ASSOCIATION OF COMMUNITY CANCER CENTERS

MULTIDISCIPLINARY MULTIPLE MYELOMA CARE

Education Project Overview

Association of Community Cancer Centers

Project Goals and Objectives

Greatly enhance the education of community providers and adoption of effective practices, including incorporation of the latest and best treatment options for patients diagnosed with multiple myeloma.

I. Raise awareness about education needs of healthcare providers in the community setting related to the management of multiple myeloma patients.

II. Educate the multidisciplinary healthcare team on how to implement effective practices in the treatment of multiple myeloma in community-based programs.

III. Establish vetted and designated resources for multiple myeloma that will be an enduring source of information for providers.

IV. Convene a strong network of advocacy and professional partners to increase peer-to-peer learning and adoption of effective practices.

Site Visits

- **Yuma Regional Medical Center Cancer Center**
  - Yuma, Arizona
  - Comprehensive Community Cancer Program
- **John Theurer Cancer Center at Hackensack University Medical Center**
  - Hackensack, New Jersey
  - Academic Comprehensive Cancer Program
- **H. Lee Moffitt Cancer Center**
  - Tampa, Florida
  - NCI-Designated Comprehensive Cancer Program

International Myeloma Working Group (IMWG)

- Incorporating the latest guidance from the International Myeloma Working Group (IMWG) to improve diagnosis, assess prognosis, and develop tailored treatment plans

  - Diagnostic workup that includes flow cytometry, immunohistochemistry, cytogenetics, and molecular diagnostics
  - Revised International Staging System (R-ISS)
  - Assess risk profiles and engage in shared decision-making conversations with each patient
  - Refer patients who are eligible candidates for transplant evaluation

imwg.myeloma.org

Skeletal-Related Events (SREs)

- Many patients with multiple myeloma have bony lesions and are often treated with either zoledronic acid (infusion) or denosumab (injection)
  - Monitor for side effects such as osteonecrosis of the jaw (ONJ)
  - Assess patient preferences
- Incorporating the 2018 ASCO Clinical Practice Guideline Update: Role of Bone-Modifying Agents in Multiple Myeloma
  - Key clinical question: “What is the role of bone-modifying agents in patients with multiple myeloma?”
- Severe SREs such as spinal cord compression or vertebral compression fractures may occur
  - Often requires surgical management to prevent permanent paralysis

Advancing Research to Improve Care

- John Theurer Cancer Center has been involved with the Multiple Myeloma Research Foundation (MMRF) CoMMpass (Relating Clinical Outcomes in MM to Personal Assessment of Genetic Profile) Study
  - Discovery of 12 different molecular types of multiple myeloma, each with its own level of risk

- Moffitt Cancer Center is a founding member of Oncology Research Information Exchange Network (ORIEN), a cross-institutional research partnership
  - Includes a longitudinal study called Total Cancer Care which examines the effects of different cancers, treatment choices, and lifestyle so that physicians can have a better understanding of patient outcomes and treatment options

Project Webpage

- Advisory Committee
- Educational resources
  - Regional lectures and recorded webinars
  - Provider Resource Portal
- Journal supplement – *Case Studies in Multiple Myeloma Care*

accc-cancer.org/multiple-myeloma-care

ASSOCIATION OF COMMUNITY CANCER CENTERS

MULTIDISCIPLINARY MULTIPLE MYELOMA CARE

Regional Lecture Series

Leveraging a Multidisciplinary Approach to Multiple Myeloma Care

ACCC
Association of Community Cancer Centers

Leveraging a Multidisciplinary Approach to Multiple Myeloma Care

Dr. Yogesh S. Jethava, MBBS, FACP

University of Iowa Hospitals & Clinics

Disclosure

- Consultancy: Celgene and Janssen

Case Scenario

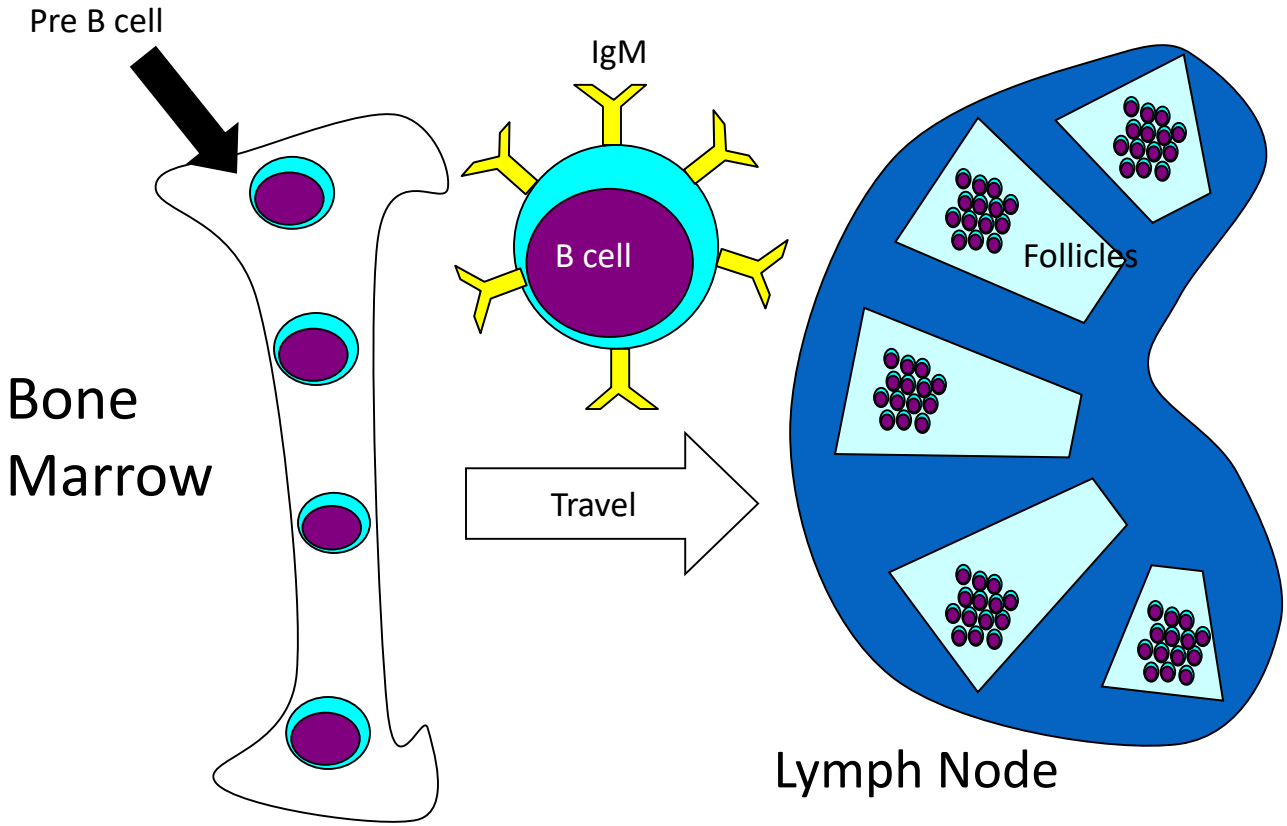
- James Bond, 45-year-old male comes for routine yearly physical
- Found to have elevated total protein
- Further work up: elevated globulins!!

Case Scenario

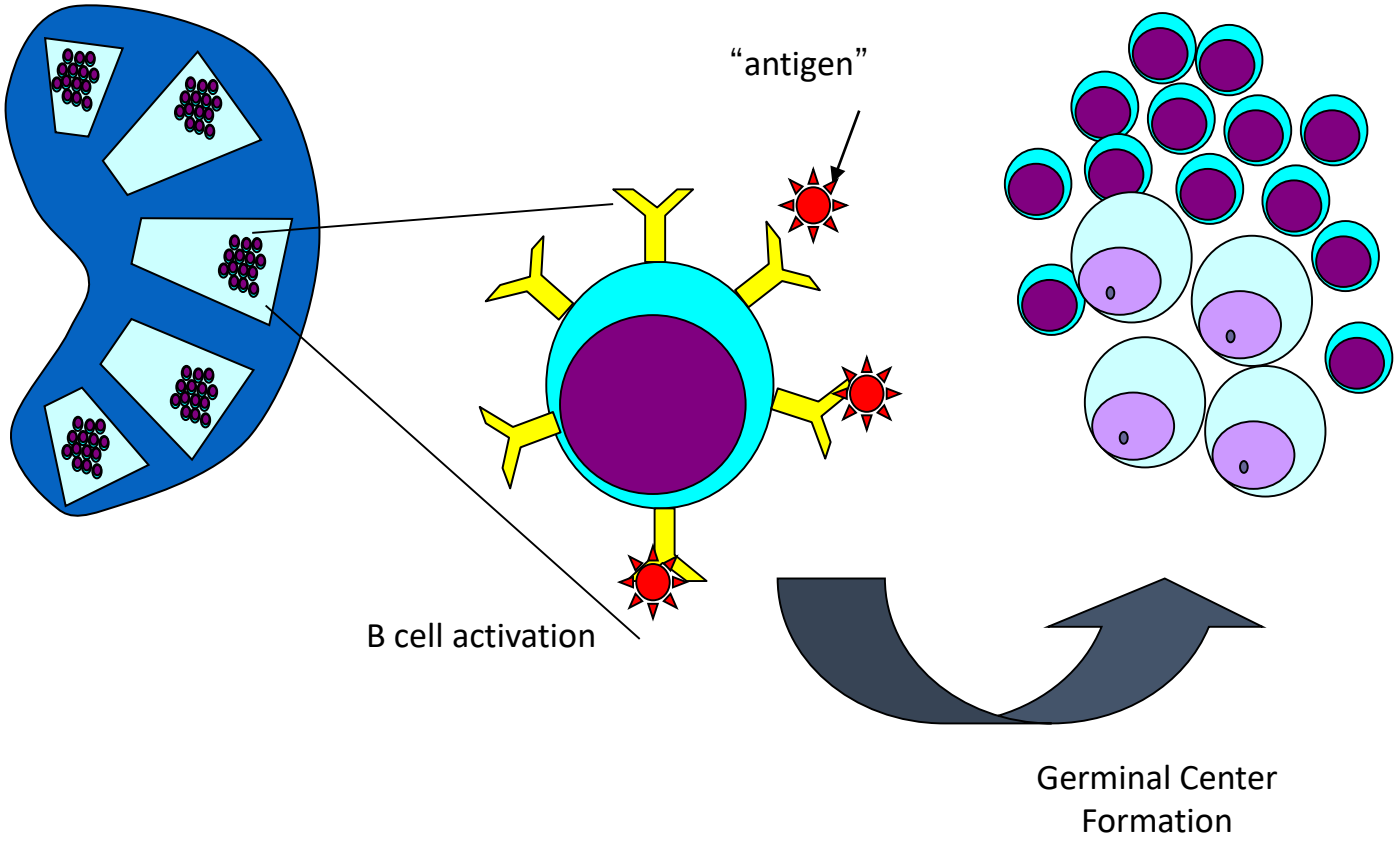
- Normal CBC
- Normal Calcium
- Normal Creatinine

- You do specific tests to find out whether this is monoclonal or polyclonal protein
  - Which are those tests?

