Multiple Myeloma:
A Primary Care Approach

NOV 19 2020

GREG DUECK
MD MSC FRCPC, MEDICAL ONCOLOGY
CLINICAL ASSOCIATE PROFESSOR, UBC

Disclosure

- Active/Recent Clinical Trial Sponsorship
  - Abbvie, Onyx, Roche
- Advisory Board/Speaker Honoraria
  - AstraZeneca, Celgene, Jannsen, Roche, Sanofi
- The use of therapeutics outside of Health Canada approval may be discussed

Outline

- Myeloma Presentation & Initial Investigations
- How to Interpret Protein Studies
- Treatment Considerations
- Supportive Care
- What Has Changed in Myeloma Management?

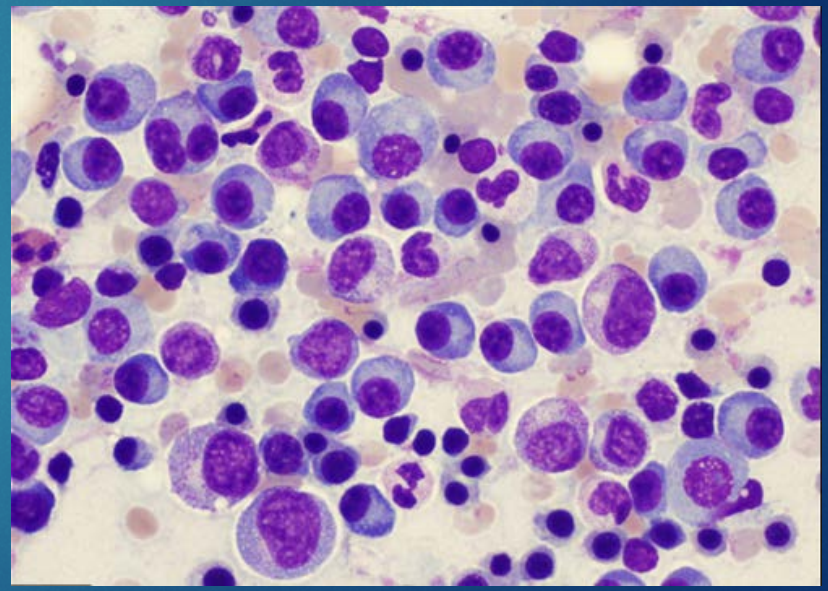


Image from Ahn & O'Donnell. 2020.
https://www.orthobullets.com/pathology/8024/multiple-myeloma

Multiple Myeloma Epidemiology

- ~ 8,000 people live with Multiple Myeloma (MM) in Canada
- 3,400 Canadians diagnosed with MM every year
  (2000 men and 1400 women diagnosed)
- 1,600 Canadians will die from MM every year

Canadian Cancer Society, 2020

Multiple Myeloma Epidemiology

- **Median age at diagnosis of 69 years**
- **15% of cases diagnosed before age 55 years**

National Cancer Institute, SEER Cancer Statistics Factsheets: Myeloma, 2016

Multiple Myeloma Presentation

Most common presenting features of MM are:

A) **Renal Dysfunction and Weight Loss**

B) **Anemia and Bone Pain**

C) **Fatigue and Hypercalcemia**

Multiple Myeloma Presentation

Most common presenting features of MM are:

A) **Renal Dysfunction and Weight Loss**

B) **Anemia and Bone Pain**

C) **Fatigue and Hypercalcemia**

Multiple Myeloma Presentation

Frequency of MM Signs/Symptoms at Diagnosis

Anemia	73%
Bone Pain	58%
↑ Creatinine	48%
Fatigue	32%
Hypercalcemia	28%
Weight Loss	24%

Kyle *et al*. Mayo Clin Proc. 2003;78:21-33.

Diagnostic Challenge

- **Symptoms of fatigue & pain are non-specific, variable**
- **Diagnostic delays relative to other cancers**

Shephard *et al*. Br J Gen Pract. 2015; e106-e113.

Diagnostic Challenge

- **Study of MM presenting to GPs found:**
  - **Positive Predictive Value for any individual presenting symptom is low, including bone pain, weight loss, nosebleeds, *etc.***
  - **With a low threshold to consider MM, standard tests including CBC, Creat, Ca, and X-ray dramatically improve predictive ability**
  - **Positive Predictive Value >10% for combinations of:**
    - **HyperCalcemia and Bone pain**
    - **Anemia and Bone pain**

Shephard *et al*. Br J Gen Pract. 2015; e106-e113.

Initial Investigations

- Patient presentation (fatigue, pain, etc)
- Consider MM on differential diagnosis
- Initial tests **CRAB:**
  - ↑ **C**alcium — Calcium
  - **R**enal dysfunction — Creatinine
  - **A**nemia — CBC diff
  - **B**one pathology — Image bone pain

- If results are abnormal/unexplained, consider serum protein electrophoresis (SPEP)

Multiple Myeloma Bone Imaging

In a case of suspected MM, the least helpful bone imaging is:

A) CT
B) Bone scan
C) MRI
D) PET

Multiple Myeloma Bone Imaging

In a case of suspected MM, the least helpful bone imaging is:

A) CT

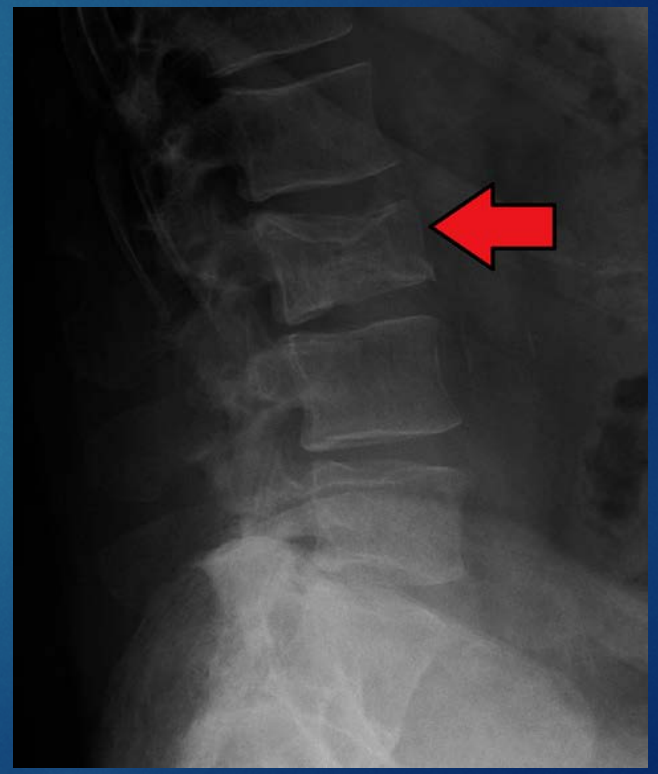
B) **Bone scan**

C) MRI

D) PET

Multiple Myeloma Bone Imaging

- Types of bone disease associated with MM:
  - Lytic lesion, Plasmacytoma, Osteopenia, Fracture incl. vertebral compression fracture
- Abnormal bone imaging ~80% at presentation
- X-ray usually first imaging modality performed
- For lytic lesion to be seen on x-ray, 30-50% of bone mass must be lost



Zamagni et al. Blood 2019; 133 (7): 644–651.
Hillengass et al. Lancet Oncol 2019; 20: e302–12.
Image from Heilman. 2016. https://en.wikipedia.org/wiki/File:PathFracMMPlainMark.png

Multiple Myeloma Bone Imaging

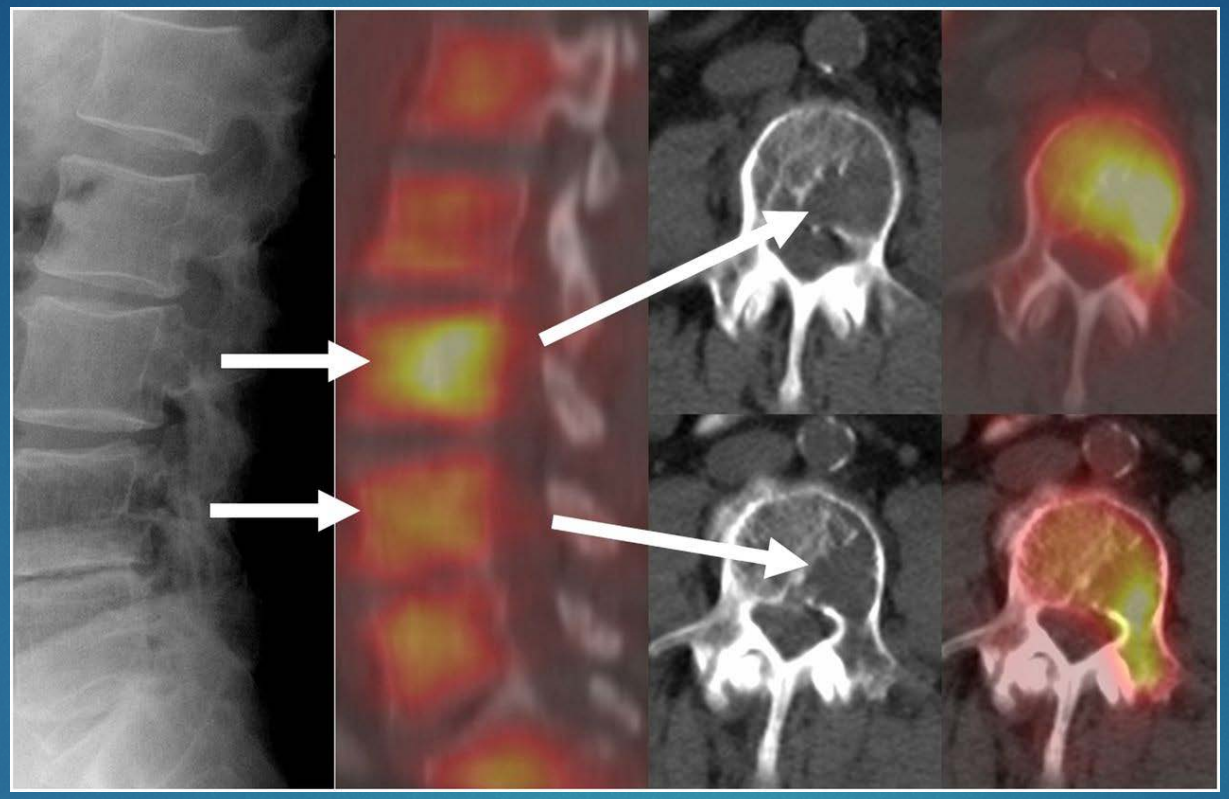
- Conventional (x-ray) skeletal survey not recommended to determine the presence or absence of bone disease in MM

- Nuclear medicine bone scan misses lytic bone disease of MM
  - Bone scans identify osteoblast activity
  - Myeloma inhibits osteoblasts, and activates osteoclasts
  - Bone scan misses ~ 30% of MM

- Most sensitive imaging studies:
  - CT skeletal survey protocol (whole body, low radiation dose, non-contrast)
  - MRI
  - PET

Zamagni et al. Blood 2019; 133 (7): 644–651.
Hillengass et al. Lancet Oncol 2019; 20: e302–12.

X-ray misses osteolytic lesions seen on CT and PET



a) b) c) d)

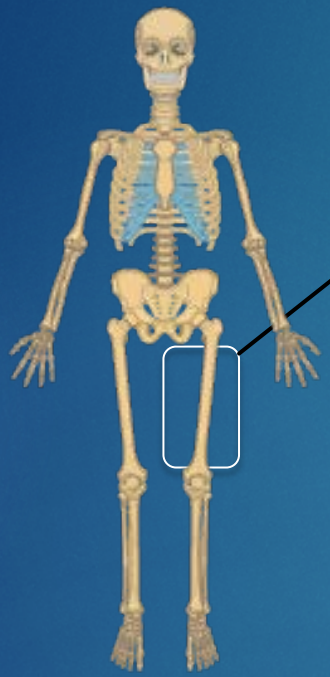
a) X-ray lumbar spine L3 and L4; b)PET-CT; c)Axial CT; d) PET-CT

Epstein & Walker. Clin Adv in Hem & Onc Vol 4, Iss 4. 2006

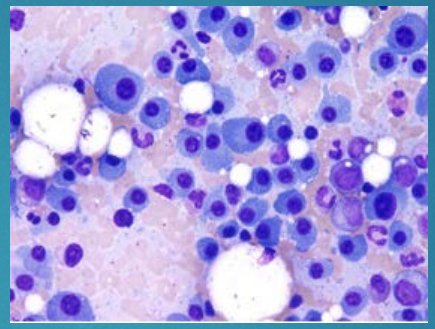
- If MM remains a possible diagnosis
  - Bone Marrow Biopsy required for diagnosis
- Consult Specialist

MM: A Plasma Cell Malignancy

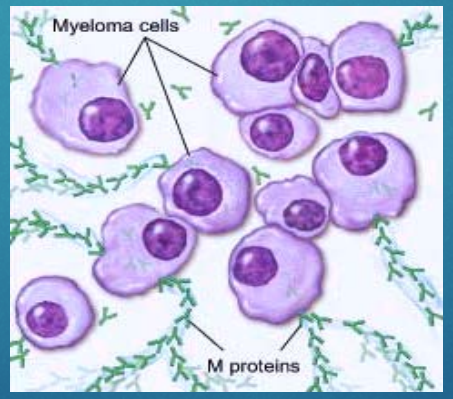
Marrow-containing bones: arms, legs, pelvis, ribs, vertebrae, skull



Interferes with the production of all types of blood cells

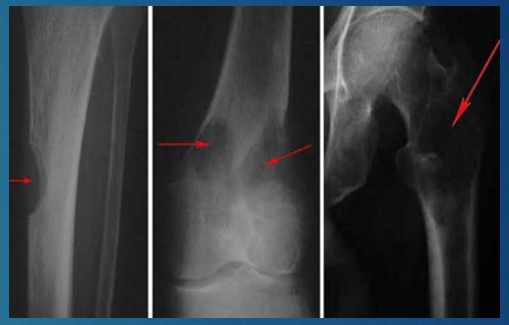


Secretion of monoclonal immunoglobulin proteins

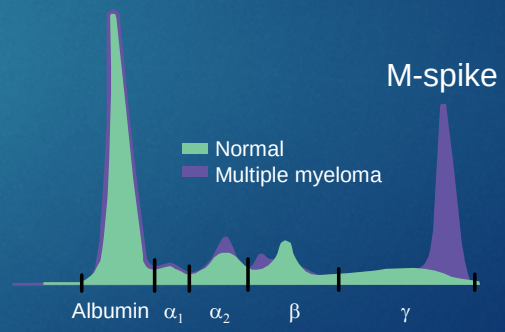


Bone destruction (lytic lesions)

- Hypercalcemia
- Fractures



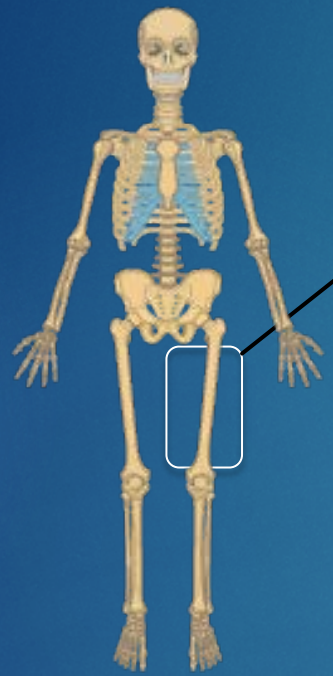
Excess M protein and calcium in the blood-kidney dysfunction



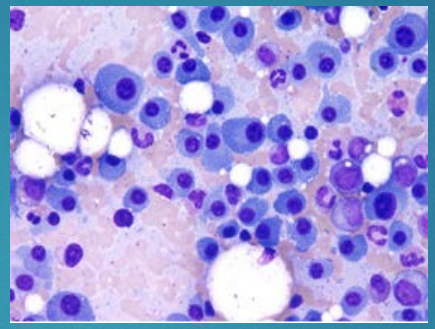
Adapted from: Durie, B. G. M. (2011) Concise Review of the Disease and Treatment Options: Multiple Myeloma. International Myeloma Foundation. Multiple Myeloma Disease Overview (2011/2012 ed.) Multiple Myeloma Research Foundation.

