



# Multiple Myeloma

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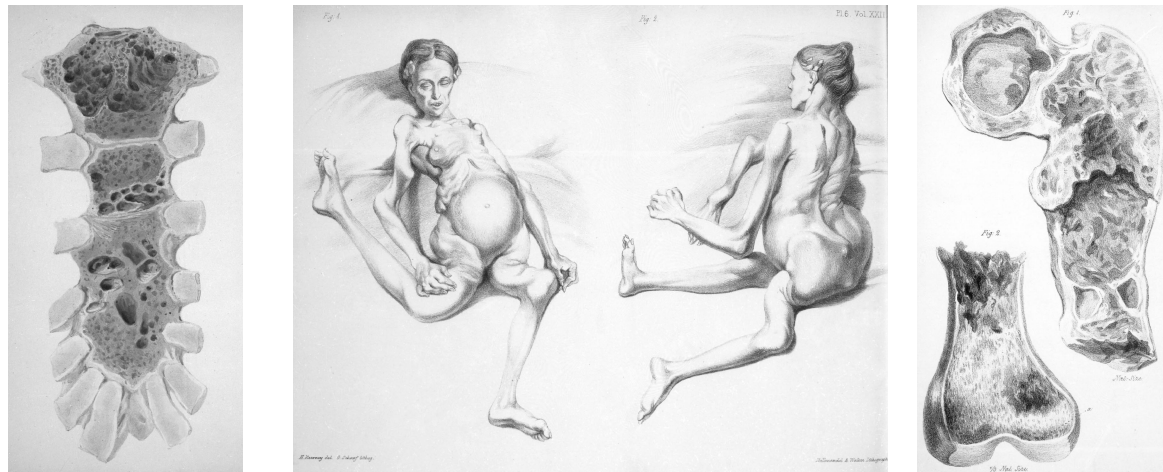
*Seattle Cancer Care Alliance*

*Fred Hutchinson Cancer Research Center*



# The first case of myeloma was described in 1844 by Dr. Samuel Solly

Dr. Solly thought that the disease was an inflammatory process that began with a “morbid action” of the blood vessels in which the “earthy matter of the bone is absorbed and thrown out by the kidneys in the urine.”



Images of the first patient, a 39-year-old woman

# Myeloma is the 24<sup>th</sup> most common cause of cancer-related mortality in Uganda

Country	Breast Cancer	Tracheal, Bronchus, and Lung Cancer	Colon and Rectum Cancer	Prostate Cancer	Stomach Cancer	Liver Cancer	Non-Hodgkin Lymphoma	Leukemia	Bladder Cancer	Cervical Cancer	Esophageal Cancer	Uterine Cancer	Pancreatic Cancer	Kidney Cancer	Up and Oral Cavity Cancer	Malignant Skin Melanoma	Thyroid Cancer	Brain and Nervous System Cancer	Ovarian Cancer	Larynx Cancer	Chronic Lymphoid Leukemia	Acute Myeloid Leukemia	Gallbladder and Biliary Tract Cancer	Other Pharynx Cancer	Acute Lymphoid Leukemia	Multiple Myeloma	Nasopharynx Cancer	Hodgkin Lymphoma	Testicular Cancer	Chronic Myeloid Leukemia	Mesothelioma
Guinea-Bissau	1	8	9	7	3	4	5	6	10	2	11	20	12	17	15	23	22	16	24	18	28	14	19	21	13	25	29	27	30	26	31
Cape Verde	3	5	11	1	2	6	7	9	13	4	8	18	12	16	10	22	24	15	25	20	23	14	26	19	17	21	28	30	29	27	31
Sao Tome and Principe	1	4	6	7	3	20	5	8	9	2	14	18	12	15	22	23	21	13	17	16	26	10	19	25	11	24	29	30	28	27	31
Eastern SSA	1	11	9	7	4	5	3	8	13	2	6	19	16	25	10	21	20	15	14	18	27	17	26	24	12	23	22	30	29	28	31
Ethiopia	1	11	6	8	4	3	5	7	15	2	9	19	14	26	10	21	18	17	13	20	27	16	25	23	12	24	22	30	29	28	31
Tanzania	1	10	8	6	7	4	3	5	14	2	9	21	17	23	12	20	19	13	15	18	27	16	26	25	11	22	24	29	31	28	30
Kenya	2	17	8	4	3	7	6	5	19	1	10	20	14	26	9	24	22	13	12	11	27	16	23	25	15	21	18	30	29	28	31
Uganda	1	10	6	4	9	7	3	8	17	2	5	18	15	22	13	21	20	14	11	23	27	16	26	25	12	24	19	30	29	28	31
Mozambique	1	9	7	12	4	3	8	5	15	2	6	20	17	24	10	22	19	14	16	18	26	13	25	21	11	23	28	29	31	27	30
Madagascar	1	11	9	6	5	3	4	8	12	2	7	19	14	25	10	21	20	16	13	18	27	17	26	24	15	23	22	30	29	28	31
Malawi	4	11	9	6	10	7	3	8	5	2	1	23	17	21	12	13	20	14	16	19	26	18	25	24	15	22	27	30	29	28	31
Zambia	1	12	6	4	7	8	3	9	11	2	5	21	16	22	10	18	20	14	13	19	27	17	26	25	15	23	24	30	29	28	31
South Sudan	1	11	8	9	3	4	6	7	12	2	5	19	13	26	10	21	20	16	15	17	27	18	25	23	14	24	22	29	31	28	30
Rwanda	1	14	7	8	6	5	3	4	17	2	9	21	16	25	10	19	20	13	12	18	27	15	26	24	11	22	23	29	30	28	31
Burundi	1	13	9	8	3	4	5	6	17	2	7	20	16	25	10	21	19	12	15	18	27	14	26	23	11	24	22	29	30	28	31
Somalia	2	12	8	9	3	4	6	7	15	1	5	16	18	27	10	21	19	13	14	20	26	17	24	22	11	25	23	29	31	28	30
Eritrea	1	11	9	8	3	4	5	6	14	2	7	18	16	25	10	21	20	15	13	19	27	17	26	24	12	23	22	30	29	28	31
Djibouti	1	10	6	3	8	5	4	9	12	2	7	20	14	24	11	19	21	16	13	15	27	17	26	25	18	22	23	30	29	28	31
Comoros	1	12	8	7	6	3	4	5	14	2	9	20	13	25	10	21	19	17	11	18	26	16	27	24	15	23	22	30	29	28	31
High-income North America	2	3	4	1	13	14	5	11	7	22	21	10	12	9	15	6	8	17	19	23	18	20	26	24	29	16	31	27	25	30	28
United States	2	3	4	1	14	13	5	11	7	23	21	9	12	10	15	6	8	17	19	22	18	20	26	24	30	16	31	27	25	29	28
Canada	2	4	3	1	7	17	5	10	9	23	21	11	12	6	20	8	13	14	18	24	16	19	22	25	29	15	31	27	26	30	28
Greenland	3	1	2	4	6	14	10	16	13	7	9	17	8	5	12	19	18	21	20	22	28	24	23	15	29	25	11	30	26	27	31

