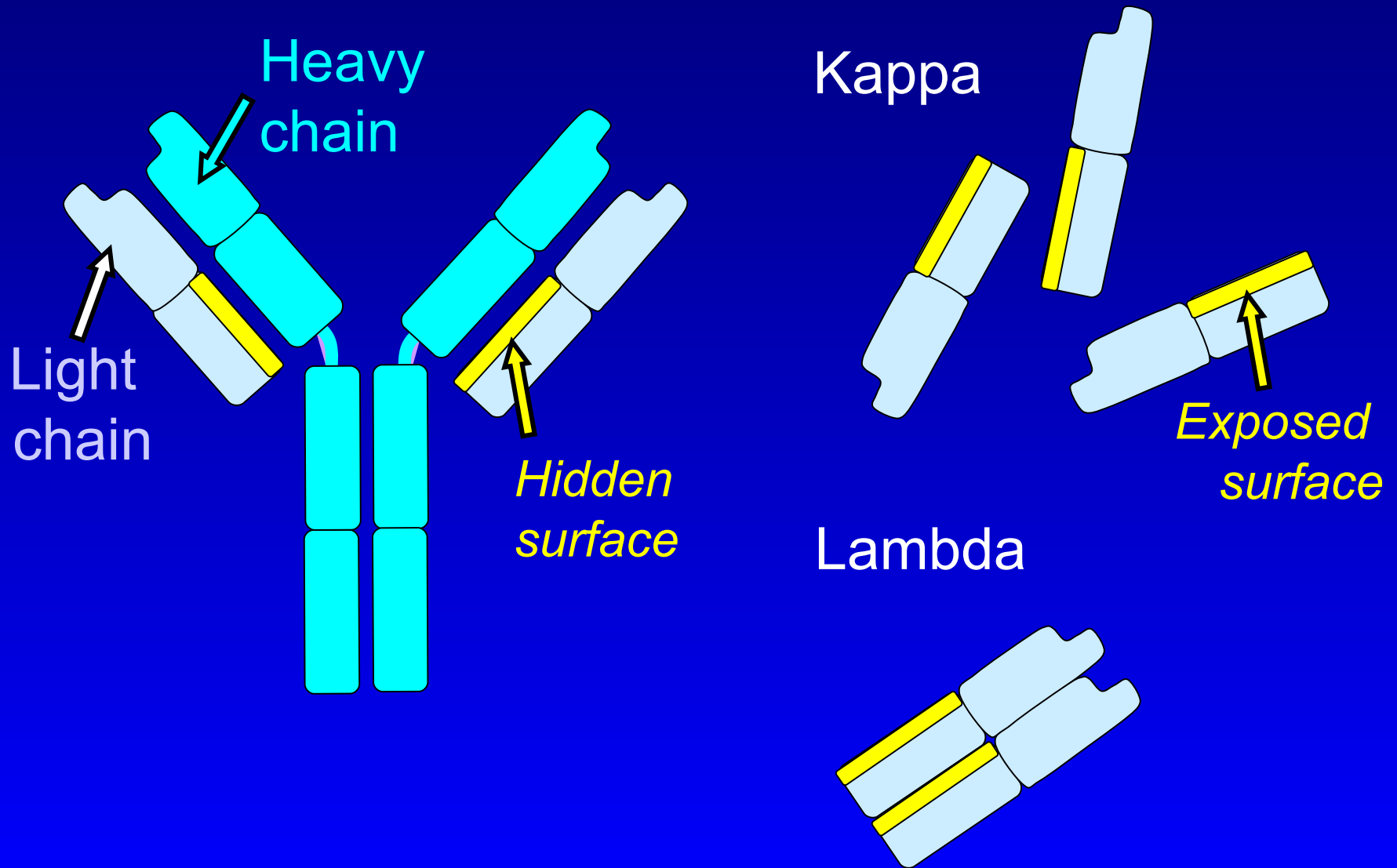


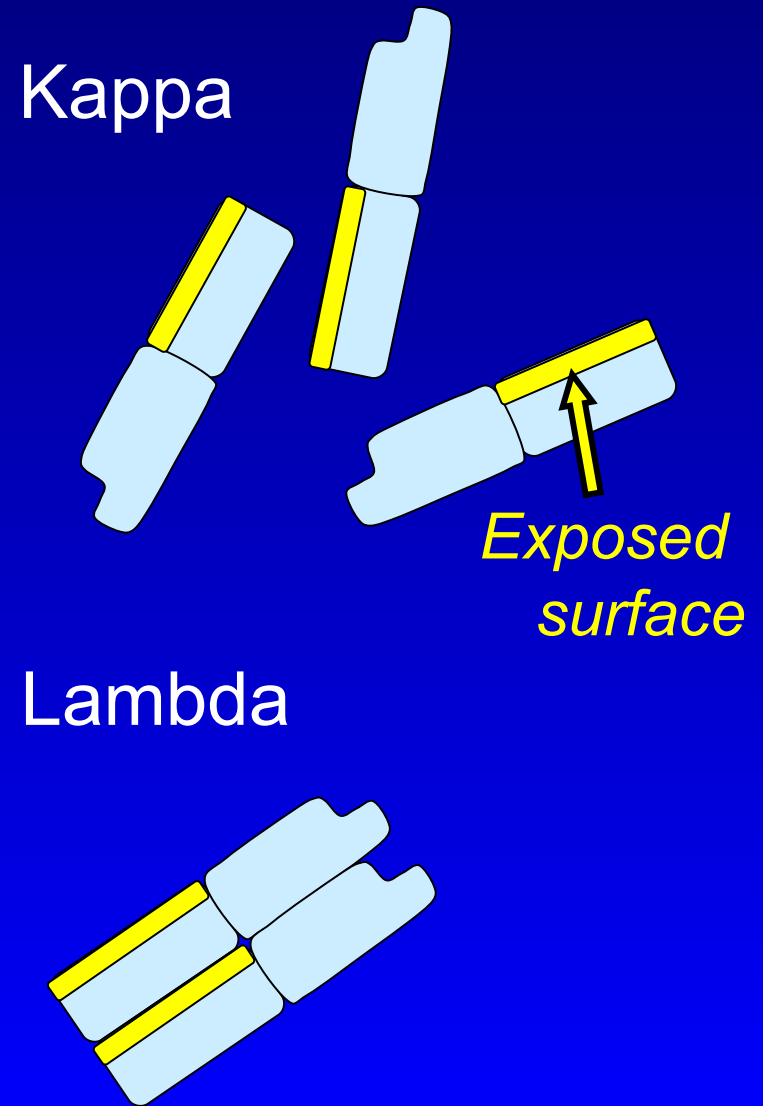
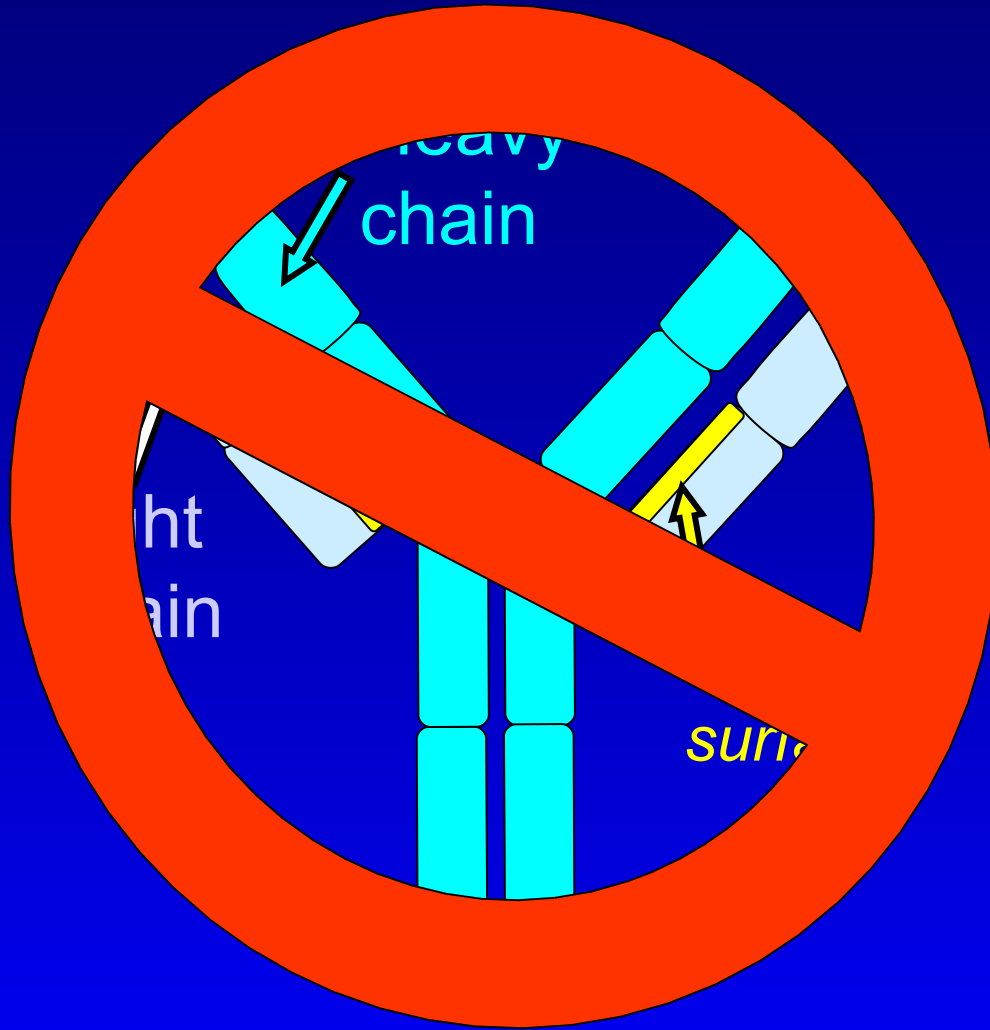
International Myeloma Working Group Guidelines for sFLC analysis