MM: A Plasma Cell Malignancy

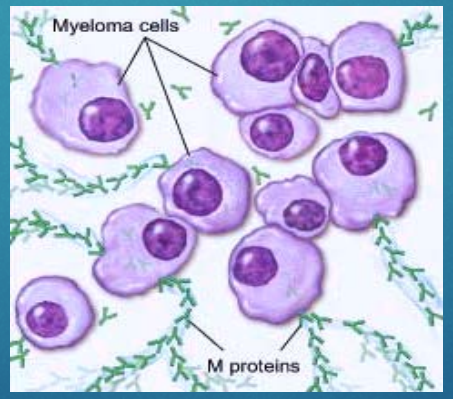
Marrow-containing bones: arms, legs, pelvis, ribs, vertebrae, skull



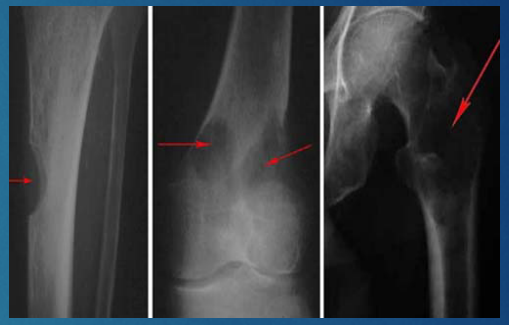
Interferes with the production of all types of blood cells



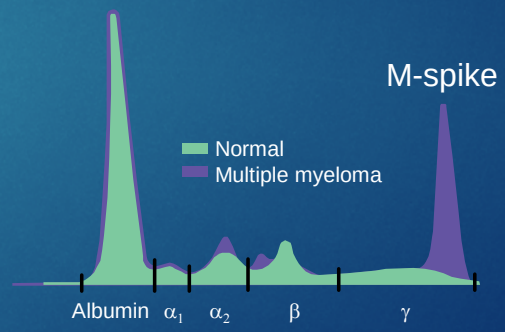
Secretion of monoclonal immunoglobulin proteins



Bone destruction (lytic lesions)
- Hypercalcemia
- Fractures



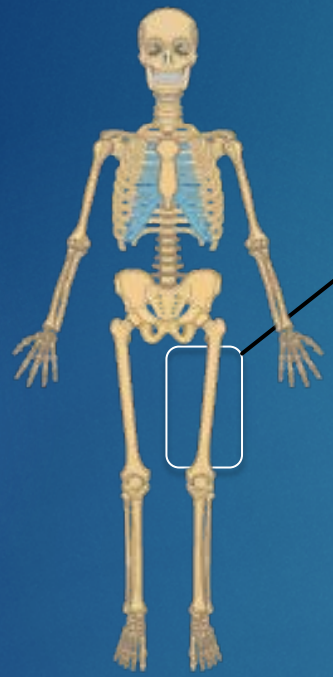
Excess M protein and calcium in the blood-kidney dysfunction



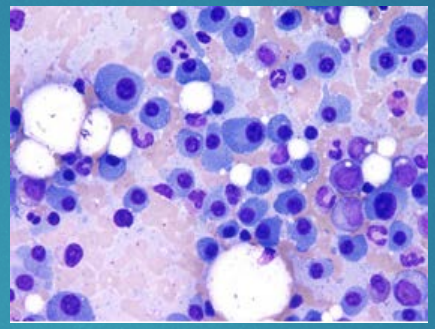
Adapted from: Durie, B. G. M. (2011) Concise Review of the Disease and Treatment Options: Multiple Myeloma. International Myeloma Foundation. Multiple Myeloma Disease Overview (2011/2012 ed.) Multiple Myeloma Research Foundation.

MM: A Plasma Cell Malignancy

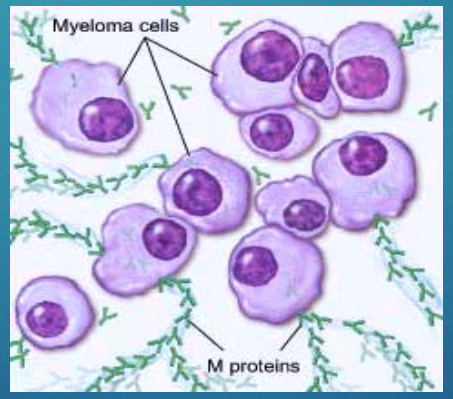
Marrow-containing bones: arms, legs, pelvis, ribs, vertebrae, skull



Interferes with the production of all types of blood cells

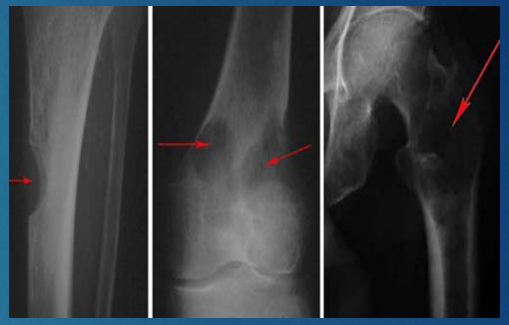


Secretion of monoclonal immunoglobulin proteins

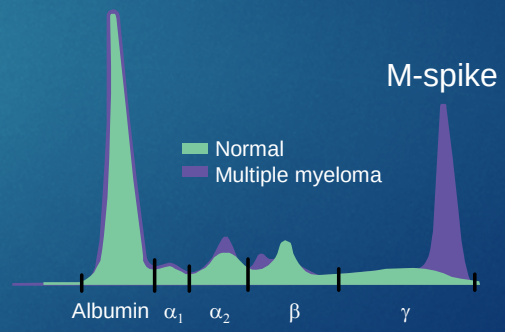


Bone destruction (lytic lesions)

- Hypercalcemia
- Fractures



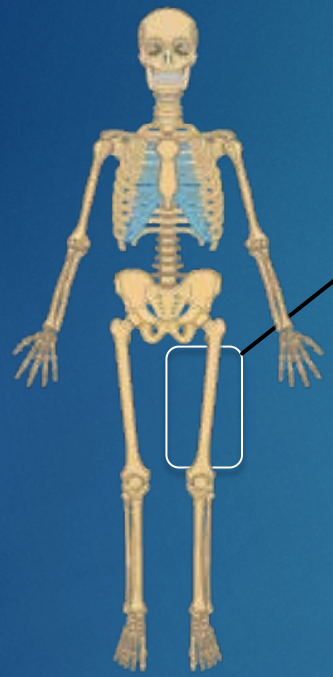
Excess M protein and calcium in the blood-kidney dysfunction



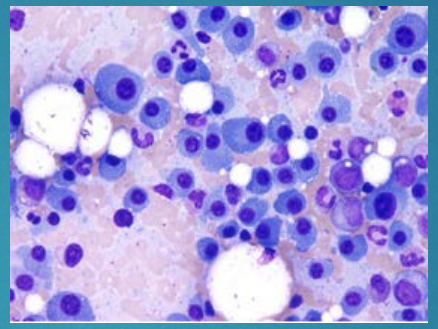
Adapted from: Durie, B. G. M. (2011) Concise Review of the Disease and Treatment Options: Multiple Myeloma. International Myeloma Foundation. Multiple Myeloma Disease Overview (2011/2012 ed.) Multiple Myeloma Research Foundation.

MM: A Plasma Cell Malignancy

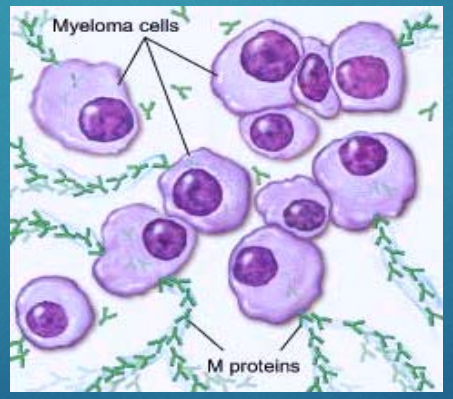
Marrow-containing bones: arms, legs, pelvis, ribs, vertebrae, skull



Interferes with the production of all types of blood cells

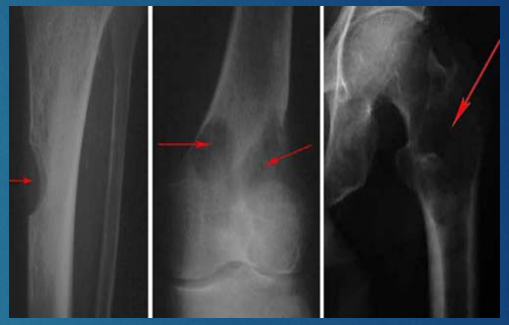


Secretion of monoclonal immunoglobulin proteins

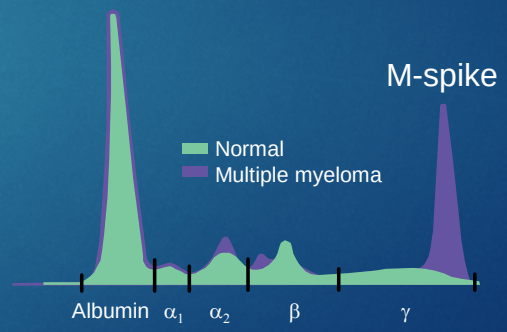


Bone destruction (lytic lesions)

- Hypercalcemia
- Fractures



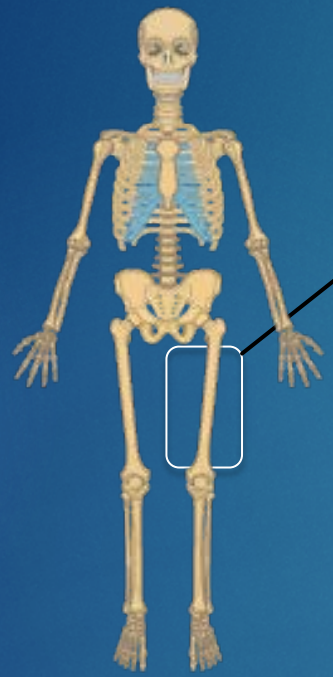
Excess M protein and calcium in the blood-kidney dysfunction



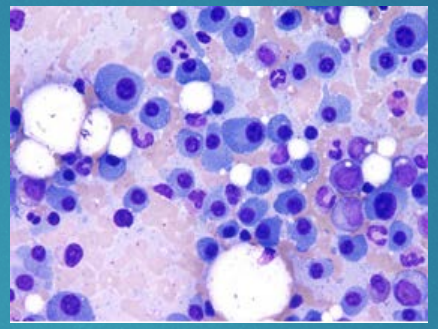
Adapted from: Durie, B. G. M. (2011) Concise Review of the Disease and Treatment Options: Multiple Myeloma. International Myeloma Foundation. Multiple Myeloma Disease Overview (2011/2012 ed.) Multiple Myeloma Research Foundation.

MM: A Plasma Cell Malignancy

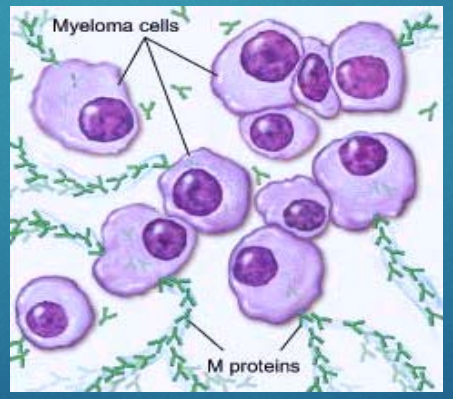
Marrow-containing bones: arms, legs, pelvis, ribs, vertebrae, skull



Interferes with the production of all types of blood cells

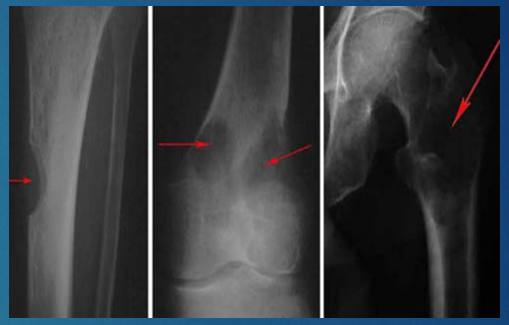


Secretion of monoclonal immunoglobulin proteins

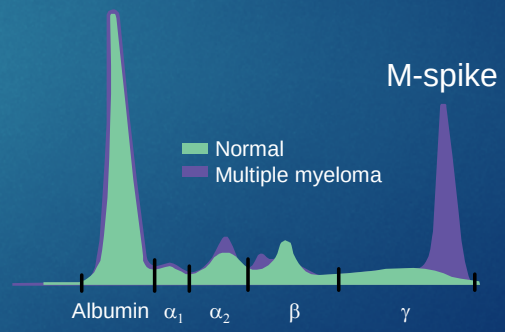


Bone destruction (lytic lesions)