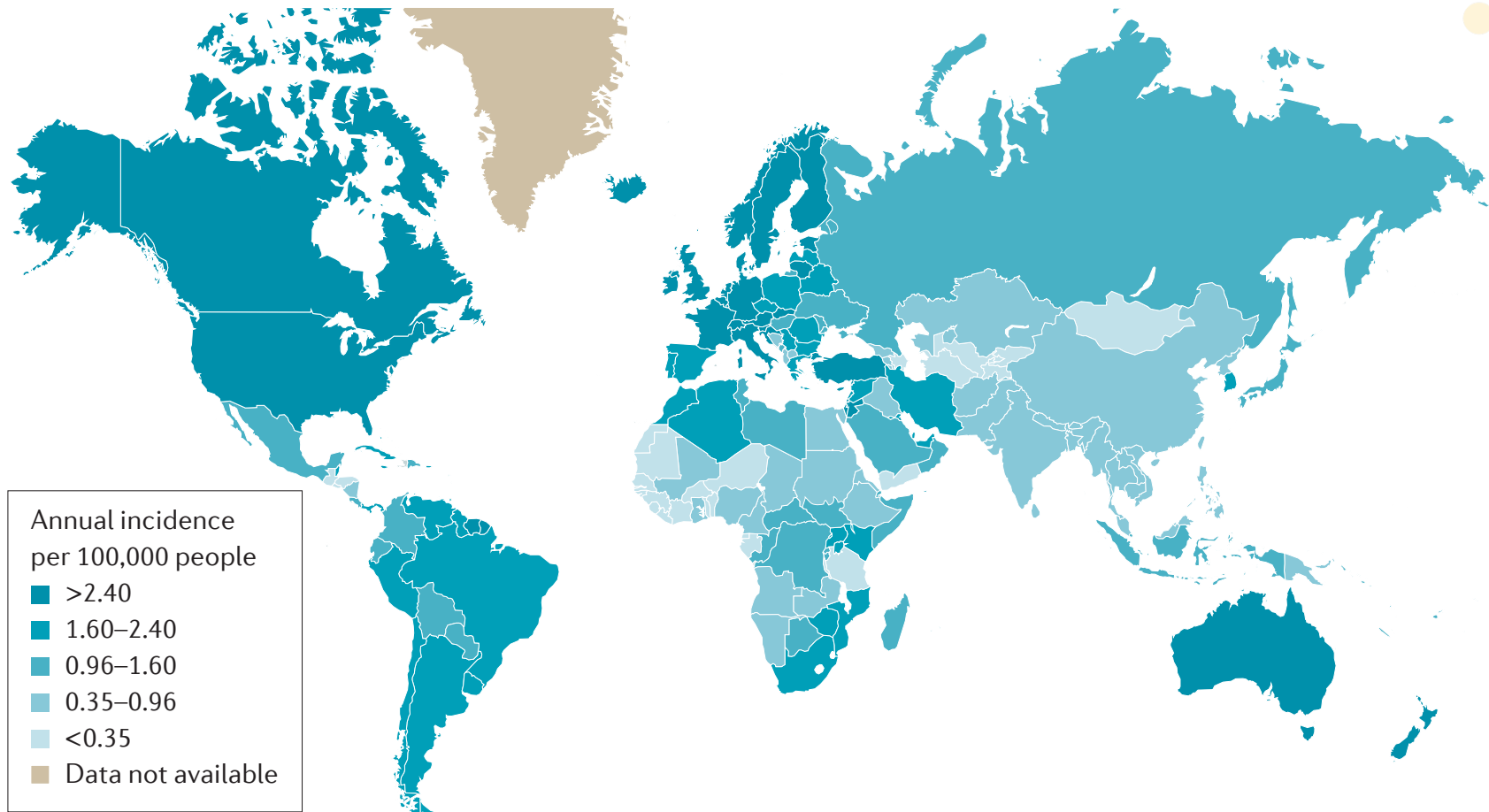
# The global incident of myeloma has increased 42% in the past decade

2005		2015		Change in A-YLLs, % (95% CI)		Change in AS-YLL Rate, % (95% CI)	
Rank	Cancer	Cancer	Rank				
1	Tracheal, bronchus, and lung cancer	Tracheal, bronchus, and lung cancer	1	14.3 (10.8 to 18.9)	-11.5 (-14.2 to -8.0)		
2	Liver cancer	Liver cancer	2	4.6 (-1.6 to 15.4)	-16.9 (-21.6 to -8.8)		
3	Stomach cancer	Stomach cancer	3	-6.9 (-10.2 to -3.7)	-27.3 (-29.8 to -24.7)		
4	Colon and rectum cancer	Colon and rectum cancer	4	17.4 (14.8 to 20.2)	-8.9 (-10.8 to -6.8)		
5	Breast cancer	Breast cancer	5	17.2 (9.3 to 24.3)	-7.5 (-13.5 to -2.2)		
6	Leukemia	Leukemia	6	6.2 (2.5 to 9.9)	-8.0 (-11.1 to -4.9)		
7	Esophageal cancer	Esophageal cancer	7	-7.8 (-12.7 to -2.3)	-28.7 (-32.5 to -24.5)		
8	Brain and nervous system cancer	Pancreatic cancer	8	26.1 (23.2 to 29.0)	-2.8 (-4.9 to -0.6)		
9	Cervical cancer	Brain and nervous system cancer	9	13.0 (4.8 to 20.8)	-5.3 (-11.8 to 1.1)		
10	Pancreatic cancer	Cervical cancer	10	2.3 (-4.4 to 10.8)	-18.6 (-24.0 to -12.0)		
11	Non-Hodgkin lymphoma	Non-Hodgkin lymphoma	11	22.7 (10.3 to 30.4)	0.3 (-9.4 to 6.0)		
12	Acute lymphoid leukemia	Prostate cancer	12	25.9 (22.0 to 29.9)	-4.2 (-7.1 to -1.3)		
13	Acute myeloid leukemia	Acute lymphoid leukemia	13	3.8 (-2.1 to 9.6)	-6.4 (-11.5 to -1.3)		
14	Prostate cancer	Acute myeloid leukemia	14	13.1 (7.8 to 18.0)	-3.1 (-7.4 to 0.9)		
15	Ovarian cancer	Ovarian cancer	15	18.0 (13.1 to 22.9)	-7.5 (-11.3 to -3.9)		
16	Lip and oral cavity cancer	Lip and oral cavity cancer	16	27.5 (23.4 to 32.2)	-0.2 (-3.5 to 3.4)		
17	Bladder cancer	Kidney cancer	17	24.6 (19.7 to 29.0)	-1.5 (-4.9 to 2.0)		
18	Kidney cancer	Bladder cancer	18	17.9 (14.3 to 21.6)	-9.6 (-12.3 to -6.8)		
19	Gallbladder and biliary tract cancer	Gallbladder and biliary tract cancer	19	6.7 (2.1 to 11.4)	-17.6 (-21.2 to -13.9)		
20	Larynx cancer	Larynx cancer	20	9.6 (6.3 to 13.2)	-15.1 (-17.6 to -12.3)		
21	Uterine cancer	Multiple myeloma	21	27.9 (22.8 to 32.5)	-1.0 (-4.8 to 2.3)		
22	Nasopharynx cancer	Uterine cancer	22	4.5 (-2.2 to 12.6)	-18.8 (-24.0 to -12.6)		
23	Multiple myeloma	Nasopharynx cancer	23	5.5 (-2.5 to 12.0)	14.6 (-20.9 to -9.4)		
24	Other pharynx cancer	Other pharynx cancer	24	20.4 (14.7 to 25.9)	-6.7 (-11.0 to -2.4)		
25	Malignant skin melanoma	Malignant skin melanoma	25	19.1 (12.6 to 23.9)	-5.0 (-10.1 to -1.2)		
26	Chronic lymphoid leukemia	Chronic lymphoid leukemia	26	5.5 (-0.1 to 11.1)	-15.4 (-19.7 to -11.1)		
27	Chronic myeloid leukemia	Chronic myeloid leukemia	27	-9.4 (-13.3 to -4.9)	-25.4 (-28.5 to -21.9)		
28	Hodgkin lymphoma	Hodgkin lymphoma	28	-12.1 (-16.2 to -7.9)	-25.7 (-29.3 to -22.1)		
29	Thyroid cancer	Mesothelioma	29	28.6 (24.1 to 33.2)	1.9 (-1.6 to 5.3)		
30	Mesothelioma	Thyroid cancer	30	18.7 (8.3 to 24.8)	-7.1 (-15.0 to -2.3)		
31	Testicular cancer	Testicular cancer	31	5.0 (-1.9 to 11.19)	-8.6 (-14.7 to -3.4)		