Alex Legg PhD
Scientific Affairs Manager

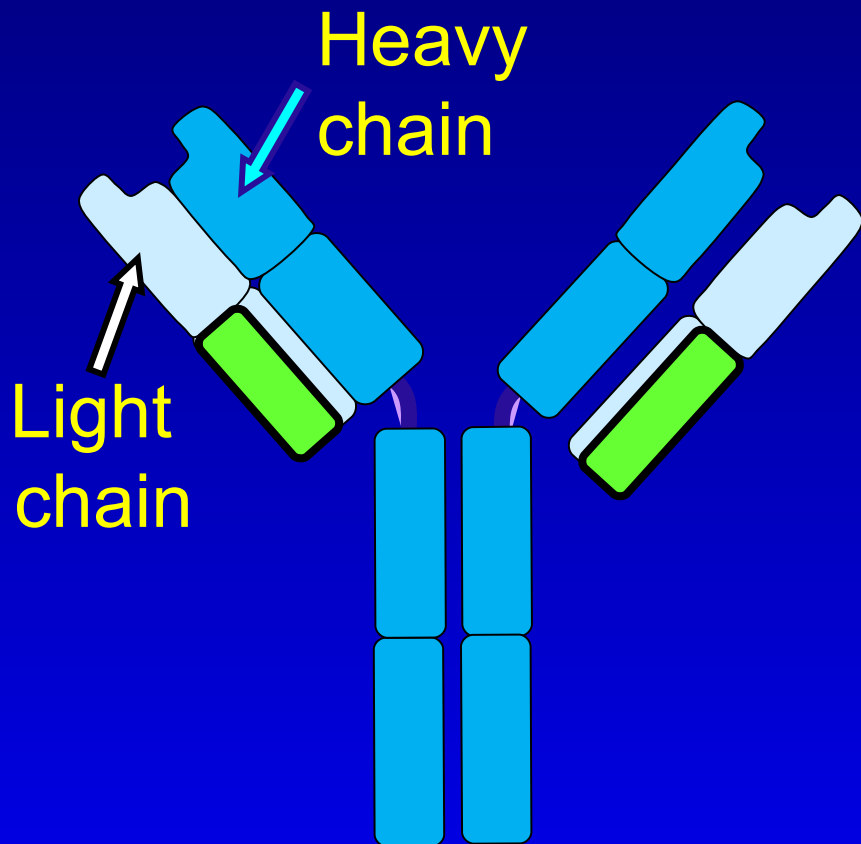
Serum free light chain immunoassay



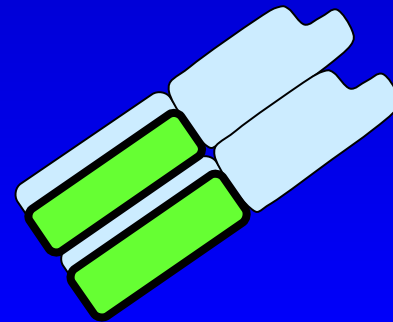
Serum free light chain immunoassay



Total light chain epitopes



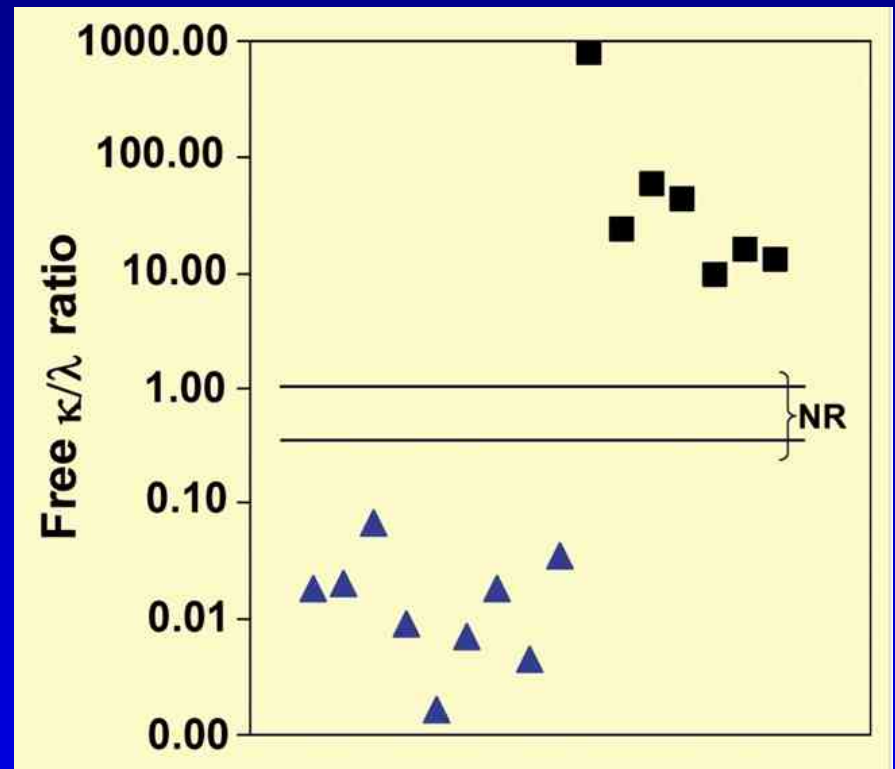
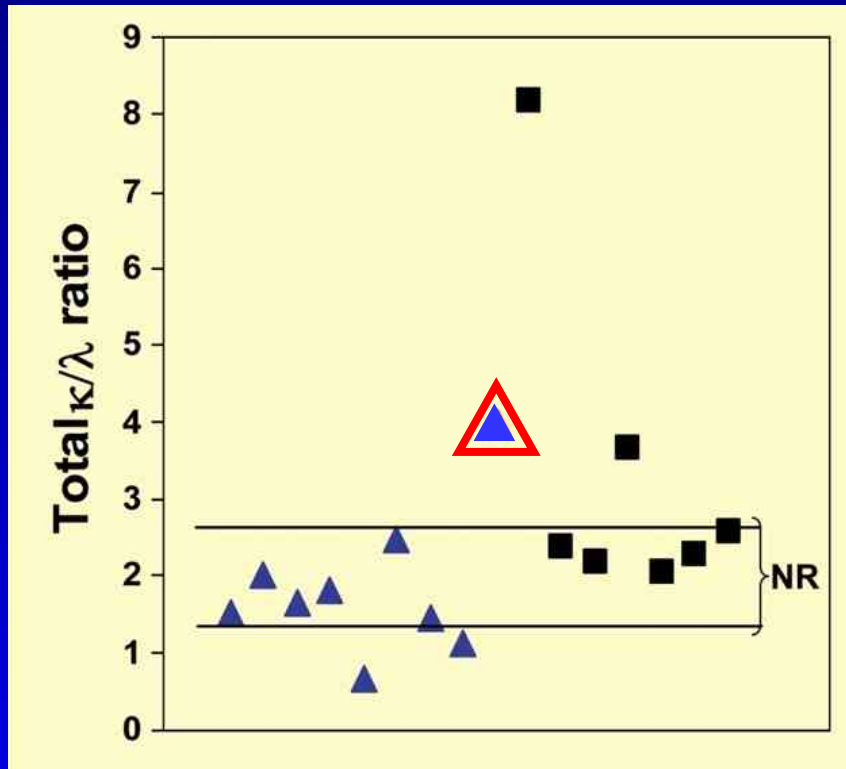
Lambda