- Hypercalcemia
- Fractures

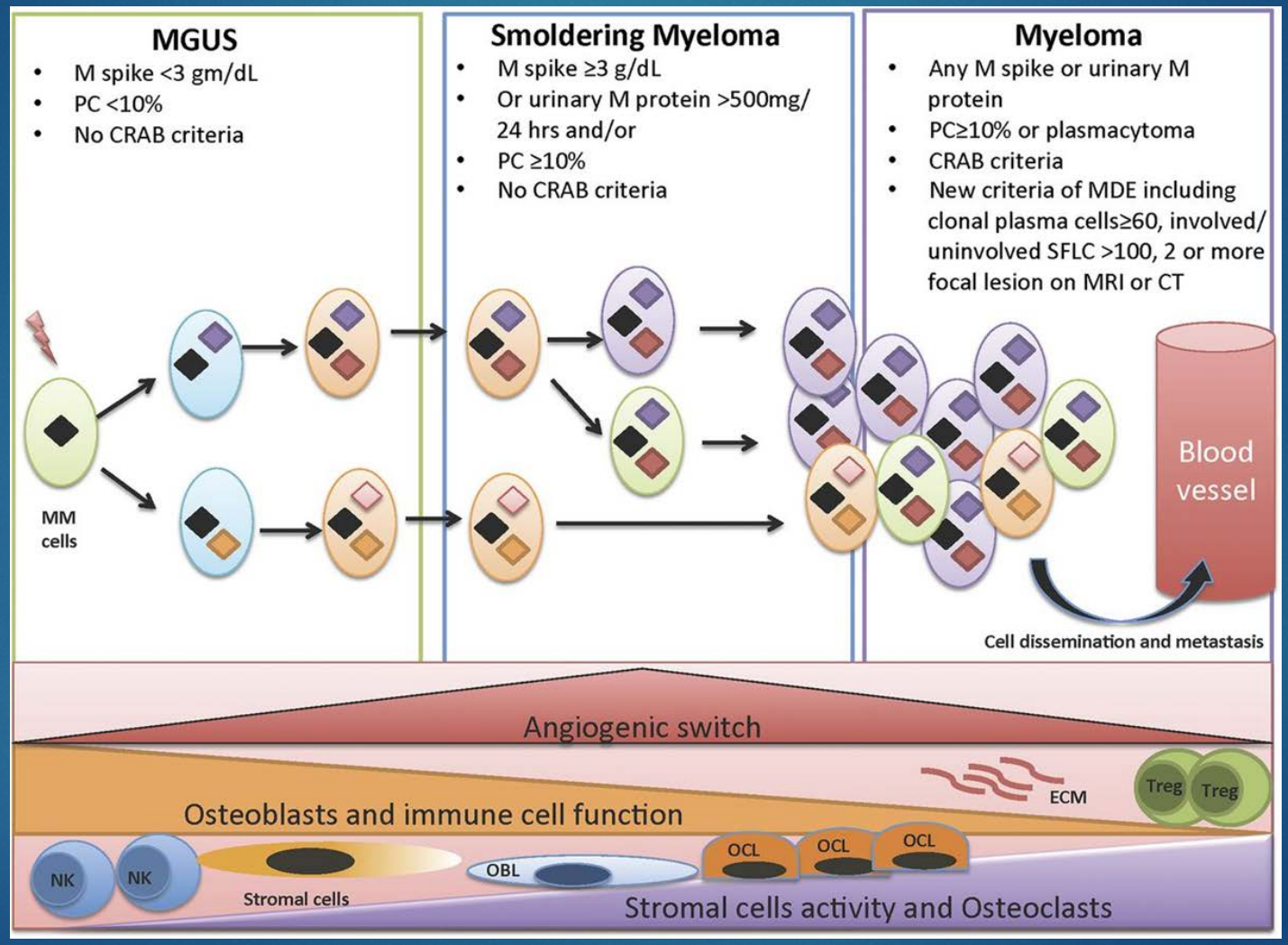


Excess M protein and calcium in the blood-kidney dysfunction



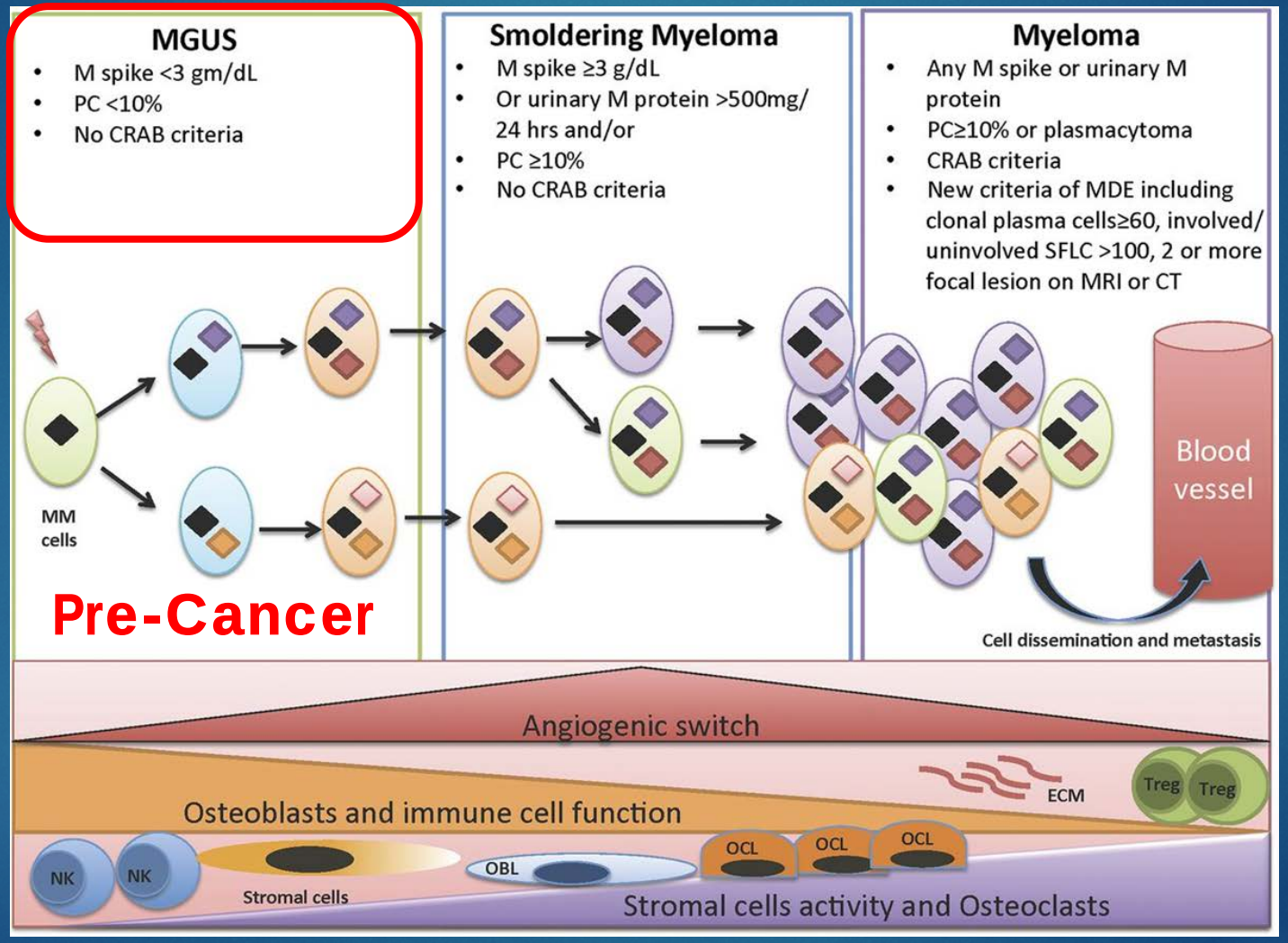
Adapted from: Durie, B. G. M. (2011) Concise Review of the Disease and Treatment Options: Multiple Myeloma. International Myeloma Foundation. Multiple Myeloma Disease Overview (2011/2012 ed.) Multiple Myeloma Research Foundation.

Clonal evolution and a spectrum of disease



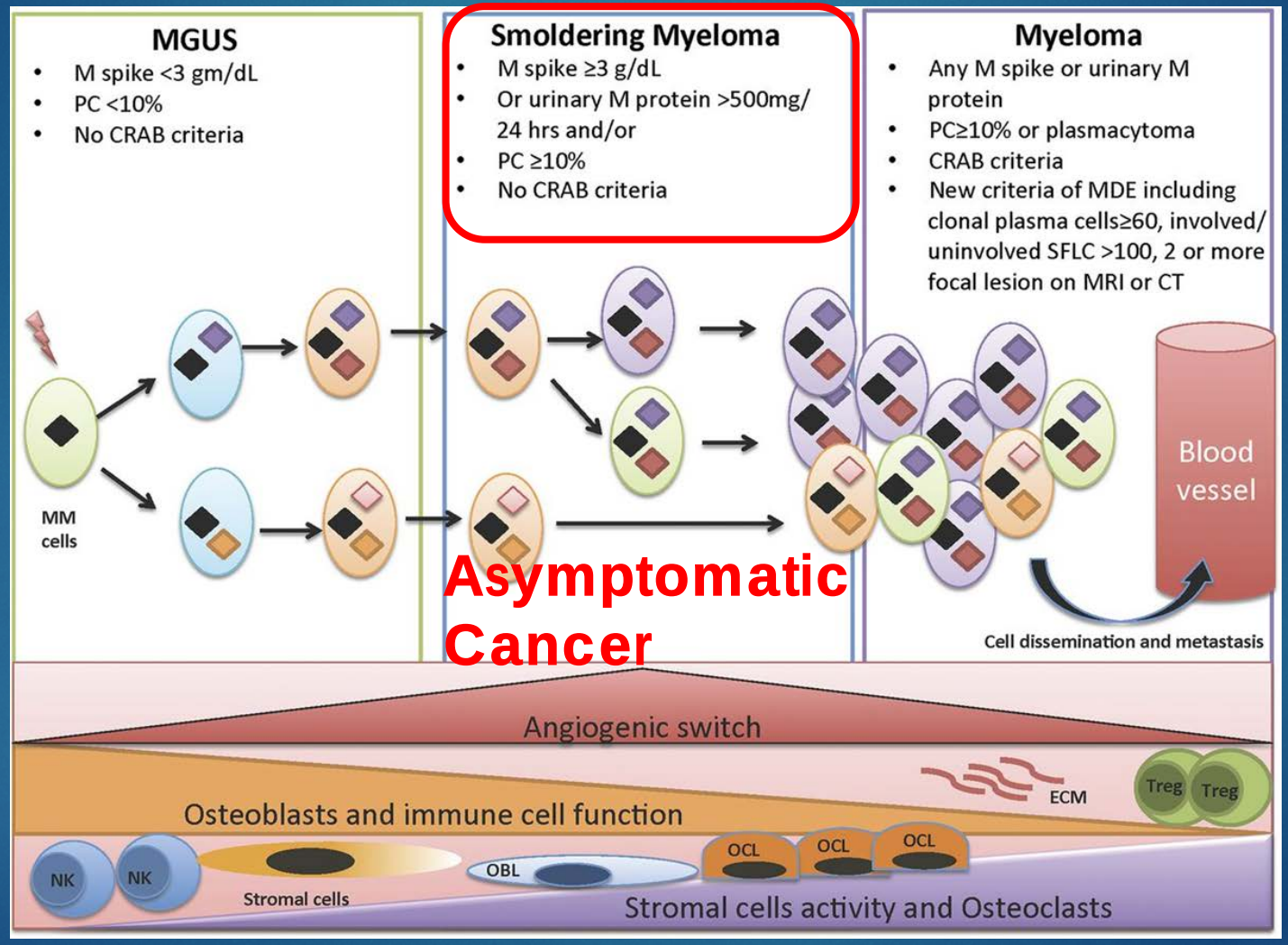
Irene M. Ghobrial, and Ola Landgren Blood 2014;124:3380-3388

Clonal evolution and a spectrum of disease



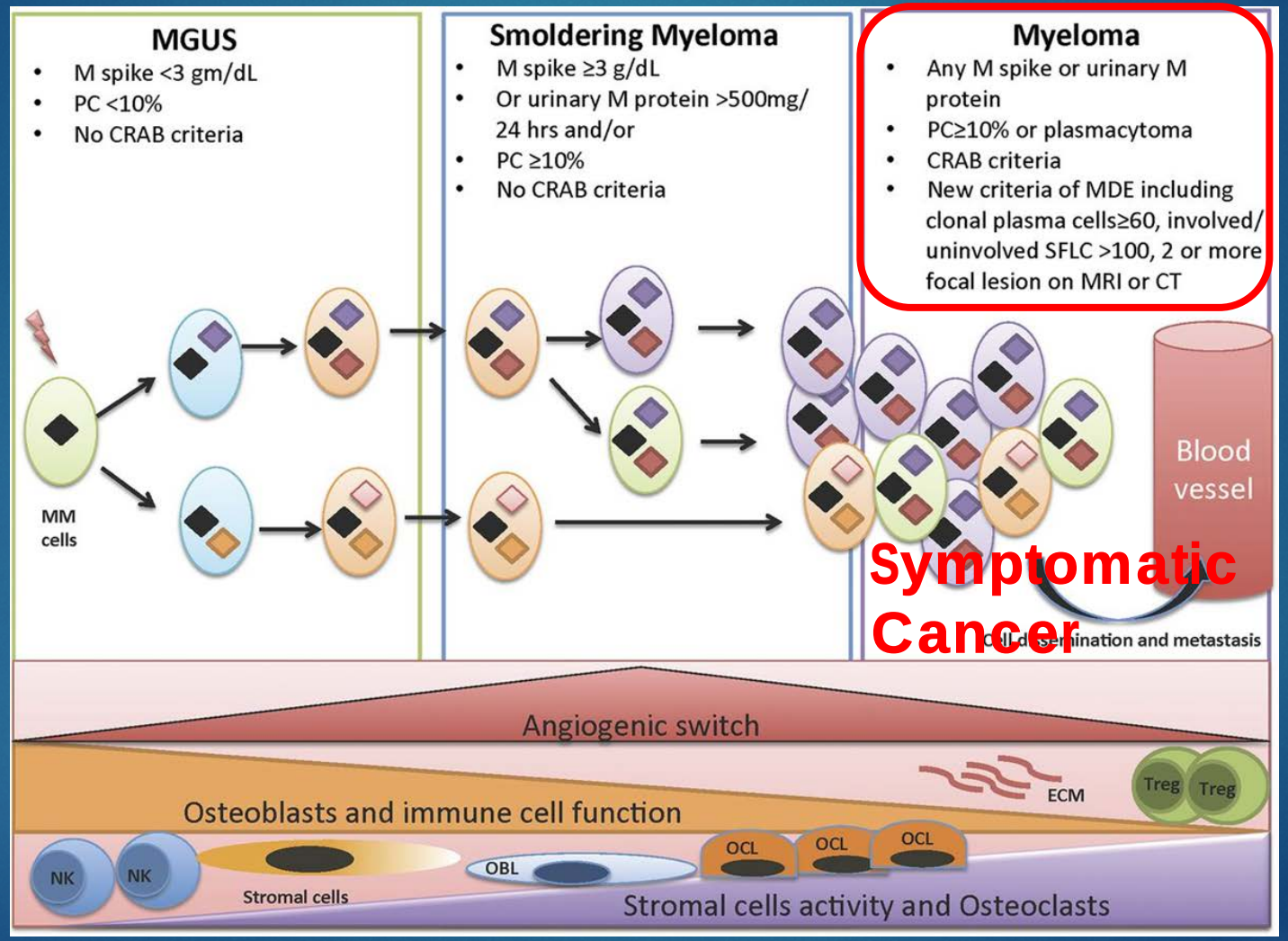
Irene M. Ghobrial, and Ola Landgren Blood 2014;124:3380-3388