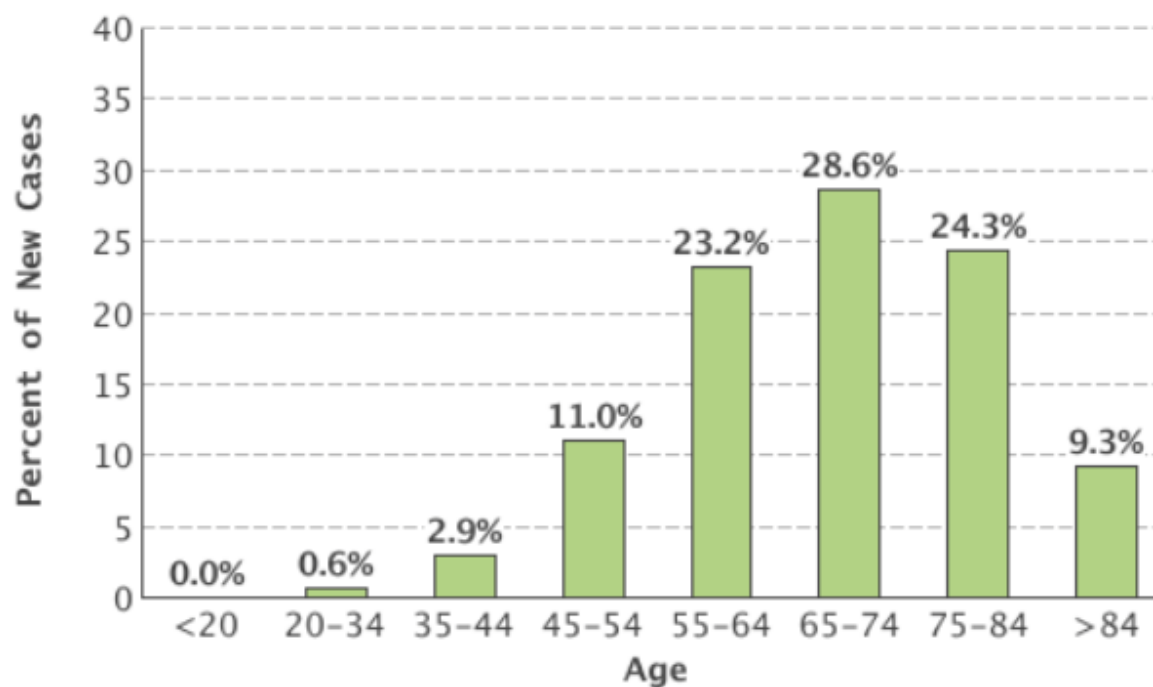
Rank increased No change Rank decreased



# The incidence of myeloma is higher in more developed countries



The median age at diagnosis is 69 years in the U.S.

