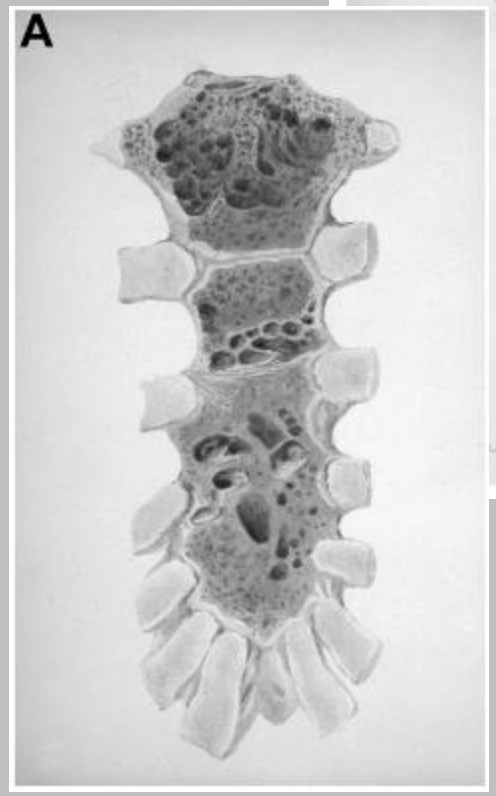
Multiple Myeloma

A Disease Overview

Monoclonal gammopathies (MG - Plasma Cell Disorders)

- Monoclonal gammopathy of undetermined significance (MGUS) – MG nejasného významu
- Multiple myeloma
  - Smoldering myeloma (SMM)
  - Indolentnt myeloma
  - Multiple myeloma stage I
  - Multiple myeloma st 2 & 3
  - Solitary plasmocytoma
    - Bone
    - Extramedular
- Primary amyloidosis (AL)
- Waldenström macroglobulinemia

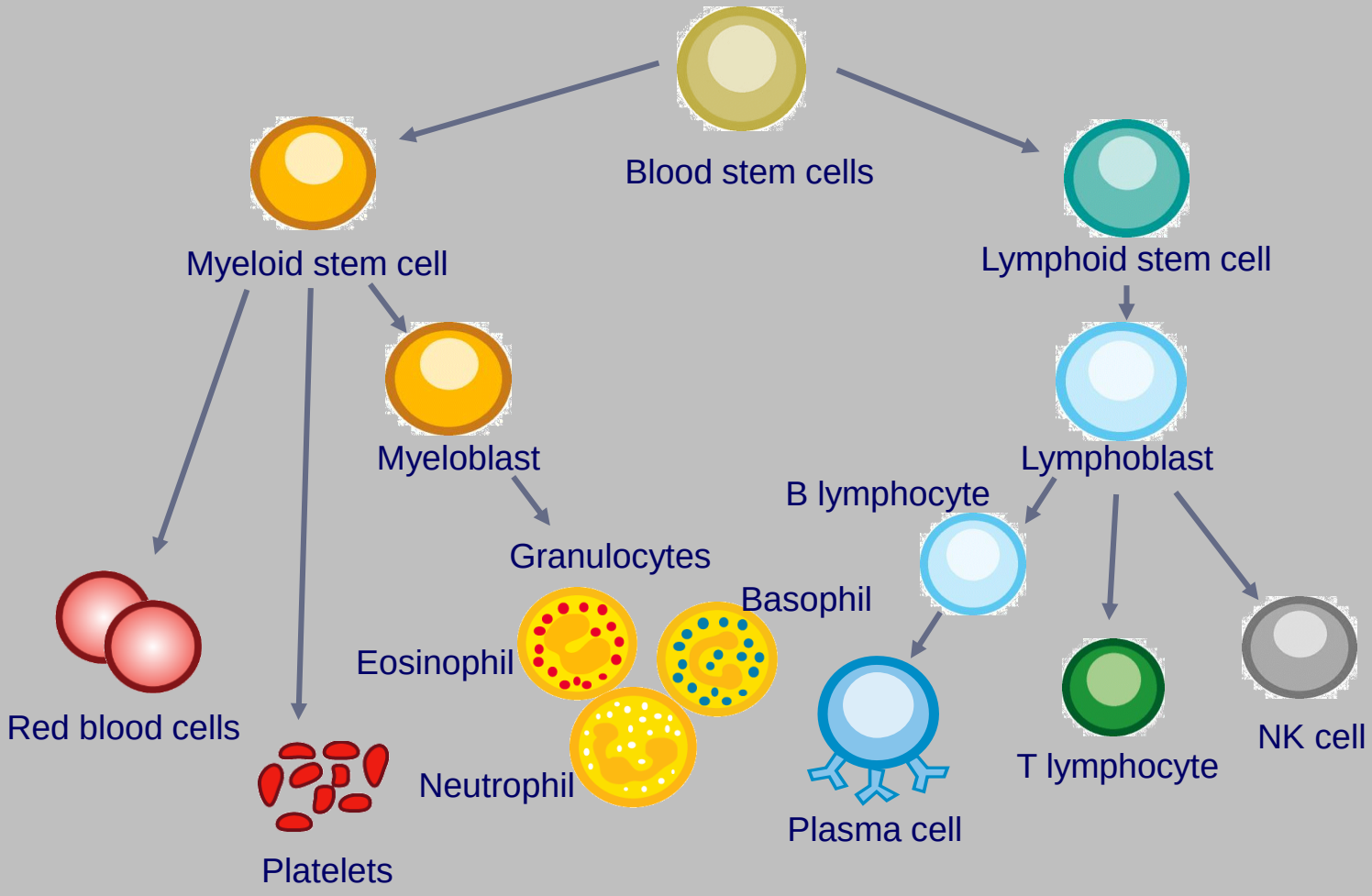


Sarah Newbury

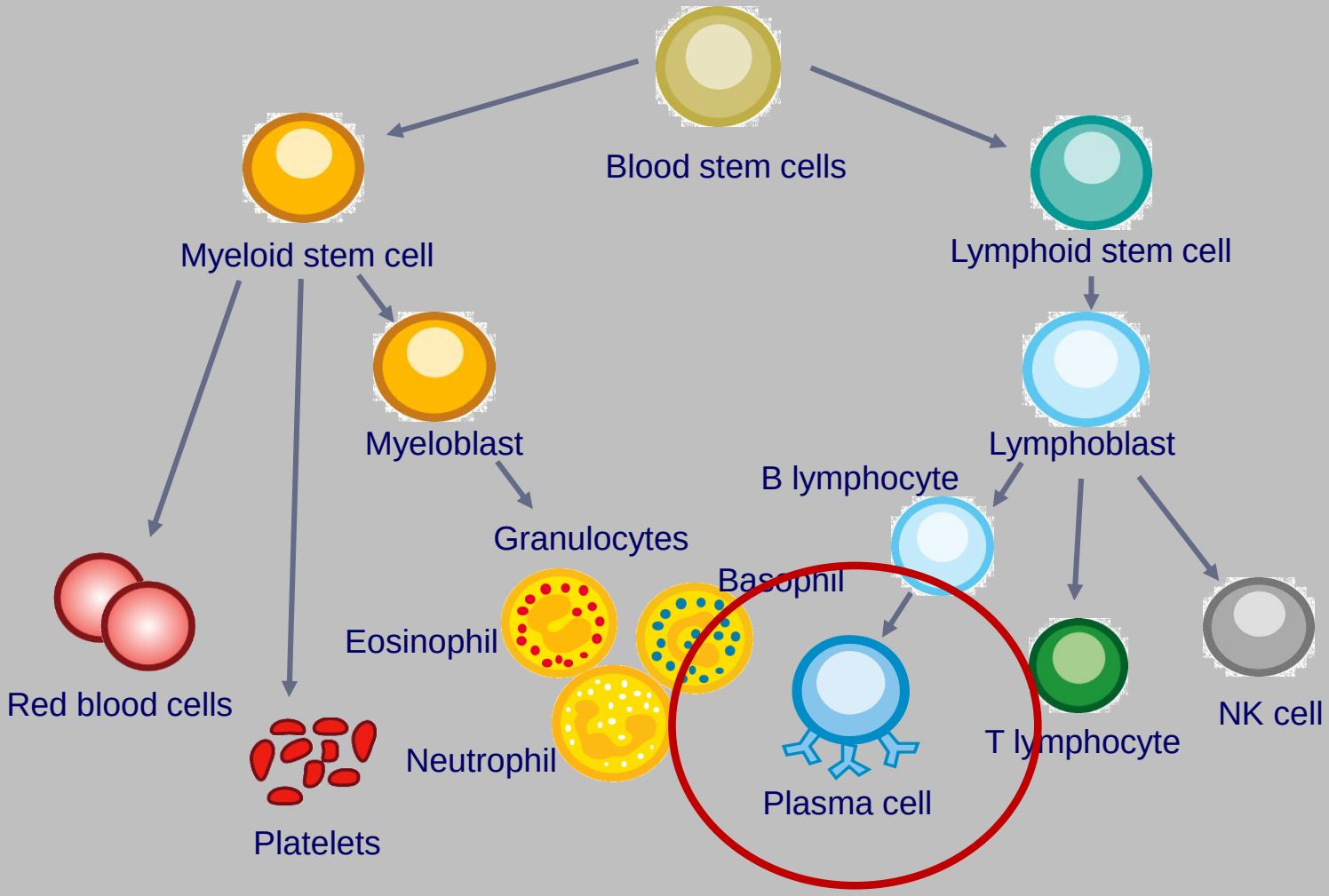
(1805-1848)

Kyle R.A., Rajkumar S. V: Multiple myeloma. Blood, 15 March 2008, Vol. 111, No. 6, pp. 2962-2972.