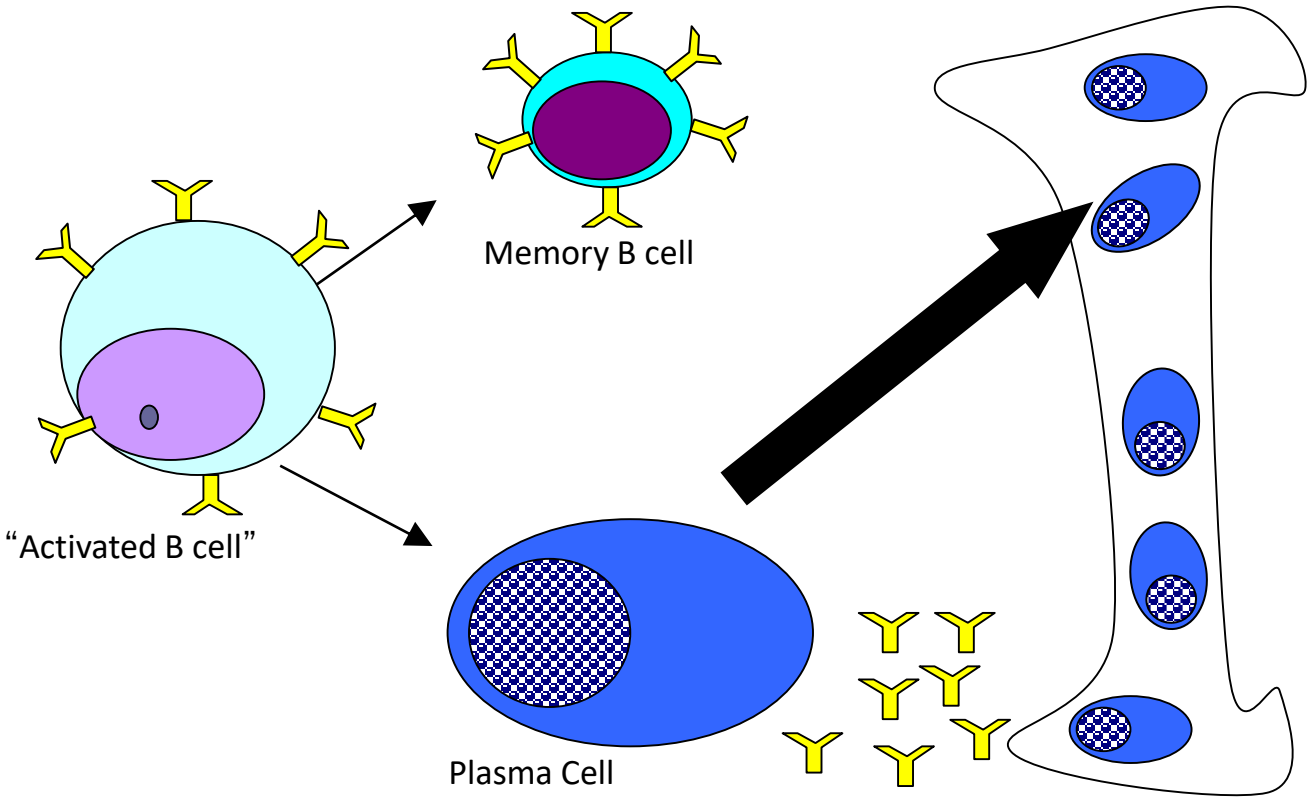
Normal B Cell Development



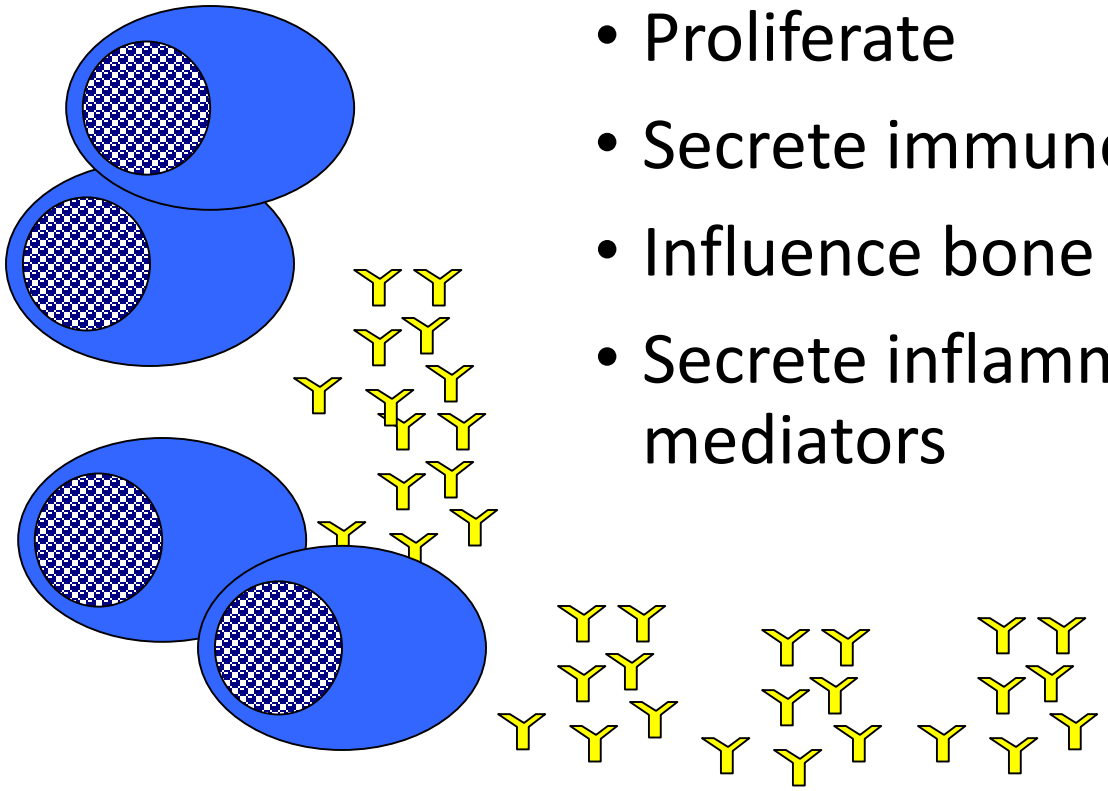
B Cell Activation



Plasma Cells Travel Back to Bone Marrow

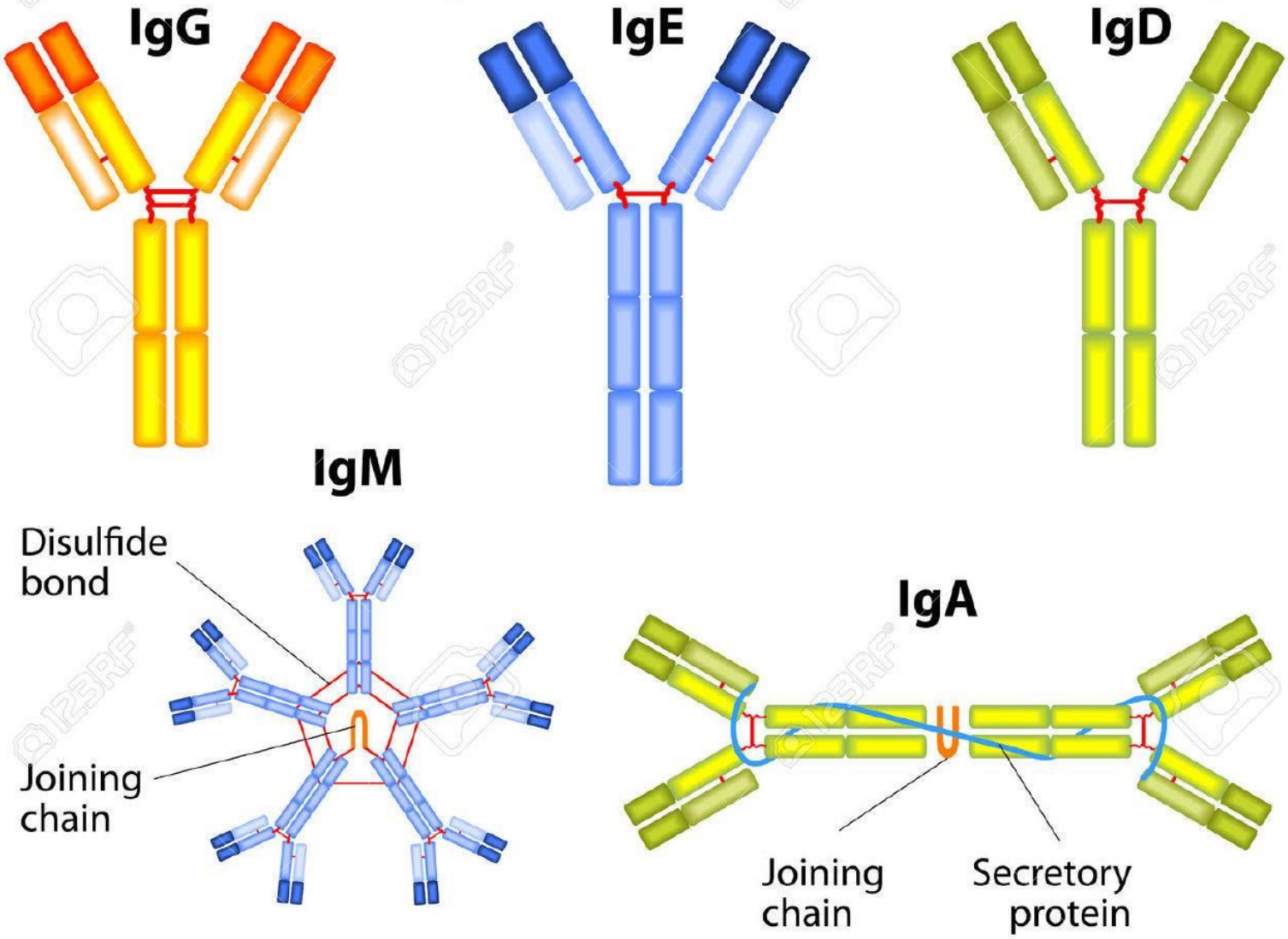


Properties of Plasma Cells



- Proliferate
- Secrete immunoglobulins
- Influence bone turnover
- Secrete inflammatory mediators

ANTIBODY CLASSIFICATION



Common Terminologies

Serum Protein Electrophoresis (SPEP)	Measures the levels of various proteins in the blood and detects abnormal monoclonal protein level.
Immunofixation (or Immunoelectrophoresis, IPEP)	This test can reveal the specific type of abnormal protein produced by the myeloma.
Immunoglobulin Levels	Active secretion of one form of immunoglobulin and suppression of normal immunoglobulin levels.

Common Terminologies

24-hour urine test for Bence Jones or light chain proteins in the urine	Actual amount of monoclonal protein secreted by the kidneys.
Serum free light chain measurement	This test measures the amount of light chains in the blood.

