Brigham and Women's Hospital
Founding Member, Mass General Brigham

Myeloma

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

DANA-FARBER
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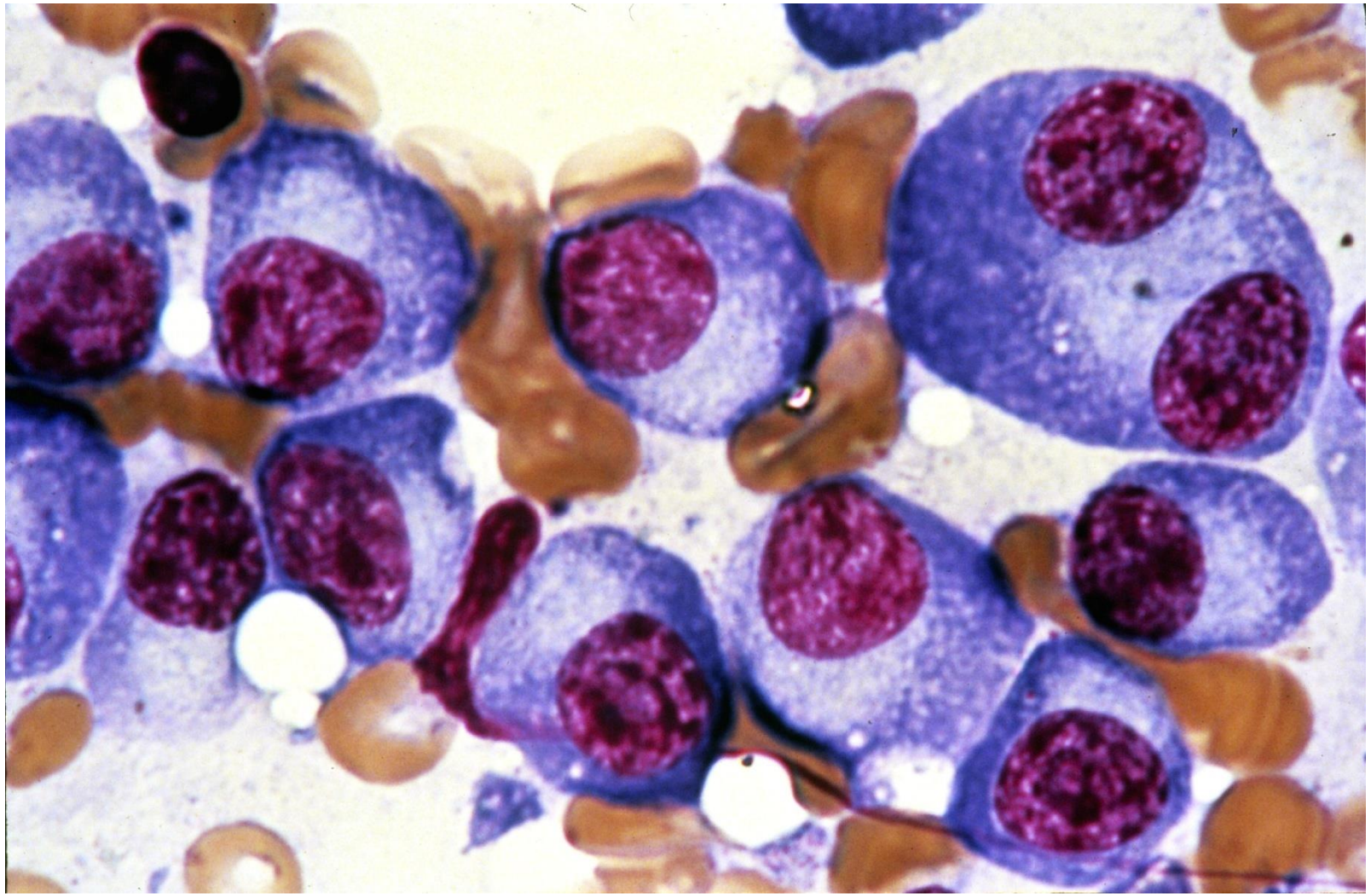
Multiple Myeloma



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Disclosures for Eric Jacobsen, MD

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Membership in Advisory Board	**No relevant conflicts of interest to declare**
Presentation includes a description of the following off-label use of a drug or medical device	**No relevant conflicts of interest to declare**