Haemopoiesis

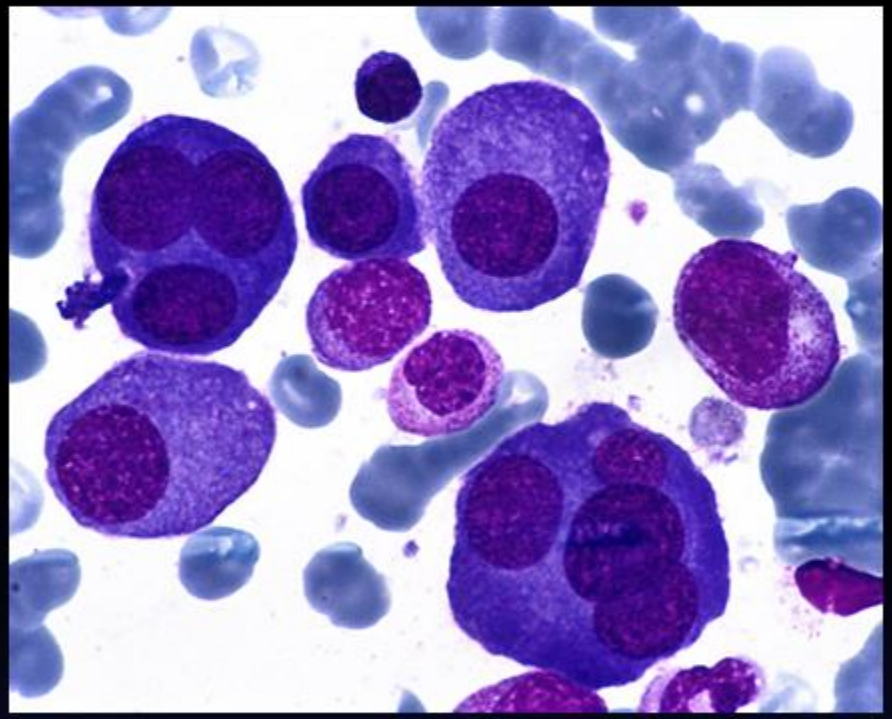


Haemopoiesis



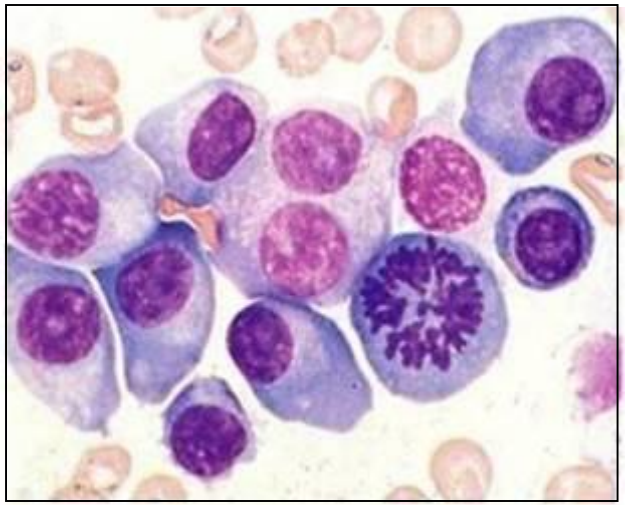
Multiple Myeloma: A Plasma Cell Malignancy

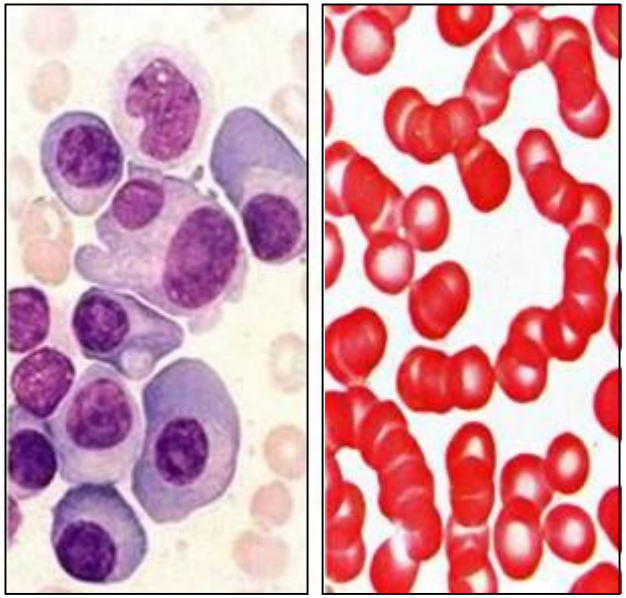
- Multiple myeloma is a B-cell malignancy derived from antibody-producing plasma cells in the bone marrow
- Myeloma cells crowd out and interfere with the development and function of normal cells in the bone marrow
- The abnormal accumulation of myeloma cells in the bone marrow and production of M-protein have direct and indirect effects on the blood, skeleton, and kidneys

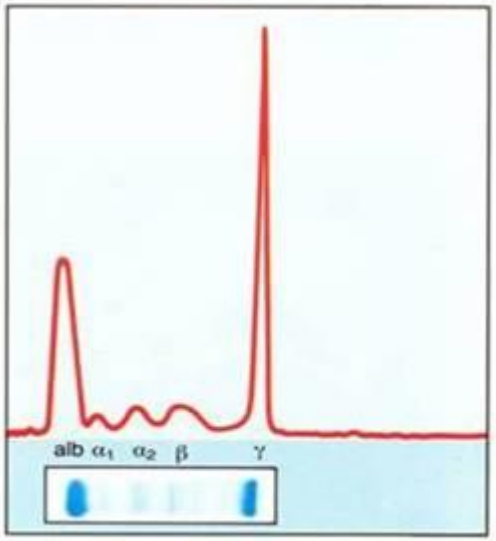


Durie. *Concise Review of the Disease and Treatment Options: Multiple Myeloma*. International Myeloma Foundation. 2011/2012 edition; Multiple Myeloma Research Foundation. *Multiple Myeloma Disease Overview*. 2011.

MNOHOČETNÝ MYELOM







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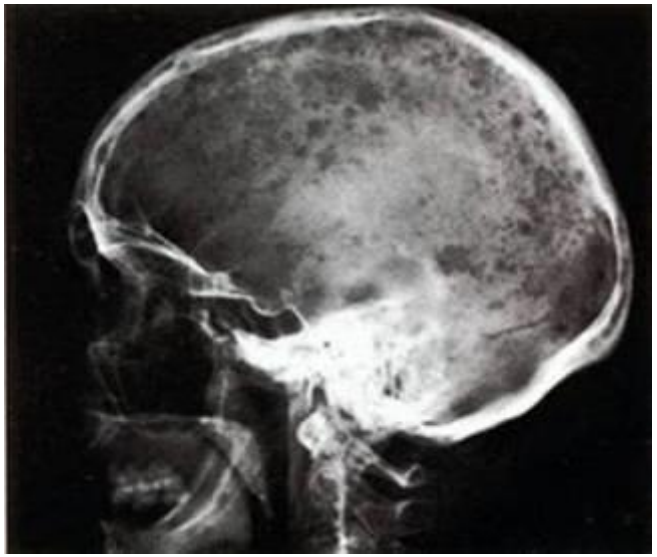
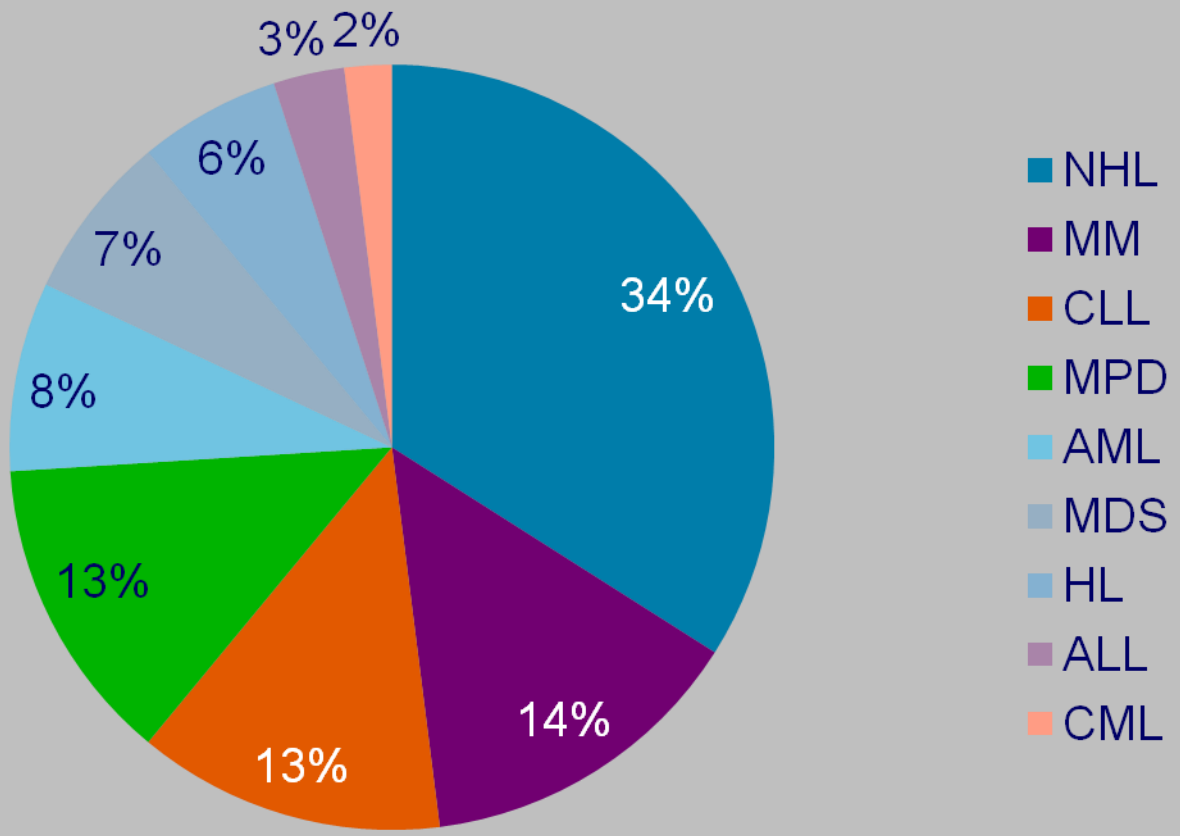


MM – klonální, nekontrolovaná proliferace a akumulace neoplasticky transformovaných el. B-buněčné linie/plazmocytů (CD_{138}+) provázená produkcí M-proteinu („paraproteinu“)

Multiple myeloma is the second most common blood cancer



ALL = acute lymphocytic leukaemia; AML = acute myeloid leukaemia; CLL = chronic lymphocytic leukaemia; CML = chronic myeloid leukaemia; HL = Hodgkin lymphoma; MDS = myelodysplastic syndromes; MPD = myeloproliferative disorders; NHL = non-Hodgkin lymphoma.