Investigations

- Serum monoclonal protein <3 g/dL
- <10 % bone marrow plasma cells
- Urinary monoclonal protein < 500 mg per 24 hours
- Absence of myeloma defining events or amyloidosis

MGUS

MGUS

- Does it need treatment? NO
- Does it progress to Myeloma? YES

2% of MGUS per year progress to MM

Patient is Being Monitored Regularly

- Now he is 50 years of age

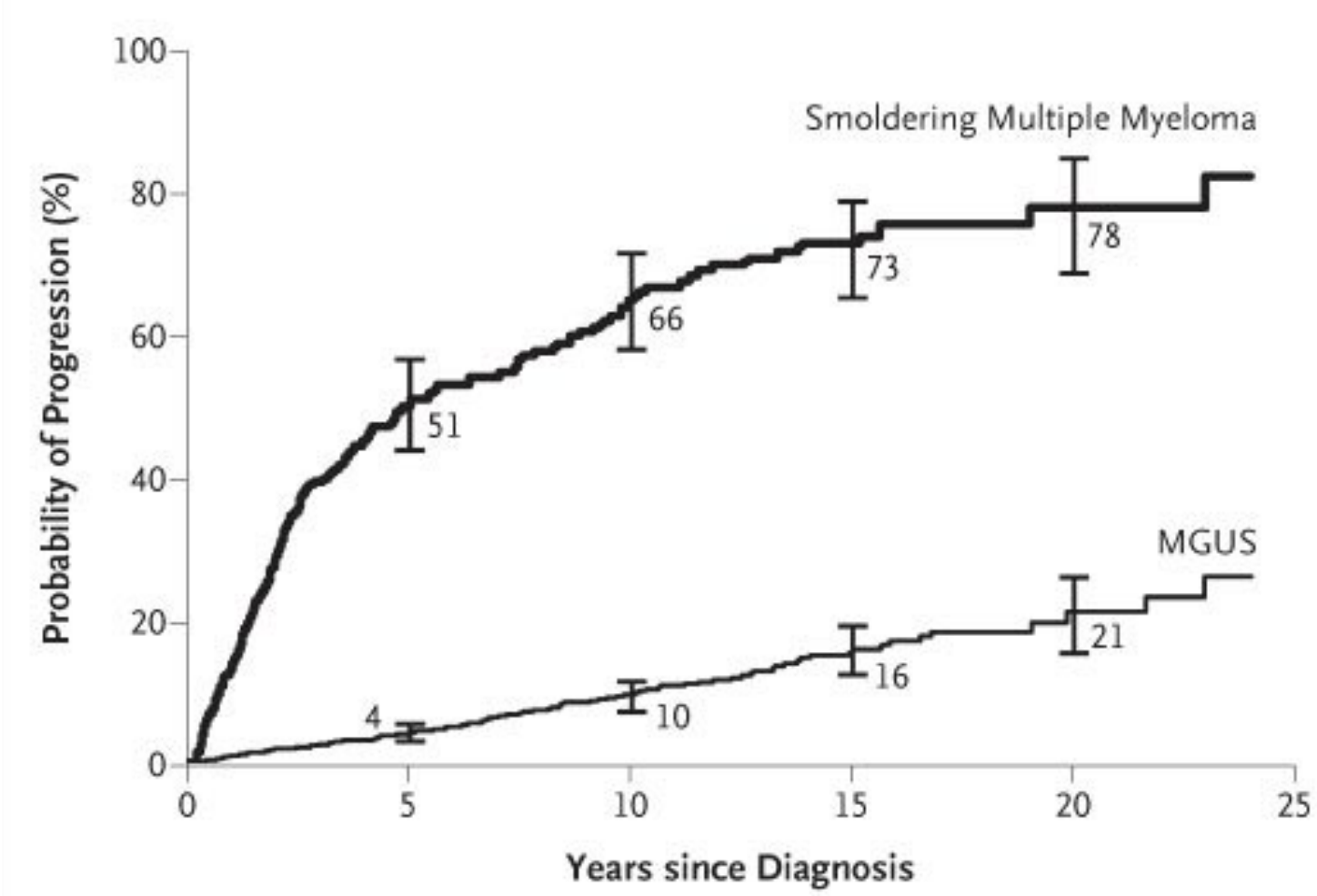
- Latest results:
  - Serum monoclonal protein (IgG or IgA) ≥3 g/dL
  - Or urinary monoclonal protein ≥500 mg per 24 h
  - Or clonal bone marrow plasma cells 10–60%
  - Absence of myeloma defining events or amyloidosis.

SMOLDERING MYELOMA

Mr. Bond Wants to Know …

- Which patients will progress early?
- What should we look for?

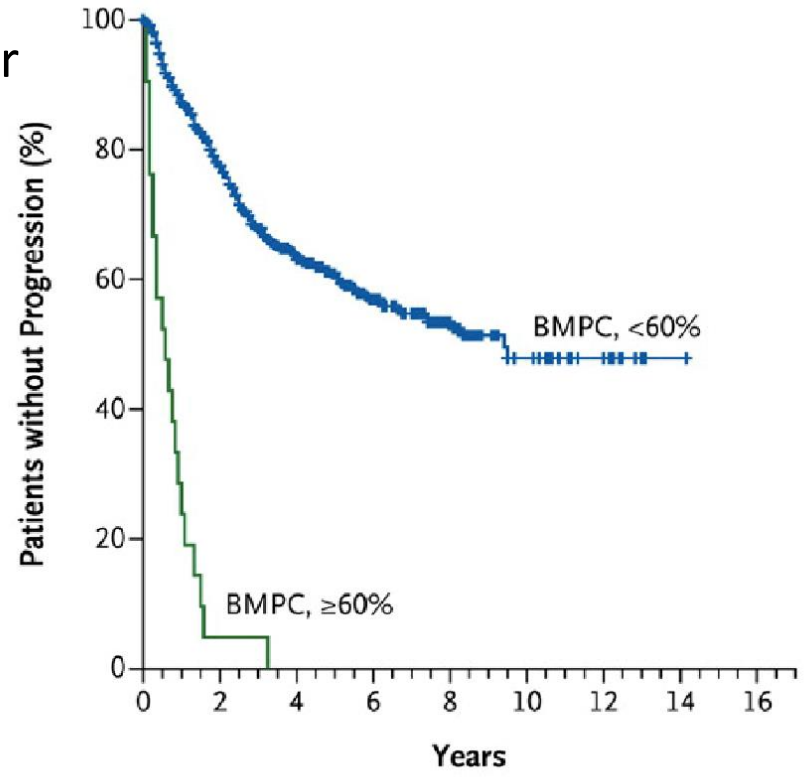
Progression to Symptomatic MM



Kyle et al. NEJM, Volume 356:2582-2590, June 21, 2007

Bone Marrow Plasma Cells

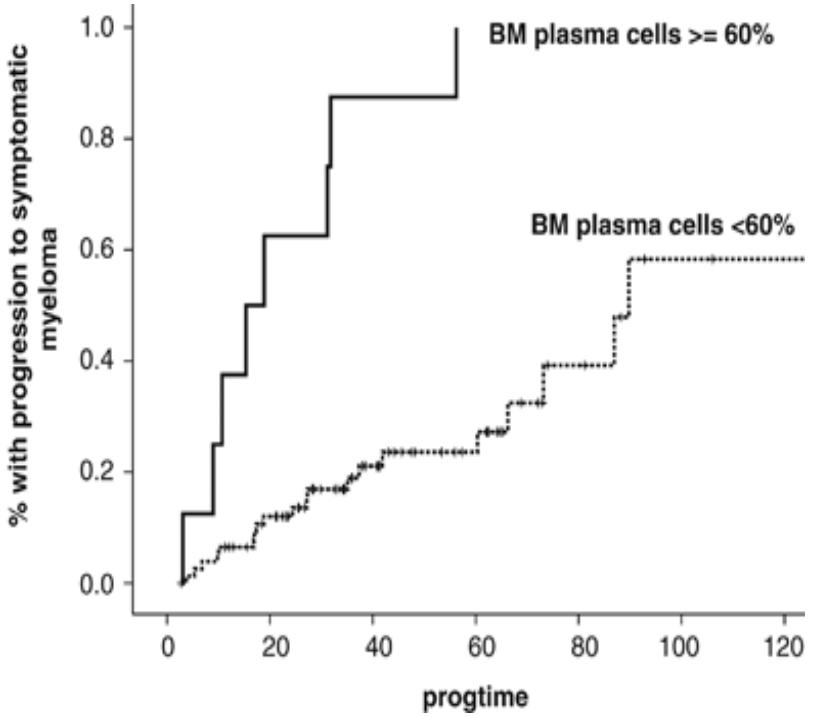
- 21 (3%) had BMPC of 60% or greater
- 95% of these progressed to MM within 2 years of diagnosis
- Median time to progression 7.0 months [95% CI 1.0–12.9])



Larson et al. NEJM, 2012

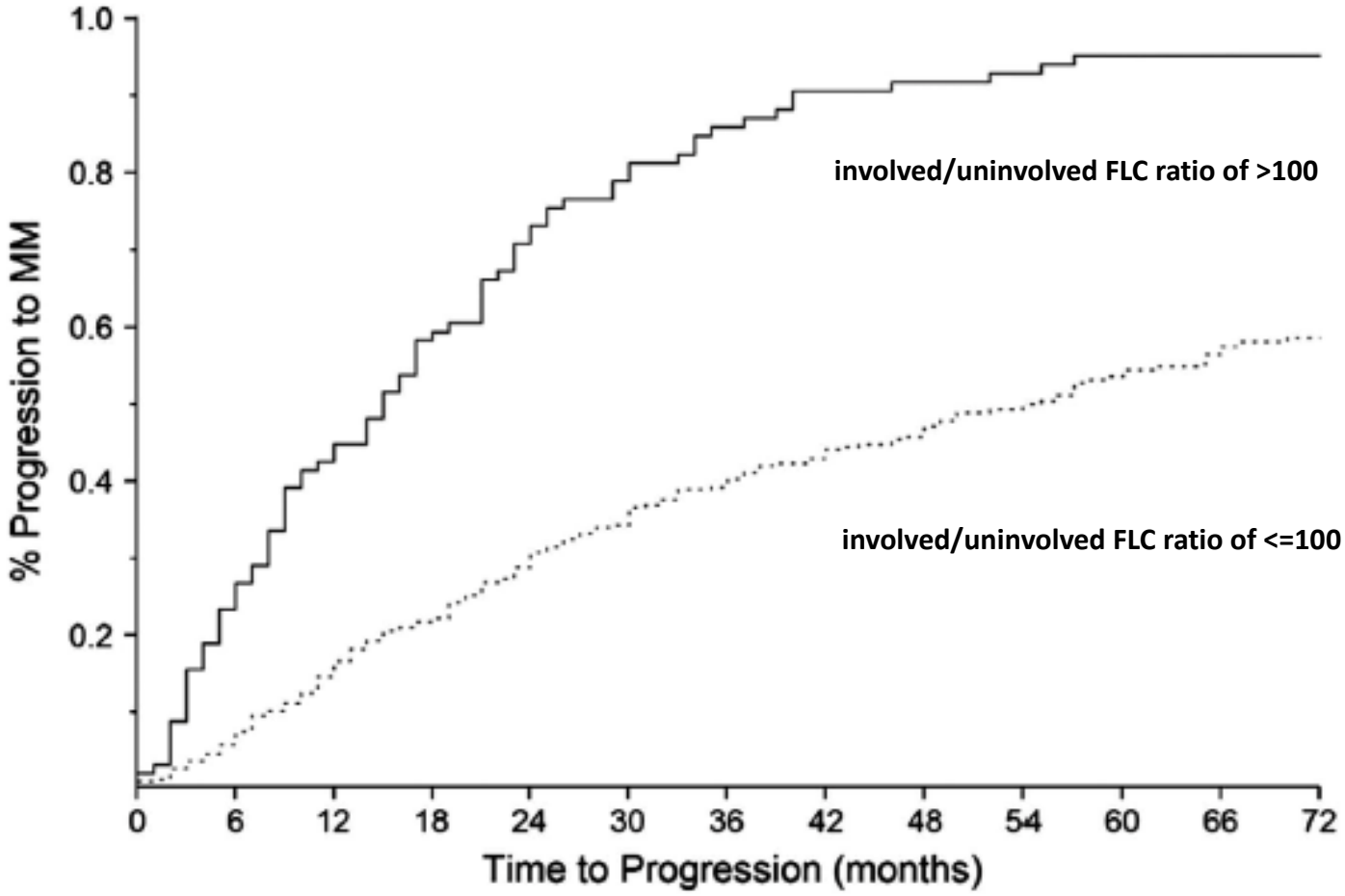
Bone Marrow Plasma Cells

- Among 8 (9%) patients with a BM infiltration ≥ 60% all have progressed to symptomatic myeloma and median time to progression to symptomatic disease was 15 months (range from 3 to 56 months)