Clonal evolution and a spectrum of disease



Irene M. Ghobrial, and Ola Landgren Blood 2014;124:3380-3388

Clonal evolution and a spectrum of disease



Irene M. Ghobrial, and Ola Landgren Blood 2014;124:3380-3388

Mono-Clonal Protein Testing

Mono-Clonal Protein Testing

- **Monoclonal Protein also called:**
  - **M-protein**
  - **Para-protein**
  - **M-spike**
  - **Bence Jones Proteins (monoclonal light chains in urine)**

Dr Henry Bence Jones
1813-1873

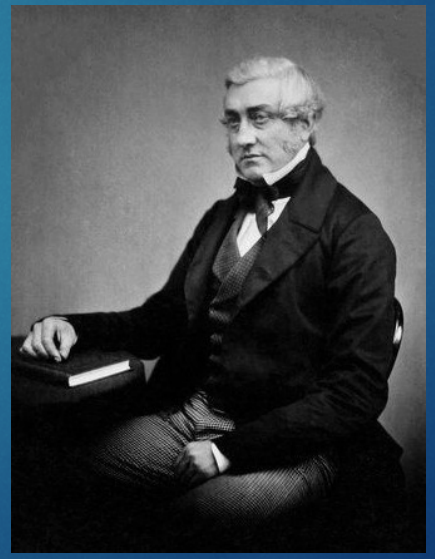


Image public domain

Mono-Clonal Protein Testing

- In MM, M-protein is assessed to:
  - Confirm diagnosis
  - Monitor disease
  - Assess response to therapy

Normal Plasma Cell Function:

- Part of Humoral Immunity
- Variety of plasma cells each produce one type of immunoglobulin/antibody (Ig)
- Each mature plasma cell produces thousands of identical Ig every second

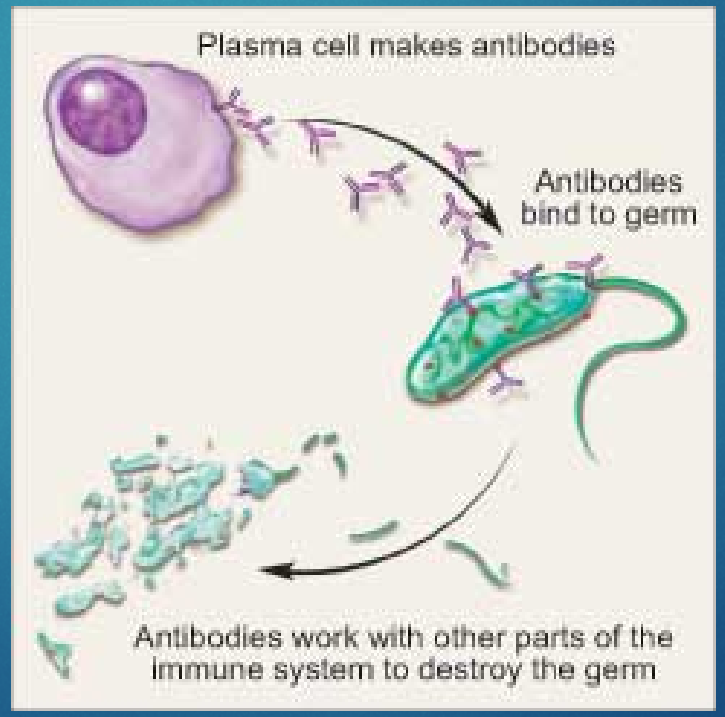


Image from National Cancer Institute, SEER Cancer Statistics Factsheets: Myeloma, 2016

Myeloma Plasma Cell:

- Malignant plasma cells from a *single clone* produce one type of Ig
- *i.e.*, billions of cancer cells each secreting thousands of identical Ig every second

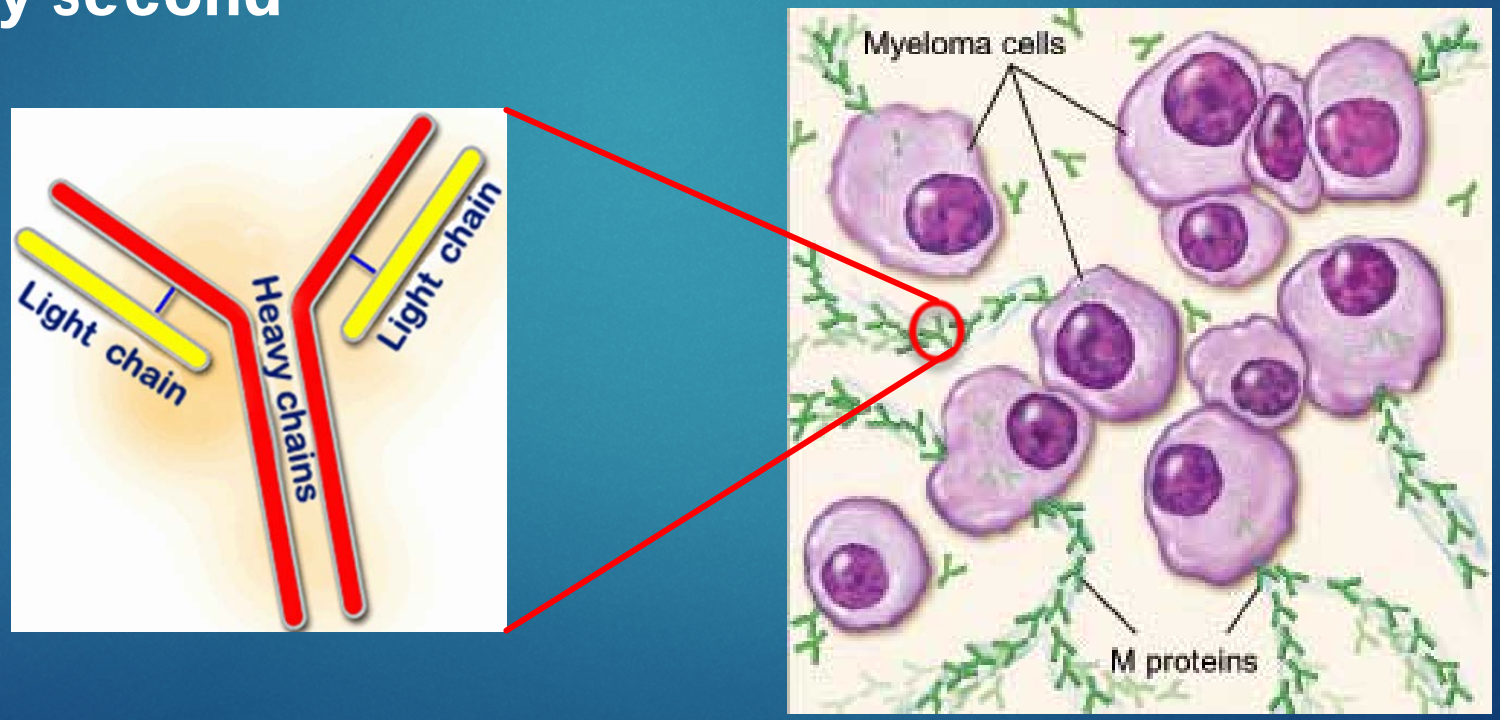
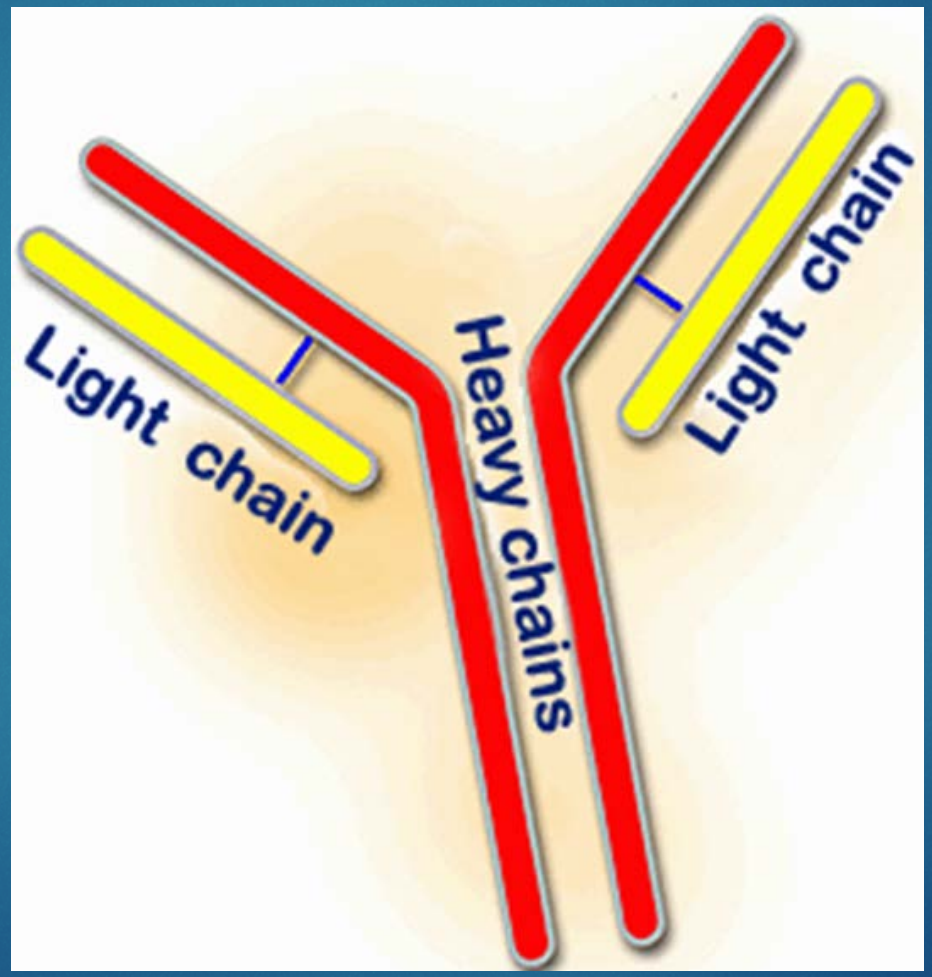


Image from National Cancer Institute, SEER Cancer Statistics Factsheets: Myeloma, 2016

Mono-Clonal Protein



Monoclonal Gammopathies

Which statement about monoclonal gammopathies is true:

A) **Multiple Myeloma is the most likely diagnosis when a monoclonal protein is found**

B) **Lymphomas do not produce a monoclonal protein**

C) **MGUS is found in about 3% of adults >50 years, and 8% of adults > 80 years**

D) **None of the above**

Monoclonal Gammopathies

Which statement about monoclonal gammopathies is true:

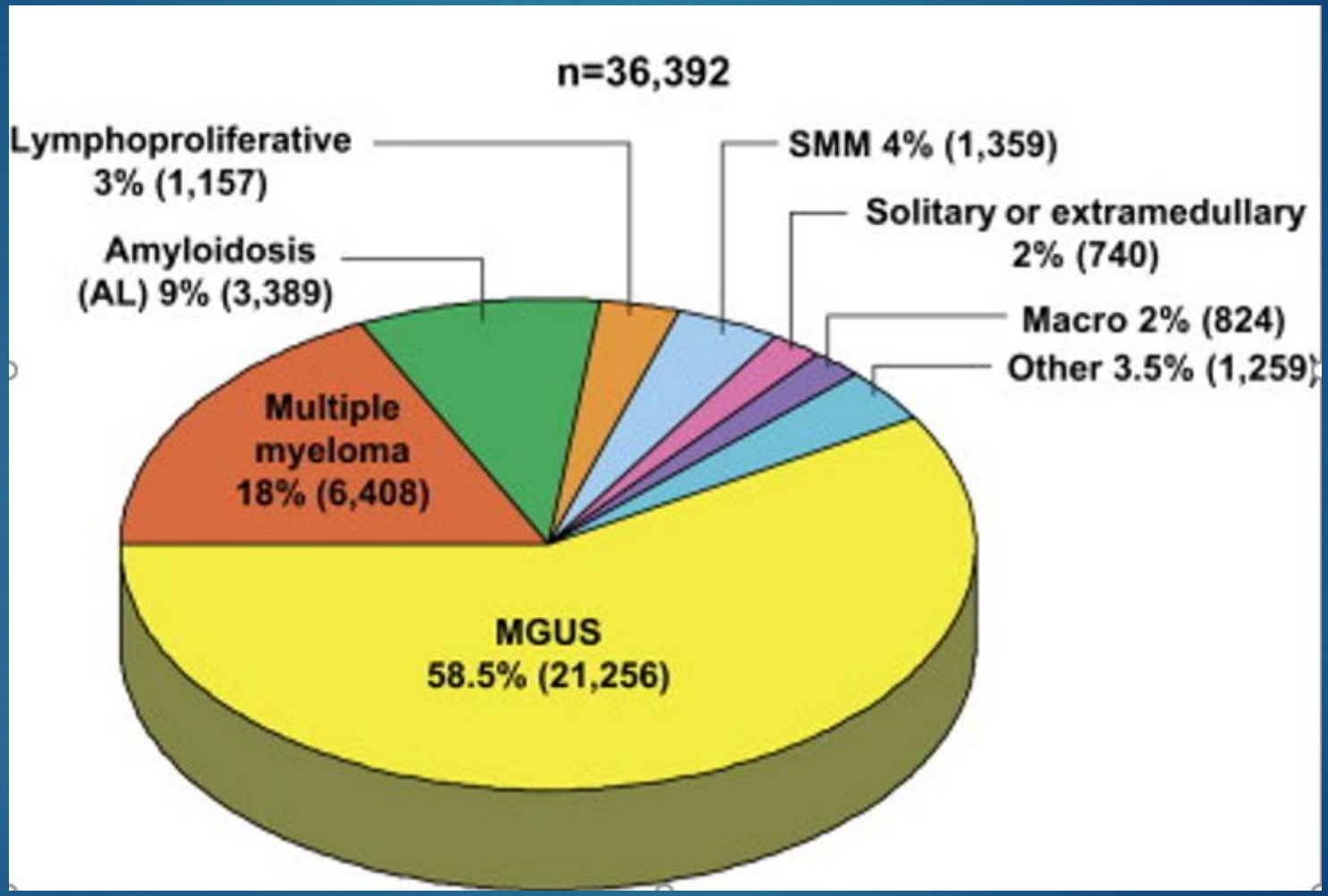
A) Multiple Myeloma is the most likely diagnosis when a monoclonal protein is found