Total LC assay

vs

Free LC assay



- Kappa LCMM
- ▲ Lambda LCMM

Total LC assay

Insensitive for detecting
free light chains

Ratio identifies intact
immunoglobulin
M-proteins

Not in guidelines

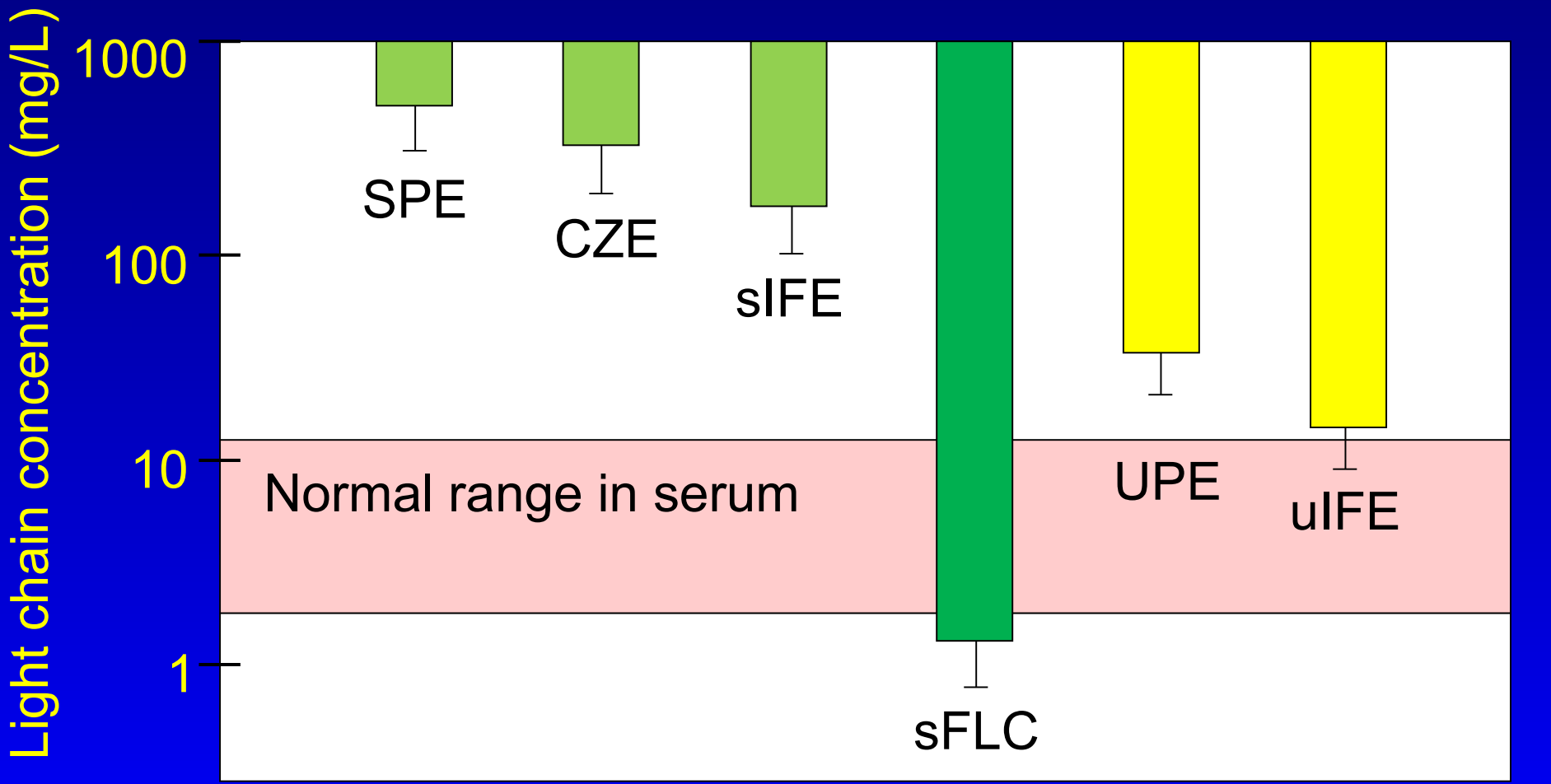
Free LC assay

Sensitive for detecting free
light chains

Ratio identifies free light
chain M-proteins

Recommended in IMWG
guidelines

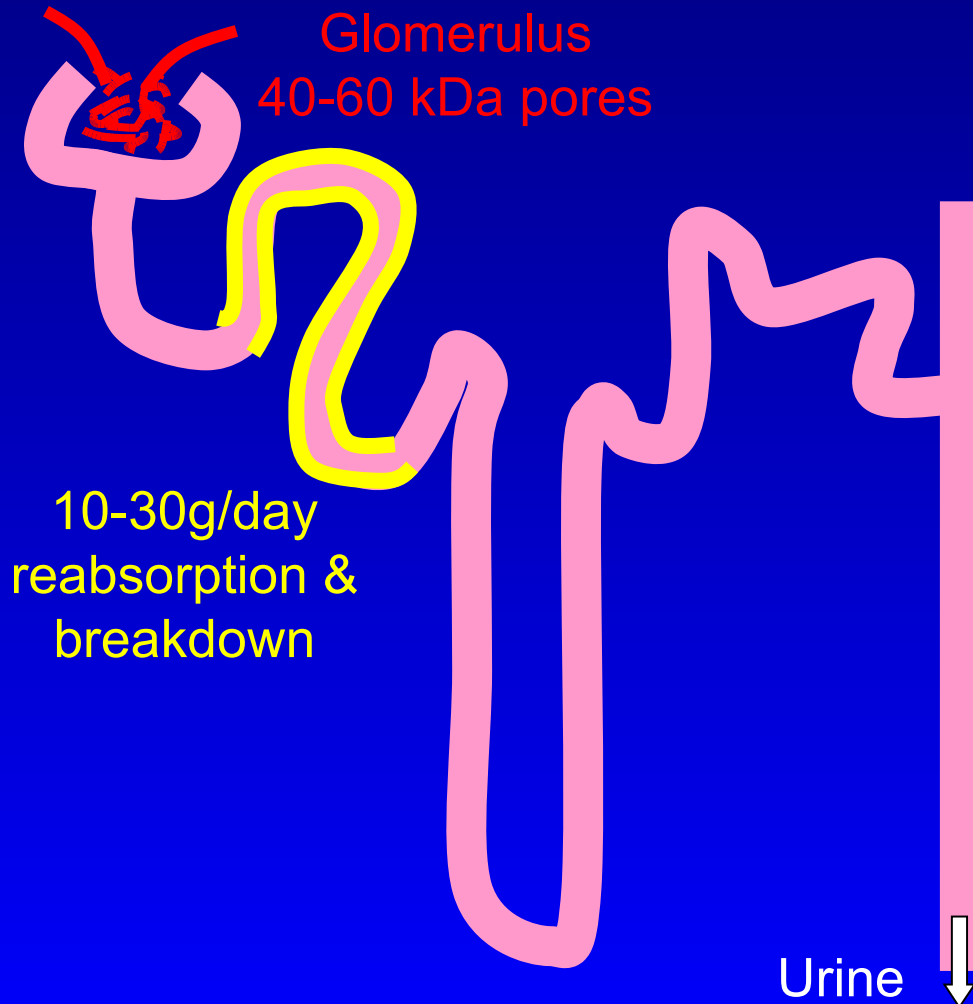
Sensitivity of light chain analysis techniques



