

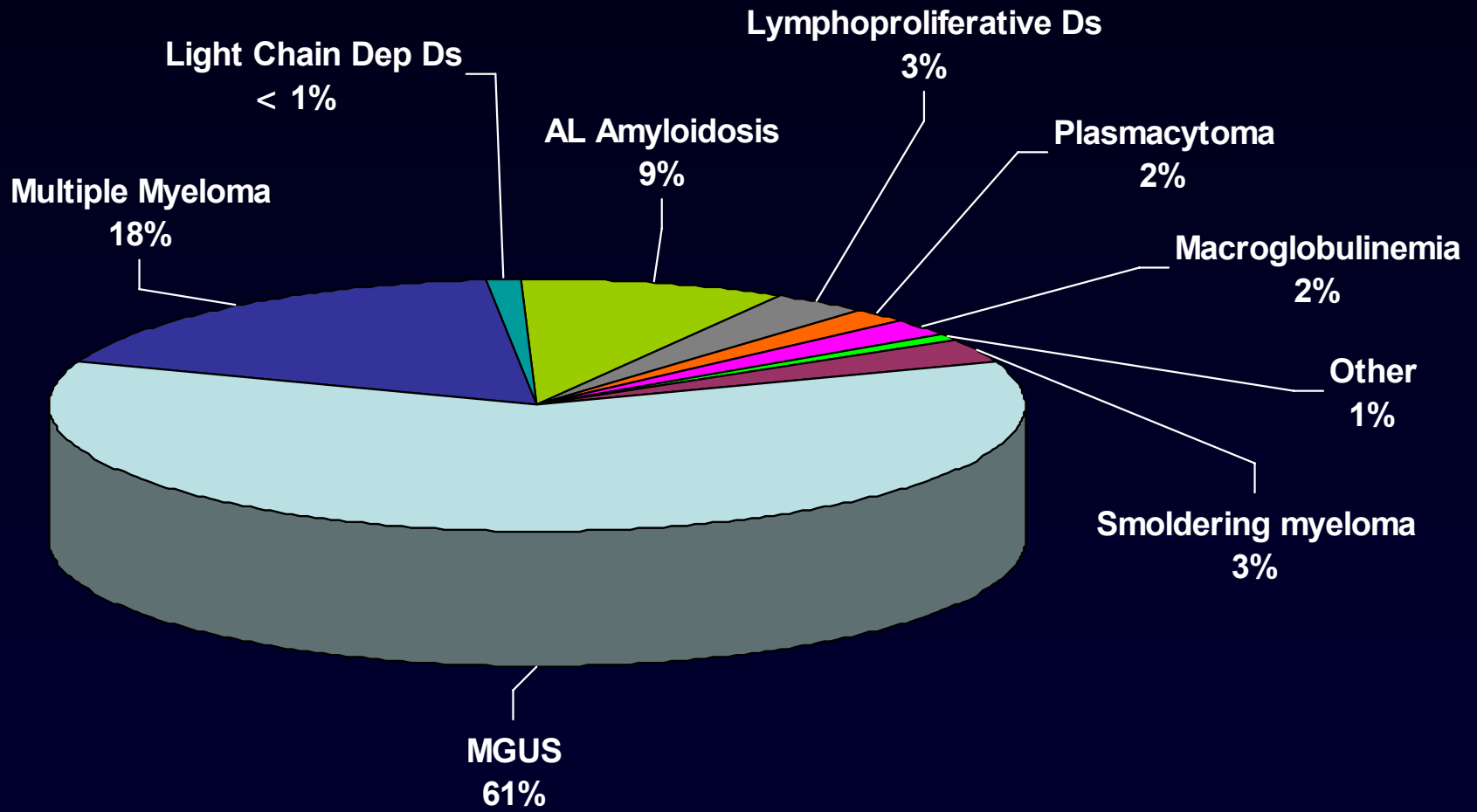
Strategies for Optimizing Outcomes in Multiple Myeloma and Other Monoclonal Gammopathies

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Cancer Hospital, Blood and Marrow Transplant and
Myeloma Program

Monoclonal Gammopathies^{1,2}



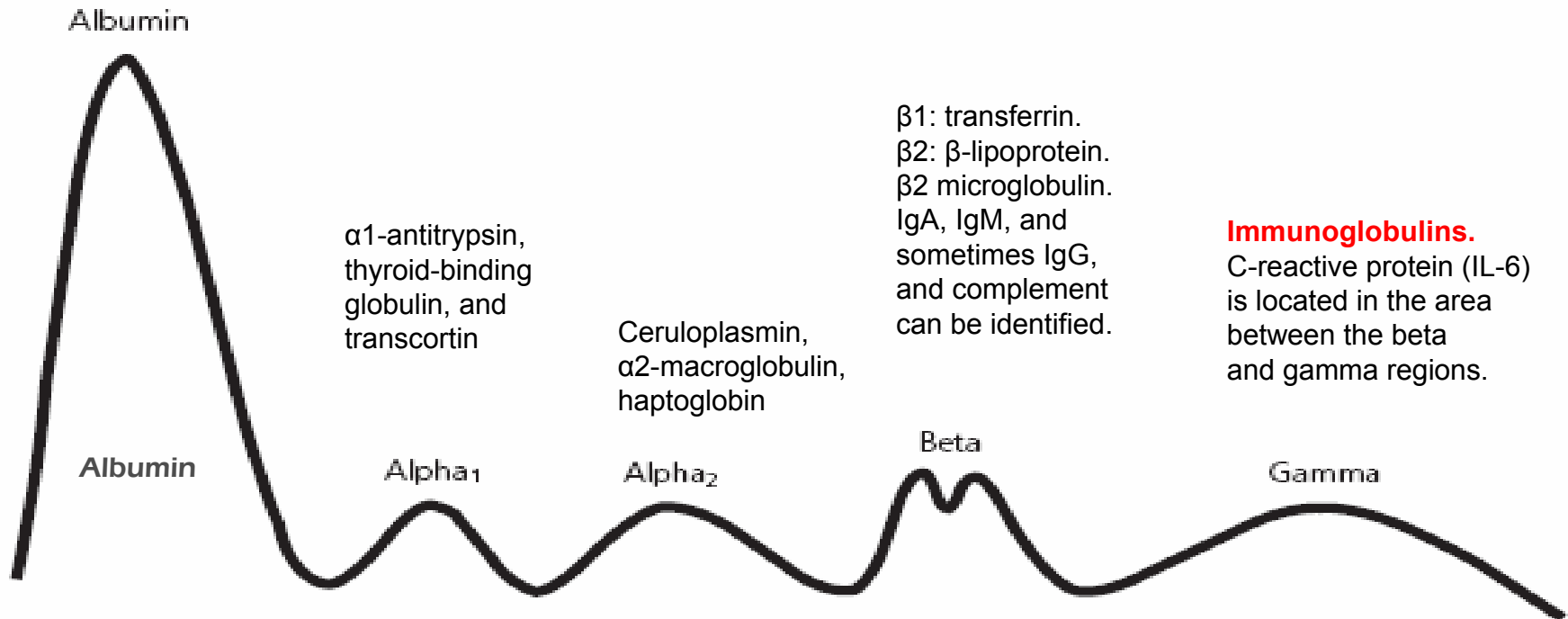
N = 29,528
Mayo Clinic Database 1960–2002

¹Katzmann JA. *Clin Lab News*. June 2006.
²Katzmann et al. *Clin Chem*. 2005;51:878-81.

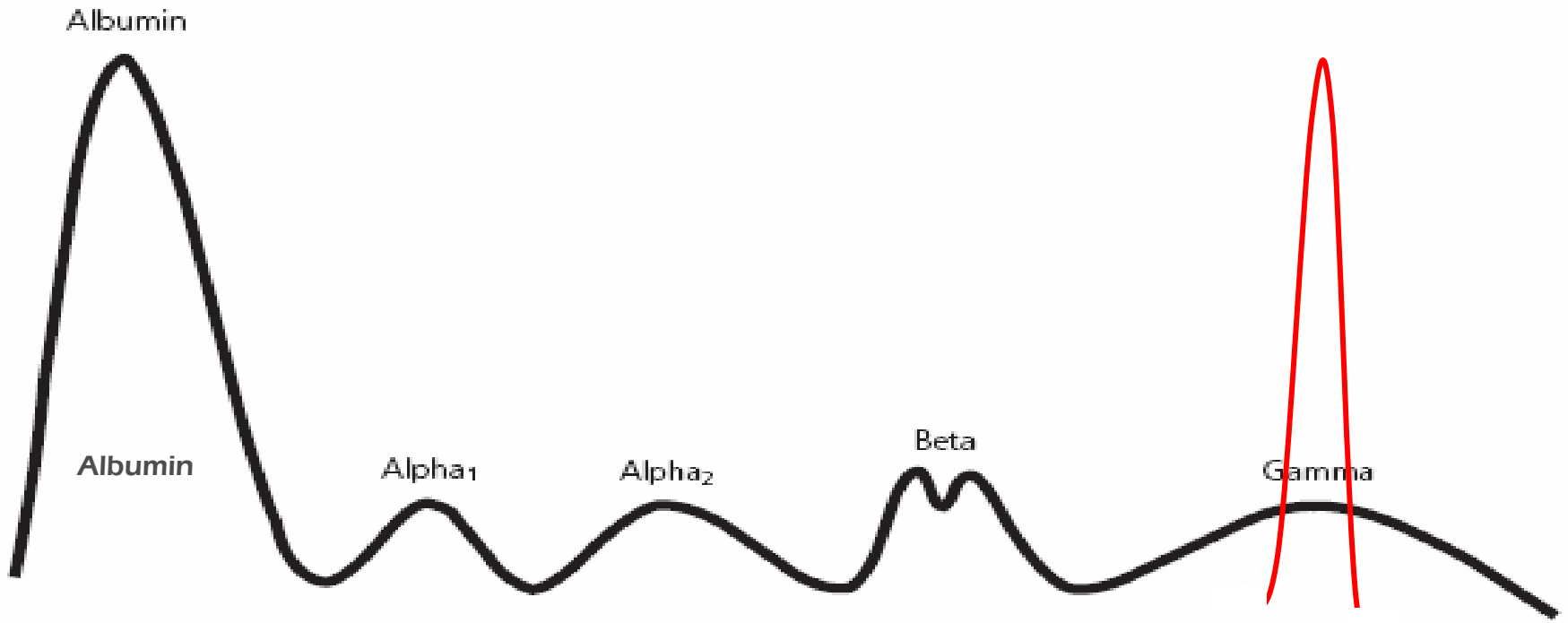
Evaluation of Monoclonal Protein

- Serum protein electrophoresis
- Immunofixation electrophoresis
- UPEP or uIFE on 24-h urine
- Serum free light chain assays

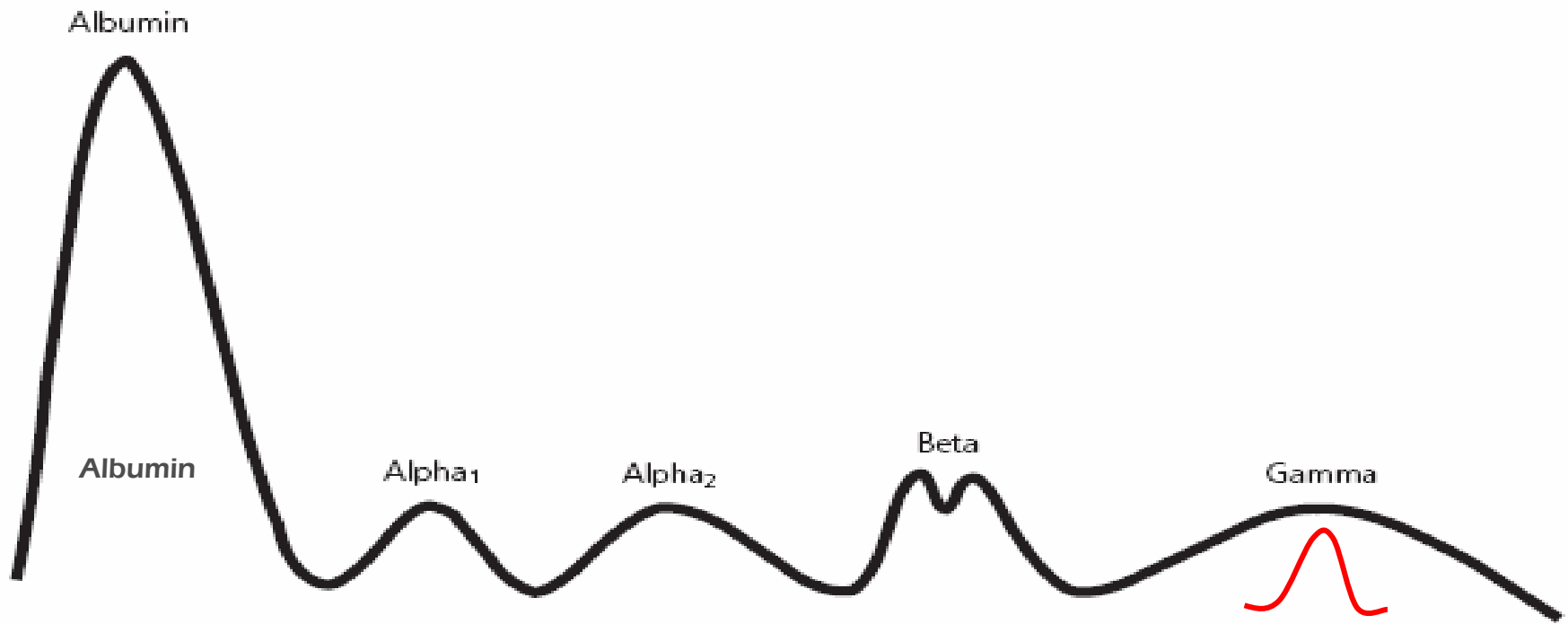
Normal Serum Protein Electrophoresis



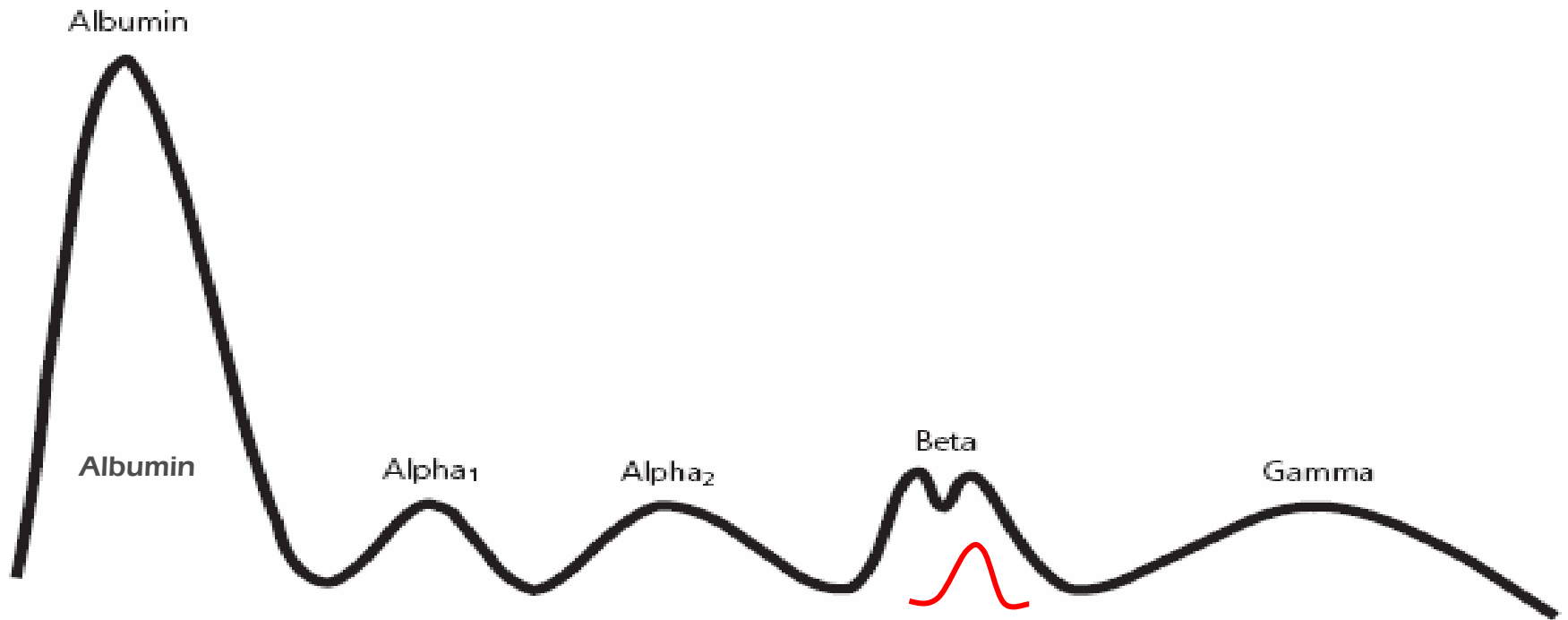
M-Spike on Serum Protein Electrophoresis



