

Multiple Myeloma and Amyloidosis: Optimism for Heretofore Incurable Diseases

Robert Vescio, MD

Director

**Multiple Myeloma & Bone Metastases Program
Samuel Oschin Comprehensive Cancer Center
Cedars-Sinai Medical Center**

**Associate Professor of Medicine
UCLA School of Medicine
Los Angeles, CA**

Multiple Myeloma



- **Malignancy of plasma cells**
- **Hallmarks:**
 - **Anemia**
 - **Renal failure**
 - **Bone destruction (lytic bone lesions)**
 - **Hypercalcemia**
 - **Presence of monoclonal immunoglobulin protein**
 - **Increased risk of infection**

Incidence of Multiple Myeloma



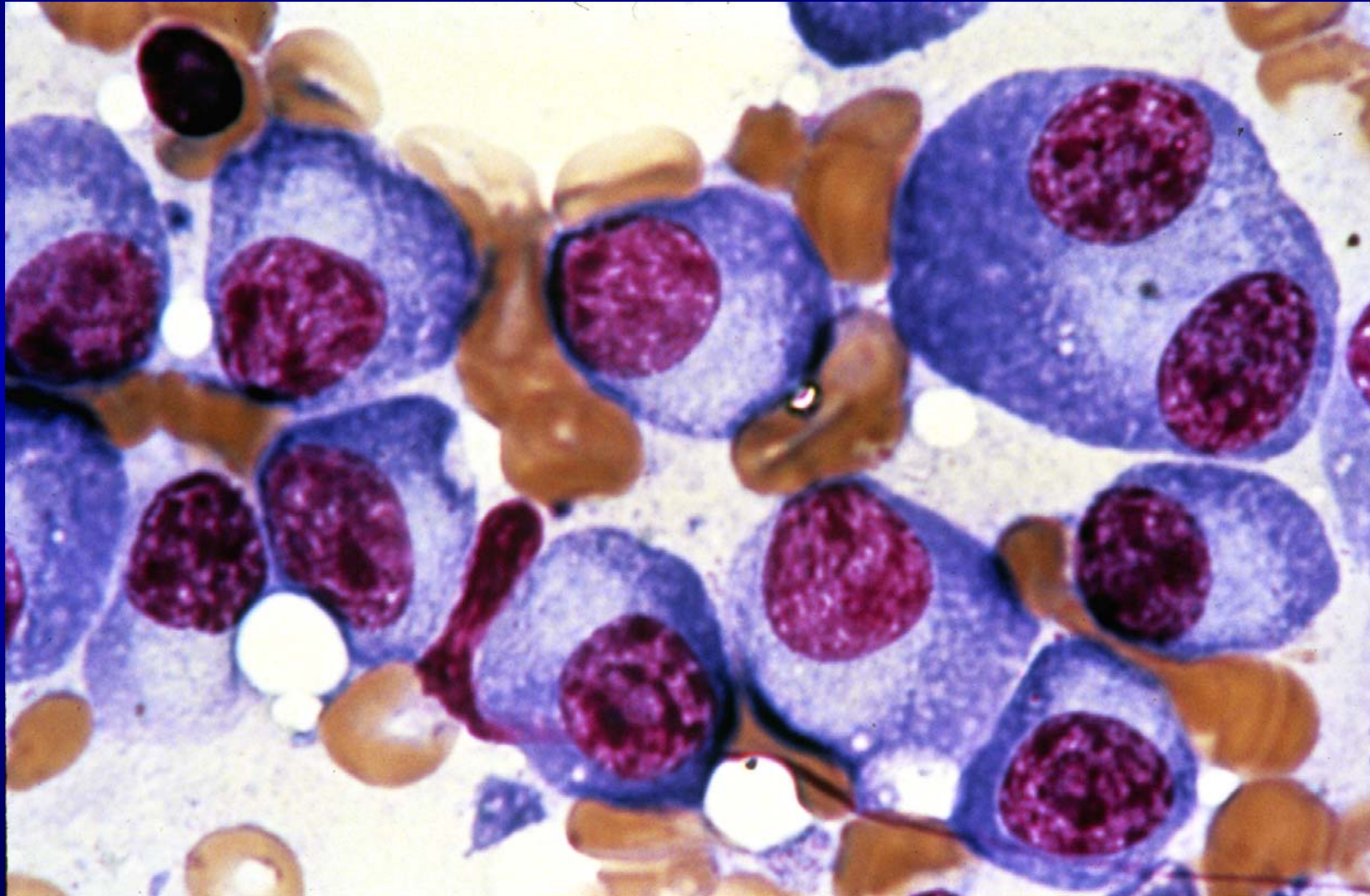
- **Estimated 19,900 new diagnoses in U.S. in 2007**
 - Equals ~ 1% of all new cancer cases
- **Prevalence = 45,000 Americans with MM**
- **Median age at diagnosis is 65 yrs**
- **Becomes more common as people get older**
- **Incidence is greater in African Americans than in Caucasians (2:1 ratio)**

Risk Factors for Multiple Myeloma



- Chronic exposure to low-dose ionizing radiation
- Occupational exposure (eg, chemical)
- Genetic factors
- Chronic antigenic stimulation (eg, recurrent infections and drug allergies)
- Silicone gel breast implants
 - Recent case-control study in California
 - RR = 2.31 (p = 0.046)
 - RR SGBI and contractures = 4.74 (p = 0.01)
- HHV-8?

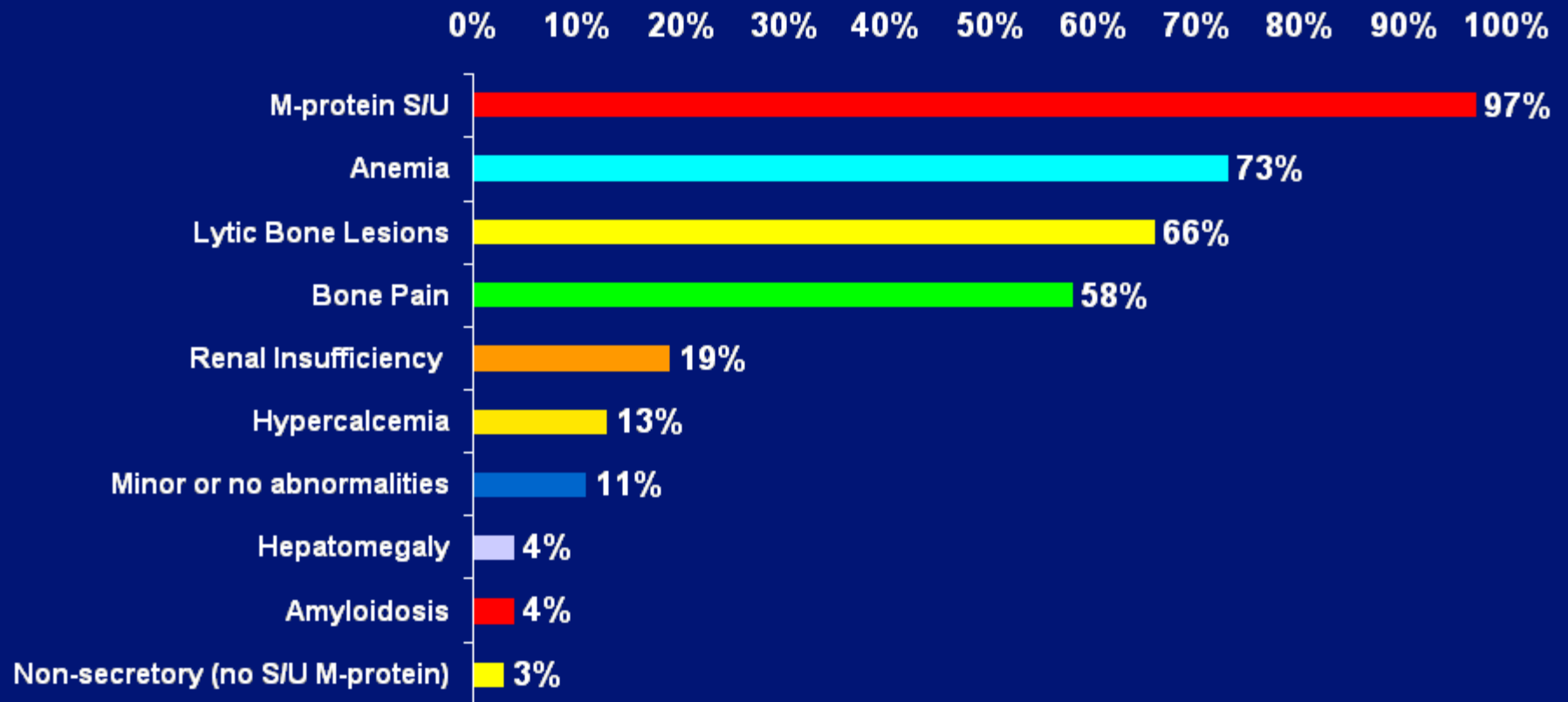
Myeloma Cells





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Presenting Features of MM



Clinical Features at Presentation



- **Monoclonal (M) protein (93%)**
- **Lytic bone lesions (67%)**
- **Increased plasma cells in the bone marrow (96%)**
- **Anemia (normochromic normocytic; 73%)**
- **Hypercalcemia ≥ 11 (13%)**
- **Renal failure, serum creatinine ≥ 2.0 (19%)**
- **Infection**