Renal Metabolism of FLC

κ FLC - 25 kDa

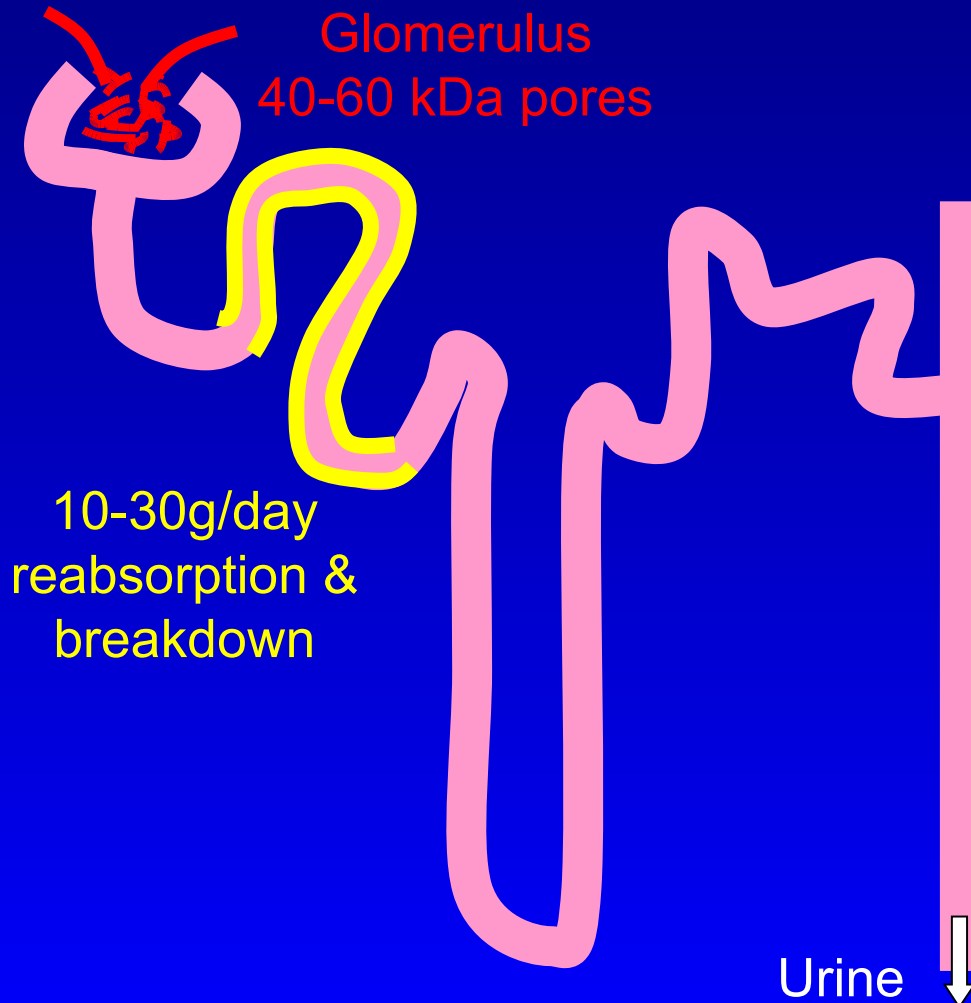
λ FLC - 50 kDa



Renal Metabolism of FLC

κ FLC - 25 kDa

λ FLC - 50 kDa



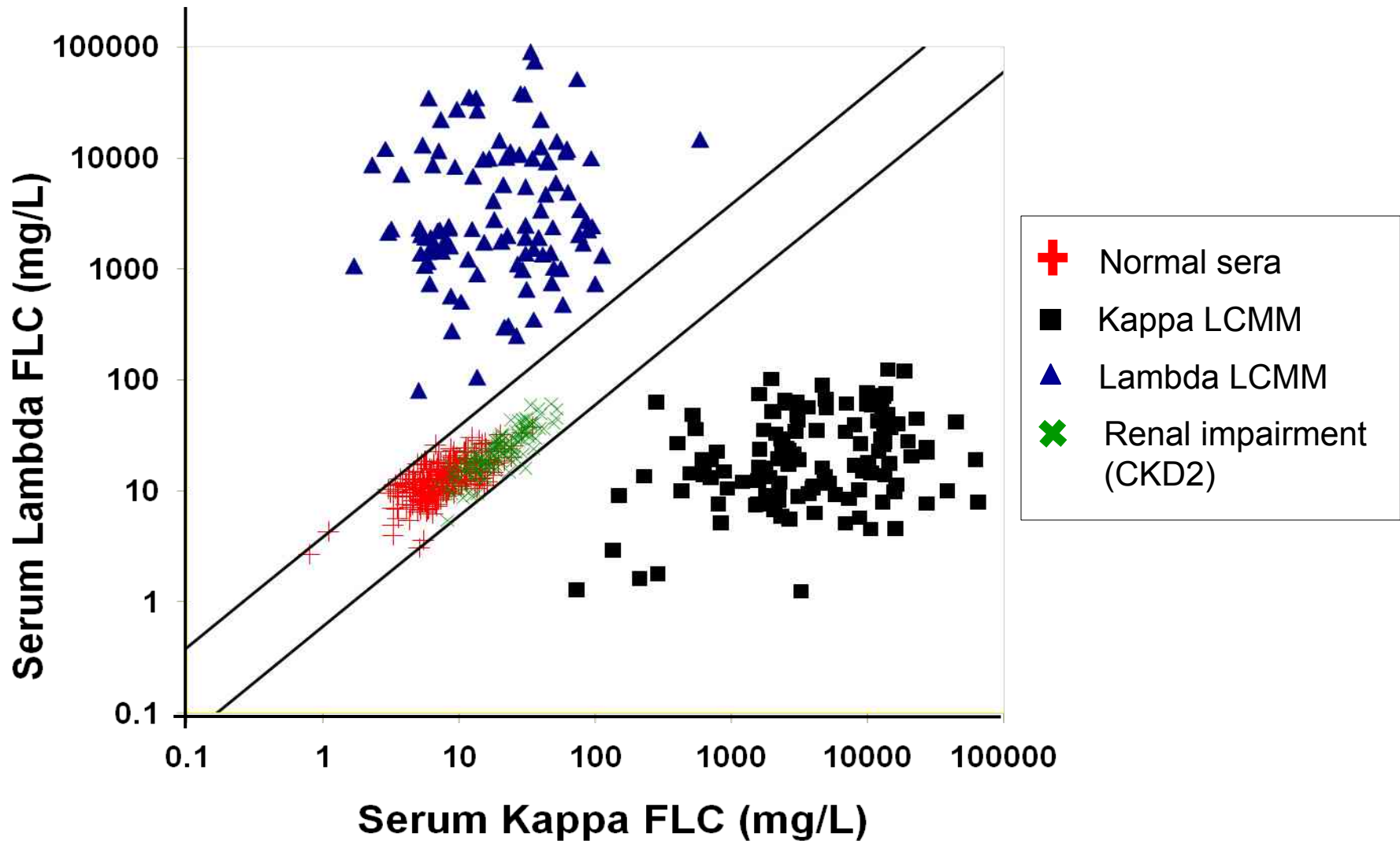
Renal metabolism results in sFLC half-life of 2-6 hours

This is in contrast to intact immunoglobulins which have half-lives of 5-21 days

Covered in this talk:

