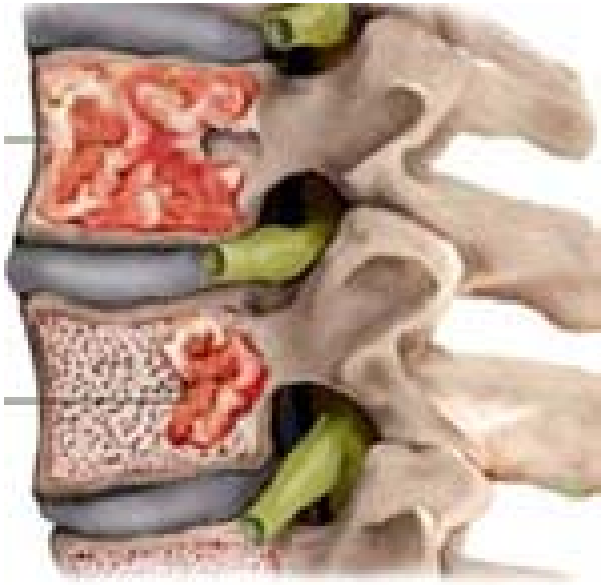
Multiple Myeloma: An Overview

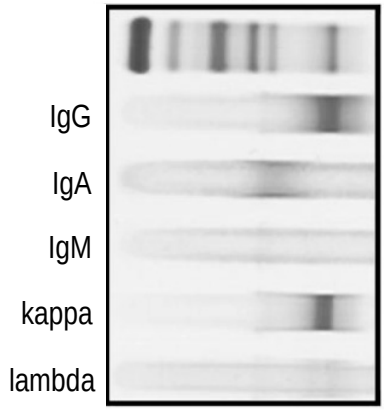


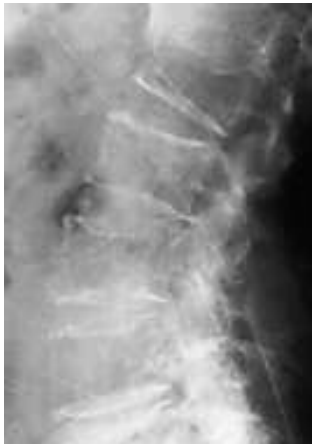
Ola Landgren, M.D., Ph.D.

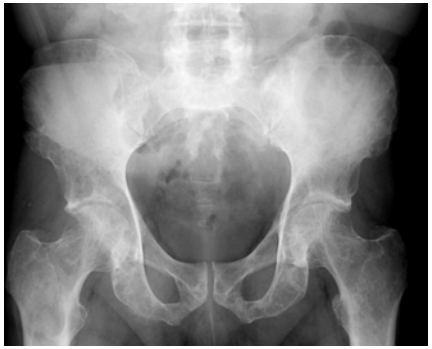
Mary Ann Yancey, RN, MSN, AOCN

Previously healthy 64-year-old man

- **Presents with persistent pain in his lower back and fatigue**
- **CBC reveals a hemoglobin level of 9.6 g/dL**
- **A monoclonal-(M)-protein is detected on serum protein electrophoresis (IgG kappa)**
- **Radiologic skeletal bone survey shows lytic bone lesions of the vertebrae and the pelvis**

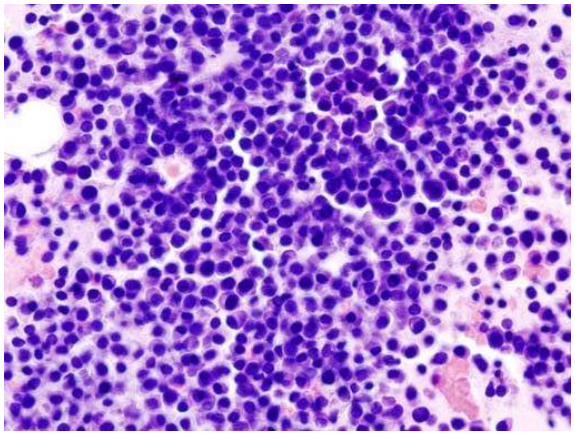


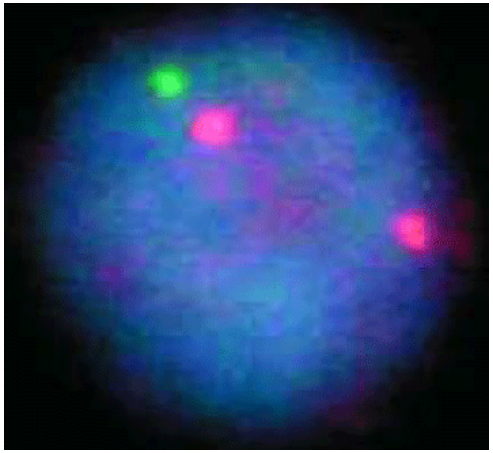




Previously healthy 64-year-old man

- **Multiple myeloma (MM) is confirmed by bone marrow aspiration showing infiltrate of plasma cells**
- **Serum calcium and creatinine levels are normal**
- **Albumin is 3.7 g/dL and beta2-microglobulin is 2.8 mg/L**
- **Fluorescence in situ hybridization (FISH) of bone marrow plasma cells shows deletion of chromosome 13**





Previously healthy 64-year-old man

- **Interpretation:**
  - **Relatively young age**
  - **Absence of coexisting illnesses**
- **A hematologist recommends:**
  - **Induction therapy followed by…**
  - **High-dose therapy with autologous hematopoietic stem-cell transplantation (ASCT) as initial treatment**

Clinical dilemma

- 20,580 new cases (11,680 men; 8,980 women) and 10,580 deaths per year
- Average age at dx 65-70 yrs (<40 yrs; ~2%)
- The 2nd most common hematologic malignancy in whites; in Blacks it is #1

MM is preceded by MGUS

Yrs prior MM dx	M-protein,* n/N (%; 95% CI)	Abnormal FLC ratio,‡ n/N (%; 95% CI)	MGUS,§ n/N (%; 95% CI)
2	25/27 (93; 76–99)	23/27 (85; 66–96)	27/27 (100; 87–100)
3	54/58 (93; 83–98)	46/58 (79; 67–89)	57/58 (98; 91–100)
4	45/48 (94; 83–99)	29/46 (63; 48–77)	47/48 (98; 89–100)
5	34/37 (92; 78–98)	25/37 (68; 50–82)	35/37 (95; 82–99)
6	25/25 (100; 86–100)	19/25 (76; 55–91)	25/25 (100; 86–100)
7	14/15 (93; 68–100)	11/15 (73; 45–92)	14/15 (93; 68–100)
> 8	13/17 (77; 50–93)	8/17 (47; 23–72)	14/17 (82; 57–96)

Landgren et al. Blood 2009; Weiss et al. Blood 2009

What causes MM?