Antibody Production by Plasma Cells in Multiple Myeloma

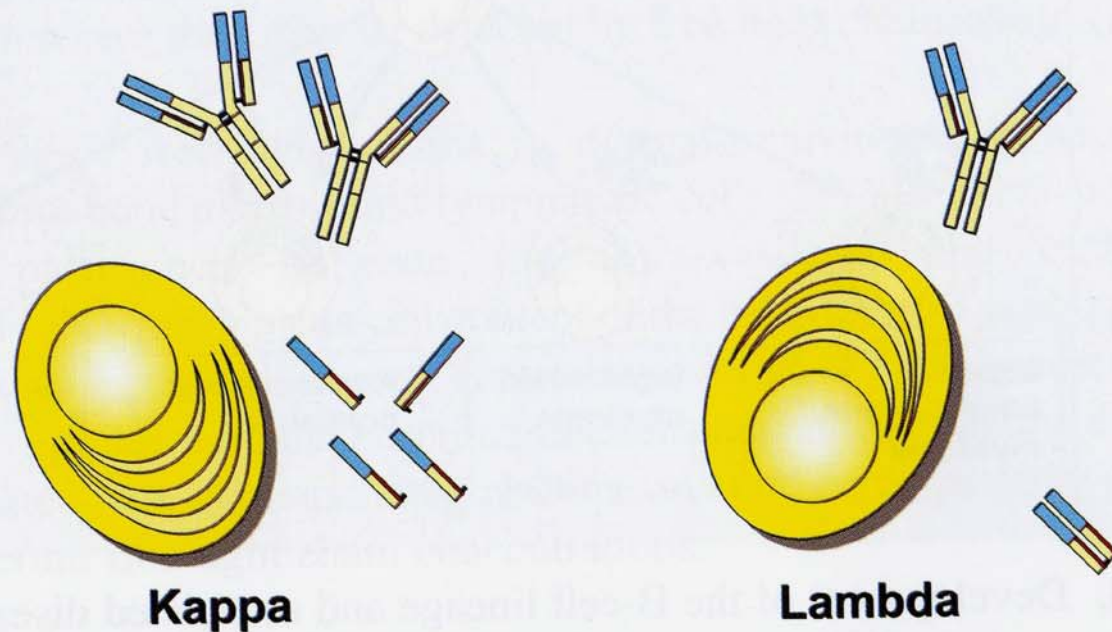
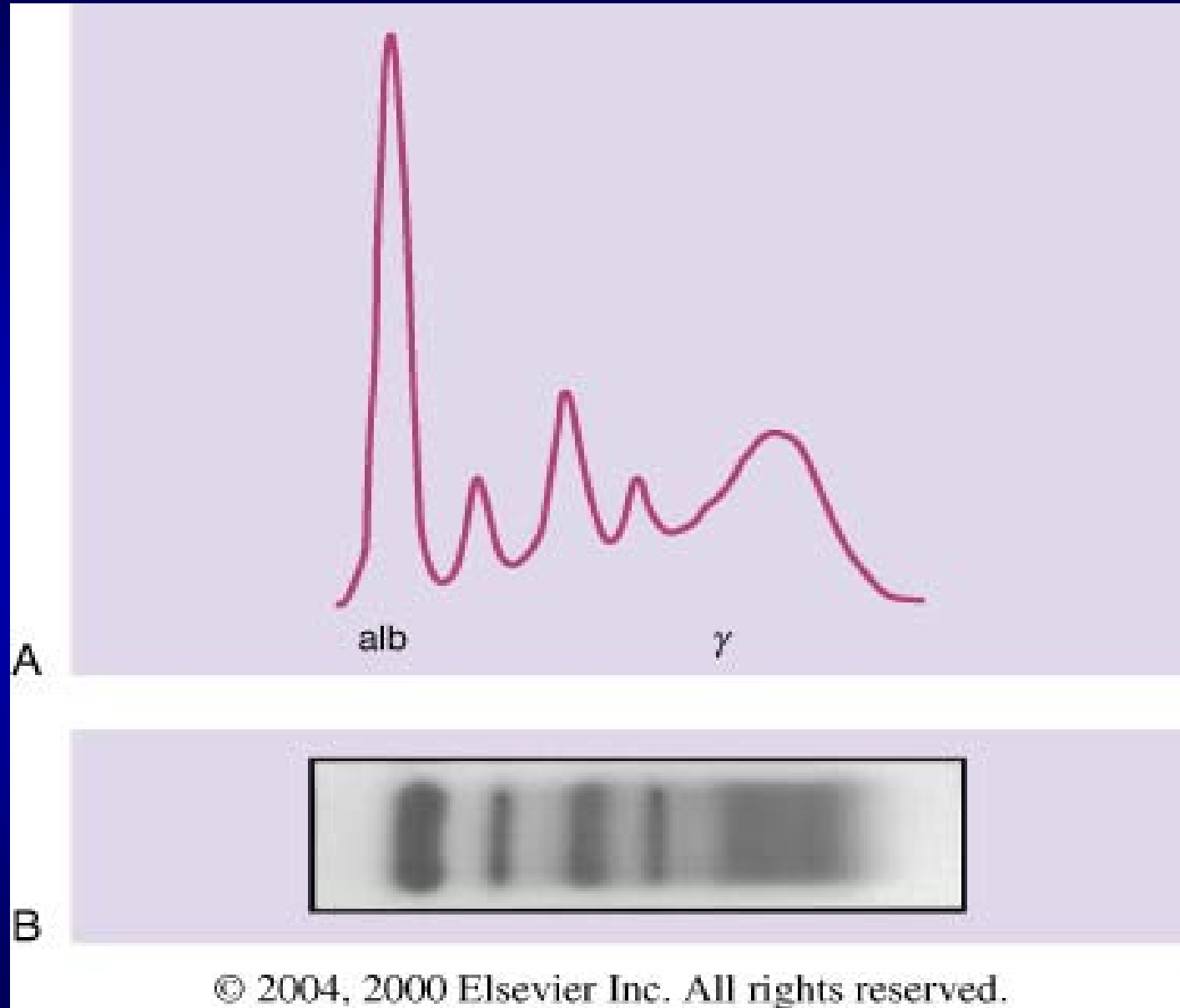
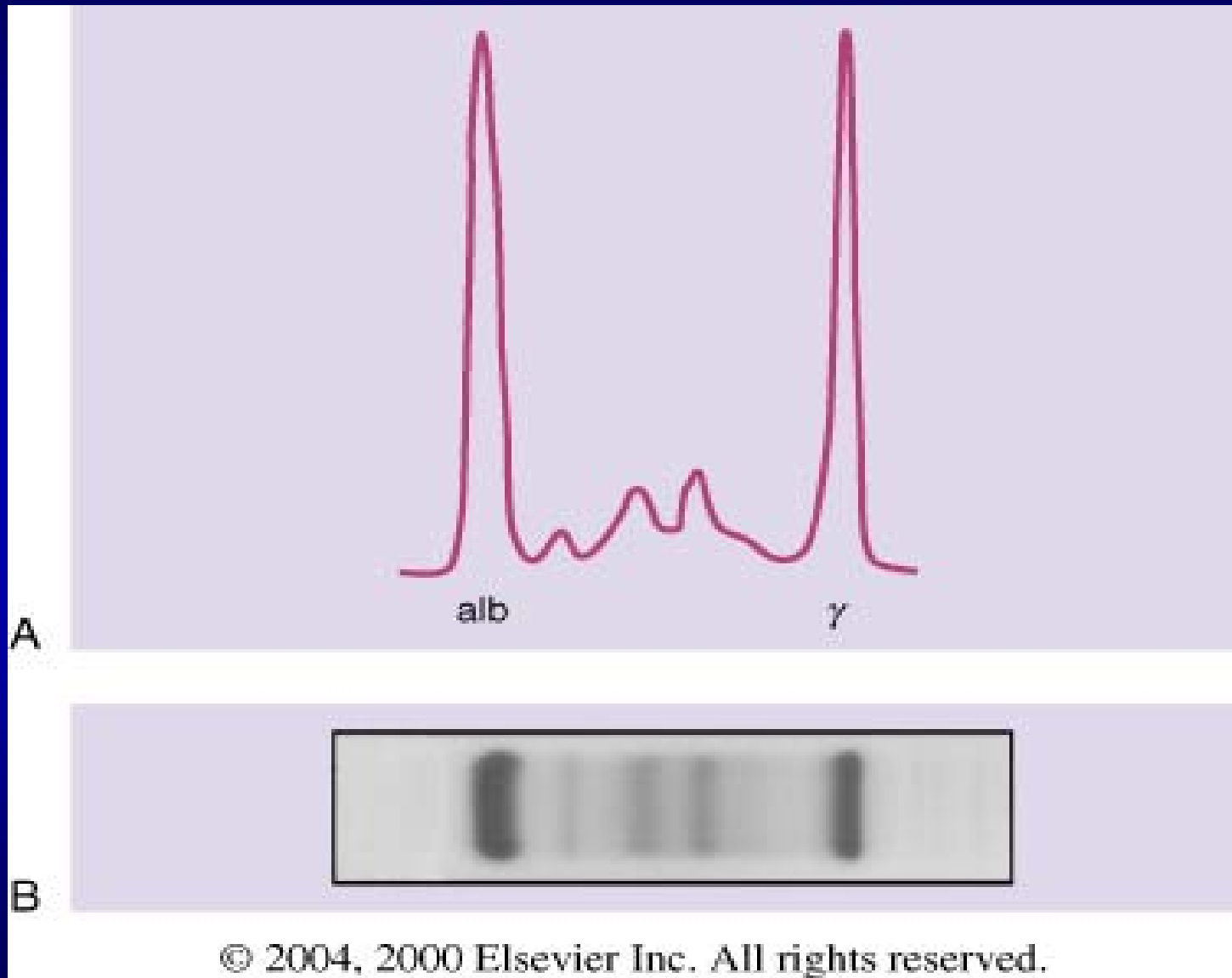


Figure 3.6. Diagrammatic representation of plasma cells producing intact immunoglobulins and free light chain molecules.

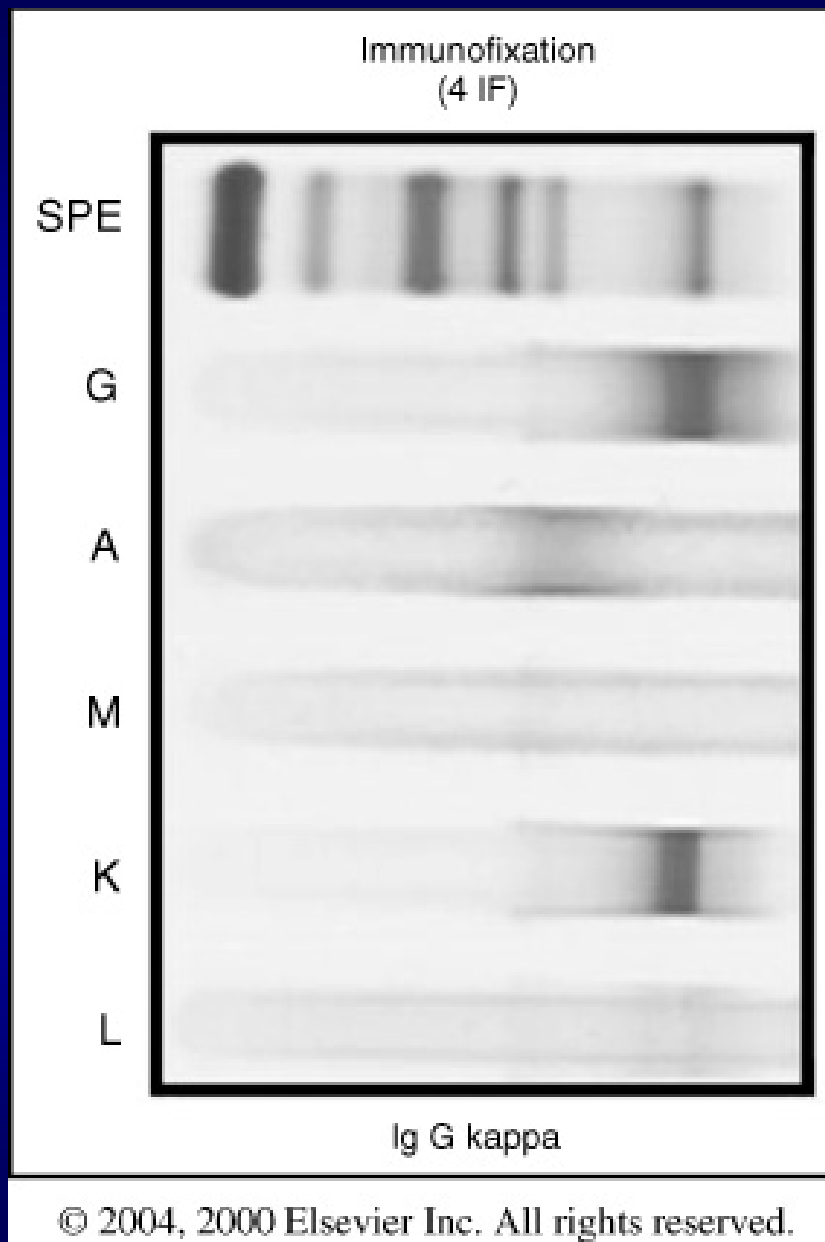
Normal Serum Protein Electrophoresis



Serum Protein Electrophoresis Showing Monoclonal Protein in Myeloma



Immunofixation to Determine Type of Monoclonal Protein

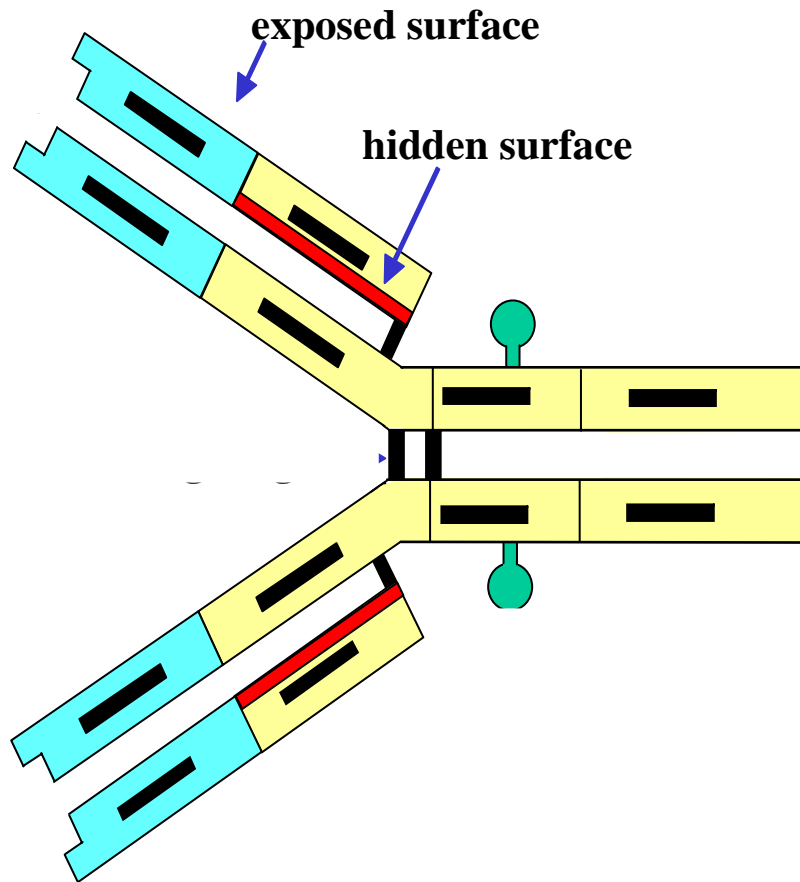


IgG kappa
M protein

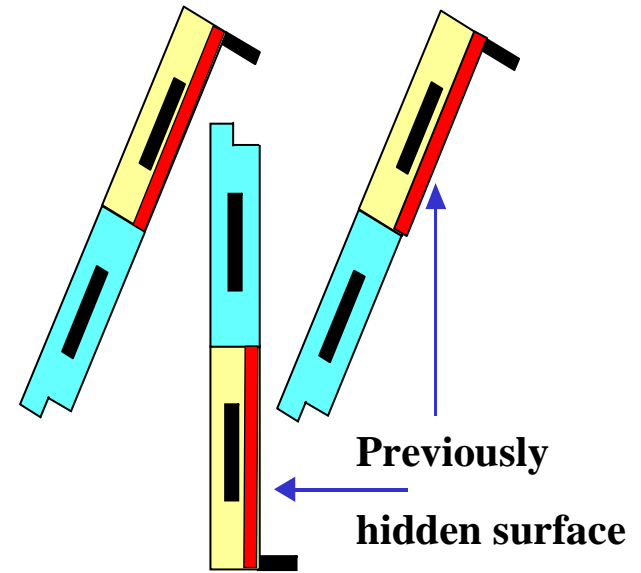
Multiple Myeloma Monoclonal Serum Proteins (%)



Protein	St. Bart's Hospital 1980-92 (n=156)	Mayo Clinic 1982-87 (n=580)
IgG	57	50
IgA	21	21
Light Chain	18	17
IgD	1	2
Non- secretory	2	3