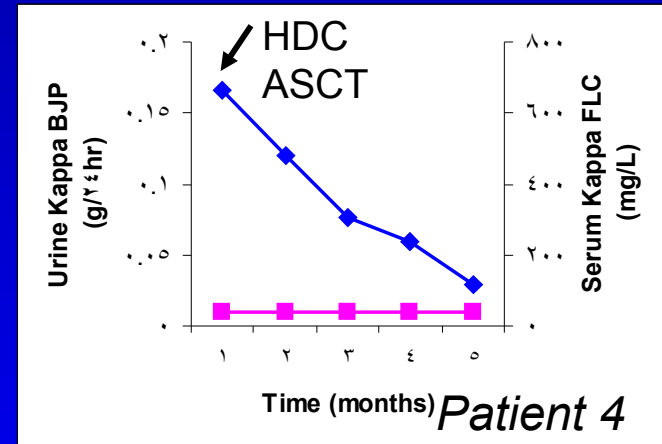
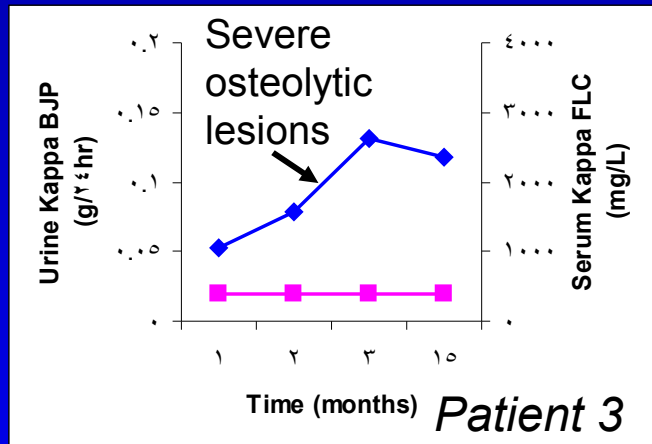
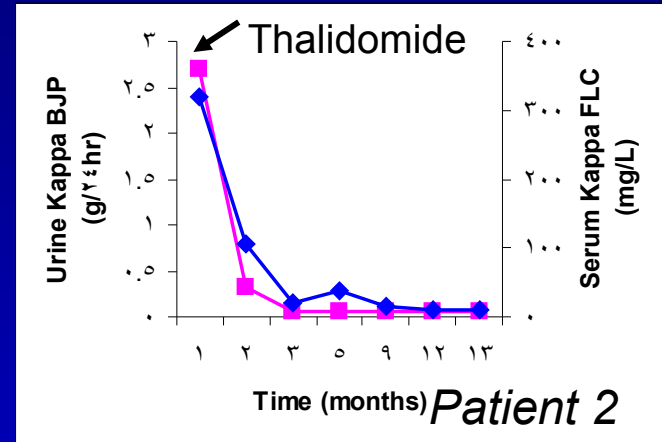
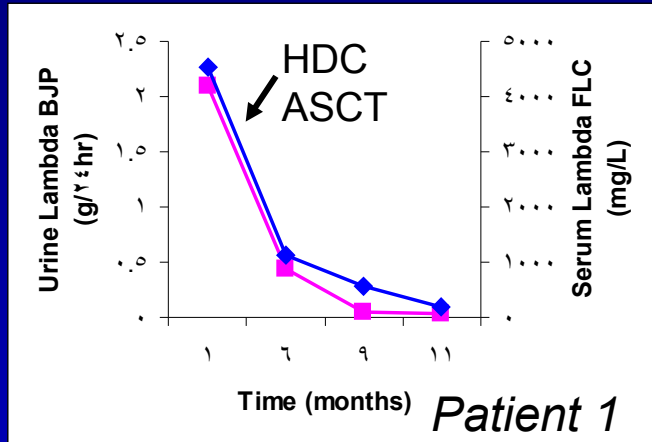
- International guidelines:
 - Monitoring
 - Screening
 - Prognosis
- Serum FLCs and renal impairment
 - Treatment of cast nephropathy
 - EuLITE trial

Light Chain Multiple Myeloma



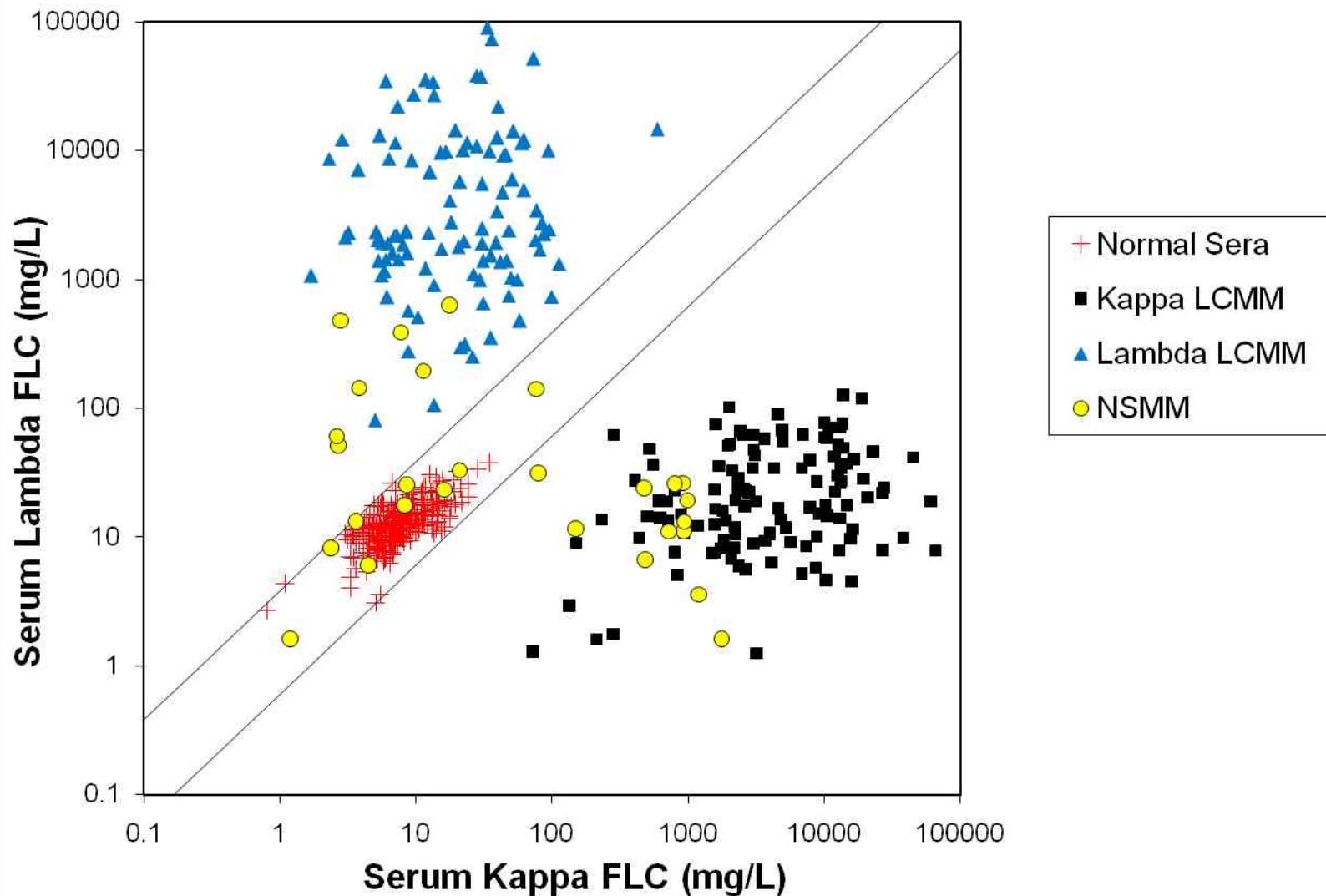
Hutchison, unpublished data; Bradwell, *Lancet* 2003; 361: 489-491