Insensitivity of Serum Protein Electrophoresis



Insensitivity of Serum Protein Electrophoresis



Sensitivity of SPEP

Myeloma¹ LCMM² AL Amy³ LCDD⁴ NSMM

**SPEP
alone**

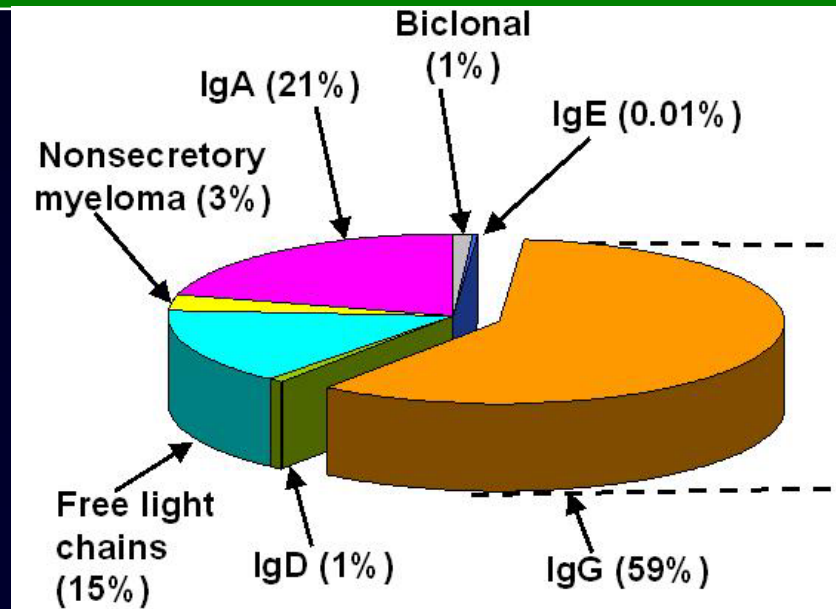
82%

45%

50%

≤ 25%

0%



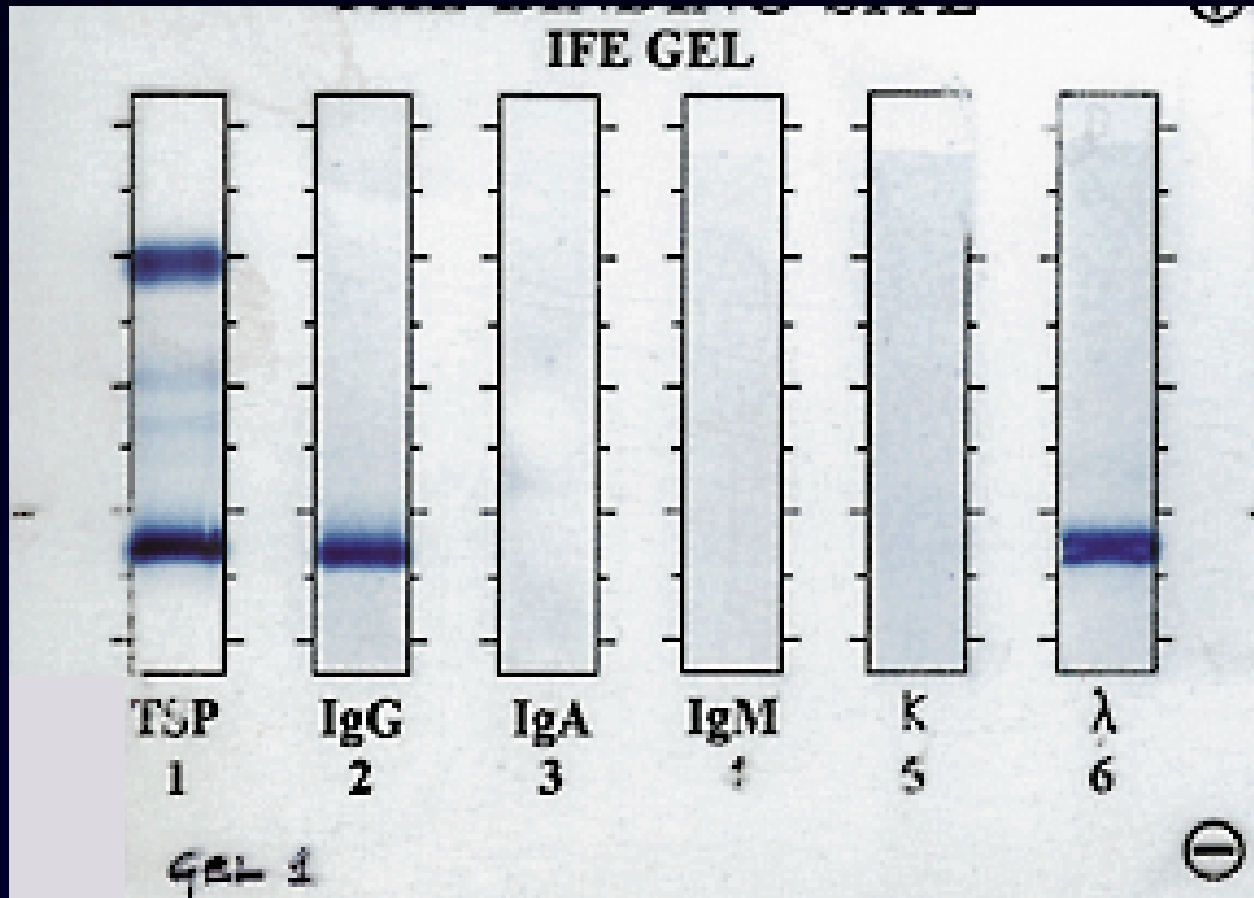
¹Kyel et al. *Mayo Clin Proc.* 2003; 78:21-33.

²Bradwell et al. *Lancet.* 2003; 361:489-491.

³Lachmann et al. *Br J Haematol.* 2003;122:78-84.

⁴Lin et al. *JASN.* 2001;12:1482-1492.

IFE - IgG λ



Immunofixation Electrophoresis

- Advantage: good sensitivity in serum (~150 mg/L) and urine (~20 mg/L)
- Disadvantages
 - Not quantitative
 - Positivity vs negativity: an “observer-dependent assessment”²
 - Manual inspection leads to variability in reported results for pts at or near CR
 - Proposal to refine response evaluation by combining CR + VGPR³

¹Sanders PW. *Lab Invest.* 1991;64:527-37.

²Durie et al. *Leukemia.* 2006;20:1467-73.

³Lonial S and Gertz M. *Blood.* 2008;111:3297-8.

Serum Free Light Chains Assays

- Highly sensitive automated assays for free light chains
- Normal reference intervals in serum¹
 - Kappa: 3.3–19.4 mg/L (0.33–1.94 mg/dL)
 - Lambda: 5.7–26.3 mg/L (0.57–2.62 mg/dL)
 - Kappa/Lambda ratio: 0.26–1.65
- “Measurable disease”: proposed as an abnormal ratio with a difference of 50 mg/L between involved and uninvolved free light chain²

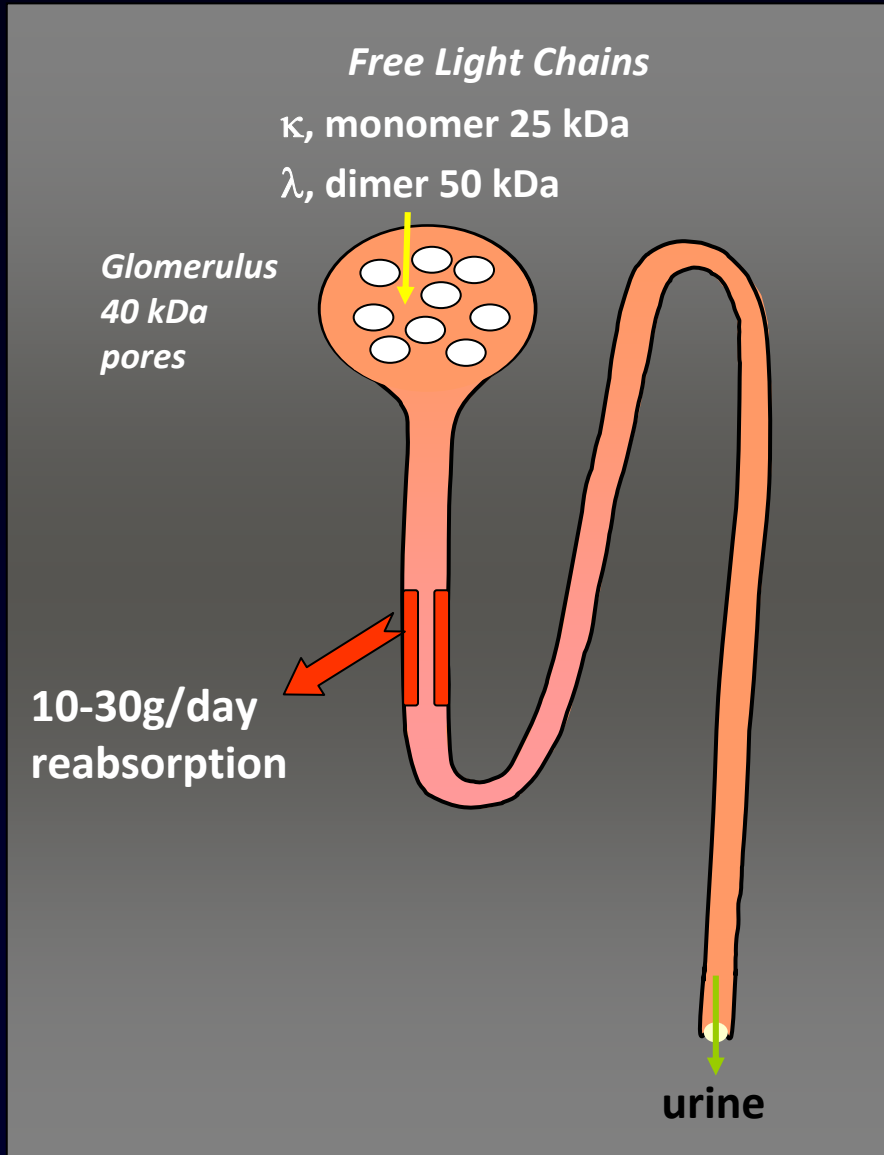
¹Katzmann et al. *Clin Chem.* 2002;48:1437–1444.

²Dispenzieri et al. *Blood.* 2008;111:4908-4915.

sFLC Sensitivity in Myeloma, AL, LCDD

Diagnosis	n	Abnormal FLC,		Reference
			%	
Multiple myeloma, NOS	488		96	Mead et al. 2004
Light chain myeloma	224		100	Bradwell et al. 2003
Light chain myeloma	28		100	Abraham et al. 2002
Nonsecretory myeloma	5		100	Katzmann et al. 2005
Nonsecretory myeloma	28		68	Drayson et al. 2001
AL amyloidosis	110		91	Katzmann et al. 2005
AL amyloidosis	262		98	Lachmann et al. 2003
AL amyloidosis	95		91	Abraham et al. 2003
Light chain deposition ds	7		100	Katzmann et al. 2005
Light chain deposition ds	19		89	Katzmann et al. 2002

Renal Handling of Free Light Chains



- FLCs in serum = production by tumor
- FLCs in urine = dept on renal function
- Serum and urine free light chain levels NOT similar during evolution and treatment of MM
- Serum is generally the more sensitive biosample for free light chains

International Guidelines for Diagnosis of Multiple Myeloma

1. M-protein in the serum and/or urine* by SPEP, 24-h UPEP, immunofixation, or an abnormal serum free light chain ratio
2. $\geq 10\%$ monoclonal plasma cells in the bone marrow [and/or presence of a biopsy-proven plasmacytoma]
3. Myeloma-related organ dysfunction (CRAB)
 - Hypercalcemia
 - Renal insufficiency
 - Anemia
 - Bone lesions (osteolytic lesions) or osteoporosis

*If none identified, need $\geq 30\%$ PC in BM or bx-proven plasmacytoma

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} MGUS if
< 3 g/dL

*If none identified, need $\geq 30\%$ PC in BM or bx-proven plasmacytoma

International Guidelines for Diagnosis of Multiple Myeloma

1. M-protein in the serum > 3 g/dL
2. $\geq 10\%$ monoclonal plasma cells in the bone marrow [and/or presence of a biopsy-proven plasmacytoma]
3. Myeloma-related organ dysfunction (CRAB)
 - Hypercalcemia
 - Renal insufficiency
 - Anemia
 - Bone lesions (osteolytic lesions) or osteoporosis

} Smoldering
myeloma
(1 and/or 2)

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Myeloma

*If none identified, need $\geq 30\%$ PC in BM or bx-proven plasmacytoma

Categories of MM¹

Classification	Characteristics	Management
MGUS (Rule of 1/3's)	<ul style="list-style-type: none">• Serum M protein <3 g/dL• Bone marrow plasma cells <10%• Absence of anemia, renal failure, hypercalcemia, and lytic bone lesions	Observation

MGUS Prevalence and Risk of Progression

- Among 21,463 residents of Olmsted County, MN, MGUS was identified in
 - 3.2 % of persons \geq 50 years of age
 - 5.3 % of persons \geq 70 years of age¹
- Prevalence of MGUS: 3-fold higher in African Americans²
- Rate of progression: 1% per year³
- Rate unchanged with time \rightarrow indefinite follow-up
- Risk assessment strategies desirable

¹Kyle et al. *N Engl J Med.* 2006;354:1362-9.

²Landgren et al. *Blood.* 2006;107:904–906.

³Kyle et al. *N Engl J Med.* 2002;346:564-9.

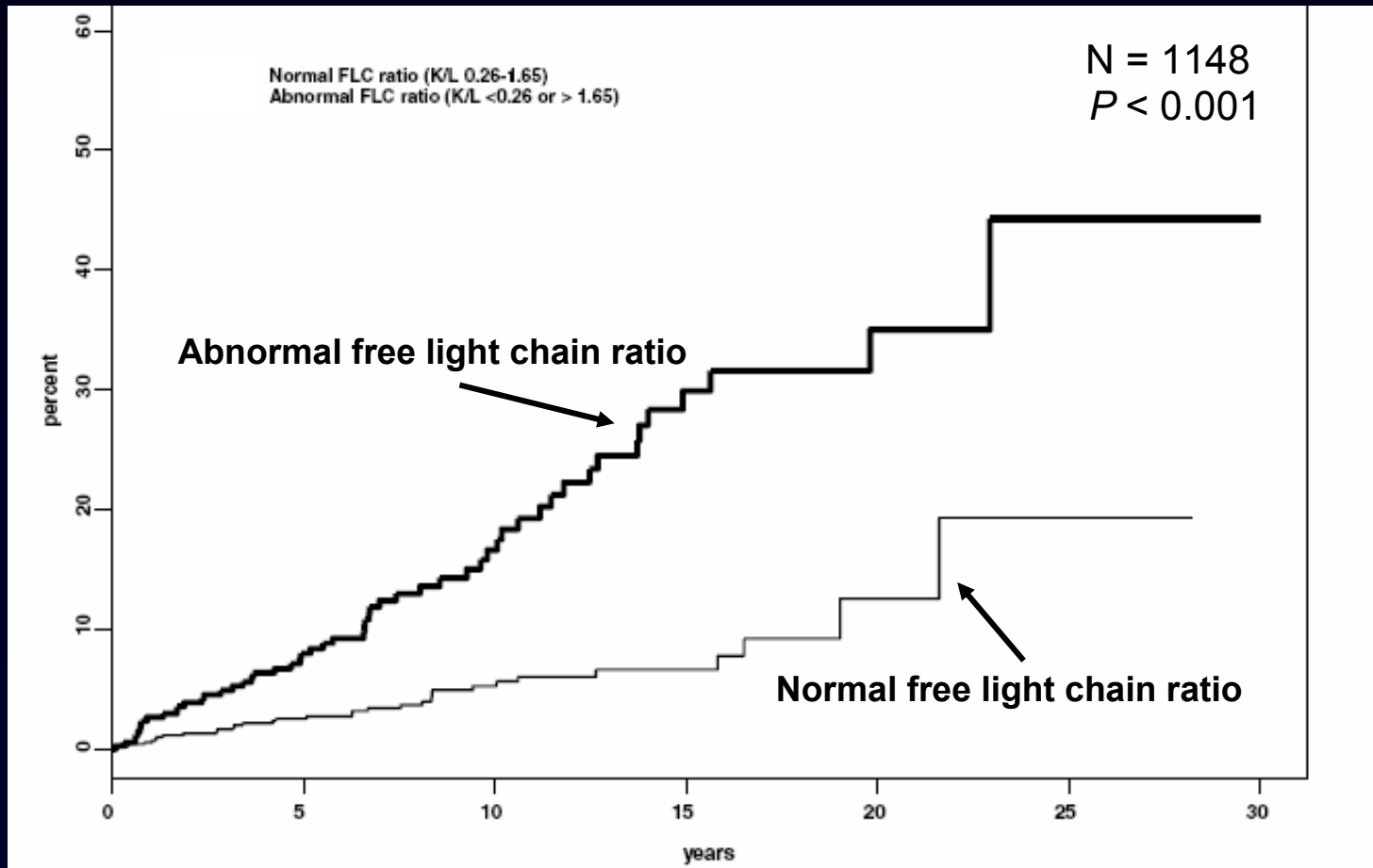
MGUS Risk Stratification Incorporating 3 Risk Factors

Risk	No. of Patients	Relative Risk (95% CI)	Absolute Risk at 20 yrs
<u>Low</u> M-spike < 1.5 g/dL IgG subtype Normal FLC ratio	449	1	5%
<u>Low-intermediate</u> Any 1 factor abnormal	420	5.4	21%
<u>High-intermediate</u> Any 2 factors abnormal	226	10.1	37%
<u>High</u> All 3 factors abnormal	53	20.8	58%