Intact Immunoglobulin



Free Light Chain

Serum Free Light Chain Assay in Myeloma and Amyloidosis

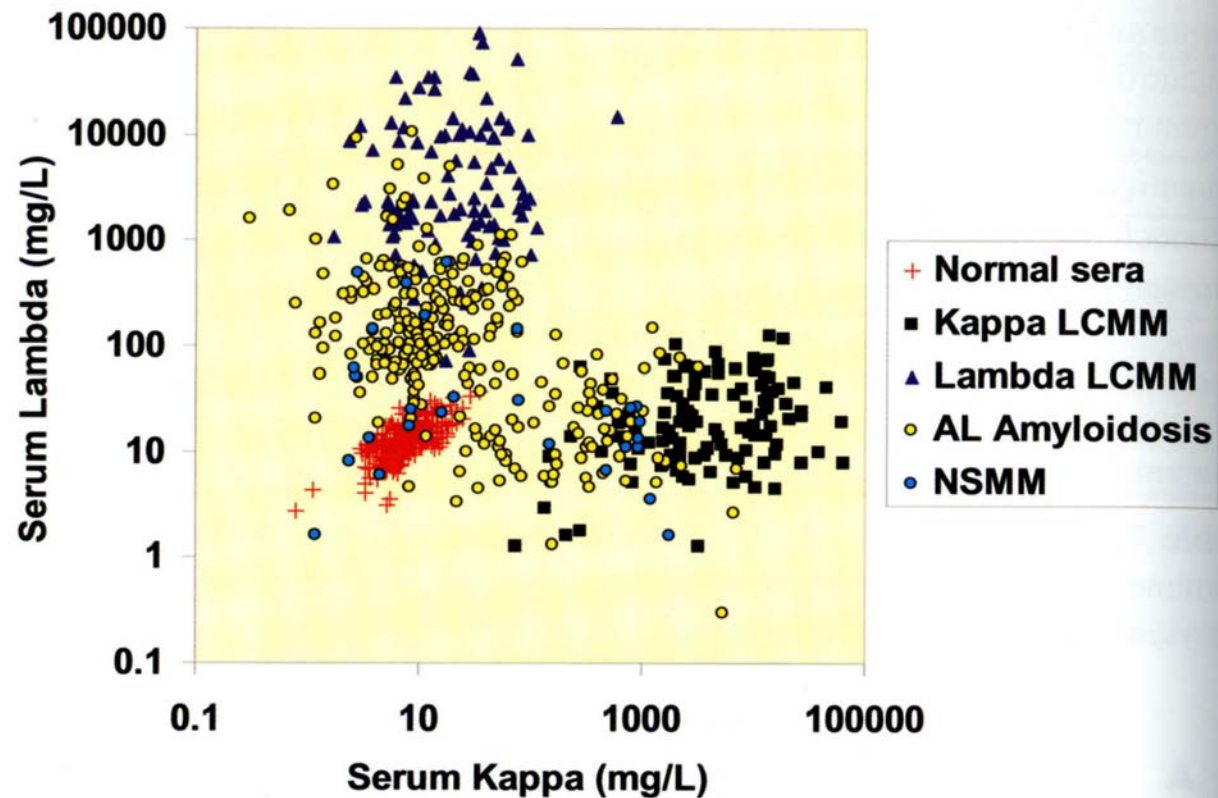


Figure 7.37. Serum free light chain concentrations in 262 patients with AL amyloidosis at the time of diagnosis. Comparison is made with 282 normal individuals, 224 patients with light chain multiple myeloma (LCMM) and 28 patients with nonsecretory multiple myeloma (NSMM).

Diagnostic Accuracy of the Free Light Chain Assay in Primary Amyloidosis

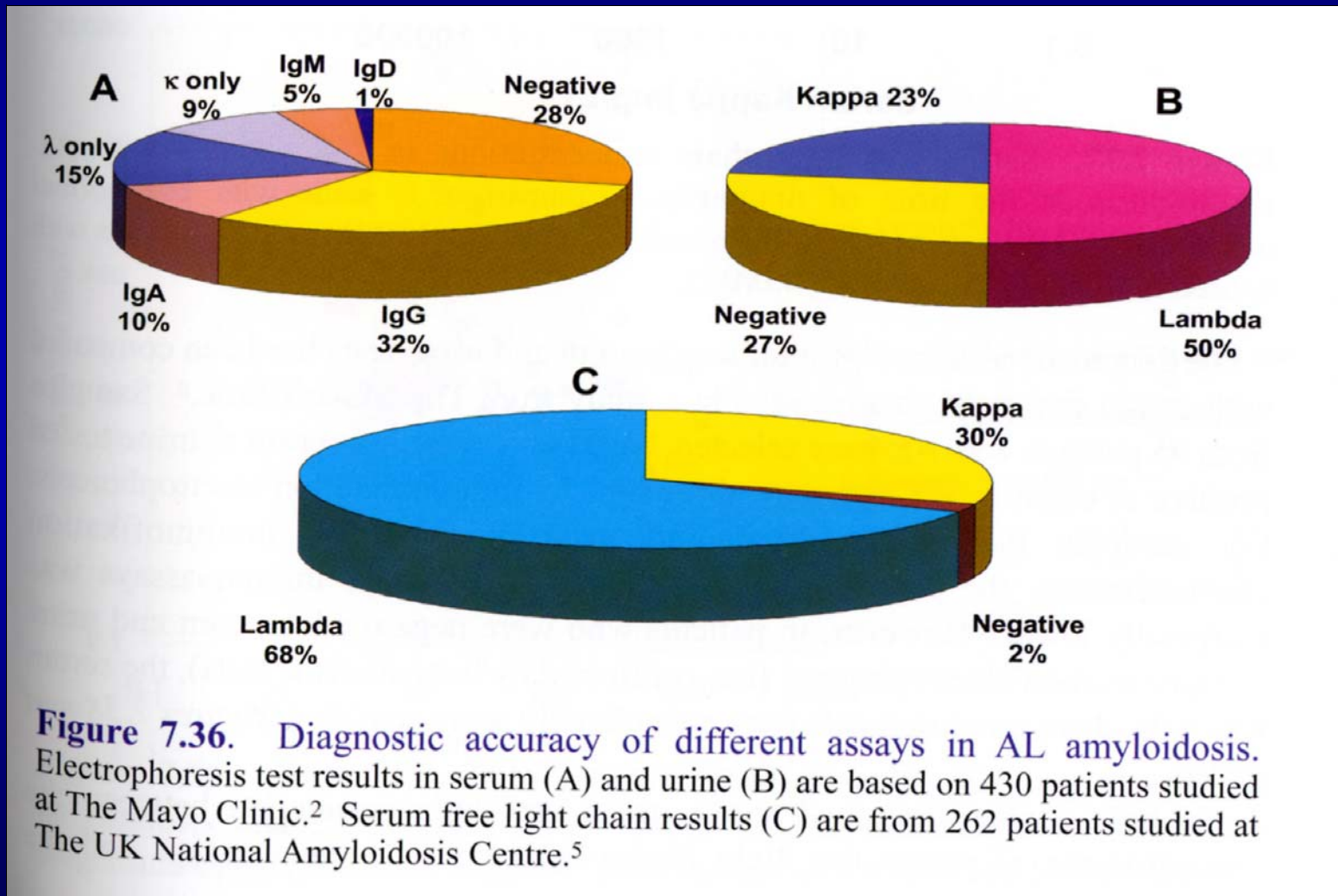


Figure 7.36. Diagnostic accuracy of different assays in AL amyloidosis. Electrophoresis test results in serum (A) and urine (B) are based on 430 patients studied at The Mayo Clinic.² Serum free light chain results (C) are from 262 patients studied at The UK National Amyloidosis Centre.⁵

Use of the Free Light Chain Assay To Monitor Disease in Amyloidosis

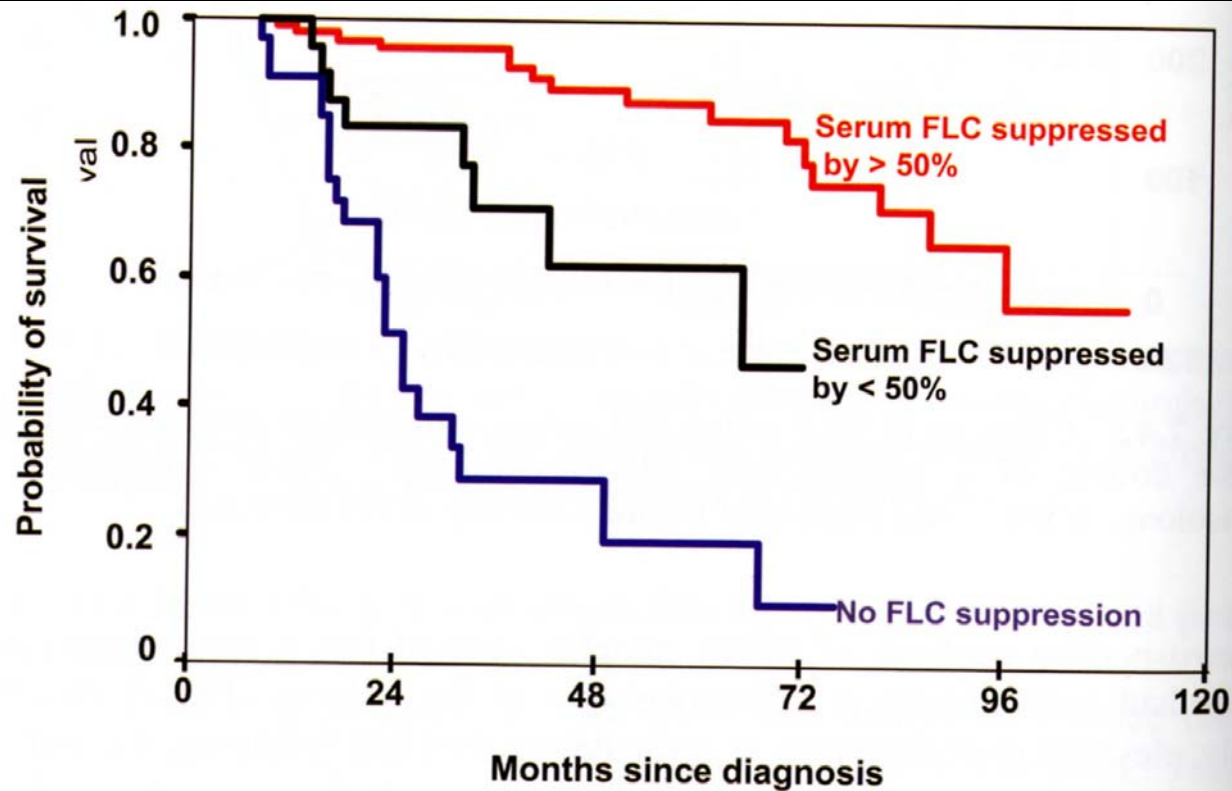


Figure 7.43. Kaplan-Meier estimate of survival in 137 patients with AL showing that a reduction of free light chain concentrations by greater than 50% following chemotherapy was associated with increased survival. FLC = free light chain. (Courtesy of PN Hawkins).

Pitfalls with the “Light Chain” Assays



- The Kappa and Lambda Light Chains tests that measure the total (free and attached to the heavy chain) amount of light chains in the serum is essentially USELESS
 - In my opinion, this test should be abandoned (confusing)
- Urine measurements of kappa and lambda light chains is of limited (? no) value
- Only the FREE Light chain test of value
 - Normal values always less than 50 mg/L for both
- Still a role for 24 hour urine and UPEP and Urine IEP

Diagnostic Tests



- **Blood and Urine Tests**
 - **M proteins**
 - **Blood—Serum protein electrophoresis and Immunofixation**
 - **24 hour urine protein electrophoresis and immunofixation**
 - **Secondary blood analysis**
 - **Complete blood cell counts (CBC)**
 - **Albumin, Beta-2-microglobulin, C-reactive protein, LDH**
 - **Quantitative Ig's, serum free light chain assay**
 - **Calcium, uric acid and creatinine**
- **Radiological**
 - **Skeletal survey; MRI/computerized tomography (CT) scanning if needed**
- **Bone Marrow**
 - **Aspirate and biopsy with karyotyping and plasma cell labeling index**

Monoclonal Gammopathy of Undetermined Significance (MGUS)