LCMM – Renal Threshold



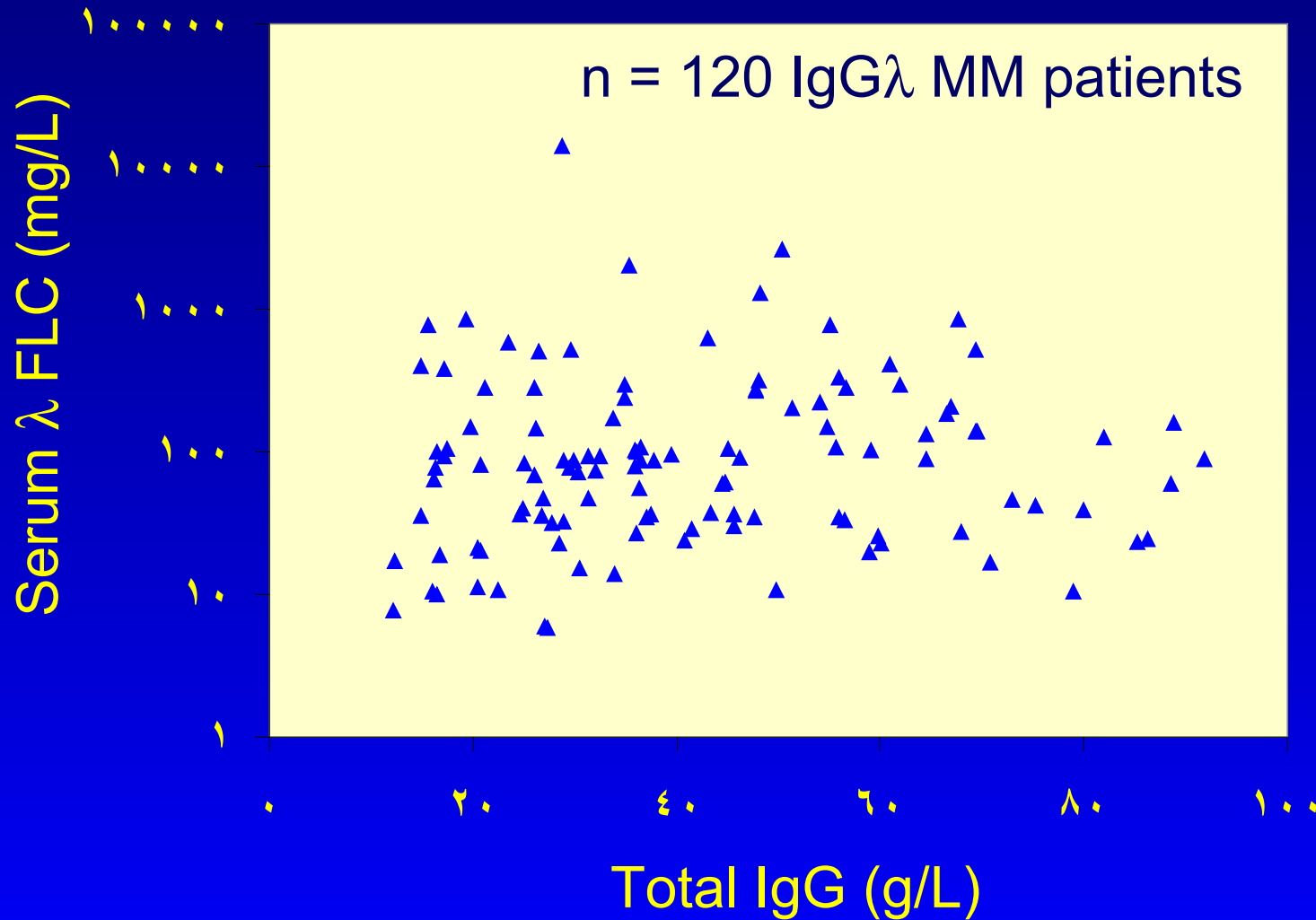
■ sFLC
■ 24 hr urine BJP excretion

Non Secretory Multiple Myeloma



Intact Immunoglobulin MM

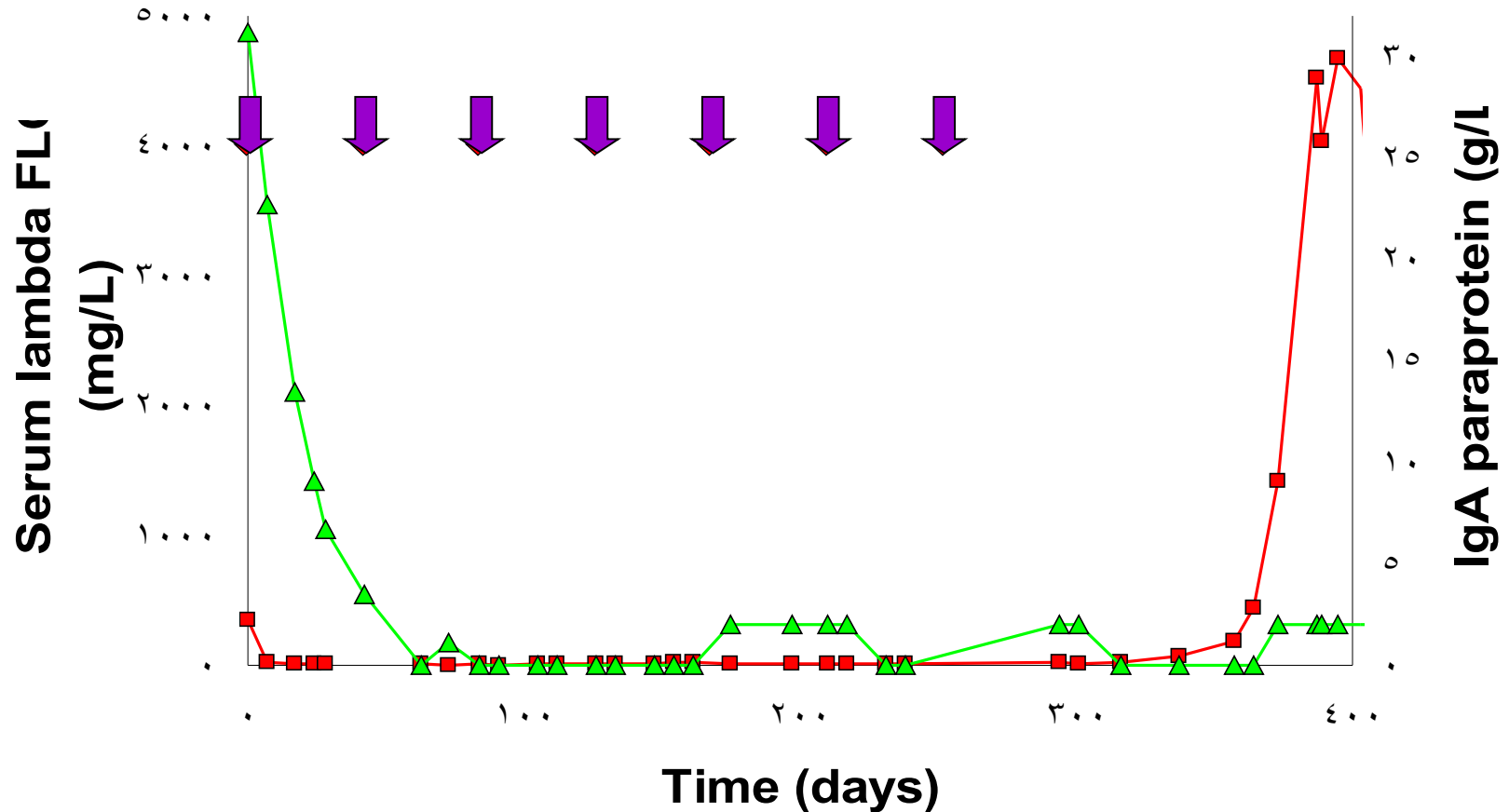
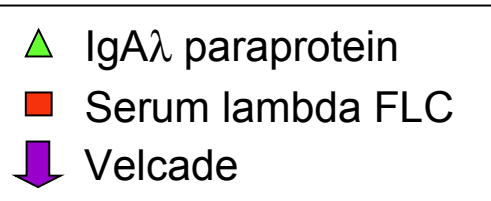
No correlation between IgG and sFLC