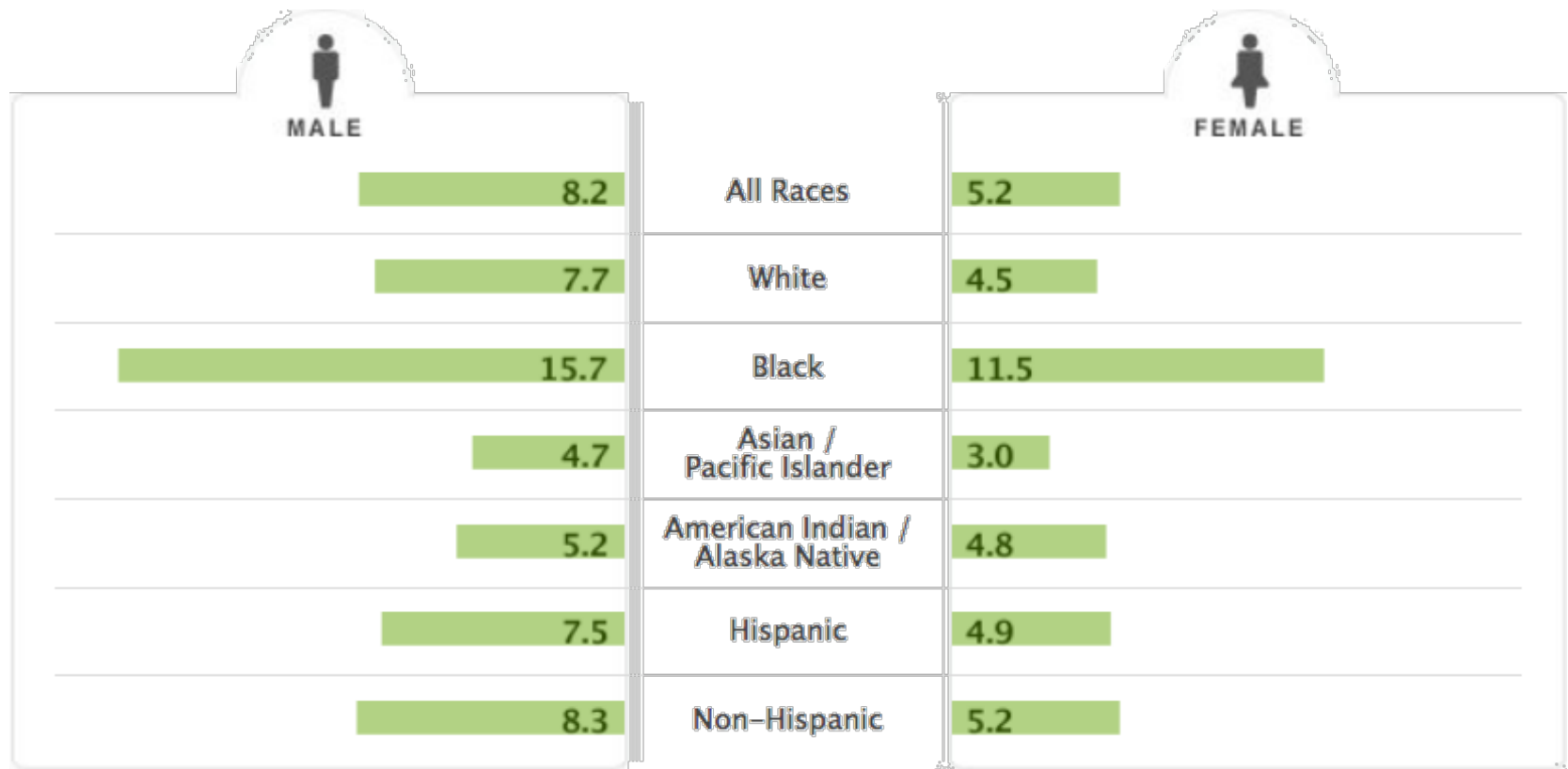


Myeloma is most frequently diagnosed among people aged 65–74.

**Median Age  
At Diagnosis**

**69**

The disease is more common in black men in the U.S.



# Symptoms of myeloma

Fatigue

Bone pain

Fractures

Neuropathy

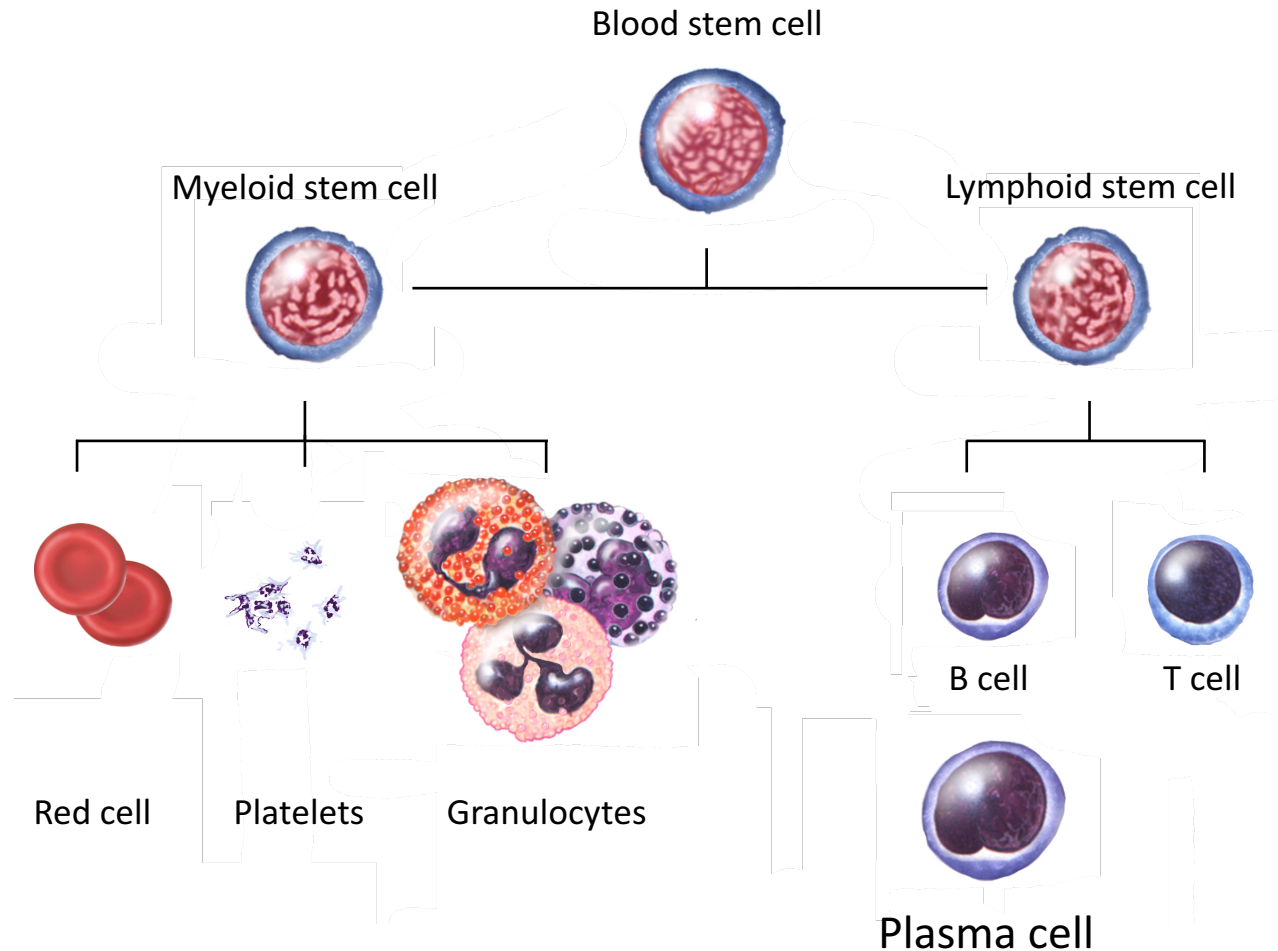
Frequent infections

Unexplained weight loss

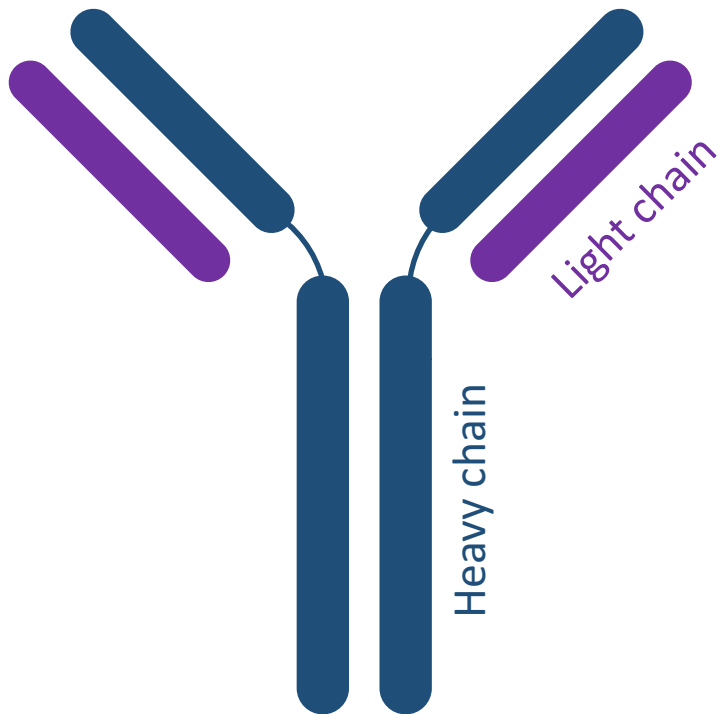
Spinal cord compression



# Myeloma is a malignancy of terminally differentiated plasma cells



# Plasma cell secrete immunoglobulin



## Types of light chains

Kappa  
Lambda

## Types of heavy chains

IgG  
IgM  
IgA  
IgD  
IgE



# Plasma cell neoplasms

Multiple myeloma

Light chain amyloidosis

- Deposition of an abnormally folded light chain protein in tissue

POEMS disease

- **P**olyneuropathy (nerve damage)
- **O**rganomegaly (enlarged organs)
- **E**ndocrinopathy (disorders involving hormone production)
- **M**onoclonal gammopathy (presence of an M-protein)
- **S**kin rash