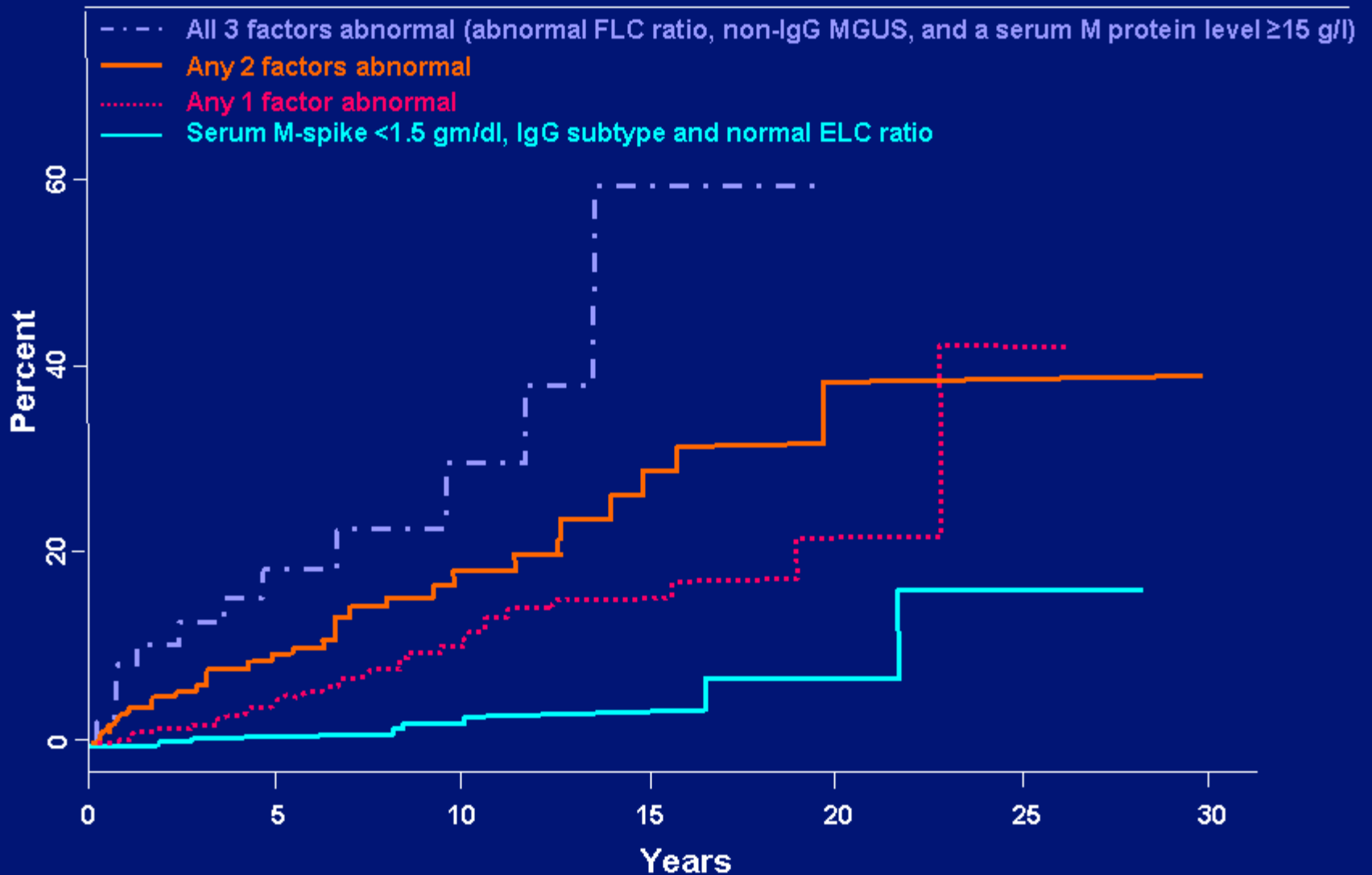
- Precursor lesion of multiple myeloma
- Presence of monoclonal protein at concentration of ≤ 3 g/dL in serum or urine without evidence of MM, Waldenström's macroglobulinemia, amyloidosis, or other lymphoproliferative disorder
- Incidence: up to 2% individuals ≥ 50 yr old
 - < 3 g/L monoclonal Ig, little or no proteinuria
 - $< 10\%$ monoclonal bone marrow plasma cells
 - No bone lesions, anemia, or hypercalcemia

MGUS: Risk of Progression to Malignancy

Table 196-2 * Size of monoclonal (M) protein and risk of progression to myeloma or related malignancy

M-Protein Size (g/dL)	Risk of Progression at 10 years (%)	Risk of Progression at 20 years (%)
≤ 0.5	6	14
1.0	7	16
1.5	11	25
2.0	20	41
2.5	24	49
3.0	34	64

Serum Free Light Chain Ratio as Independent Risk Factor for Progression in MGUS



Distinguishing MM from MGUS and Smoldering MM

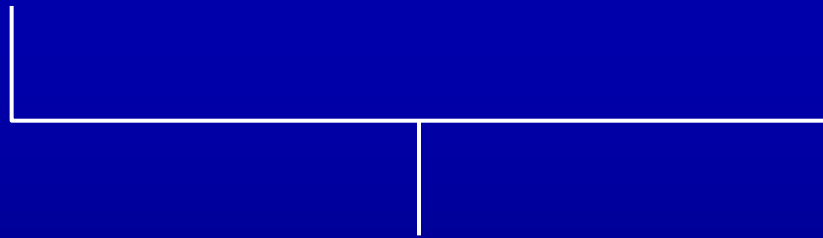
MGUS

- <3 g M spike AND <10% PC

SMM (AMM)

- ≥ 3 g M spike OR $\geq 10\%$ PC

AND



No anemia, bone lesions
normal calcium and
kidney function

MM

- $\geq 10\%$ PC
- M spike +

AND

Anemia, bone lesions,
high calcium or
abnormal
kidney function

Durie-Salmon Staging System

Stage	Criteria	Myeloma cell mass (x 10 ¹² cells/m ²)
I	<p>All of the following:</p> <p>Hemoglobin >10 g/dL</p> <p>Serum calcium level ≤12 mg/dL (normal)</p> <p>Normal bone or solitary plasmacytoma on x-ray</p> <p>Low M-component production rate:</p> <p> IgG <5 g/dL; IgA <3 g/dL</p> <p> Bence Jones protein <4 g/24</p>	<0.6 (low)
II	Not fitting stage I or II	0.6–12 (intermediate)
III	<p>Any or more of the following:</p> <p>Hemoglobin <8.5 g/dL</p> <p>Serum calcium level >12 mg/dL</p> <p>Multiple lytic bone lesions on x-ray</p> <p>High M-component production rate:</p> <p> IgG >7 g/dL; IgA <5 g/dL</p> <p> Bence Jones protein >12 g/24 h</p>	>1.2 (high)
	Subclassification	Criteria
	A	Serum Creatinine < 2.0 mg/dL
	B	Serum Creatinine ≥ 2.0 mg/dL

International Staging System (ISS) for Multiple Myeloma

Stage	Criteria	Median Survival (mo)
I	$\beta 2m < 3.5 \text{ mg/L}$ Albumin $\geq 3.5 \text{ g/dl}$	62
II*	Not stage I or III	44
III	$\beta 2m > 5.5 \text{ mg/L}$	29

* $\beta 2m < 3.5 \text{ mg/L}$ and albumin $< 3.5 \text{ g/dL}$ or
 $\beta 2m 3.5 - < 5.5 \text{ mg/dL}$, any albumin

Chromosomal Aberrations in Myeloma



- All MM cases have chromosome abnormalities
- Karyotype: 8-30% of patients
 - Poor prognosis: monosomy 13 or hypodiploidy
 - Good prognosis: normal karyotype or hyperdiploidy
- Interphase FISH: ~ 100% of cases
 - Poor prognosis; t(4;14), t(14;16) or -17p13
 - Intermediate prognosis
 - Good prognosis; hyperdiploidy

Incidence of Chromosomal Abnormalities in MM

- n = 1064 patients
- Chromosomal changes observed in 90% of patients

Genomic Aberrations	Incidence of aberration
Del (13)	48%
t(11;14) (q13;q32)	21%
t(4;14) (p16;q32)	14%
Hyperdiploidy	39%
MYC translocations	13%
Del(17p)	11%

Median follow-up 41 months

- del(13), t(4;14), nonhyperdiploidy, and del(17p) negatively impacted both the event-free survival and the overall survival
- t(11;14) and *MYC* translocations did not influence the prognosis
- Only t(4;14) and del(17p) retained prognostic value for both the event-free and overall survivals

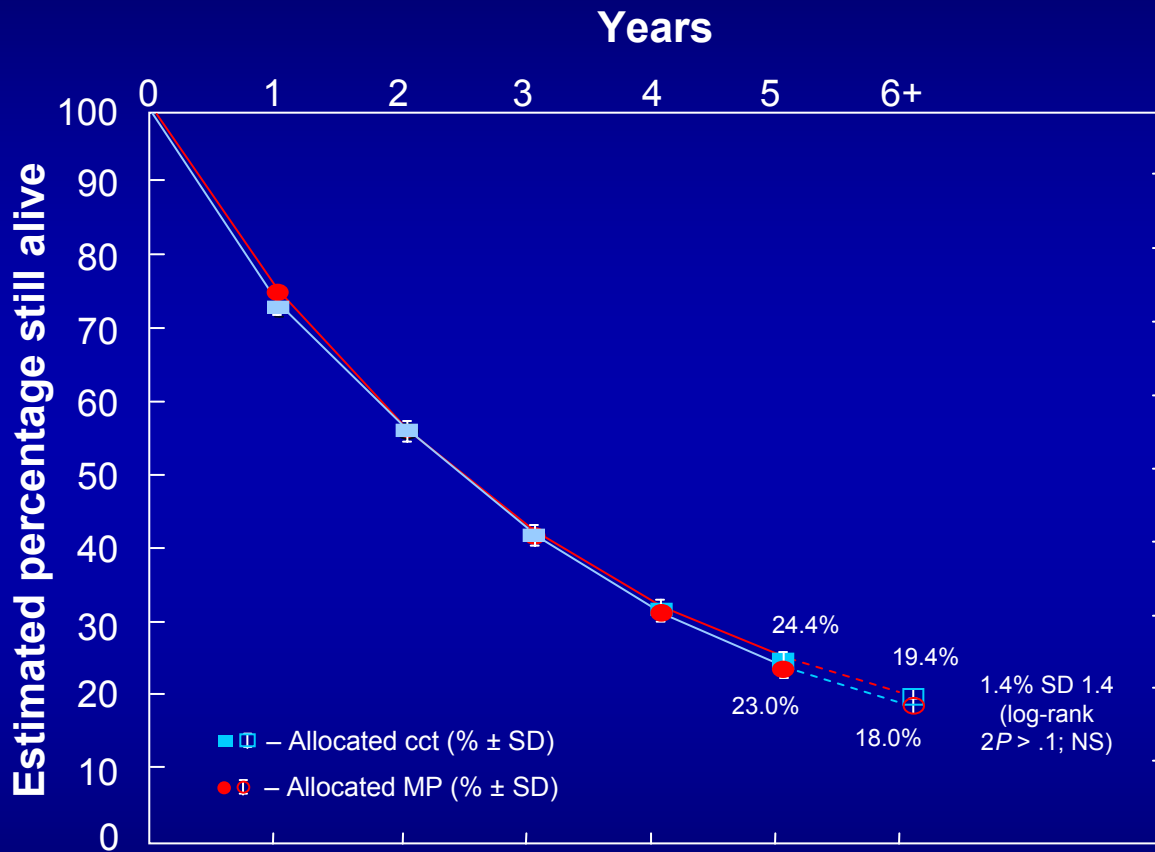
Initial Treatment of Multiple Myeloma

Historical Perspective: 1970 - 1990



- **5 year survival did not improve during this time period**
 - 1974 – 1976 = 24%
 - 1980 – 1982 = 28%
 - 1983 – 1990 = 27%
- **Median survival up until 1990 = 32 months**
- **Why?**
 - Only drugs = Chemotherapy agents and Steroids
 - Could just mix and match different drugs
 - No growth factors
 - No high-dose chemotherapy

Combination Chemotherapy vs Melphalan/Prednisone: Mortality



Deaths/person-years:

CCT	642/1999	392/1456	305/1044	196/724	133/506	255/1130
MP	576/1968	407/1423	294/983	194/652	130/444	215/839

Reprinted with permission from Myeloma Trialists' Collaborative Group. *J Clin Oncol.* 1998;16;3832

Historical Challenges in Management of MM



- **Currently incurable in most patients**
- **Chemotherapy response rates = 50% to 70%**
 - Long-term complete responses = rare
 - Median survival with standard therapy = 3 years
- **Stem cell transplant prolongs survival, but not curative**
- **Treatment of relapse**
 - No standard therapy
 - Existing options have high response rates but short duration of effect
- **New treatment options needed**