Kastritis et al. Leukemia (2013) 27, 947–953

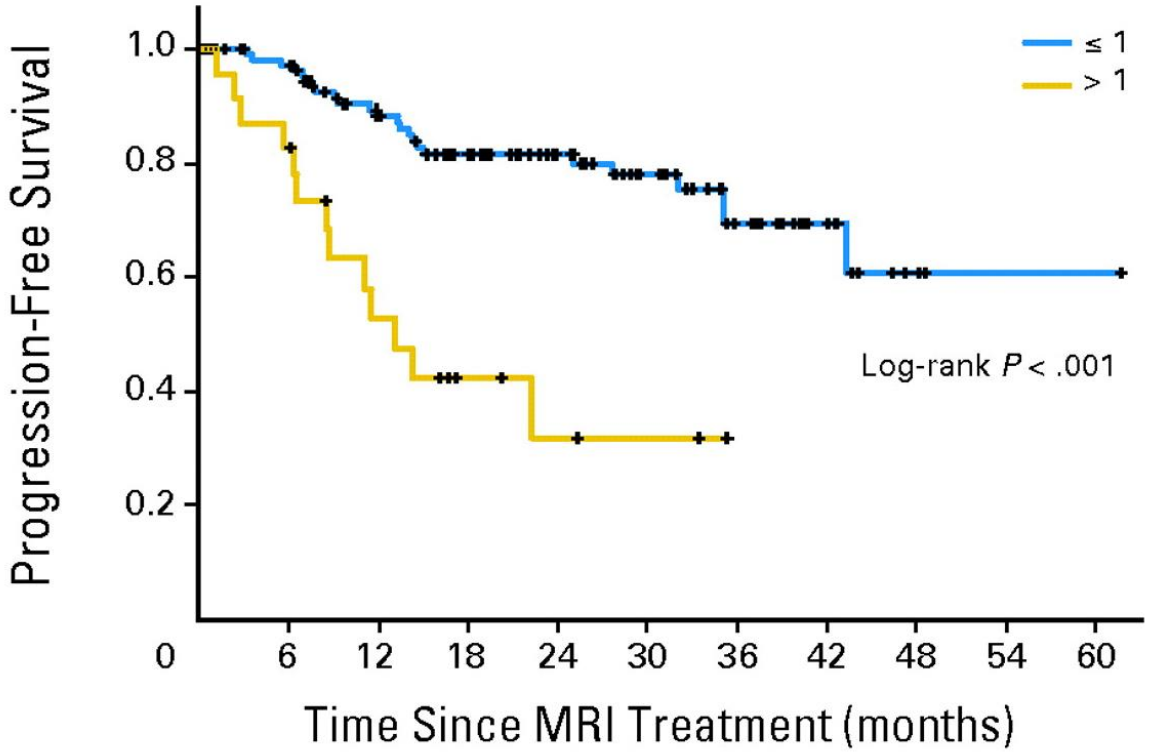
Free Light Chain Ratio



Larsen et al. Leukemia, 2012

MRI Lesions

- 23/149 patients had >1 lesion; median TTP not patients with ≤1 FL and 13 months for those with >1 FL



Jens Hillengass et al. JCO 2010;28:1606-1610

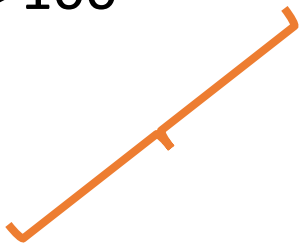
Active (symptomatic) Multiple Myeloma

Classical Definition

- Hyper**C**alcemia
- **R**enal Insufficiency
- **A**nemia
- **B**one Disease

Expanded Definition

- BMPC ≥60%
- >1 PET/MRI lesions
- FLC ratio >100



Predicts an 80% or more risk of progression in 2 years

Current IMWG Definition

Clonal BMPC ≥10% or biopsy-proven plasmacytoma PLUS

- *Either a myeloma defining event*:

C: Hypercalcemia: serum calcium >1 mg/dL higher than the upper limit of normal or >11 mg/dL

R: Renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >2 mg/dL

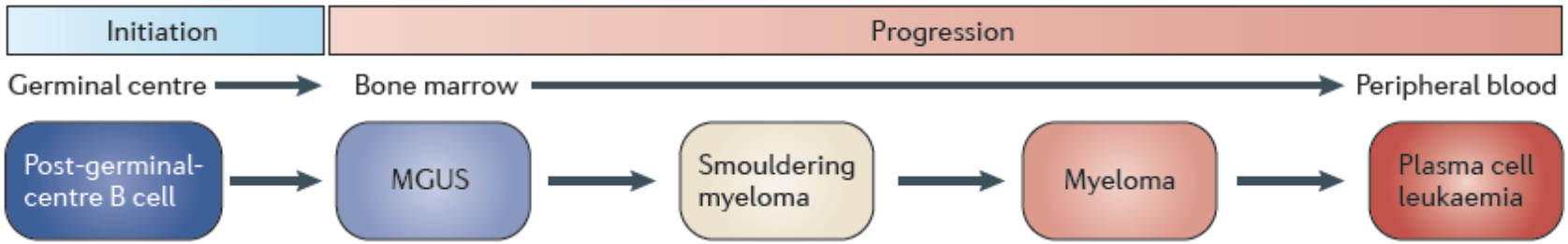
A: Anemia: hemoglobin >20 g/L below the lower limit of normal, or a hemoglobin <100 g/L

B: Bone lesions: osteolytic lesions on x-ray, CT, or PET-CT

- OR *a biomarker of early progression*

- Clonal bone marrow plasma cell percentage ≥60%
- Involved: uninvolved serum free light chain ratio ≥100
- >1 focal lesions on MRI studies

Unique Disease with Precursor Conditions



Mr. Bond Continues to Follow Up with Your Clinic

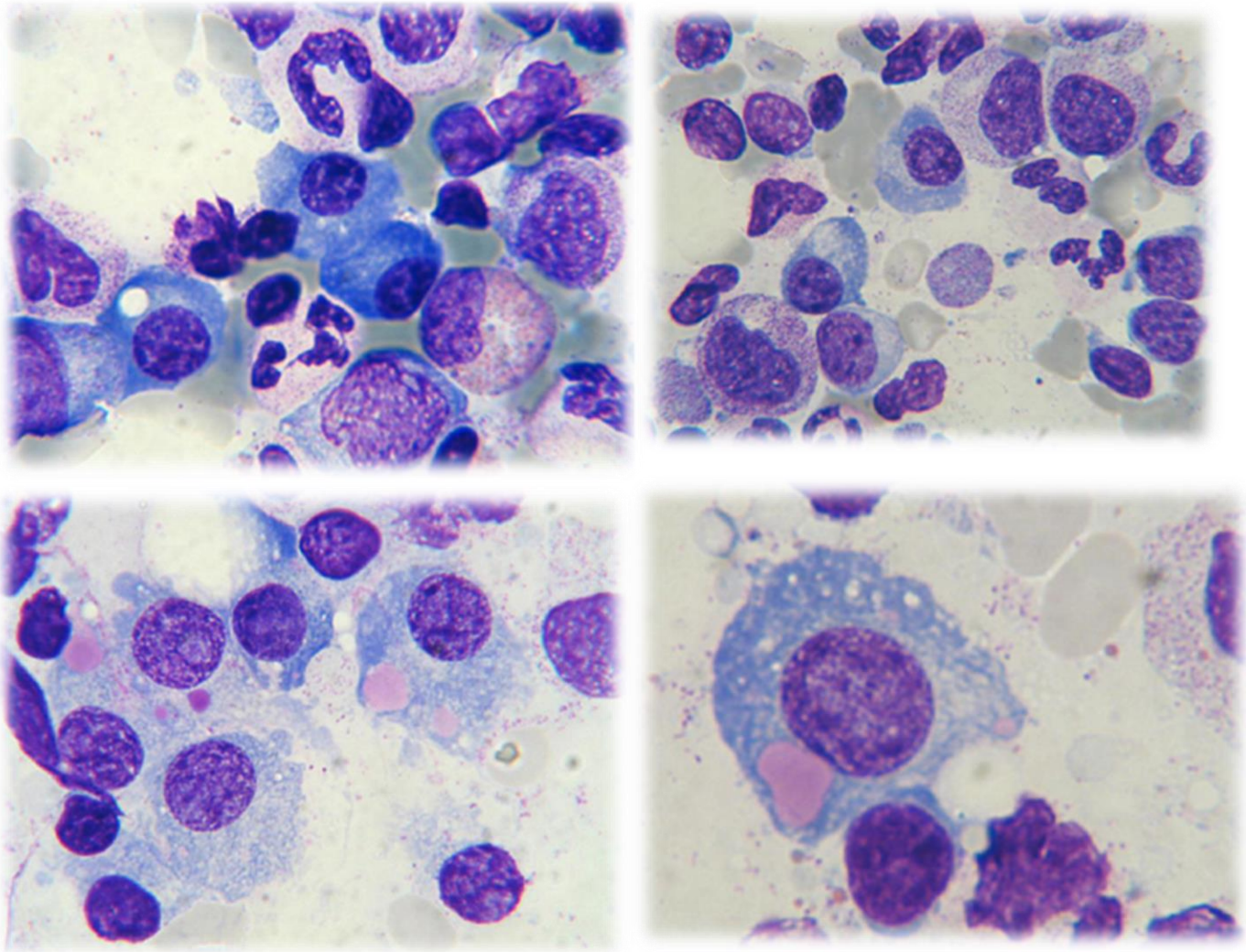
- One day, he presents with following symptoms:
  - ✓Back Pain
  - ✓Fatigue
  - ✓Anorexia
  - ✓Recurrent infection
  - ✓Constipation
  - ✓Somnolence
  - ✓Fracture
  - ✓Neuropathy

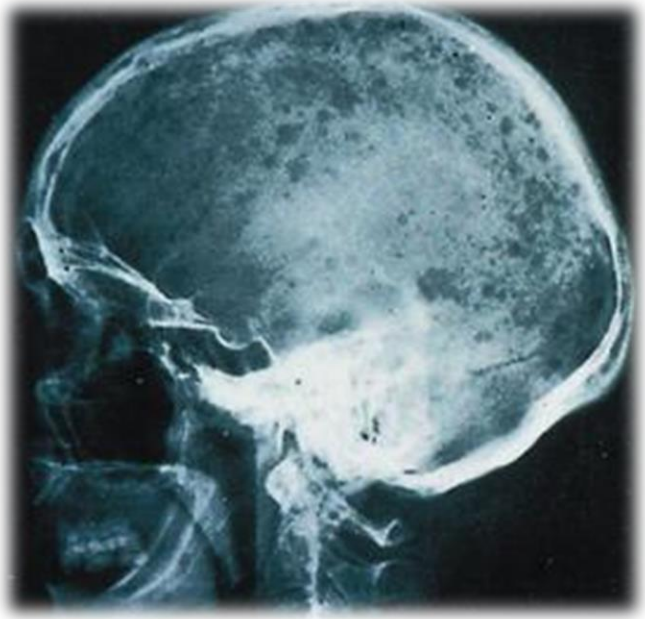
Initial Diagnostic Workup

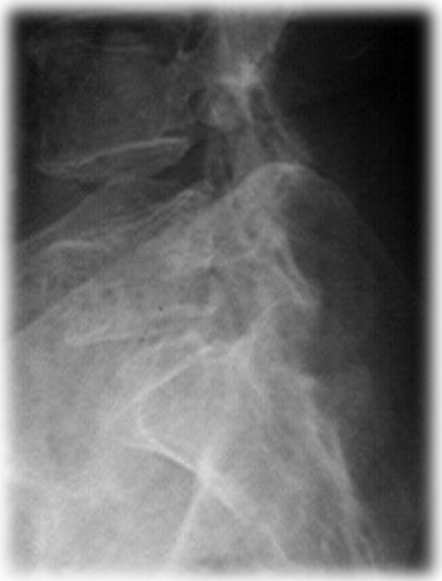
- H&P
- CBC
- BUN/create.
- Calcium/albumin
- Quant Ig
- SPEP/immunofix.
- Bone marrow biopsy
- 24-hour urine
- UPEP/immunofix.
- Beta2-microglobulin
- Skeletal survey
- PET/MRI
- **FISH on BM plasma cells**
- **Gene expression profiling**

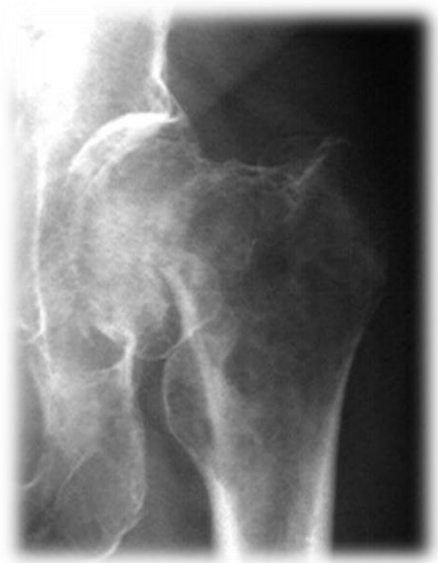
Tests Results!