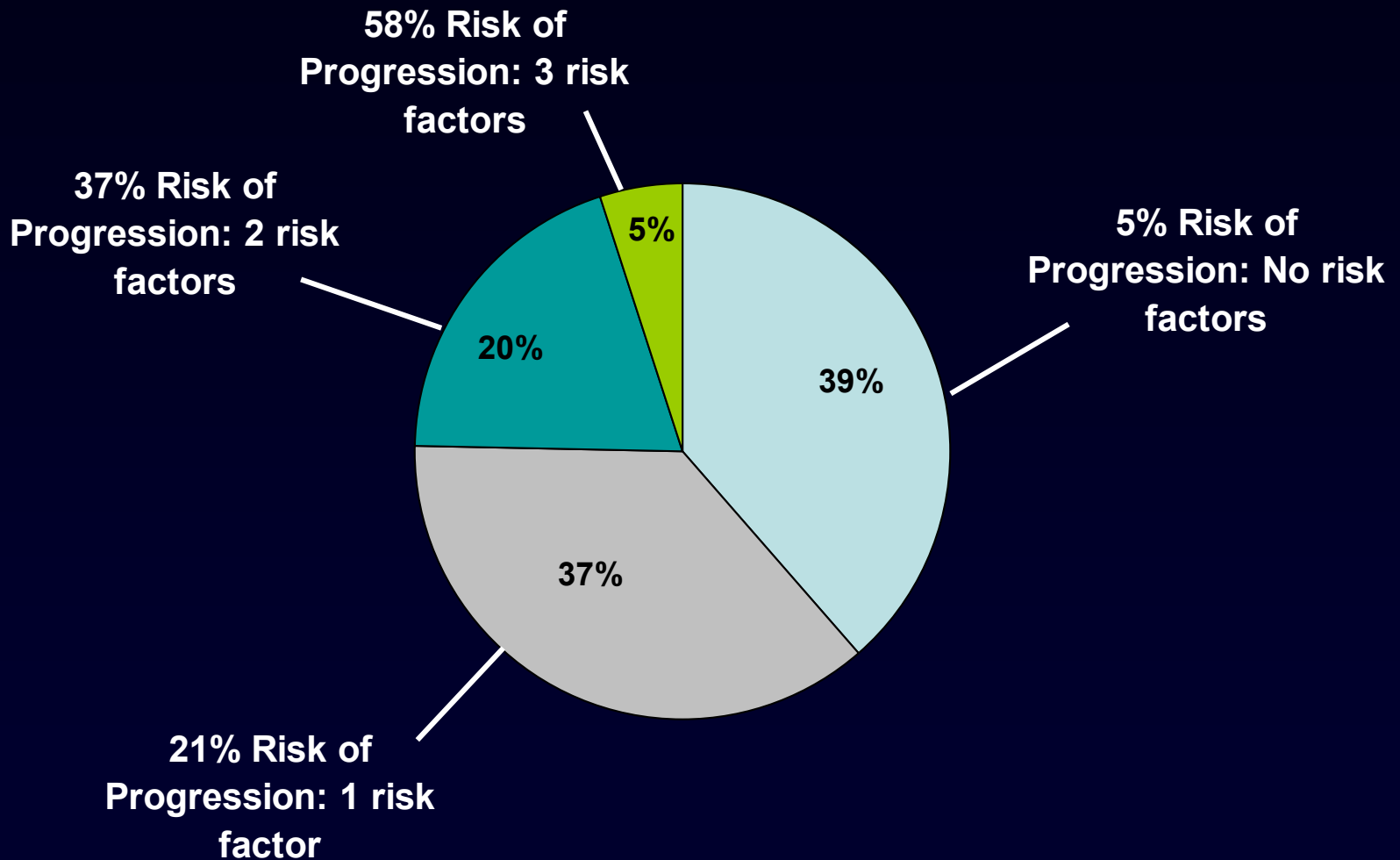
N = 1148

Risk of Progression from MGUS Based on an Abnormal Serum Free Light Chain Ratio

1/3 of pts with MGUS had abnormal sFLC ratio at baseline



Percentages in Risk Groups



MGUS Monitoring

- SPEP, sIFE and sFLC assays performed routinely at baseline
- More frequent monitoring warranted in patients with
 - Abnormal serum free light chain ratio
 - Non-IgG subtype
 - ≥ 1.5 g/dL M-protein
- Algorithm clinically recommended but not FDA-cleared

Categories of MM²

Classification

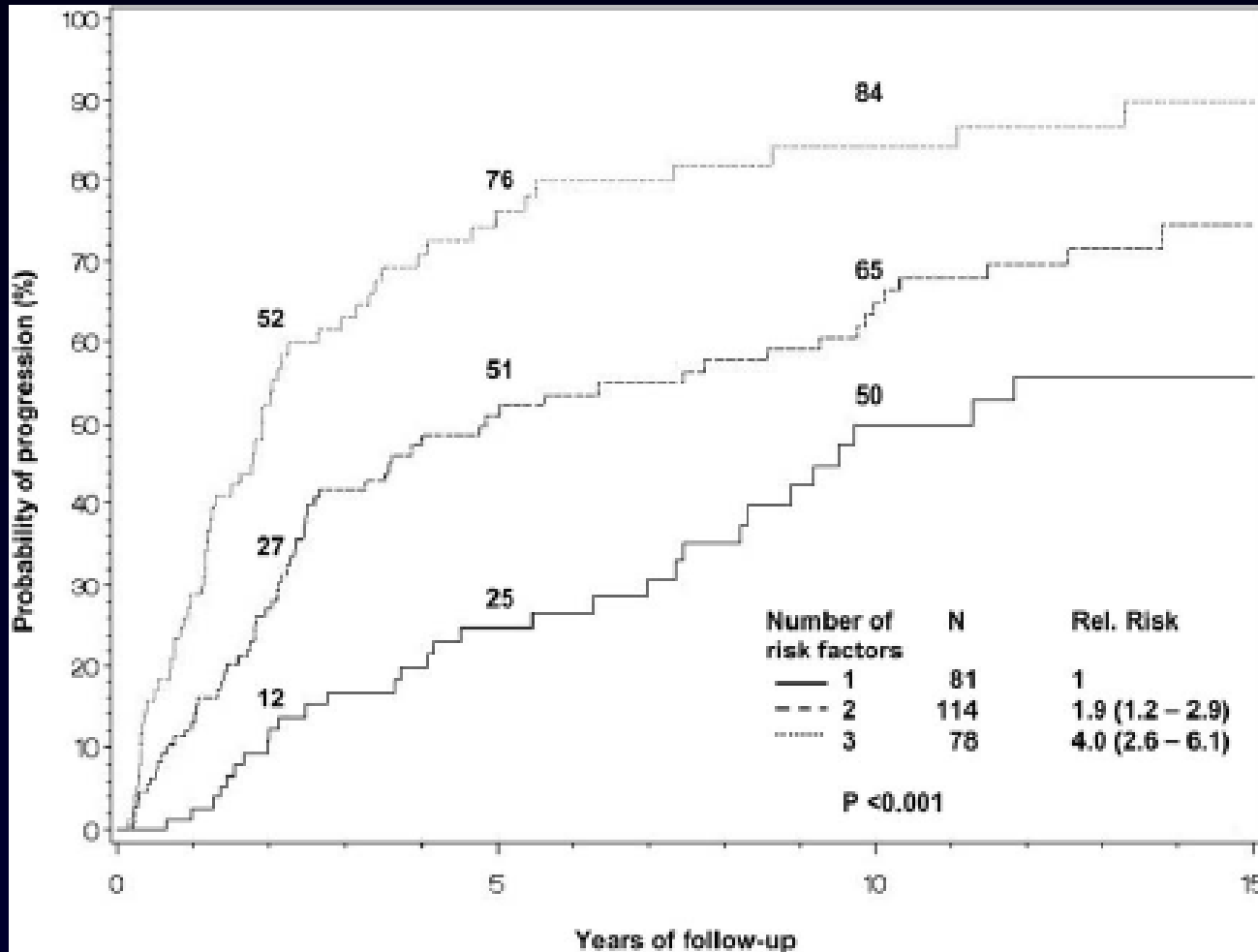
Characteristics

Management

Smoldering MM Serum M protein ≥ 3 g/dL *and/or*

- Bone marrow plasma cells $\geq 10\%$
 - Absence of anemia, renal failure, hypercalcemia, and lytic bone lesions
Observation, with treatment beginning at disease progression
-

Smoldering Myeloma: Risk Stratification Model, Mayo Clinic

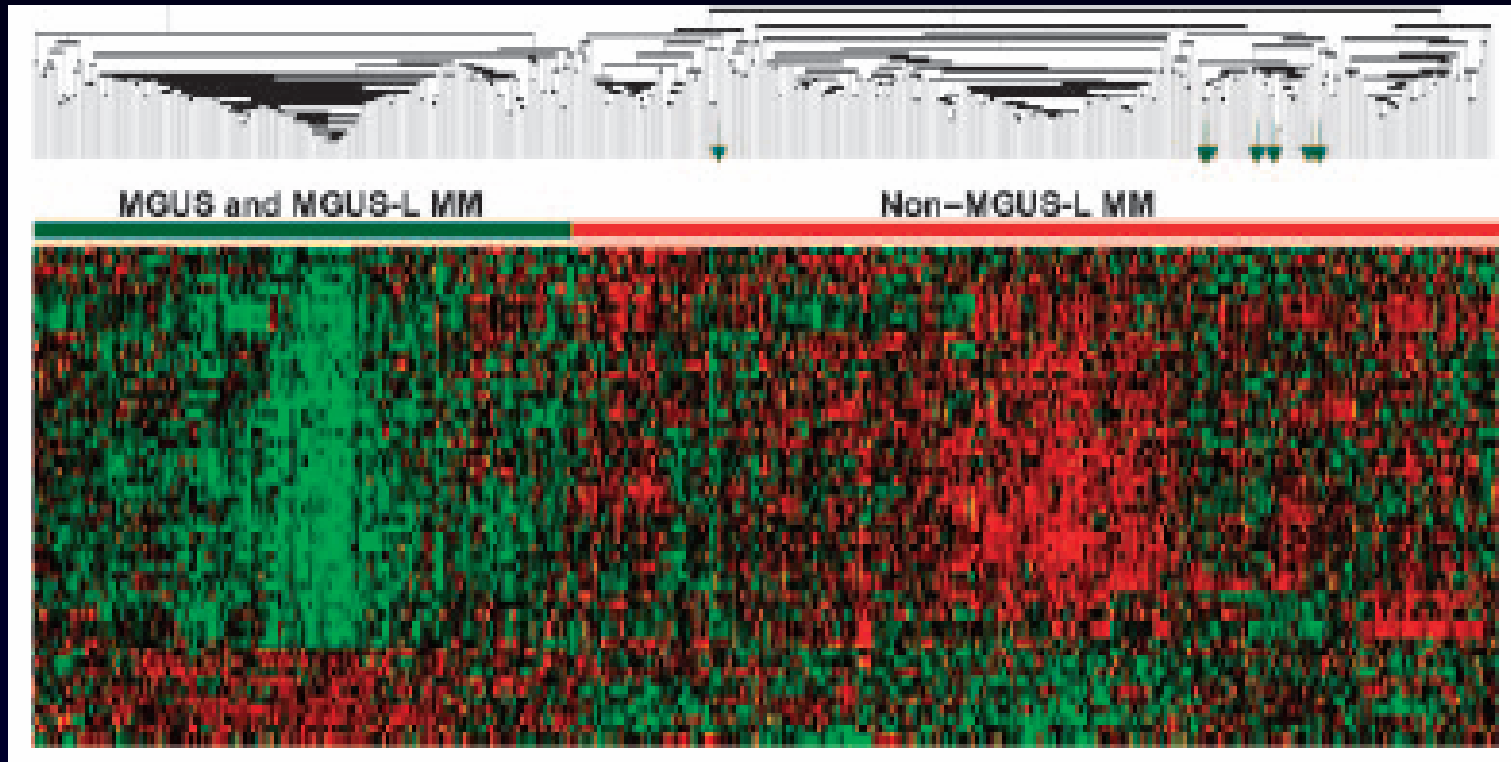


Risk factors:

- BMPC \geq 10%
- M-protein \geq 3 g/dL
- Serum free light chain ratio:
 < 0.125 or > 8.0

Gene Expression Profiling:

Unique Signature of MGUS/SMM/Low-risk MM vs High-risk MM



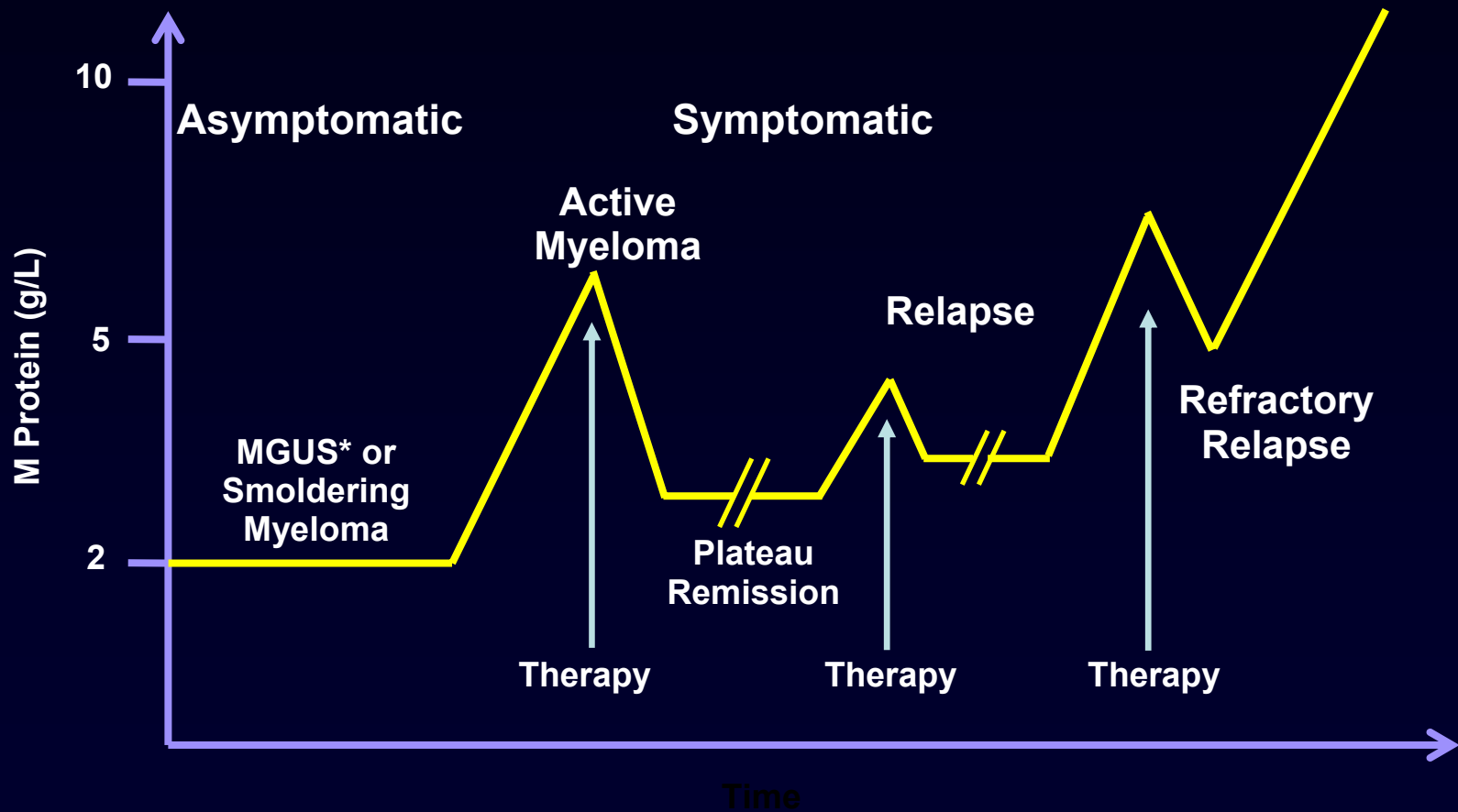
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Myeloma

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MM Disease Progression



*Monoclonal gammopathy of uncertain significance.

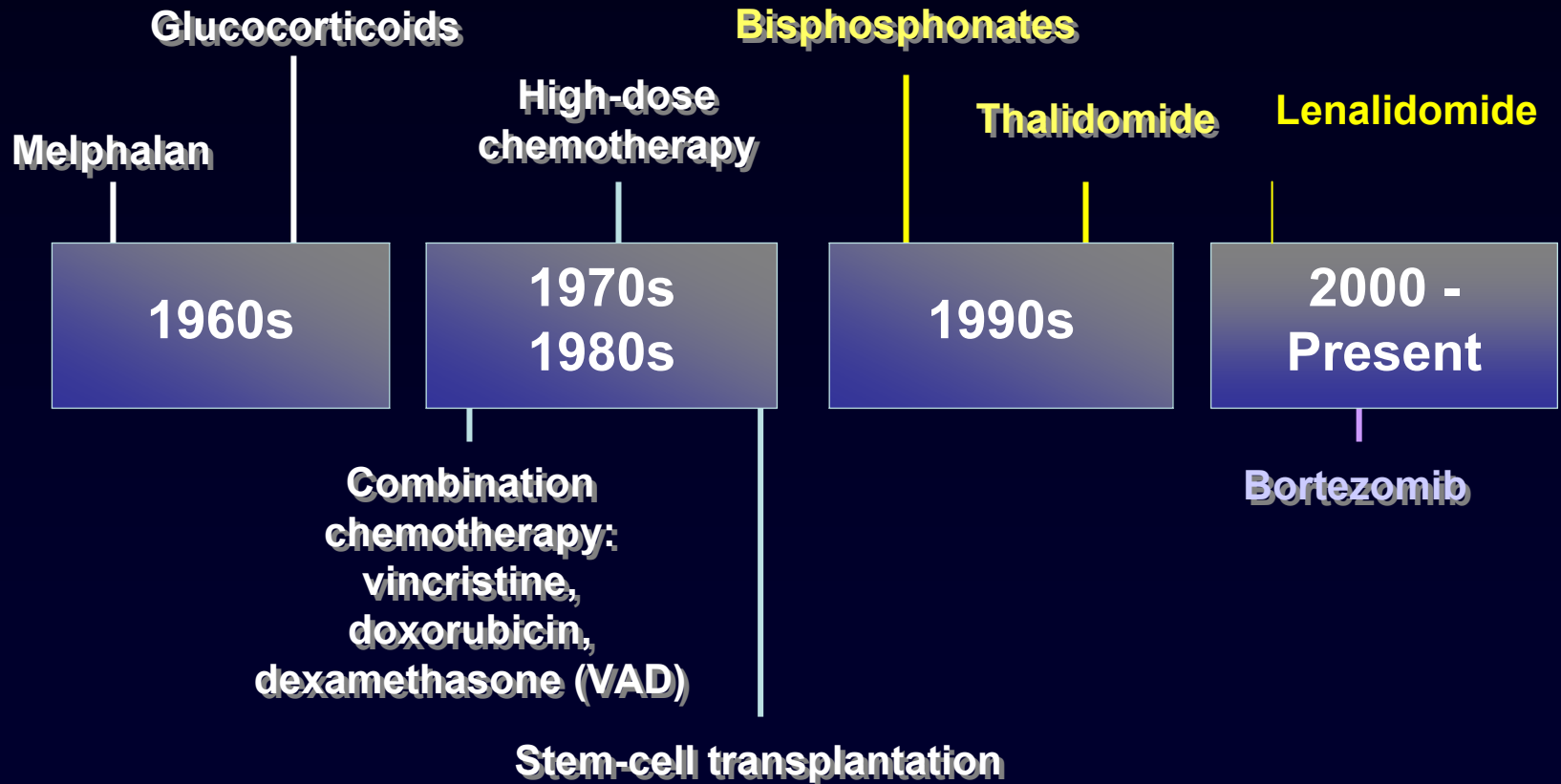
Adapted from International Myeloma Foundation. Concise review of the disease and treatment options. 2006.
<http://www.myeloma.org/pdfs/ConciseReview2006.pdf>. Accessed April 30, 2007.