Data from Leukaemia and Lymphoma Research. Facts about blood cancers; 2010. Available from: http://www.beatbloodcancers.org/facts-about-blood-cancers.

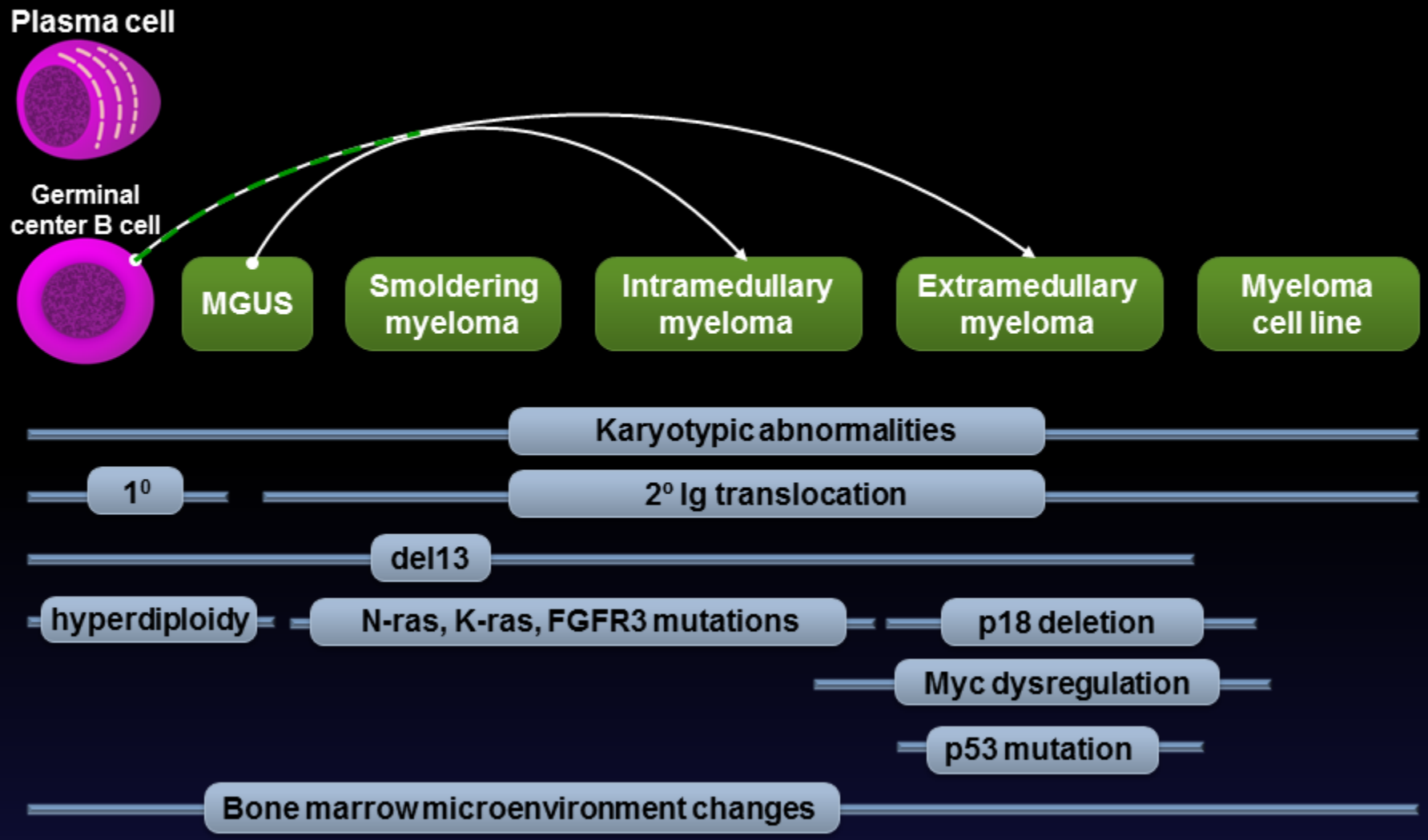
Incidence and Mortality by Race/Ethnicity and Gender

SEER (2005-2009)

	Male		Female	
Rates Per 100,000	**Incidence**	**Mortality**	**Incidence**	**Mortality**
All Races	7.4	4.4	4.7	2.7
White	6.9	4.1	4.1	2.5
Black	14.3	8.0	10.1	5.4
Asian/Pacific Islander	4.2	2.1	2.9	1.4
American Indian/Alaska Native	4.9	3.8	4.2	2.5
Hispanic	6.3	3.3	4.7	2.3

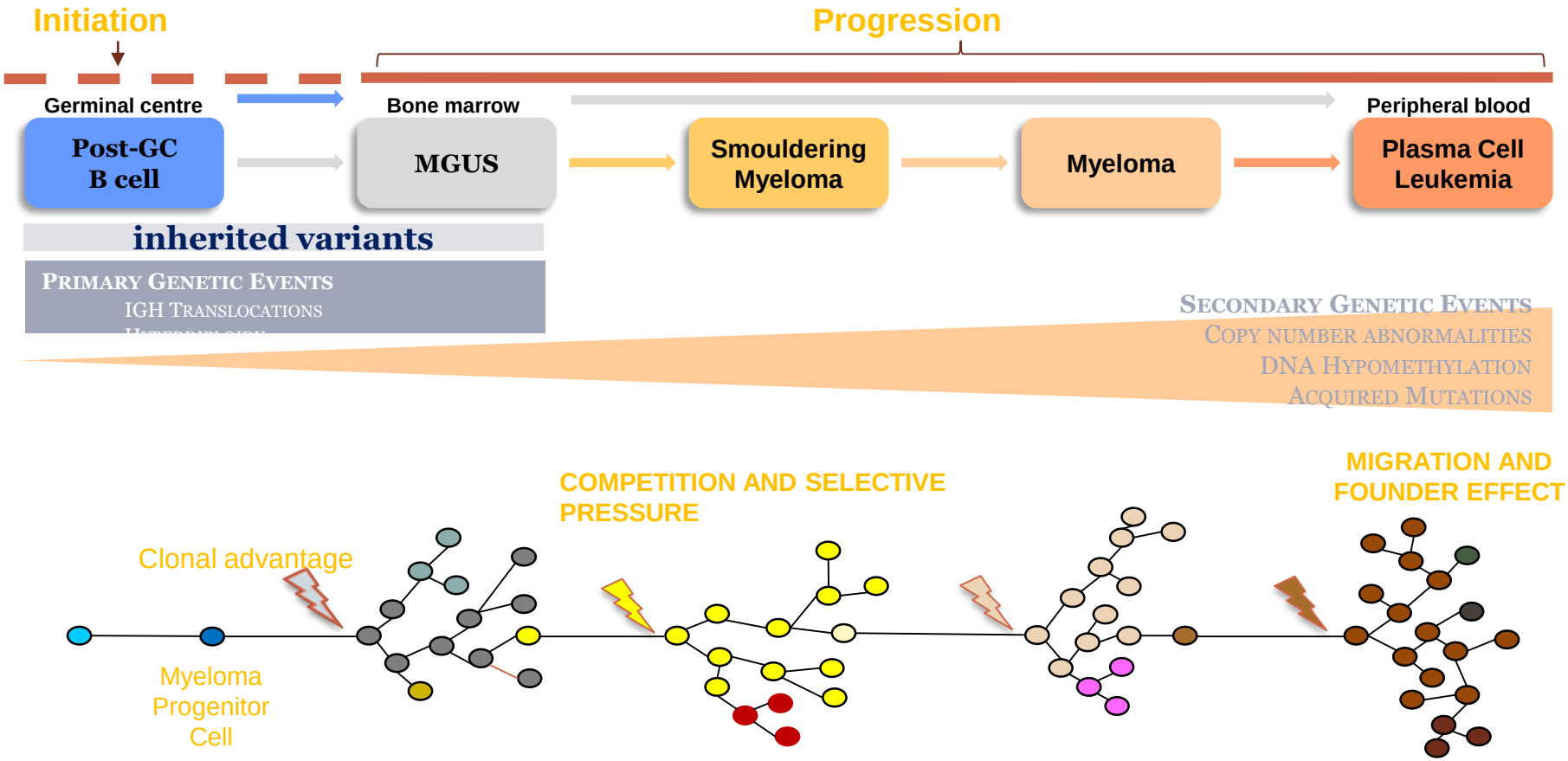
[1]http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed June 2012.