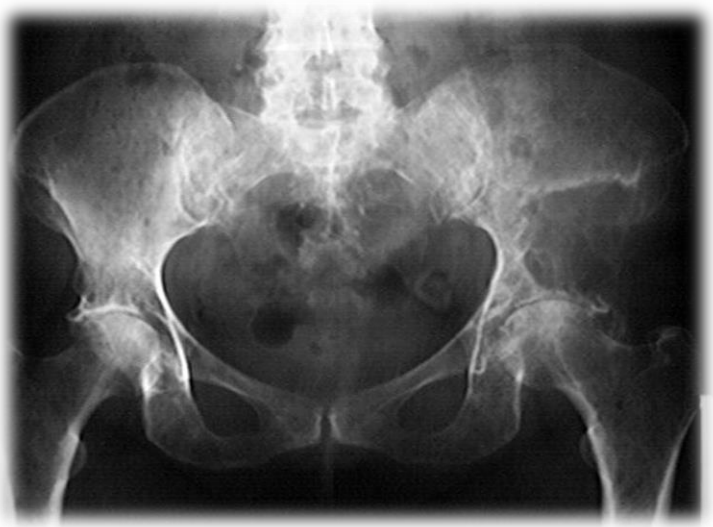
- Anemia
- Hyper Calcemia
- Renal insufficiency
- Hypogammaglobulinemia
- X-ray: lytic bone lesions
- PET/MRI: focal lesions/extramedullary disease/fractures/ bone damage
- Bone marrow examination and FISH testing











What Type of Myeloma Do I Have?

- Myeloma is classified by the type of immunoglobulin production

- Immunoglobulins (Ig) are made up of 2 components: light chains and heavy chains
  - light chains- kappa or lambda
  - Heavy chains- alpha [IgA], gamma [IgG], mu [IgM], delta [IgD], and epsilon [IgE]) chains.

- If there is excess of IgG and kappa, then it is called IgG kappa myeloma

What Type of Myeloma Do I Have?

- Light chain myelomas-
  - Incomplete immunoglobulin consisting of light chains only.
  - Identified by free light chain assays and urinary free light chain assay.
- Non secretory myeloma occurs in about 1% of myelomas

Is this a common disease?

Age-Adjusted Incidence per 100,000

	Male	Female
White	6.2	4.1
Black	11.8	10.0

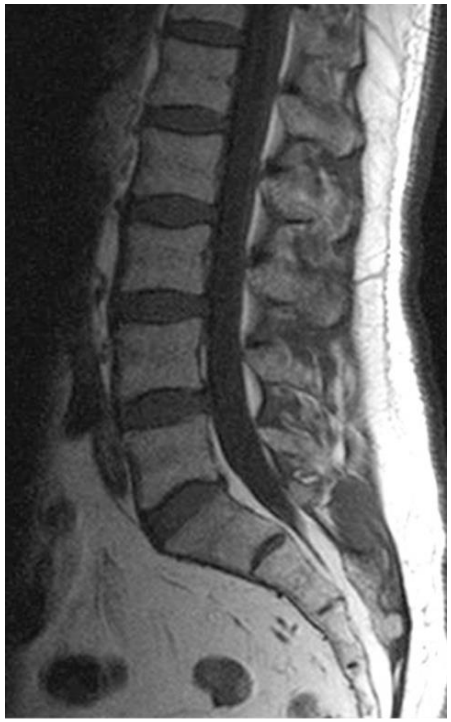
Etiology

- Familial clustering
- African Americans
- Radiation
- Agriculture, benzene, radiation, sheet metal work
- Chronic inflammatory disorders

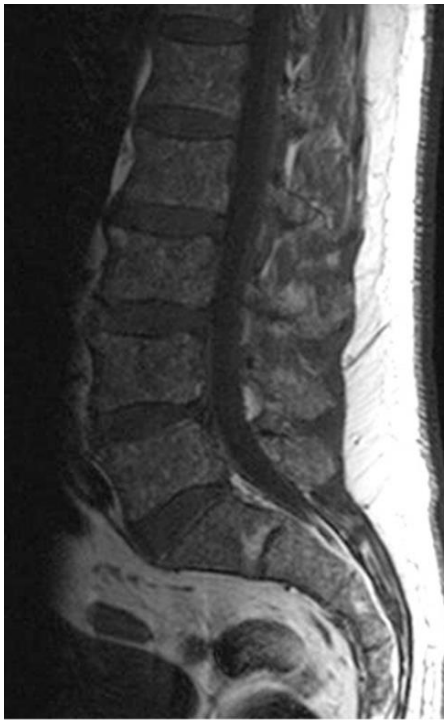
Why do I need PET or MRI? Does it help in treatment?

Disadvantages of Conventional Radiography

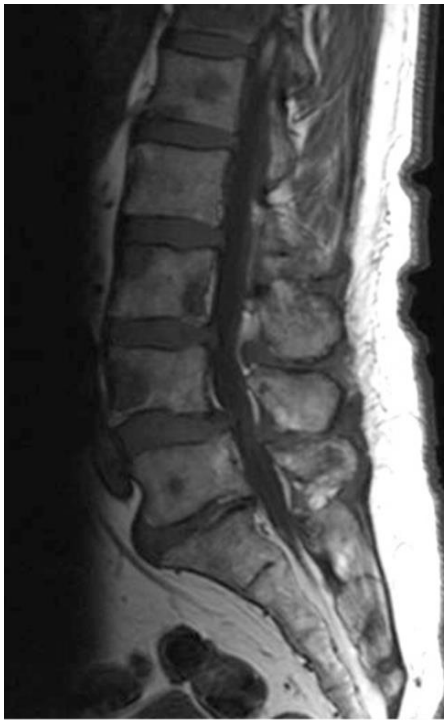
- Reveals lytic disease when over 30% of the trabecular bone has been lost; ~20-30% of patients at diagnosis have normal skeletal survey
- Lack of accurate visualization
- Reduced specificity
- Observer dependency
- Lengthy period for exam
- Poor tolerance
- Cannot be used for response assessment