International Staging System in MM

N = 10,750 previously untreated symptomatic patients with myeloma

Stage	Criteria	Median survival (mo)
1	Serum β 2 microglobulin < 3.5 mg/dL Serum albumin \geq 3.5 g/dL	62
2	Neither 1 nor 3	44
3	Serum β 2 microglobulin > 5.5 mg/dL	29

Multiple Myeloma Therapies Are Continuously Evolving



Results of 2 Phase III Studies (MM-009, MM-010)

Relapsed or refractory MM

>1 prior lines of tx

No dex resistance

Creatinine <2.5 mg/dL

LFTs ≤3 x normal

**Lenalidomide 25 mg/day, days 1-21
Dex 40 mg/day, days 1-4, 9-12, 17-20***

× 4 courses → Dex d 1-4 → Continue until PD

**Placebo on days 1-21
Dex 40 mg, d 1-4, 9-12, 17-20***

MM-009/010: Response & duration of response

Best response, n (%)	MM-009		MM-010	
	Len/Dex (n=177)	Placebo/Dex (n=176)	Len/Dex (n=176)	Placebo/Dex (n=175)
Overall response	108 (61)*	35 (20)	106 (60)*	42 (24)
CR	25 (14)*	1 (1)	28 (16)*	6 (3)
Near CR	18 (10)	2 (1)	15 (9)	3 (2)
PR	65 (37)	32 (18)	62 (35)	33 (19)
Stable disease	54 (31)	102 (58)	53 (30)	97 (55)
Duration of response (months)	16	5	17	8

24%

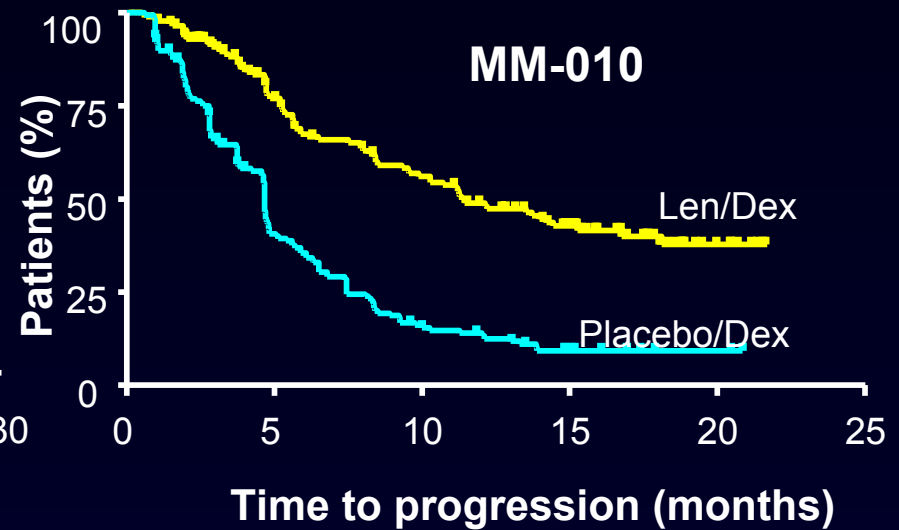
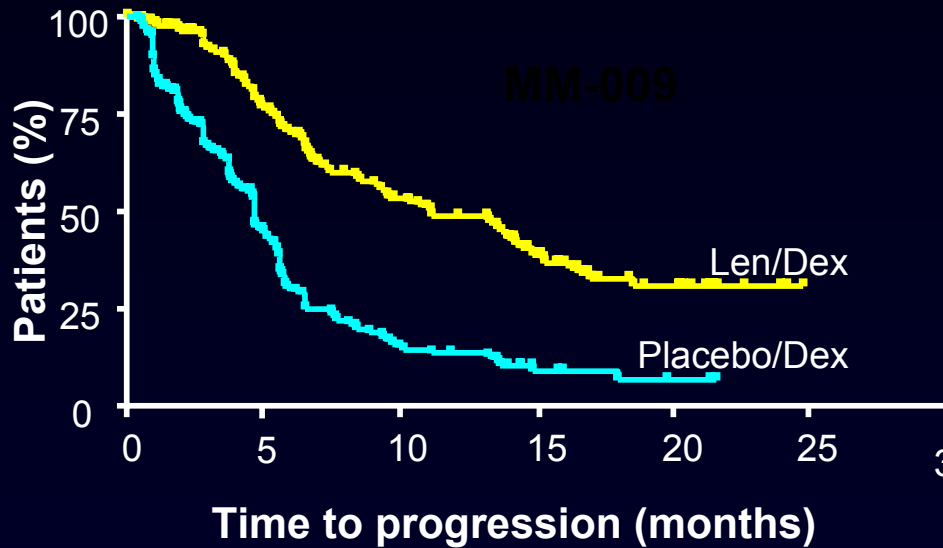
2%

25%

5%

*P-value <0.001 for comparison with Placebo/Dex counterpart,

MM-009/010: Time to progression

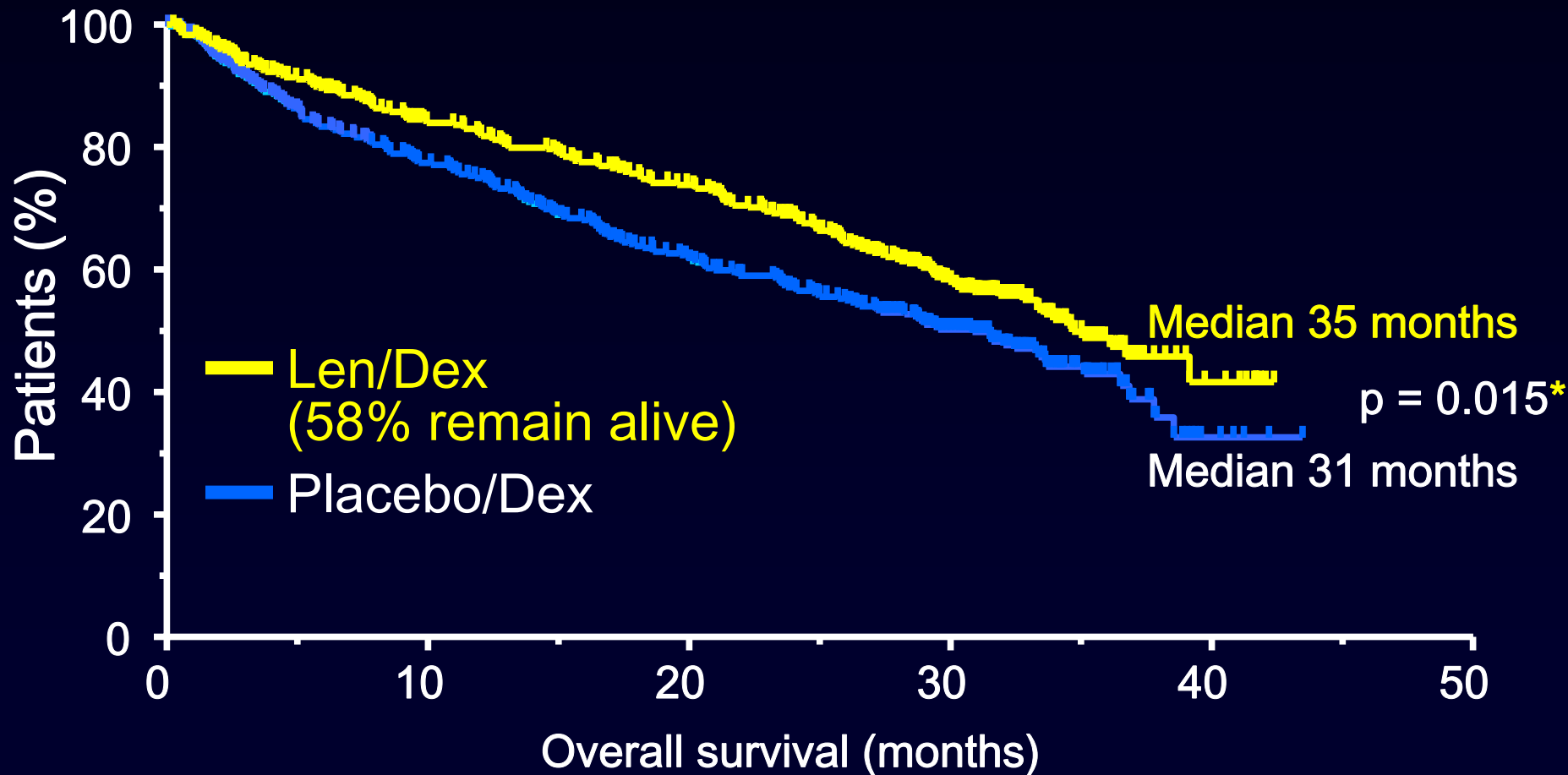


	Median time to progression (months)		<i>P</i> *
	Len/Dex	Placebo/Dex	
MM-009	11.1	4.7	<0.001
MM-010	11.3	4.7	<0.001

*`P-value from log-rank test.

MM-009/010 pooled analysis: Updated overall survival

Survival benefit retained despite 47% cross-over

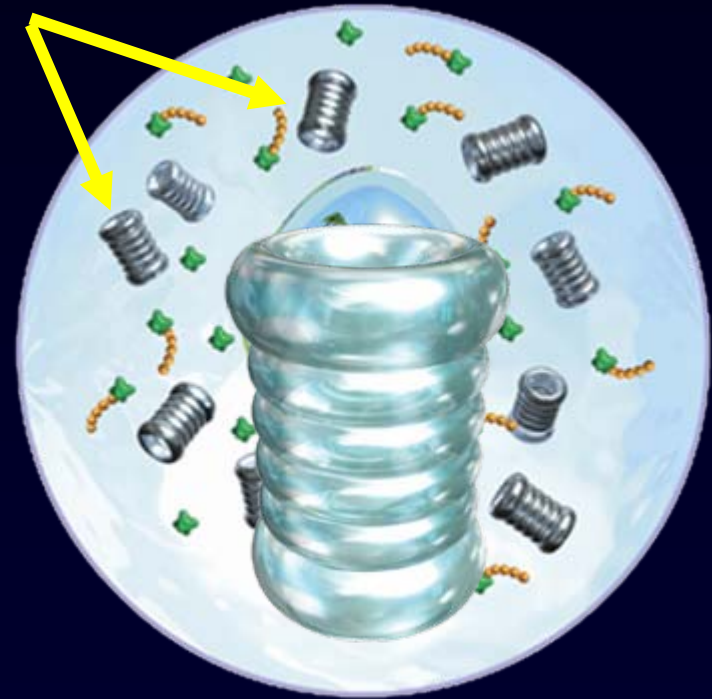


*p-value from log-rank test (patients analysed for extended follow-up remained in original groups despite cross-over).

BORTEZOMIB: A Reversible Inhibitor of the 26S Proteasome

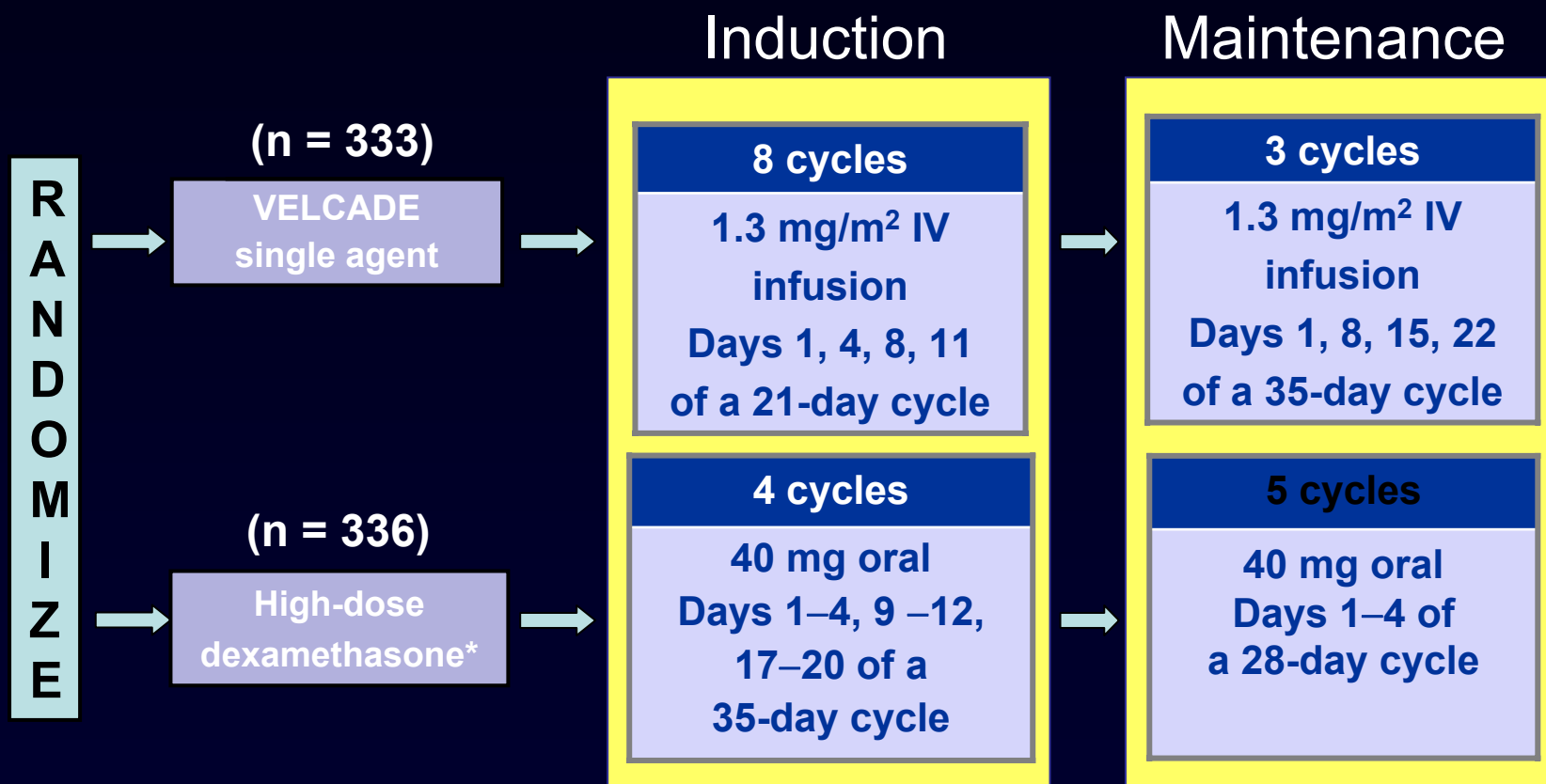
Proteasomes are enzyme complexes present in all cells that degrade intracellular proteins in a regulated manner in both healthy and cancerous cells