Multiple Myeloma

General Concepts: Historical Treatment



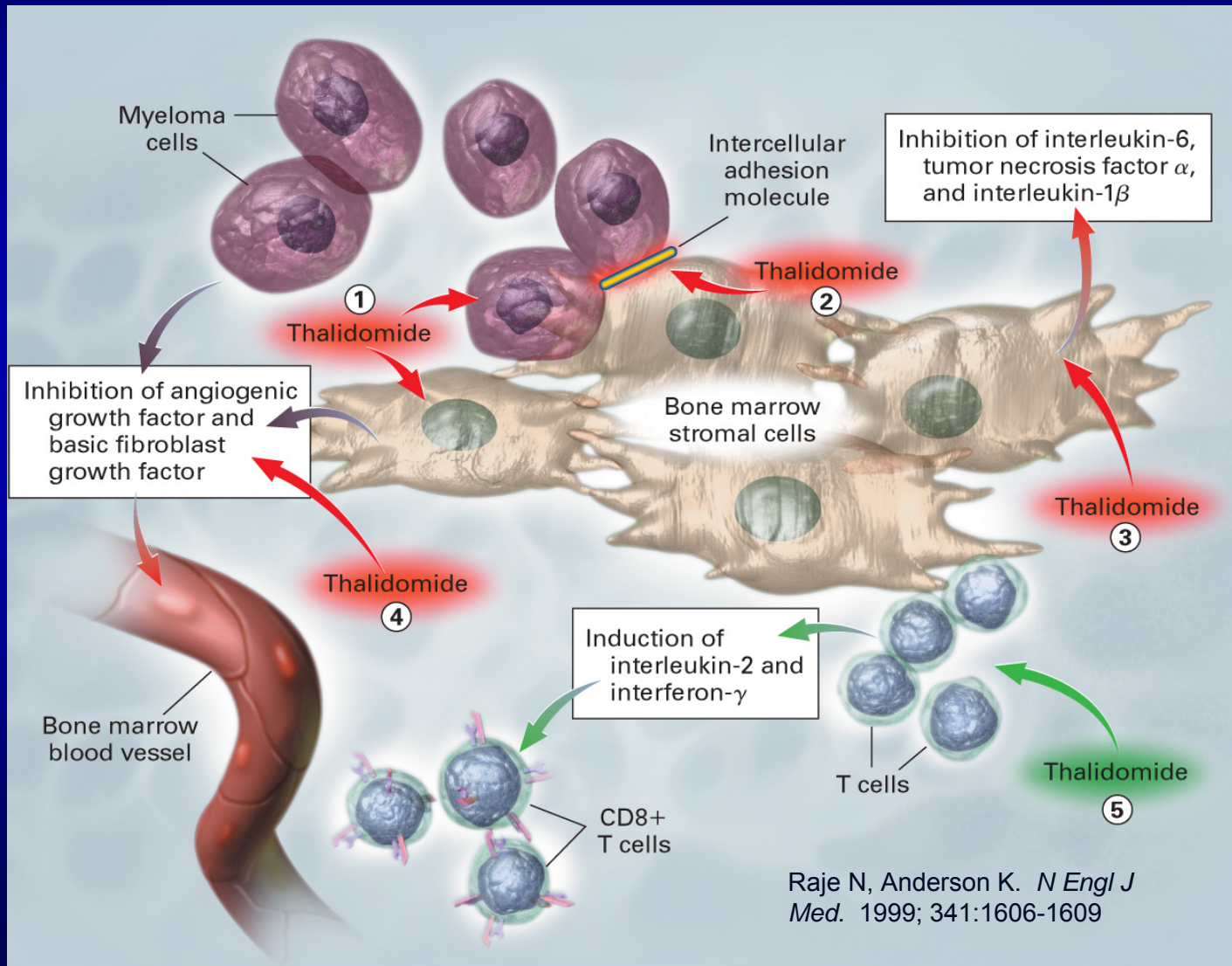
- **Melphalan and Prednisone**
 - Advantages
 - Inexpensive
 - Well tolerated
 - Disadvantages
 - **MP associated with long-term bone marrow suppression + leukemia**
 - **Do not use if Stem Cell Transplant Considered**
- **Newer regimens may be better tolerated or more effective**
 - Pegylated Liposomal Doxorubin instead of Doxorubicin in VAD
 - Thalidomide + Dexamethasone
 - (Lenalidomide and Bortezomib containing regimens)

History of Thalidomide



- **Used in late 1950s in Europe as sedative**
 - Good sleep quality and low risk of fatal overdose
- **Also used for “morning sickness” associated with pregnancy**
- **Teratogenicity**
 - >10,000 malformed children born
 - Malformation of limbs (dysmyelia, phocomelia, radial aplasia), digestive tract, heart, eyes, ears, kidney, nervous system

Actions of Thalidomide Against Multiple Myeloma



Single-Agent Thalidomide in Recurrent/ Refractory Multiple Myeloma



Study	Patient Population	Dose	No. Pts.	Response Rate
Singhal	Refractory	200-800 mg/d	84	32%*
Barlogie	Advanced, refractory	200-800 mg/d	169	30%†
Grosbois	Advanced	200-400 mg/d	121	41% minor response

* >25% ↓ in paraprotein

† 2-yr event-free survival and overall survival rates of 20% and 48%, respectively

Clinical Experience With Thalidomide in Multiple Myeloma: Safety Summary



- **Generally well tolerated**
- **Major toxicities are nonhematologic**
 - Constipation
 - Fatigue/sedation
 - Skin toxicity/rash
 - Peripheral neuropathy
- **Dose reduction can often relieve symptoms yet remain effective**

Thalidomide With Melphalan and Prednisone in Elderly Patients With MM

Phase III Randomized Controlled Trial

Newly
diagnosed MM patients,
aged >65 yr
(n=255 as of 3/05)

MPT Arm (Median age 72)

Melphalan, 4 mg/m² (7 days/mo)

Prednisone, 40 mg/m² (7 days/mo)

Thalidomide, 100 mg/d (continuously)*

(n=129)

→ ×6 courses

MP Arm (Median age 72)

Melphalan, 4 mg/m² (7 days/mo)

Prednisone, 40 mg/m² (7 days/mo)

(n=126)

*Thalidomide dose reduced to 50% if grade 2 toxicity enoxaparin prophylaxis added to protocol December 2003. Follow-up ≥6 mos.

Palumbo A et al. *Blood*. 2005;106:230a [abstract 779]

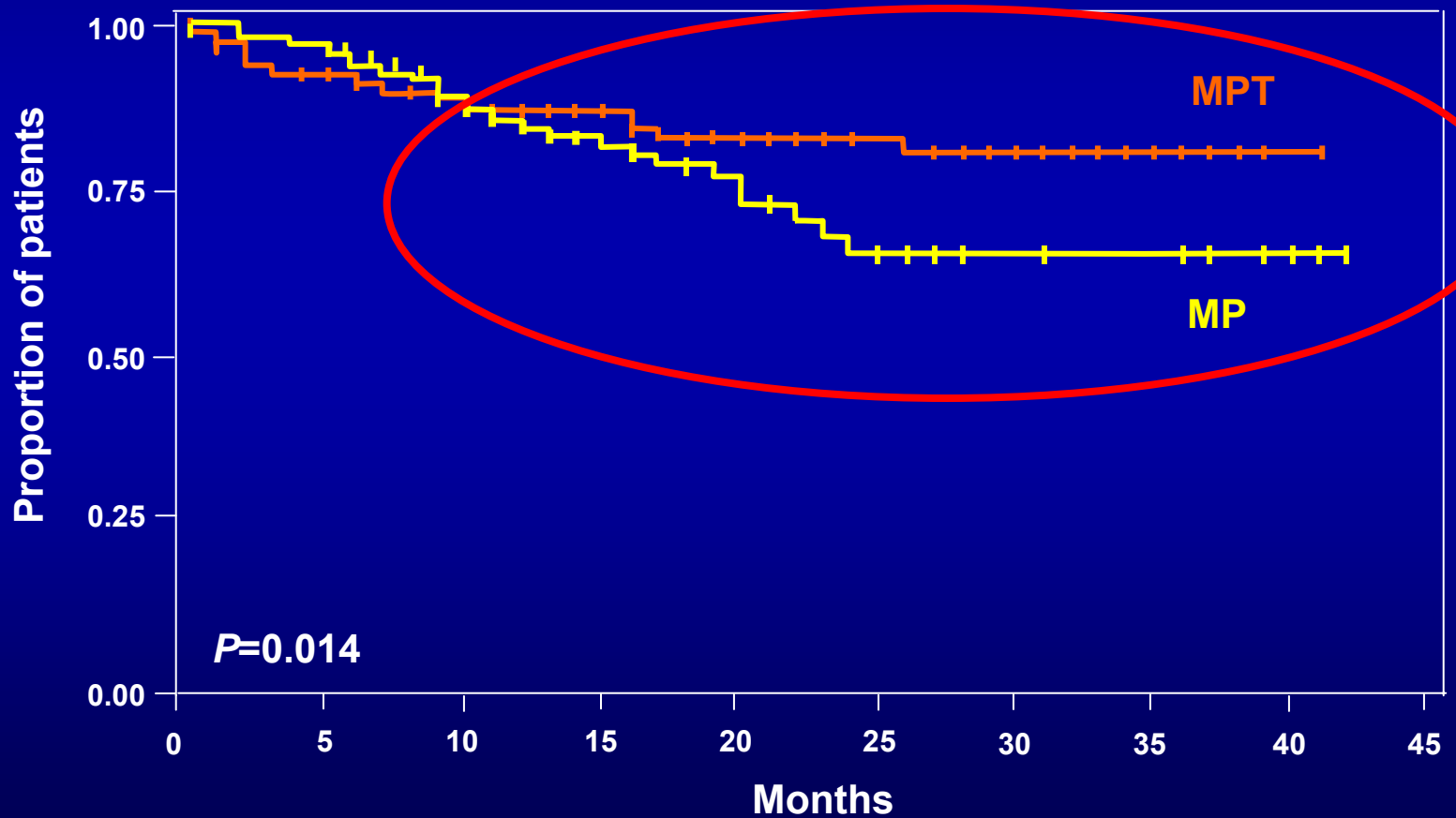
MPT in Elderly Patients With MM: Response

Response	MPT, % (n=129)	MP, % (n=126)	P value
CR + nCR	28	7	<0.001
CR	16	2	
nCR	12	5	
PR	60	45	
ORR	76	47	<0.001
Median EFS, mo	29.2	13.6	<0.001
OS at 36 mo	80	64	NS
0-9 mo			NS
9-40 mo			<0.02

PR (>50%), nCR (IF+), CR (IF-)

MPT vs MP: Overall Survival

65% decrease in the risk of death after 9 months



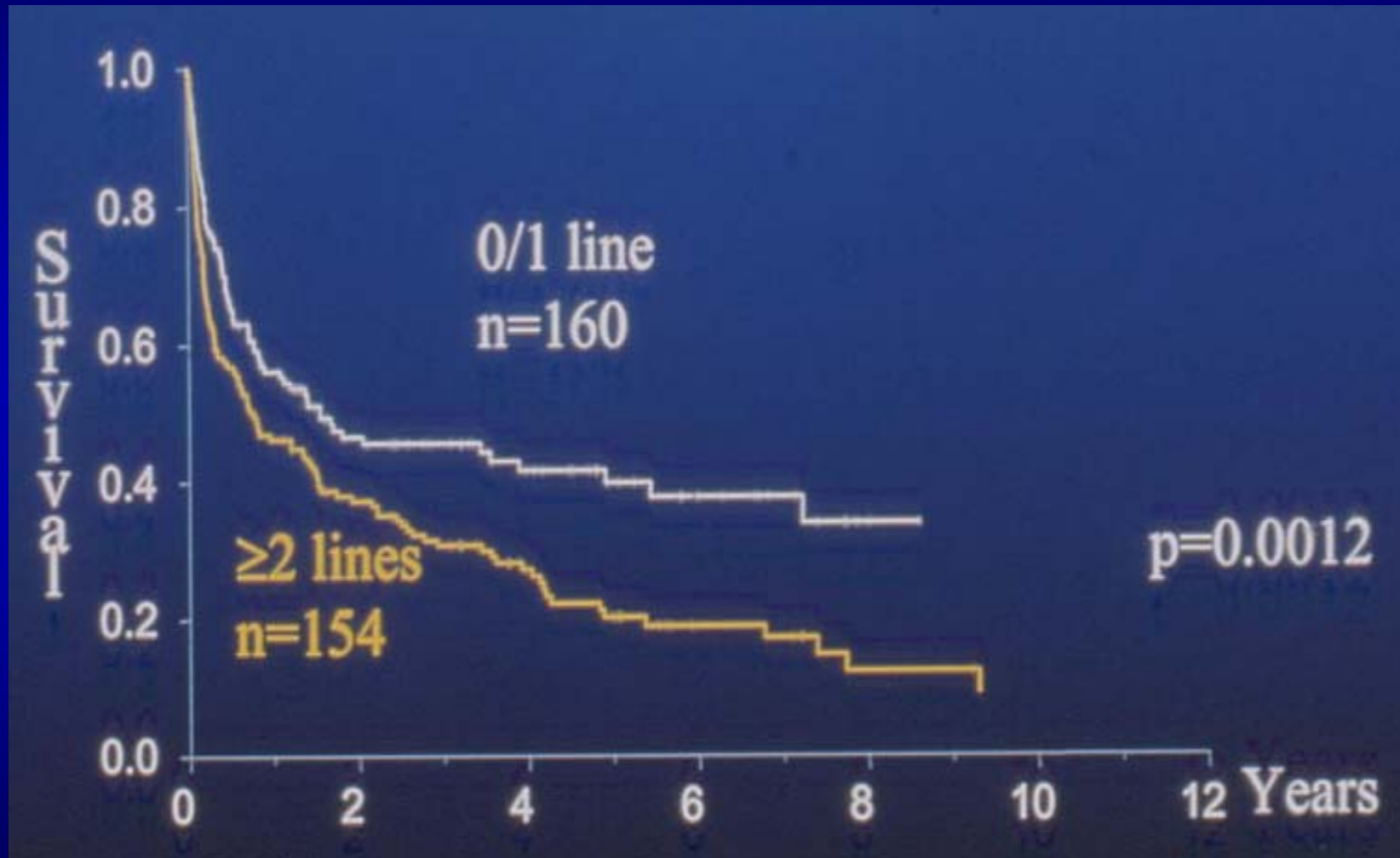
Multiple Myeloma

Rationale for High Dose Therapy



- **Myelosuppression is limiting for most standard chemotherapy regimens**
 - Dose intensity of standard chemotherapy can only be increased a couple fold even with growth factors
- **Multiple myeloma may be curable**
 - Long term survivors following syngeneic bone marrow transplantation

