Plasma Cell Neoplasms

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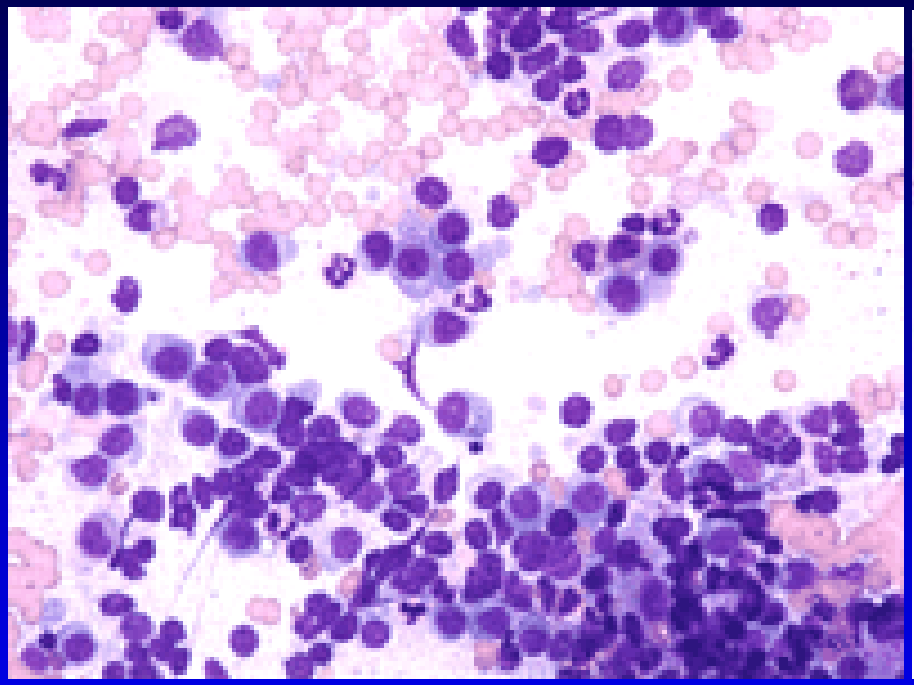
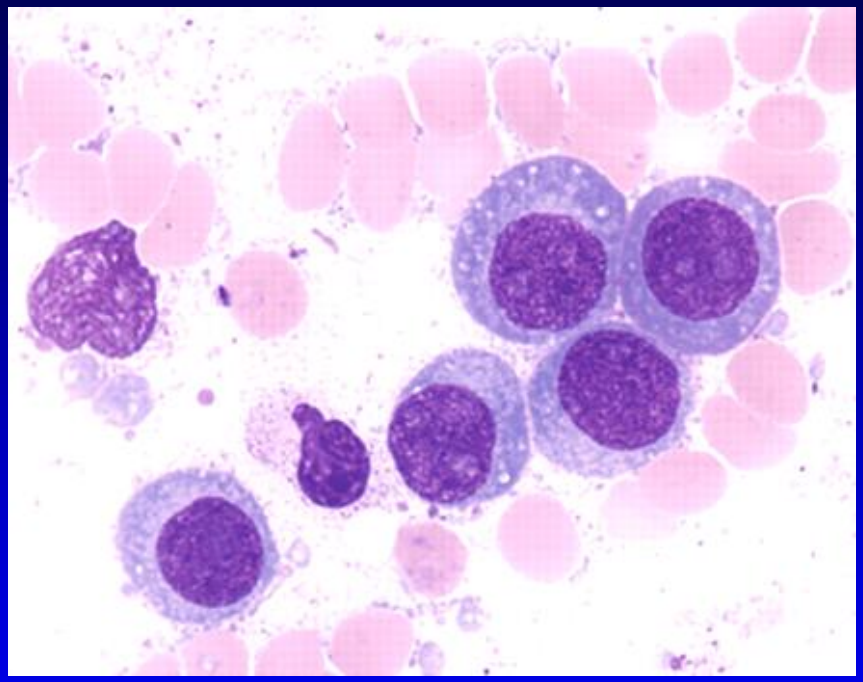
MULTIPLE MYELOMA
A plasma cell neoplasm





- Malignant plasma cell proliferation in the BM
- Monoclonal Immunoglobulin (or kappa or lambda light chain) in serum ± urine

Criteria for Diagnosis of Myeloma

Kyle RA. *N Engl J Med* 2002; 346: 564

MGUS
<3 g M spike
<10% PC

Smouldering MM
≥3 g M spike
OR ≥10% PC

Active MM
M spike +
≥10% PC

AND

No end organ damage
MGUS ➔ MM 1%/yr
Smouldering MM ➔ MM 10%/yr

Treatment
Watchful waiting, serial monitoring M protein

End organ damage (CRAB)
Hyper**C**alcemia
Renal failure
Anemia
Bone lesions
Recurrent bacterial infection, hyperviscosity, amyloidosis

Risk Stratification Model for MGUS

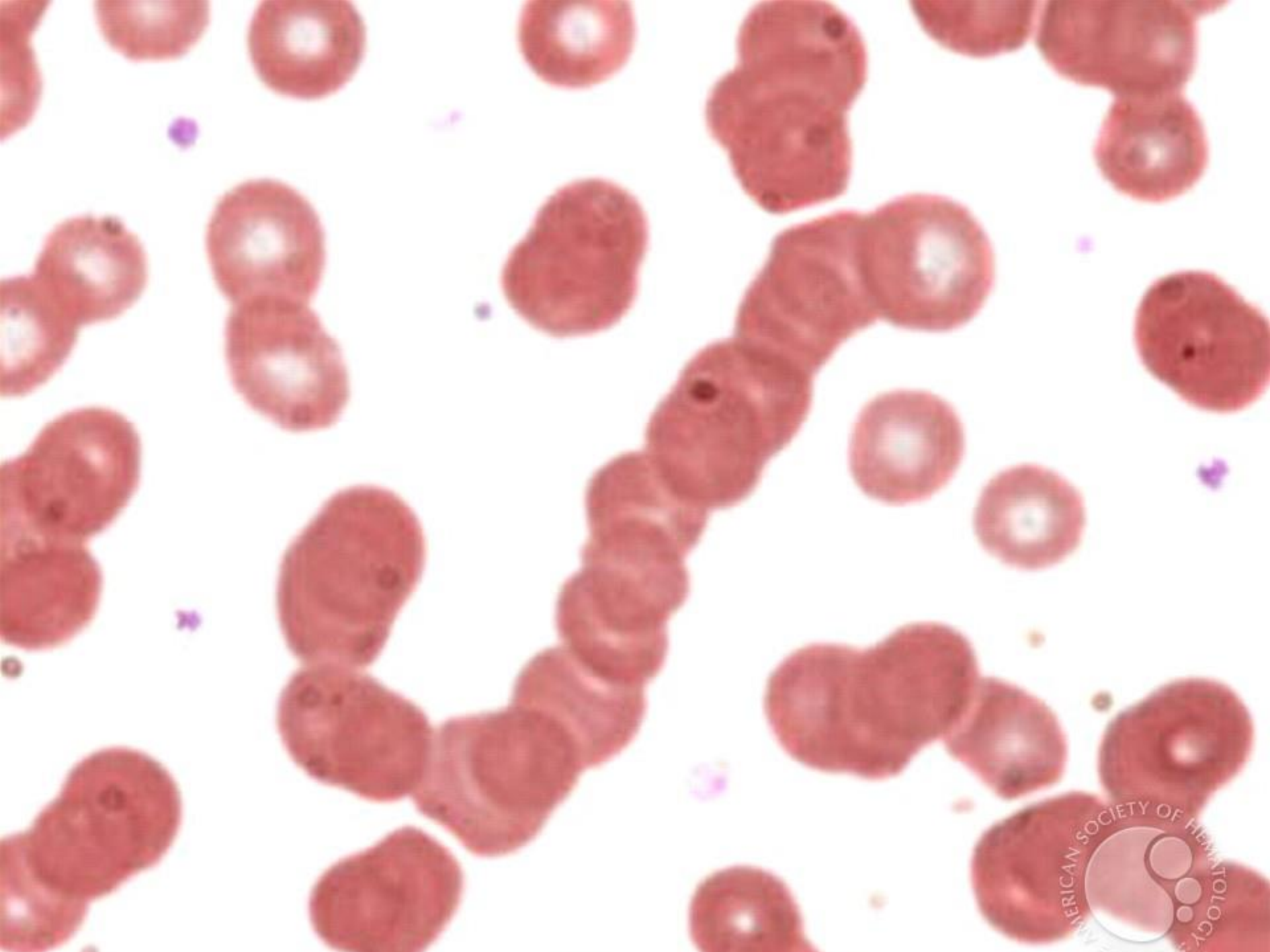
Risk Group	No. of patients	Relative risk	Absolute risk of progression (ARP) at 20 years	ARP at 20 years with death as a competing risk
Risk stratification model				
Low-risk (serum M spike <1.5g/dL, IgG subtype, normal FLC ratio 0.26-1.65)	449	1	5%	2%
Low-Intermediate-risk (Any 1 factor abnormal)	420	5.4	21%	10%
High-Intermediate-risk (Any 2 factors abnormal)	226	10.1	37%	18%
High-risk (All 3 factors abnormal)	53	20.8	58%	27%