Objectives

Prevalence

Diagnosis

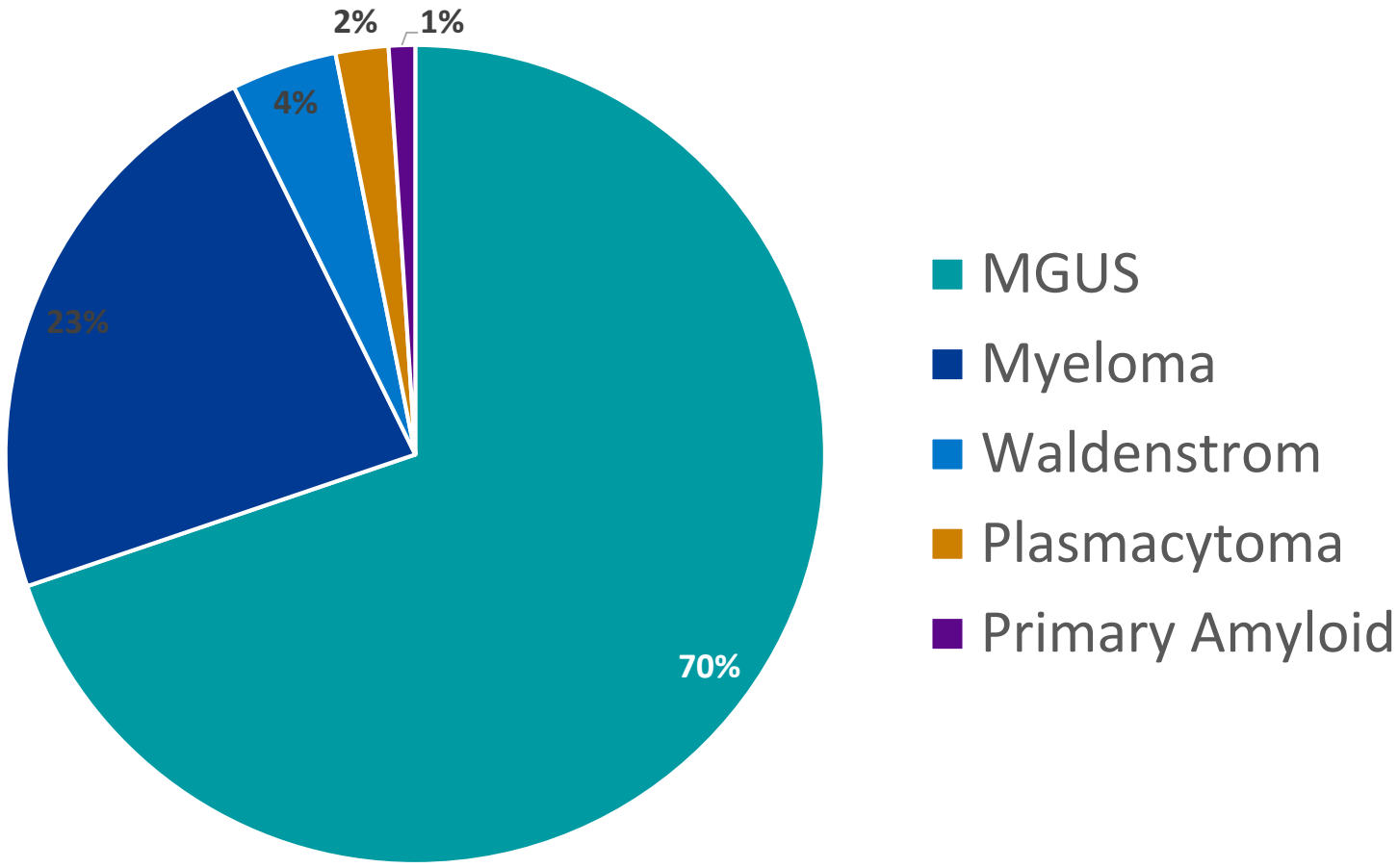
Classification

Risk Stratification

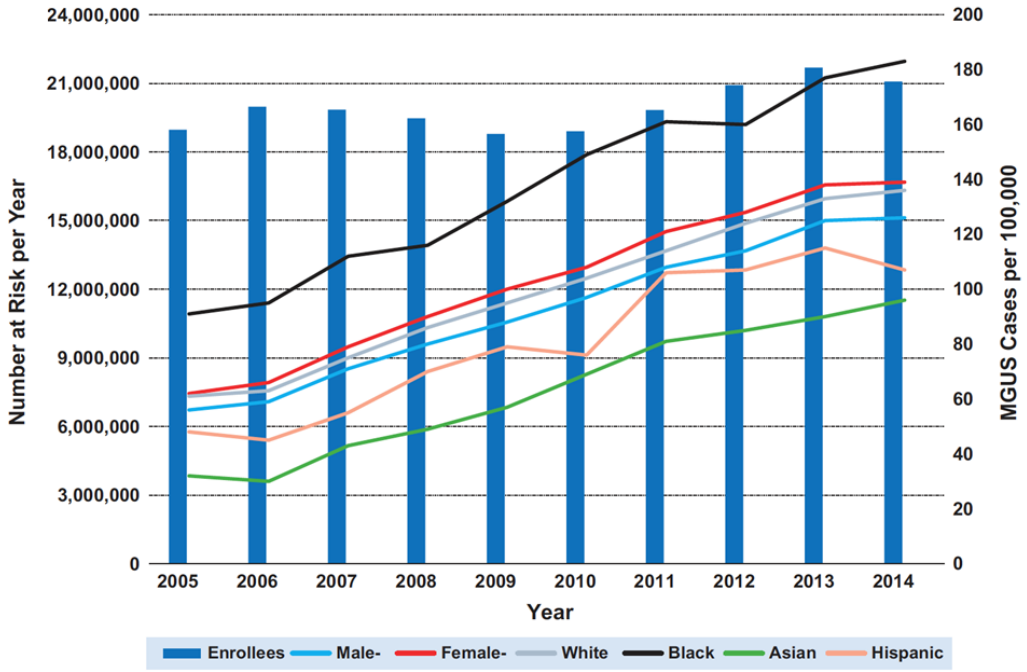
Complications

Management

Plasma Cell Disorders



MGUS is a very common condition



- 3% of population at age 50
- Increases with age

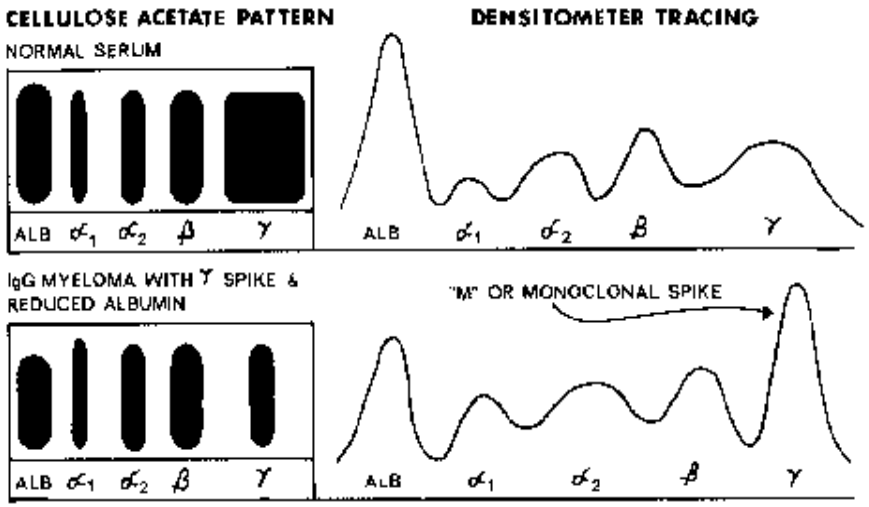
- 3 times more common in AA
- Younger age for AA

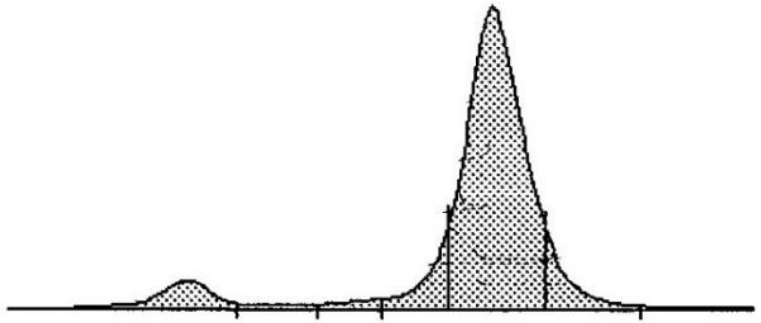
- 3 times more in familial cases

G. RS et al., *Leukemia*, 2016

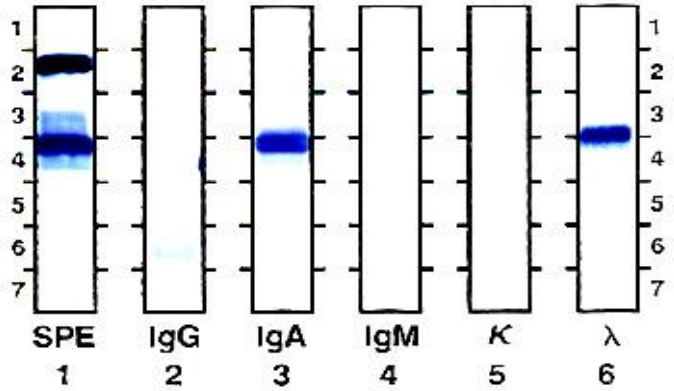
Monoclonal Proteins (Paraprotein)