B) Lymphomas do not produce a monoclonal protein

C) MGUS is found in about 3% of adults >50 years, and 8% of adults > 80 years

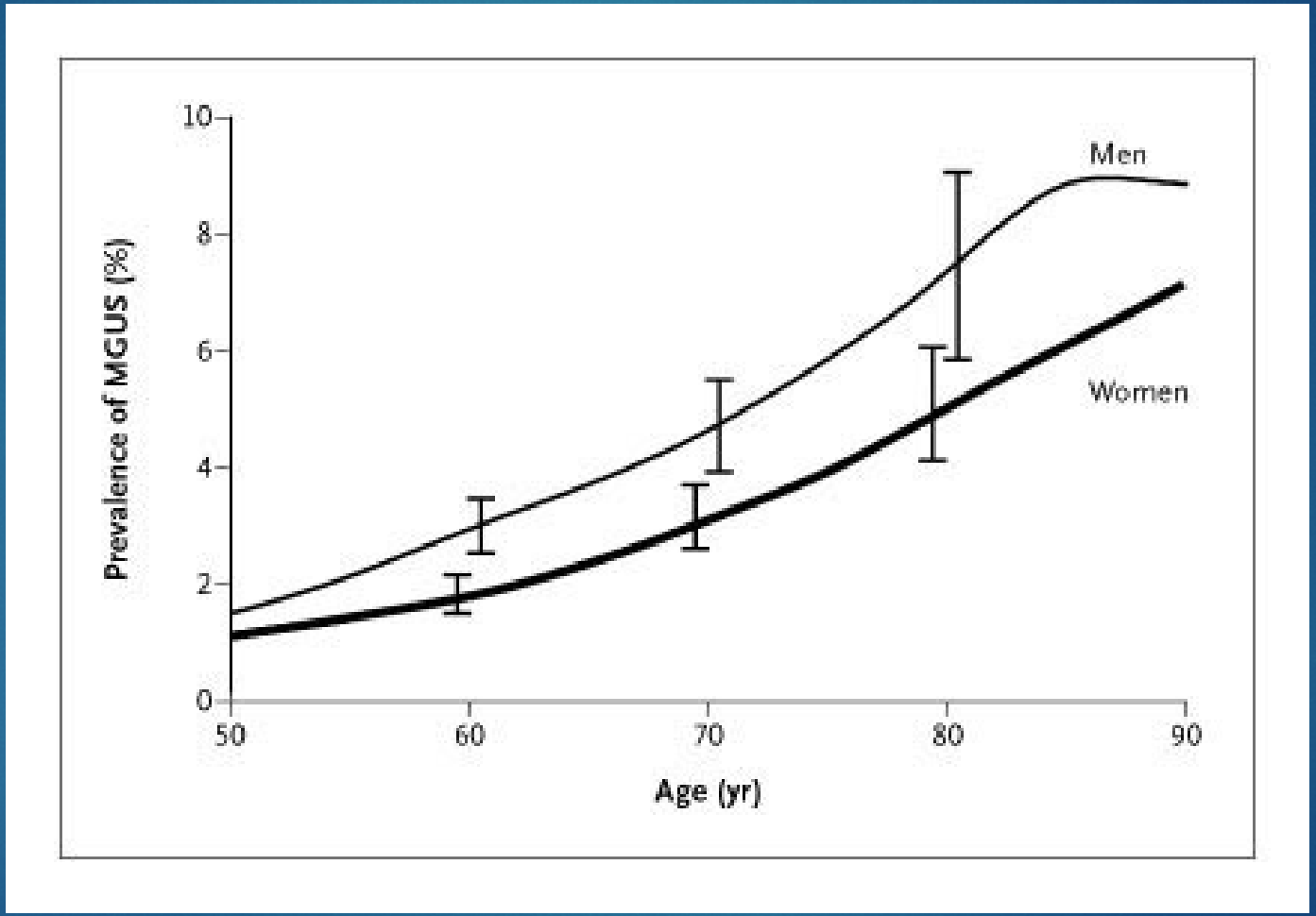
D) None of the above

Monoclonal Gammopathies



Kyle RA, Rajkumar SV. Monoclonal gammopathy of undetermined significance. Br J Haematol 2006;134:573-89

Prevalence of Monoclonal Gammopathy by Age



Kyle et al. N Engl J Med 2006; 354:1362-1369

Mono-Clonal Protein Testing

- **Serum Protein Electrophoresis**

Protein Electrophoresis Panel				
Protein	**83**	**H**	63-82	g/L
Albumin; Electrophoresis	**32**	**L**	35-54	g/L
Alpha 1 Globulin	3.4		2.0-4.0	g/L
Alpha 2 Globulin	6.1		4.0-10.0	g/L
Beta 1 Globulin	3.5		3.0-6.0	g/L
Beta 2 Globulin	3.2		2.0-5.0	g/L
Gamma Globulin	**34.9**	**H**	7.0-15.0	g/L
Protein Monoclonal Band 1	32.1			g/L
Pathologist Comment; Electrophoresis				

There is a large abnormal gamma peak; an immunofixation study will be performed (result to follow under the immunology heading of the Meditech EMR).

- **M-protein is 32.1 g/L**
- **Immunofixation pending, so we don't know the type of M-protein**

Mono-Clonal Protein Testing

- **Serum Protein Electrophoresis**

Protein Electrophoresis Panel

Protein	**83**	**H**	63-82	g/L
Albumin; Electrophoresis	**32**	**L**	35-54	g/L
Alpha 1 Globulin	3.4		2.0-4.0	g/L
Alpha 2 Globulin	6.1		4.0-10.0	g/L
Beta 1 Globulin	3.5		3.0-6.0	g/L
Beta 2 Globulin	3.2		2.0-5.0	g/L
Gamma Globulin	**34.9**	**H**	7.0-15.0	g/L
Protein Monoclonal Band 1	32.1			g/L

Pathologist Comment; Electrophoresis

There is a large abnormal gamma peak; an immunofixation study will be performed (result to follow under the immunology heading of the Meditech EMR).

- **M-protein is 32.1 g/L**
- **Immunofixation pending, so we don't know the type of M-protein**

Mono-Clonal Protein Testing

- **Serum Protein Electrophoresis**

Protein Electrophoresis Panel				
Protein	**83**	**H**	63-82	g/L
Albumin; Electrophoresis	**32**	**L**	35-54	g/L
Alpha 1 Globulin	3.4		2.0-4.0	g/L
Alpha 2 Globulin	6.1		4.0-10.0	g/L
Beta 1 Globulin	3.5		3.0-6.0	g/L
Beta 2 Globulin	3.2		2.0-5.0	g/L
Gamma Globulin	**34.9**	**H**	7.0-15.0	g/L
Protein Monoclonal Band 1	32.1			g/L

Pathologist Comment; Electrophoresis

There is a large abnormal gamma peak; an immunofixation study will be performed (result to follow under the immunology heading of the Meditech EMR).

Immunofixation; Serum

IgG kappa monoclonal protein identified.

Immunofixation confirms monoclonal IgG kappa

Mono-Clonal Protein Testing

- **Serum Free Light Chain Assay**

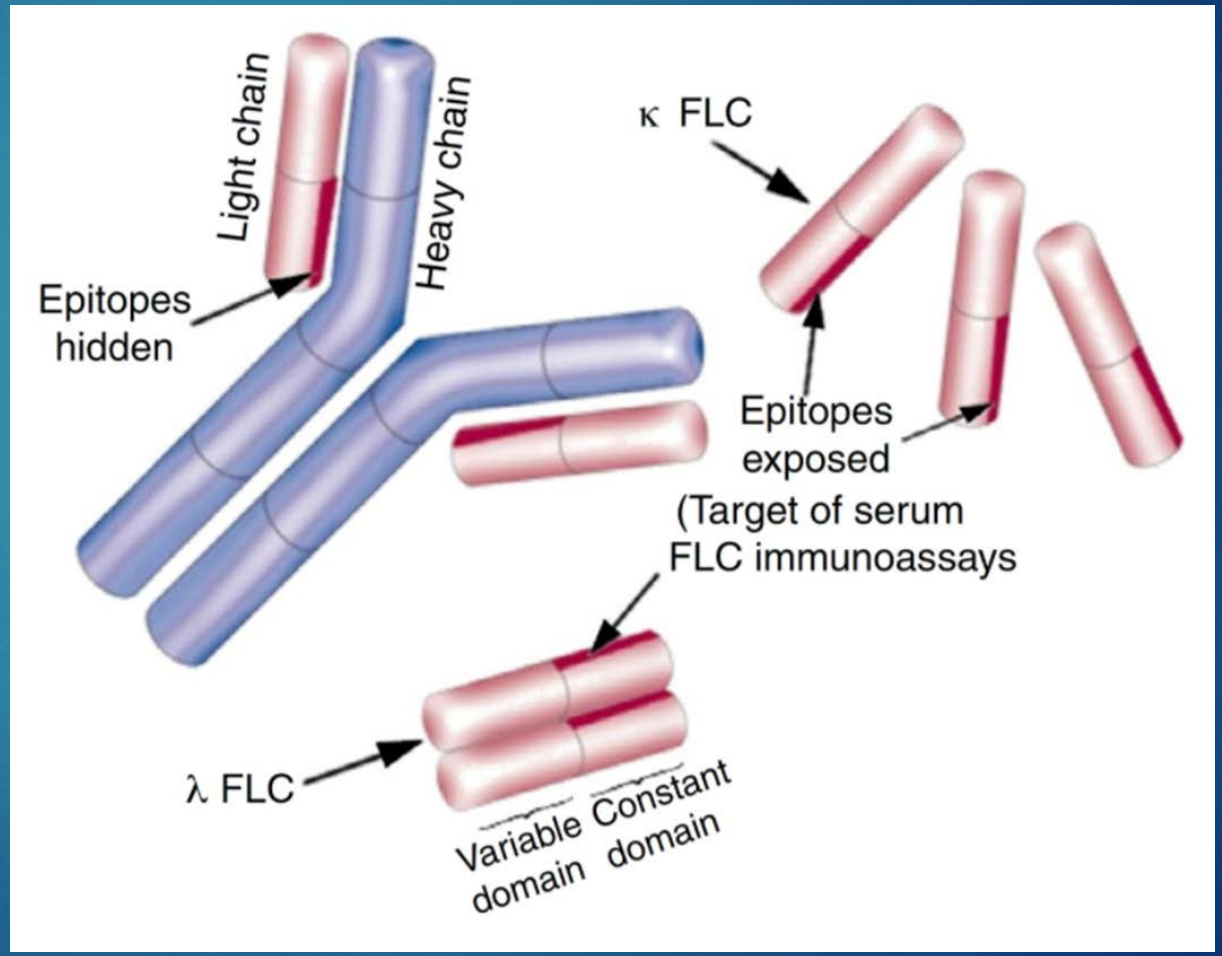


Image source: https://www.bindingsite.com/en

Abnormal serum free light chains before MM therapy

Immunoglobulin Light Chains Free Panel				
Light Chains Kappa Free	**6190.0**	**H**	3.3-19.4	mg/L
Light Chains Lambda Free	**4.9**	**L**	5.7-26.3	mg/L
Light Chains Kappa Free/Light Chains Lambda Free	**1263.27**	**H**	0.26-1.65	

Abnormal serum free light chains before MM therapy

Immunoglobulin Light Chains Free Panel				
Light Chains Kappa Free	**6190.0**	**H**	3.3-19.4	mg/L
Light Chains Lambda Free	**4.9**	**L**	5.7-26.3	mg/L
Light Chains Kappa Free/Light Chains Lambda Free	**1263.27**	**H**	0.26-1.65	

Abnormal serum free light chains before MM therapy

Immunoglobulin Light Chains Free Panel				
Light Chains Kappa Free	**6190.0**	**H**	3.3-19.4	mg/L
Light Chains Lambda Free	**4.9**	**L**	5.7-26.3	mg/L
Light Chains Kappa Free/Light Chains Lambda Free	**1263.27**	**H**	0.26-1.65	

Serum free light chains type is kappa

Serum kappa free light chains quantity is 6190 mg/L

Immunoglobulin Light Chains Free Panel				
Light Chains Kappa Free	**6190.0**	**H**	3.3-19.4	mg/L
Light Chains Lambda Free	**4.9**	**L**	5.7-26.3	mg/L
Light Chains Kappa Free/Light Chains Lambda Free	**1263.27**	**H**	0.26-1.65	

	Test Result	Result Flags	Reference Range	Result Units
Routine Chemistry				
Immunoglobulin Light Chains Free Panel				
Light Chains Kappa Free	14.9		3.3-19.4	mg/L
Light Chains Lambda Free	14.9		5.7-26.3	mg/L
Light Chains Kappa Free/Light Chains Lambda Free	1.00		0.26-1.65	

Normalized serum free light chains after MM therapy

Immunoglobulin Light Chains Free Panel				
Light Chains Kappa Free	**6190.0**	**H**	3.3-19.4	mg/L
Light Chains Lambda Free	**4.9**	**L**	5.7-26.3	mg/L
Light Chains Kappa Free/Light Chains Lambda Free	**1263.27**	**H**	0.26-1.65	

	Test Result	Result Flags	Reference Range	Result Units
Routine Chemistry				
Immunoglobulin Light Chains Free Panel				
Light Chains Kappa Free	14.9		3.3-19.4	mg/L
Light Chains Lambda Free	14.9		5.7-26.3	mg/L
Light Chains Kappa Free/Light Chains Lambda Free	1.00		0.26-1.65	

Normalized serum free light chains after MM therapy

Immunoglobulin Light Chains Free Panel				
Light Chains Kappa Free	**6190.0**	**H**	3.3-19.4	mg/L
Light Chains Lambda Free	**4.9**	**L**	5.7-26.3	mg/L
Light Chains Kappa Free/Light Chains Lambda Free	**1263.27**	**H**	0.26-1.65	

	Test Result	Result Flags	Reference Range	Result Units
Routine Chemistry				
Immunoglobulin Light Chains Free Panel				
Light Chains Kappa Free	14.9		3.3-19.4	mg/L
Light Chains Lambda Free	14.9		5.7-26.3	mg/L
Light Chains Kappa Free/Light Chains Lambda Free	1.00		0.26-1.65	