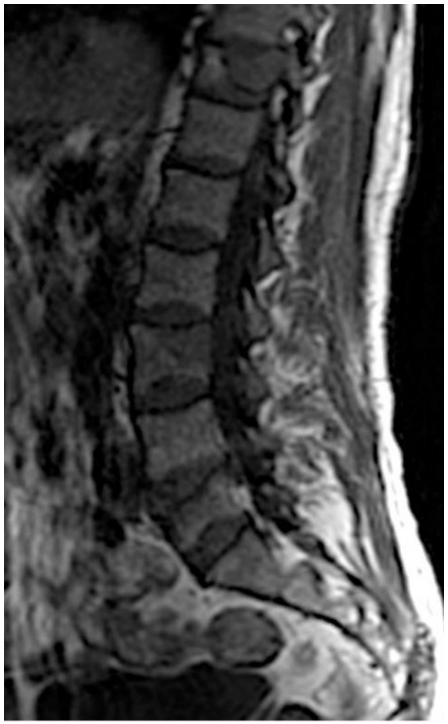
minimal



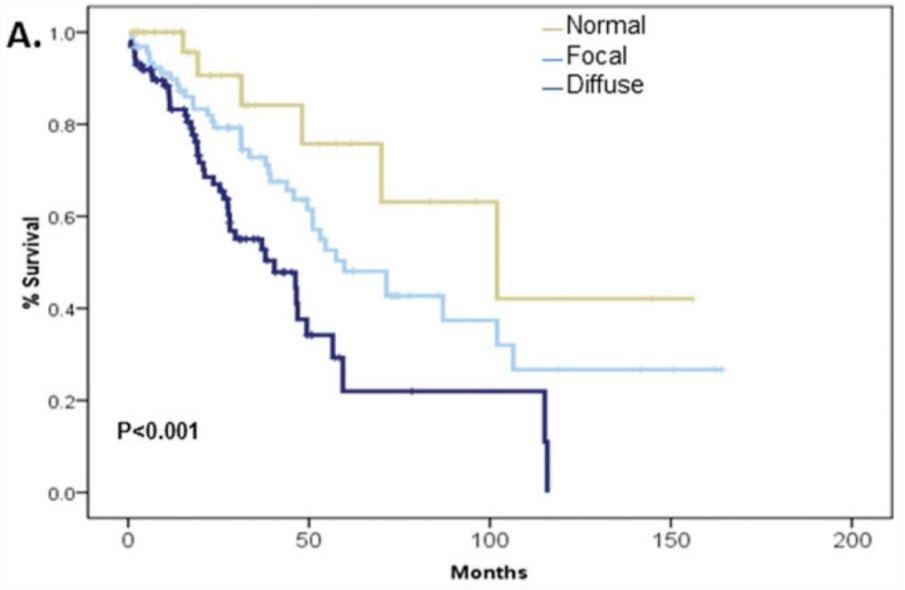
diffuse



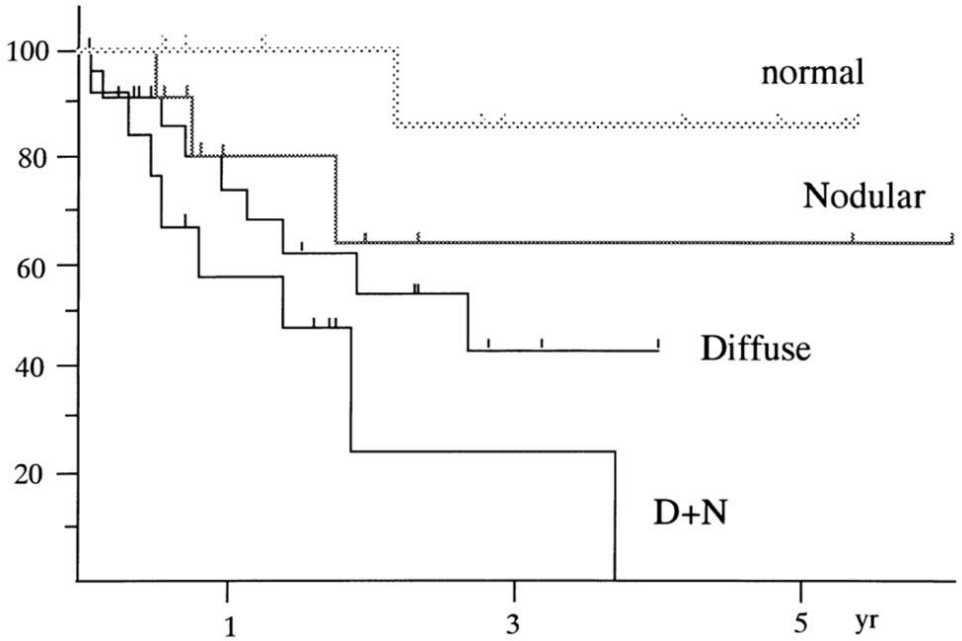
focal



mixed

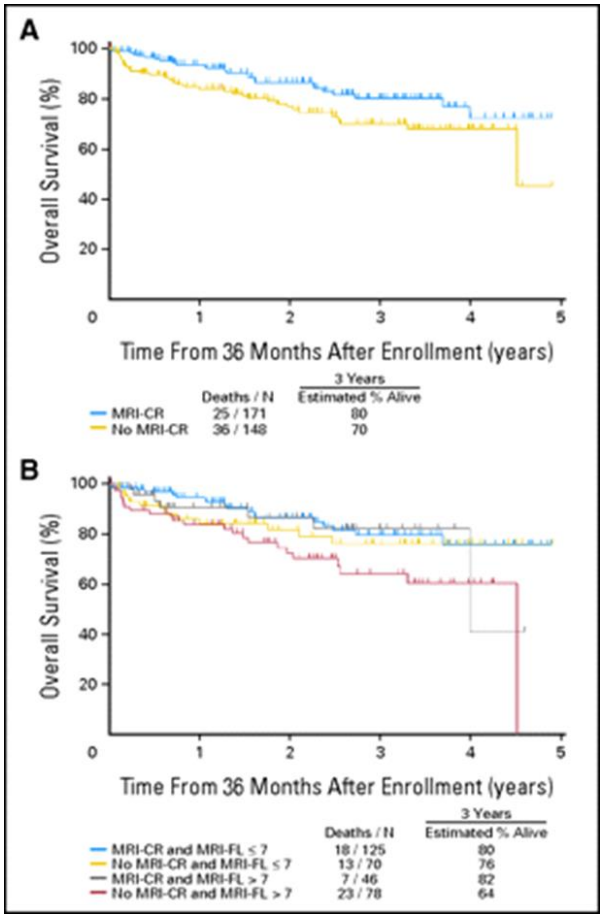


Moulopoulos 2012 AJR



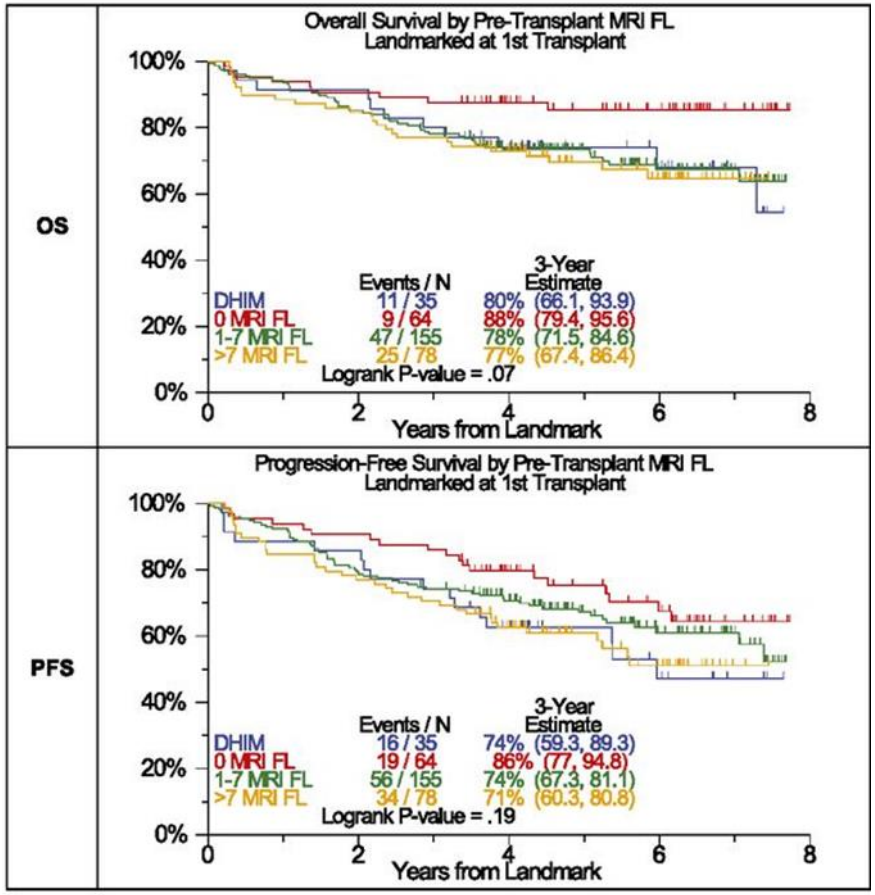
Kusumoto 1997 Br J Haematol

POST-ASCT



Walker R., et al. JCO 2007

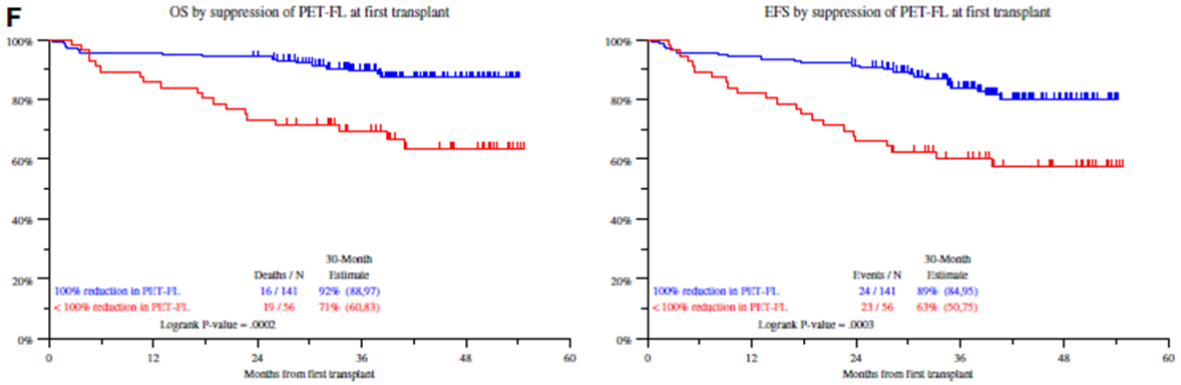
PRE-ASCT



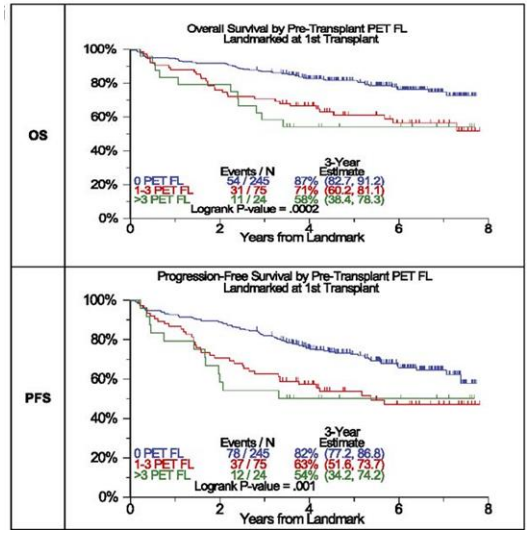
Usmani S.Z., et al. Blood 2013

PET in MM

Prognostic Value of PET/CT Before ASCT



Bartel. TB, et al. Blood 2009



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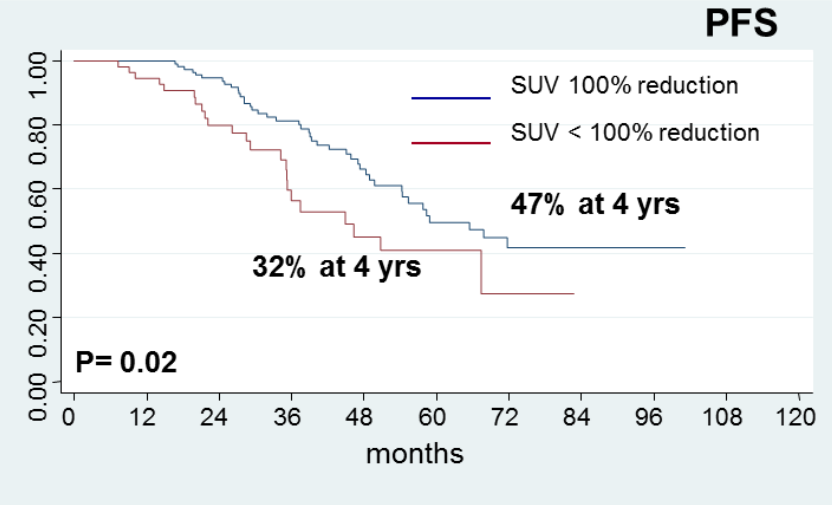
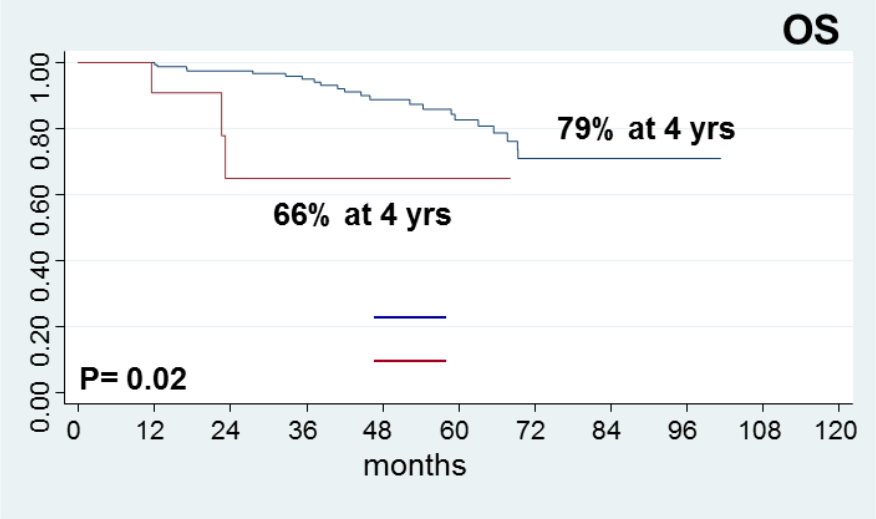


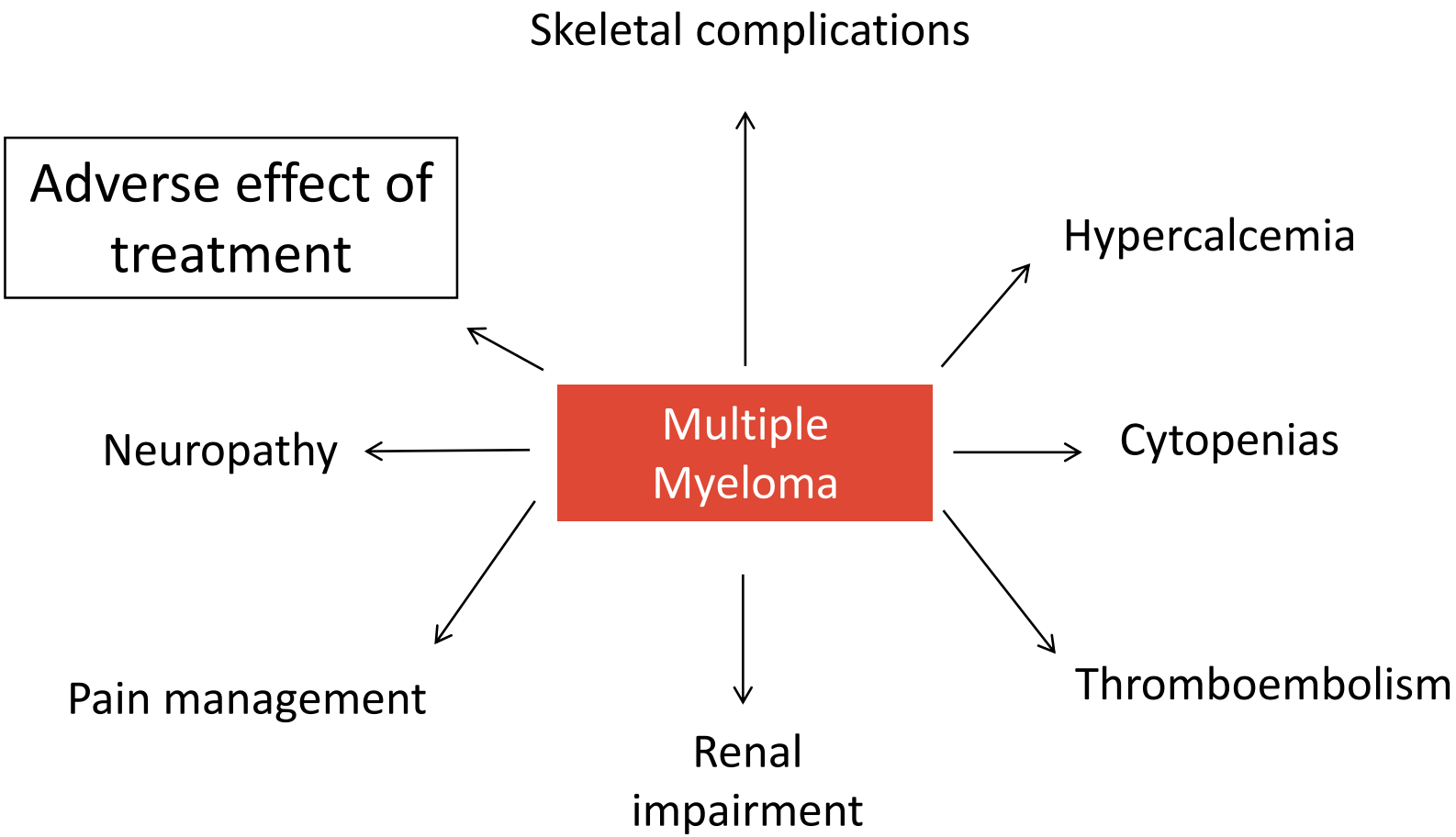


Myeloma –
A Truly Multi-Organ Disease

Mr. Bond Wants to Know…

- *Is this curable cancer? I am just 51 years old! I want to live to see my grandkids!*