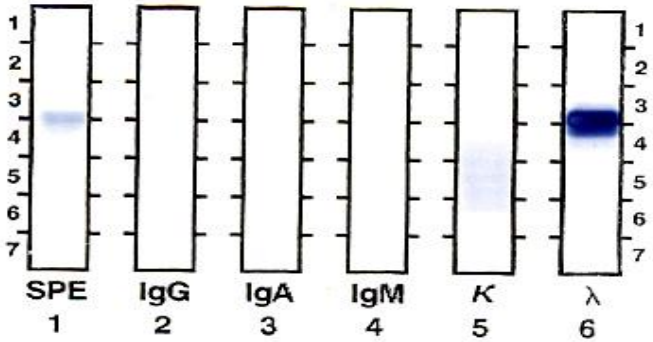
Electrophoresis





Immunofixation





Serum

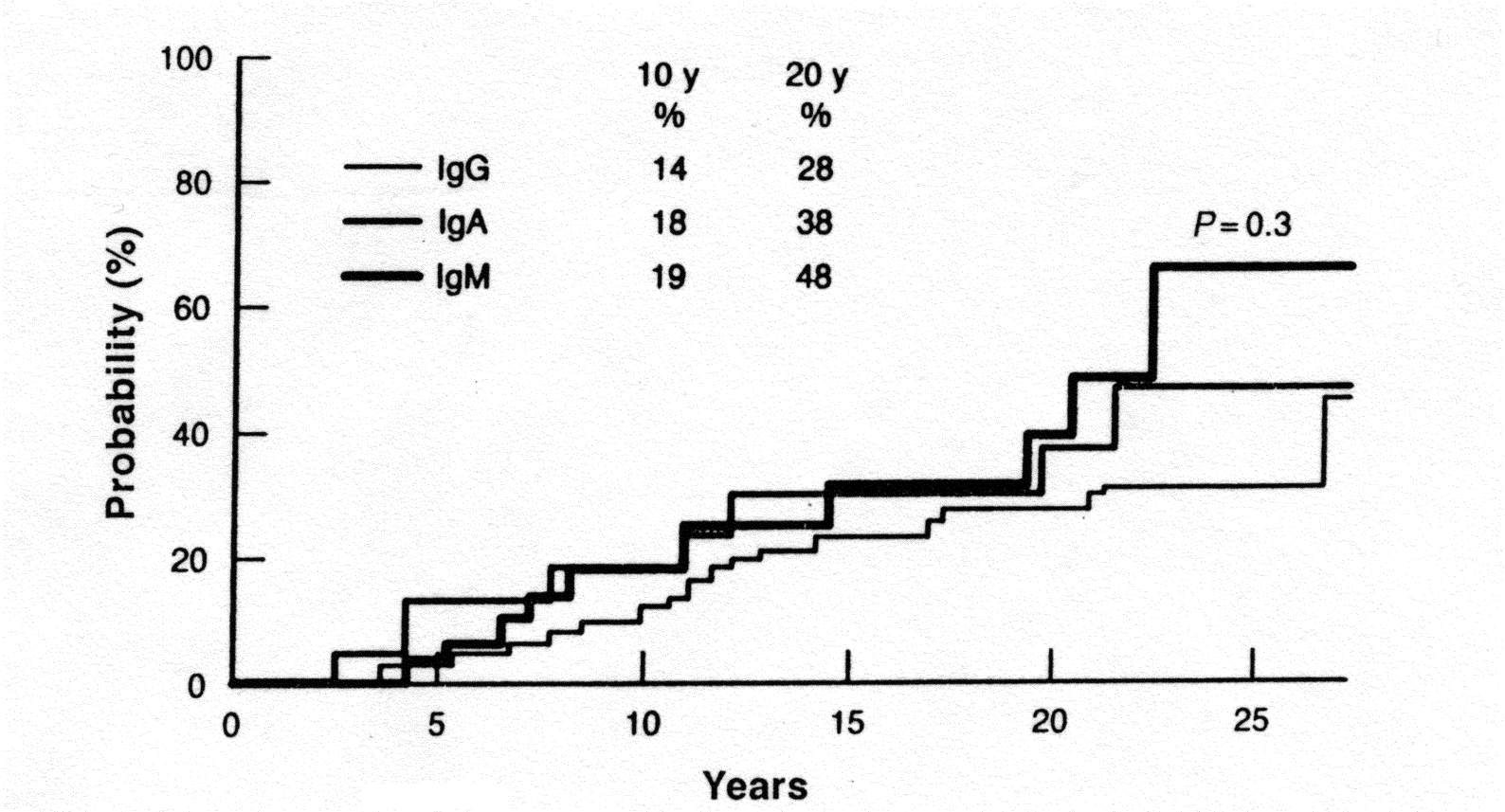
Urine

MGUS: Subtypes

IgA/IgG	IgM	Light-chain
<3 g/dL M-protein	Any M-protein	Abnormal FLC ratio; elevated serum LC
<10% Plasma Cells	No histological infiltrate	<10% Plasma Cells
No end organ damage*	No end organ damage*	No end organ damage*
		No IgH expression

Korde et al, Blood 2011; Owen et al, Semin Oncol 2003

MGUS: Natural History

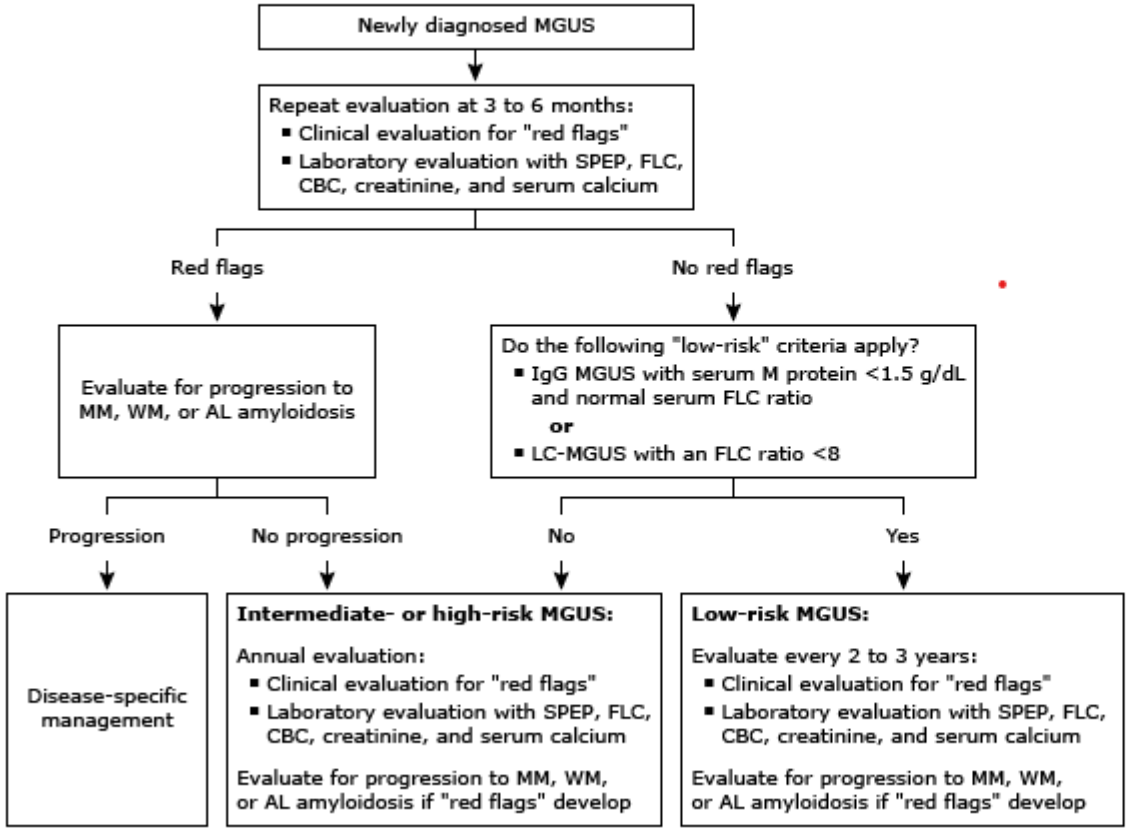


Rate of development of lymphoplasmacytic disease in 241 patients with a serum monoclonal protein, stratified by immunoglobulin class. (*From* Kyle RA: "Benign" monoclonal gammopathy—after 20 to 35 years of follow-up. Mayo Clin Proc 68:26, 1993; with permission.)