Oncogenic Events in Myelomagenesis



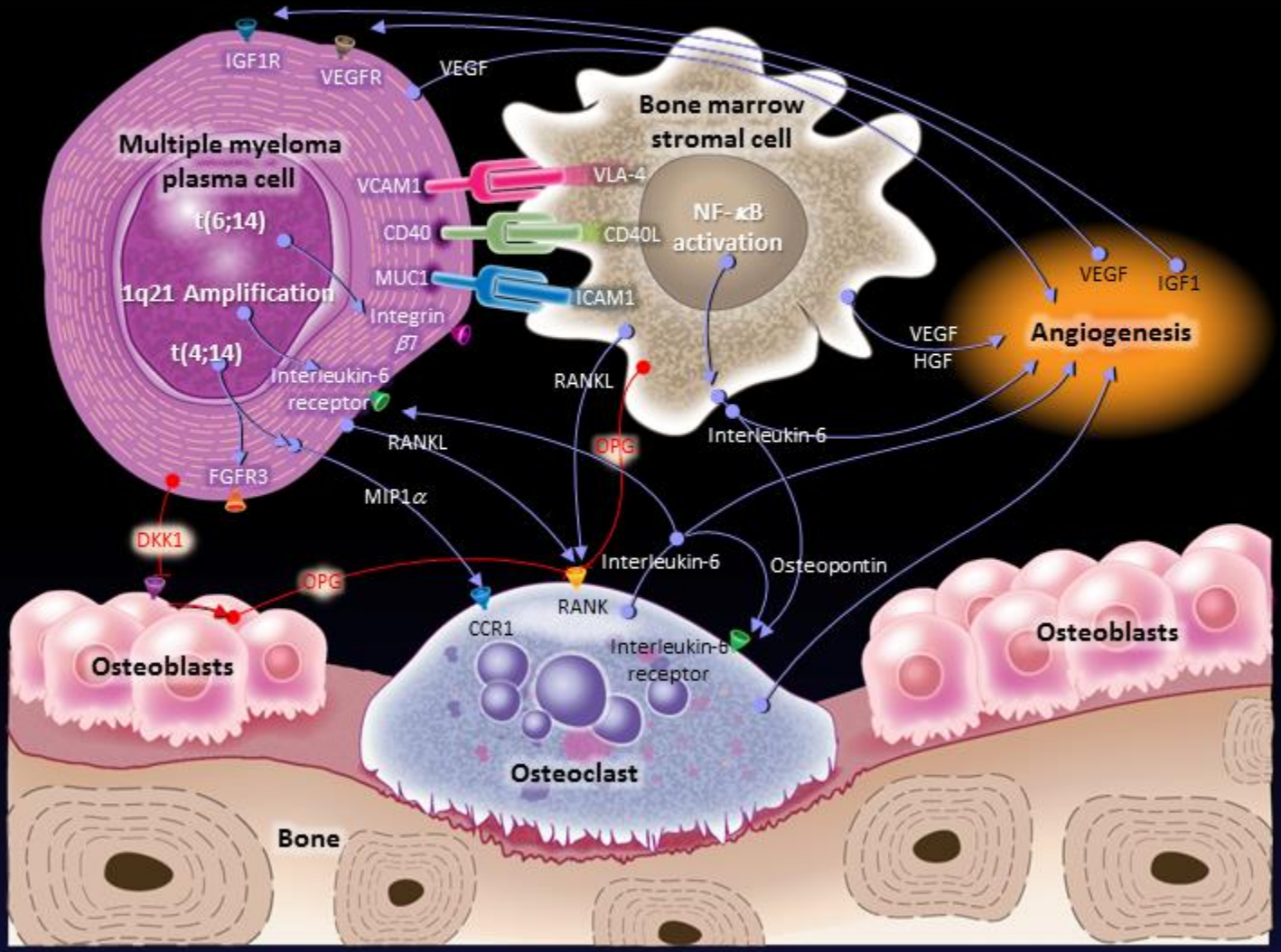
Kuehl. *Nat Rev Cancer*. 2002;2:175; Bergsagel. *J Clin Oncol*. 2005;23:6333; Landgren. *JAMA*. 2010;304:2397.

Multiple stepwise genetic alterations and clonal evolution lead to non-responsive aggressive multiple myeloma



Morgan G, et al. Nat Rev Cancer. 2012;12:335-48.

Myeloma Cells Interact with the Bone Marrow Microenvironment



Palumbo. *N Engl J Med*. 2011;364:1046.

Clinical Findings

Multiple Myeloma: Effects on Major Body Systems

Blood: anemia, abnormal clotting, immunosuppression, infection, hyperviscosity

Fatigue, dizziness, headache, dyspnea, growth factor dependency, infection, organ infarction, VTE

Renal: proteinuria, amyloidosis, hypercalcemia, renal impairment or failure

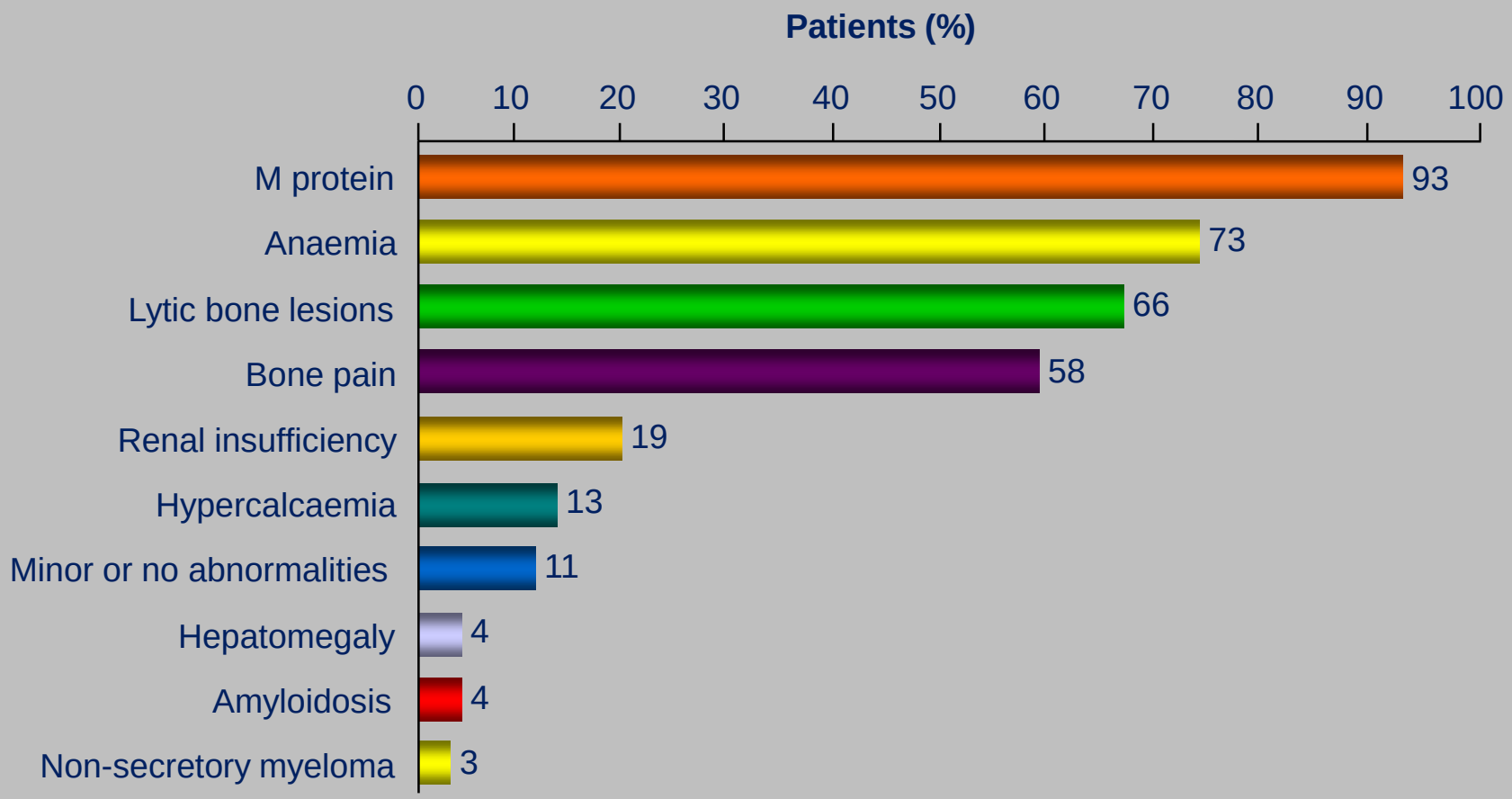
Hypercalcemic coma, dialysis dependency

Bone: lytic lesions, osteopenia, hypercalcemia (commonly skull, vertebrae, ribs, long bones)

Pain, immobility, pathologic fractures

Durie. *Concise Review of the Disease and Treatment Options: Multiple Myeloma.* International Myeloma Foundation. 2011/2012 edition; Multiple Myeloma Research Foundation. *Multiple Myeloma Disease Overview.* 2011; Snowden. *Br J Haematol.* 2011;154:76; Littlewood. *Semin Oncol.* 2002;29:40.