- *What treatment options do I have?*
  - Triplets: PI, IMiD, and steroid
  - Early stem cell transplant
  - Sequential transplants (tandem approach)
  - Post transplant maintenance


Skeletal complications
Adverse effect of treatment
Hypercalcemia
Neuropathy
Multiple Myeloma
Cytopenias
Pain management
Renal impairment
Thromboembolism

Important to Recognize Skeletal Complications

- 40% of newly diagnosed patients: elevated Alkphos.
- Other tests:
  - Bone specific alkaline phosphatase
  - Bone metabolites
    - propeptides of type I collagen (P1NP, P1CP)
    - telopeptides of type I collagen (NTX and CTX)
      - levels go down with improved bone health
- Not widely measured on a regular basis

Supportive Care: Bone Disease

- Vitamin D – > 50 y.o. 800-1000 IU daily
- Measure 25 (OH) D level: <20 ng/ml (50nmol/L) defined as deficient; 21-29 insufficient
- Oral supplementation-
  - Ergocalciferol D2
  - Cholecalciferol (D3): better at raising 25 (OH) Vit D

Supportive Care: Bone Disease

- Stop smoking, limit alcohol intake
- Supplements: Institute of Medicine recommends calcium intake, 1200 mg/daily
- EXERCISE IS KEY!
  - Movement, 30 min daily: walking, dancing, tai chi, weight training, PT

Bisphosphonates: Duration

- Bisphosphonates recommended for all patients with lytic bone disease, monthly for 24 months
- Restart at time of relapse
- After two years of continuous use, unclear what should be recommended
  - ?
  - Every 3 - 6 months

Bisphosphonates: Duration

- In patients who do not have active myeloma and are on maintenance therapy, the physician may consider a 3-monthly bisphosphonate administration.

Bisphosphonates: Monitoring

- Creatinine should be monitored before each dose of pamidronate or zoledronic acid
- 24 hr. urine albumin: ideal tests
- > 500 mg/24 hours of urinary albumin - discontinue bisphosphonates

Bisphosphonates: Monitoring

- If renal deterioration, hold zoledronic acid or pamidronate
- Resume bisphosphonates at the same dosage when serum creatinine returns to within 10% of the baseline level
- Monitor serum calcium and vitamin D levels regularly

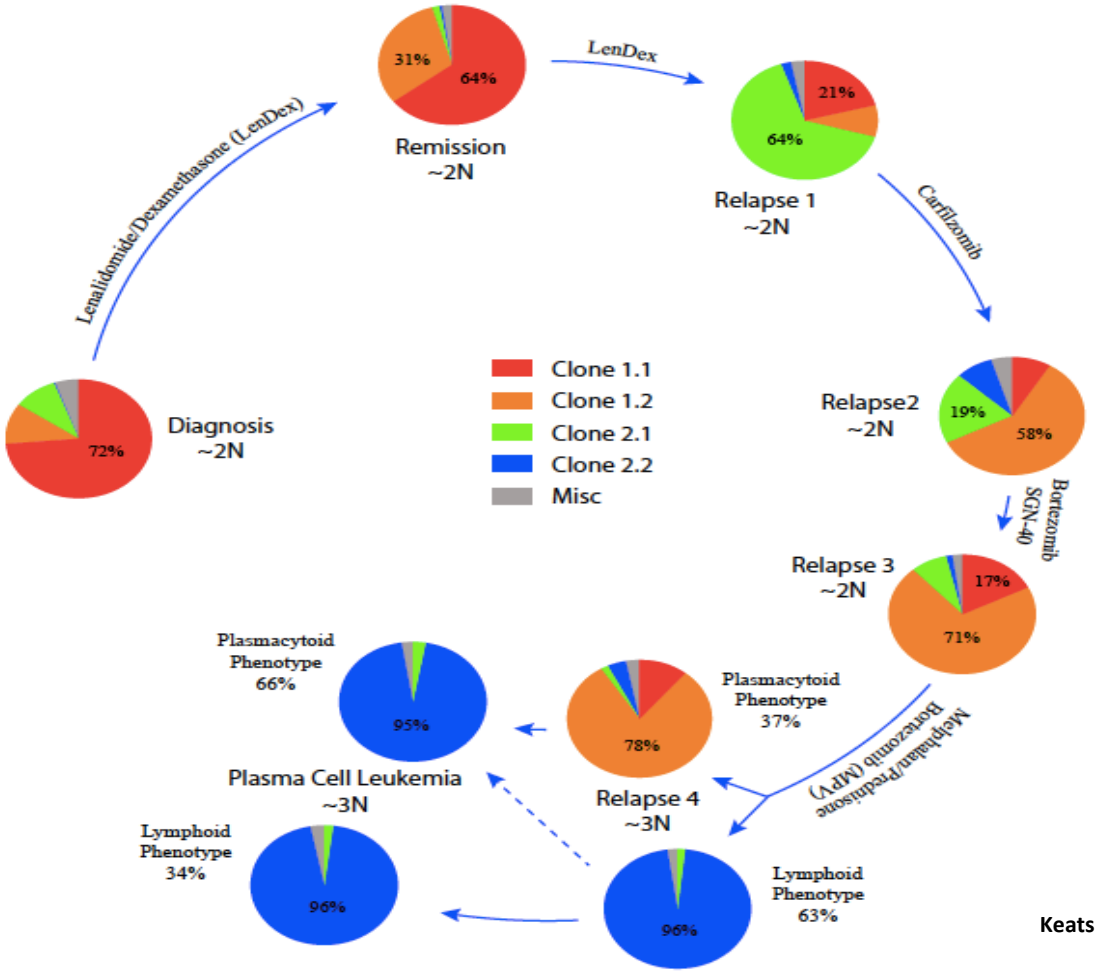
Xgeva

- Xgeva inhibits the RANK ligand mediated osteoclastic over activity
- Does not require monitoring of renal function
- More pronounced hypocalcemia
- Should not be stopped abruptly
- Contraindicated in HypoCa: check Ca levels
- Jaw problems can happen!

Should I consider early transplant in MM?

- Absolutely, yes!

Clonal Tiding Over Multiple Treatment Relapse Cycles:



Keats JJ, et al. Blood. 2012;120:1067-76.