Multiple Myeloma Allogeneic Transplantation: Survival



EBMT Data 2001

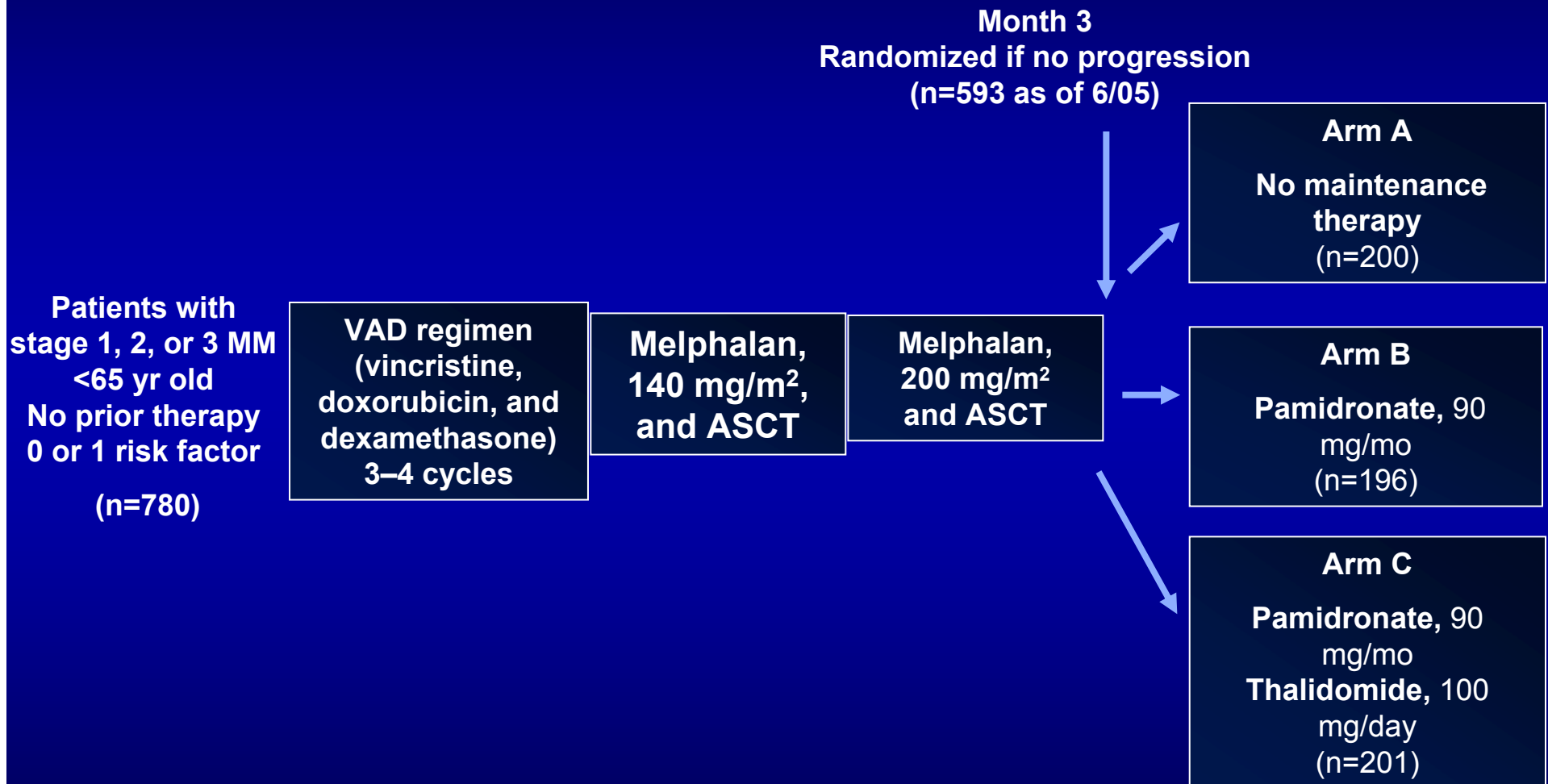
French Randomized Comparison of Conventional Therapy to High-Dose Therapy in Myeloma

- Attal et al, NEJM 1996
- Conventional dose arm
 - VMCP alt BVAP X 12 → INF
- High-Dose Arm
 - VMCP alt BVAP X 4-6
 - Mel 140, 800cGy TBI, BMT
 - INF

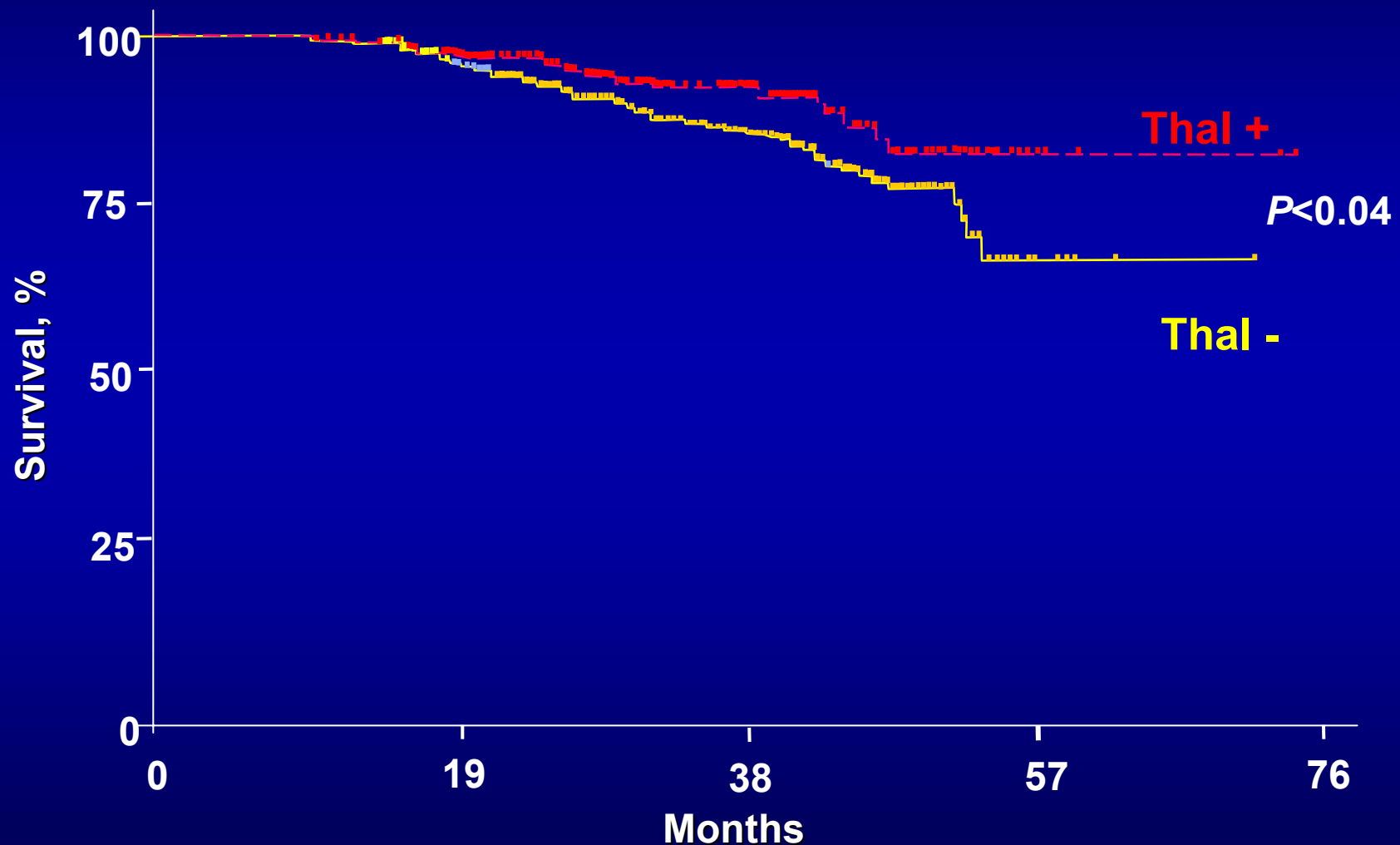
- HDC Superior (p=0.03)

– Survival	Conventional	BMT
– 5-yr EFS	10%	28%
– 5-yr OS	38%	52%
– 7-yr EFS	8%	16%
– 7-yr OS	25%	43%

Maintenance With Thalidomide After ASCT for MM (IFM 99 02)



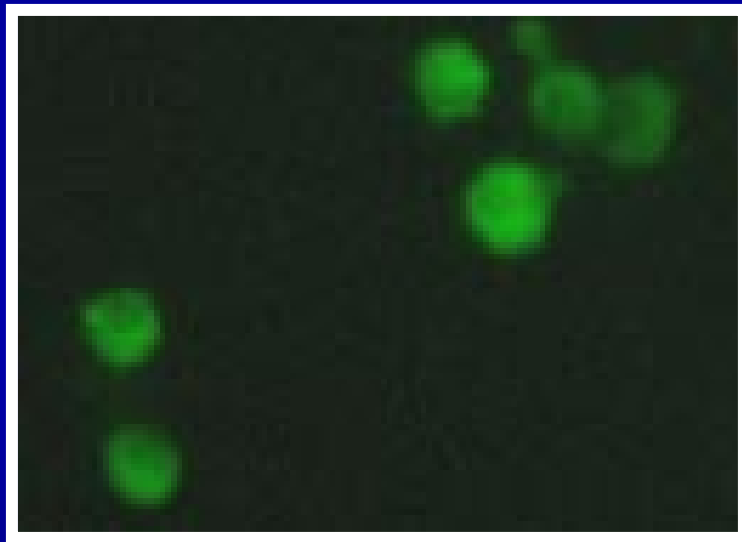
Maintenance With Thalidomide After ASCT for MM (IFM 99 02): Overall Survival



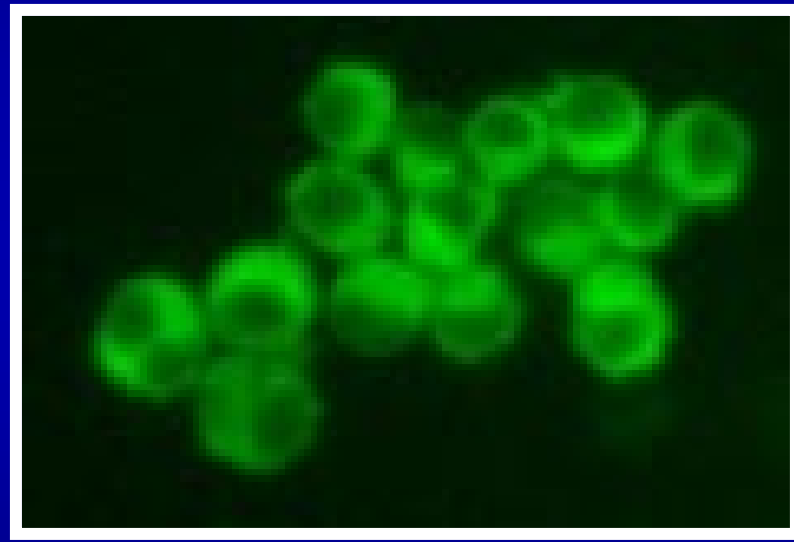
Attal M et al. *Blood*. 2005;106:335a [abstract 1148]

Bortezomib Reduces the Translocation of NF- κ B to the Nucleus in a Myeloma Cell Line