Rajkumar SV et al. Blood 2005;106:812-817

Multiple Myeloma

Presenting Features **Kyle RA, Mayo Clin Proc 1975:50:29**

98%	>40 years old
61%	Males
68%	**Bone pain (back, ribs)**
62%	**Anemia (normochromic normocytic, Rouleaux)**
88%	Proteinuria
49%	Bence Jones Proteinuria
79%	Lytic bone lesions, pathologic fractures
	Bone X-RAY survey, MRI (most sensitive) or CT
55%	Renal Failure (2^{nd} to light chain deposition $\pm$ high Ca)
30%	Hypercalcemia (confusion, disorientation, constipation, polyuria, polydipsia, weakness, suppressed PTH)
21%	Hepatomegaly
Others	Recurrent bacterial infections, hypogamma, hyperviscosity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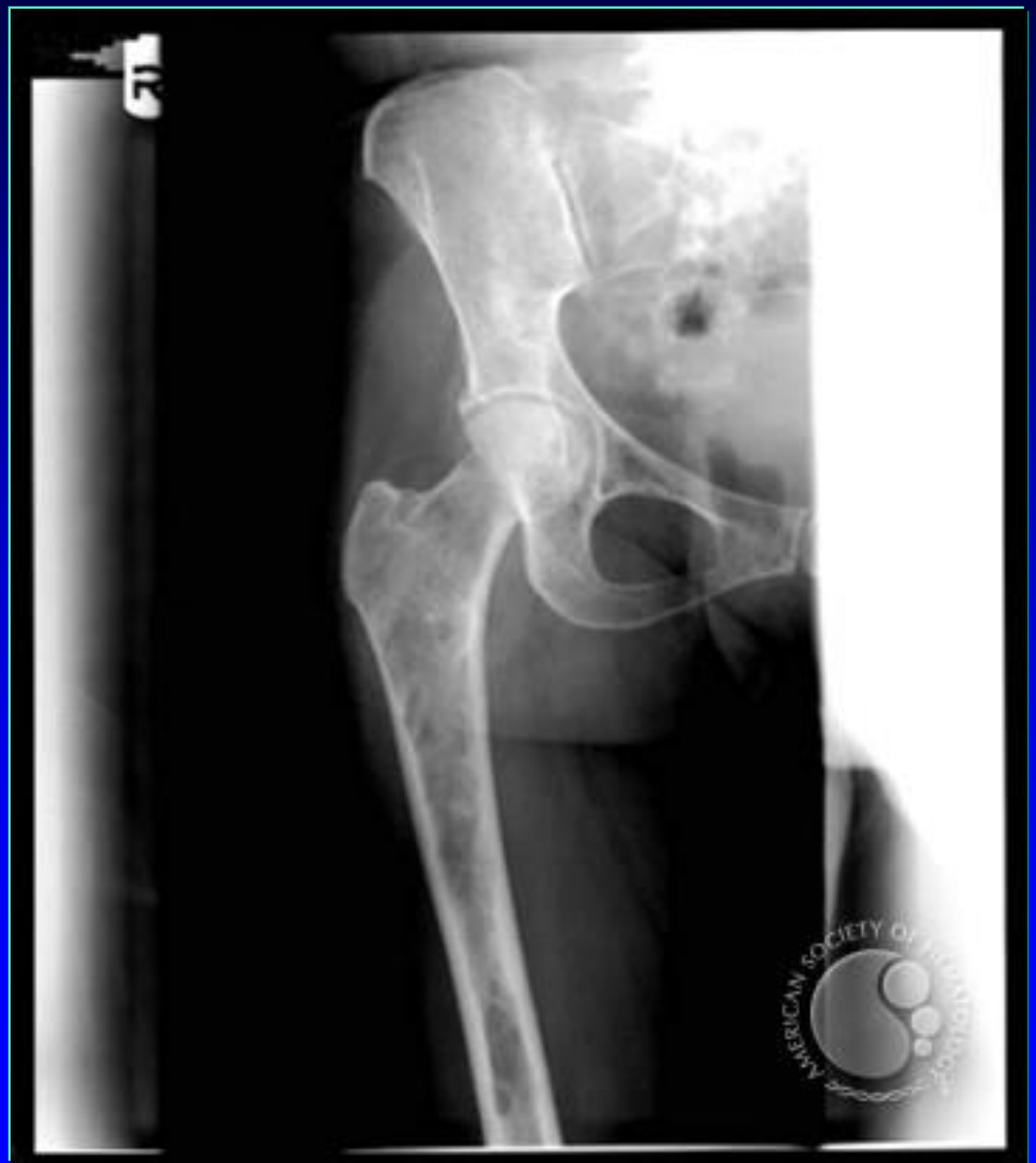
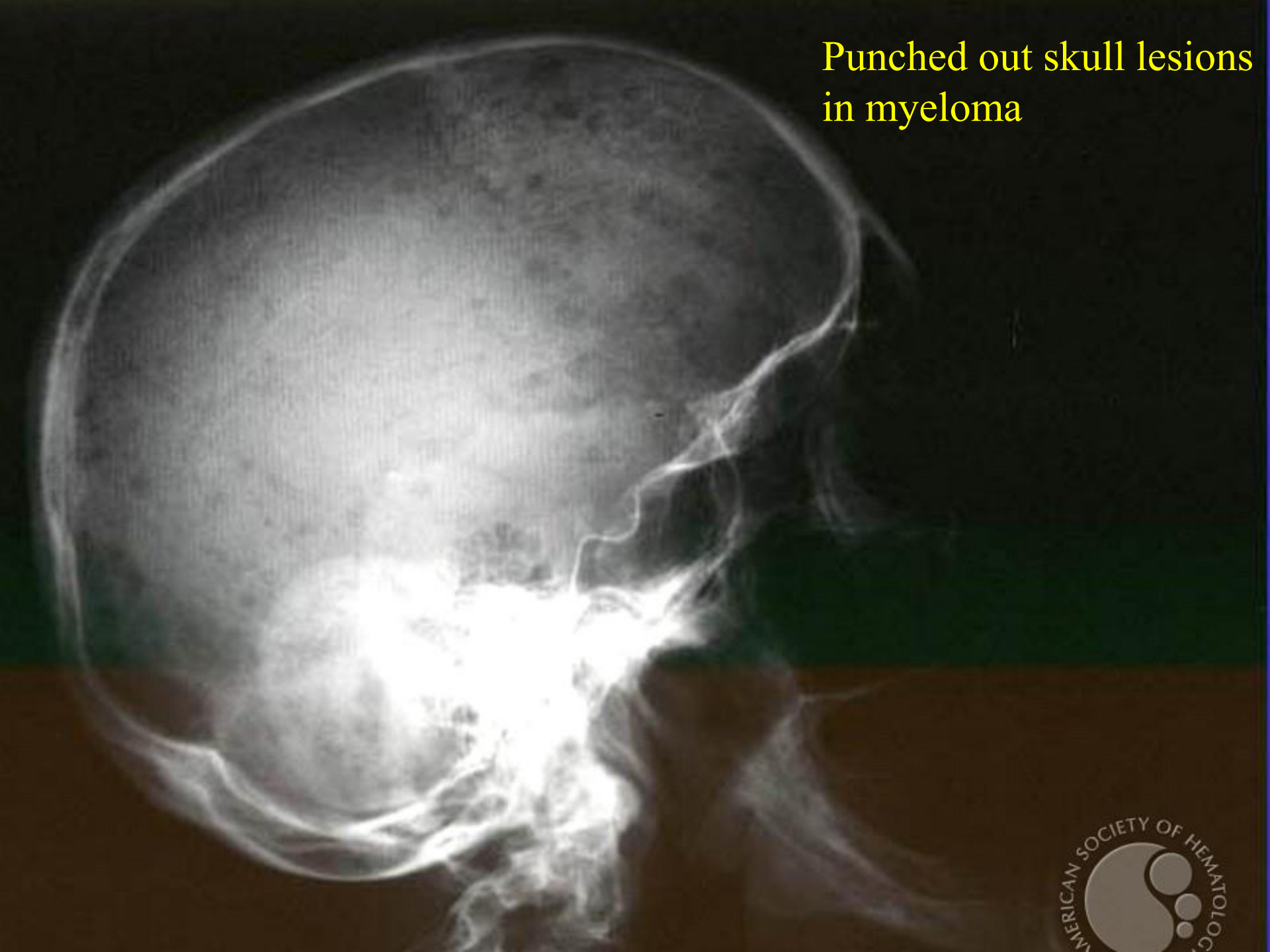
Lytic bone lesions in Multiple Myeloma




Punched out skull lesions
in myeloma

Myeloma Work-up

- **Blood work**
  - CBC, diff
  - CRP quantitative
  - CMP, LDH, Ca, Uric acid, **albumin**
  - SPEP and immunofix
  - Serum IgG, A, M ± D and E
  - Serum free-kappa and lambda
  - **Beta-2 microglobulin**
  - Erthropoietin level (if anemic)
- **Urine**
  - 24-hour UPEP, immunofix, free LC
- **BM asp/bx**
  - Wright-Giemsa + k/l immunostain
  - Flow (CD34, 38, 138, 10, 19, 20)
  - Cytogenetics and FISH
    - Hyperdiploid, t(11:14)
    - 13q-, 17p-, t(4:14)
  - Oncogenomics

Check to see if

1. Bone disease, hyper Ca
2. Renal failure
3. Dehydration
4. Anemia
5. Hyperviscosity
6. Infection
7. Amyloid signs and sx
   - Heart failure
   - Neuropathy
   - Macroglossia
   - Nephrotic syndrome
   - Racon eyes