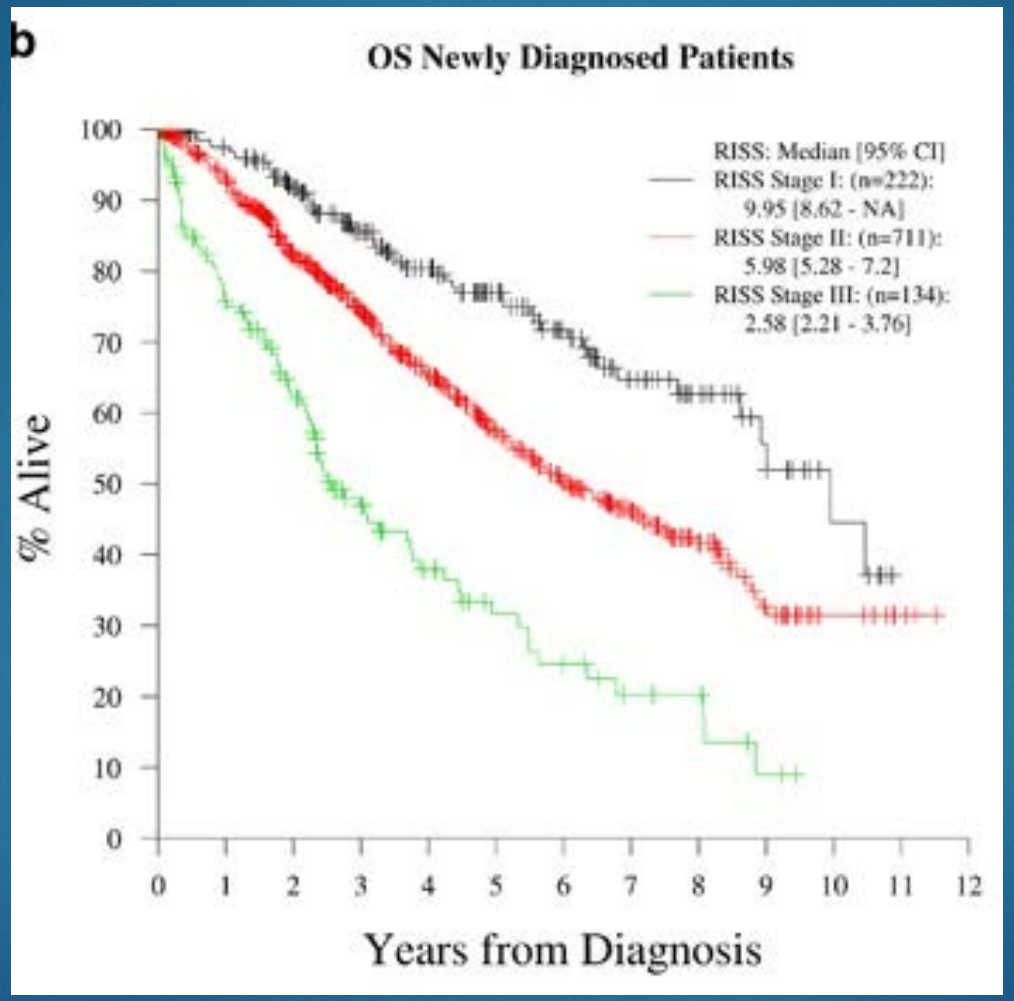
Normalized serum free light chains after MM therapy

MM Survival

- MM remains incurable with current treatments
- Survival is variable, based on:
  - Cytogenetics*
  - LDH*
  - Albumin*
  - Beta-2 microglobulin*
  - Age
  - Gene expression profiling

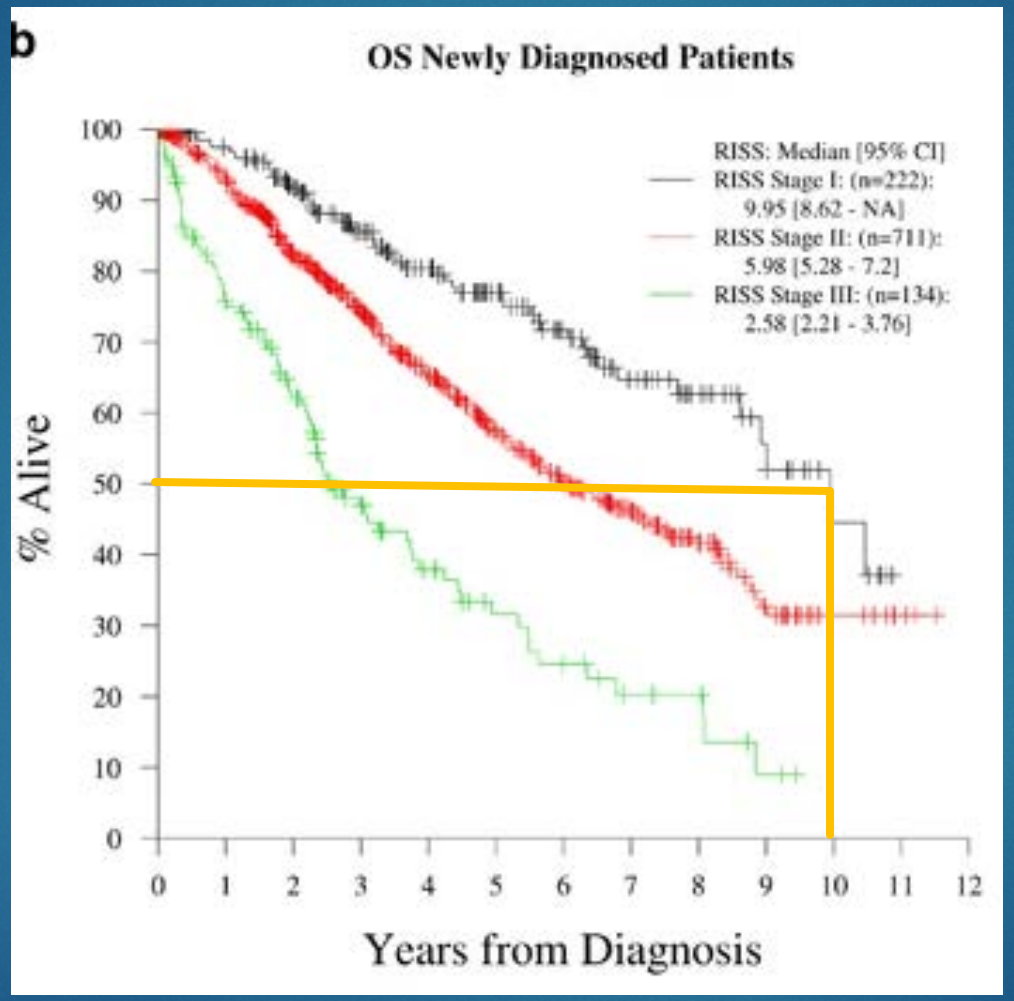
*Revised International Staging System - Palumbo *et al*. J Clinic Oncol. 2015; 33(26):2863-2869

Survival of Newly Diagnosed MM Patients



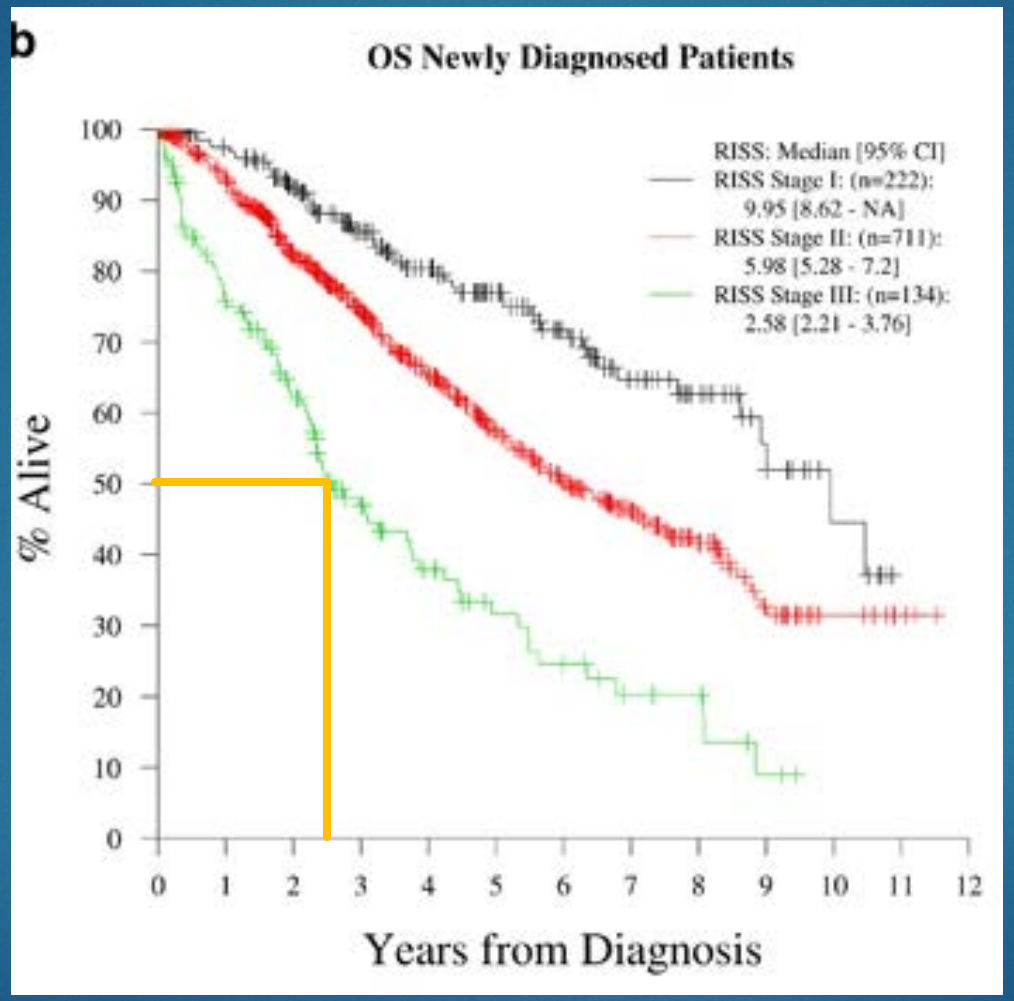
Tandon, et al. Clinical utility of the Revised International Staging System in unselected patients with newly diagnosed and relapsed multiple myeloma. Blood Cancer Journal 7, e528 (2017).

Survival of Newly Diagnosed MM Patients



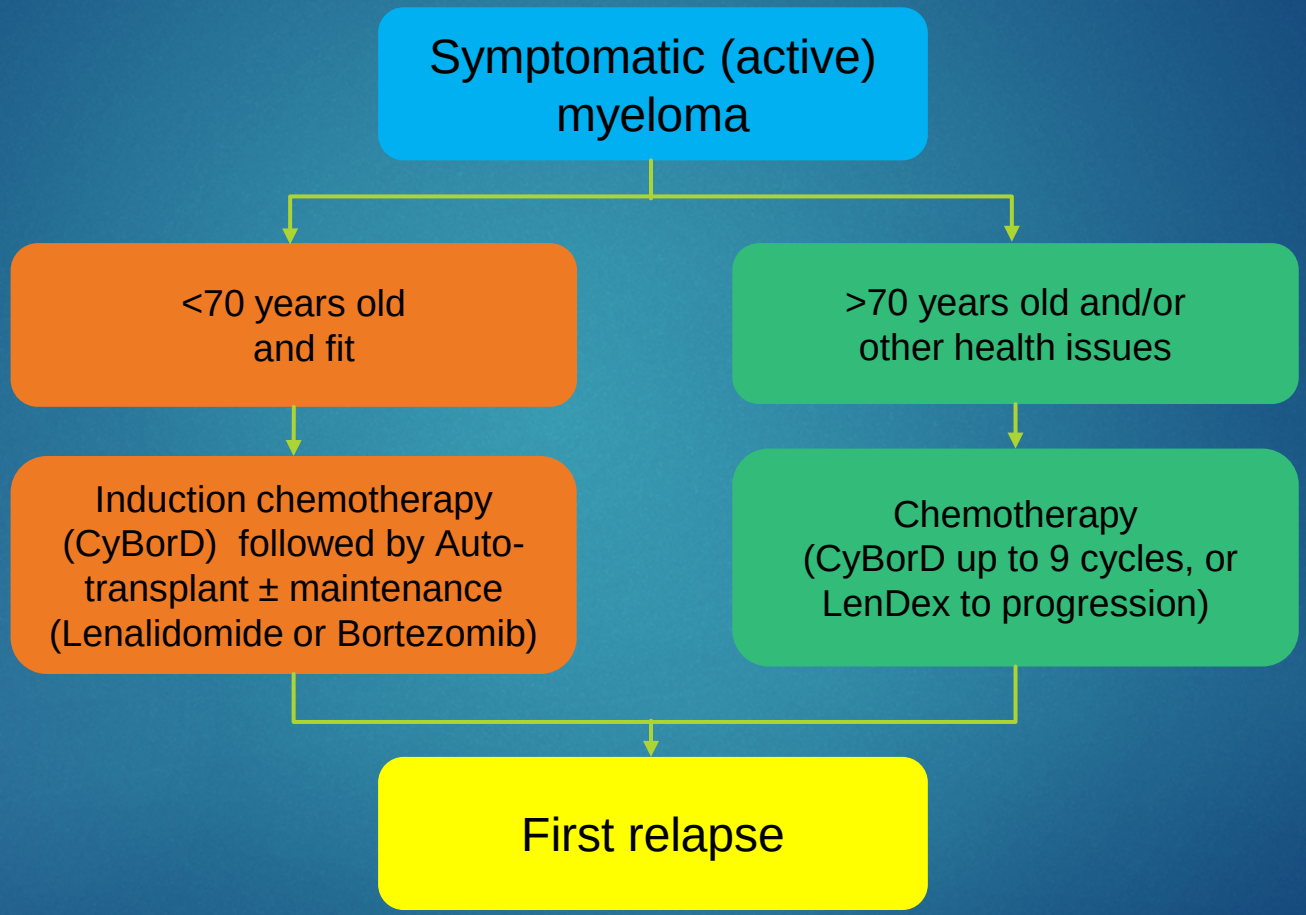
Tandon, et al. Clinical utility of the Revised International Staging System in unselected patients with newly diagnosed and relapsed multiple myeloma. Blood Cancer Journal 7, e528 (2017).

Survival of Newly Diagnosed MM Patients



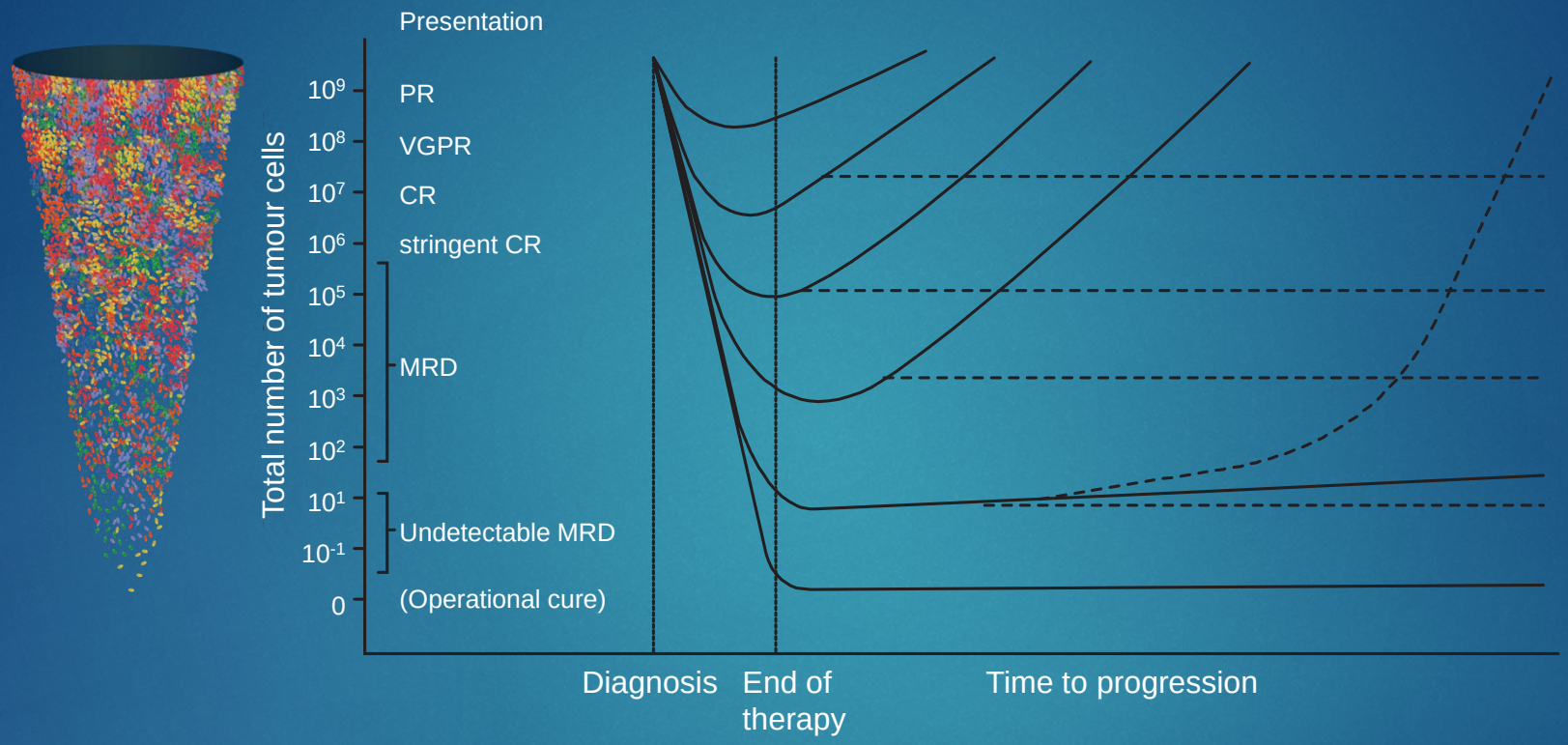
Tandon, et al. Clinical utility of the Revised International Staging System in unselected patients with newly diagnosed and relapsed multiple myeloma. Blood Cancer Journal 7, e528 (2017).

