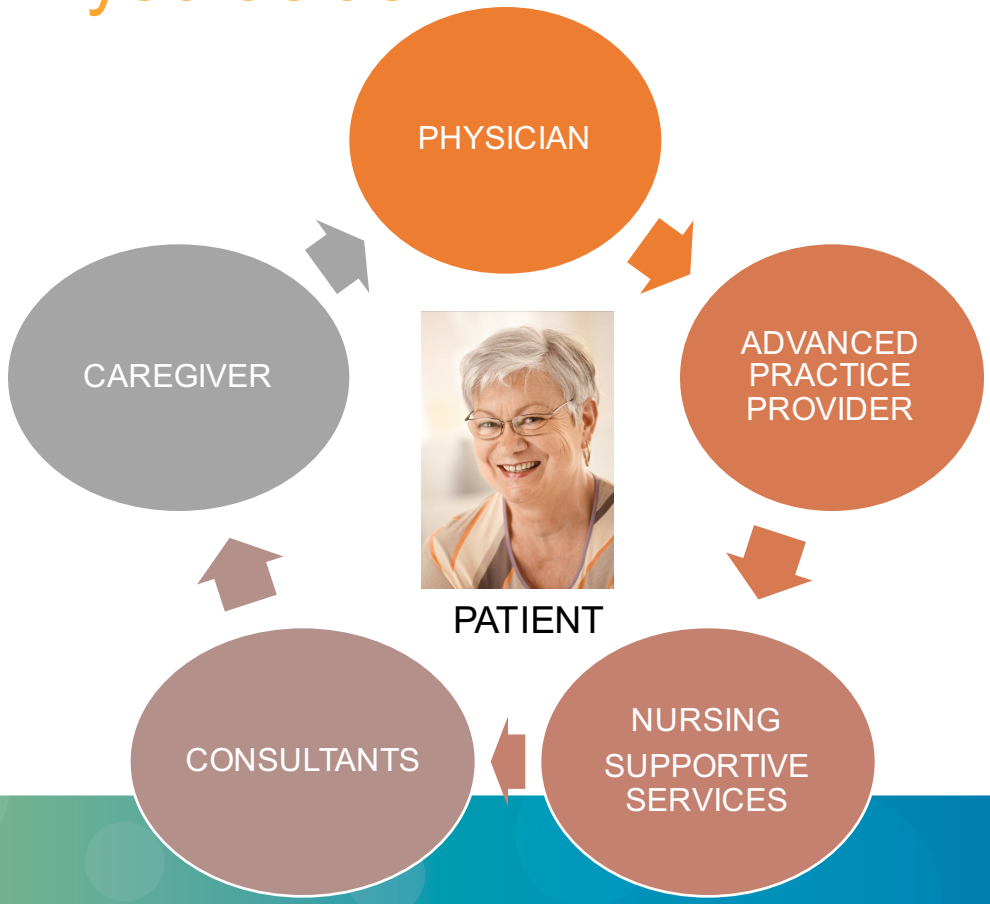
Diagnosis and Treatment

- Diagnosis: Systemic AL amyloidosis, lambda light chain type
- Cardiology referral
  - Started on torsemide and beta-blocker
- Nephrology referral
- Nurse education re: diuretic management, heart failure
- Bortezomib, cyclophosphamide and dexamethasone
  - Watch blood sugars w/ T2DM history
- Evaluation for HSCT

Exciting Updates on Amyloidosis

- Dr. Giampaolo Merlini gave a key lecture on AL amyloidosis – unprecedented!
- Abstracts 507 and 508 (ASH 2017): Daratumumab in Previously-Treated Systemic Light-Chain (AL) Amyloidosis (Sanchorawala and Roussel et al.)
- Abstract 1819 (ASH 2017) Daratumumab Is Safe and Highly Effective in AL Amyloidosis (Khouri et al)
  - DARA is generally safe, well tolerated
- Pooled analysis of "IMiD" drugs
- Ixazomib in relapsed amyloid: hematologic (52%) and organ (56%) response rates (Sanchorwala et al. *Blood* 2017)

Importance of a Collaborative Approach to Plasma Cell Dyscrasias



Conclusion

- Explosion of new therapies to treat MM and are used to treat amyloidosis
- APPs are positioned to educate patients, identify and intervene side effects
- Knowledge of the drugs and class effects allow for better education, surveillance and continued therapy
- Research is needed to inform sequencing of agents and use of drugs in amyloidosis

SMARTIE

This has been a SMARTIE presentation.

SMARTIE participants, you can now go to smartie2018.com or visit the SMARTIE booth to answer the post-session questions for this presentation.

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