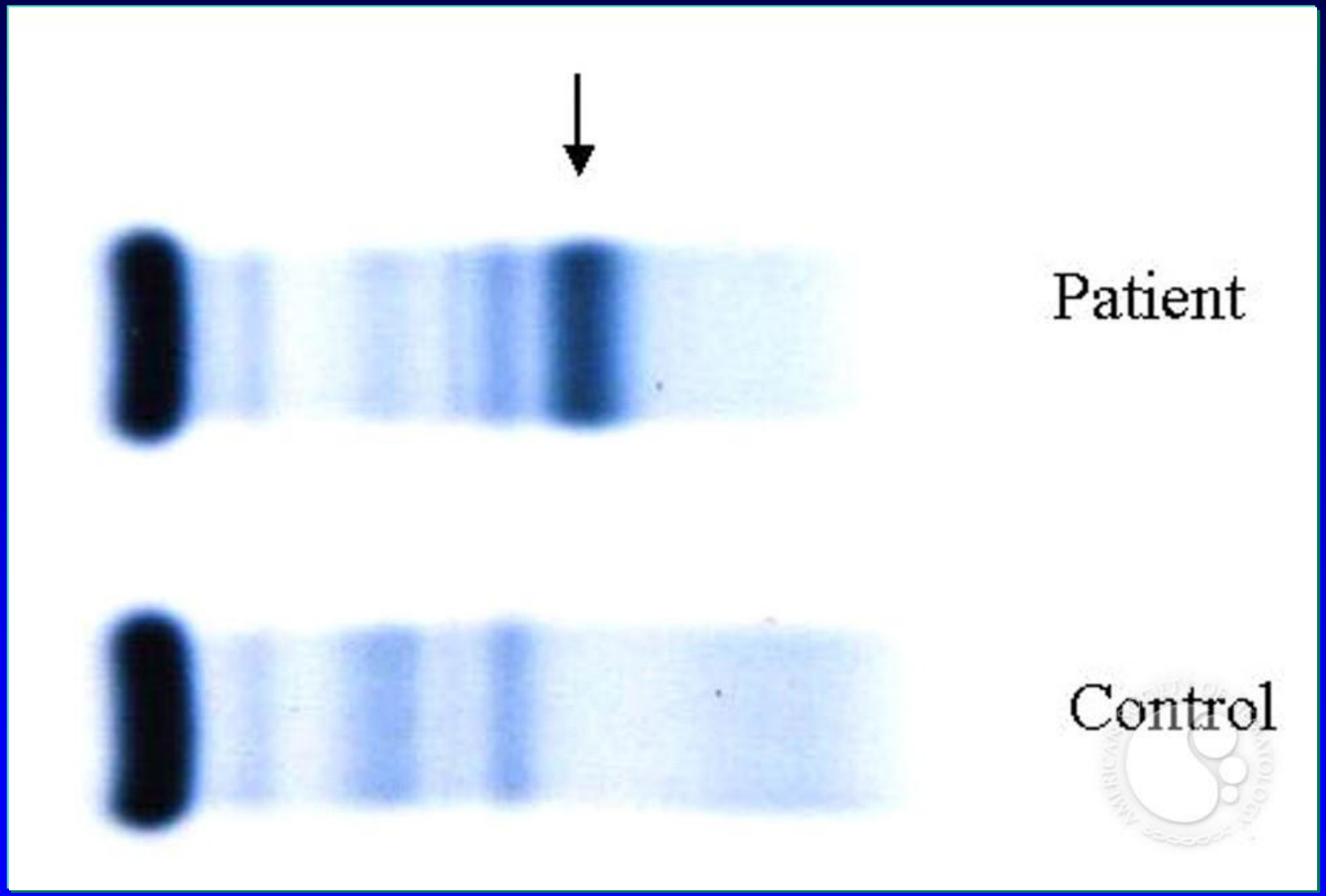
- **Imaging**

  Skeletal survey

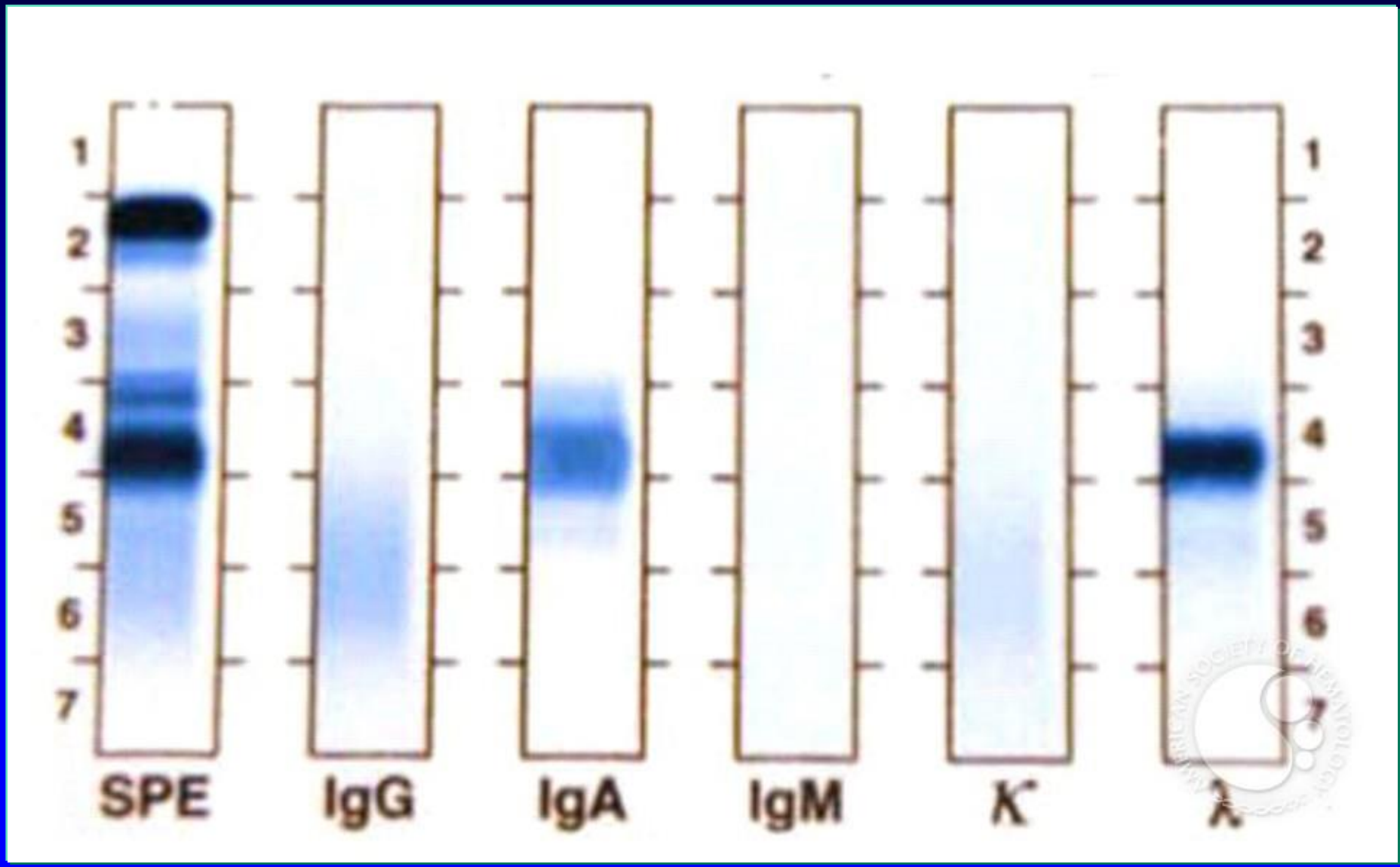
  PET

  MRI

SPEP - Serum Protein Immunoelectropheresis

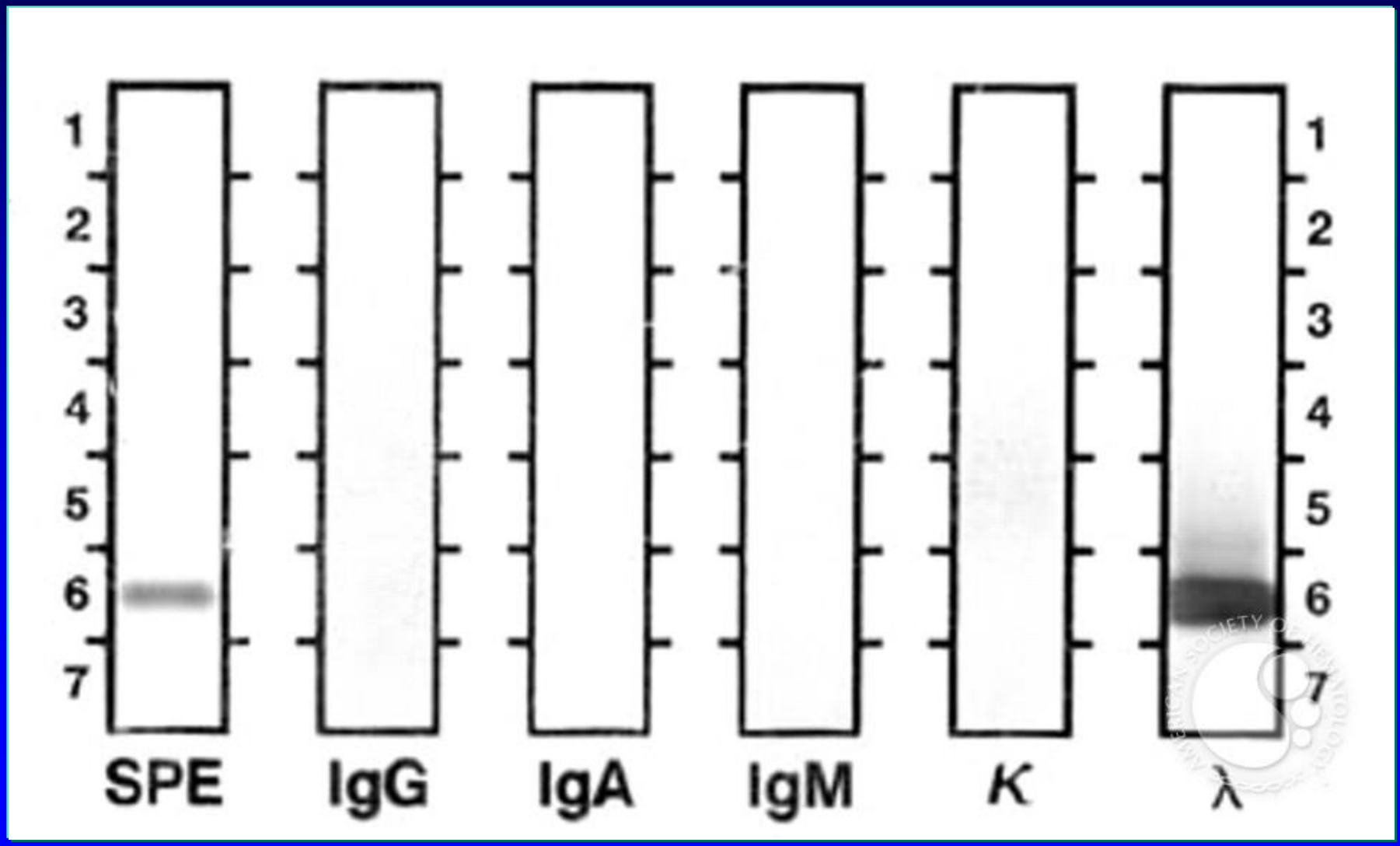


Serum Protein Immunofixation

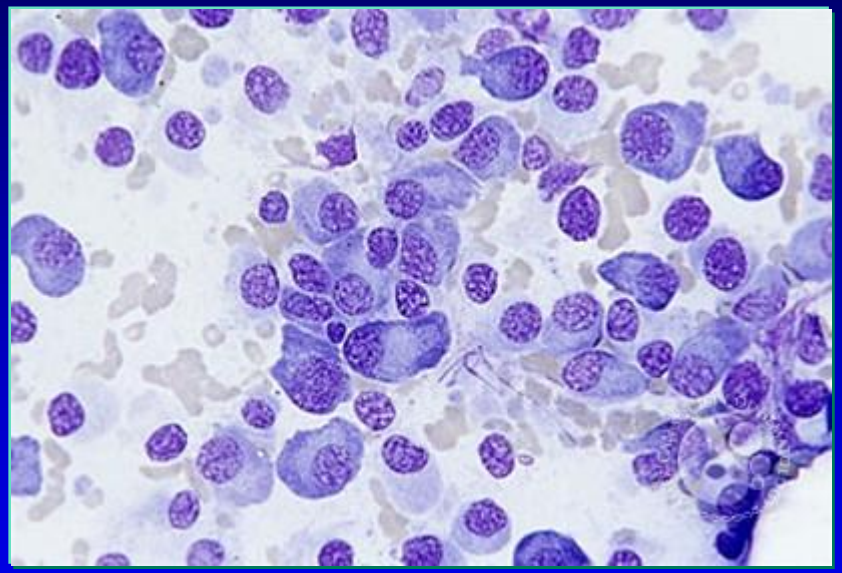


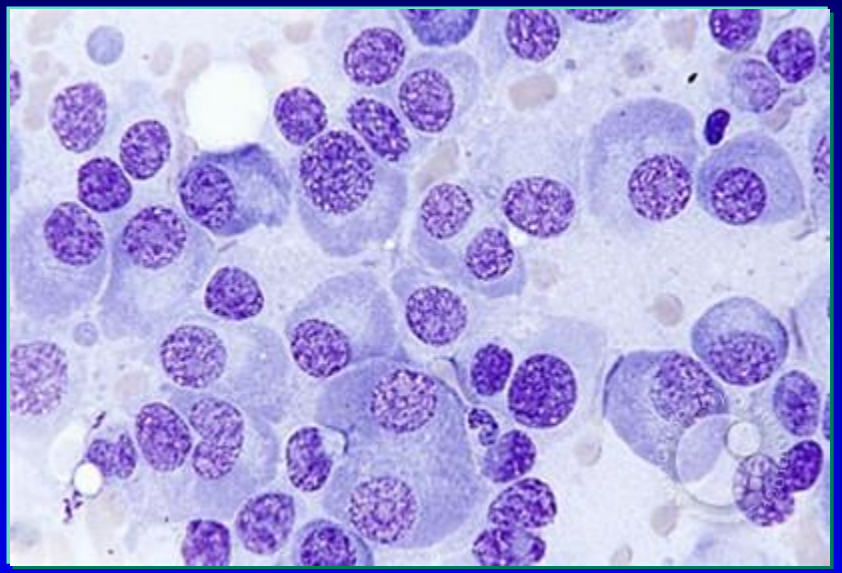
Serum Protein Immunofixation

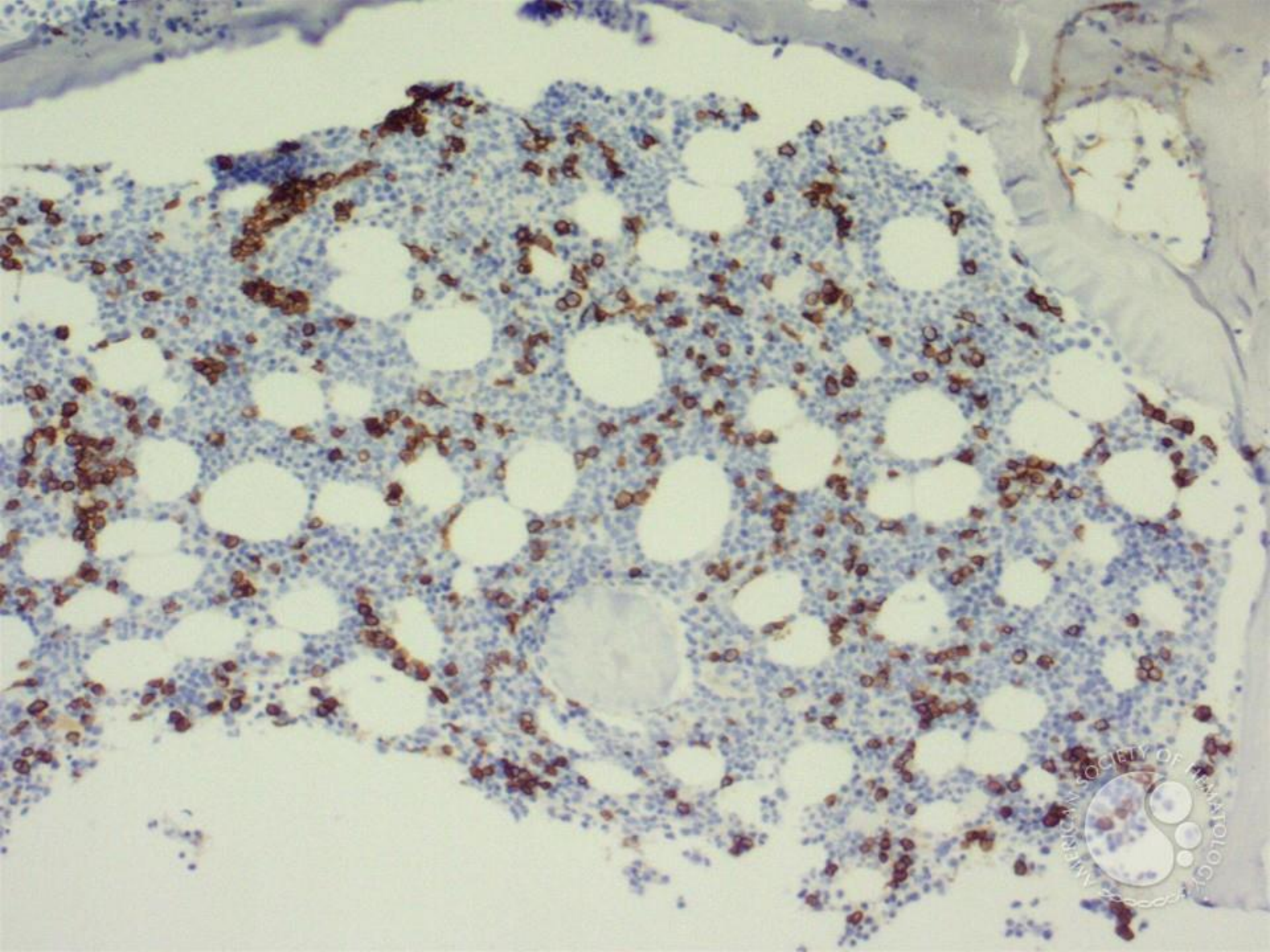
(Light-chain myeloma)