Treatment for Newly Diagnosed MM in BC



CyBorD, cyclophosphamide, bortezomib and dexamethasone

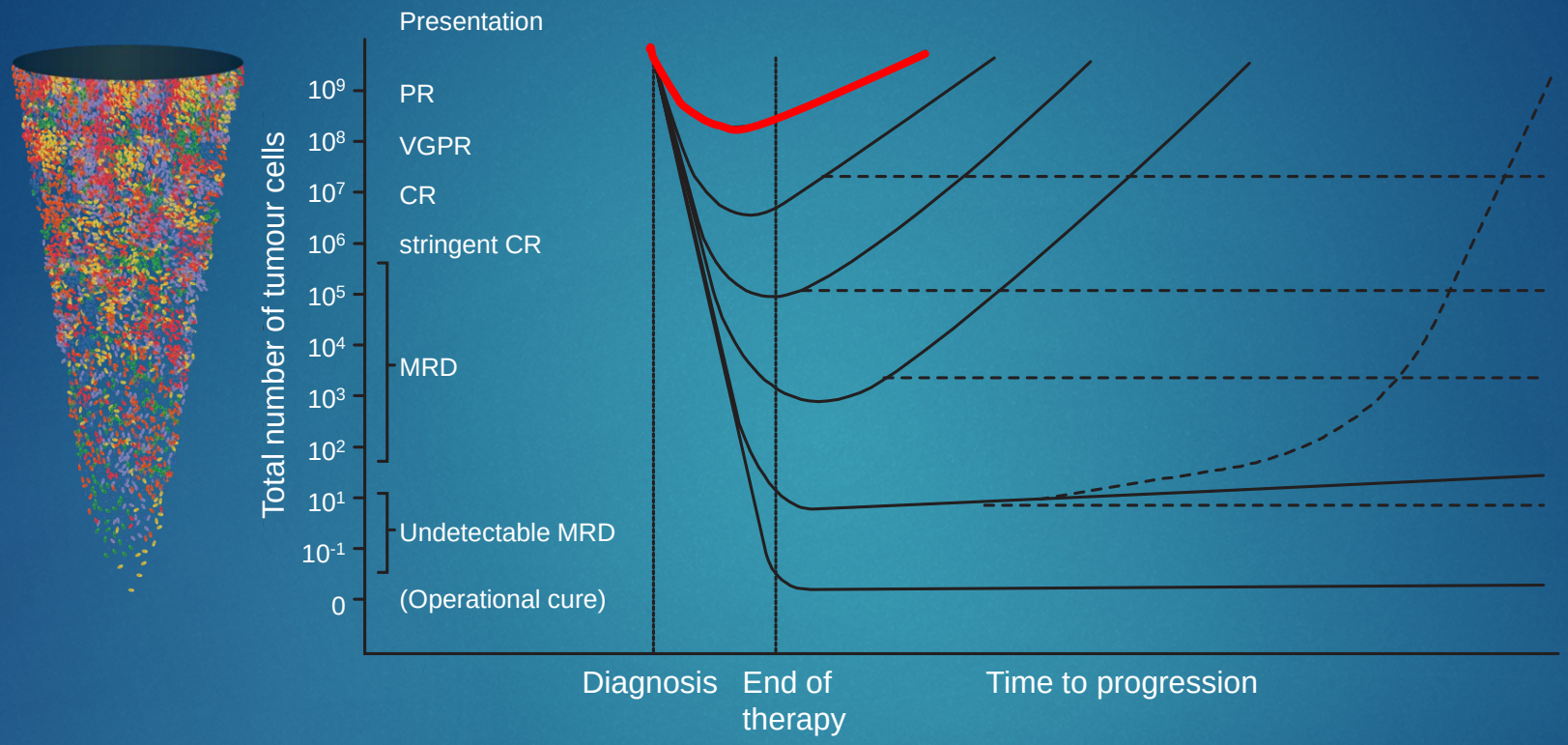
Deeper response leads to more durable remission



Even in a Complete Response, patients still have residual clonal disease that will lead to relapse. Combination therapies can achieve deeper responses.

CR, complete remission; MRD, minimal residual disease; sCR, stringent complete response

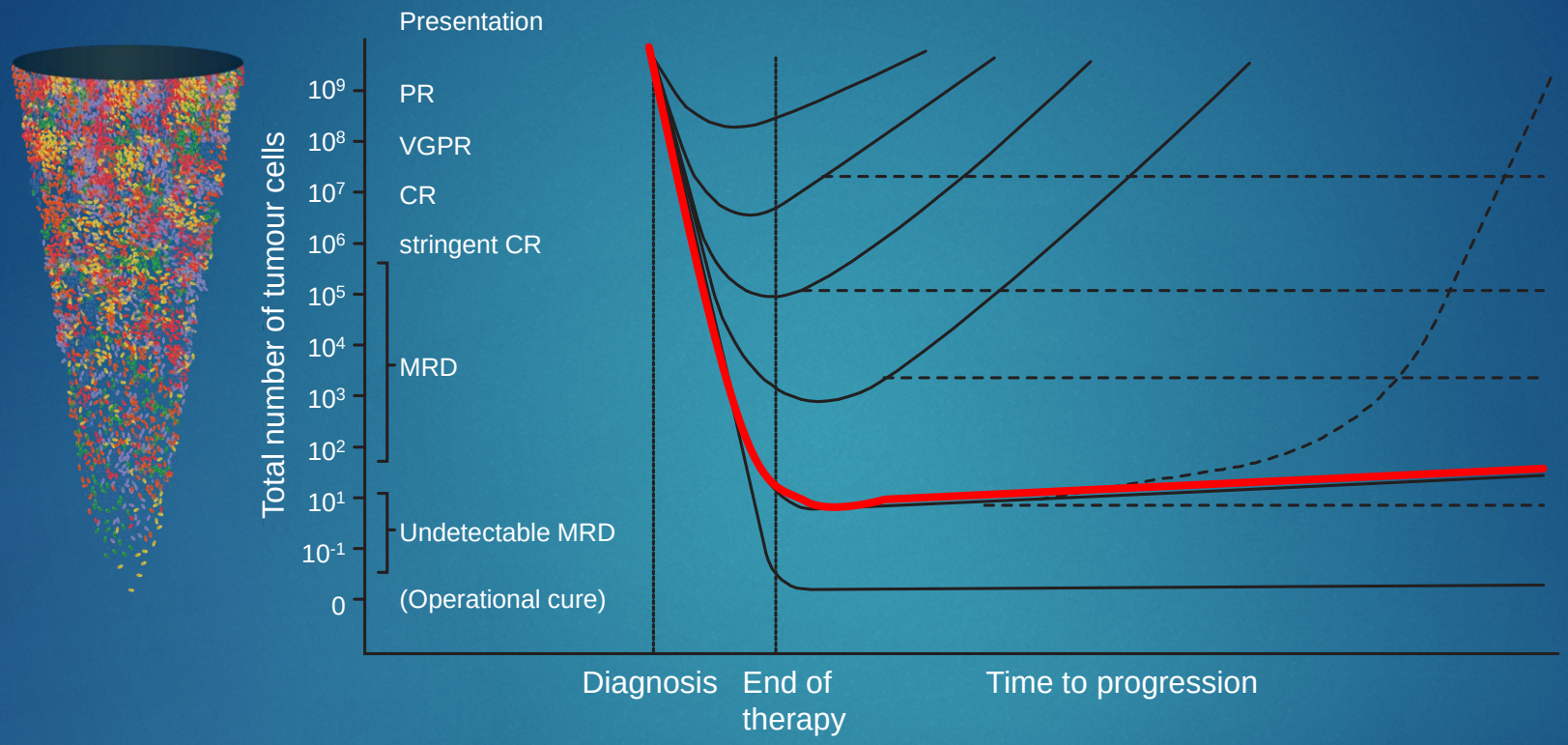
Deeper response leads to more durable remission



Even in a Complete Response, patients still have residual clonal disease that will lead to relapse. Combination therapies can achieve deeper responses.

CR, complete remission; MRD, minimal residual disease; sCR, stringent complete response

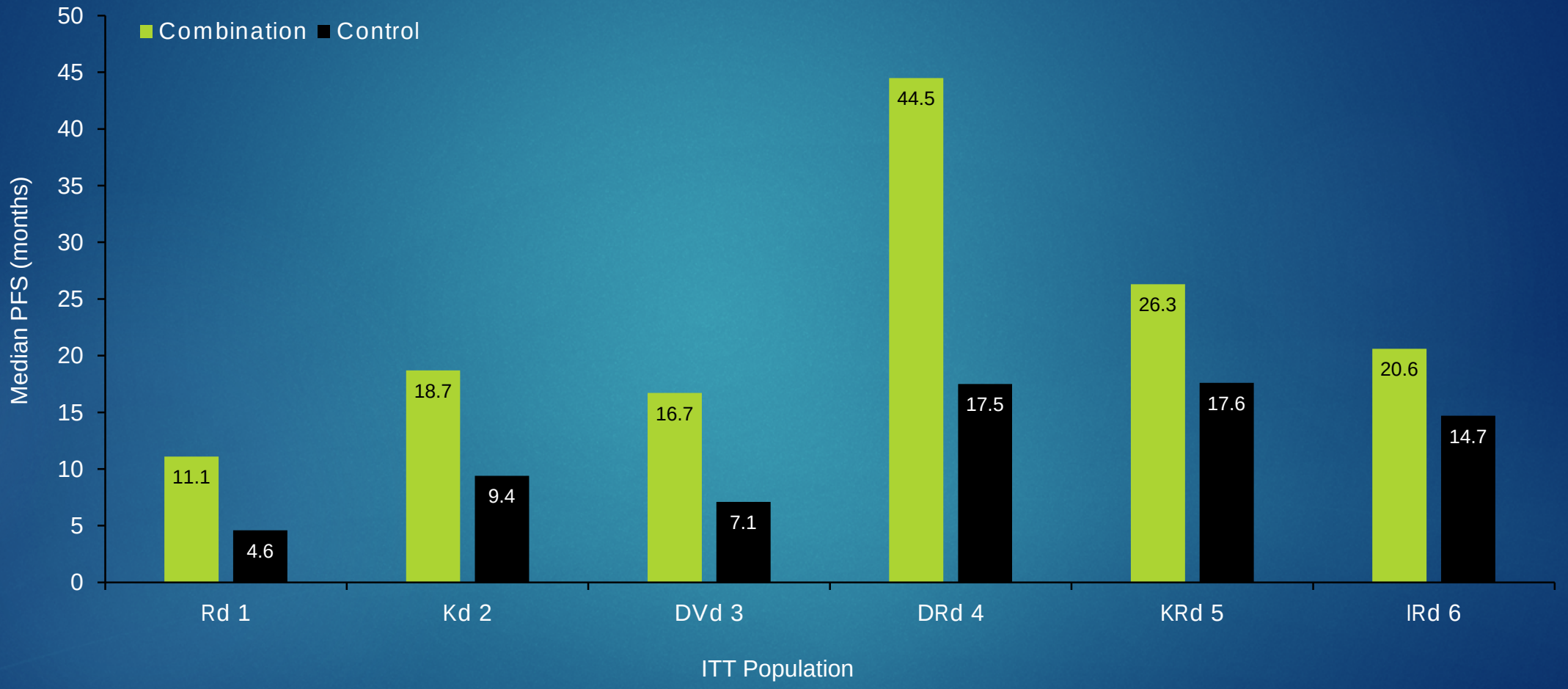
Deeper response leads to more durable remission



Even in a Complete Response, patients still have residual clonal disease that will lead to relapse. Combination therapies can achieve deeper responses.

CR, complete remission; MRD, minimal residual disease; sCR, stringent complete response

PFS in Combination therapy trials



ITT, intention-to-treat; PFS, progression-free survival

1. Dimopoulos, M. A., et al. (2009) Leukemia, 23(11),2147-2152; 2. Dimopoulos, M. A., et al. (2016) Lancet Oncol, 17(1),27-38; 3. Spencer, A., et al. (2018) Haematologica, 103(12):2079-2087; 4. Bahlis, N., et al. ASH 2018, [Abstract 1996]; 5. Dimopoulos, M. A., et al. (2017) Blood Cancer J, 7:e554; 6. Mateos, M. V., et al. (2017) Haematologica 102(10), 1767-1775.

Factors to consider when selecting treatment at relapse

Disease-related factors[1,2]

- Type and risk status of disease
- Presence of refractory disease
- Aggressiveness of current relapse

Treatment-related factors[1,2]

- Type of prior therapy and prior response
- Prior treatment related toxicity
- Bone marrow reserve
- Expected efficacy & toxicity of proposed treatment
- Expectations of the patient

Patient-related factors[1,2,3]

- Age, frailty and performance status
- Comorbidities
- Renal insufficiency/hepatic impairment
- Preference of mode of administration
- Drug availability

Goals of Treatment

- Maximize response and maintain disease control[4,5]
- Delay or prevent disease progression
- Balance efficacy with tolerability and Quality of Life[4,5]
- Prolong survival[5]
- Stable disease may be beneficial

1. Sonnevald, P., Broil, A. (2016) Haematologica, 101(4),396-406; 2. Nooka, A. K., et al. (2015) Blood, 125(20), 3085-3099; 3. Laubach, J., et al. (2016) Leukemia, 30(5),1005-1017;
4. Mohty, B., et al. (2012) Leukemia, 26(1) 73-85; 5. Pratt, G., et al. (2014) Br J Haematol, 167(1),131-133.