Support for genetic factors

- 3-fold increased relative risk of developing MM among first-degree relatives of MM and MGUS pts[7]

- Twice as common among Blacks (compared to whites); earlier age of onset in Blacks

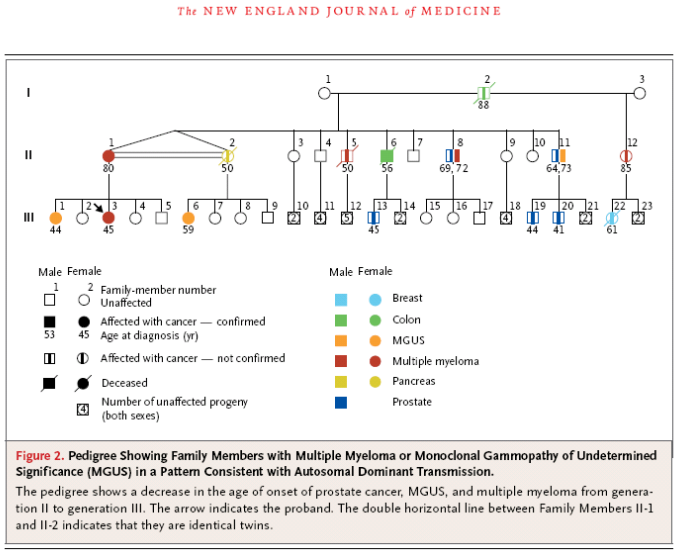


Figure 2. Pedigree Showing Family Members with Multiple Myeloma or Monoclonal Gammopathy of Undetermined Significance (MGUS) in a Pattern Consistent with Autosomal Dominant Transmission.

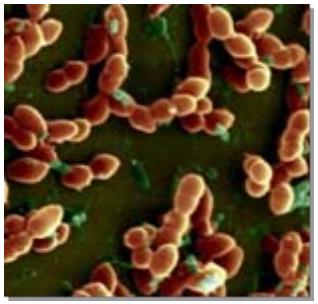
The pedigree shows a decrease in the age of onset of prostate cancer, MGUS, and multiple myeloma from generation II to generation III. The arrow indicates the proband. The double horizontal line between Family Members II-1 and II-2 indicates that they are identical twins.

Lynch et al. NEJM 2008; Landgren et al. Blood 2009

What causes MM?

<u>Support for environmental factors</u>

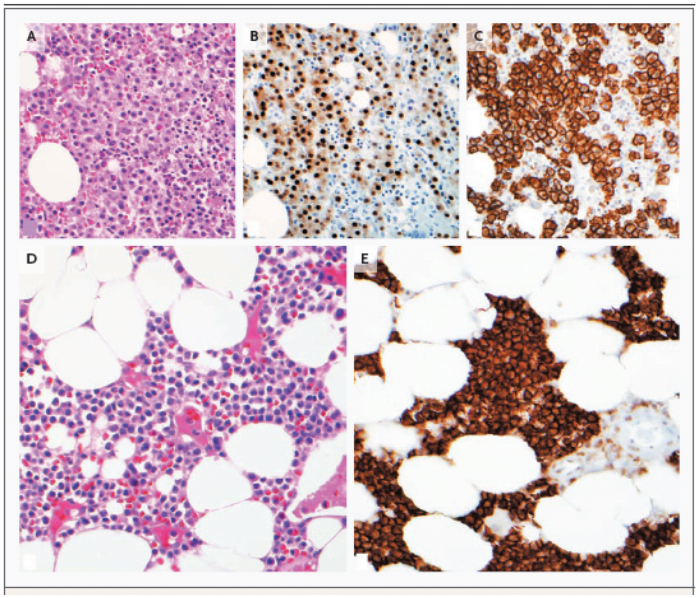
- Exposure to pesticides and radiation associated with increased risk
- Chronic immune stimulation (e.g. infections, autoimmunity, obesity) associated with increased risk



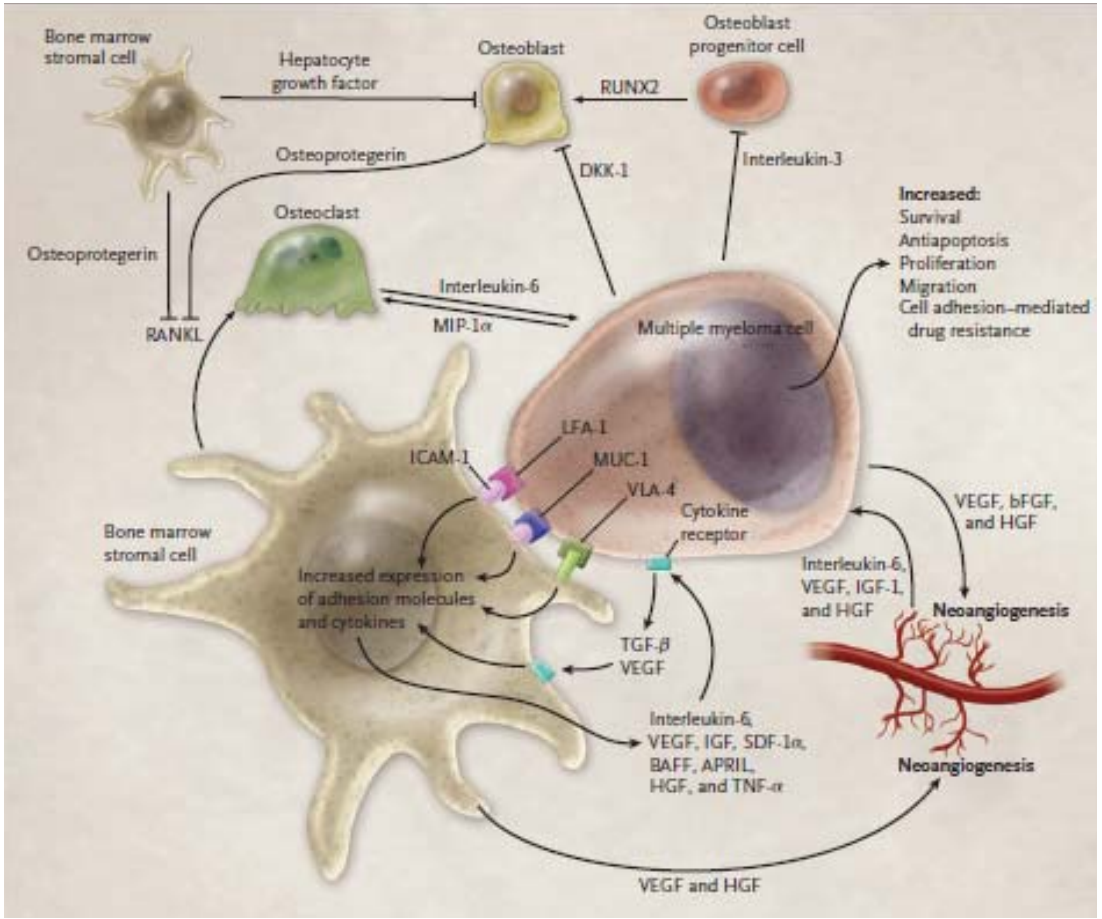
Alexander et al. Int J Cancer 2007; Brown et al. Blood 2008; Iwanaga et al. Blood 2009; Landgren et al. Blood 2009

Pathophysiology of MM

- Clonal B-cell tumor of plasma cells in the bone marrow
- Most malignant plasma cells express
  - CD38, CD56/58, CD79a, CD138
- Most malignant plasma cells do not express the pan-B cell antigens CD19 and CD20
- Cytokine and signaling alterations in the bone marrow microenvironment
  - IL-6, tumor necrosis factor (TNF)-alpha, IL-1-beta, VEGF, fibroblast growth factor-beta, DDK-1, etc…