Bone marrow aspirate in Multiple Myeloma

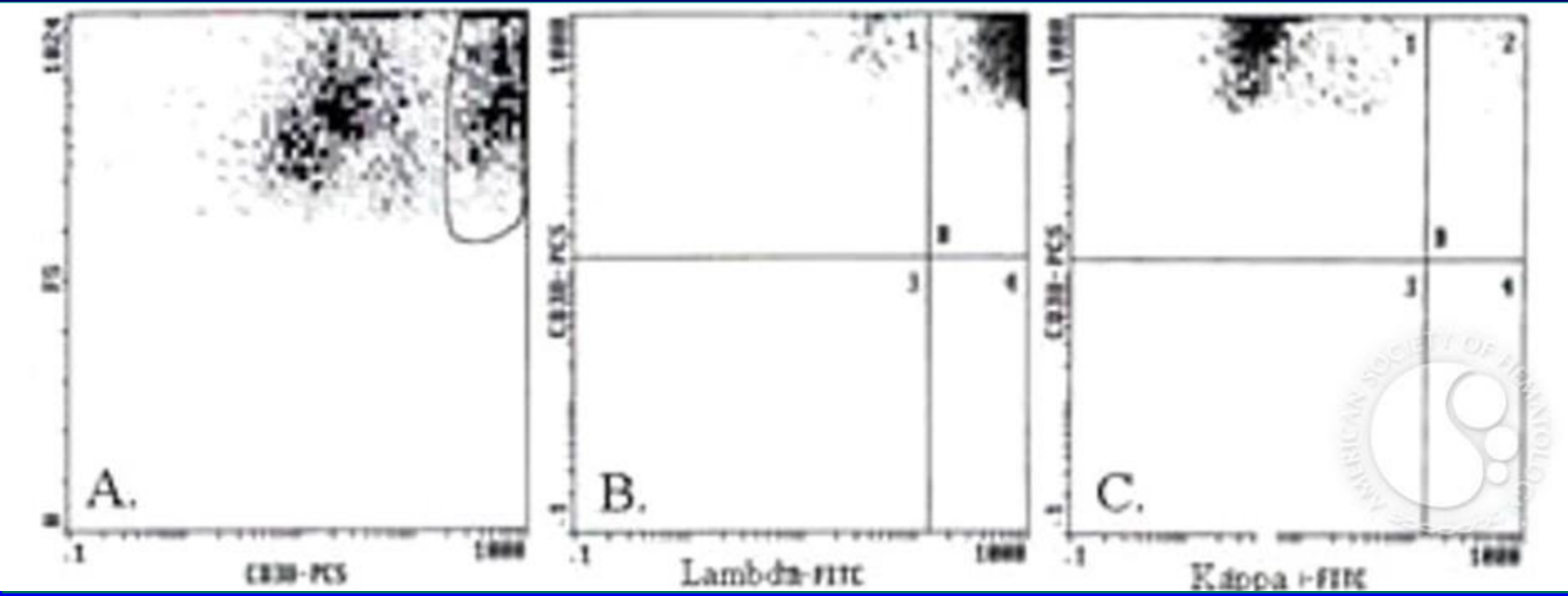






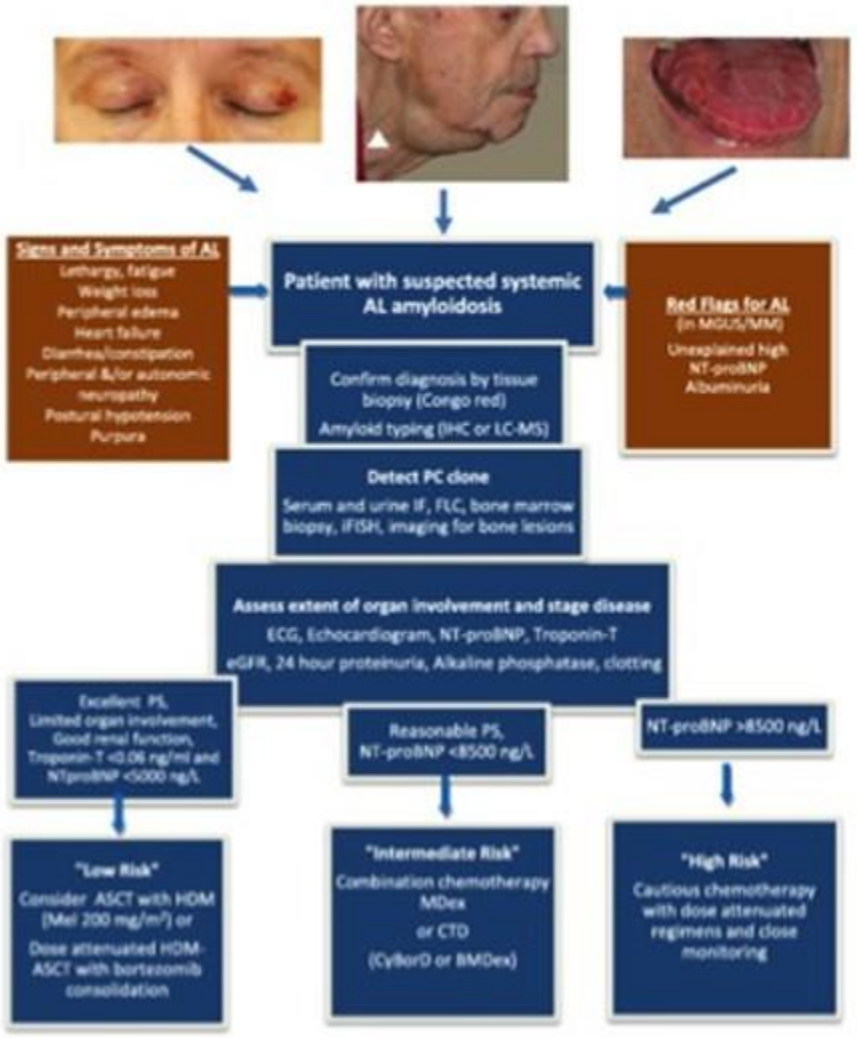
Bone marrow flow cytometry in Multiple Myeloma

CD38+, lambda+, kappa- population

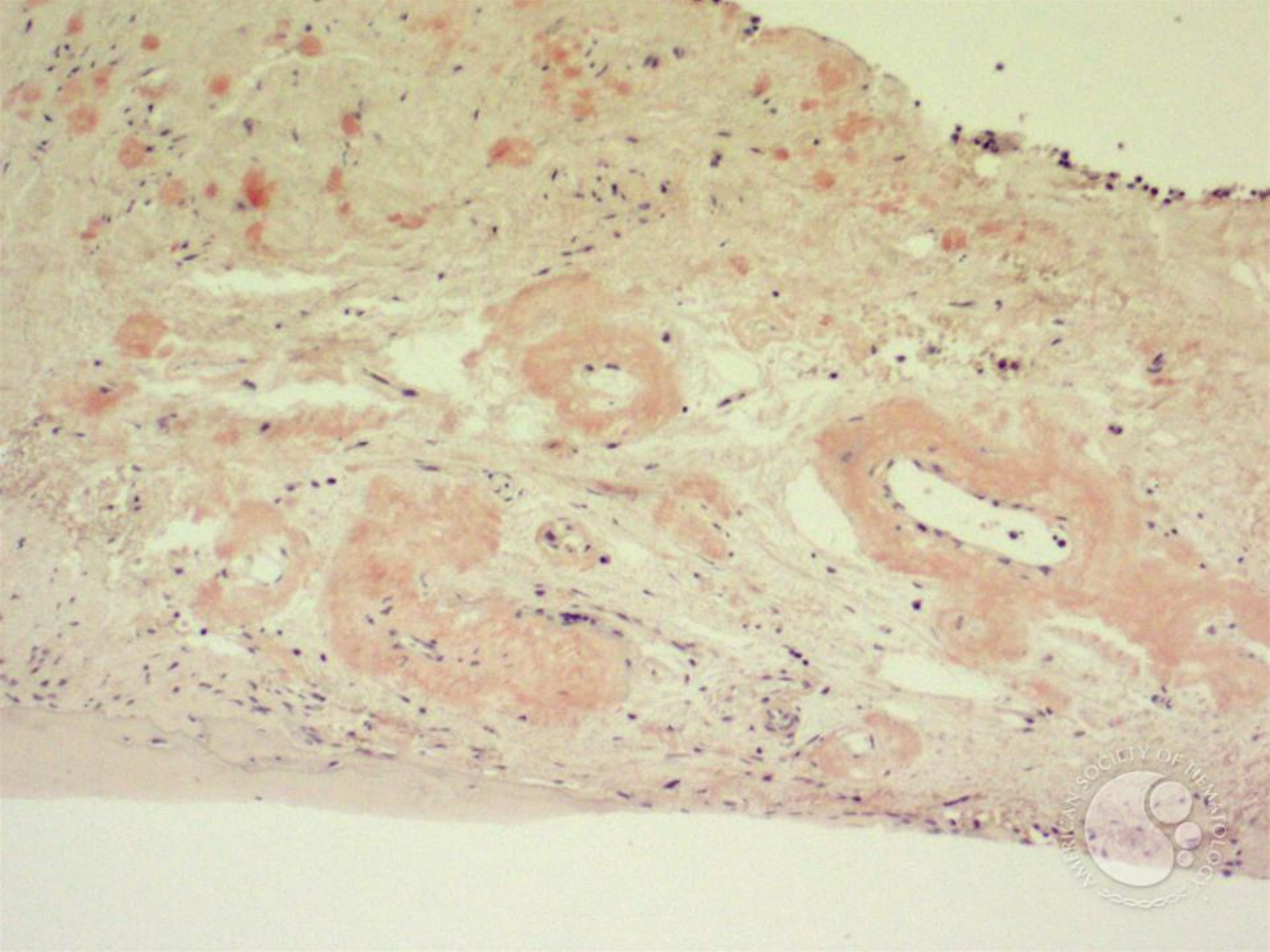


blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Pathway for a patient with suspected AL amyloidosis.



Merlini G et al. Blood 2013;121:5124-5130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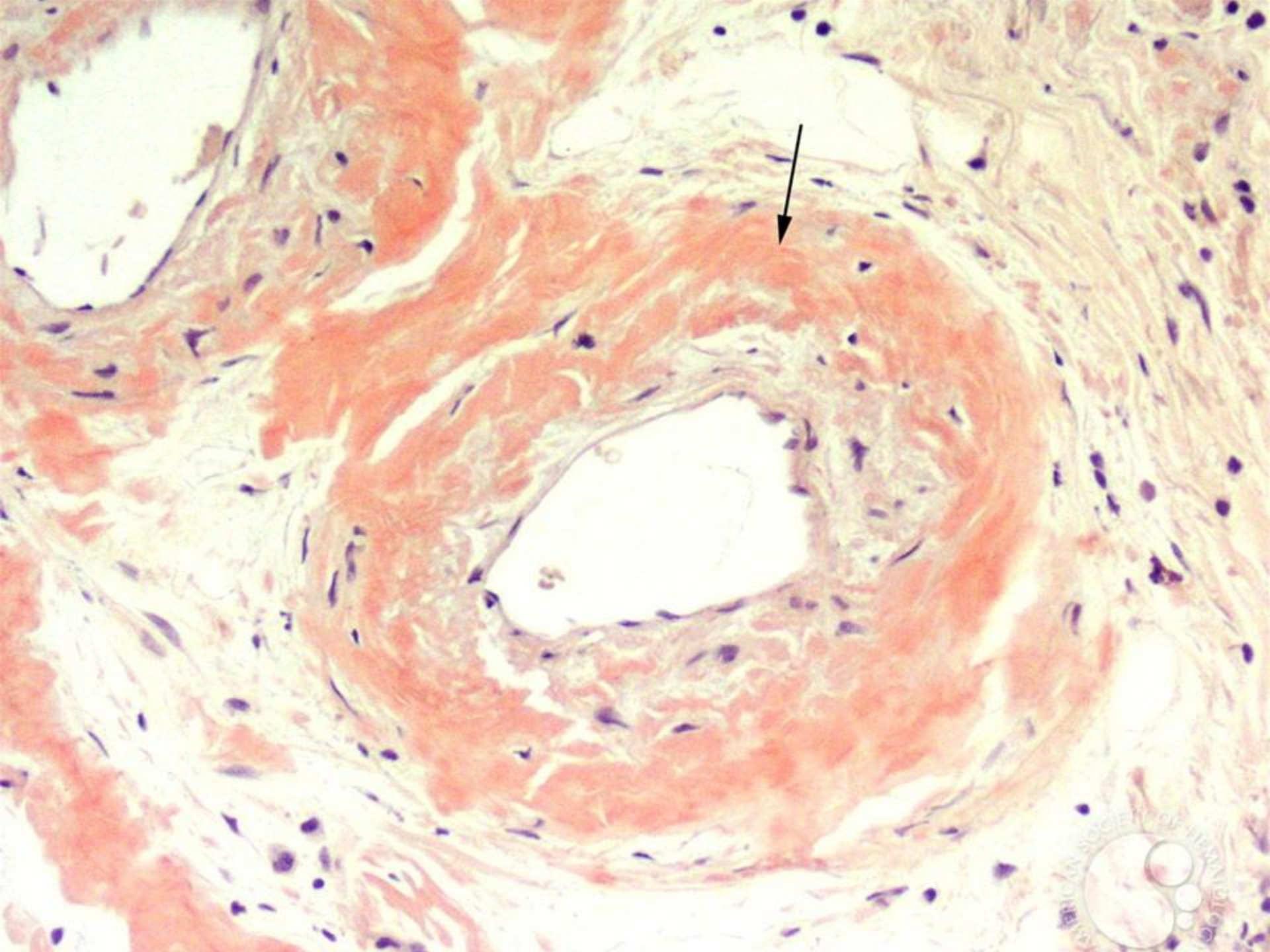
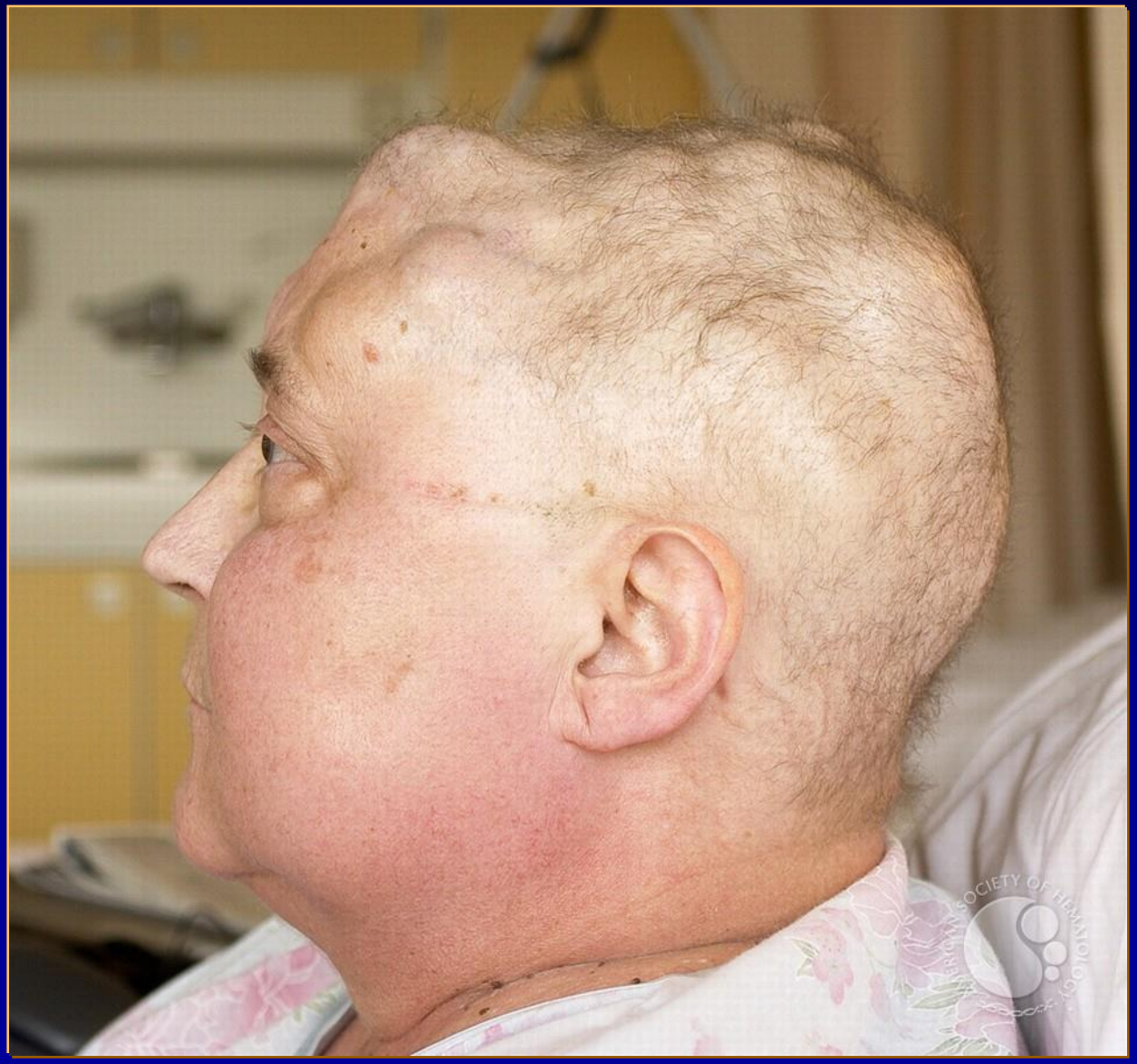