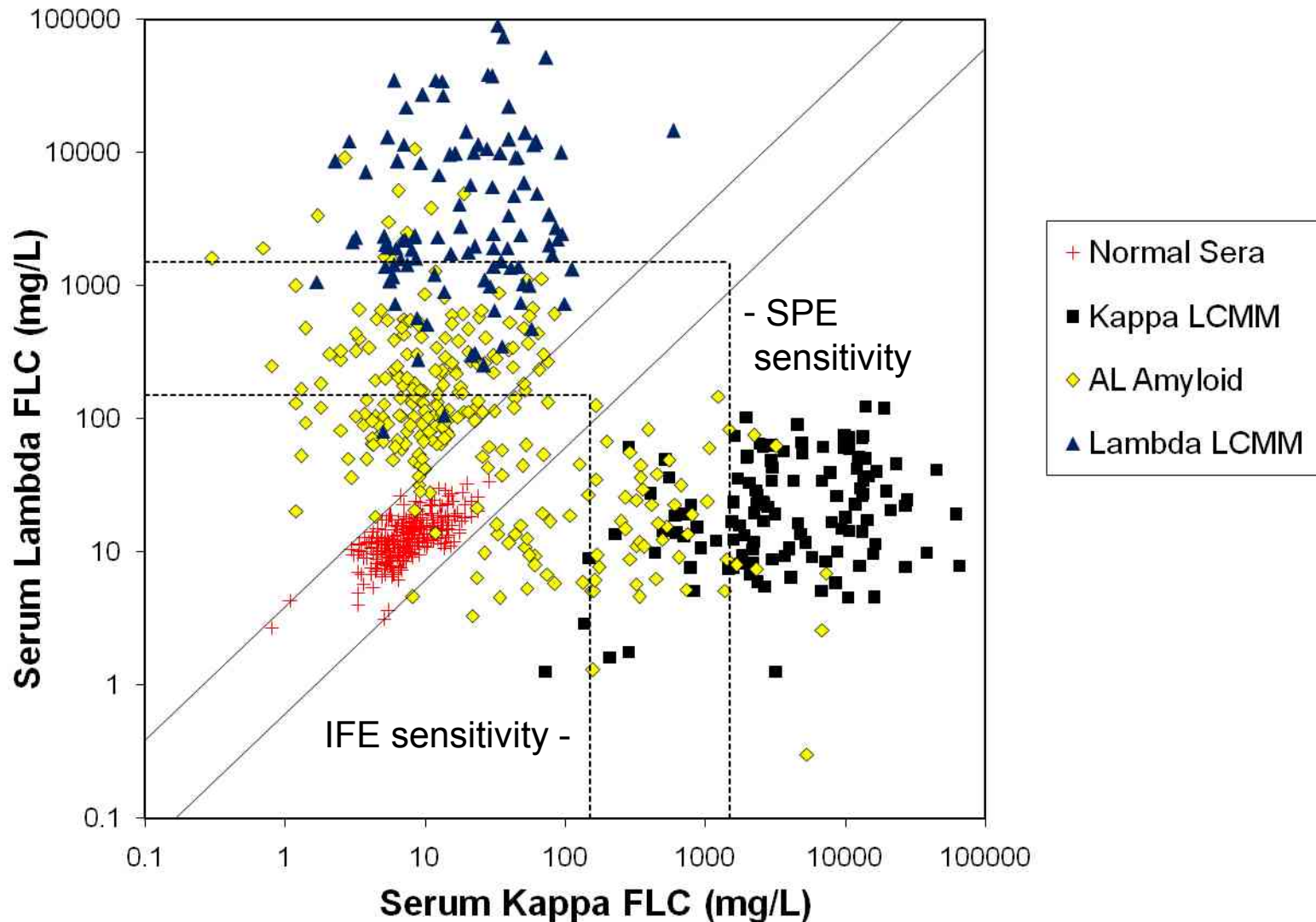
Light chain escape

- *“Rising monoclonal free light chain production at relapse without increased monoclonal intact immunoglobulin”*
- Analysis of MRC I trial:
 - 167 patients
 - 60 relapsed: 15 with LC escape

Light chain escape

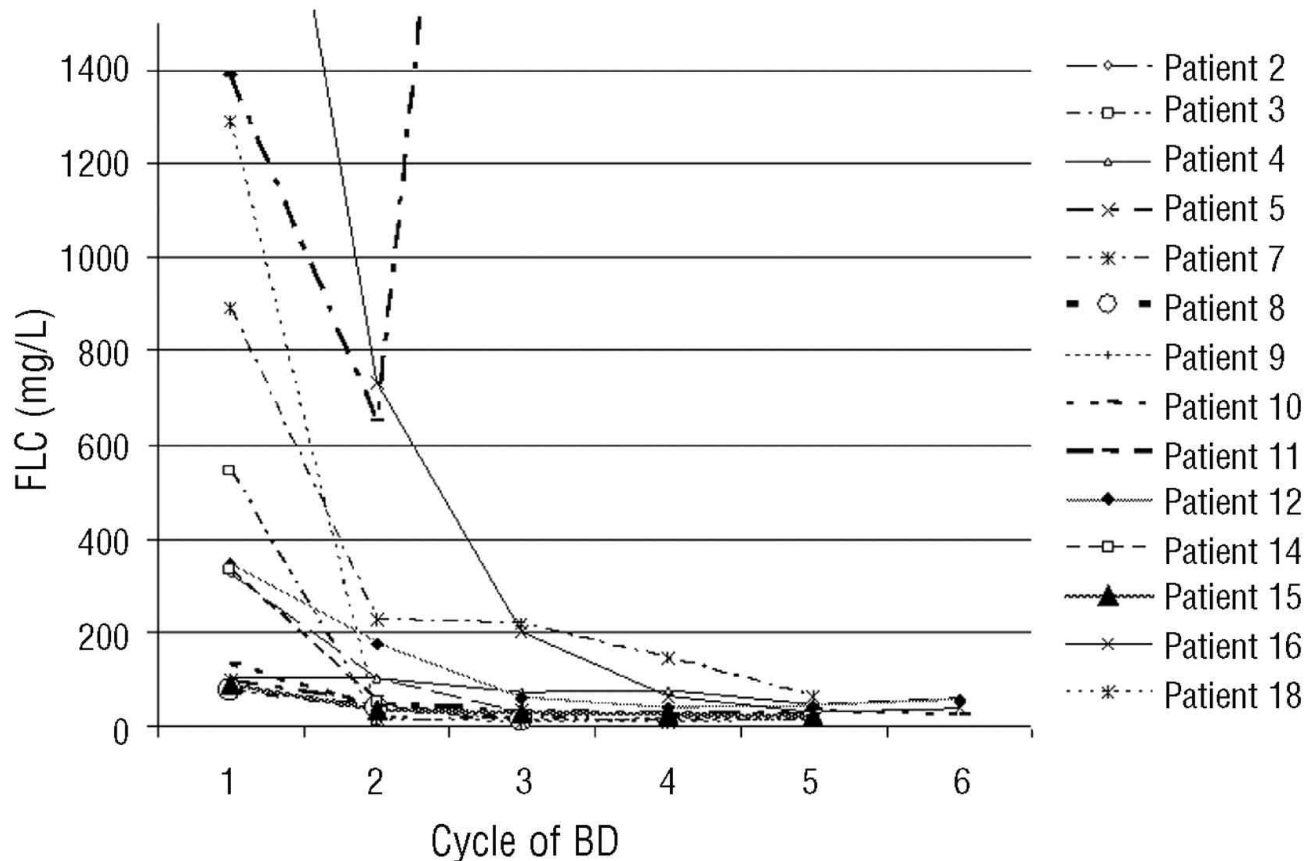


AL Amyloidosis



AL amyloidosis: BD response

“..at least a 50% reduction occurred in all [responding] patients within two courses of treatment.”