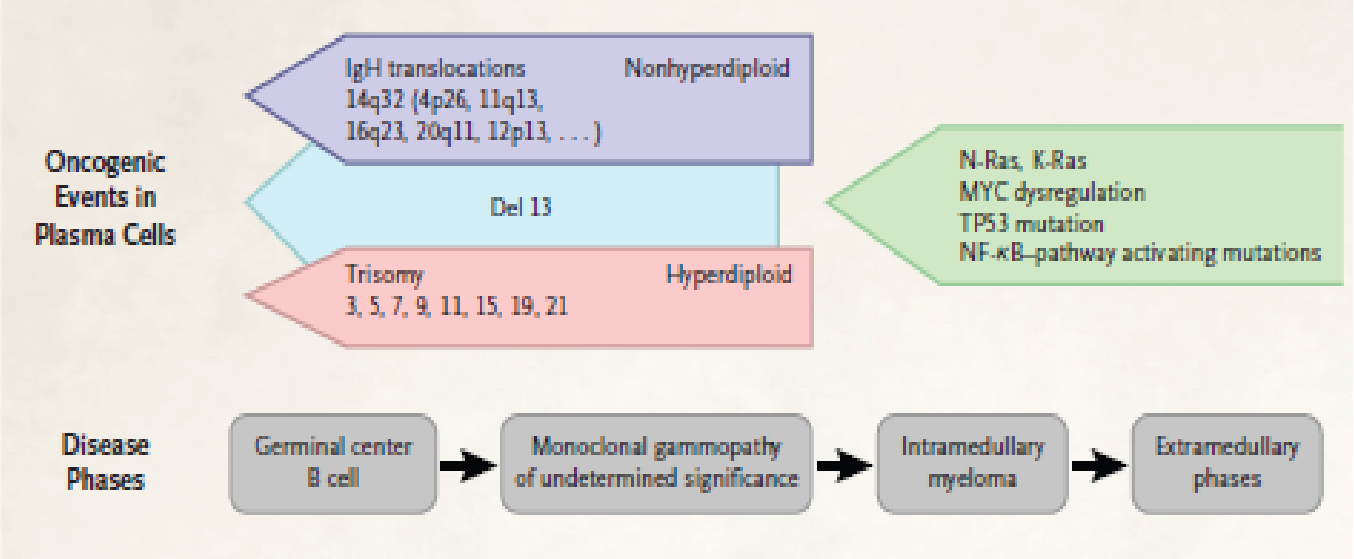


In MM, the bone marrow micro-environment plays a key role!



Harousseau and Moreau, *NEJM 2009*

Molecularly, MM is <u>not</u> one disease!



Non-hyperdiploid (translocations)

Hyperdioploid (trisomies)

Harousseau and Moreau, *NEJM 2009*

Gene expression reveals 7 molecular MM subtypes

Associated with genetic lesions

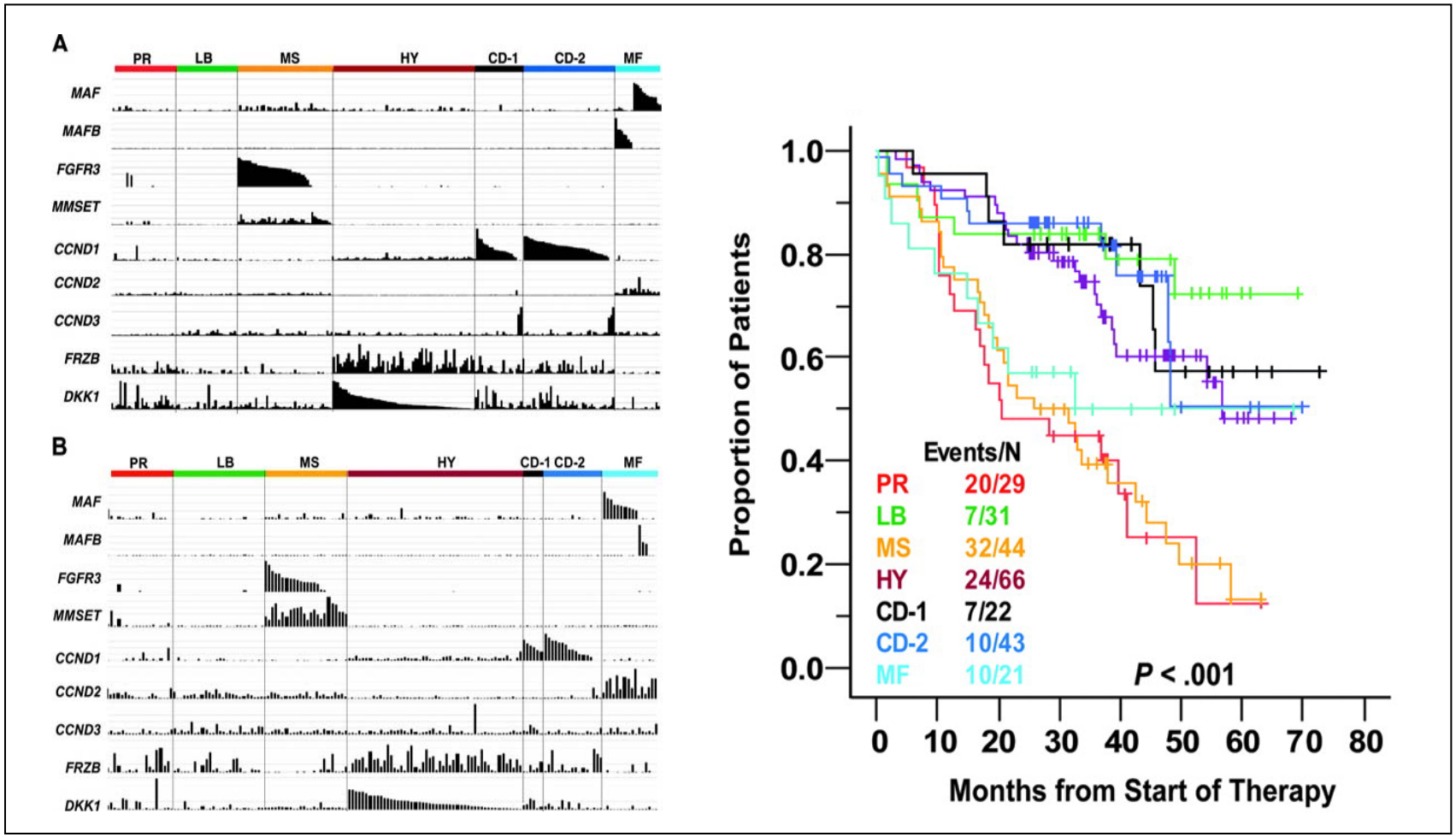
- **MF (MAF translocation)**
- **MS (MMSET/FGFR3 translocation)**
- **CD1 (Cyclin D1 or D3 translocation)**
- **CD2 (Cyclin D1 or D3 translocation)**
- **Hyperdiploid**