Plasmacytoma



International Staging System (ISS) for Myeloma

Stage	Criteria	Median Survival (mo)
I	β2m < 3.5 mg/L albumin ≥ 3.5 g/dL	62
II*	Not stage I or III	44
III	β2m > 5.5 mg/L	29

*β2m < 3.5 mg/L and albumin < 3.5 g/dL or
β2m 3.5 - < 5.5 mg/dL, any albumin

Others prognostic indicators: LDH, Cytogenetics/FISH, DNA microarray

Greipp et al. J Clin Oncol 2005; 23: 3412-20

Chromosomes and Prognosis in Multiple Myeloma

Nonhyperdiploid worse prognosis than hyperdiploid

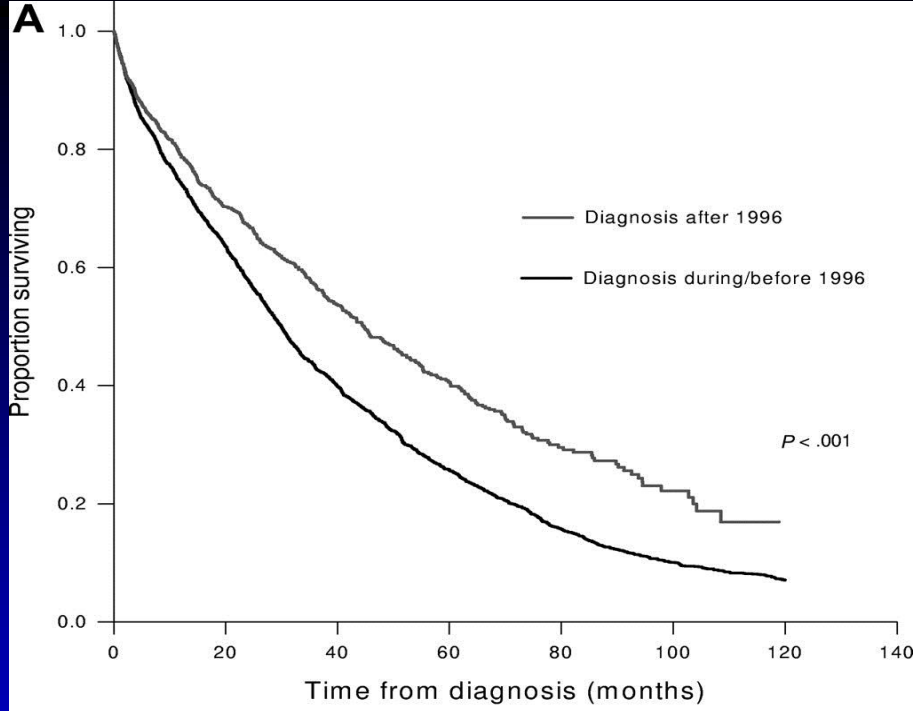
<u>For conventional therapy</u>
t(11;14), hyperdiplody → standard risk
t(4;14), del(17p), del(13q14) → high risk

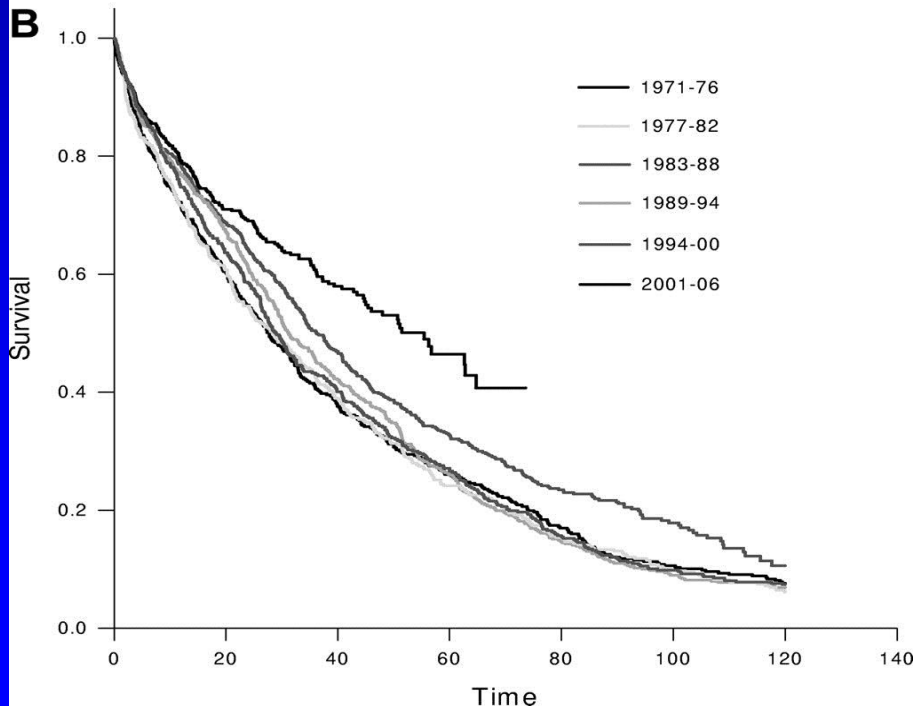
Novel treatment approaches can overcome high risk cytogenetic abnormalities, i.e. bortezomib

Life expectancy is doubled in MM
Now, average 5 years after diagnosis

Kumar S K et al. Blood 2008;111:2516-20

Longer survival is directly related
to depth of response to therapy





International Myeloma Working Group Uniform Response Criteria: CR and Response Categories

Response subcategory	*Response criteria*[a]
sCR	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and $\leqslant$5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level $<$100 mg per 24 h
PR	$\geqslant$50% reduction of serum M-protein and reduction in 24-h urinary M-protein by $\geqslant$90% or to $<$200 mg per 24 h If the serum and urine M-protein are unmeasurable,[d] a $\geqslant$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, $\geqslant$50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was $\geqslant$30% In addition to the above listed criteria, if present at baseline, a $\geqslant$50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

[a]All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

[b]Confirmation with repeat bone marrow biopsy not needed.

[c]Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of $>$4:1 or $<$1:2.

[d]Refer to Table 4 for definitions of measurable disease.

Durie BGM et al. Leukemia 2006

Improvement in survival of patients with myeloma is due to

- Initial (Induction) therapy with **novel agents** (3-4 months)
- Stem Cell Transplantation → Highest CR rate
- Post-transplant Maintenance → Some additional benefit
- Supportive Care (Critical)
- Treatment of Relapsed Disease (Possible but expensive)

Thalidomide

- Marketed as a sedative in the 1950s
- In 1961, it was discovered to be teratogenic, affecting 10,000 infants and was taken off the market
- In 1997, Dr. Barlogie found that it was antiangiogenic in myeloma
- In 84 patients treated, response rate was 32% (Singhal S et al. NEJM 1999)

Lenalidomide

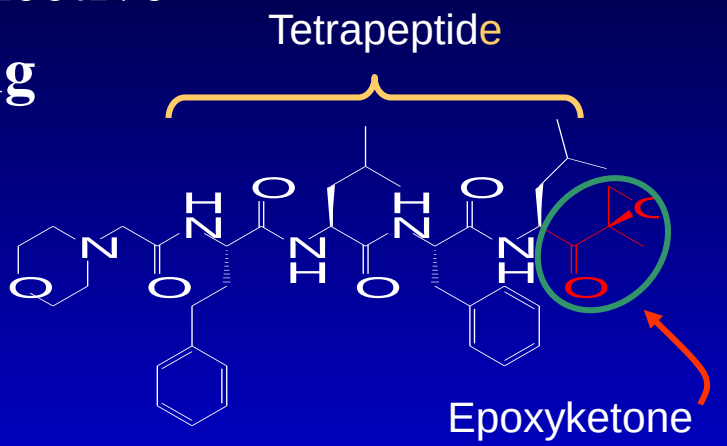
- An analog of thalidomide , immunomodulator
- Overall response rate was 71% in patients with relapsed or refractory myeloma
- In an upfront trial, lenalidomide + dexamethasone ➔ RR: 31/34 (91%) (Rajkumar SV et al. Blood 2005)
- Approved by the FDA in 2006
- Preferred in the setting of peripheral neuropathy

Bortezomib

- Inhibition of proteasome causes apoptosis, predominantly in the malignant and proliferating cells
- Robert Orlowski showed striking anti-myeloma (9/9 patients) activity (Orlowski RZ et al. JCO 2002)
- Approved by the FDA for myeloma in 2003
- Preferred in the setting of renal impairment, t(4;14), or advanced disease