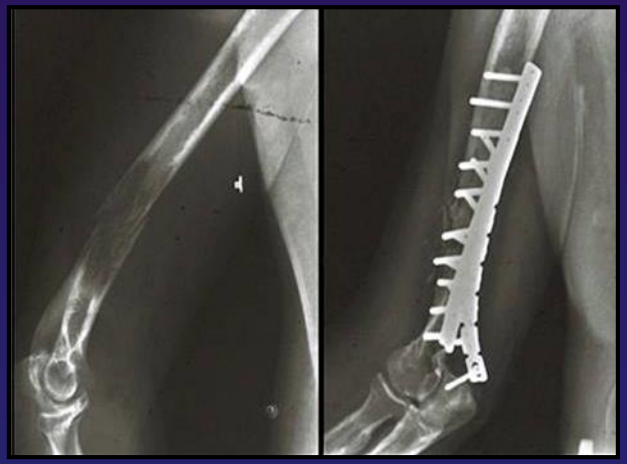
Patients with multiple myeloma have a range of signs and symptoms



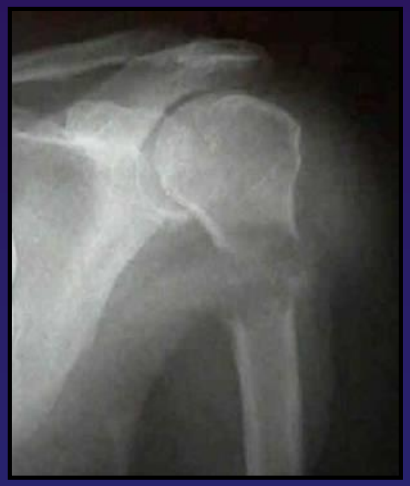
Kyle RA, et al. Mayo Clin Proc. 2003;78:21-33.

Metastases to Bone Contribute to Significant Skeletal Morbidity by Causing Skeletal Related Events (SREs)

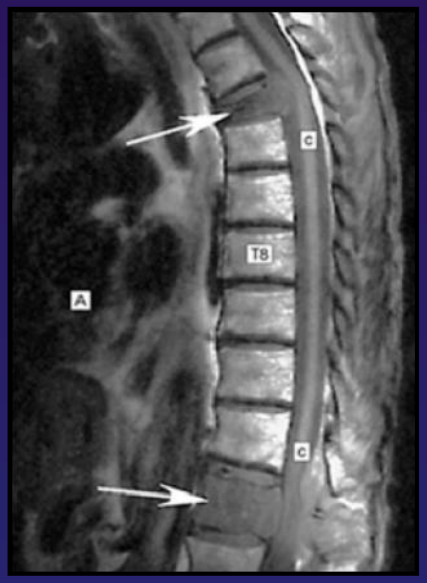
- Surgery to bone[1]



- Pathologic fracture[2]



- Spinal cord compression[3]



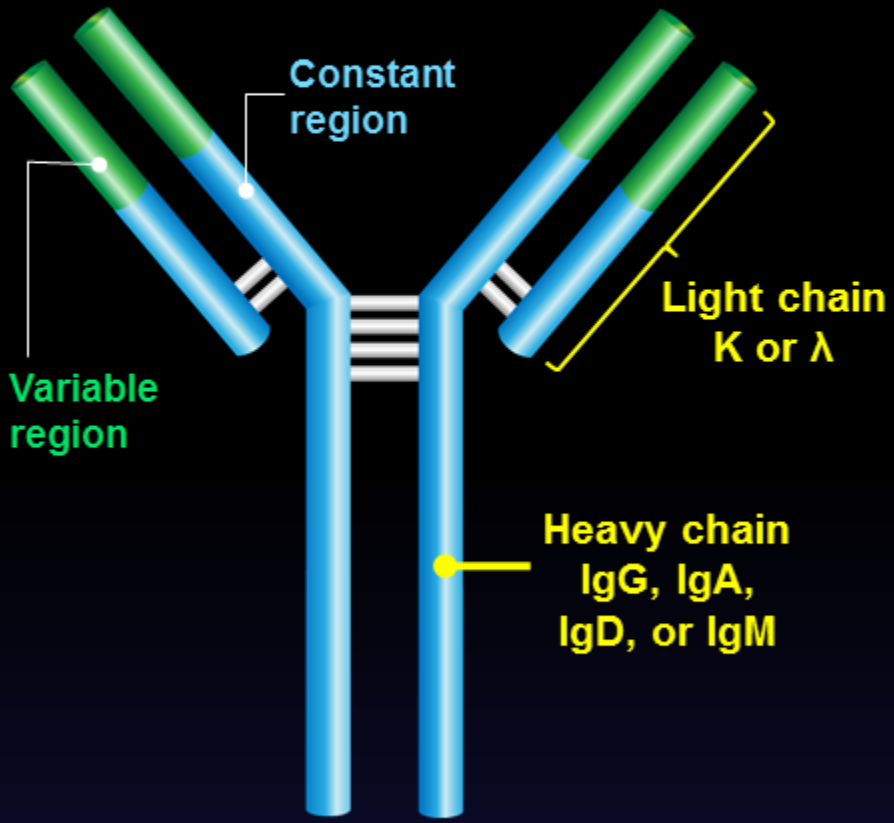
- Radiotherapy to bone for pain[4]

- 1. Available at: http://www.hopkins-arthritis.org/rheumrounds/metastatic_bone_disease_rheumrounds2.html. Accessed 8/2007 Provided by John Hopkins Arthritis Center at John Hopkins University
2. Wheeless' Textbook of Orthopaedics. www.wheelessonline.com © 2007 Data Trace Publishing Company. All rights reserved
3. Higdon ML, et al. *Am Fam Physician* 2006;74:1873-80 Permission obtained
4. This image is licensed under the GNU Free Documentation License

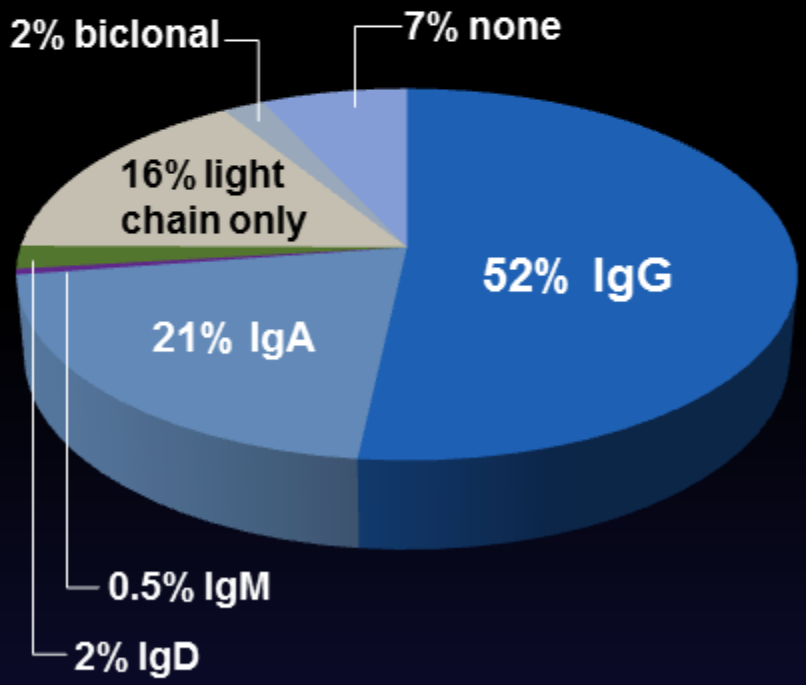
Diagnosis

Multiple Myeloma Cells Produce a Single Monoclonal Antibody

Immunoglobulin

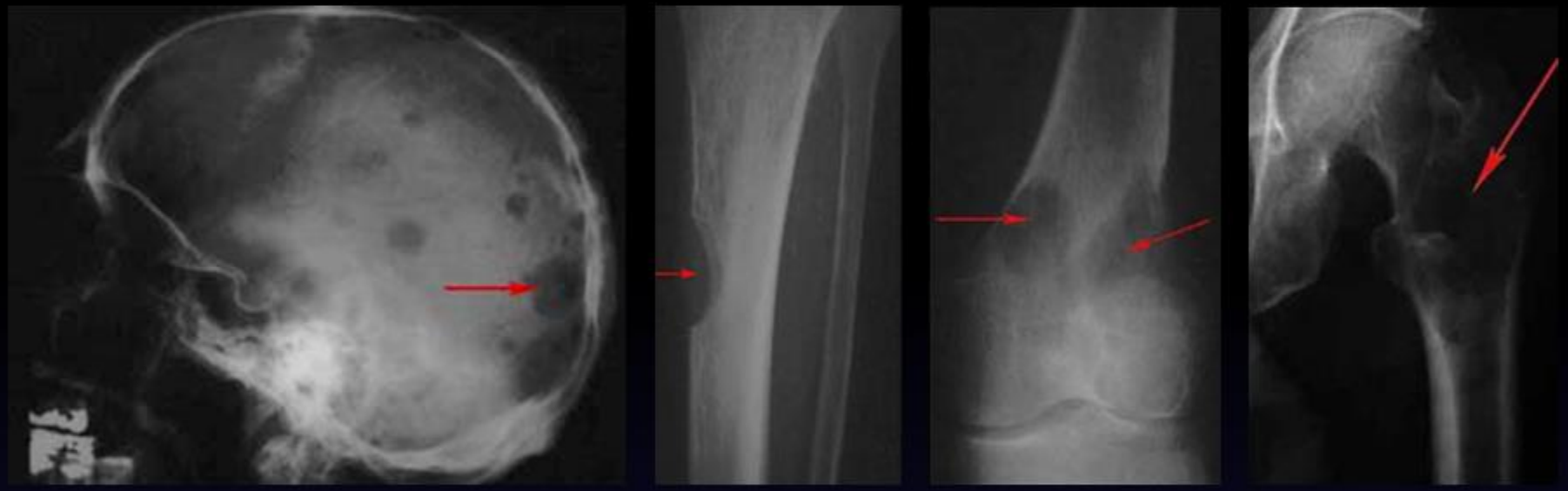


Types of Serum M-Protein in Multiple Myeloma



Durie. *Concise Review of the Disease and Treatment Options: Multiple Myeloma.* International Myeloma Foundation. 2011/2012 edition; Kyle. *Mayo Clin Proc.* 2003;78:21.