Selected Multiple Myeloma Drugs

Steroids	Alkylators	Proteasome Inhibitors	Immuno-modulators	Monoclonal Antibodies
• Dexamethasone • Prednisone	• Melphalan • Cyclophosphamide	• Bortezomib • Carfilzomib • Ixazomib	• Thalidomide • Lenalidomide • Pomalidomide	• Daratumumab • Elotuzumab • Isatuximab

Selected Multiple Myeloma Treatments

Steroids	Alkylators	Proteasome Inhibitors	Immuno-modulators	Monoclonal Antibodies
• Dexamethasone • Prednisone	• Melphalan • Cyclophosphamide	• Bortezomib • Carfilzomib* • Ixazomib*	• Thalidomide • Lenalidomide • Pomalidomide	• Daratumumab* • Elotuzumab* • Isatuximab^

*Health Canada Approved in 2016
^Health Canada Approved in 2020

“In order to achieve optimal treatment outcomes with novel agents, …it may be important to continue treatment until disease progression.”

“If [adverse] events are not properly managed, they can lead to treatment discontinuation and undermine the efficacy of treatment.”

Durie BG. Role of new treatment approaches in defining treatment goals in multiple myeloma--the ultimate goal is extended survival. Cancer Treat Rev. 2010 May;36 Suppl 2:S18-23.

Optimize comorbidities prior to starting MM therapy

- **Examples:**
  - **Poorly controlled COPD increases respiratory risks of infusion reactions to antibody treatments, e.g., daratumumab**

Optimize comorbidities prior to starting MM therapy

- **Examples:**
  - **Poorly controlled COPD increases respiratory risks of infusion reactions to antibody treatments, e.g., daratumumab**
  - **Poorly controlled HTN or CHF increases cardiovascular risks associated with proteasome inhibitor treatment, especially carfilzomib**

Optimize comorbidities prior to starting MM therapy

- **Examples:**
  - **Poorly controlled COPD increases respiratory risks of infusion reactions to antibody treatments, e.g., daratumumab**
  - **Poorly controlled HTN or CHF increases cardiovascular risks associated with proteasome inhibitor treatment, especially carfilzomib**
  - **Other conditions may contribute to hypercalcemia, anemia, or renal dysfunction -- e.g., parathyroid, thyroid, iron deficiency, DM2, HTN, medications, etc.**

Managing Complications of MM & Therapy

Complications of MM & Therapy

Which statement is true:

A) About 1/3 of patients treated with bortezomib develop neuropathy

B) Lenalidomide associated diarrhea often responds to bile acid sequestrants

C) Within 1st year after diagnosis MM patients have 30x risk of sepsis compared to control population

D) Lenalidomide and dexamethasone has venous thrombosis rate of ~ 15% with no prophylaxis

E) All of the above

Complications of MM & Therapy

Which statement is true:

A) **About 1/3 of patients treated with bortezomib develop neuropathy**

B) **Lenalidomide associated diarrhea often responds to bile acid sequestrants**

C) **Within 1st year after diagnosis MM patients have 30x risk of sepsis compared to control population**

D) **Lenalidomide and dexamethasone has venous thrombosis rate of ~ 15% with no prophylaxis**

E) **All of the above**

Systemic Steroid Toxicities

- Psychiatric effects: Anxiety, Insomnia, Irritability, Labile mood, Memory deficits, Mania, Depression, Psychosis
- Hyperglycemia
- Thrombosis
- Immunosuppression
- Osteoporosis and Avascular necrosis of bones

Infections

- Within 1st year after diagnosis MM patients have 30x risk of sepsis compared to control population
- Low threshold for investigating and treating possible infection

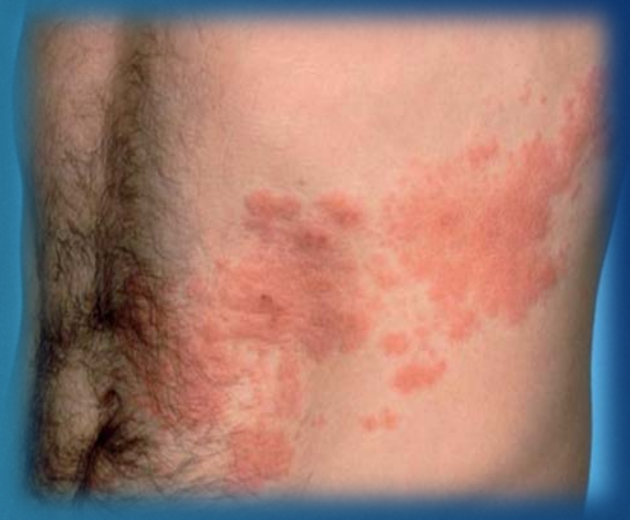
Blimark C, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. Haematologica. 2015;100(1):107-113.

Infections

- No standard antibacterial prophylaxis recommendation
- IV immunoglobulin as prophylaxis if recurrent serious infections
- Filgrastim/G-CSF may be used to maintain safe neutrophil count while on treatment
- Seasonal flu vaccine, pneumococcal vaccine, no live vaccines

Infections

- **MM patients have 25x risk of shingles compared to control population**
- **Shingles prophylaxis valacyclovir 500 mg PO daily while taking daratumumab or PI, and for 4 weeks after its discontinuation**



Blimark C, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. Haematologica. 2015;100(1):107-113.

Cardiovascular toxicity

- MM patients 5x risk of heart failure & arrhythmia compared to control population
- Cardiotoxicity with PI's usually HTN or heart failure; more common with carfilzomib
  - 18% any grade CV adverse event
  - 4-6% high grade heart failure or HTN
- Prior to initiating carfilzomib, manage CV risk factors: HTN, CHF, DM, CKD, CAD…

(Kistler, Clin Lymphoma Myeloma Leuk 2017, Waxman JAMA Oncology 2018, and Chari, Blood Advances 2018)

Thrombosis

- Lenalidomide + dexamethasone has venous thrombosis rate of ~ 15% with no prophylaxis, and <10% with prophylaxis
- Low threshold to investigate DVT/PE

(Palumbo, et al. Leukemia. 2008 Feb;22(2):414-23.)

Renal Dysfunction

- Avoid NSAIDs and IV contrast
- Hydration
- Renal dysfunction sometimes reversible with MM treatment

Bone disease and Hypercalcemia

- Treat underlying MM
- Analgesics and steroids
- Bisphosphonate, IV hydration, calcitonin
- Radiation therapy
  - Bone pain not responding to systemic therapy and analgesics
  - Pathologic fractures/impending fractures
- Surgery
  - Kyphoplasty/Vertebroplasty for recent vertebral compression fractures
  - Orthopedic management of fractures/impending fractures of femur, tibia, spinal cord compression.

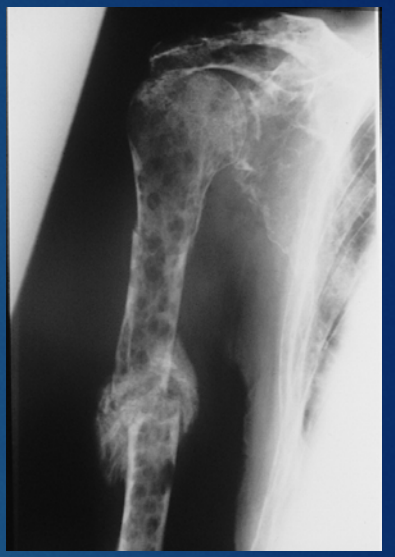


Image from Singer *BMJ* 1997;314:960

Neuropathy

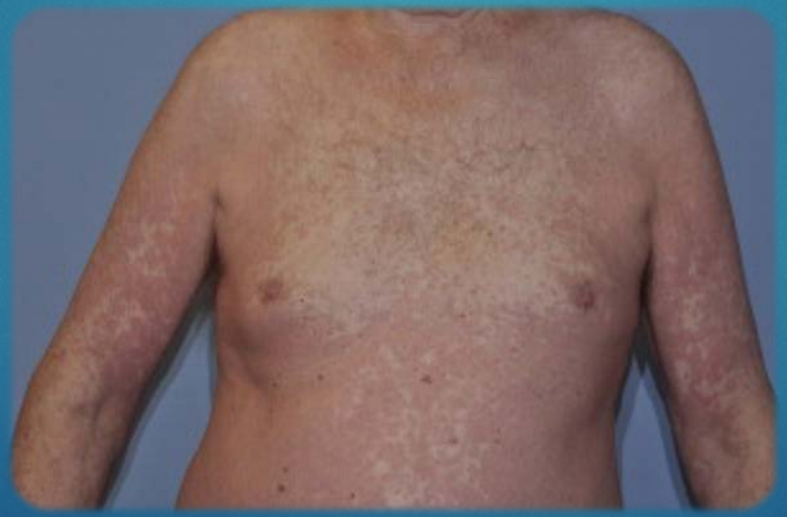
- Peripheral and/or autonomic neuropathy
- ~ 1/3 of patients treated with bortezomib develop neuropathy
- Subclinical diabetic neuropathy increases risk
- Symptom management with antiseizure meds or TCAs
- Adjust anti-hypertensives for autonomic neuropathy

Diarrhea

- Diarrhea often a late onset side effect of lenalidomide
- Usually low grade diarrhea, often daily
- Evidence that lenalidomide diarrhea caused by bile acid malabsorption
- Anti-diarrheal like loperamide may be helpful
- Bile acid sequestrant cholestyramine (5 g po/d) often improves diarrhea, especially in those without benefit from loperamide
- Diarrhea often a cyclic effect of bortezomib

Lenalidomide Rash

- One of the most common non-hematologic side effects of IMiD therapy in MM
- A rash of any grade in 25-30% of patients, and high grade <5%



Lenalidomide Rash Management

- Hold lenalidomide
- Short course of systemic steroids if needed
- After rash improves, restart lenalidomide, consider a dose reduction
- Switch from weekly dexamethasone to three times per week prednisone

(Barley *et al* Leuk Lymphoma. 2016 Nov;57(11):2510-5)

Health Related Quality of Life improves when effective treatment begins

- Outcomes include: usual activities, pain, mobility, depression, anxiety
- Best evidence in first line treatment
- Growing evidence with novel treatments in relapsed myeloma

(Nielsen et al. Eur J Haematol. 2017;99:3–17, Richardson et al. Blood Cancer J. 2018 Nov; 8(11): 109.)

What's new in MM?

- Daratumumab (anti CD38 MoAb)
  - IV form currently available for relapsed MM, in combination therapy with lenalidomide or bortezomib
  - SC form approved in Canada August 2020
  - Access in front line combination therapy?
- Isatuximab (anti CD38 MoAb)
  - Recently approved by Health Canada, in combination with pomalidomide and dexamethasone for relapsed MM

What's new in MM?

- CAR-T cell therapies
  - Early studies in heavily pre-treated MM, response rates 60-100%
- Bispecific antibodies
- Antibody drug conjugates
  - Belantamab mafodotin (FDA approved August 2020)
- Cereblon E3 ligase modulators
- Selinexor (FDA approved July 2019)

Outcomes are improving for MM patients

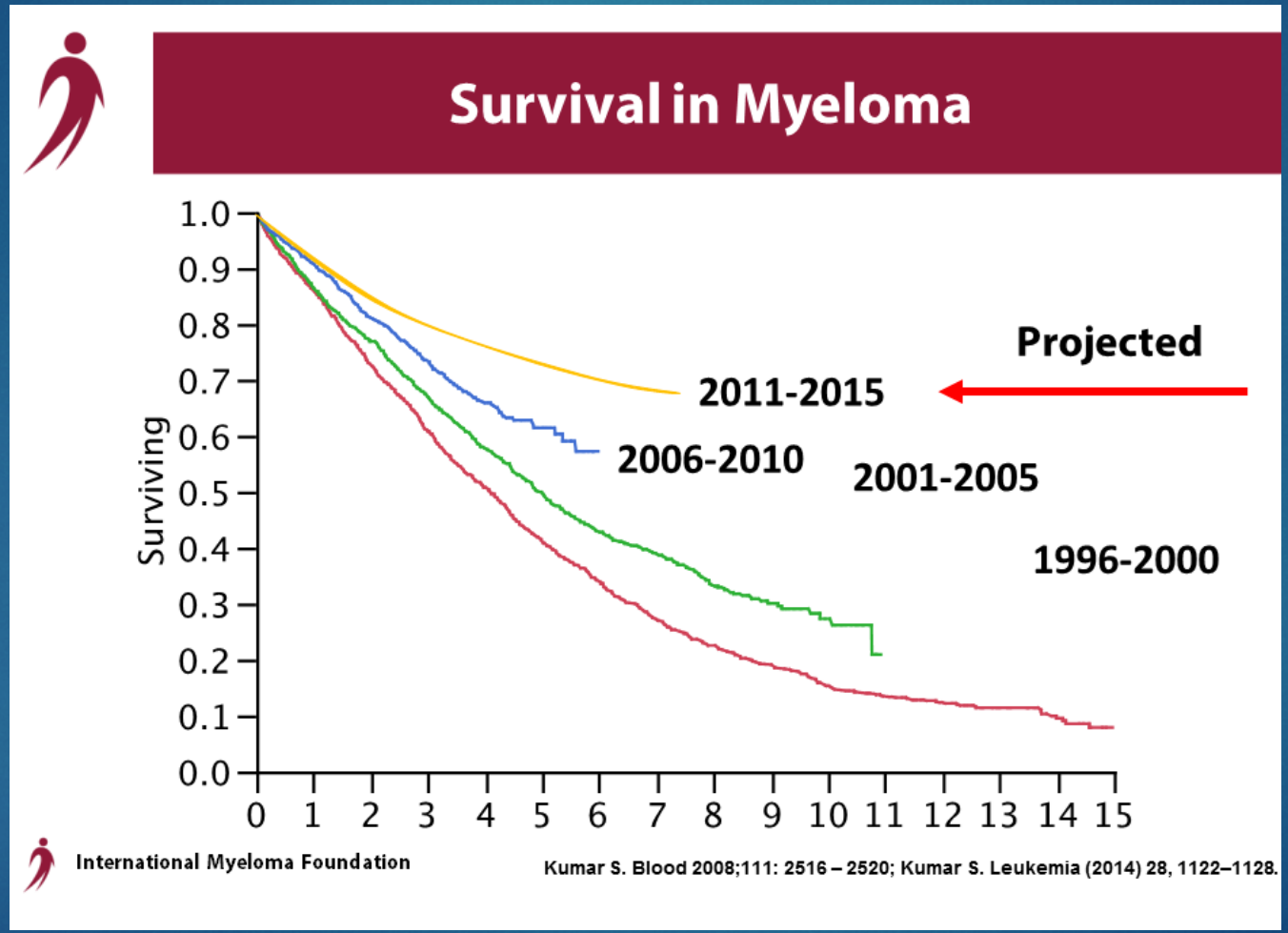


Image from https://www.myeloma.org/blog/dr-duries/new-future-myeloma-patients

Questions? Comments?