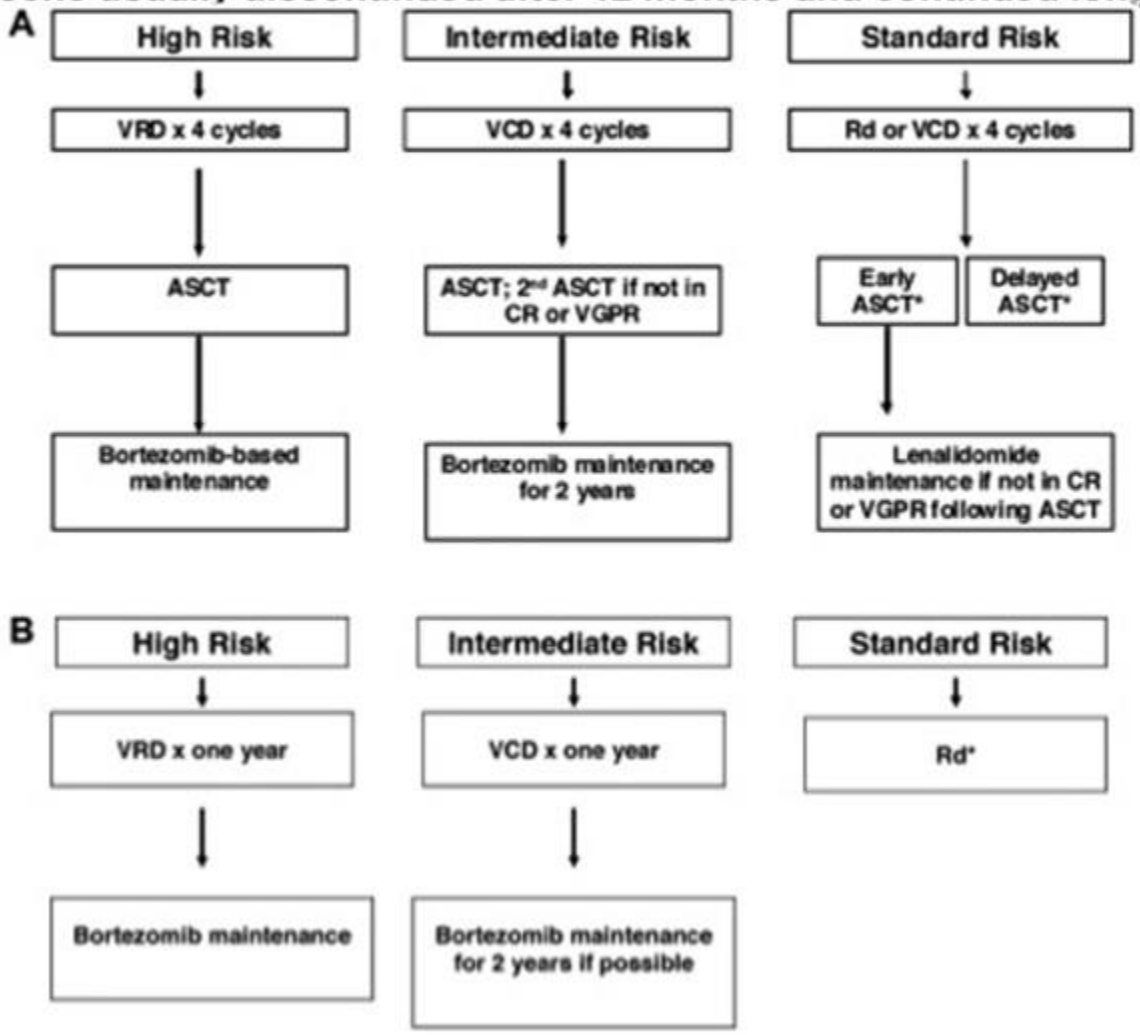
Carfilzomib: A Novel Proteasome (Chymotryptic) Inhibitor

- Novel chemical class with highly selective and irreversible proteasome binding
- Improved antitumor activity with consecutive day dosing
- No neurotoxicity in animals
- Durable responses in relapsed/refractory MM w/o neuropathy
- Carfilzomib lenalidomide Dex versus lenalidomide Dex phase III trial for new drug approval



[1]Demo et al. (2007), Cancer Research, 67:6383 [2]Kirk et al, (2008) Blood, 112: 2765 Siegal et al ASH 2010

Approach to the treatment of newly diagnosed myeloma in patients eligible for transplantation (A) and not eligible for transplantation (B). *For patients who choose delayed ASCT, dexamethasone usually discontinued after 12 months and continued long-term len...



Rajkumar S V Hematology 2012;2012:354-361

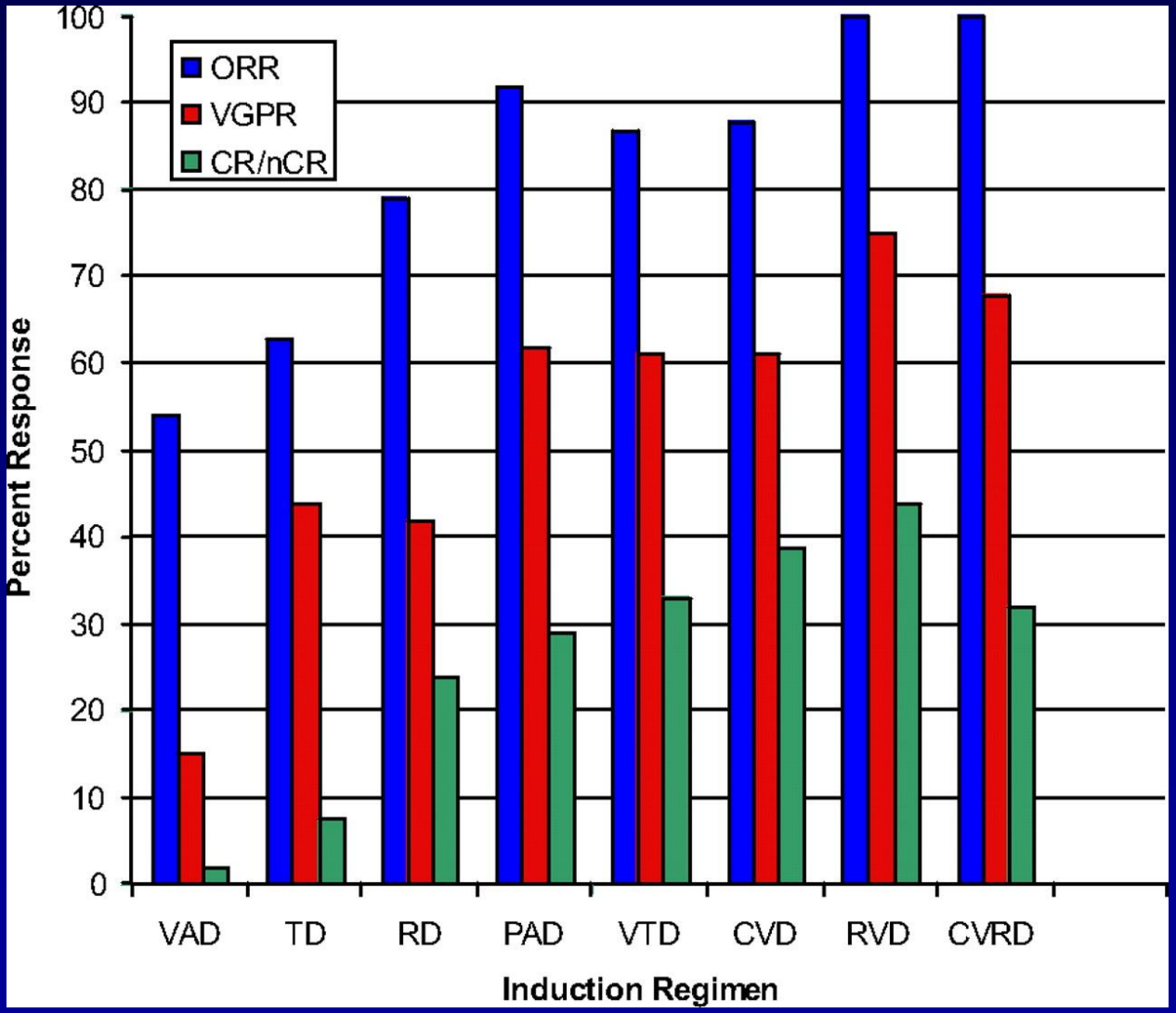
Response to First ASCT

Evaluable Patients

Harousseau et al, ASH 2008

	VAD (A1+A2) N=213	Vel-Dex (B1+B2) N=212	P value
CR	9%	17%	0.016
CR + nCR	19%	37%	<0.0001
≥ VGPR	38%	57%	0.0003
≥ PR	79%	84%	NS
MR/SD/PD	4%	3%	
No ASCT	17%	13%	

Upfront Induction Treatments of MM



Stewart AK, Richardson PG, San Miguel JF *Blood* 2009

Summary of Results of Randomized Trials Comparing Single Autotransplant with Conventional Therapy

		IFM90[1]	MRC7[2]	PETHEMA[3]	USIG[4]	IMMSG[5]	
CR %	CC 10%	5	9	11	15	7	4/5 studies - improvement in CR with ASCT
	ASCT 30%	21	44	30	17	26	
Improvement in EFS with ASCT (9 months)		9	12	8	4	12	•4/5 studies - improvement in EFS with ASCT
Improvement in OS with ASCT (12 months)		>23	12	5	5	15	•3/5 studies - improvement in OS with ASCT

References:

1 – Attal et al; 2 – Child et al; 3- Blade et al; 4- Barlogie et al; 5- Italian Study Group, Turin 2004

NOTE: colored values indicate statistical significance

Double Autotransplantation Improves Survival in MM

IMF 94 399 pts

	autotransplant (m 140 mg/m^2 8Gy)	vs	autotransplant (m 140 mg/m^2) autotransplant (m 140 mg/m^2 8Gy)	
CR/VGPR	42%		50%	*p*=0.10
7 yr prob EFS	10%		20%	*p*=0.03
7 yr prob OS	21%		42%	*p*=0.01
7 yr prob OS (no VGPR)	11%		43%	*p*<0.001

Low β2m, young age, low LDH, and treatment are associated with longer survival

Attal et al N Engl J Med 2003; 349: 2495

Pamidronate With or Without Thalidomide as Post-transplantation Maintenance Therapy

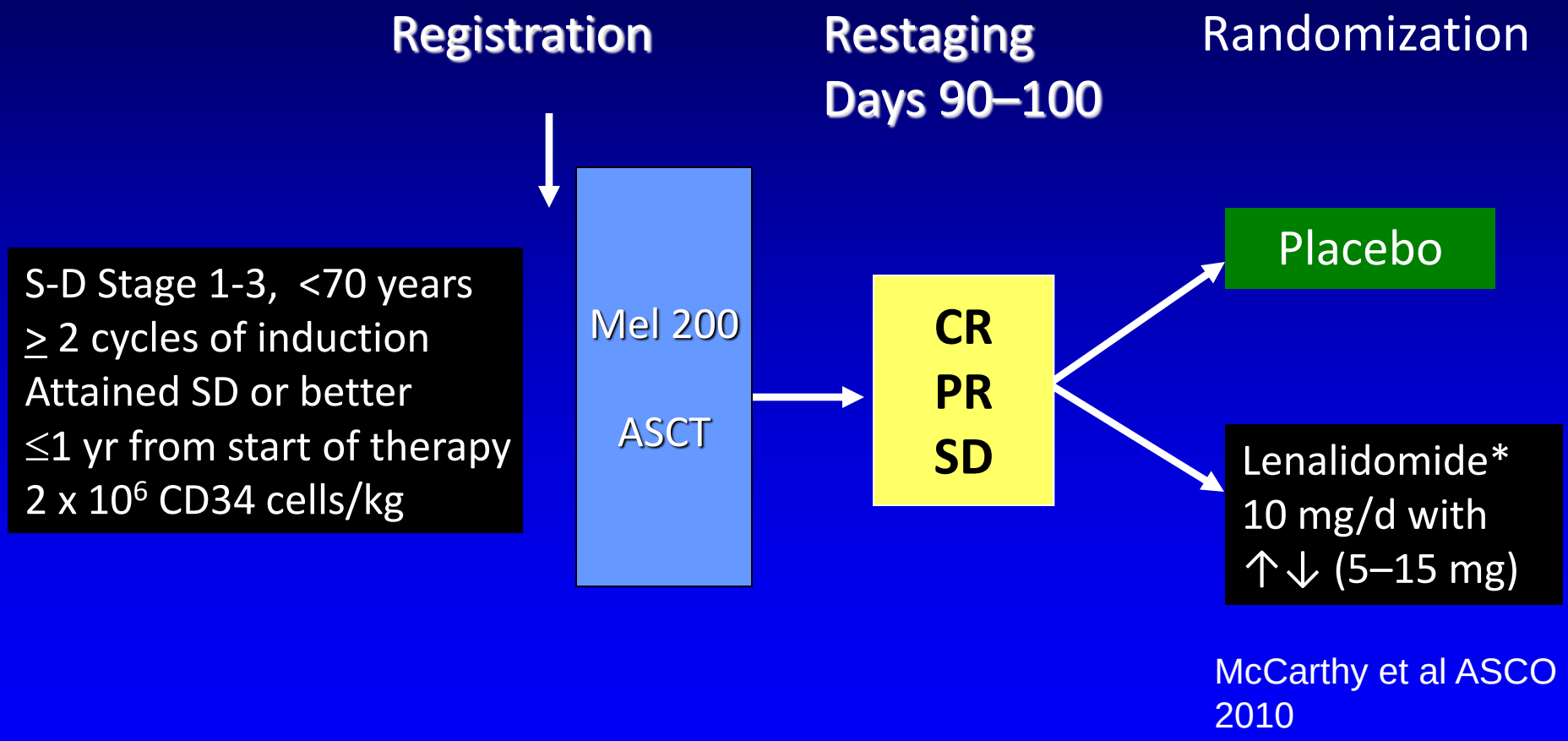
	No maintenance	Pamidronate	Pamidronate+Thal	
CR/VGPR	55%	57%	67%	P=0.03
3yr EFS	36%	37%	52%	p<0.009
4 yr OS	77%	74%	87%	p<0.04

Longer EFS significantly associated with: low beta2m (p<0.03); treatment arm (p<0.02); lack of del 13 (p<0.03); and lack of VGPR to transplant (p<0/004).