Proteasomes



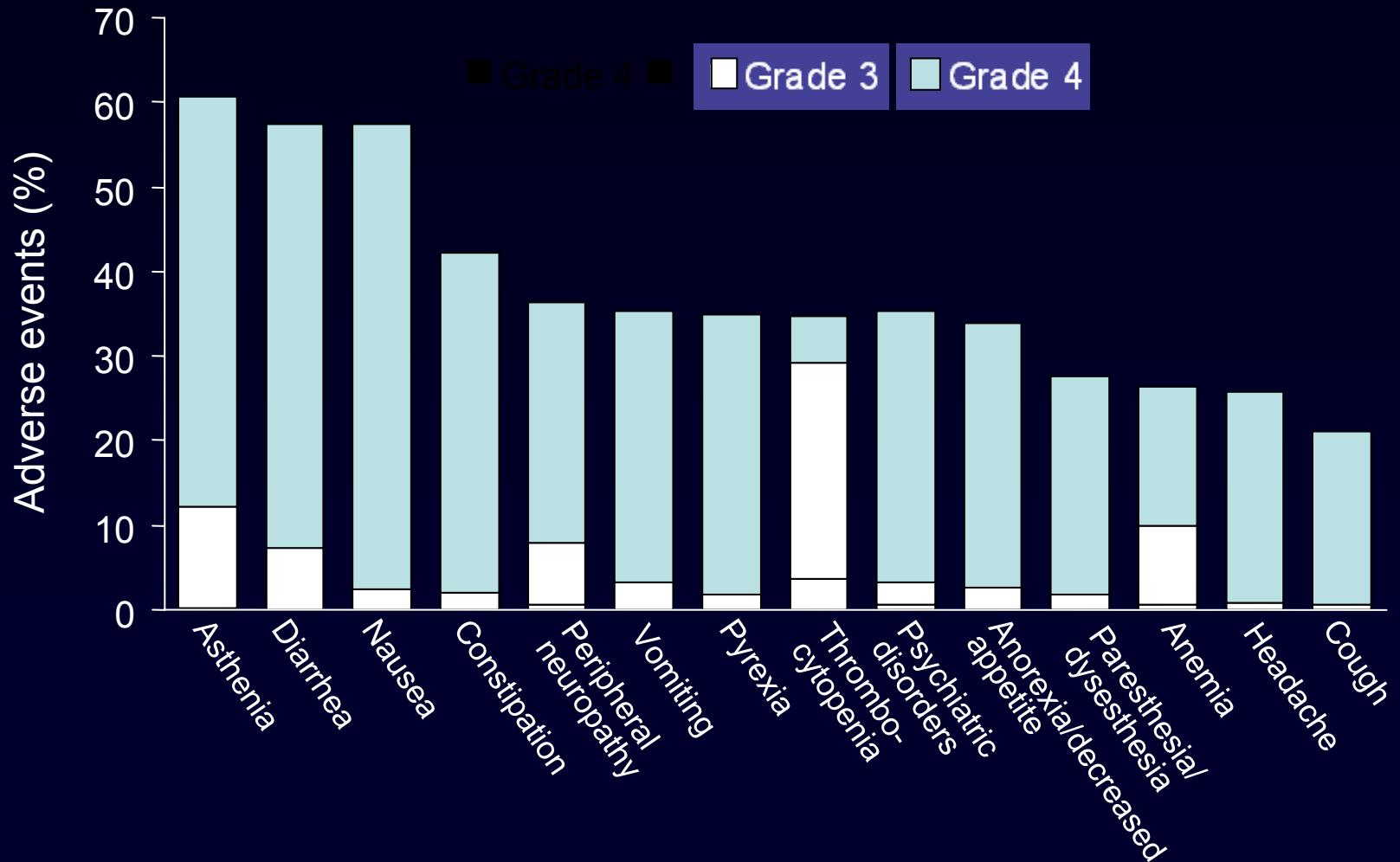
Cell

APEX Phase III Trial: Largest in Relapsed MM



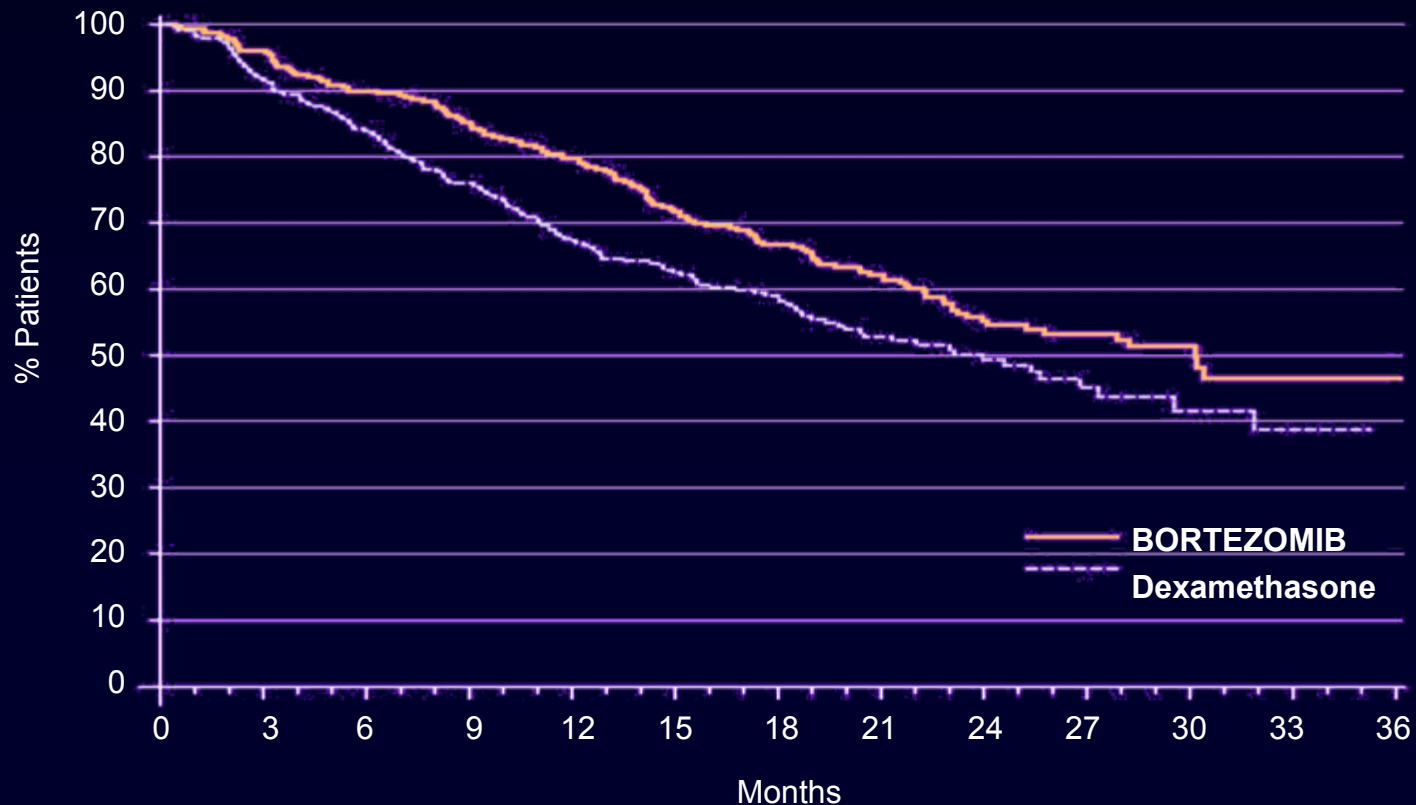
Adverse Events (>20%) With BORTEZOMIB in APEX (n=331)

Low incidence of Grade 3/4 AEs in APEX

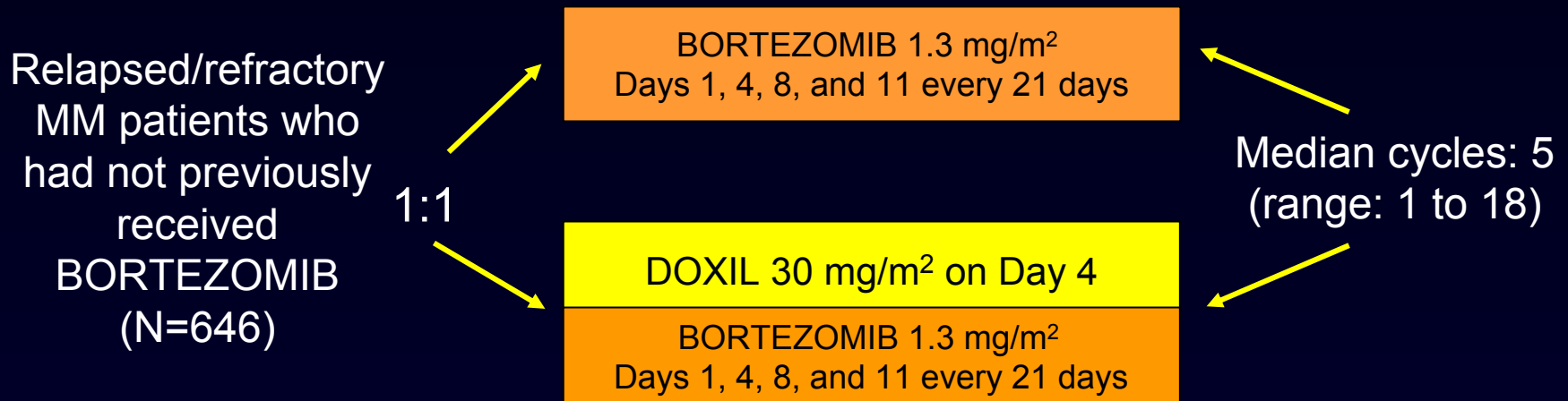


6-Month Survival Advantage With Single-Agent BORTEZOMIB in APEX (N = 669)

- 30-month median overall vs 24 months with high-dose dexamethasone ($P = 0.0272$)

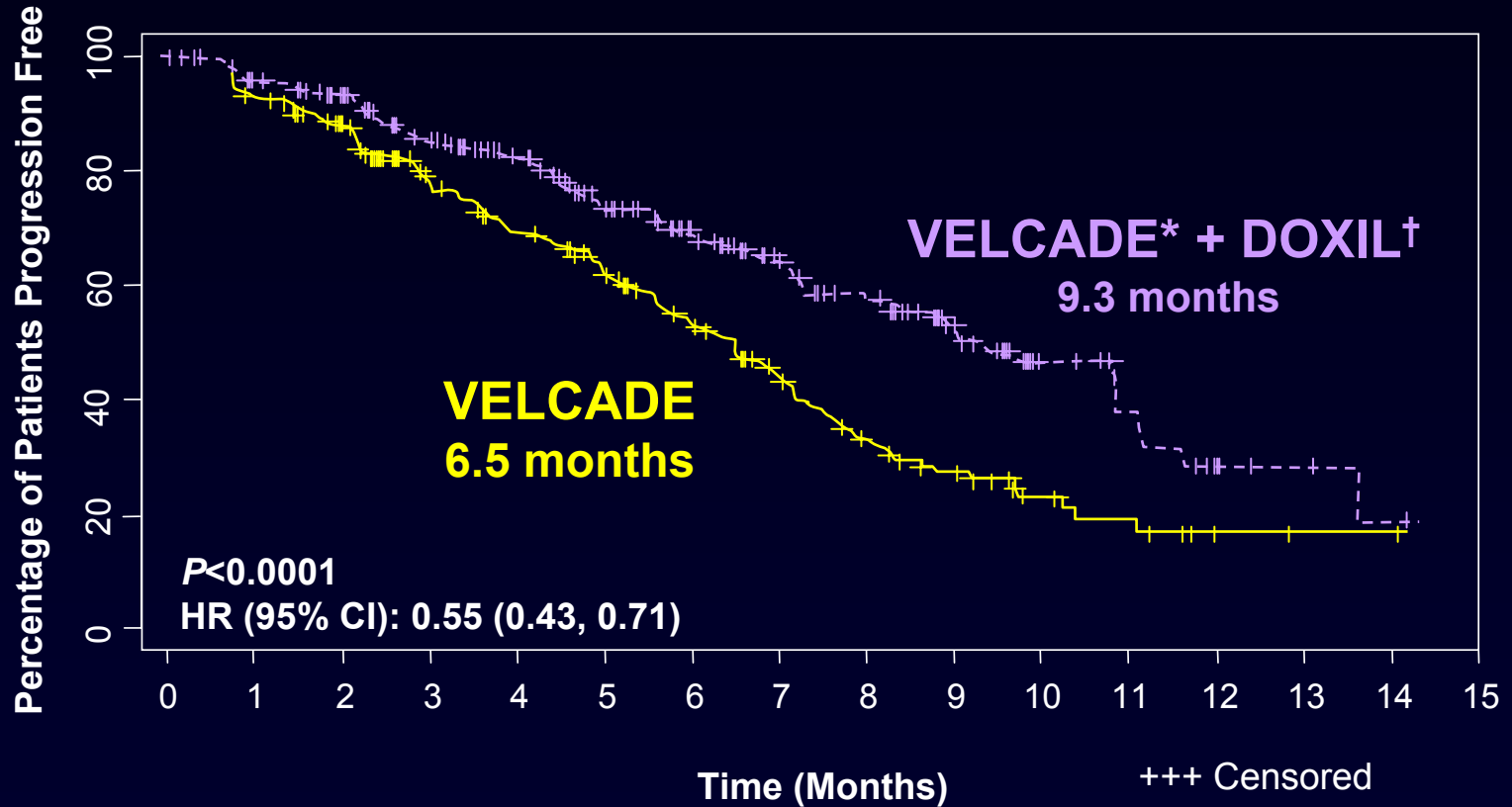


Randomized, Multicenter Study of BORTEZOMIB+ DOXIL[®] (doxorubicin HCl liposome injection) or BORTEZOMIB Monotherapy for Relapsed MM



- Primary endpoints
 - TTP
- Secondary endpoints
 - OS, ORR, safety

Time to Progression



MP versus MP plus thalidomide (MPT) Patients With Multiple Myeloma (Age >65 years)

Newly diagnosed MM patients,
Age >65 years
(median age: 72 years)
n=255

```
graph LR; A["Newly diagnosed MM patients, Age >65 years (median age: 72 years) n=255"] --> B["MPT Arm"]; A --> C["MP Arm"];
```

MPT Arm

Melphalan, 4 mg/m² (7 days per month)
Prednisone, 40 mg/m² (7 days per month)
Thalidomide, 100 mg/d (continuously)*

(n=129)

→ ×6 courses

MP Arm

Melphalan, 4 mg/m² (7 days per month)
Prednisone, 40 mg/m² (7 days per month)

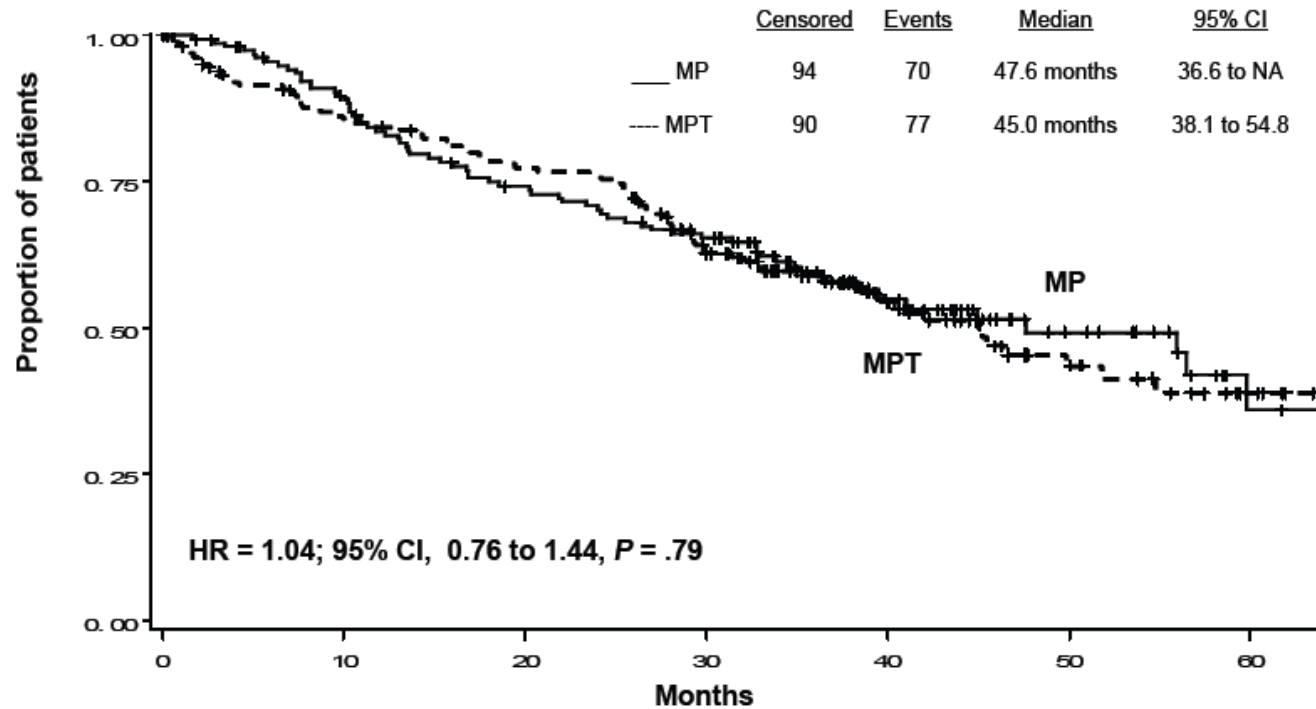
(n=126)

*Thalidomide dose reduced to 50% if grade 2 toxicity. Enoxaparin prophylaxis added to protocol in December 2003.

MPT vs MP

Improved Response Rates, No Diff in OS with MPT in Newly Diagnosed MM

	MPT	MP
CR, %	15.6	3.7
VGPR, %	29.3	11.0
PR, %	68.9	47.6
Med TTP, mo	24.7	15
Med PFS, mo	21.8	14.5
Med OS, mo	45.0	47.6



No. at risk	0	10	20	30	40	50	60
MP	164	135	109	92	47	20	6
MPT	167	135	120	89	49	23	10

Overall Survival (N = 331)

MP vs MPT vs Mel100 in Patients Aged 65–75 Years with Newly Diagnosed Myeloma (IFM-PP06)

Newly diagnosed
MM patients;
Age 65–75 years
(N=436)



MP Arm

Standard MP: Melphalan (0.25 mg/kg) plus prednisone (2 mg/kg) given orally for 4 days repeated every 6 weeks for a total of 12 cycles

MP-Thal Arm

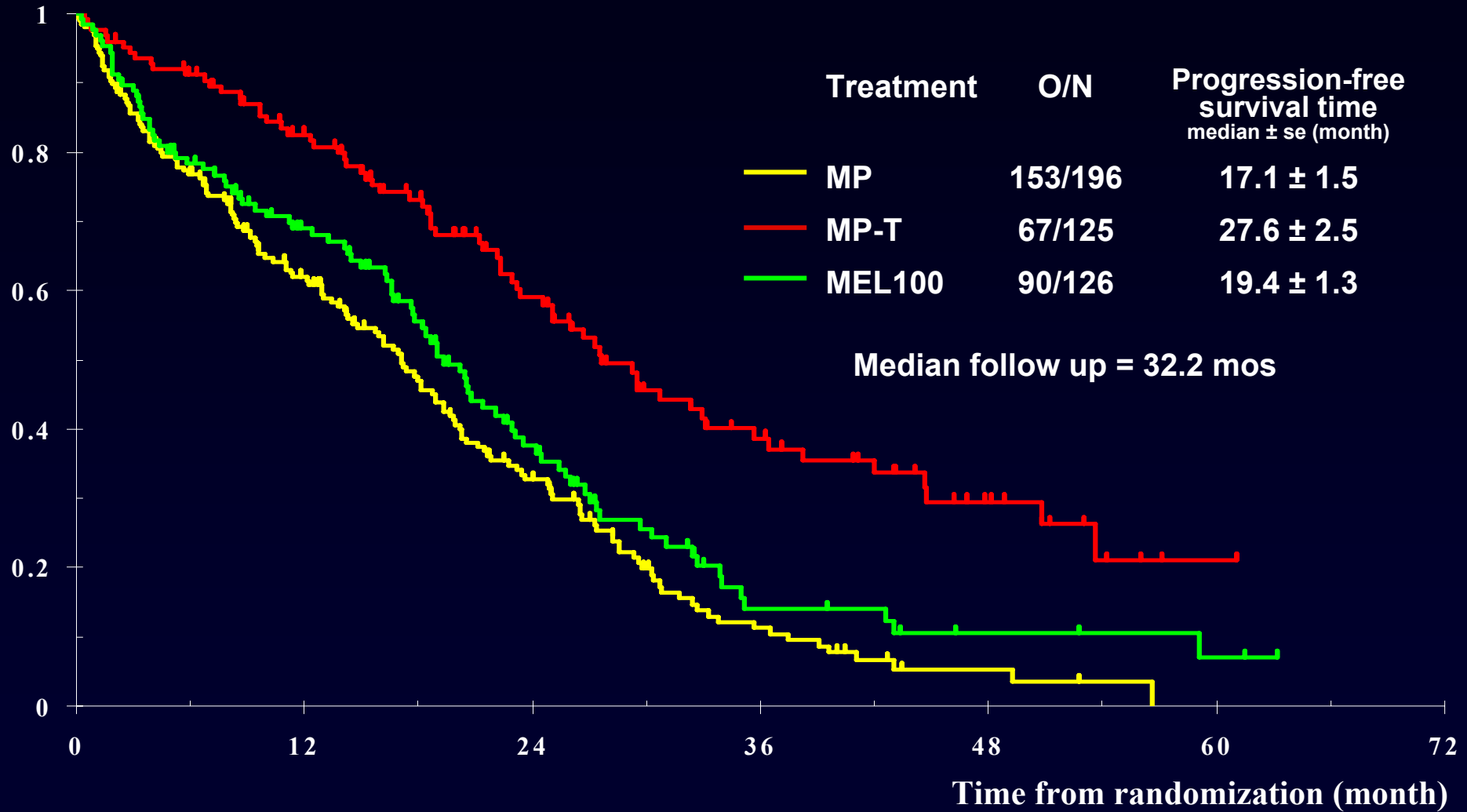
MP as Arm 1 + Thal at MTD* but ≤ 400 mg/day, stopped at end of MP