Lymphoplasmacytic lymphoma

- Plasma cell disease involving the lymph nodes

Waldenström's macroglobulinemia

- A type of lymphoplasmacytic lymphoma that makes IgM M-protein

Solitary plasmacytoma

Plasma cell leukemia

- Greater than 20% plasma cells in the blood

# Diagnostic work-up for myeloma

## Recommended in all patients

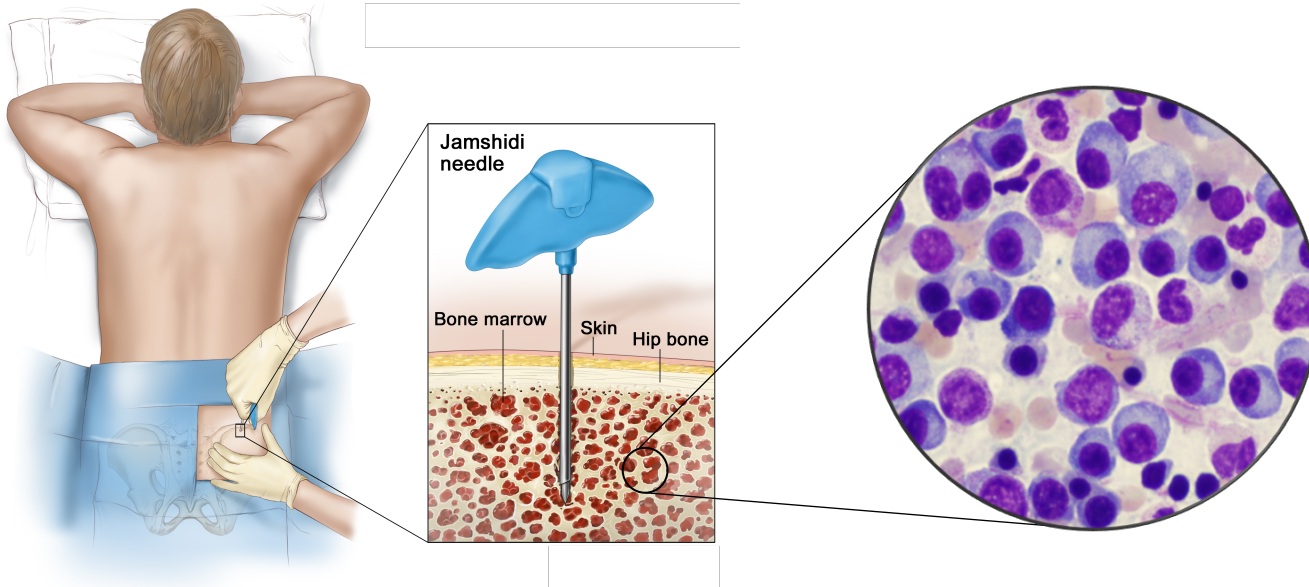
- ✓ Bone marrow biopsy and aspirate
  - ✓ Flow cytometry and immunohistochemistry
  - ✓ Cytogenetics
  - ✓ FISH
- ✓ Serum protein electrophoresis
- ✓ Serum free light chains
- ✓ 24-hour urine protein electrophoresis
- ✓ X-rays

## Recommended in certain patients

- ✓ MRI scan
- ✓ CT scan
- ✓ PET scan

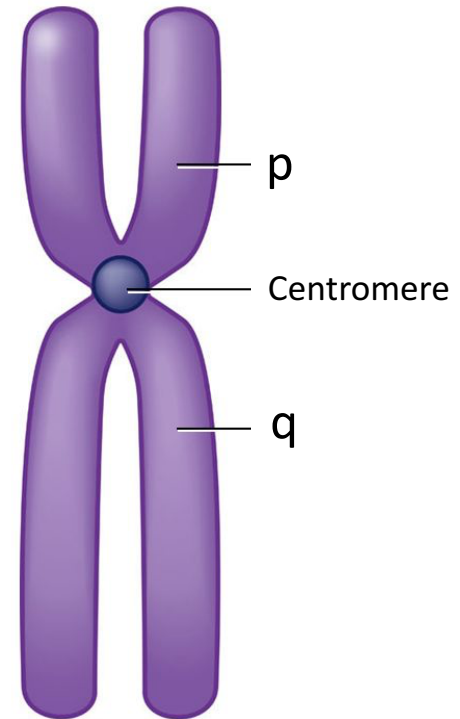
# Myeloma immunophenotype

Marker	Normal plasma cell	Myeloma cell
CD138	+	+
CD38	+	+
CD19	+	-
CD45	+	-
CD56	+	-
Kappa:Lambda	2:1	> 4:1 or < 1:2



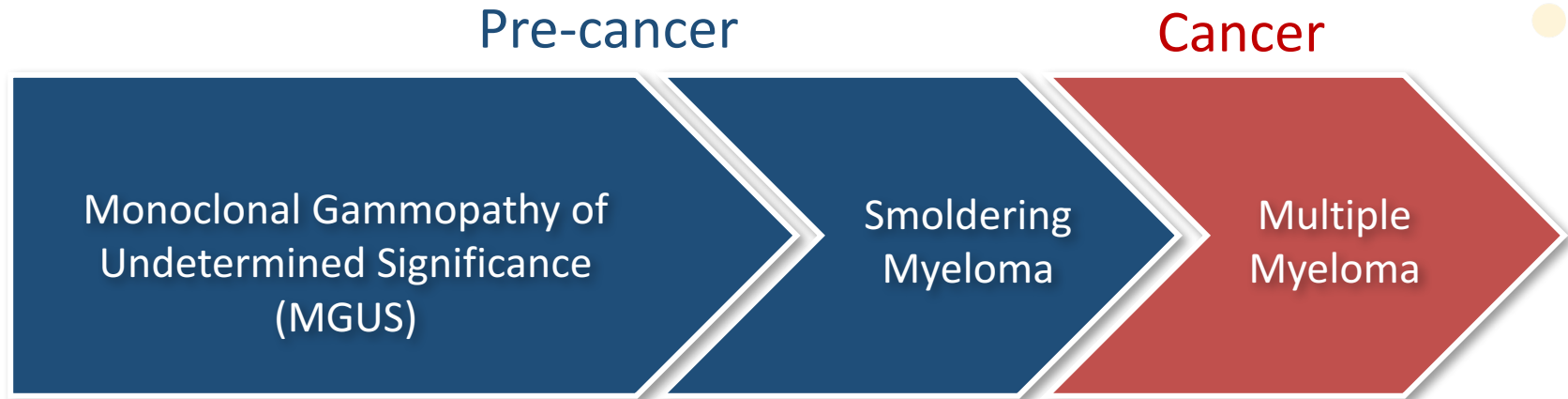
# Common chromosomal abnormalities in myeloma