MGUS monitoring

- Studies have suggested that monitoring improves survival and decreases morbidity in patients who develop MM

Monoclonal gammopathy of undetermined significance: Monitoring for progression



Clinical "red flags" for progression:

- Bone pain
- Fatigue/generalized weakness
- Constitutional "B" symptoms (unintentional weight loss, fever, night sweats)
- Neurologic symptoms (neuropathy, headache, dizziness, loss of vision/hearing)
- Bleeding
- Symptoms suggestive of amyloidosis (macroglossia, nephrotic range proteinuria, restrictive cardiomyopathy, unexplained elevated NT-proBNP)
- Lymphadenopathy, hepatomegaly, or splenomegaly

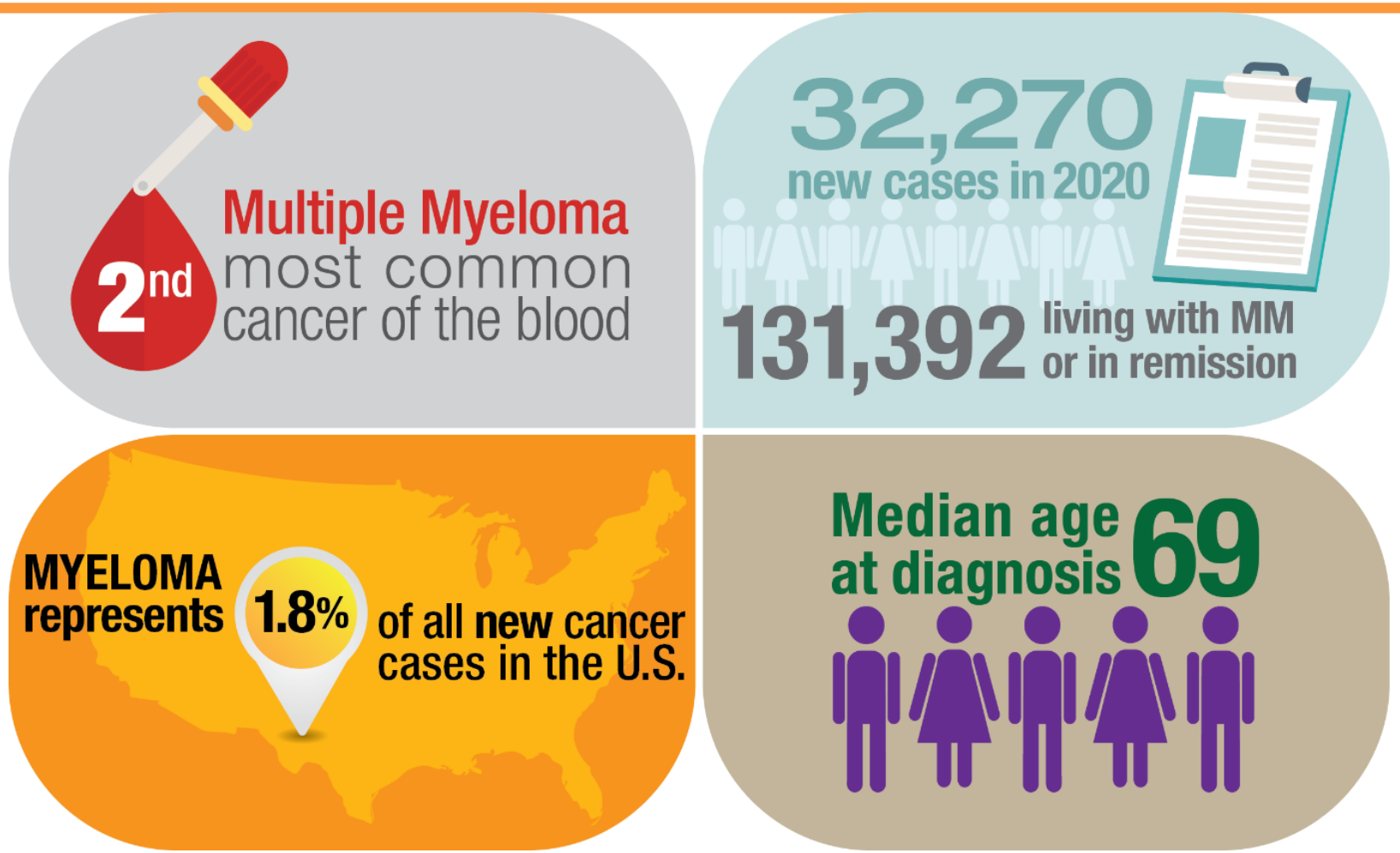
Laboratory "red flags" for progression:

- Increase in serum M-protein level ≥50% (provided absolute increase ≥0.5 g/dL)
- Increase in serum FLC level ≥50% (provided involved FLC level is at least 100 mg/L)
- Involved/uninvolved FLC ratio of 100 or more (provided involved FLC level is at least 100 mg/L)
- Serum M-protein ≥3 g/dL
- Urine M-protein ≥500 mg in 24 hours

Adapted from: Go RS, Rajkumar SV. How I manage monoclonal gammopathy of undetermined significance. Blood 2018; 131:163.

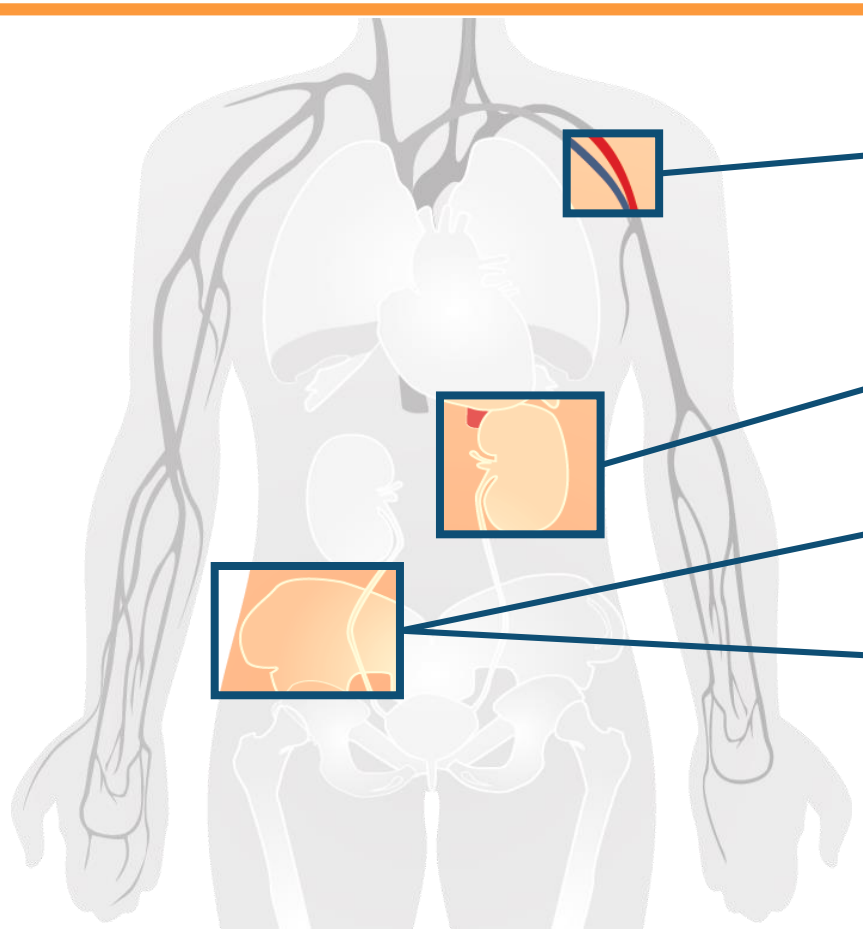
Graphic 118785 Version 3.0

How common is multiple myeloma?



SEER Cancer Stat Facts: Myeloma. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/mulmy.html

Effects of Myeloma and Common Symptoms



- **Low blood counts** → Weakness, Fatigue, Infection
- **Decreased kidney function** → Weakness
- **Bone damage** → Bone pain
- **Bone turnover** → Loss of appetite, Weight loss

About 10% to 20% of patients with newly diagnosed myeloma do not have any symptoms.

MMRF. Multiple myeloma symptoms, side effects, and complications. https://themmrf.org/multiple-myeloma/symptoms-side-effects-and-complications/.
Campbell K. *Nurs Times*. 2014;110:12.
Kyle R et al. *Mayo Clin Proc.* 2003;78:21.