No decrease in bone events with maintenance pamidronate

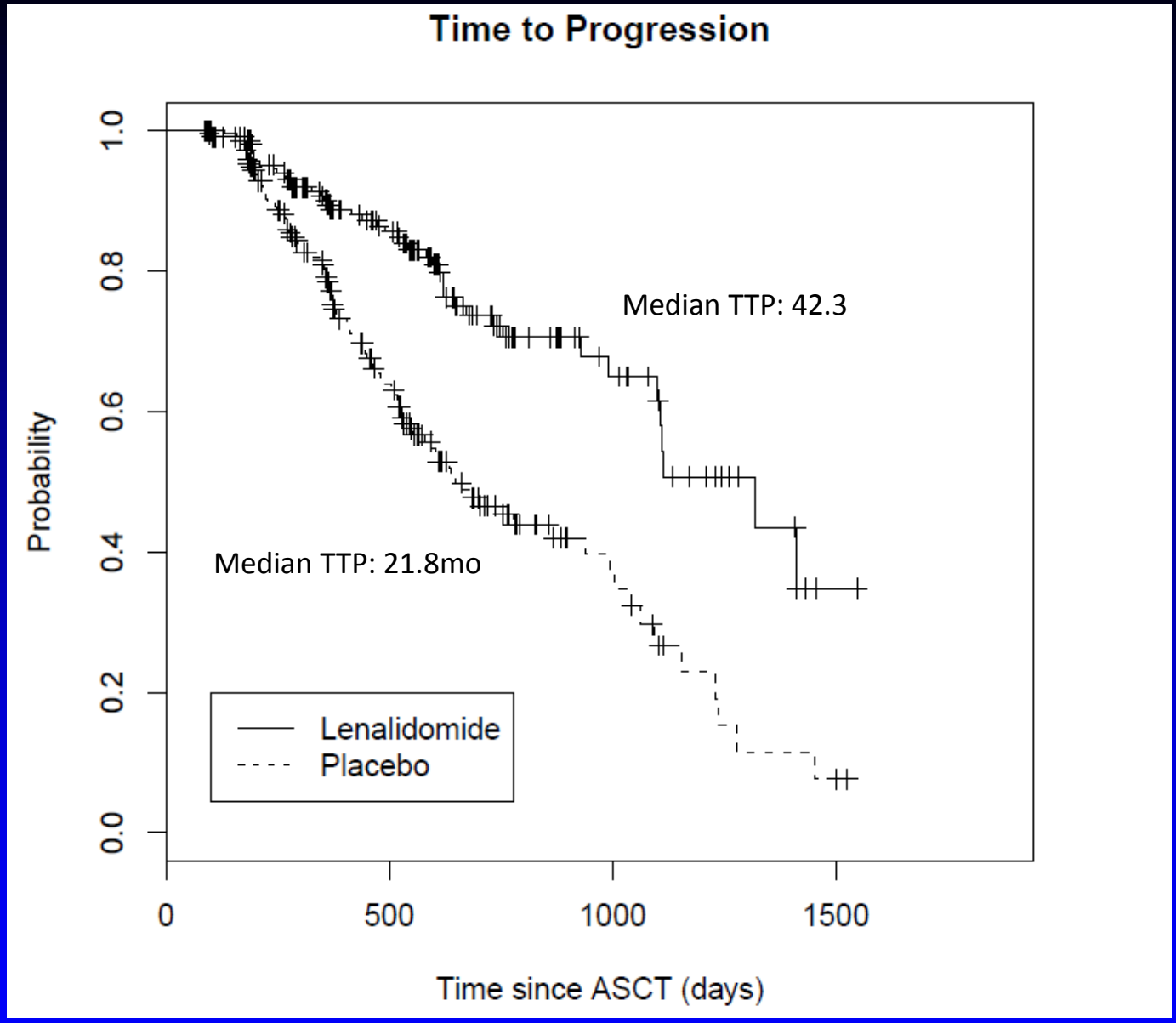
Attal M et al. Blood 2006; 106:3289-94.

CALGB 100104 Schema



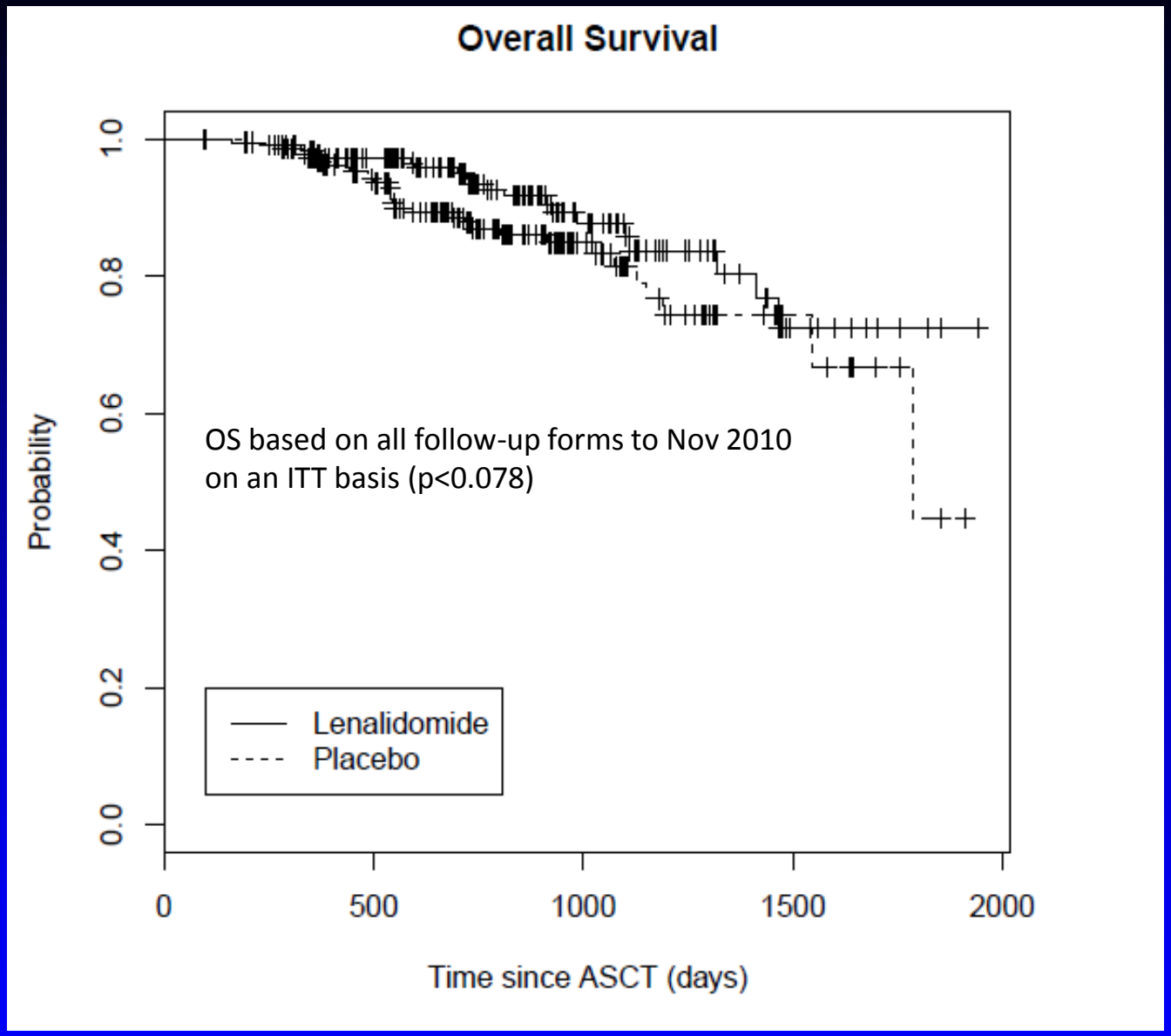
McCarthy et al ASCO 2010

Stratification based on diagnostic β-2M and thalidomide and lenalidomide use during Induction



CALGB 100104

ITT Analysis with a Median Follow-up from transplant of 18 months as of 12/17/2009 ($p < 0.0001$)



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Continued Therapy, Second Cancers

- In January, 2010, 122 lenalidomide patients and 86 placebo patients were receiving lenalidomide
- As of Feb 2011, 101 lenalidomide patients have received lenalidomide within 6 months and 26 have not for > 6 months
- As of Feb 2011, 52 placebo patients have received lenalidomide within 6 months and 34 have not received lenalidomide for > 6 months
- No 2nd cancers in cross over placebo patients as of Feb 2011
- 30 new cancers reported out of 568 registered patients (5.3%, 4.0% excluding all skin cancers) at a median follow-up of 26 months (Feb 2011)
- **Lenalidomide 14/231 (6%) versus Placebo 4/229 (2%)** excluding pre randomization and non-melanoma skin cancers (Feb 2011)

IFM 2005-02: Study design

Phase III randomized, placebo-controlled trial
N= 614 patients, from 78 centers, enrolled between 7/2006 and 8/2008

Patients < 65 years, with non-progressive disease, ≤ 6 months after ASCT in first line

Randomization: stratified according to Beta-2m, del13, VGPR

Consolidation:
Lenalidomide alone 25 mg/day p.o.
days 1-21 of every 28 days for 2 months

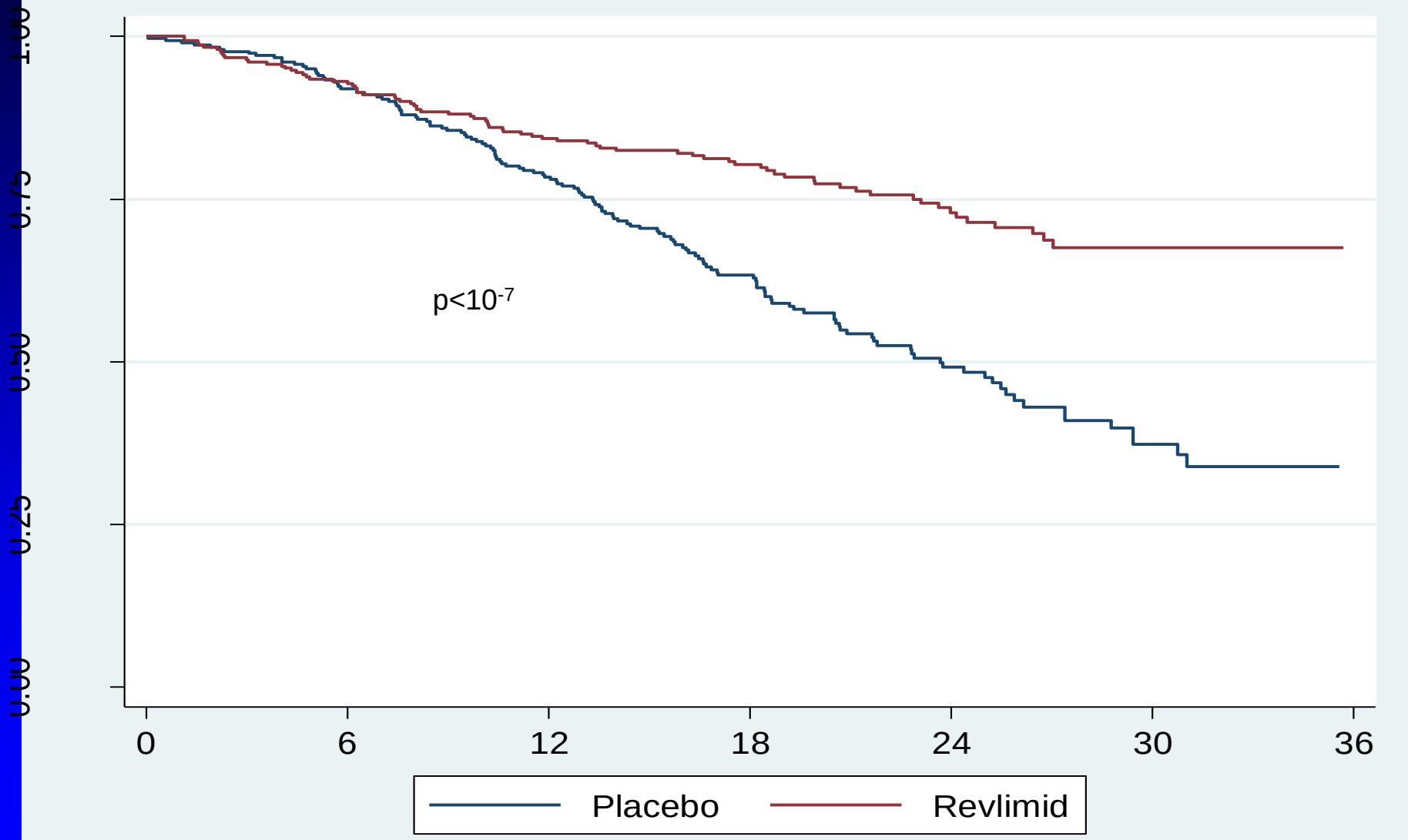
Arm A=
Placebo
(N=307)
until relapse

Arm B=
Lenalidomide
(N=307)
10-15 mg/d until relapse

Primary end-point: PFS.
Secondary end-points: CR rate, TTP, OS, feasibility of long-term lenalidomide….