Abnormality	Frequency	Prognosis
Deletion 13q	45-50%	Neutral
Gain 1q	35-40%	Poor
Deletion 1p	30%	Poor
Translocation (11;14)	15-20%	Neutral
Translocation (4;14)	15%	Poor
Deletion 17p	10%	Poor
Translocation (14;16)	5-10%	Poor
Translocation (6;14)	2%	Neutral
Translocation (14;20)	1%	Neutral



p = short arm of chromosome; q = long arm of chromosome

# Myeloma diagnostic criteria



M-protein	< 3.0 g/dl	> 3.0 g/dl	Any
Light chain ratio	< 100	< 100	> 100
Bone marrow plasma cells	< 10%	10-59%	> 60%
End organ damage	No	No	Yes "CRAB criteria"

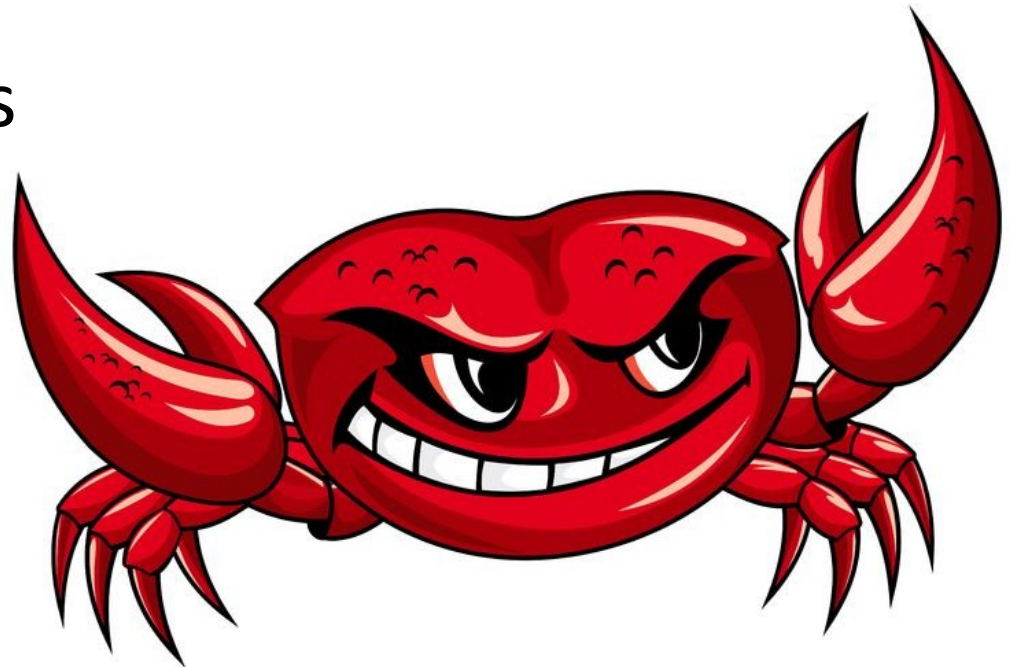
# Myeloma end-organ damage

**C**alcium level elevated

**R**enal failure

**A**nemia

**B**ony lytic lesions





# Revised International Staging System (ISS)

## Stage I

Beta-2 microglobulin < 3.5 mg/L **and**  
Albumin  $\geq$  3.5 g/dL **and**  
LDH normal **and**  
No high risk cytogenetics

## Stage II

Not stage I or II

### High risk cytogenetics

Deletion(17)p

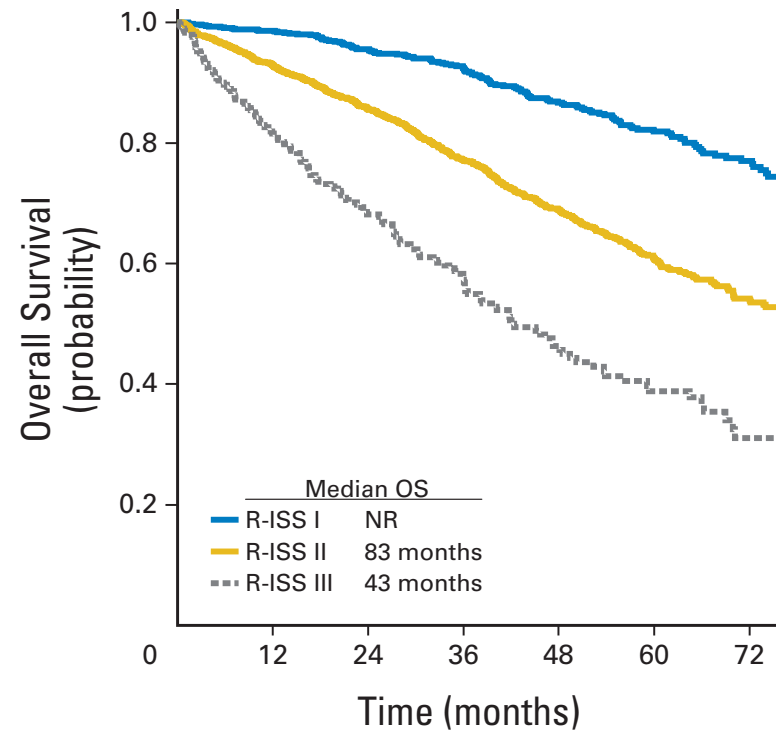
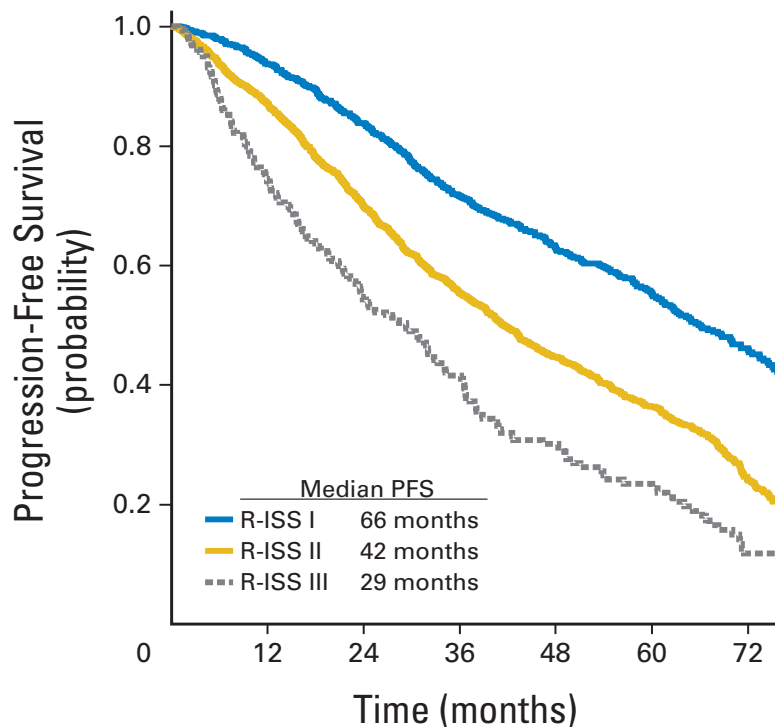
Translocation(4;14)