Stain for NF- κ B



ARH77



ARH77 + Bortezomib

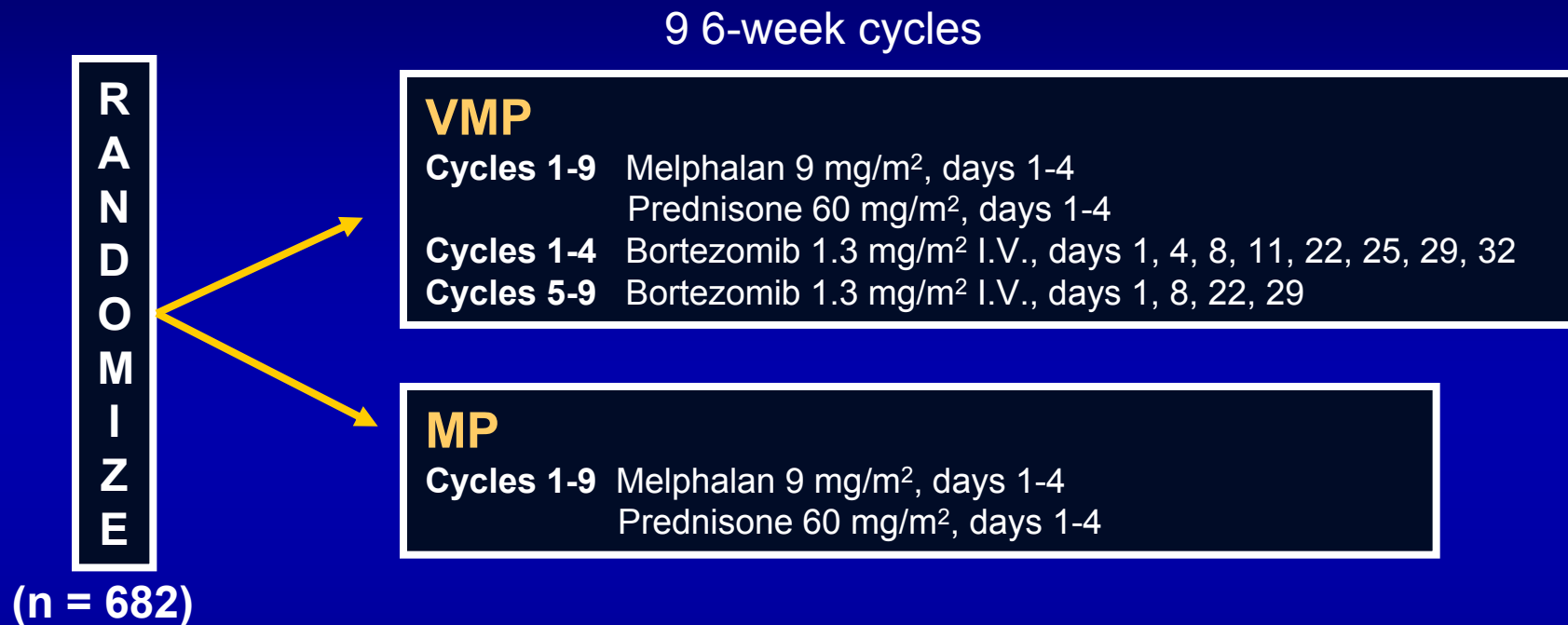
Frequency, Characteristics, and Reversibility of PN in the APEX trial



▶ PN Reversibility

- PN is reversible in the majority of pts: 64% (58/91) of pts with \geq Grade 2 PN experienced improvement or resolution
 - 55% (50/91) had complete resolution (return to baseline)
 - 9% (8/91) experienced improvement by at least one CTC grade
- Median time to improvement or resolution was 110 days from initial diagnosis

Phase III Trial of Melphalan/Prednisone \pm Bortezomib in MM



Primary endpoint:

Time to progression

Secondary endpoints:

Response rate

Time to response

Duration of response

Progression-free survival

Overall survival

Melphalan/Prednisone ± Bortezomib: Efficacy

	VMP	MP
Time to Progression	24 months	16.6 months
	HR 0.483; <i>P</i> < .000001	
Progression-Free Survival	HR 0.609; <i>P</i> = .00001	
Overall Survival	Not reached (45 deaths)	Not reached (76 deaths)
	HR 0.607; <i>P</i> = .0078	
Time to Next Treatment	Not reached	20.8 months
	HR 0.522; <i>P</i> = .000009	
Complete Response	35%	5%
	Odds ratio 11.2; <i>P</i> < .000001	
Duration of Complete Response	24 months	12.8 months

Phase II MM Trial of Bortezomib/Dexamethasone With Cyclophosphamide Then Thalidomide as Frontline Therapy

Newly Diagnosed
Symptomatic Myeloma

3 - 21-Day Cycles

Bortezomib 1.3 mg/m², days 1, 4, 8, 11
Cyclophosphamide 300 mg/m², days 1 and 8
Dexamethasone 40 mg, days 1, 2, 4, 5, 8, 9,
11, 12

3 - 21-Day Cycles

Bortezomib 1.0 mg/m², days 1, 4, 8, 11
Thalidomide 100 mg/day
Dexamethasone 40 mg, days 1, 4, 8, 11

- Primary endpoints:
 - Response rate
 - Achieve \geq CR/nCR of \geq 40%
- Secondary endpoints:
 - Safety, tolerability, and VGPR rate vs. bortezomib/dexamethasone

Bortezomib/Cyclophosphamide/Dexamethasone With or Without Thalidomide: Efficacy and Toxicity

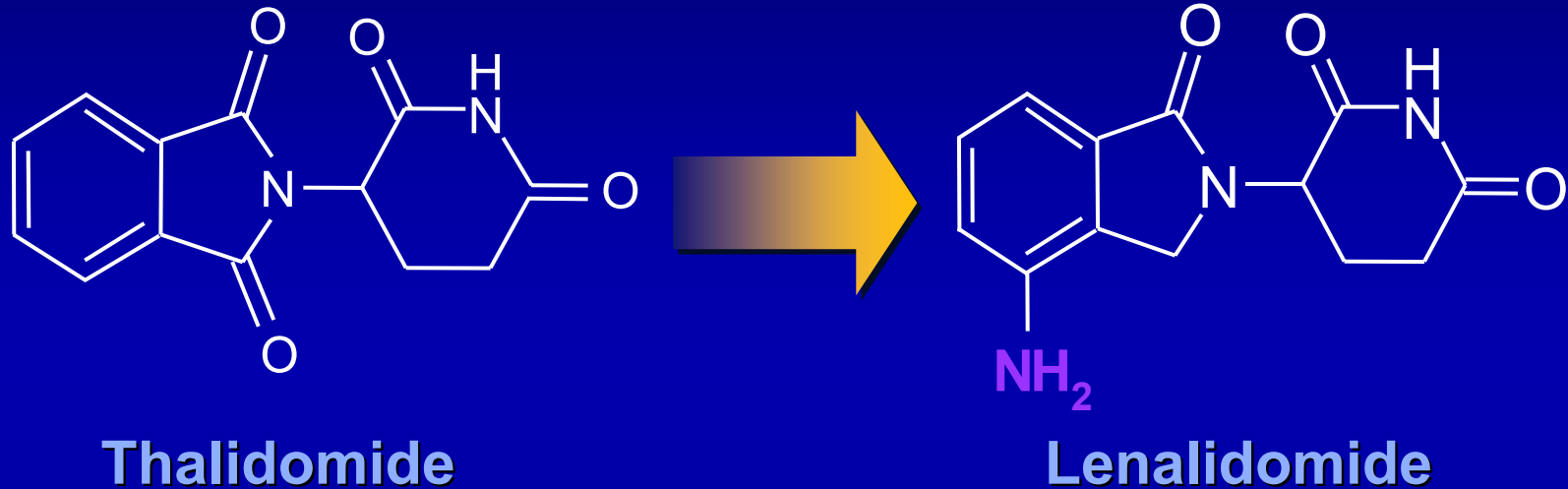
Efficacy	BCD	BCD + BDT
Overall Response Rate	92%	92%
CR/nCR rate	19%	42%
VGPR rate	35%	19%
PR rate	38%	31%

Grade ≥ 2 Adverse Events	First 26 Patients
Bortezomib	
Neuropathy	5 (20%)
Thalidomide	
Neuropathy	4 (15%)
Dexamethasone	
Insomnia/hyperglycemia	15%
Cyclophosphamide	
Neutropenia/pneumonia	12%

No treatment-related mortality

Jagannath *et al*, Abstract 188, ASH 2007

Lenalidomide: Pharmacologic Evolution

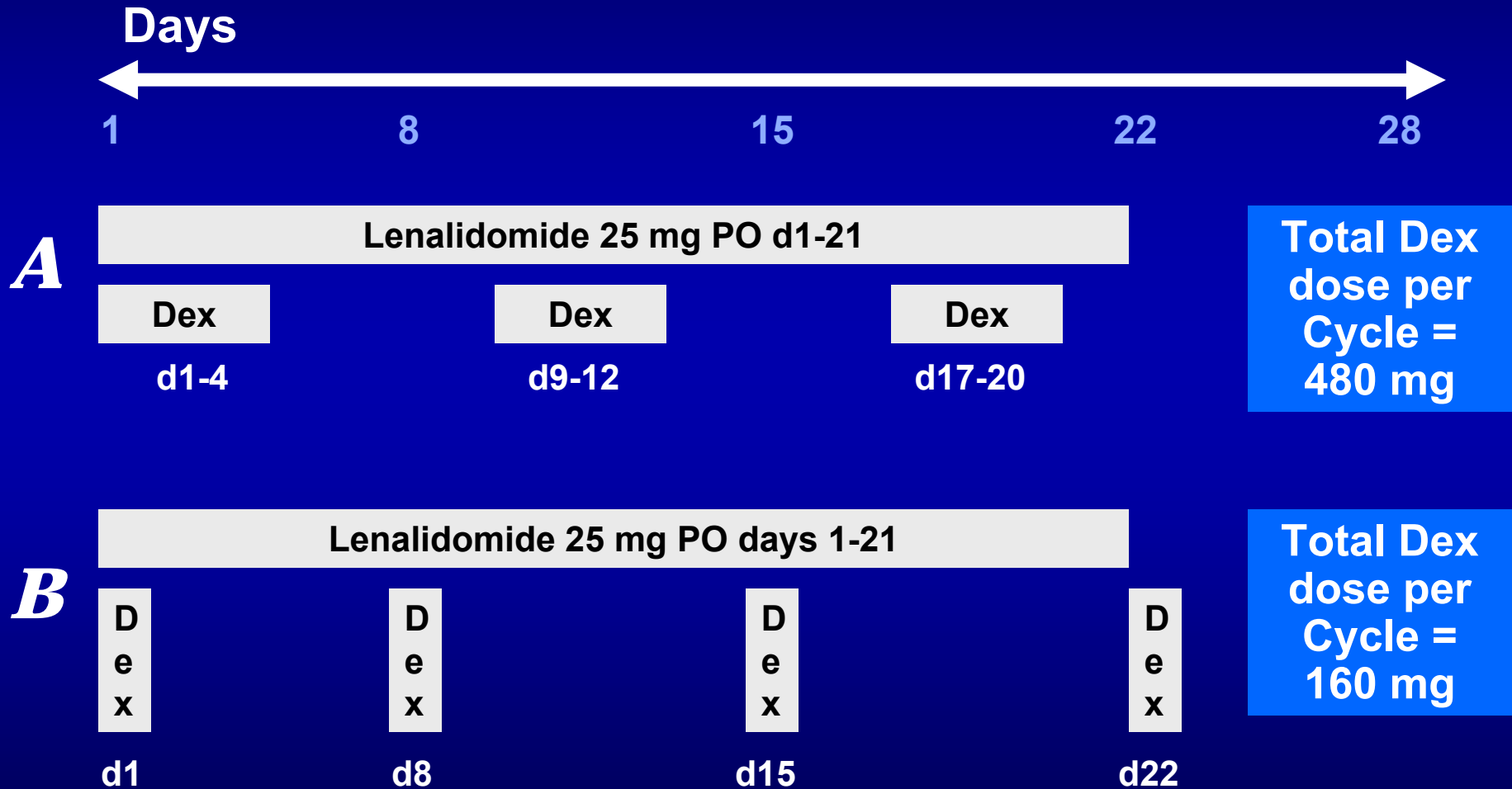


- **More “potent” immunomodulator than thalidomide**
 - Up to 50,000 times more potent inhibitor of $\text{TNF}\alpha$
 - Increased stimulation of T-cell proliferation
 - Augmented stimulation of IL-2 and $\text{IFN}\gamma$ production

Bartlett JB et al. *Nat Rev Cancer*. 2004;4:314

Stirling D. *Semin Oncol*. 2001;28:602

E4A03: Phase III trial of Lenalidomide plus Either High-dose or Low-dose Dexamethasone in Newly Diagnosed MM: Schema