Atal et al, ASCO, 2010

IFM 2005-02 : PFS from randomization



Grade 3-4 Adverse Events during treatment

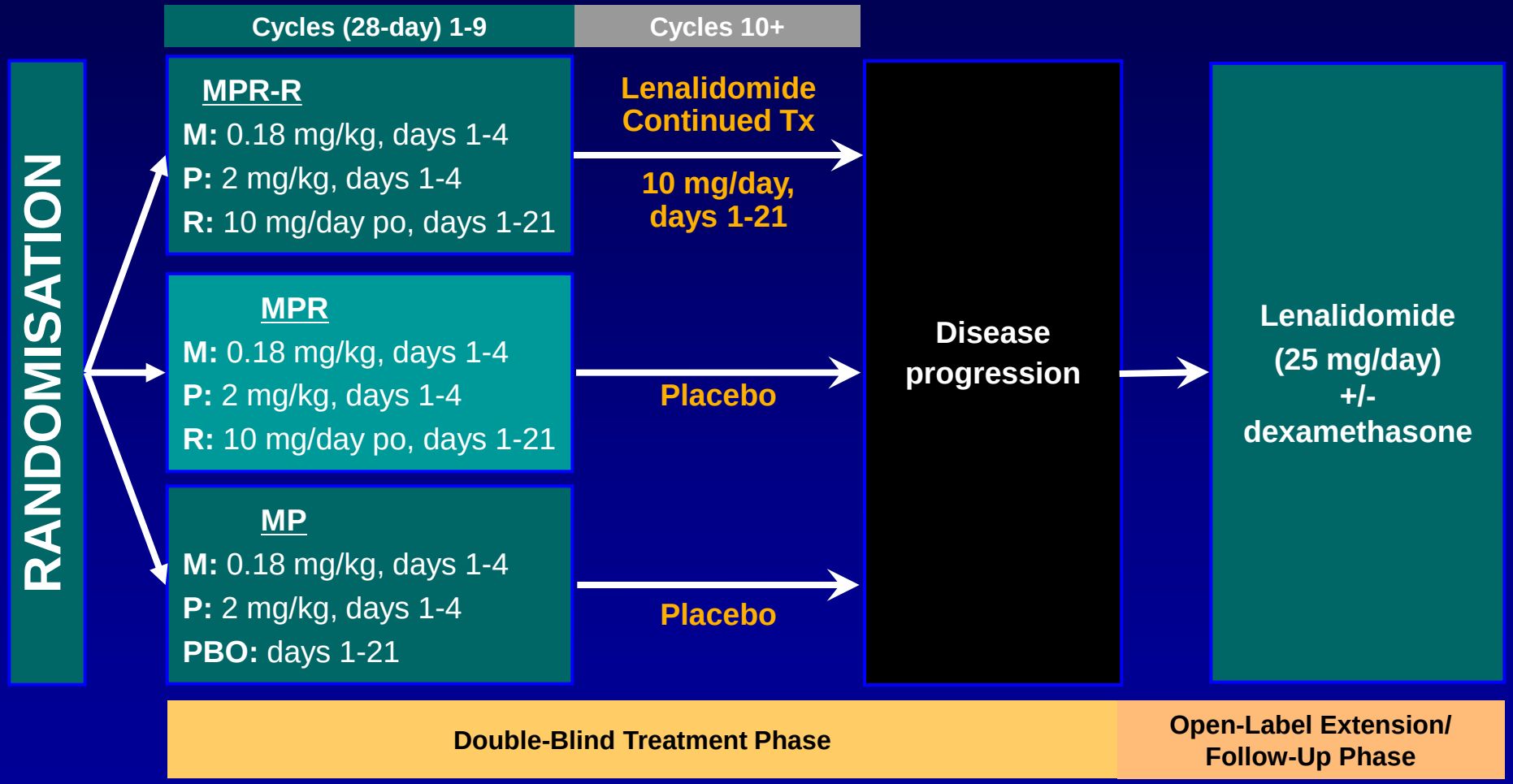
AE (grade 4)	Arm A	Arm B
Anemia	2% (1%)	4% (2%)
Thrombocytopenia	6% (2%)	12% (5%)
Neutropenia	14% (3%)	43% (11%)
Febrile Neutropenia	0%	2% (1%)
Infections	5% (1%)	10% (1%)
DVT	0%	2% (0.3%)
Skin disorders	4%	6%
Fatigue	0%	1%
Peripheral Neuropathy	0.3%	0.7%
Hematologic malignancies (n)	2	10
Non hematologic malignancies (n)	1	6

Discontinuation for AE: placebo = 15% vs lenalidomide = 21%

Treatment in transplant ineligible patients

Phase III Trial: MP vs MPR vs MPR-R

N=459, 82 centers in Europe, Australia and Israel



Stratified by age (≤ 75 vs. > 75 years) and stage (ISS 1,2 vs. 3)

Palumbo et al, ASH 2009

M, melphalan; P, prednisone; R, lenalidomide; PBO, placebo.

Best Response: MP vs MPR vs MPR-R

Best Overall Response[a]	MPR-R N = 152	MPR N = 153	MP N = 154	*P* Value (MPR-R vs. MP)
ORR	77%	67%	49%	<0.001
CR[b]	18%	13%	5%	<0.001
≥ VGPR[c]	32%	33%	11%	<0.001
PR	45%	34%	37%	---
Progressive Disease	0%	1%	0%	---
Median time to first response, months	1.9	1.9	2.8	<0.001

a. As measured using EBMT criteria[1]

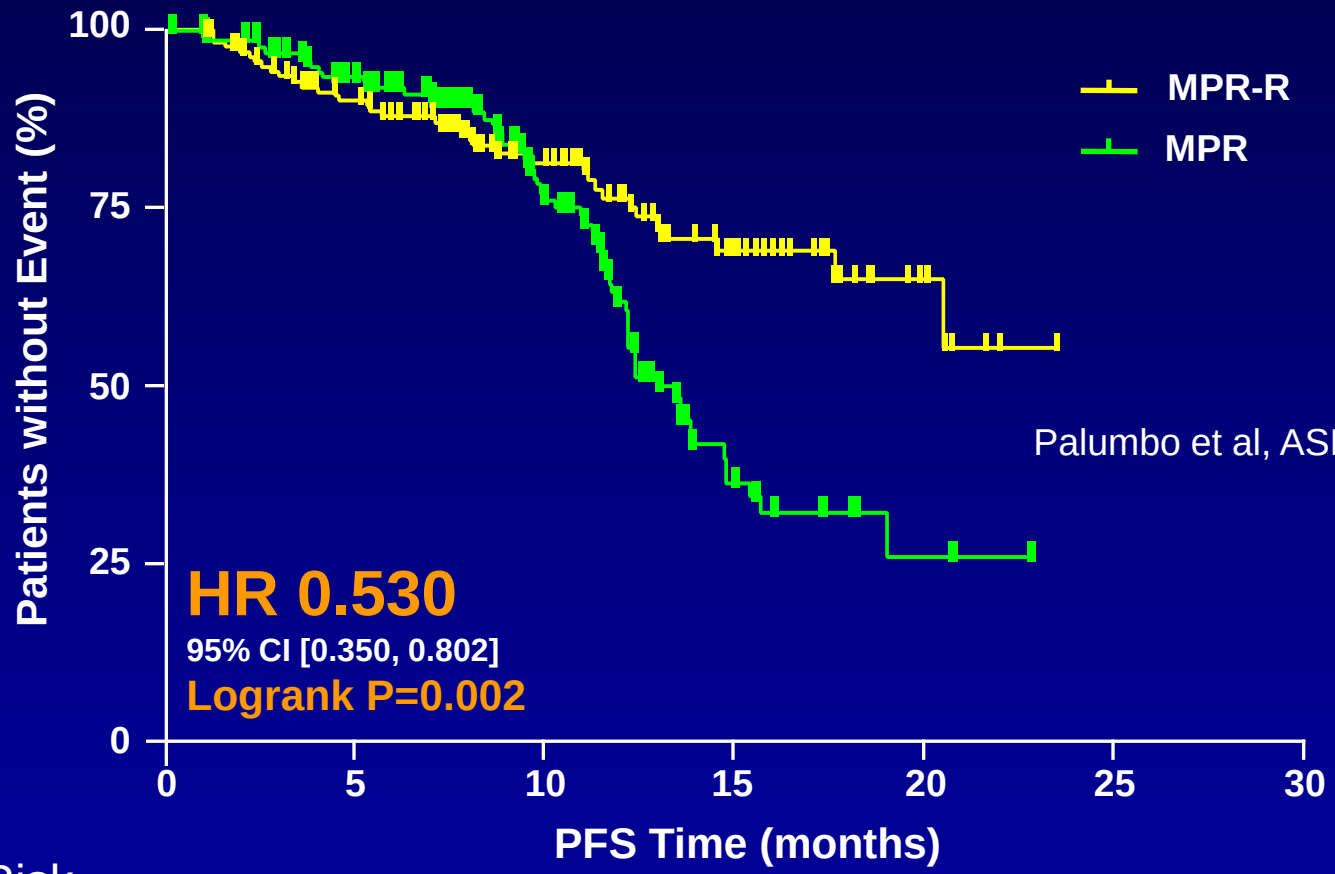
b. Immunofixation negative with or without bone marrow confirmation

c. VGPR: >90% reduction in M-protein

Palumbo et al, ASH 2009

1. Bladé J et al. *Br J Haematol.* 1998;102:1115-1123.

MPR-R vs. MPR
47% Reduced Risk in PFS



Median PFS

MPR-R	Not reached
MPR	13.2 months

Palumbo et al, ASH 2009

No. at Risk							
MPR-R	152	115	70	36	11	2	1
MPR	153	122	78	20	5	1	1

VISTA: VELCADE as Initial Standard Therapy in multiple myeloma: Assessment with melphalan and prednisone

- Randomized, international, phase III trial of VMP vs MP in previously untreated MM patients who were not candidates for HDT-ASCT
- Patients: Symptomatic multiple myeloma/end organ damage with measurable disease
  - ≥65 yrs or <65 yrs and not transplant-eligible; KPS ≥60%

RANDOMIZE

VMP

Cycles 1-4

Bortezomib 1.3 mg/m^2 IV: days 1,4,8,11,22,25,29,32
Melphalan 9 mg/m^2 and prednisone 60 mg/m^2 days 1-4

Cycles 5-9

Bortezomib 1.3 mg/m^2 IV: days 1,8,22,29
Melphalan 9 mg/m^2 and prednisone 60 mg/m^2 days 1-4

9 x 6-week cycles (54 weeks) in both arms

MP

Cycles 1-9

Melphalan 9 mg/m^2 and prednisone 60 mg/m^2 days 1-4

- Primary Endpoint: TTP
- Secondary Endpoints: CR rate, ORR, TTR, DOR, PFS, TNT, OS, QoL (PRO)

San Miguel et al, ASH 2008 Abstr 650

VISTA: VMP vs MP Updated Follow-Up and Results of Subsequent Therapy

Mateos et al ASH 2009

- Updated data with over 3-year follow-up confirm that VMP results in **significantly longer OS** vs. MP
- Subsequent salvage therapies were similarly effective in pts from both arms, demonstrating that use of bortezomib does not preclude use of novel agents at relapse
- Retreatment with bortezomib-based therapies resulted in a 47% ORR

Supportive Care

- Bisphosphonates
  - Reduces SREs
    - Morgan G. MRC Myeloma IX. Lancet Oncol.2011
  - Associated with improved survival in the MRC trial
    - Morgan G. MRC Myeloma IX. Blood.2012
- Vertebroplasty/Kyphoplasty
  - Pain control in vertebral compression and collapse
- Anti-microbials

ASCO Clinical Practice Guidelines
Bisphosphonates:

- Indicated for MM pts w/ lytic bone disease or osteopenia
- Reduce skeletal events such as fractures
- Useful as an adjunct for pts w/ bone pain
- The bisphosphonates recommended are either
  - Zoledronic acid: 4 mg over 15 mins, IV q 3-4 wks
  - Pamidronate (PAM): 90 mg over $\geq$ 2 hrs, IV q 3-4 wks
- Monitoring serum creatinine (both BPs) and/or urine albumin (for palmidronate only)
- PAM preferred in setting of renal dysfunction
- Re-evaluate after 2 years and stop if stable disease
- Potential side effects:
  - Hypocalcemia
  - Renal dysfunction
  - Osteonecrosis of jaw (ONJ)

Kyle R, et al. JCO. 200725: 2464-2472

Questions?