Translocation(14;16)

## Stage III

Beta-2 microglobulin > 5.5 mg/L **and**  
High risk cytogenetics **or**  
Elevated LDH

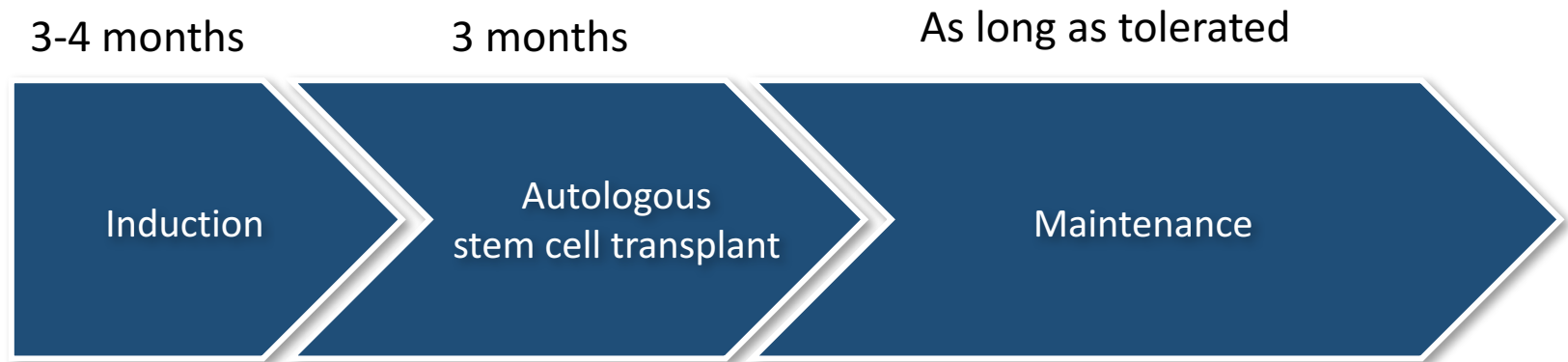
# Higher stage predicts more aggressive disease



NR = not reached (i.e. beyond the duration of the study)

*Journal of Clinical Oncology* (2015)

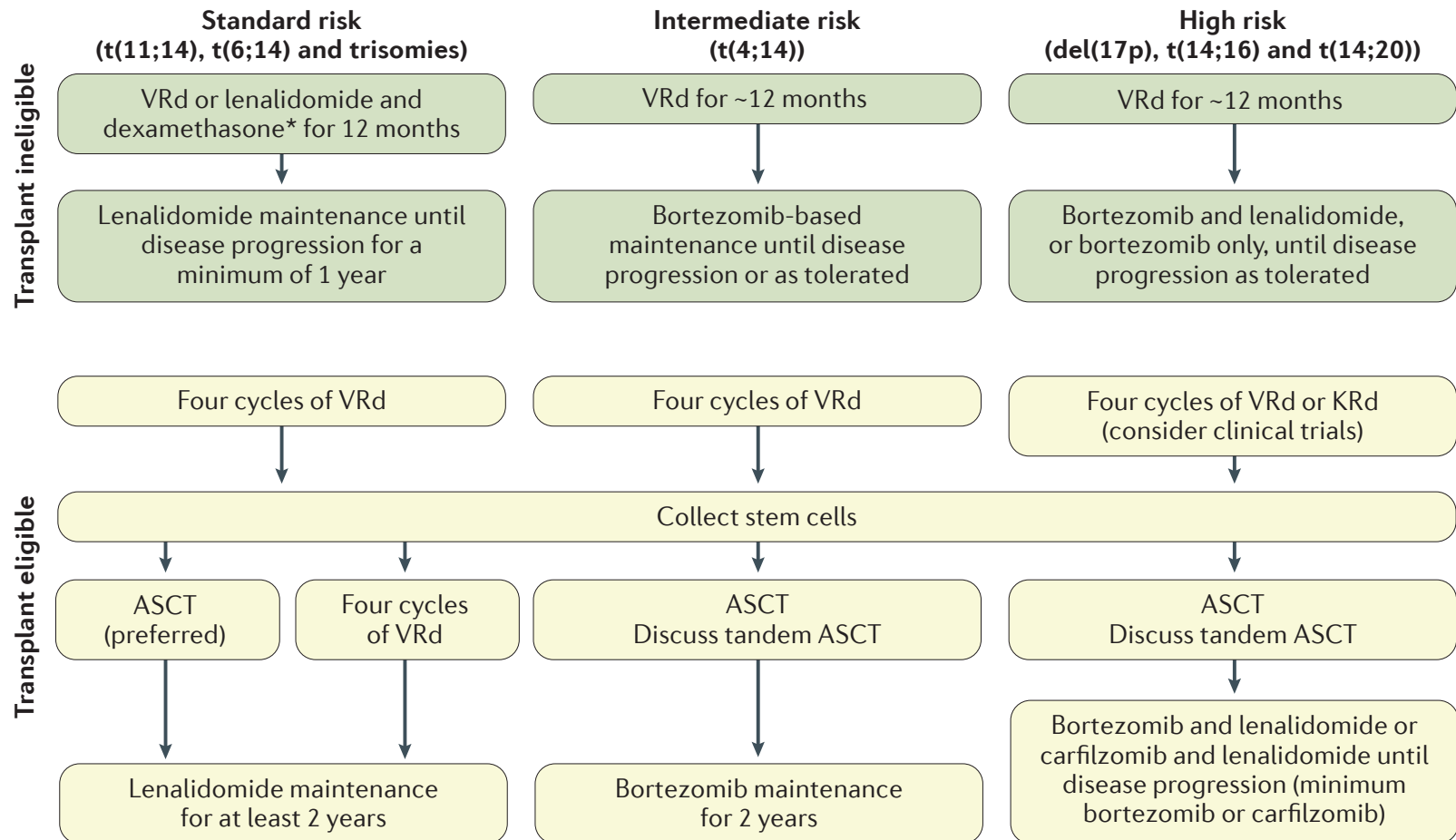
# Treatment overview



# International Myeloma Working Group Response Criteria

<b>Response</b>	<b>M-protein</b>	<b>Immunofixation</b>	<b>Urine light chains</b>	<b>Bone marrow plasma cells</b>	<b>Light chain ratio</b>
Stringent complete	Undetectable	Undetectable	Undetectable	Undetectable	Normal
Complete	Undetectable	Undetectable	Undetectable	< 5%	Any
Very good partial	90-100% ↓	Any	< 100 mg	Any	Any
Partial	50-89% ↓	Any	90-100% ↓	Any	Any
Minimal	25-49% ↓	Any	50-89% ↓	Any	Any
Progressive disease	25% ↑	Any	25% ↑	Any	Any