Diagnostic Studies

	Test/Procedure	Case specific
Serum/blood	CBC with manual diff CMP SPEP+IF sFLC LDH β2 microglobulin	•Serum viscosity •Cryogobulins •Peripheral blood flow cytometry
Urine	UPEP+IF	
Radiology	Bone survey (long bones+skull)	•PET-CT and/or MRI • MRI brain and/or spine
Pathologic specimens	BM aspirate and biopsy and/or Biopsy of plasmacytoma	•IHC •Flow cytometry •Cytogenetics+FISH •(Congo red stain)
	Fat pad aspirate	AL amyloidosis

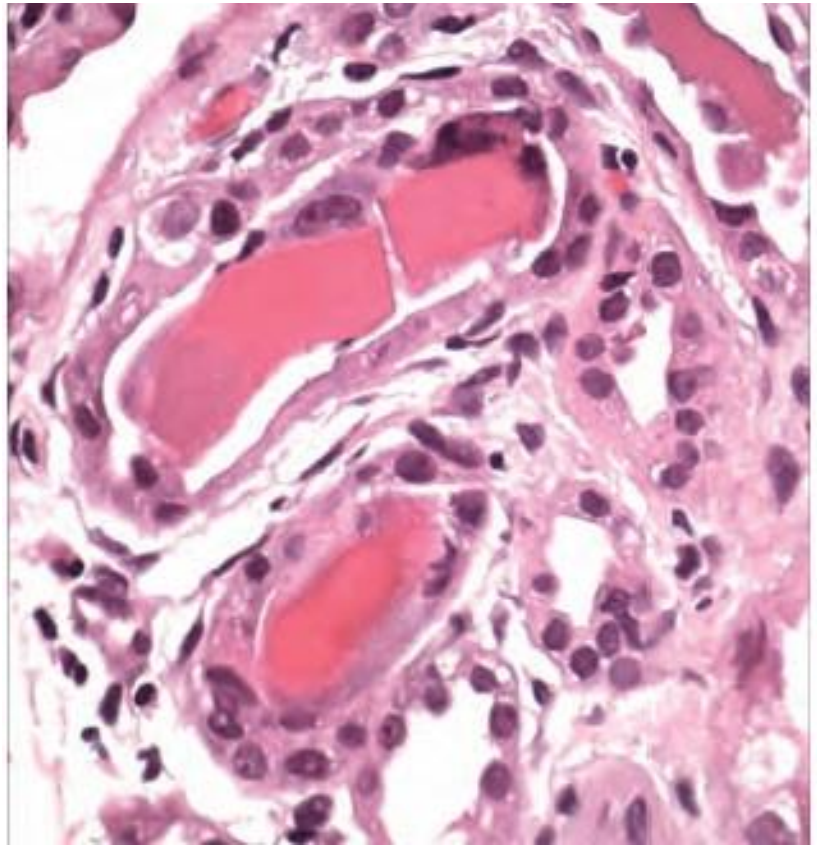
Bianchi and Anderson, CA J 2014

Complications

- Bone disease/hypercalcemia
- Hyperviscosity-IgM, IgG3, IgA
- Recurrent infections
- Renal failure: hypercalcemia, myeloma kidney, hyperuricemia, IV urography, dehydration, plasma cell infiltration, pyelonephritis, amyloidosis
- Cardiac failure: amyloid, hyperviscosity, anemia
- Anemia: BM tumors, renal dysfunction, myelosuppression, low endogenous erythropoietin
- Neuropathy: sensory ±motor, amyloid, anti-myelin Ab
- Daratumumab interferes with type and screen

Myeloma Complications: Renal disease

- Light-chain cast nephropathy →
- Amyloidosis
- Cryoglobulinemia
- Hypercalcemic nephropathy
- Hyperviscosity
- Infiltrative interstitial nephropathy
- Plasma cell infiltration
- Urate nephropathy



Updated IMWG criteria for diagnosis of multiple myeloma

MGUS

- M protein <3 g/dL
- Clonal plasma cells in bone marrow <10%
- No myeloma-defining events

Smoldering myeloma

- M protein ≥3 g/dL (serum) or ≥500 mg/24 hrs (urine)
- Clonal plasma cells in bone marrow ≥10% to 60%
- No myeloma-defining events

Multiple myeloma

- Underlying plasma cell proliferative disorder

AND

1 or more myeloma-defining events:

- ≥1 CRAB* feature
- Clonal plasma cells in bone marrow ≥60%
- Serum free light chain ratio ≥100
- >1 MRI focal lesion

*C: Calcium elevation (>11 mg/dL or >1 mg/dL higher than ULN)
R: Renal insufficiency (creatinine clearance <40 mL/min or serum creatinine >2 mg/dL)
A: Anemia (Hb <10 g/dL or 2 g/dL < normal)
B: Bone disease (≥1 lytic lesions on skeletal radiography, CT, or PET-CT)

Rajkumar SV et al. *Lancet Oncol.* 2014;15:e538.

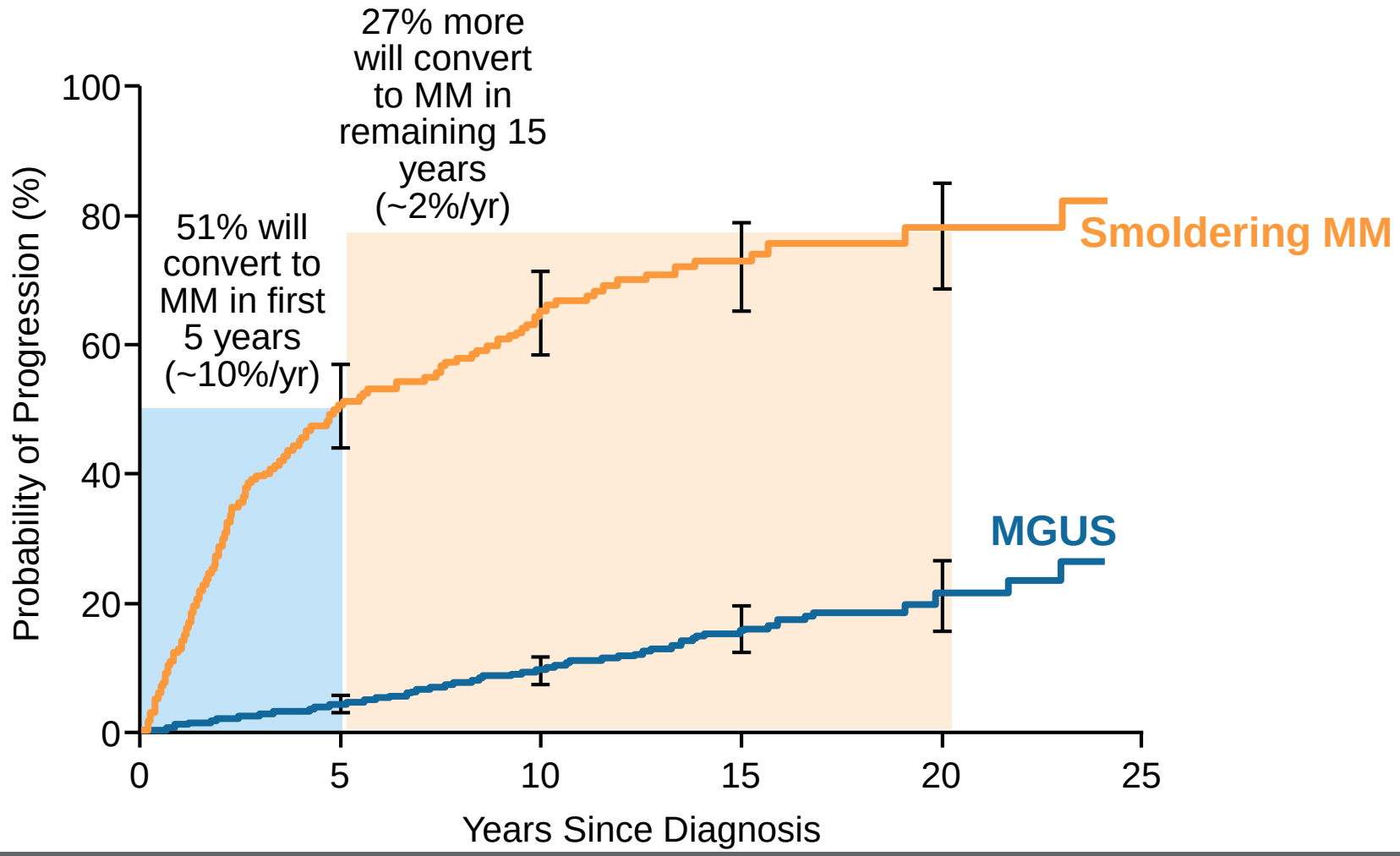
High-risk MGUS

- Non-IgG M protein
- Abnormal serum free light chain ratio
- M protein >1.5 g/dL

SMM

Current standard of care is to observe only for low- and intermediate-risk patients.