Establishing Diagnosis: Skeletal Survey



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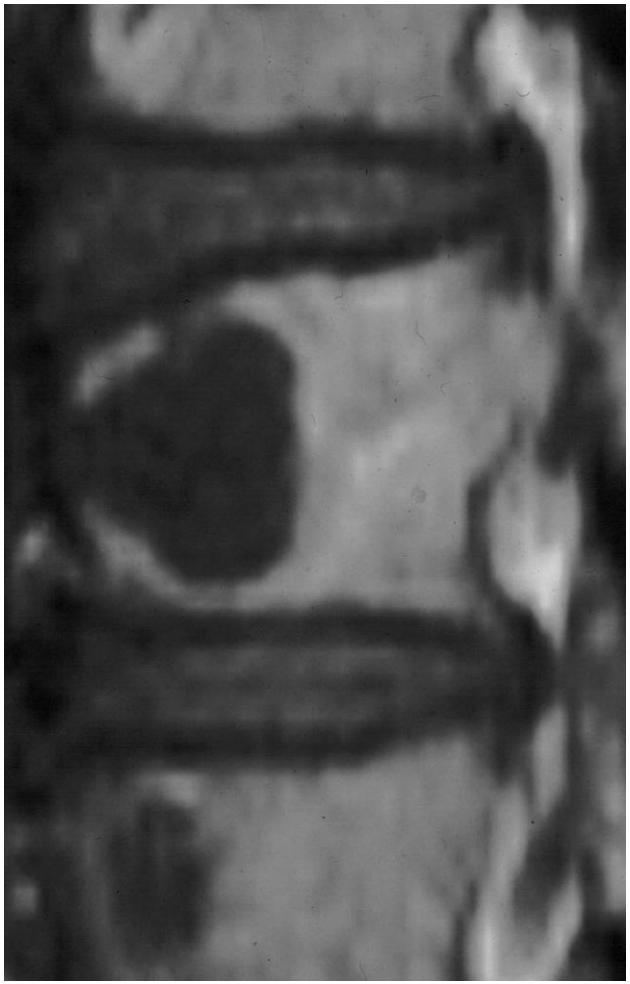
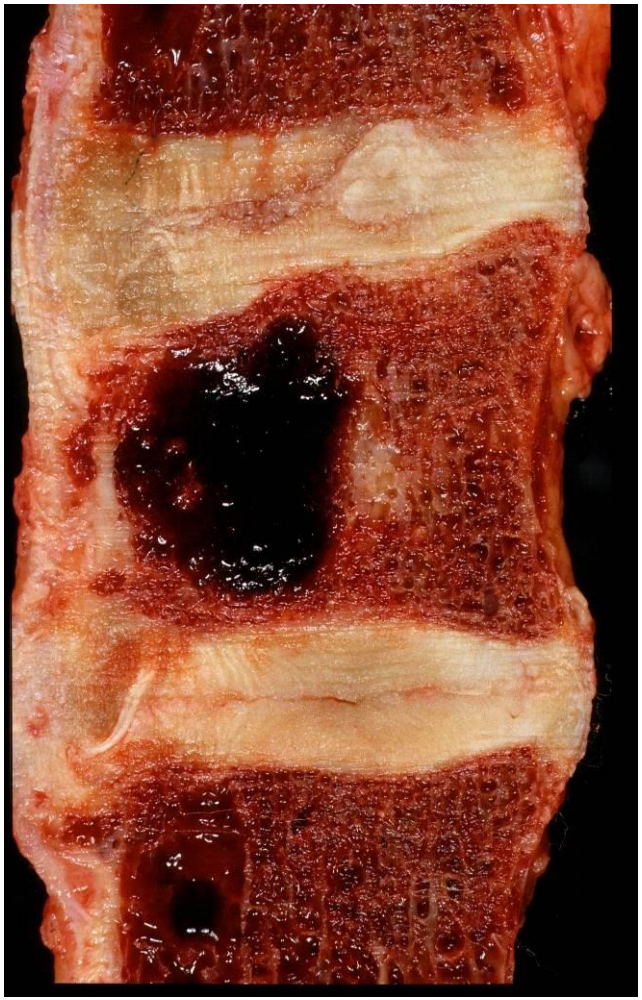
- IRM, détection des métastases osseuses





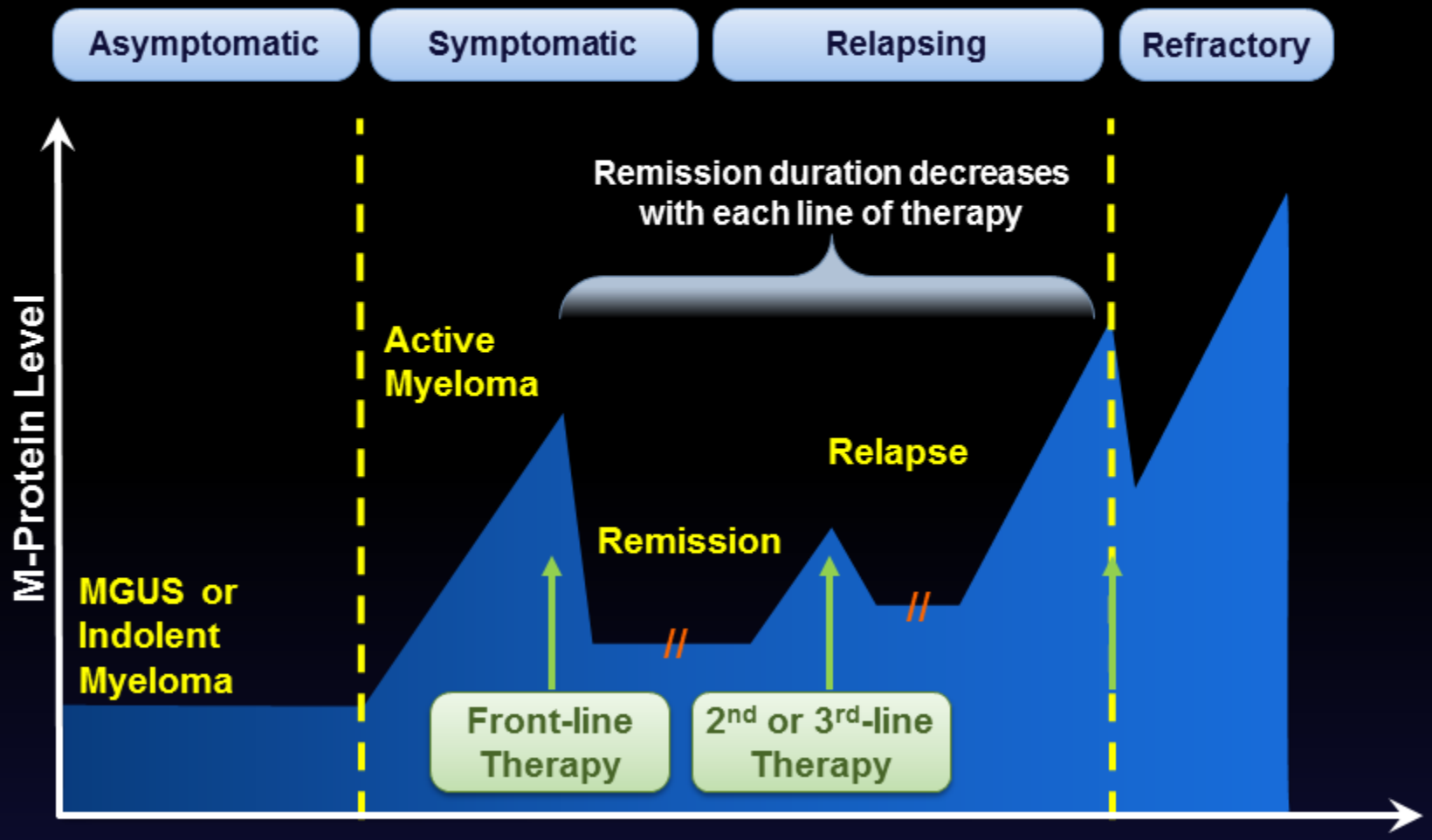
IMWG Diagnostic Criteria for Symptomatic MM

Criteria for Symptomatic MM (all 3 required)		
1	≥ 10% monoclonal plasma cells in bone marrow	
2	Monoclonal protein in serum and/or urine	
3	Presence of end-organ damage (at least one of the below)	
	Calcium	Serum calcium ≥11.5 mg/100 mL
	Renal	Serum creatinine >1.73 mmol/L
	Anemia	Hb <10 g/100 mL or >2 g/100 mL below normal
	Bone	Lytic lesions, severe osteopenia, pathologic fractures

Palumbo. *Leukemia*. 2009;23:1716.