Associated with phenotype

- **PR (proliferative)**
- **LB (low incidence of bone disease)**

Zhan et al, *Blood 2006*

Gene expression MM subtypes have different outcomes



Zhan et al, *Blood 2006*

Common symptoms at MM diagnosis

- **Bone pain**
- **Fatigue**
- **Weight loss**
- **Parasthesias**

- **~10% are asymptomatic/have only mild symptoms at dx**

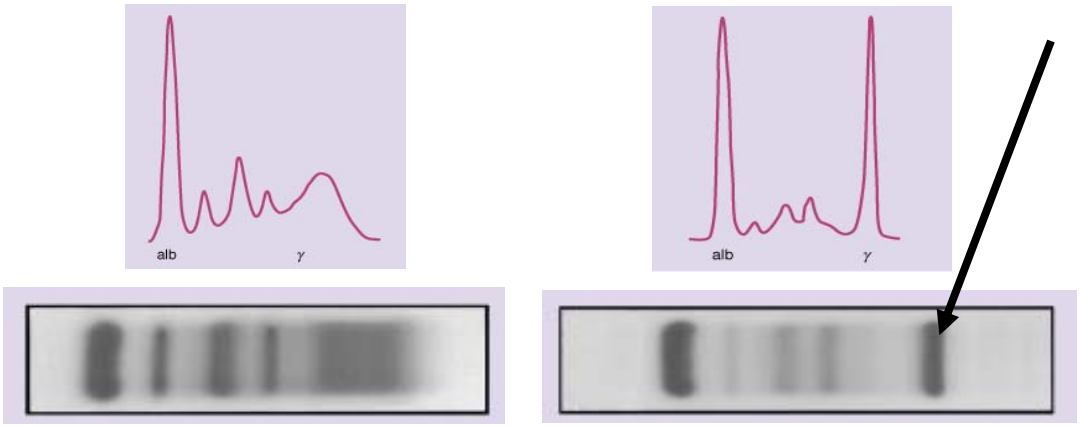
Kyle and Rajkumar, *N Engl J Med* 2004

Clinical hallmarks of MM

- **Hypercalcemia**
- **Renal failure**
- **Anemia**
- **Bone destructions (lytic lesions)**
- **Increased risk of infections**
- **Presence of *monoclonal protein***

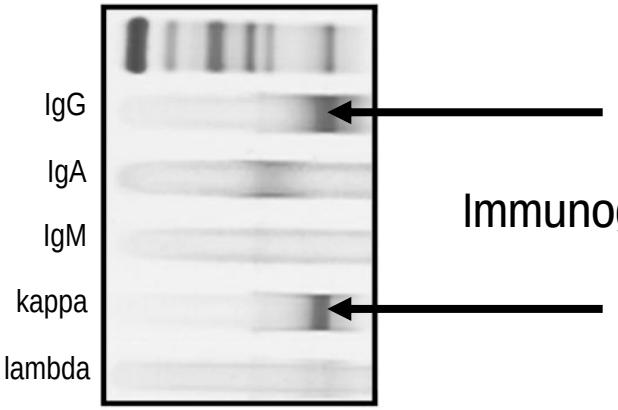
Kyle and Rajkumar, *N Engl J Med* 2004

Serum protein electrophoresis



Normal

Monoclonal protein

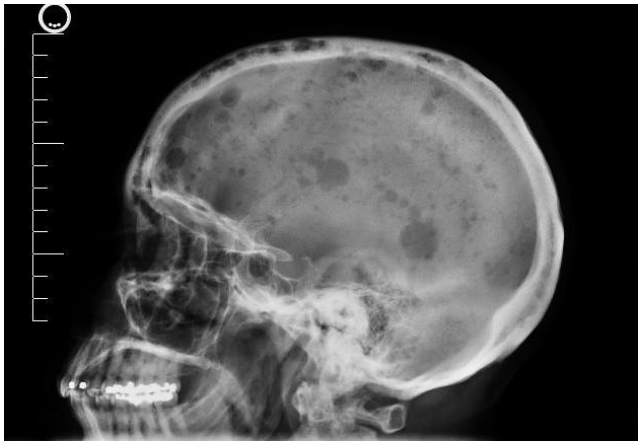


Immunoglobulin (Ig) G kappa

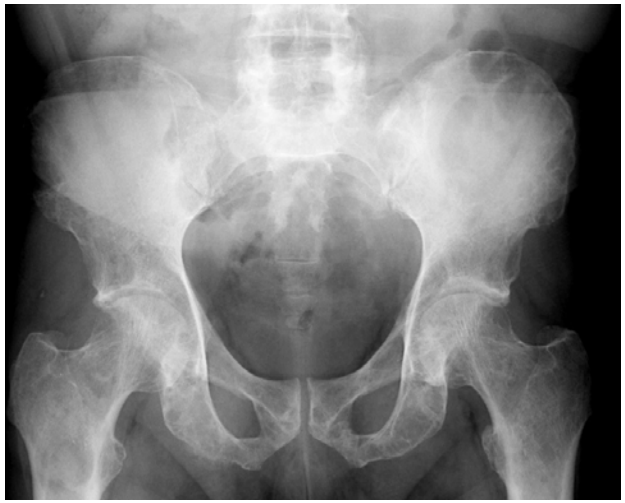
Immunofixation

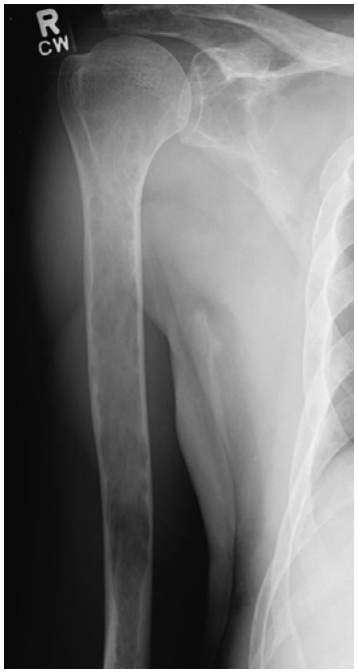
Katzmann et al, *Electrophoresis* 1997

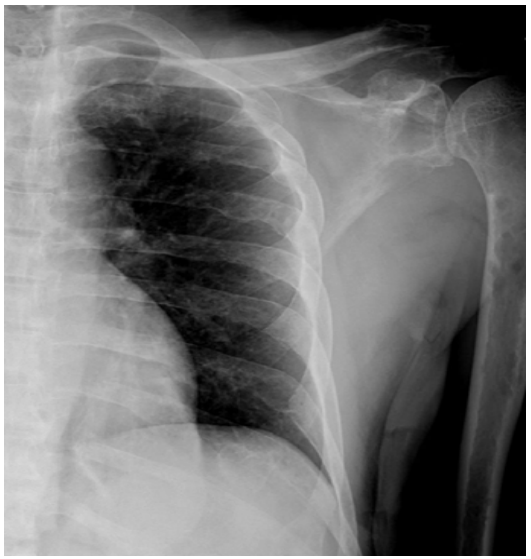
Skeletal X-ray shows punched-out lytic lesions, diffuse osteoporosis, and fractures