Smoldering Multiple Myeloma: Heterogeneous Disease



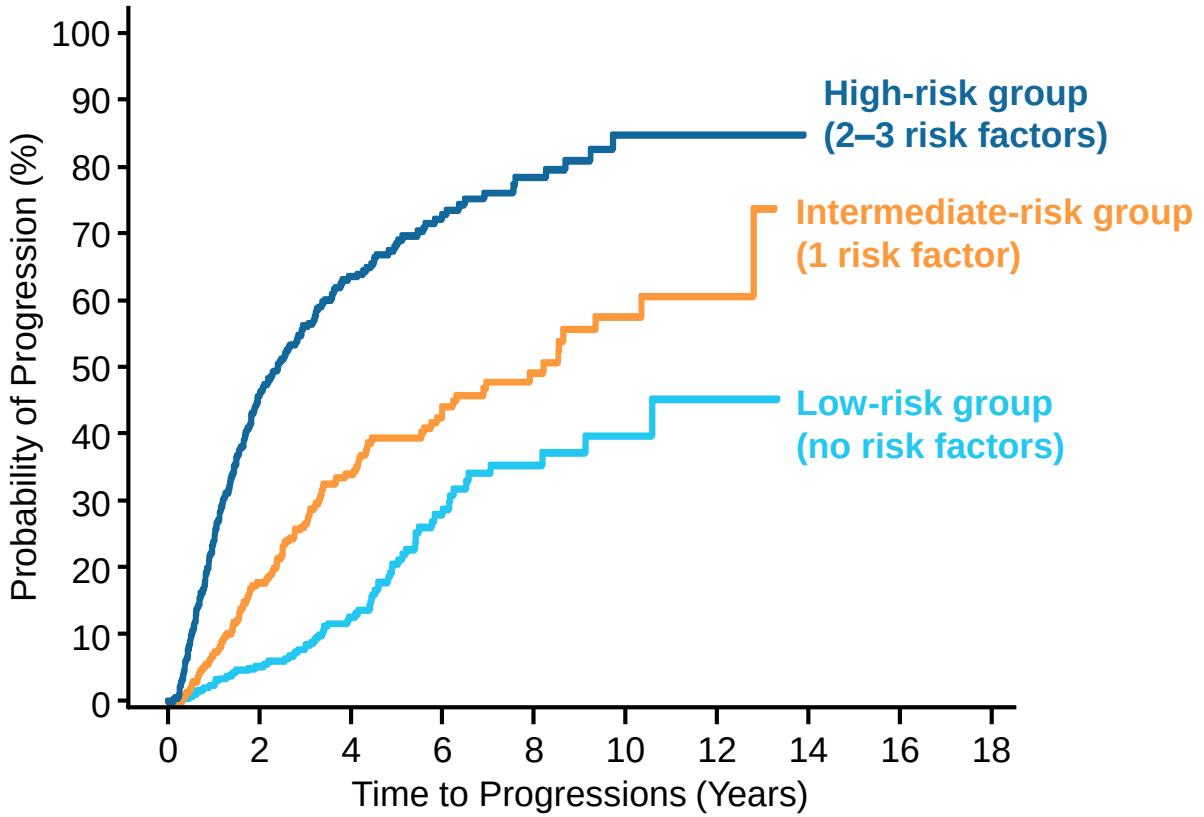
Kyle RA et al. *N Engl J Med.* 2007;356:2582.
Greipp PR et al. *J Clin Oncol*. 2005;23:3412.

2/20/20 Model to Identify High-Risk SMM Patients

2/20/20 Risk assessment for SMM

- **2** >2 g/dL M protein
- **20** >20 free light chain ratio
- **20** >20% bone marrow plasma cells

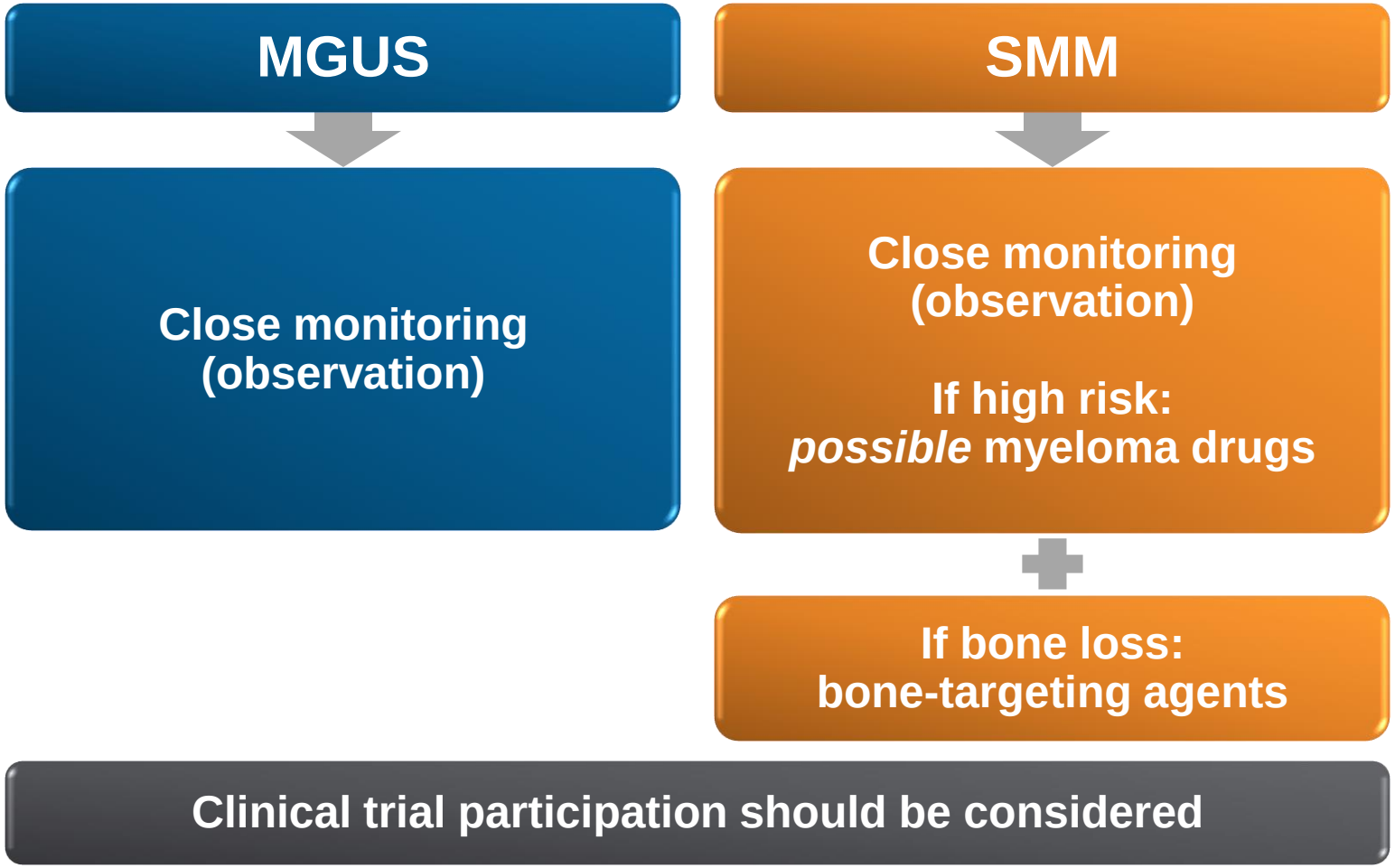
Model does not include any biological or immune factors that may account for interpatient heterogeneity.