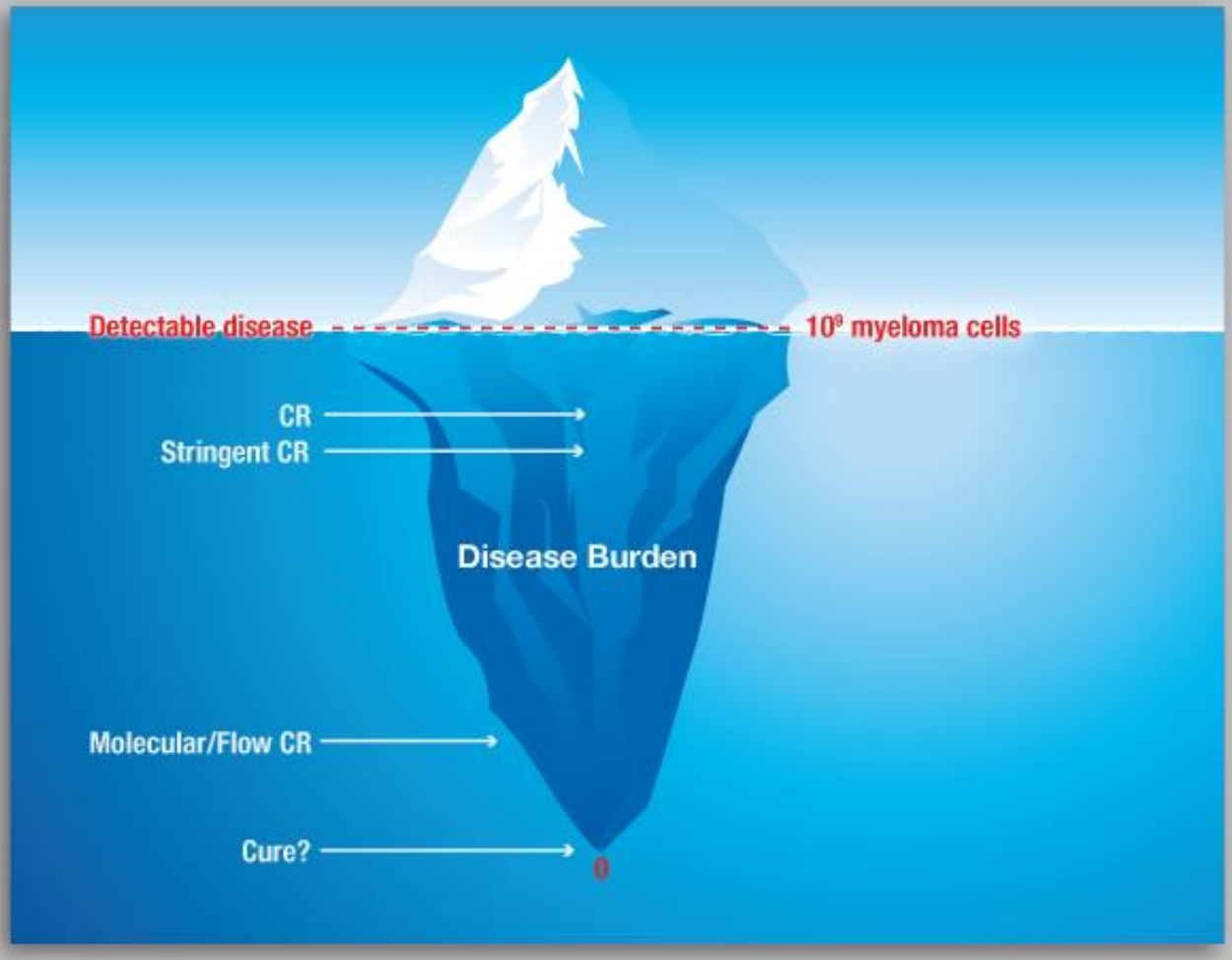
Treatment

Multiple Myeloma is Characterized by a Pattern of Remission and Relapse



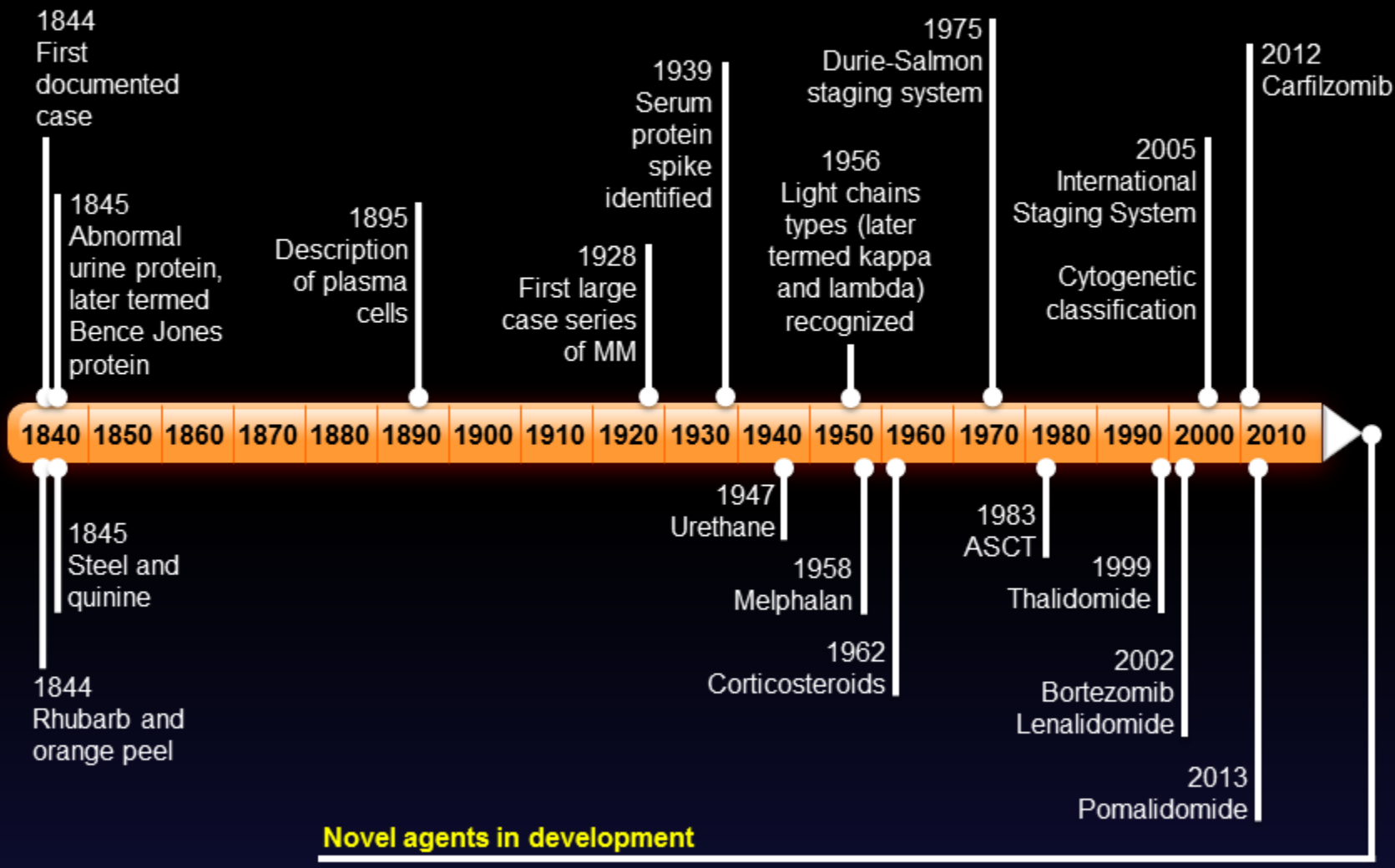
Durie. *Concise Review of the Disease and Treatment Options: Multiple Myeloma.* International Myeloma Foundation; 2011/2012 edition; Kumar. *Mayo Clin Proc.* 2004;79:867.

Is treating to a CR enough?



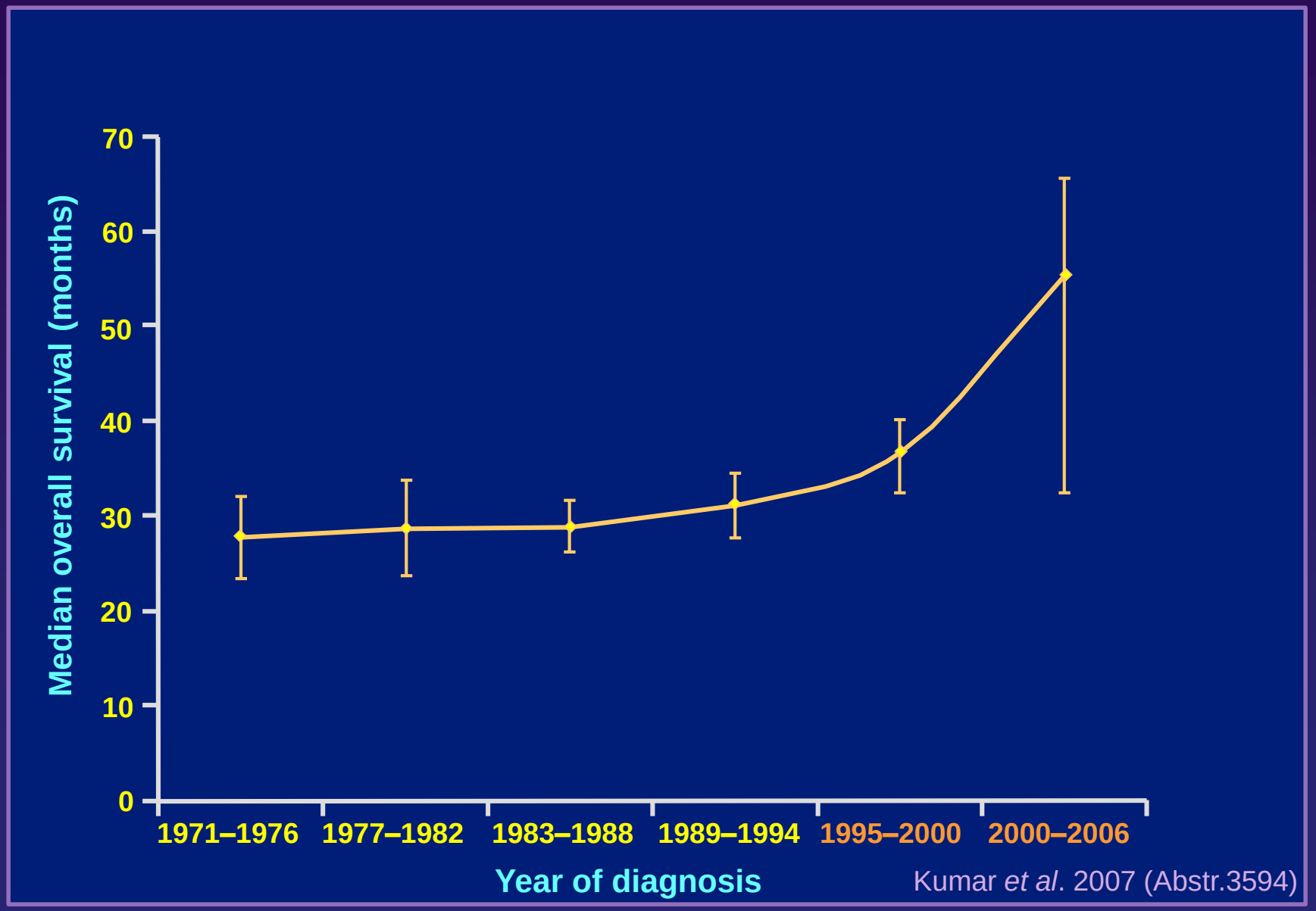
References: 1. Dingli D et al. *Cancer Sci.* 2007;98(7):1035-1040. **2.** Dingli D et al. *J Clin Oncol.* 2007;25(31):4933-4937. **3.** Munshi NC et al. *J Clin Oncol*. 2013;31:2523-2526.