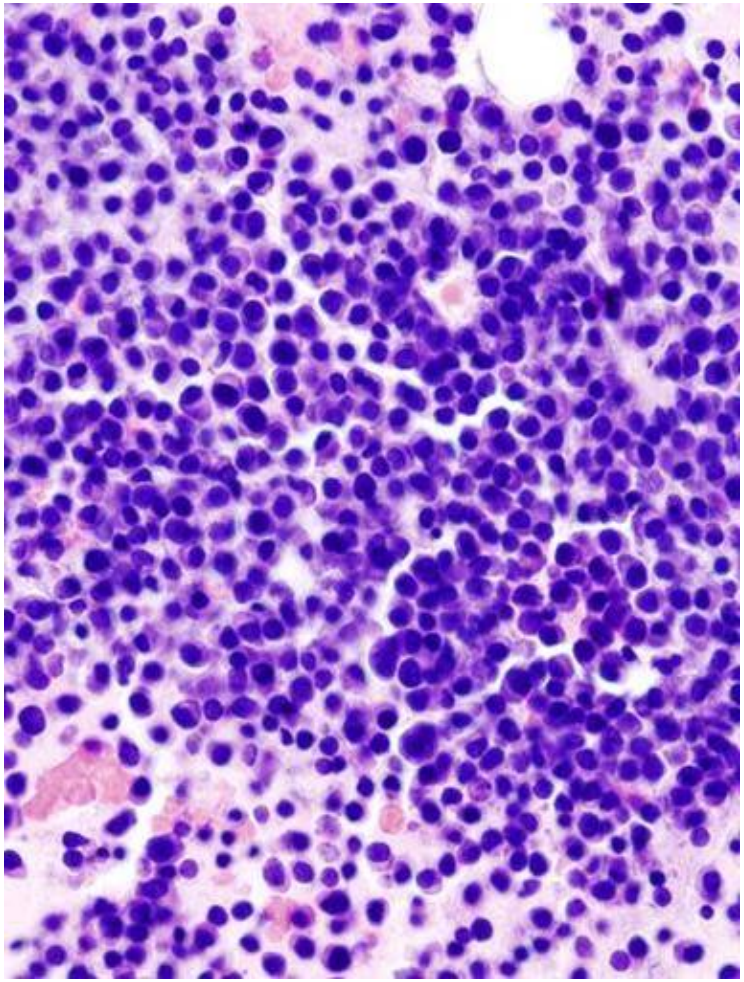


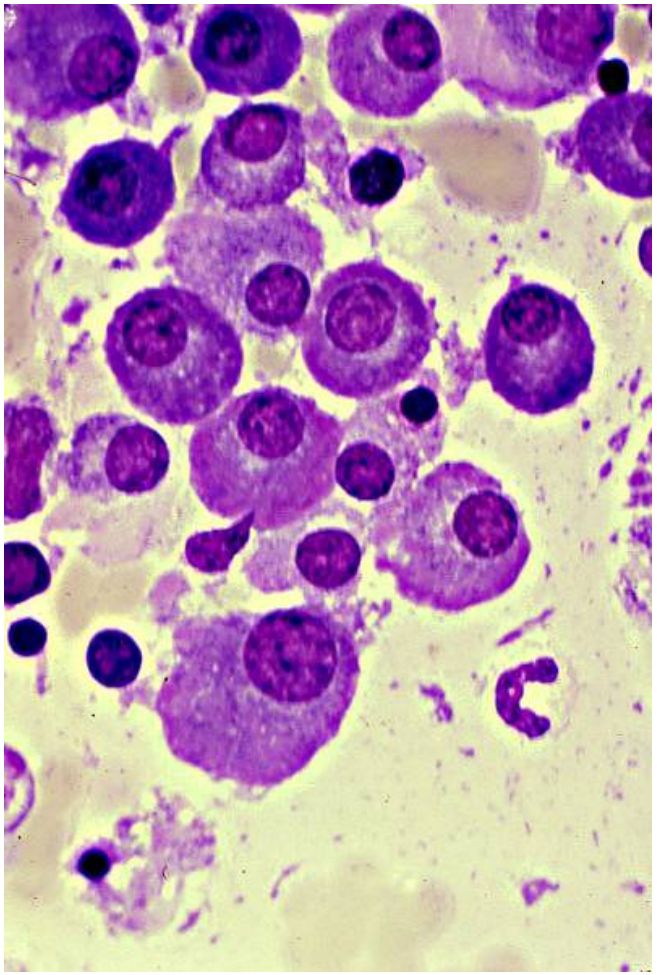
For MM work-up, bones should be evaluated with a complete “skeletal survey”, including:
- Skull
- Spine
- Pelvis
- Extremities (including forearms and legs)











Diagnostic criteria

	Monoclonal gammopathy of undetermined significance (MGUS)	Smoldering myeloma (SMM)	Multiple myeloma (MM)
Monoclonal (M)-protein in serum	<3 g/dL	>3 g/dL	Any
Monoclonal plasma cells in bone marrow	*AND* <10%	*OR* >10%	Any
End-organ damage	No	No	Yes
Comment	Requires exclusion of all other B-cell lymphoproliferative disorders	Indolent MM is a non-standard term to refer to disease with end-organ damage but minimal symptoms	*End-organ damage:* • Hypercalcemia • Renal failure • Anemia • Lytic bone lesions

Int'l Myeloma Working Group. Br J Haematol 2003

Differential diagnosis

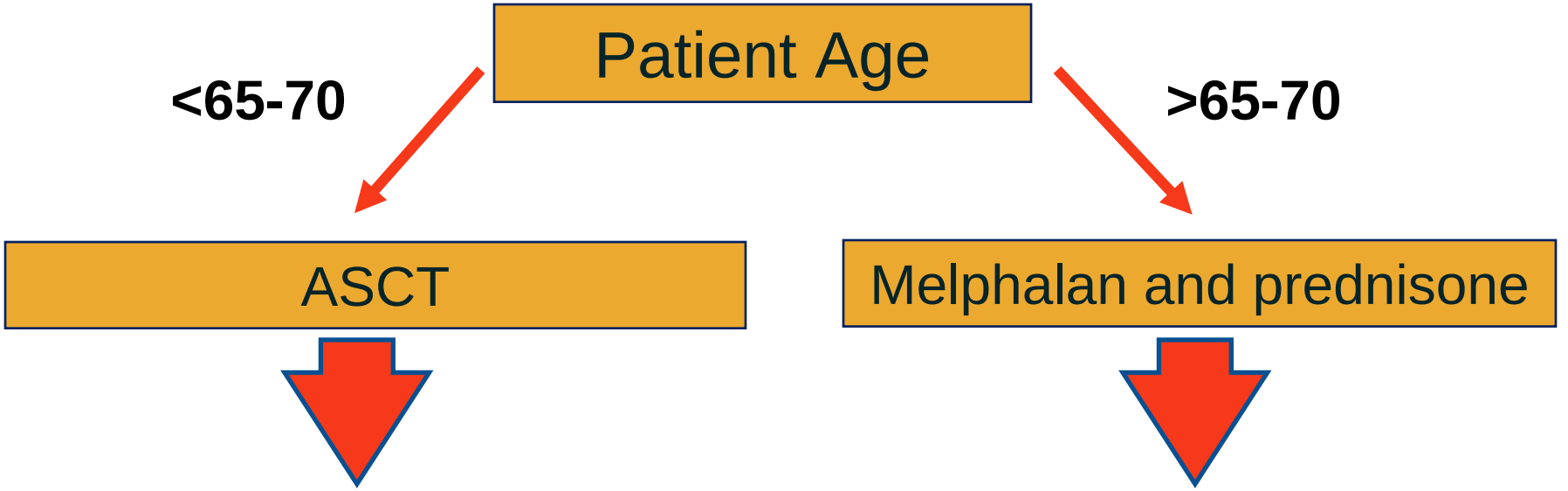
- MGUS
- SMM
- Solitary plasmacytoma
- Amyloidosis
- Light chain deposition disease
- Waldenström's macroglobulinemia
- Lymphoproliferative disorders
- Infections (e.g. CMV)
- Rheumatologic autoimmune disorders
- Certain skin or neurologic disorders