MEL100 x 2 Arm

VADx2; cyclophosphamide 3 g/m²; SCT x2 with Melphalan 100 mg/m²

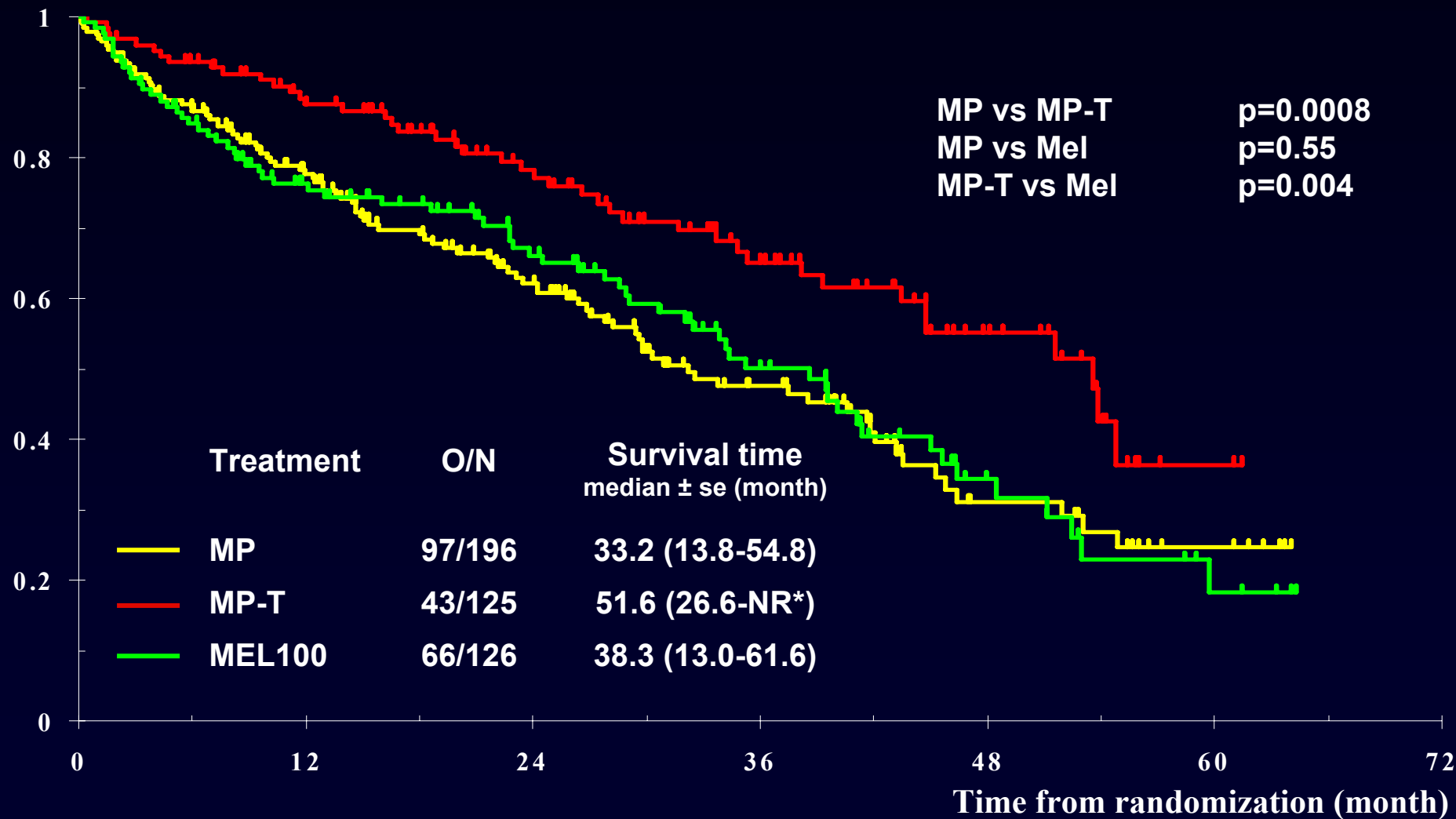
IFM 99-06: Progression-Free Survival

Proportion

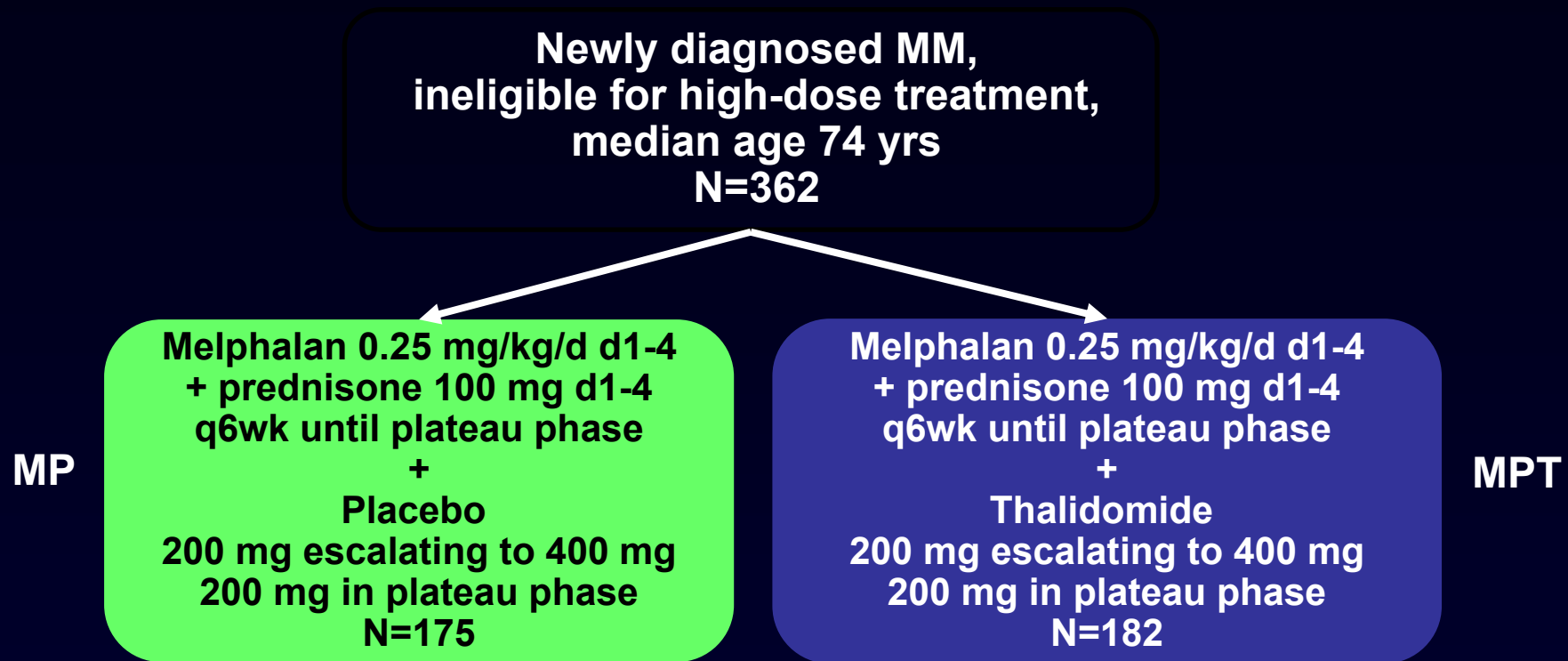


IFM 99-06: Overall Survival

Proportion



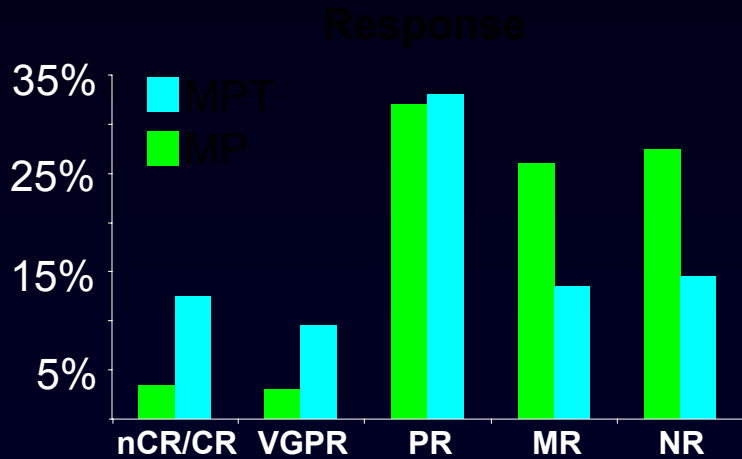
Phase III Trial: MPT vs MP



- No DVT prophylaxis
- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, TTP, TTR, safety, and QOL

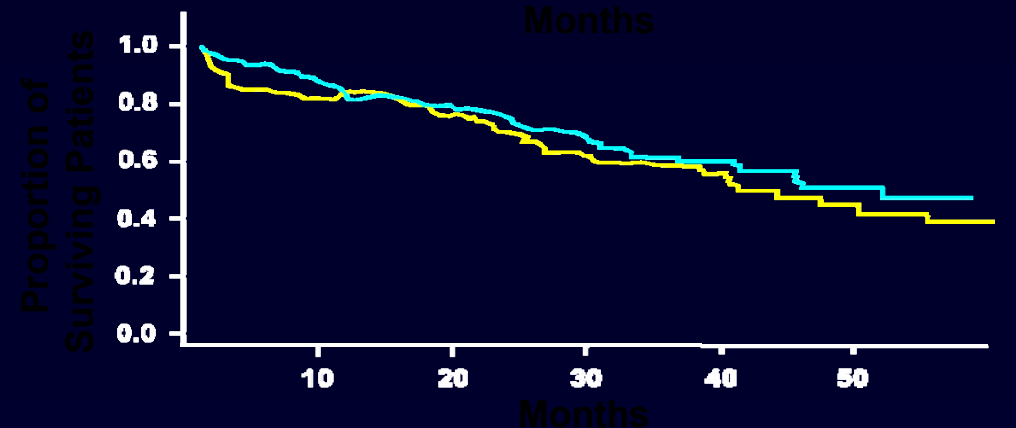
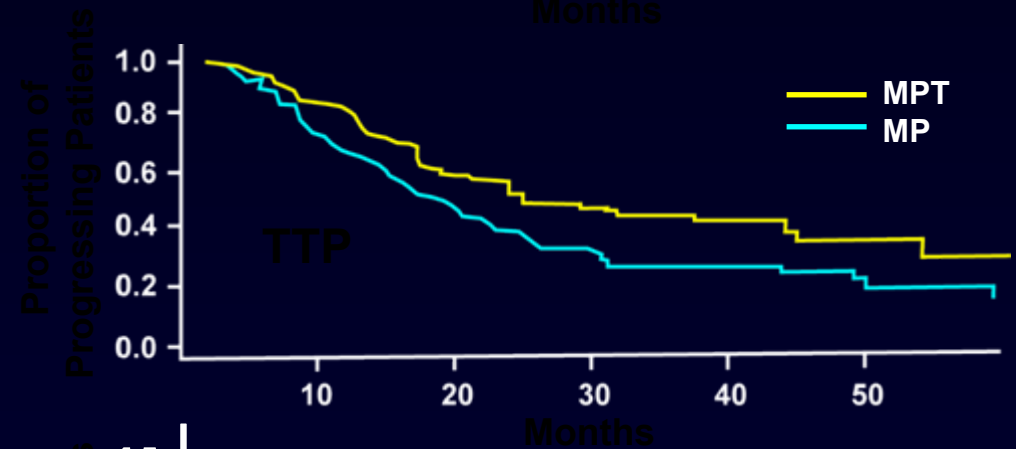
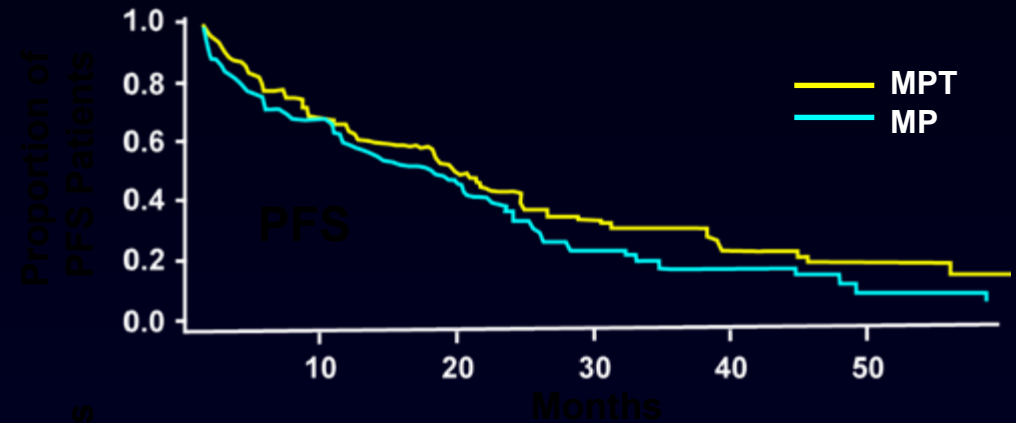
QOL=quality of life; TTR=time to response.

Phase III MPT vs MP: Results and Toxicity



Adverse Events	MPT	MP
DVT/LE	8%	9%
Deaths Within 6 Months, Age >75 Years	23	12
Deaths Within 6 Months, Age <75 Years	12	9

LE=lower extremity



VISTA: BORTEZOMIB as Initial Standard Therapy in multiple myeloma: Assessment with melphalan/prednisone