Multiple Myeloma: History



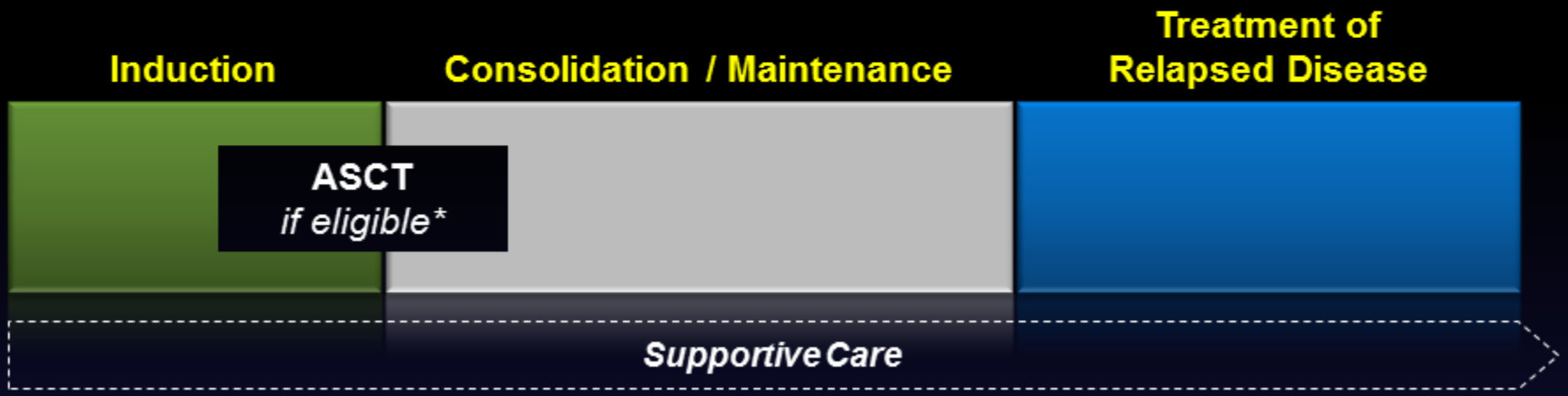
Kyle. *Blood*. 2008;111:2962; Durie. *Concise Review of the Disease and Treatment Options: Multiple Myeloma*. International Myeloma Foundation; 2011/2012 edition; KYPROLIS [package insert]. Onyx Pharmaceuticals, Inc. July 2012; POMALYST [package insert]. Celgene Corporation. February 2012.

Vliv nových léků na OS u pacientů s nově diagnostikovaným MM (n=2981)



Available Therapies for Multiple Myeloma

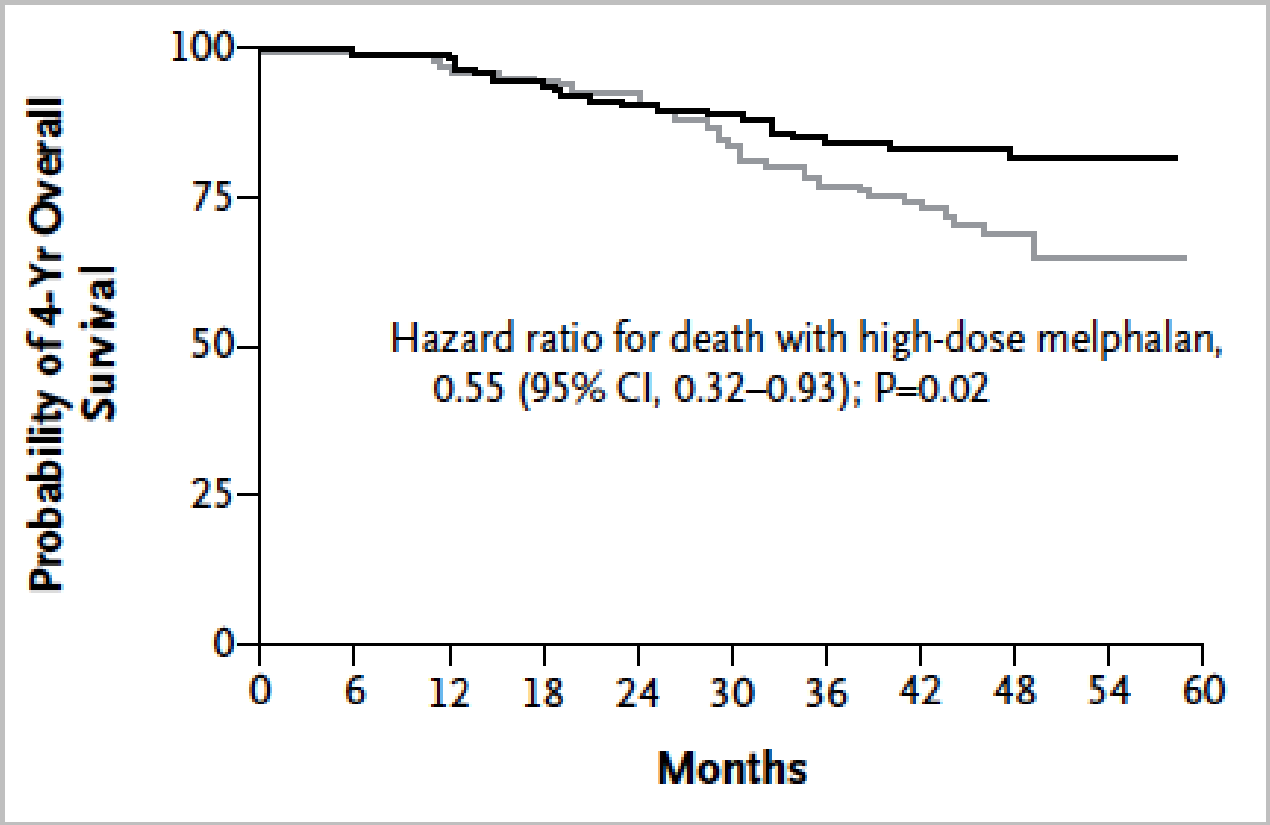
Treatment Options
Conventional chemotherapy (e.g., alkylating agents)
Steroids (corticosteroids)
Autologous stem cell transplant (ASCT)
"Novel" agents (proteasome inhibitors, immunomodulatory agents, etc)



*Transplant eligibility may impact initial treatment decisions

Multiple Myeloma Research Foundation. *Multiple Myeloma Disease Overview*. 2011.
Rajkumar. ASCO 2012 Education Session.

HDT-ASCT improves OS compared with novel agent-based induction therapy



Reference: Palumbo A et al. N Engl J Med. 2014;371(10):895-905.

Summary

- Multiple myeloma is a chronic, progressive disease of plasma cells, characterized by a pattern of remission and relapse
- Pathogenesis is dependent on the interaction of myeloma cells with components of the bone marrow microenvironment
- Hallmark clinical features are anemia, renal impairment, and lytic bone disease.
- Staging and prognosis have evolved due to a better understanding of disease biology
- Response criteria have evolved based on improvements in treatment efficacy with novel agents
- Treatment strategy is individualized based on patient and tumor factors.

Immunoglobulin Light-Chain Amyloidosis

- **Organ dysfunction due to accumulation of misfolded Ig light chain**

Signs and Symptoms	Evaluation
• Fatigue • Cardiomyopathy: dyspnea on exertion, edema • Albuminuria in non-diabetic patient • Sensorimotor peripheral neuropathy • Hepatomegaly	• Immunofixation & electrophoresis of serum and urine • Free light chain analysis • Biopsy of subcutaneous fat and bone marrow if above are positive

Prognosis depends on extent of cardiac involvement and level of Ig light chain at diagnosis

Gertz. *Oncology*. 2012;26:152.