Risk of progression at 2 Years
44.2%
17.9%
6.2%

Mateos MV et al. *Blood Cancer J*. 2020;10:102.

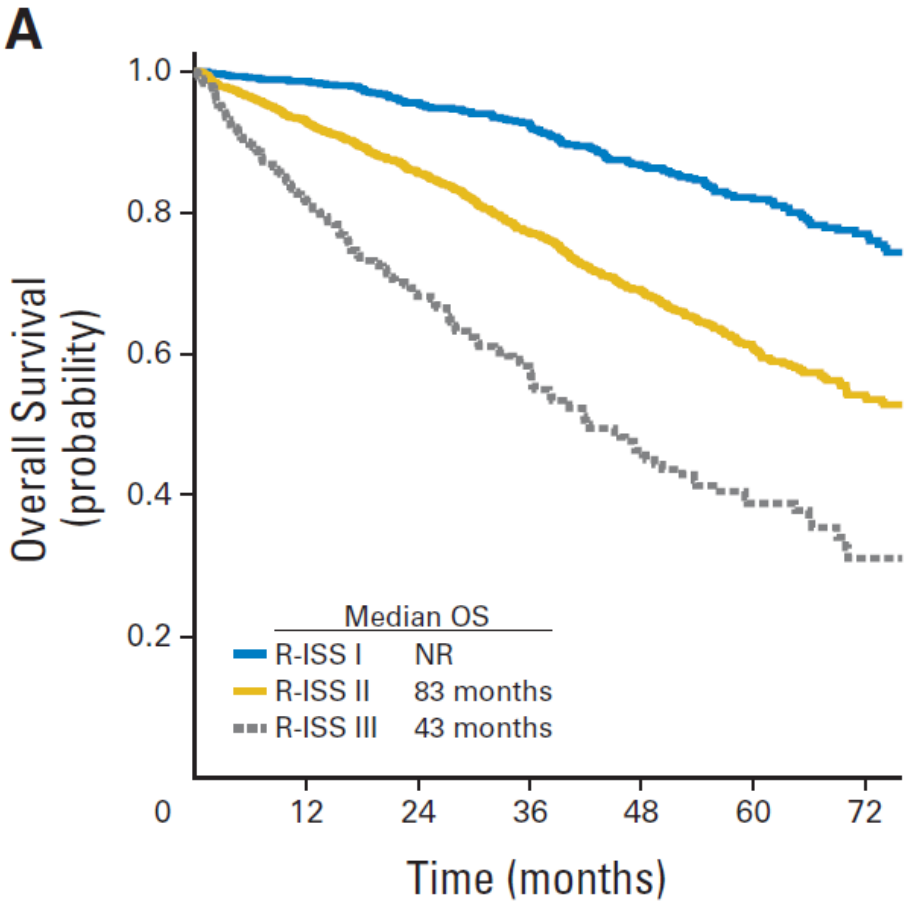
Overview of Treatment Approach



The Revised International Staging System

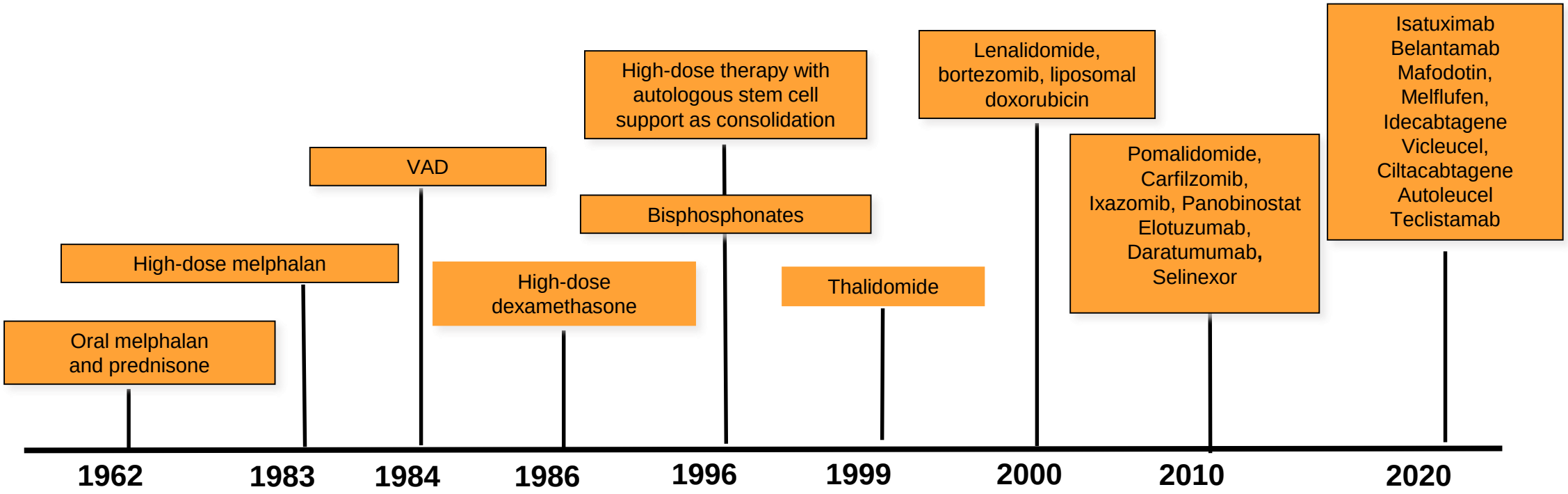
Table 1. Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