R
A
N
D
O
M
I
Z
E

VMP

Cycles 1-4

Bortezomib 1.3 mg/m² IV: days 1,4,8,11,22,25,29,32

Melphalan 9 mg/m² and prednisone 60 mg/m² days 1-4

Cycles 5-9

Bortezomib 1.3 mg/m² IV: days 1,8,22,29

Melphalan 9 mg/m² and prednisone 60 mg/m² days 1-4

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

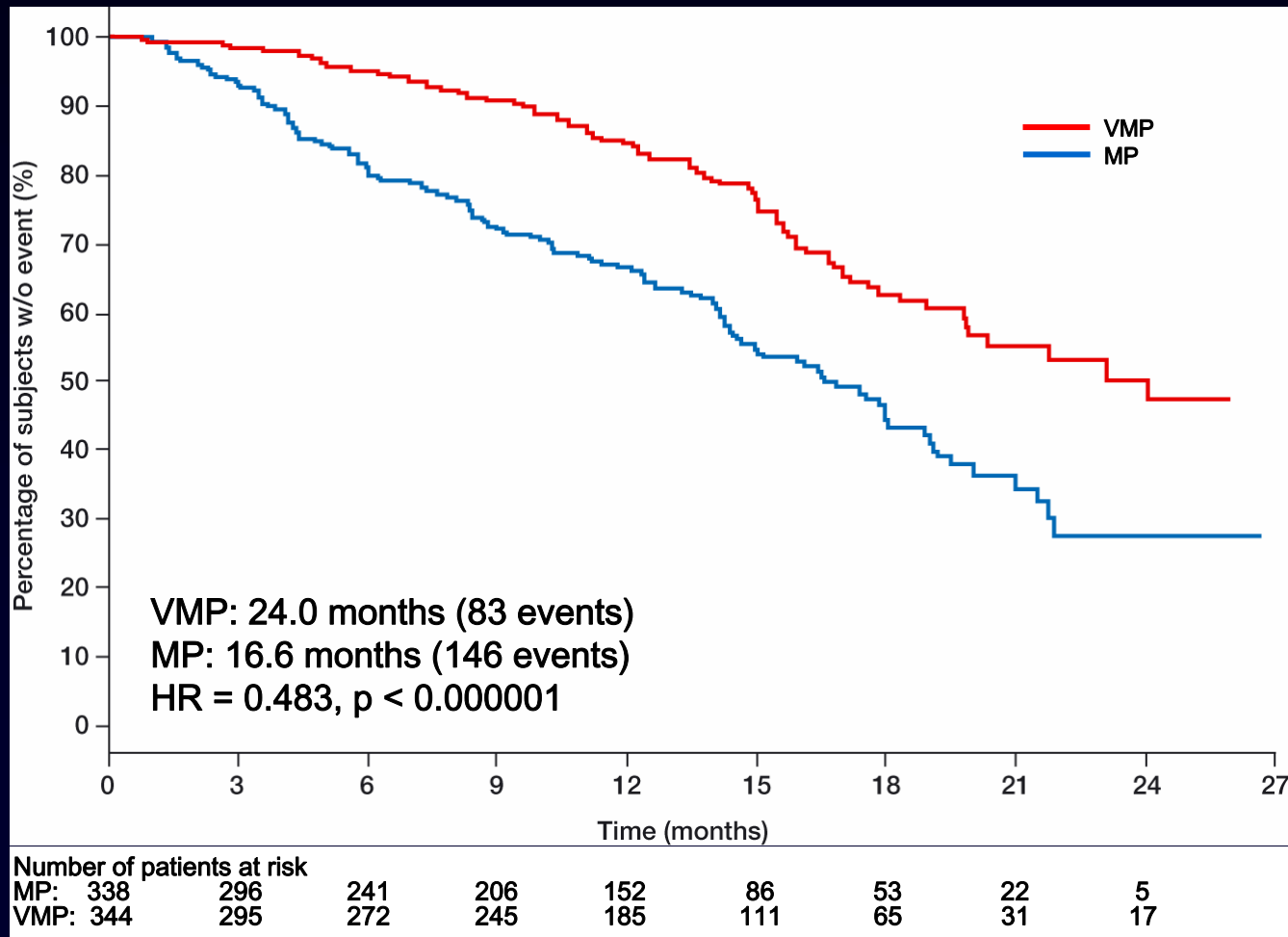
MP

Cycles 1-9

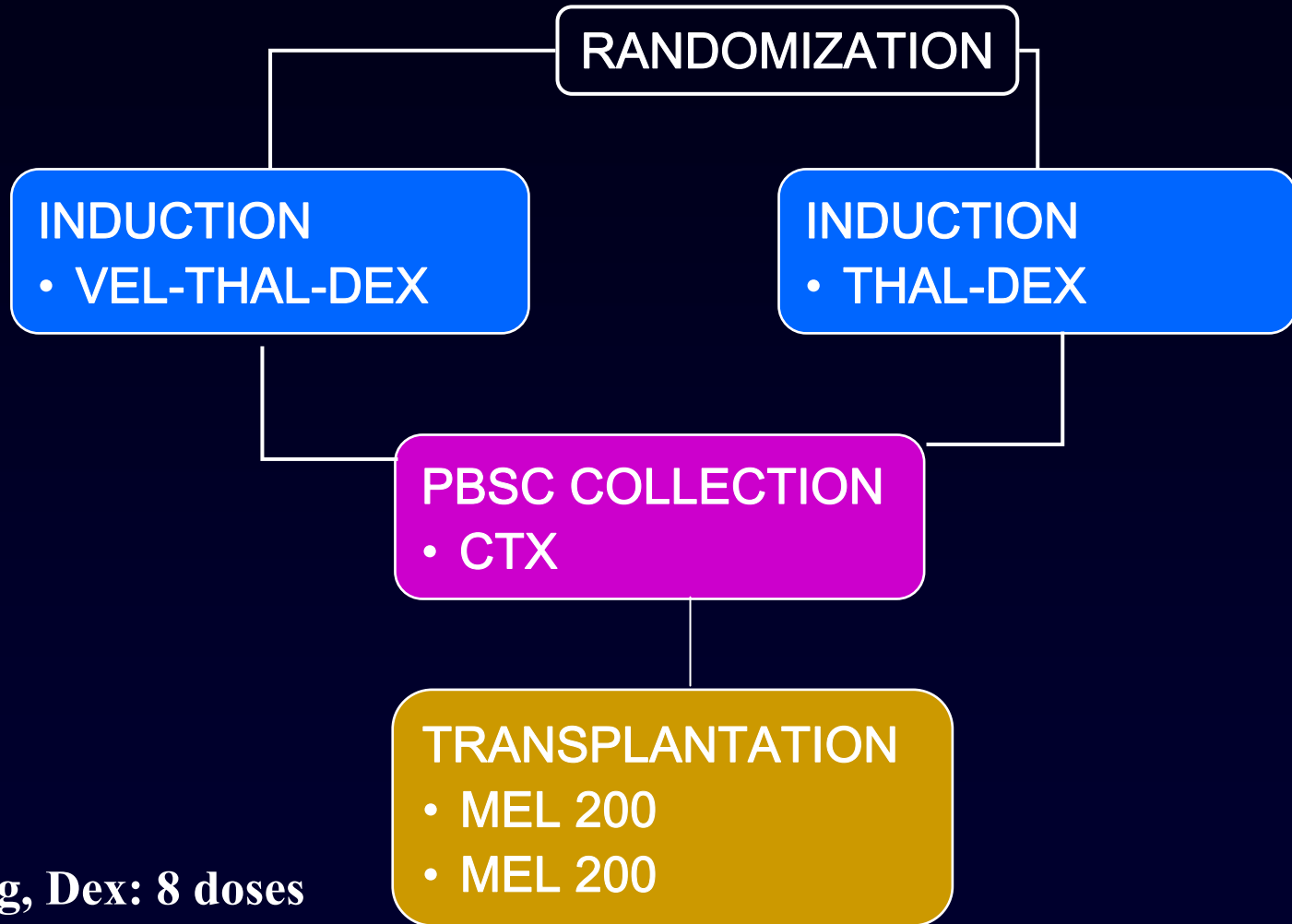
Melphalan 9 mg/m² and prednisone 60 mg/m² days 1-4

Time to progression

~52% reduced risk of progression on VMP



VTD vs TD incorporated into double ASCT for MM (351 pts)



Thal: 200 mg, Dex: 8 doses

Velcade-Thalidomide-Dex vs. Thal-Dex

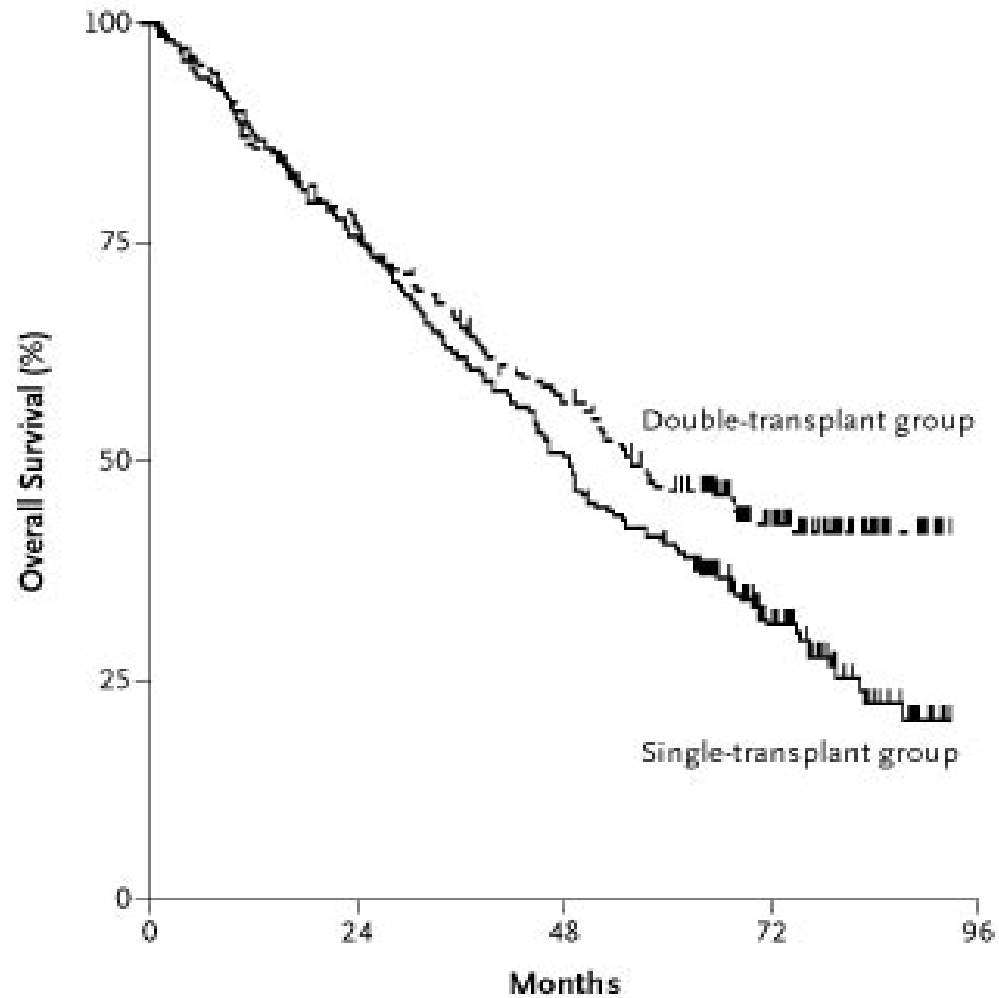
	VTD (%)	TD (%)	
Responses after Induction (n = 256)			P
CR/nCR	36	9	< 0.001
≥ VGPR	60	27	< 0.001
< PR	7	20	0.003
Progres.	0	5,5	0.008
Responses after ASCT-1 (n = 153)			P
CR	45	19	< 0.001
CR/nCR	57	28	< 0,001
≥ VGPR	77	54	0.003

Single Versus Tandem Auto SCT: IFM 94 trial

399 pts	Single SCT (M 140 mg/m ² ; 8Gy)	vs	Tandem SCT (M 140 mg/m ² ; then (M 140 mg/m ² ; 8Gy)	
CR/VGPR	42%		50%	<i>p</i> =0.10
7 yr prob EFS	10%		20%	<i>p</i> =0.03
7 yr prob OS*	21%		42%	<i>p</i> =0.001

*Survival benefit with tandem SCT restricted to patients failing to achieve CR or VGPR with first SCT

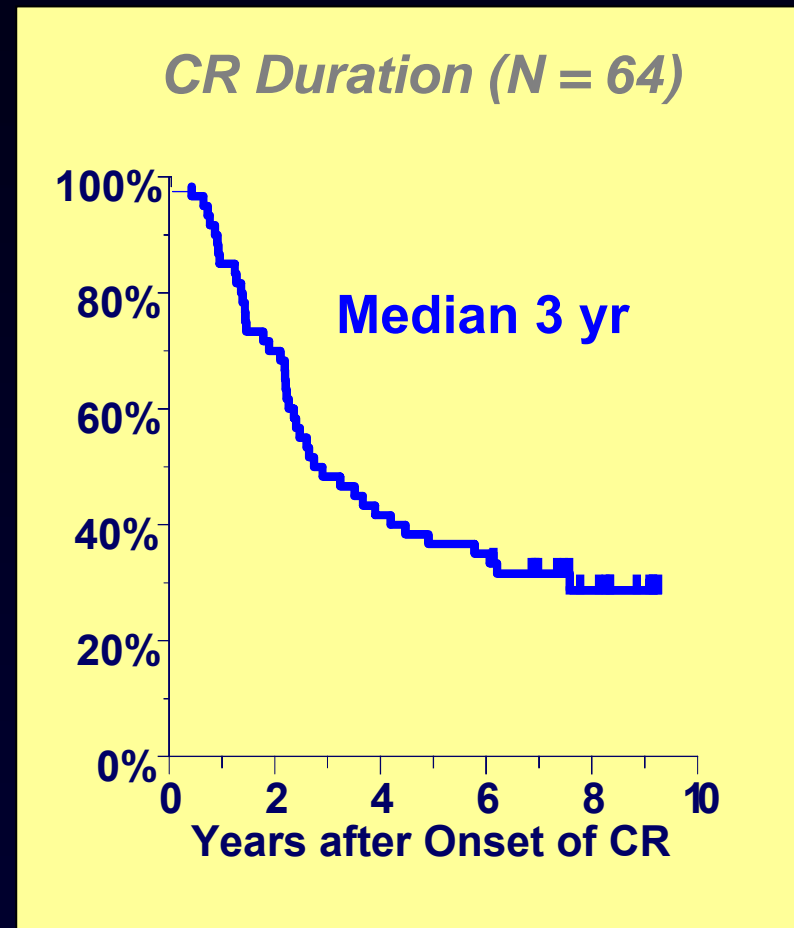
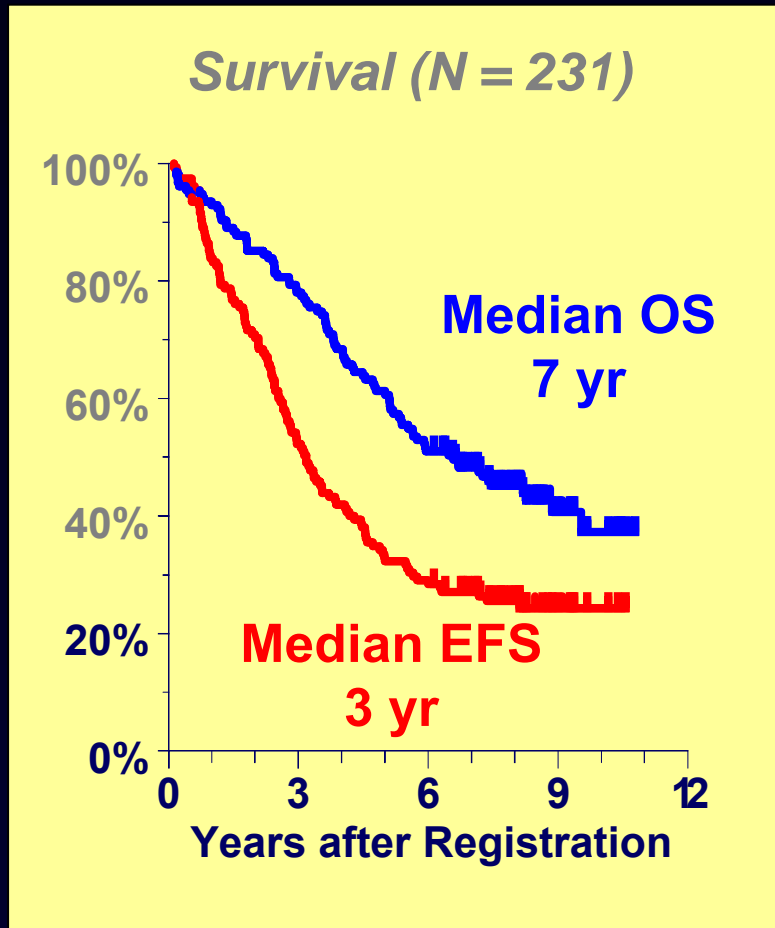
IFM 94: Overall Survival



Probability of Overall Survival (95% CI)

Single-transplant group	50 (43-57)	31 (24-38)	20 (13-29)
Double-transplant group	57 (49-64)	42 (35-50)	42 (34-49)

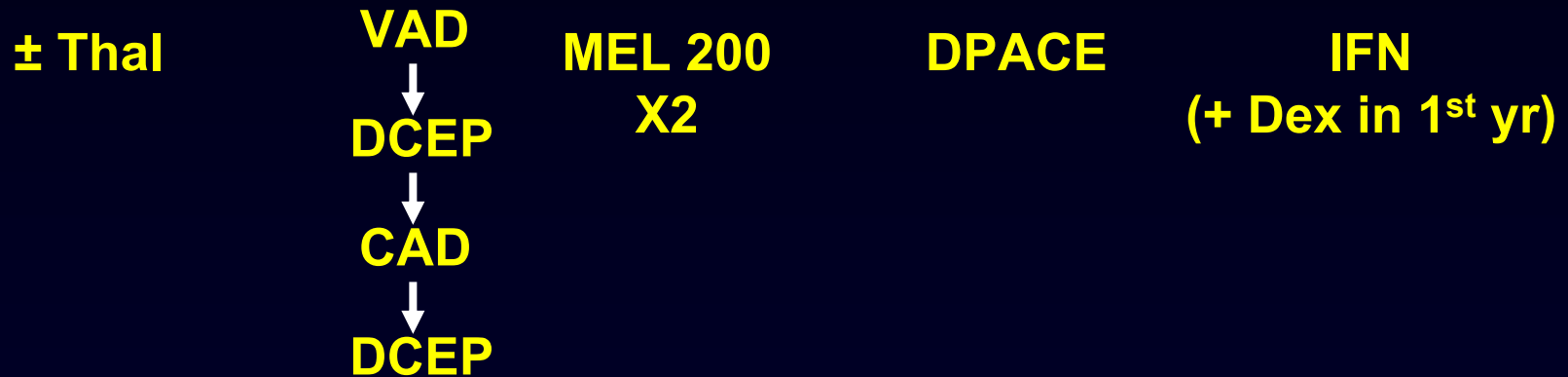
Total Therapy 1*: Long-term F/U



***Tandem transplant followed by interferon maintenance therapy**

Phase III Total Therapy II (TT2) Trial for MM

RANDOMIZATION INDUCTION TRANSPLANT CONSOLIDATION MAINTENANCE



- Untreated MM patients stratified by β_2 M and plasma cell labeling index randomized to \pm Thal, administered until relapse
- 668 patients enrolled; 345 –Thal, 323 +Thal
- Trial powered to test whether Thal could \uparrow 5-yr EFS from 40% to 50% (primary endpoint; 80% power, 2-sided 0.05 level test)
- Median follow up total therapy = 3 years