Treatment

- Initial treatment for MM depends if the patient is a candidate for Autologous Stem Cell Transplant (ASCT)

- Typically, eligibility is determined by
  - Age
  - Performance status
  - Comorbidity

Treatment strategy before novel drugs



- VAD, Dex or Thal/Dex induction
- Melphalan 200 mg/m^2
- Overall response rate 80%
  - CR/nCR rate 20%
- Median PFS 20-36 mos
- Median OS 48-60 mos

- Overall response rate 40-50%
  - CR/nCR 5%
- Median PFS 12-15 mos
- Median OS 30-36 mos

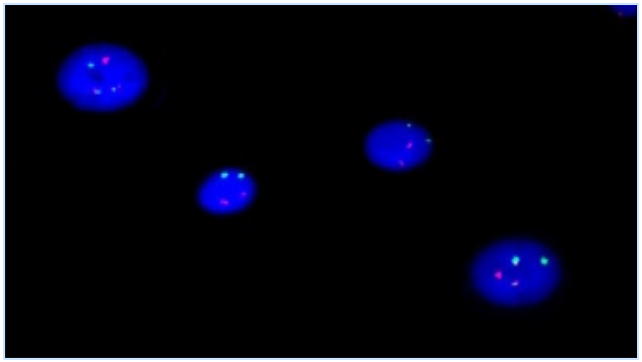
Kyle and Rajkumar. Clin Lymphoma & Myeloma 2009

Advances in prognosis

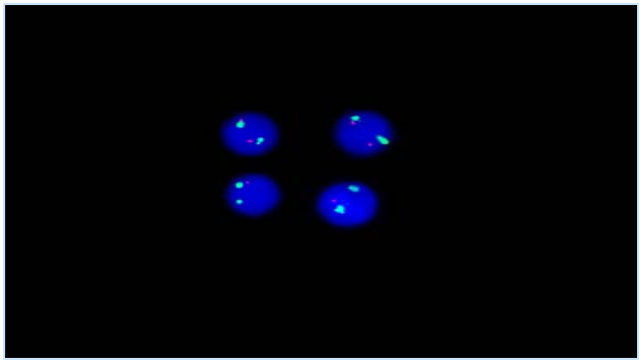
- International Staging System (ISS)

Stage	Criteria	Median
I	Serum β_2-microglobulin <3.5 mg/L Serum albumin ≥ 3.5 g/dL	62 mo.
II	Not stage I or III	44 mo.
III	Serum β_2-microglobulin ≥ 5.5 mg/L	29 mo.

- Adverse cytogenetic abnormalities (by FISH)



t(4;14)=15% of MM
(dysregulation of FGFR3 and MMSET)



p53 deletion=10% of MM
(loss of tumor suppressor gene)

Mayo Clinic “mSMART classification”of active MM

High-Risk (25%)

- FISH
  - Del 17p
  - t(4;14)*
  - t(14;16)
- Cytogenetic Deletion 13
- Cytogenetic hypodiploidy
- PCLI ≥3%

Standard-Risk (75%) *

All others including:

- Hyperdiploid
- t(11;14)
- t(6;14)

*Patients with t(4;14), b2M<4 mg/l and Hb≥10g/dl may have intermediate risk disease

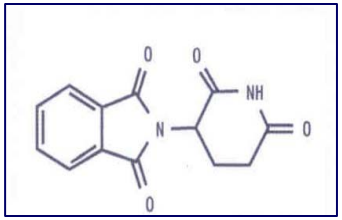
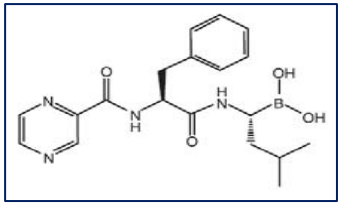
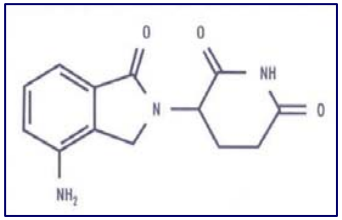
Dispenzieri, et al. *Mayo Clin Proc* 2007 (revised and updated Jan 2009, v5)

Int'l Myeloma Working Group response criteria

Response subcategory	*Response criteria*
Complete response[a] (CR)	Negative immunofixation of serum and urine and Disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow
Stringent complete response (sCR)	CR as defined above plus Normal FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Very good partial response (VGPR)[a]	Serum and urine M-component detectable by immunofixation but not on electrophoresis or ⩾90% or greater reduction in serum M-component plus urine M-component <100 mg per 24 h
Partial response (PR)	⩾50% reduction of serum M protein and reduction in 24-h urinary M protein by ⩾90% or to <200 mg per 24 h If the serum and urine M protein are unmeasurable, a ⩾50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M protein criteria If serum and urine M protein are unmeasurable, and serum free light assay is also unmeasurable, ⩾50% reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was ⩾30% In addition to the above criteria, if present at baseline, ⩾50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive disease (PD)[a]	Increase of 25% from lowest response value in any one or more of the following: Serum M-component (absolute increase must be ⩾0.5 g/100 ml)[c] and/or Urine M-component (absolute increase must be ⩾200 mg per 24 h) and/or Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >100 mg/l) Bone marrow plasma cell percentage (absolute % must be ⩾10%) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/100 ml) that can be attributed solely to the plasma cell proliferative disorder

Durie, et al. *Leukemia* 2007; Anderson, et al. *Leukemia* 2008

Novel agents in MM

Agent	Main Toxicities
• Thalidomide 	• Teratogenicity, peripheral neuropathy, constipation, sedation, rash, venous thromboembolism
• Bortezomib 	• Fatigue, GI toxicity, peripheral neuropathy, decrease in platelets and neutrophils
• Lenalidomide 	• Myelosuppression, venous thromboembolism

Current treatment options for newly dx non-transplant eligible MM pts

- **Add novel agent to melphalan + prednisone**
- **IMiD + dexamethasone**
- **3-4 drug regimens +/- maintenance[1-5]**

[1]Morgan G, et al. Blood 2007;110: abstract 3593 [2]Richardson PG, et al. Blood 2008;112: abstract 92; [3]Reeder CB, et al. Leukemia 2009;23: 1337-1341; Kumar S et al. Blood 2008;112: abstract 91; [5]Offandini M. et al. Br J Haematol 2009;144: 653-659.