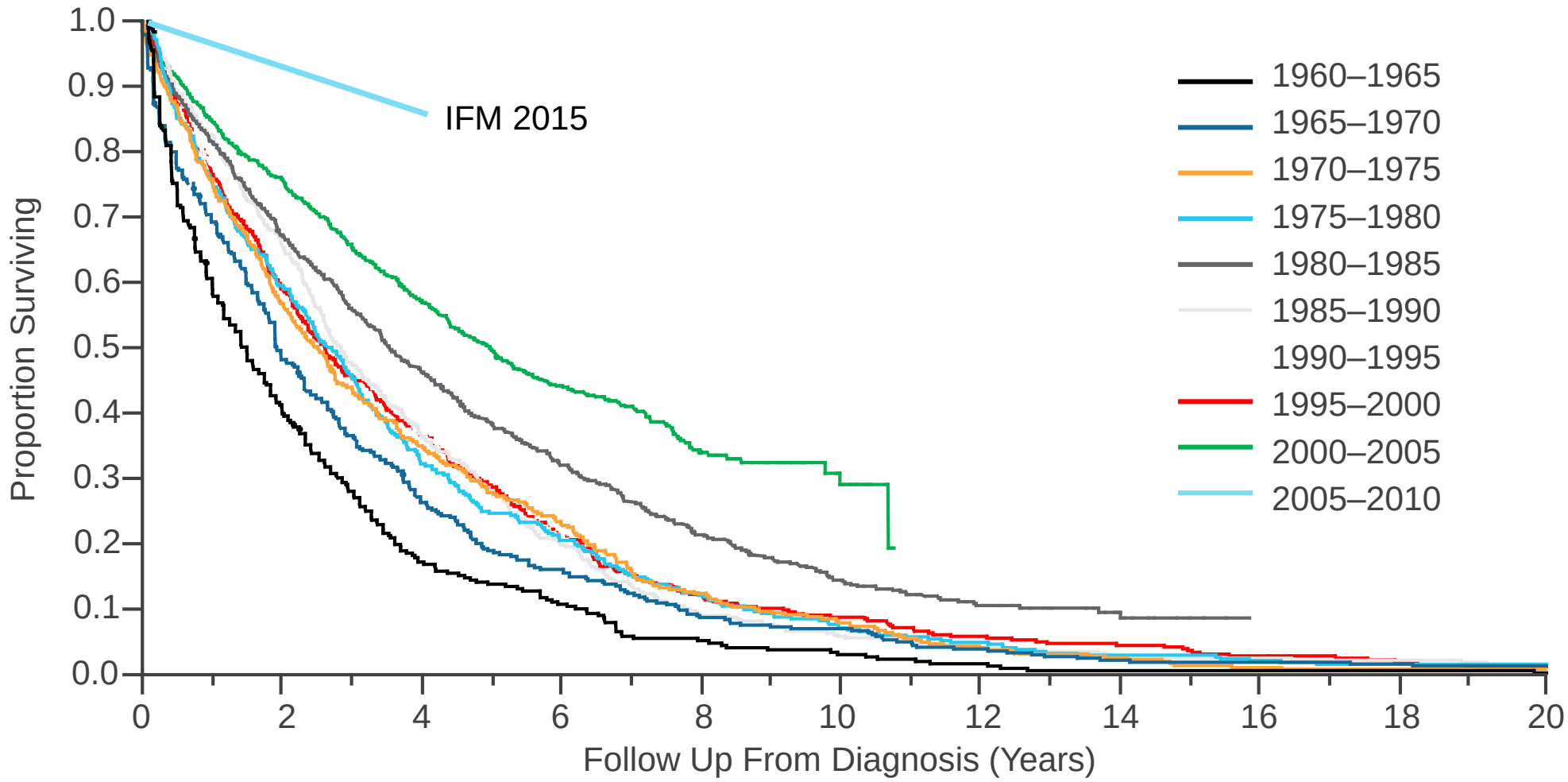


Palumbo et al. J Clin Oncol 2015

Evolution of Myeloma Therapy

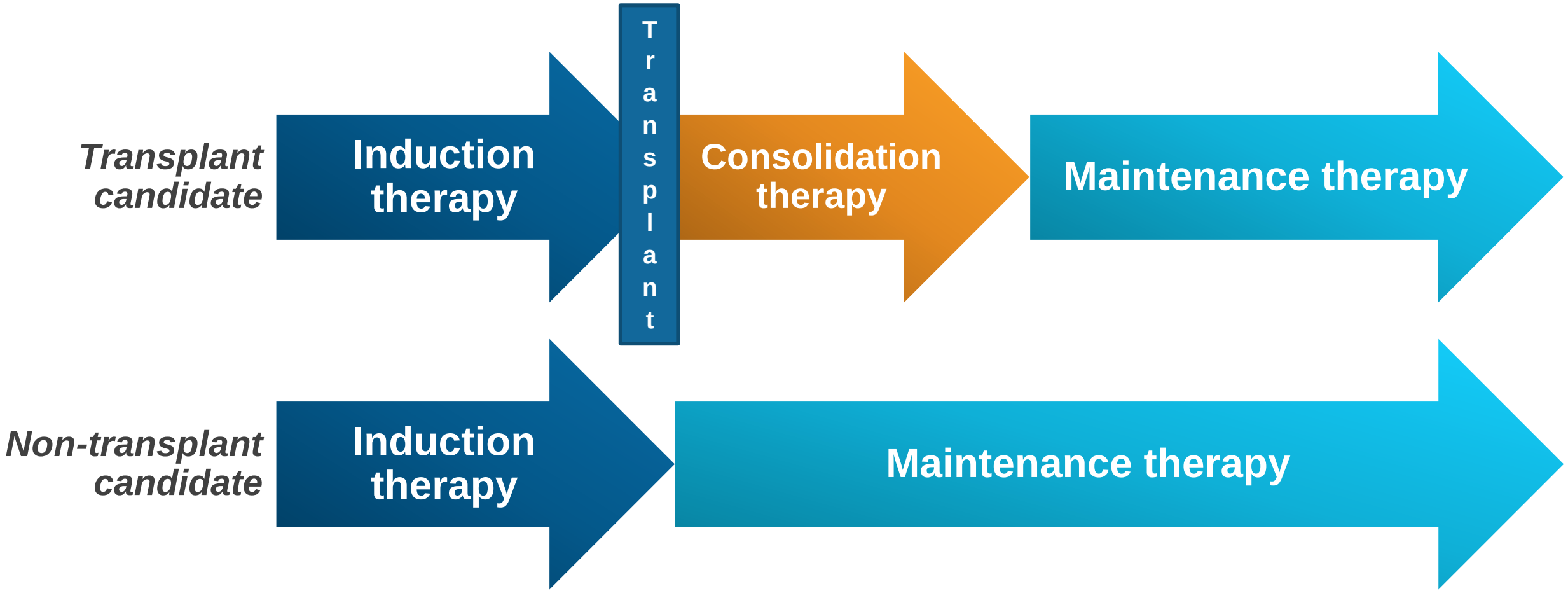


Current Drugs Have Improved Survival in MM



Adapted from Kumar SK et al. *Leukemia*. 2014;28:1122.

Current Treatment Paradigm for Newly Diagnosed Multiple Myeloma



Question 1

Which of the following concerning MGUS is true:

A) The prevalence is higher in Caucasian than African-American patients

B) A family history of MGUS or other plasma cell neoplasm is not associated with an increased risk of MGUS

C) Any level of IgM can qualify as MGUS if there is no histologic infiltrate of plasma cells or lymphoma cells and there is no end-organ damage

D) Patients with MGUS frequently have anemia

E) Approximately 10% of patients between the ages of 50 and 60 have MGUS

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D) Patients with MGUS frequently have anemia

E) Approximately 10% of patients between the ages of 50 and 60 have MGUS

Question 1

The prevalence of MGUS is higher in African-American patients and patients with a family history of MGUS or plasma cell dyscrasia. Approximately 3% of patients in their 50s will have MGUS. By definition, MGUS does not result in end-organ damage such as anemia. Any level of IgM can be considered MGUS if there is no histologic evidence of neoplasm or end-organ damage.

Question 2

A 65-year-old male has an elevated total protein on routine laboratory evaluation. His CBC, renal function and electrolytes are normal, and he is asymptomatic. A serum protein electrophoresis and IFE identify an IgG kappa monoclonal gammopathy with an M spike of 3.5 gm/dl. He is referred to a hematologist. A bone marrow biopsy and aspirate demonstrate a population of kappa restricted plasma cells constituting 20% of the marrow cellularity. The serum free light chain ratio (kappa:lambda) is 5. A skeletal survey demonstrates no evidence of lytic bone lesions. This process is best classified as:

A) Monoclonal gammopathy of undetermined significance (MGUS)

B) Smoldering multiple myeloma (SMM)

C) Multiple myeloma

D) Amyloidosis

E) Waldenstrom macroglobulinemia

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- This patient has an M spike of greater than 3 gm/dl and has greater than 10% plasma cells on bone marrow biopsy but does not have any end organ damage or myeloma defining events. This is consistent with smoldering multiple myeloma. MGUS would require an M spike of less than 3 gm/dl and less than 10% plasma cells on bone marrow examination. Multiple myeloma would require a plasma cell disorder and at least one of the following: 1 or more myeloma-defining events; ≥1 CRAB feature; clonal plasma cells in bone marrow ≥60%; serum free light chain ratio ≥100; or >1 MRI focal lesion. Waldenstrom macroglobulinemia is associated with elevated IgM, not IgG, and lymphoplasmacytic lymphoma. The patient has no end organ damage or biopsy evidence to suggest amyloidosis.