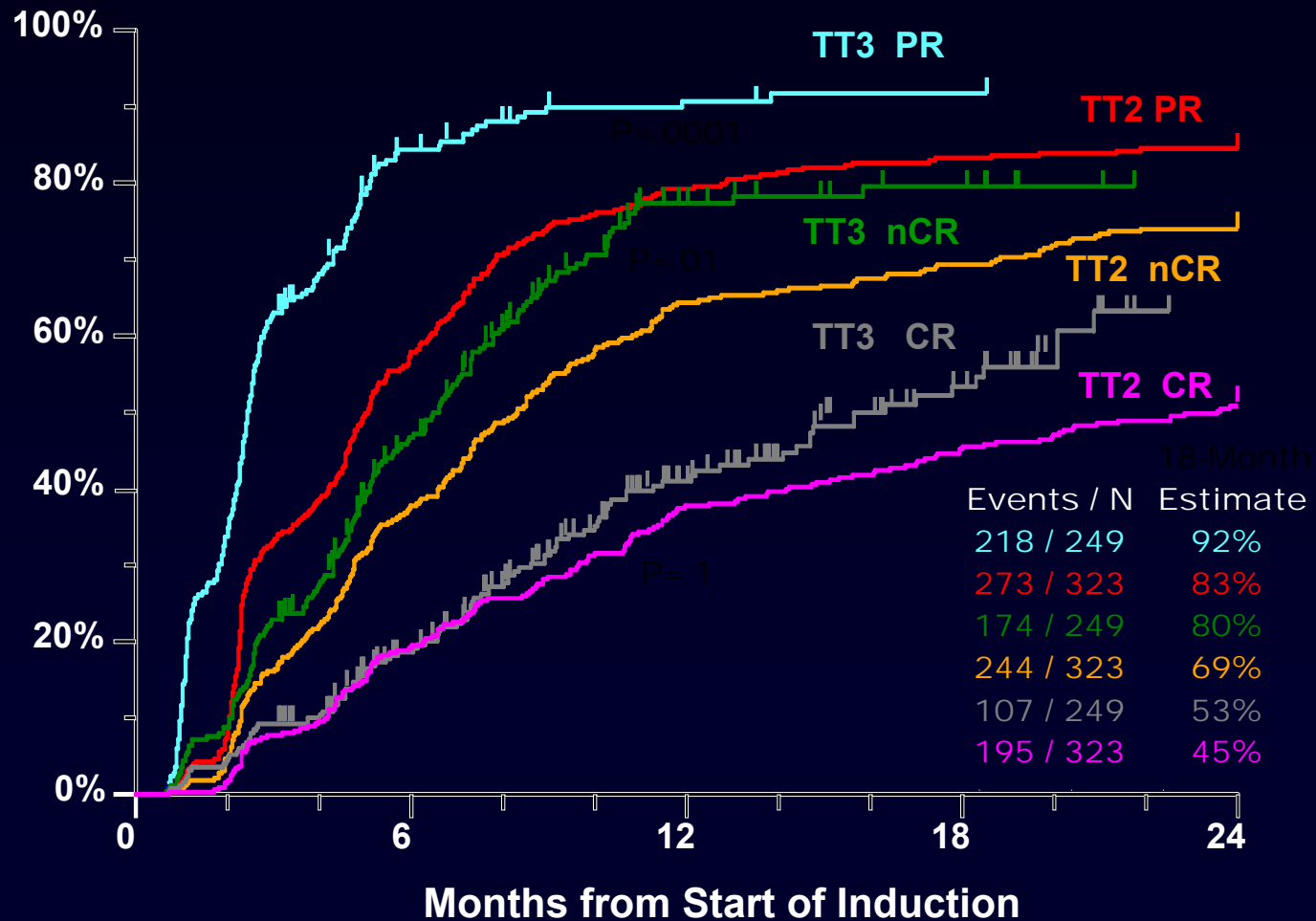
TT2: Results

Parameter	-Thal (%)	+Thal (%)	<i>P</i> value
CR	43	62	<0.001
5-yr EFS	40	55	<0.029
5-yr OS	63	68	0.90

Barlogie B et al. *J Clin Oncol*. 2005;23(suppl 16S):1049s [abstract LBA 6502]

Tricot G et al. *Blood*. 2005;106:127a [abstract 423]

Cumulative Response Rates



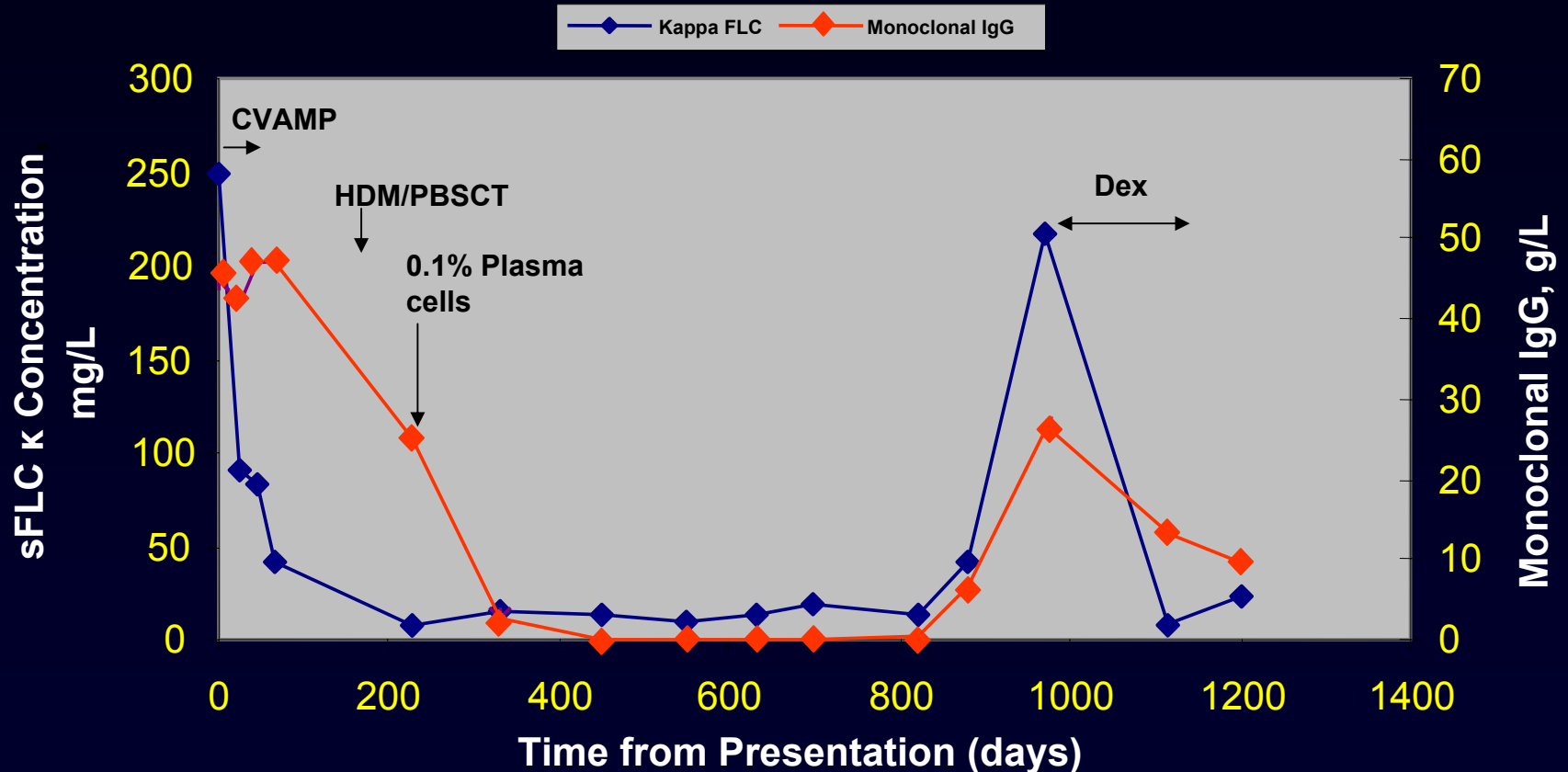
Monitoring Response to Treatment

Immunoglobulin Half-Life

<u>Protein</u>	<u>Half Life</u>
IgG	20–25 days
IgA	6 days
IgM	6–8 days
Free Kappa	2–4 hours
Free Lambda	3–6 hours

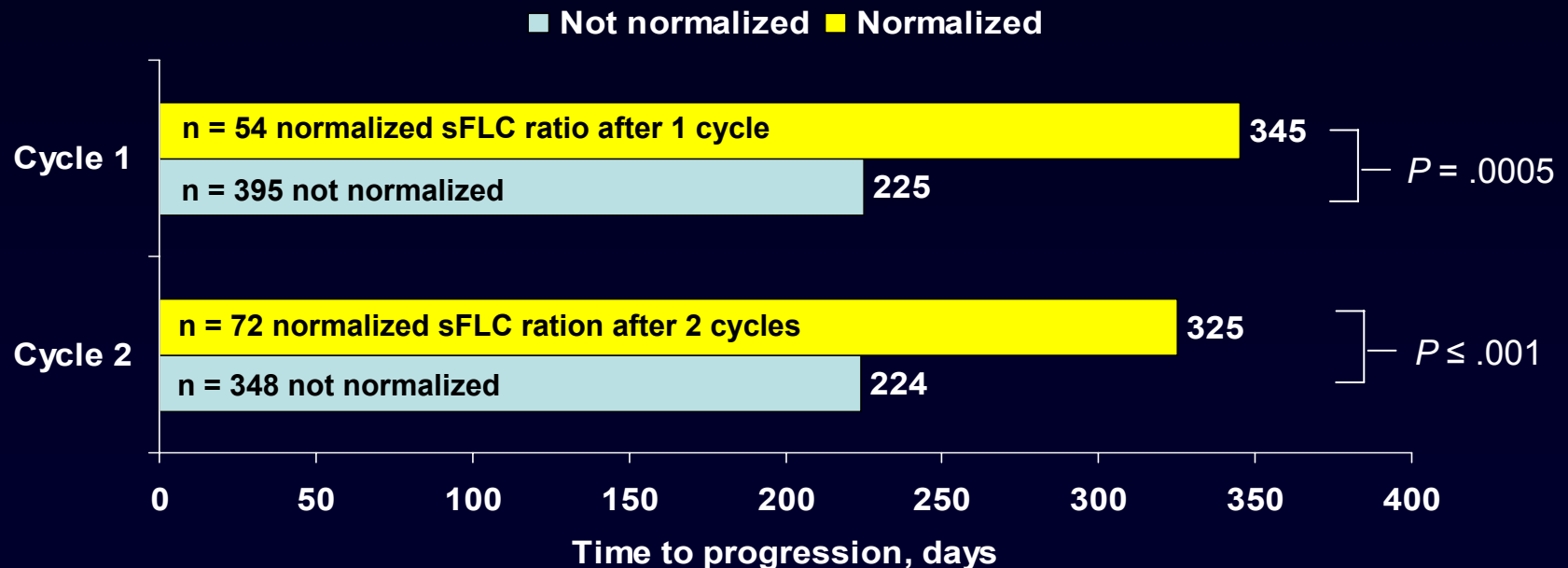
Serum Free Light Chain Levels Fall Faster Than IgG

IgG κ Multiple Myeloma

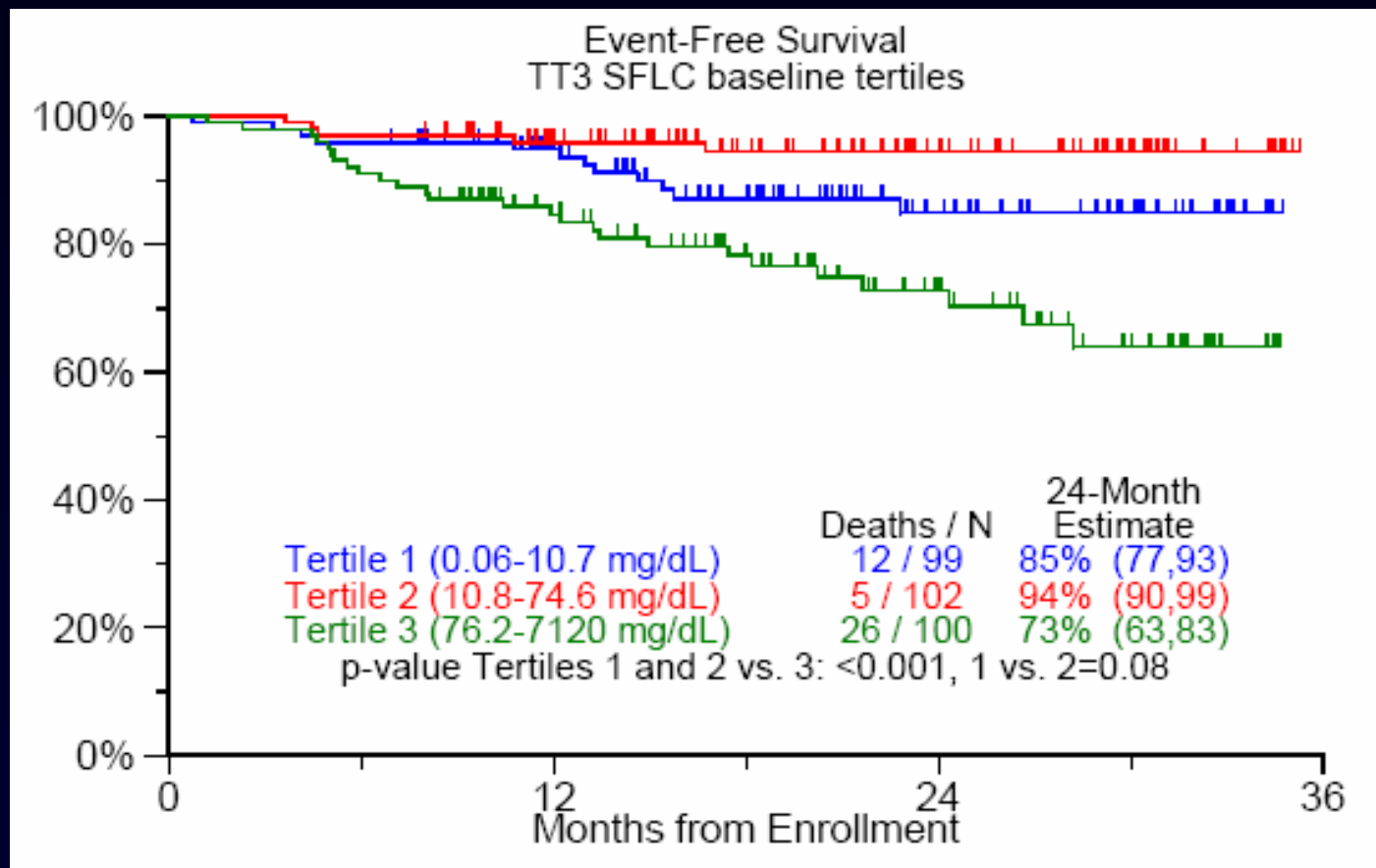


Early Normalization of sFLC Ratio Associated with Improved TTP

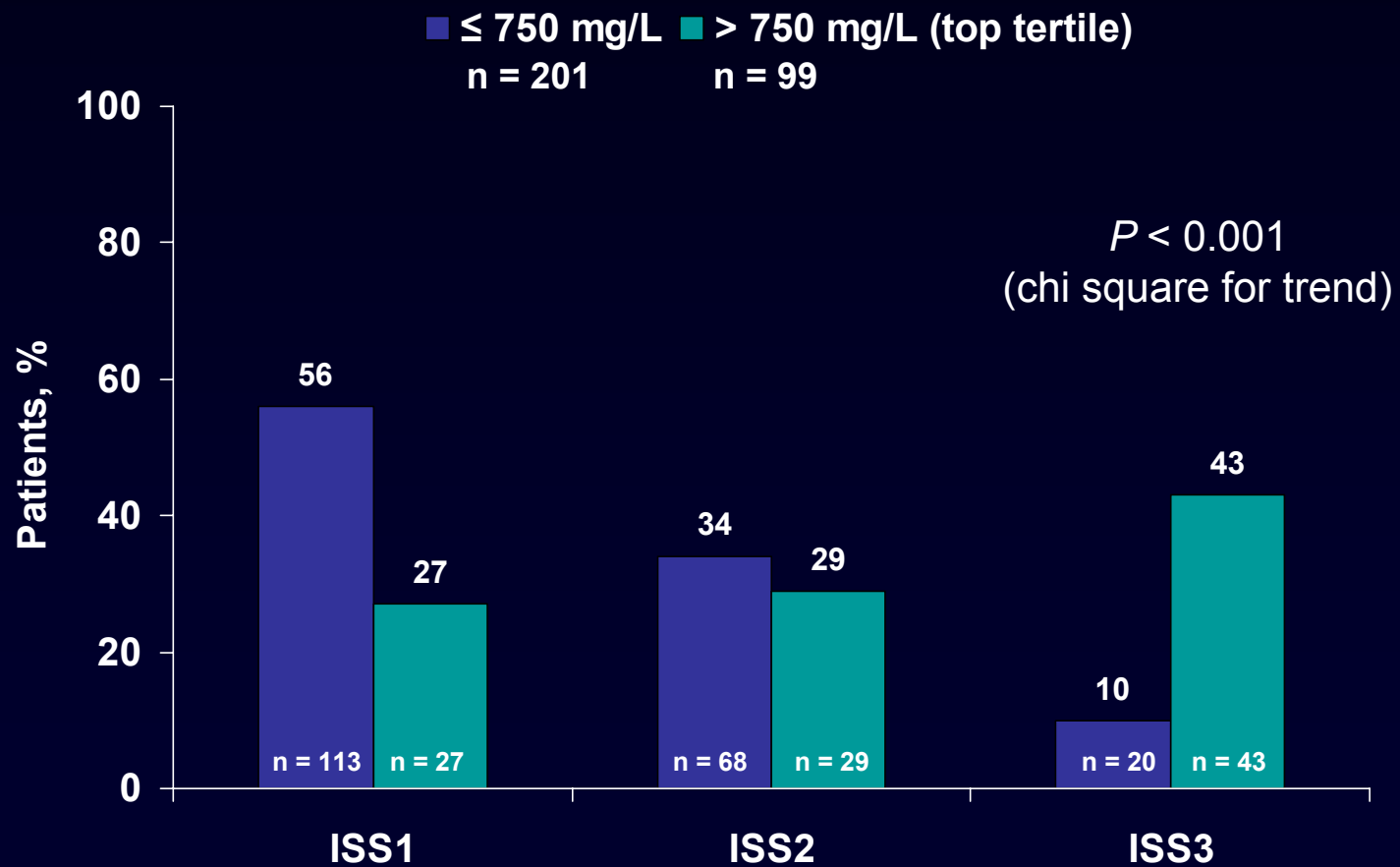
- Analysis of RCT of bortezomib ± PLD in R/R MM
- 458/487 (94%) had abnormal κ/λ ratio at baseline



Baseline Involved Free Light Chain ≥ 750 mg/L: A Poor Prognostic Sign for OS and EFS in TT3



Serum Free Light Chain Testing Provided Prognostic Data Independent of Stage



Optimizing the Approach

- New diagnostic criteria in MM
- Understanding value and limitations of SPEP, UPEP, IFE, and serum free light chain assays
- Risk assessment in MGUS, SMM
- New International Uniform Response Criteria in multiple myeloma
- More treatment options to individualize the approach
- New prognostic markers