# Myeloma treatment algorithm



# VTD is superior to VCD as induction therapy

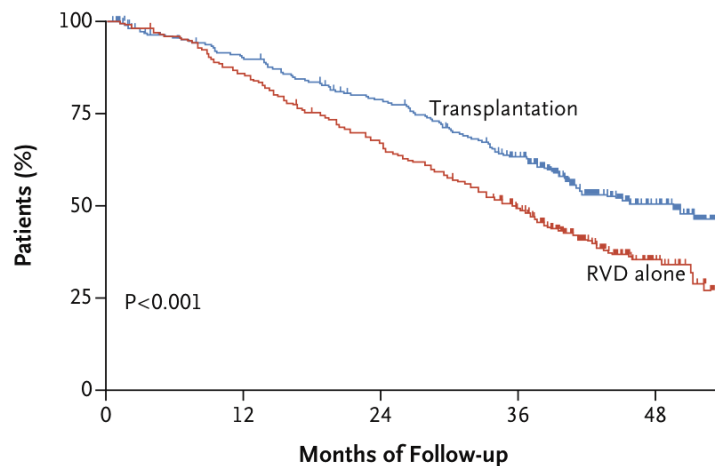
	VTD (n = 169)	VCD (n = 169)	P value
<b>Intent to treat</b>			
≥CR	13.0%	8.9%	.22
≥VGPR	66.3%	56.2%	.05
≥PR	92.3%	83.4%	.01
<b>Per protocol</b>			
	n = 157	n = 154	
≥CR	14.0%	9.1%	.17
≥VGPR	70.7%	60.4%	.05
≥PR	98.7%	90.3%	.001

Moreau, P. *et al. Blood* **127**, 2569–2574 (2016)



# Early autologous stem cell transplant is superior to RVD alone

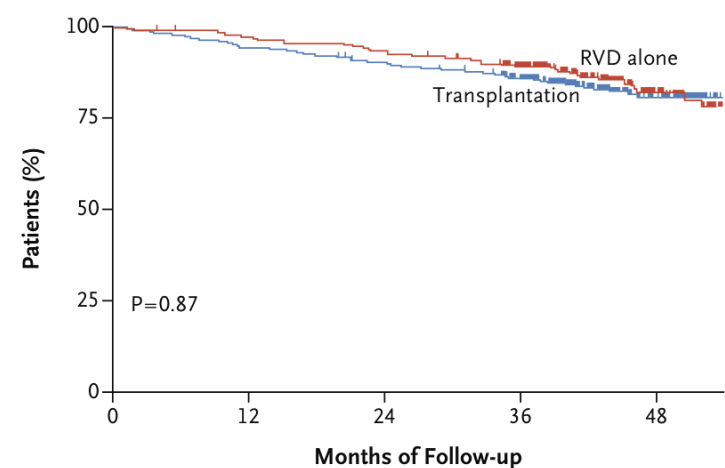
Progression-free Survival



No. at Risk

RVD alone	350	294	228	157	32
Transplantation	350	308	264	196	50

Overall Survival



No. at Risk

RVD alone	350	339	325	293	95
Transplantation	350	330	313	281	89

Attal, M. *et al.* *The New England journal of medicine* **376**, 1311–1320 (2017)

# Maintenance therapy improves PFS and OS

**Table 1** Lenalidomide-based Maintenance Strategies

Trial	N	Regimen	Outcomes
IFM 2005-02 <sup>7</sup>	614	ASCT → Rm vs. ASCT → placebo	Median PFS (Rm vs. placebo): 46 vs. 24 mo (HR, 0.52; $P < .001$ ) Median OS (Rm vs. placebo): NR vs. 90 mo (HR, 0.92; $P = .52$ )
CALGB 100104 <sup>8</sup>	460	ASCT → Rm vs. ASCT → placebo	Median TTP (Rm vs. placebo): 53 vs. 26 mo (HR, 0.54; $P < .001$ ) Median OS (Rm vs. placebo): NR vs. 76 mo (HR, 0.60; $P < .001$ )
RV-MM-PI-209 <sup>9</sup>	402	MPR → Rm vs. MEL200 → Rm vs. MPR vs. MEL200	Median PFS (Rm vs. no R): 41.9 vs. 21.6 mo (HR, 0.47; $P < .001$ ) 3-y OS (Rm vs. no R): 88% vs. 80% (HR, 0.64; $P = .14$ )
Gay et al <sup>10</sup>	389	CRD → Rm vs. MEL200 → Rm vs. CRD → Rm + P vs. MEL200 → Rm + P	Median PFS (Rm + P vs. Rm): 37.5 vs. 28.5 mo (HR, 0.84; $P = .34$ ) 3-y OS (Rm + P vs. Rm): 83% vs. 88% (HR, 1.51; $P = .21$ )
IFM/DFCI <sup>13</sup>	700	RVD → ASCT → Rm vs. RVD → Rm → ASCT	Median PFS (ASCT → Rm vs. Rm): 43 vs. 34 mo (HR, 1.5; $P < .001$ ) 4-y PFS (ASCT → Rm vs. Rm): 47% vs. 35% (HR 1.5, $P < .001$ ) 4-y OS (ASCT → Rm vs. Rm): 83% vs. 81% (HR 1.2, $P = NS$ )
FIRST <sup>15</sup>	1623	Rd vs. Rd18 vs. MPT	Median PFS (Rd vs. Rd18 vs. MPT): 25.5 vs. 20.7 vs. 21.2 mos (HR, Rd vs. MPT, 0.72; $P = .00006$ ; Rd vs. Rd18, 0.70; $P = .00001$ ; Rd18 vs. MPT, 1.03; $P = .7$ ) 4-y OS (Rd vs. Rd18 vs. MPT): 59.4% vs. 55.7% vs. 51.4% (HR, Rd vs. MPT: 0.78; $P = .017$ ; Rd vs. Rd18: 0.90; $P = .31$ ; Rd18 vs. MPT: 0.88; $P = .18$ )
MM-015 <sup>16</sup>	460	MPR → Rm vs. MPR vs. MP	Median PFS (MPR → Rm vs. MPR vs. MP): 31 vs. 14 vs. 13 mo (HR, MPR → Rm vs. MPR, 0.49; $P < .001$ ; MPR → Rm vs. MP, 0.40; $P < .001$ ) Median OS (MPR → Rm vs. MPR vs. MP): 56 vs. 52 vs. 54 mo (HR, MPR → Rm vs. MPR, 0.88; $P < .43$ ; MPR → Rm vs. MP, 0.95; $P < .74$ )

Abbreviations: ASCT = autologous stem cell transplant; Bm = bortezomib maintenance; CR = complete response; CRD = cyclophosphamide, dexamethasone, and lenalidomide; HR = hazards ratio; nCR = near complete response; OS = overall survival; P = prednisone; PAD = bortezomib, Adriamycin, and dexamethasone; PFS = progression-free survival; Rm = lenalidomide maintenance; RVDm = RVD maintenance; Tm = thalidomide maintenance; TTP = time to progression; VAD = vincristine, adriamycin, and dexamethasone.