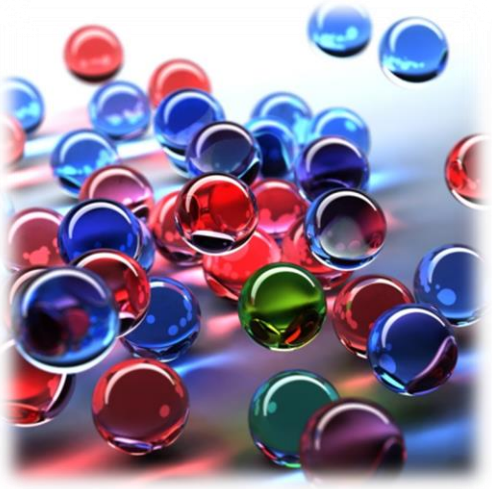
Intraclonal Heterogeneity

No heterogeneity

All myeloma cells are the same

Intraclonal heterogeneity

Different MM clones sharing features

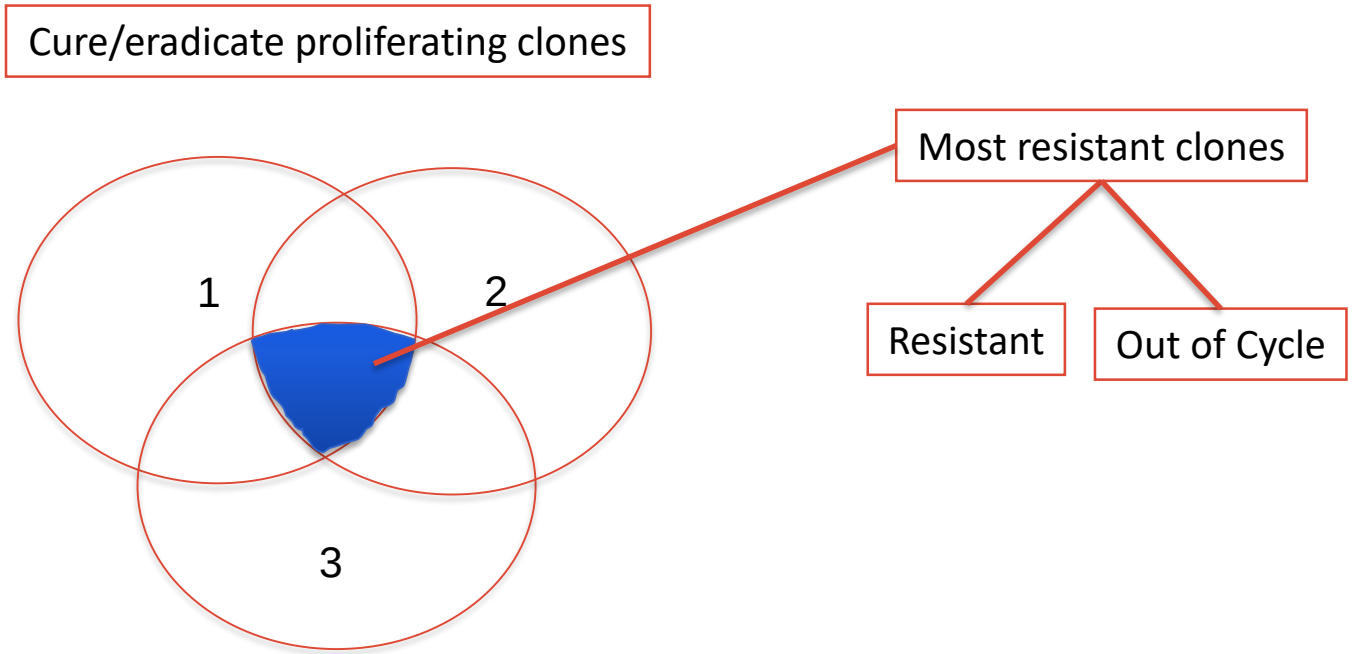


Interclonal heterogeneity

Different MM clones NOT sharing features

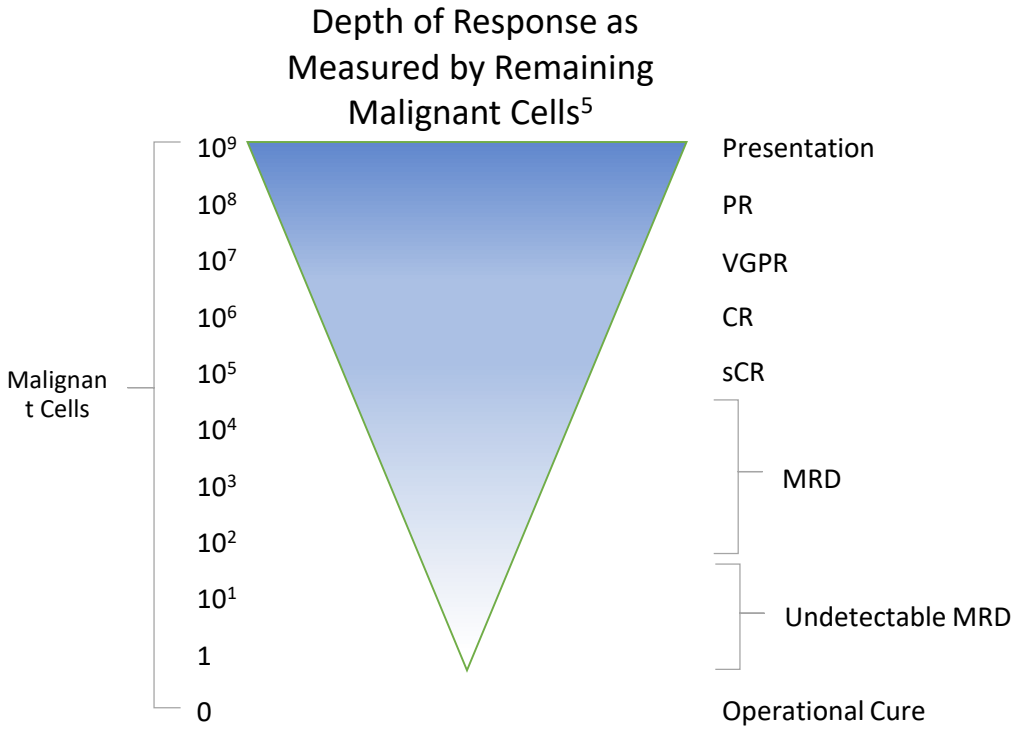
Why does disease keep relapsing?

Composition of Residual Clonal Populations Post-Induction Chemotherapy



Minimal Residual Disease (MRD)

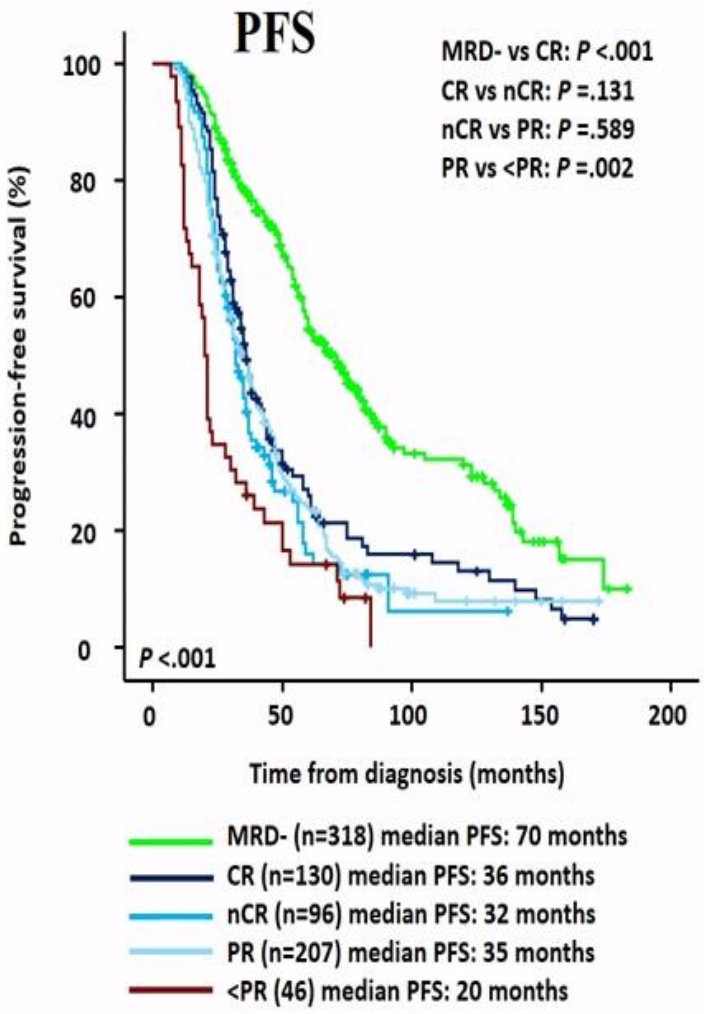
- In MM, MRD describes detectable malignant cells that remain after treatment; these indicate a remaining tumor burden, even in the presence of confirmed response[1]
- MRD can be present in patients who achieved a CR[2,3]
- These remaining malignant cells can contribute to relapse[4]

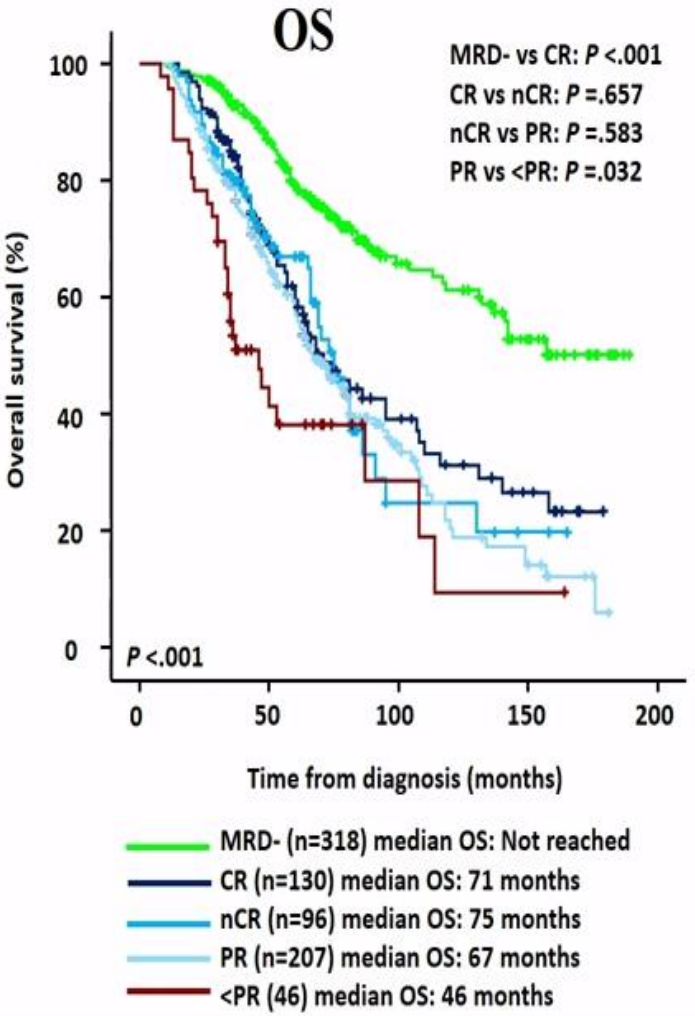


1. Kumar S et al. *Lancet Oncol*. 2016;17(8):e328-e346. **2.** Paiva B et al. *Blood.* 2008;112(10):4017-4023. **3.** Rawstron AC et al. *J Clin Oncol.* 2013;31(20):2540-2547. **4.** Martinez-Lopez J et al. *Blood.* 2014;123(20):3073-3079. **5.** Paiva et al. *Blood.* 2015;125(20):3059-3068.

Depth of Response correlate with Survival

MRD is the best biomarker to predict outcome





GEM2000, GEM2005MENOS65, GEM2005MAS65, GEM2010MAS65

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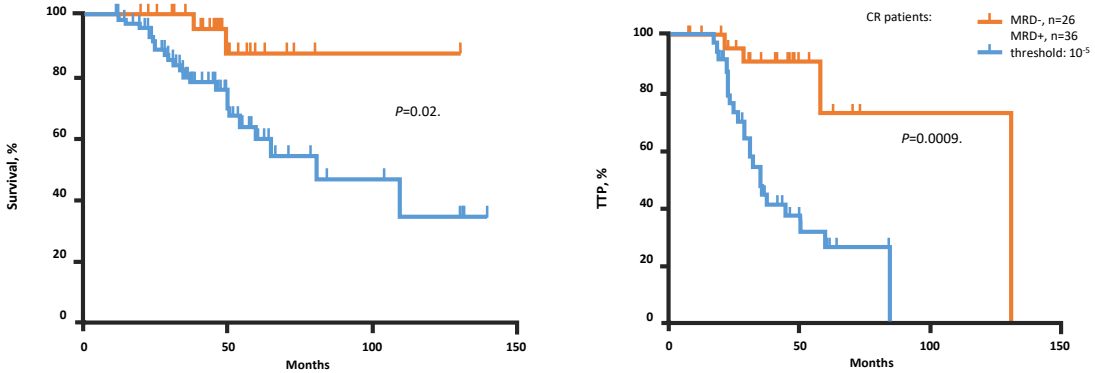
MRD Is Associated with Improved Patient Outcomes

- Measurement of MRD is used to qualify increasingly robust or deep responses that are observed with novel agents and combination treatment[1-3]
  - MRD is associated with longer OS in newly diagnosed patients[2,3]
  - MRD vs. MRD+ status is associated with longer OS and TTP[3] in patients who achieved CR

Impact of MRD status on survival and time to progression[3]*



TTP = time to progression.
*In 133 patients included in the GEM clinical trials. Patients <65 years were treated within the GEM2000 or GEM05 <65 protocols, whereas elderly patients were treated within the GEM05 ≥65 or GEM10 ≥65 trials. Patients were newly diagnosed and had untreated symptomatic MM.[3-6]

1. Kumar S et al. *Lancet Oncol*. 2016;17(8):e328-e346. **2.** Landgren O et al. *Bone Marrow Transplant*. 2016;51(12):1565-1568. **3.** Martinez-Lopez J et al. *Blood*. 2014;123(20):3073-3079. **4.** Lahuerta JJ et al. *J Clin Oncol*. 2008;26(35):5775-5782. **5.** Mateos MV et al. *Lancet Oncol*. 2010;11(10):934-941. **6.** Rosiñol L et al. *Blood*. 2012;120(8):1589-1596.alig

Newer Approaches

Approaches that address immune suppression in MM may allow the patient's own immune system to identify and eradicate cancer cells[1]

Several proteins relevant to suppressive or effector immune cells have demonstrated therapeutic utility or are being investigated as targets for the treatment of MM[2-6]

BCMA	**CD38**	**SLAMF7**	**PD-1/PD-L1**
Expressed by MM cells; implicated in the expression of immunosuppressive	Expressed by MM cells and subsets of immune	Expressed by MM cells; also functions as an activating receptor	PD-1 and its ligand PD-L1 are overexpressed in MM and contribute to suppression of

BCMA = B-cell maturation antigen; SLAMF7 = signaling lymphocytic activation molecule family member 7; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1.

1. Feyler S et al. *Blood Rev.* 2013;27(3):155-164. **2.** Tai UT et al. *Blood*. 2016;127(25):3225-3236. **3.** Krejcik J et al. *Blood*. 2016;128(3):384-394. **4.** Hsi ED et al. *Clin Cancer Res*. 2008;14(9):2775-2784. **5.** Cruz-Munoz ME et al. *Nat Immunol*. 2009;10(3):297-305. **6.** Hallet WH et al. *Biol Blood Marrow Transplant.* 2011;17(8):1133-1145.

Closing Thoughts

- MGUS/Smoldering needs regular follow-up
- FISH/MRI or PET at diagnosis
- Early ASCT
- MRD negativity - important
- Post ASCT maintenance
- **New options available!**

Questions?

Thank You!