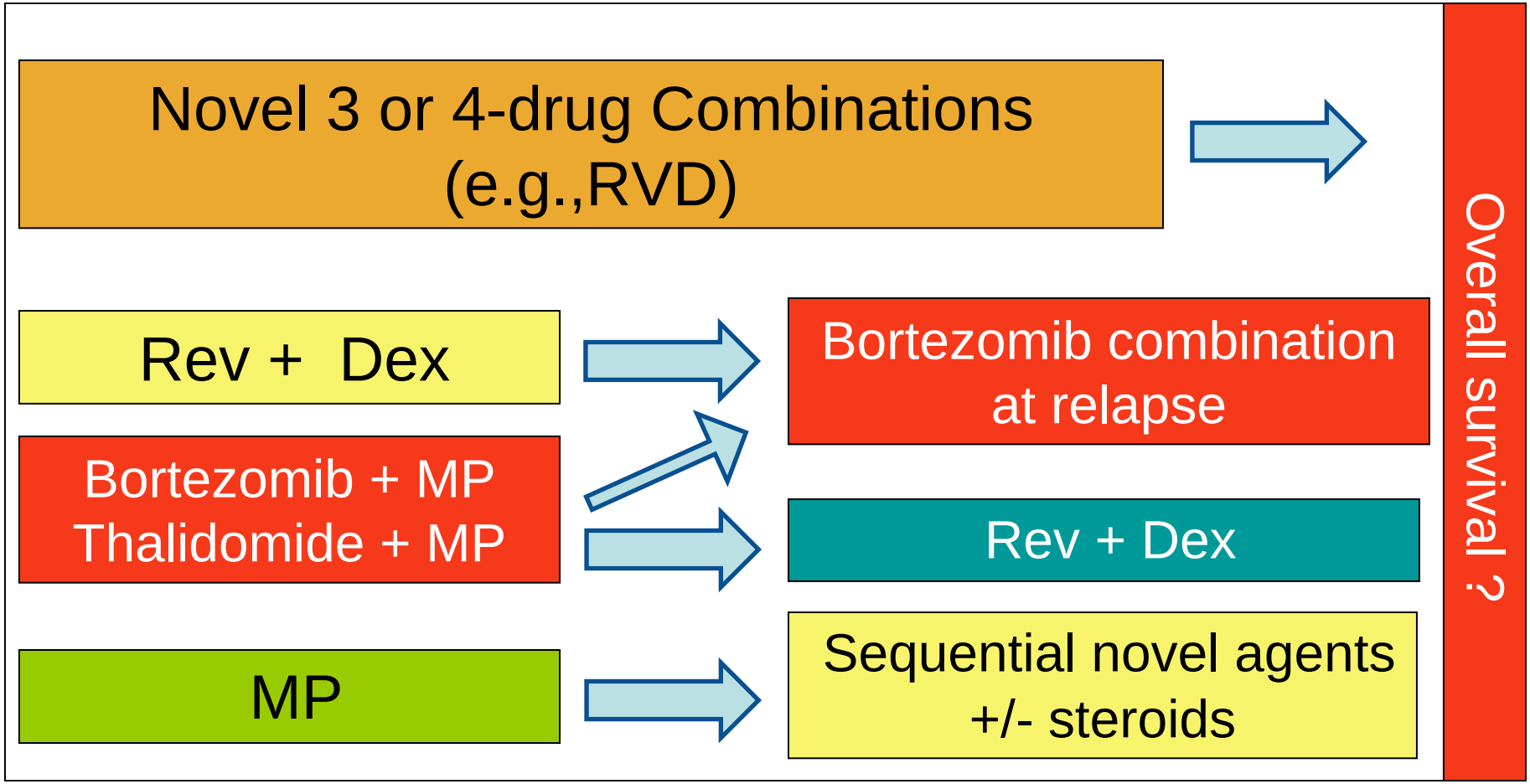
Current best outcomes with non-ASCT regimens in phase III trials

Reference	Rx	Duration of therapy (wks)	Overall response rate (CR+nCR) (%)	Median PFS (mos)	Median OS (mos)	2 year OS (%)
Facon[1]	MPT	72	76 (18)	27.5*	51.6*	78
Palumbo[2]	MPT	24+	76 (28)	21.8*	45	82
Hulin[3]	MPT	72	61 (7)	24*	45*	70
San Miguel[4]	VMP	54	71 (35)	24*	NYR*	83
Rajkumar[5]	Len+ dex	Until prog	70 (14 CR)	~24	NYR	93

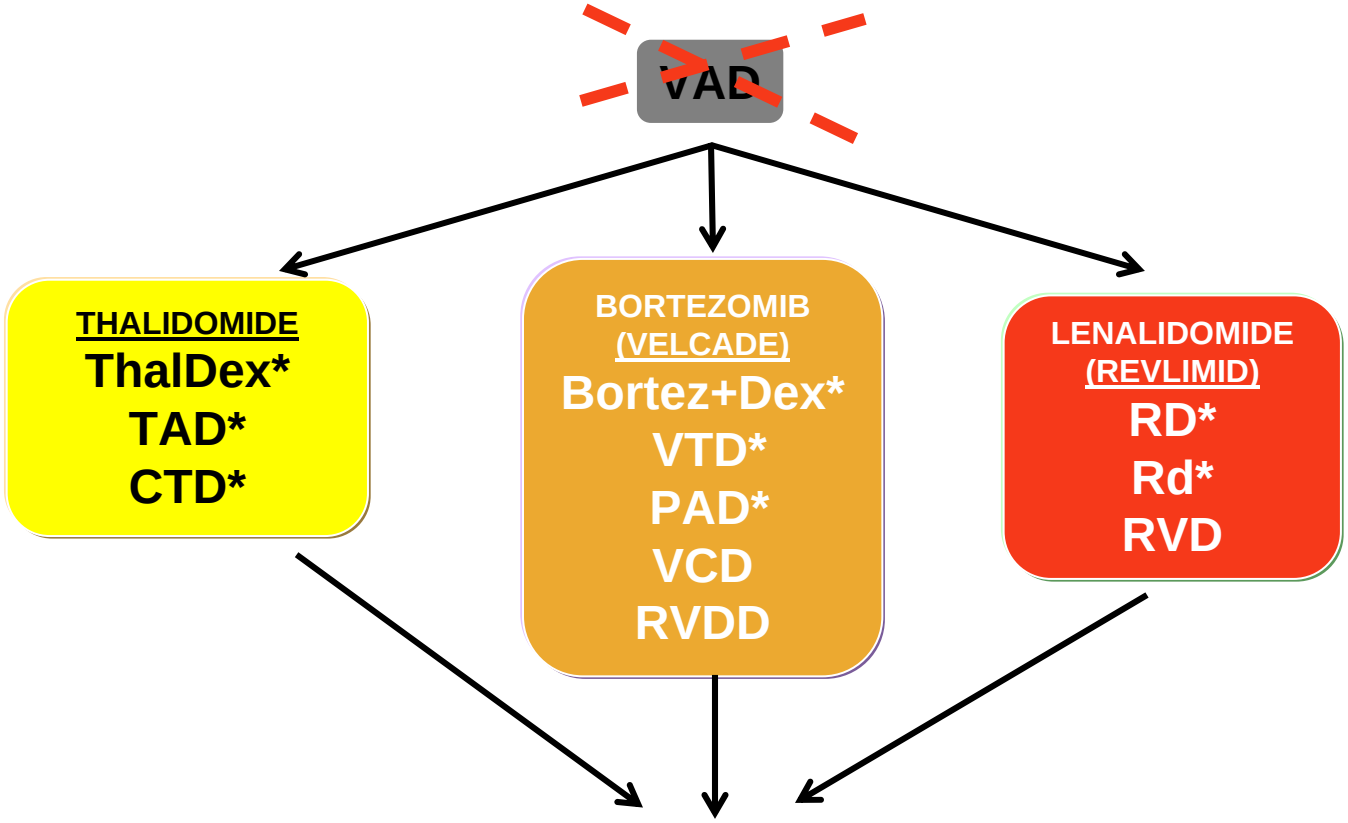
*** P<0.05 (when compared to MP alone)**

[1]Facon T, et al. Lancet 2007:370; 1209-1218; [2]Palumbo A , et al. Blood 2008;112: 3107-3114; [3] Hulin C, et al. Blood 2007; 110: abstract 75;[4]San Miguel JF, et al. N Engl J Med 2008; [5] Rajkumar V, et al; Blood 2007; 110: Abstract 74.