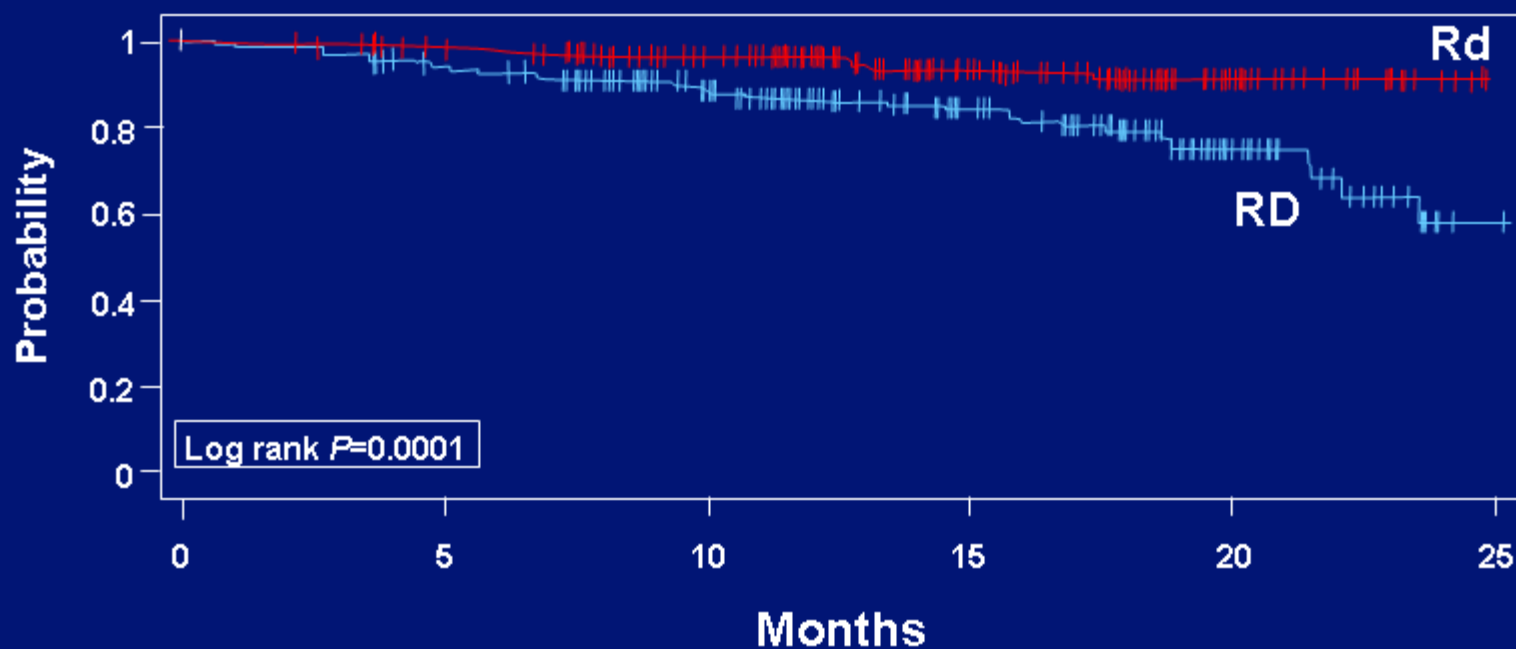


Serious Adverse Events Non-Hematologic Toxicity



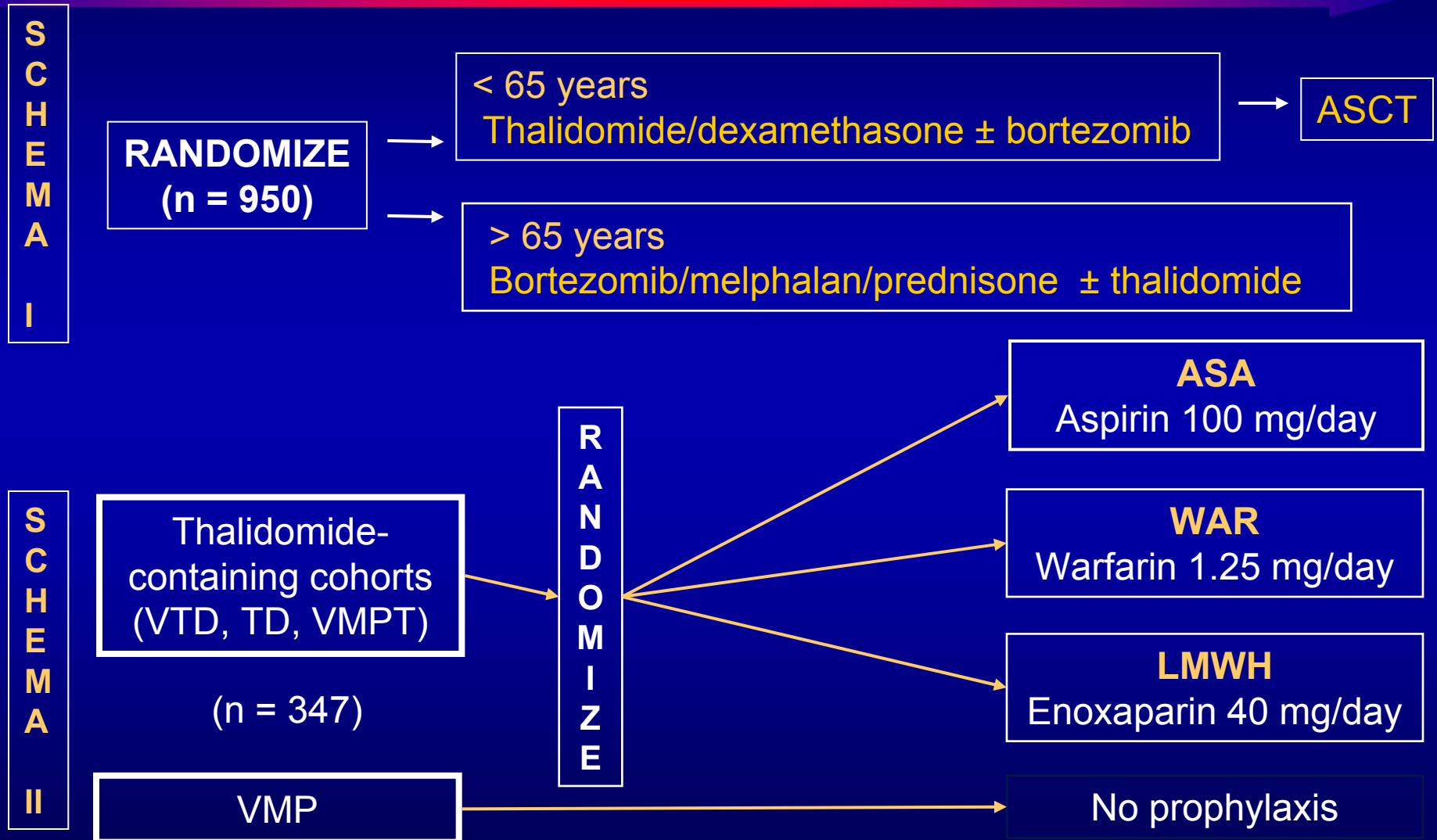
Toxicity (N=433 Ever Reported)	Arm A High Dose Dex (N=217)	Arm B Low Dose Dex (N=216)	P value
DVT/PE (AdEERS*)	23.8%	9.1%	<0.001
Infection/Pneumonia	14.7%	5.1%	<0.001
Hyperglycemia	9.7%	6%	0.05
Cardiac ischemia	2.8%	0.5%	0.05
Atrial fibrillation/flutter	2.3%	0.5%	0.09
Neuropathy	1.4%	0.9%	0.31

E4A03: Overall Survival on Len/Std-Dose Dex (RD) and Len/Low-Dose Dex (Rd)



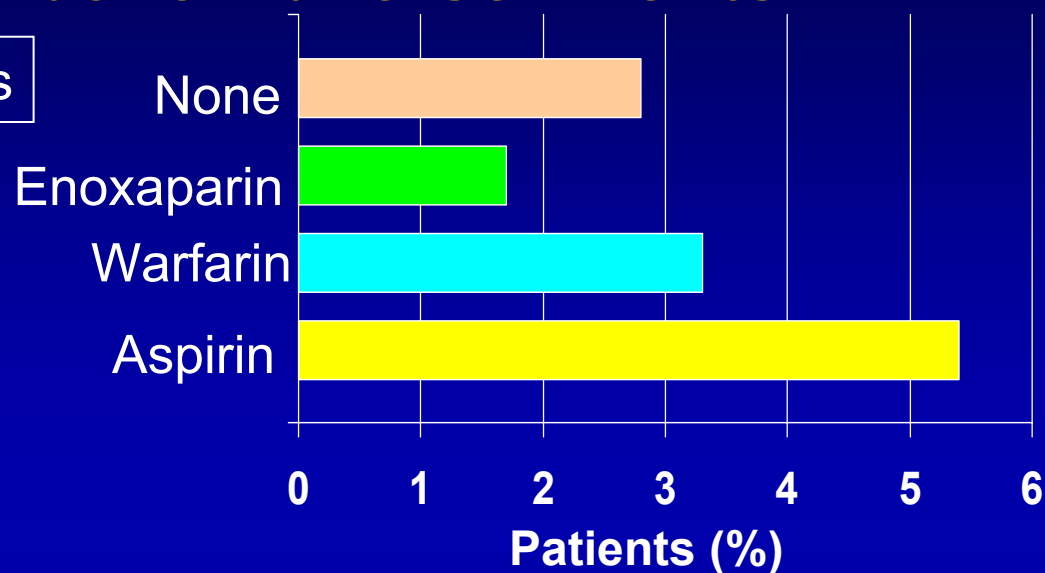
	No. of Subjects	Event	Censored	Median Survival (95% CI)
RD	223	18% (41)	82% (182)	NA (23.56 NA)
Rd	222	6% (13)	94% (209)	NA (NA NA)

Phase III Trial of Enoxaparin Versus Aspirin Versus Warfarin (GIMEMA): Newly Diagnosed

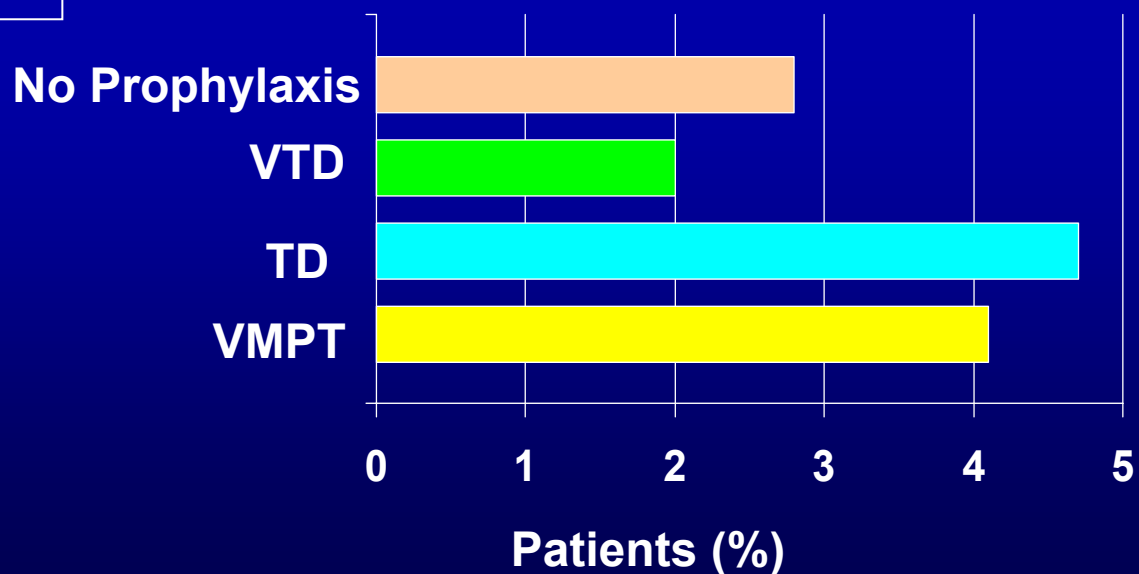


Aspirin/Warfarin/Enoxaparin: Grade 3/4 Thromboembolic Adverse Events

By Prophylaxis



By Regimen



Primary Amyloidosis Treatment



- **Treatments mirror (although lag) those for multiple myeloma**
 - Etiologies similar
 - Patients tend to tolerate treatment less well
 - Disease less common so randomized studies difficult
- **Must reduce production of pathogenic amyloid Ig protein**
 - Treat monoclonal proliferation of pre-malignant plasma cells
- **If protein production falls, disease pace will slow**
 - Follow paraprotein levels in blood or urine
- **Clinical improvement may take months following successful reduction in serum/urine paraprotein**
- **Clinical symptoms related to protein already in organ tissue**

Multiple Myeloma Treatment Conclusions



- Initial therapy improving (RR 90%, 1 yr OS = >95%)
 - Lenalidomide and Bortezomib containing regimens
- Stem Cell Transplant is still treatment of choice for patients < 65 years of age
 - Large studies with > 85% four year survival
 - Bortezomib + Dex superior to VAD (and ? Thal/Dex)
- Older Patients
 - MPT or Lenalidomide + dex (Bortezomib if renal failure)
- Maintenance therapy
 - Combination of thalidomide + steroids better
 - ? Lenalidomide + steroids

Osteonecrosis of the Jaw (ONJ): Clinical Presentation



Clinical Features of Suspected ONJ

- Exposed bone in maxillofacial area that occurs in association with dental surgery or occurs spontaneously, with no evidence of healing*

Working Diagnosis of ONJ

- No evidence of healing after 6 weeks of appropriate evaluation and dental care
- No evidence of metastatic disease in the jaw or osteoradionecrosis

*Refer for appropriate dental evaluation and care as soon as possible.

Incidence of Osteonecrosis of the Jaw (ONJ) in Multiple Myeloma



- ASH Abstract #637 *Blood*, 106(11) 2005
- Meletios Dimopoulos, Efsthios Kastritis, Lia Moulopoulos et.al., Athens, Greece
- Study Group: **137 patients treated with bisphosphonates**
 - Treated since 1995 with minimum 6 mos. treatment
 - Zoledronic Acid = 50 patients
 - Pamidronate + Zoledronic Acid = 50 patients
 - Pamidronate = 29 patients
 - Bondronate = 2 patients
 - Other combination = 5 patients
- Prospective study after initial patient developed a diagnosis of ONJ

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- Ten patients (6.7%) developed ONJ
- Median number of treatment cycles with a bisphosphonate higher in those with ONJ ($p=0.05$)
 - ONJ Diagnosis (36 infusions)
 - No ONJ present (19 infusions)
- Cumulative hazard increased with duration of treatment
 - 0% if bisphosphonate treatment < 1 year
 - 13% if bisphosphonate treatment > 5 years
- Higher risk with zoledronic acid use ($p=0.022$)
 - No cases occurred in patients using pamidronate alone
- Seven of ten cases occurred in an area of prior dental extraction