What is the optimal non-ASCT strategy in MM?



Current induction regimens before ASCT



***Studied in phase III trials**

RD: Lenalidomide + high-dose dex
Rd: Lenalidomide + low-dose dex

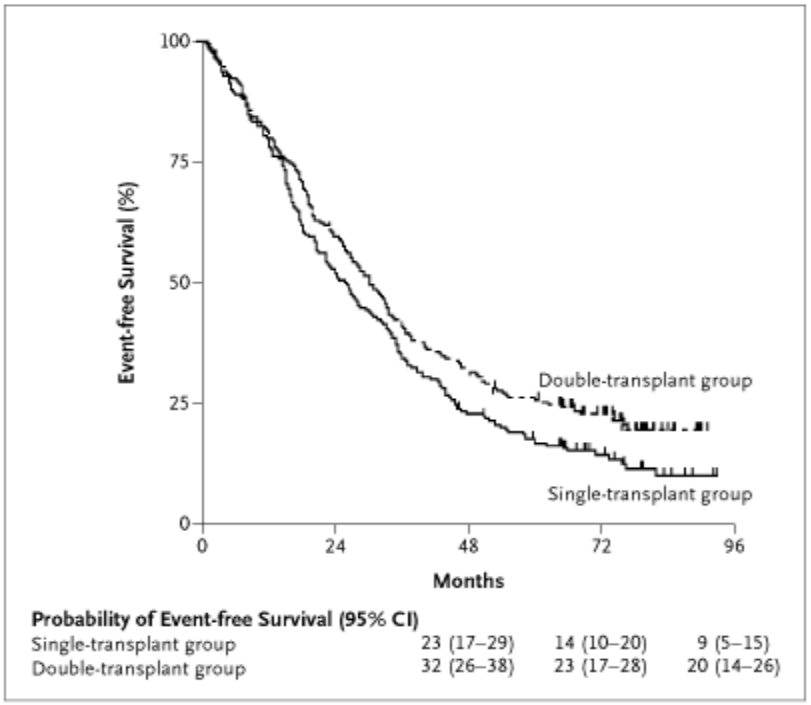
Strategies to improve ASCT results

- Risk stratification
  - Cytogenetics
  - Molecular classification
- Improved induction therapy
- Improved consolidation therapy
  - New regimens
  - Tandem ASCT
- Maintenance therapy

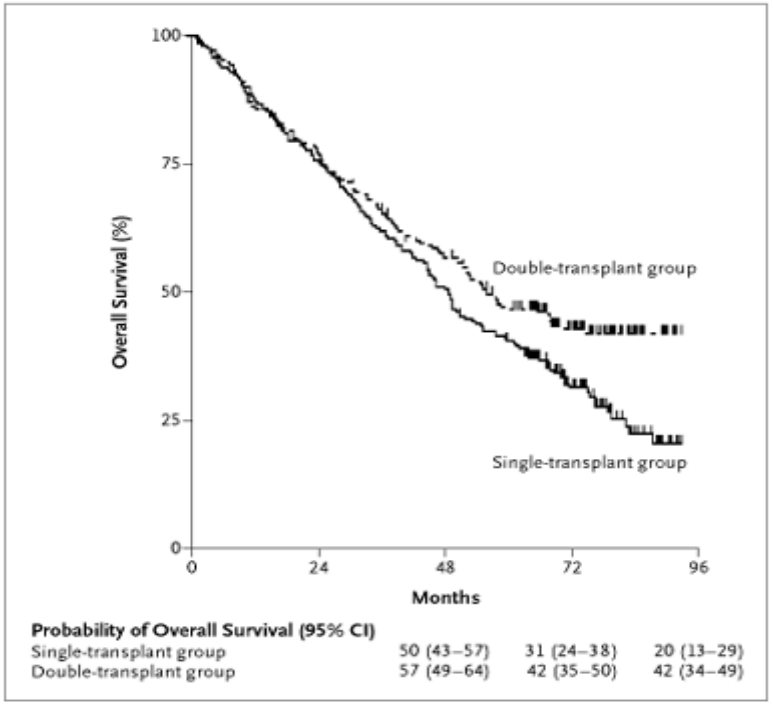
- ASCT followed by alloSCT

Tandem ASCT reportedly beneficial if <VGPR after first ASCT

EFS



Overall survival



Attal M, et al. *N Engl J Med* 2003;349:2405

Randomized tandem ASCT trials

	N	CR/VGPR rate (%) Single	CR/VGPR rate (%) Tandem	Median PFS (mo) Single	Median PFS (mo) Tandem	Median OS (mo) Single	Median OS (mo) Tandem
Attal, 2003	399	42	50	*25*	*30*	*48*	*58*
Fermand, 2003	277	39	37	31	33	49	73
Goldschmidt, 2005	268	--	--	*22*	*NYR*	23	NYR
Sonneveld, 2004	303	13	28	*20*	*22*	55	50
Cavo, 2007	321	38	48	*23*	*35*	65	71

Values highlighted in red indicate $p<0.05$

Thalidomide maintenance after ASCT

Reference	N	Thalidomide dose (mg)/duration	PFS/ EFS	Overall survival
Attal, 2006	597	**Thal 200 (median dose) vs. obs** /progression	+	+
Spencer, 2006	243	**Thal 200 + pred vs. pred** /12 months	+	+
Maiolino, 2008	212	**Thal 200 + dex vs. dex** /12 months	+	NS
Barlogie, 2006*	668	**Thal 400** /progression	+	NS*
Morgan, 2008*	--	**Thal 100** /progression	+/-	NS*
NCIC, 2009	325	**Thal 200 + pred vs. obs** /48 months	?	?

*Thalidomide also given as part of induction therapy

Treatment strategies in 2010

ASCT

- Preceded by novel induction regimens
- Melphalan 200 mg/m^2
  +/- second ASCT
  +/-maintenance
- Overall response rate 80-90%
- CR/nCR rate 35-50%
- 2 year PFS 69-93%
- 2 year OS 90-93%

MPT or MPV or Lenalidomide + Dex

- Overall response rate 65-75%
- CR/nCR 20-25%
- Median PFS 24-30 mos
- Median OS 48-50 mos
- 2 year OS 70-93%

Treatment strategies for relapsed/refractory patients

- **Initial treatment can be repeated in selected patients**
  - Commonly used with alkylating agents (cyclophosphamide + prednisone is alternative to repeated MP)
  - Also high-dose melphalan + ASCT
  - Data emerging that novel agents can be used again

- **Novel agents can be introduced**
  - As single agents
  - With steroids
  - In 3-4 drug regimens with conventional chemotherapy and/or other novel agents

Clinical myeloma studies at NCI in 2010-

- Precursor disease
  - Natural history study (individualized profiling)
- Smoldering myeloma
  - Early treatment
- Relapsed multiple myeloma
  - MEK inhibitor
  - HDAC/mTOR inhibitors
- From precursor to multiple myeloma
  - Imaging study

-Thank you very much
for your attention!