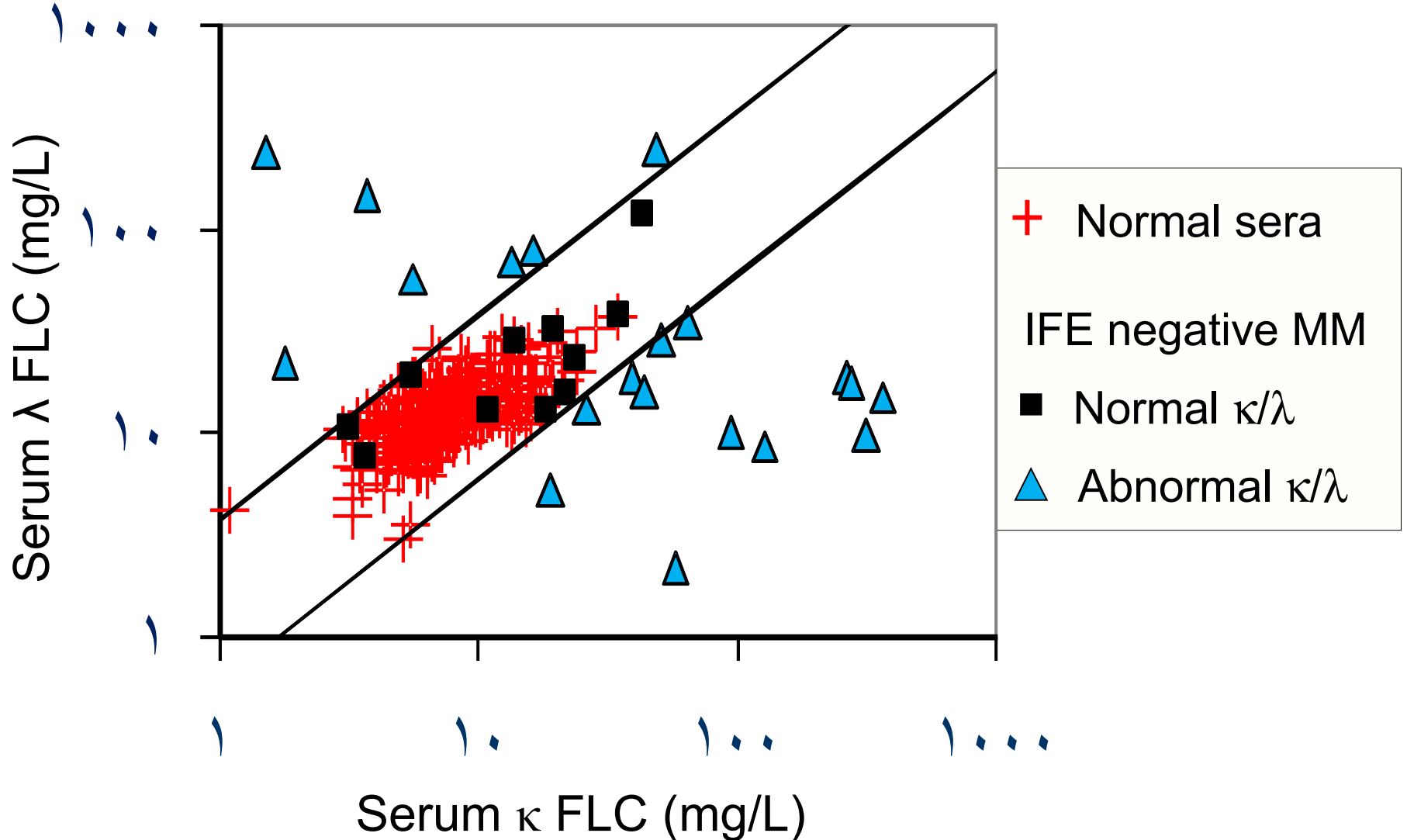


Progressive disease

International guidelines for sFLC analysis in MM and related disorders

- Assessment of response
 - Serial sFLC should be routinely performed in:
 - AL amyloidosis
 - Oligosecretory MM
 - LCDD (personal experience of authors)
 - Periodic urine or sFLC assessment for LCE

sFLC identify residual disease



International guidelines for sFLC analysis in MM and related disorders

- Assessment of response

- All MM patients to define a *stringent CR*

CR	Stringent CR
Negative S/U IFE BM plasma cells $\leq 5\%$	Negative S/U IFE Normal sFLC ratio Absence of clonal cells in BM

Screening for Monoclonal Gammopathy



Serum electrophoresis



Urine electrophoresis

***Can the sFLC increase detection of MG and
replace the need for urine electrophoresis?***

Replacement of urine tests with sFLC

- 428 urine samples positive by uIFE
- On paired serum samples:

Serum electrophoresis + sFLC missed only 2 urine positive light chain MGUS patients

No significant pathology was missed

International guidelines for sFLC analysis in MM and related disorders

- Screening

- Recommended in combination with serum electrophoresis
- sFLC can replace 24 h urine IFE*

**For AL screening, 24 h urine IFE still recommended*

Dispenzieri et al *Leukemia* (2009) 23, 215–224

Serum FLCs are prognostic in:

- MGUS progression
- Myeloma outcome
- Smouldering MM progression
- Plasmacytoma progression
- AL amyloidosis outcome
- B-CLL outcome
- Waldenstrom's outcome

Monoclonal gammopathy of undetermined significance

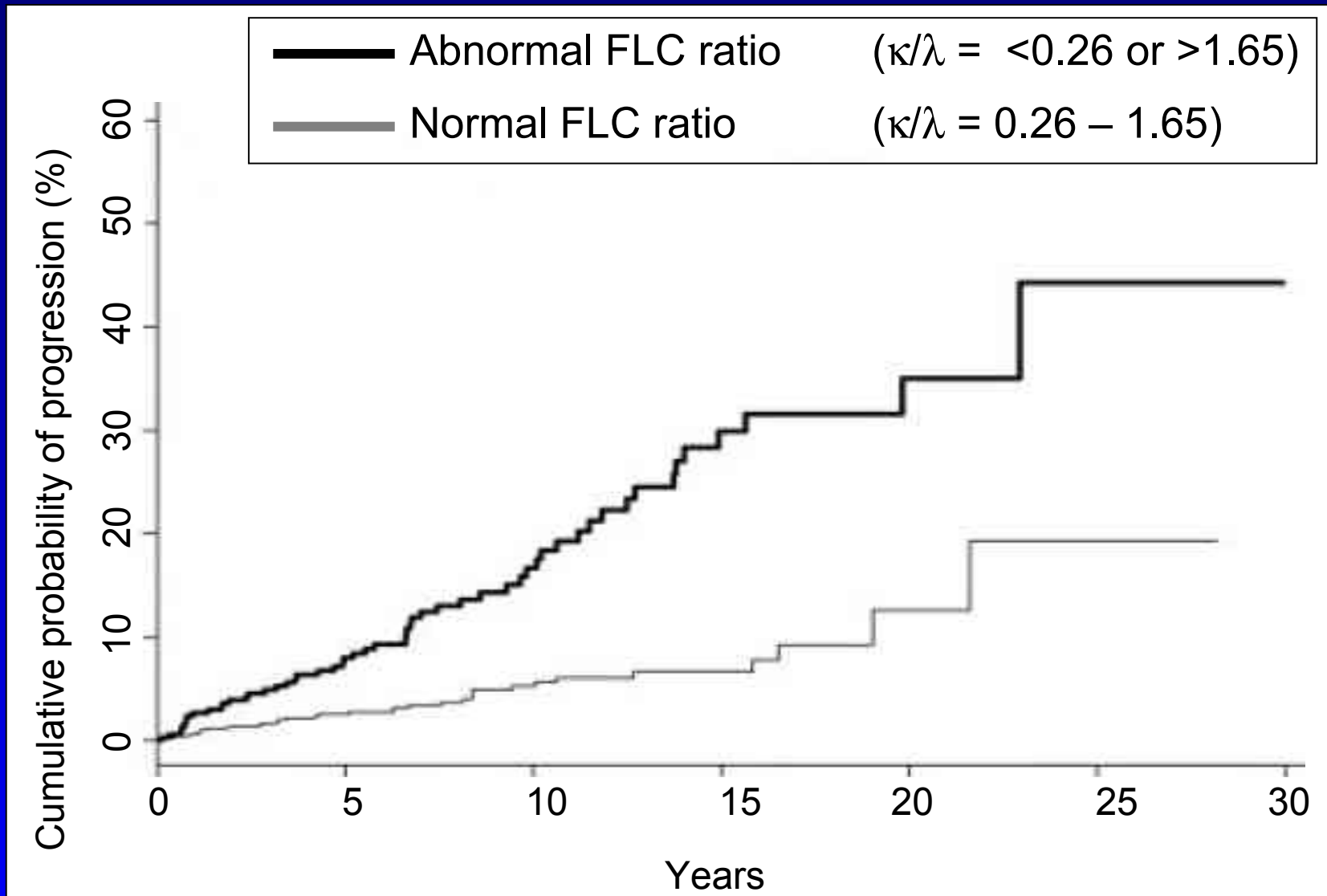
Incidence: 1-2 % of individuals > 50 years

Risk of progression 1% per year

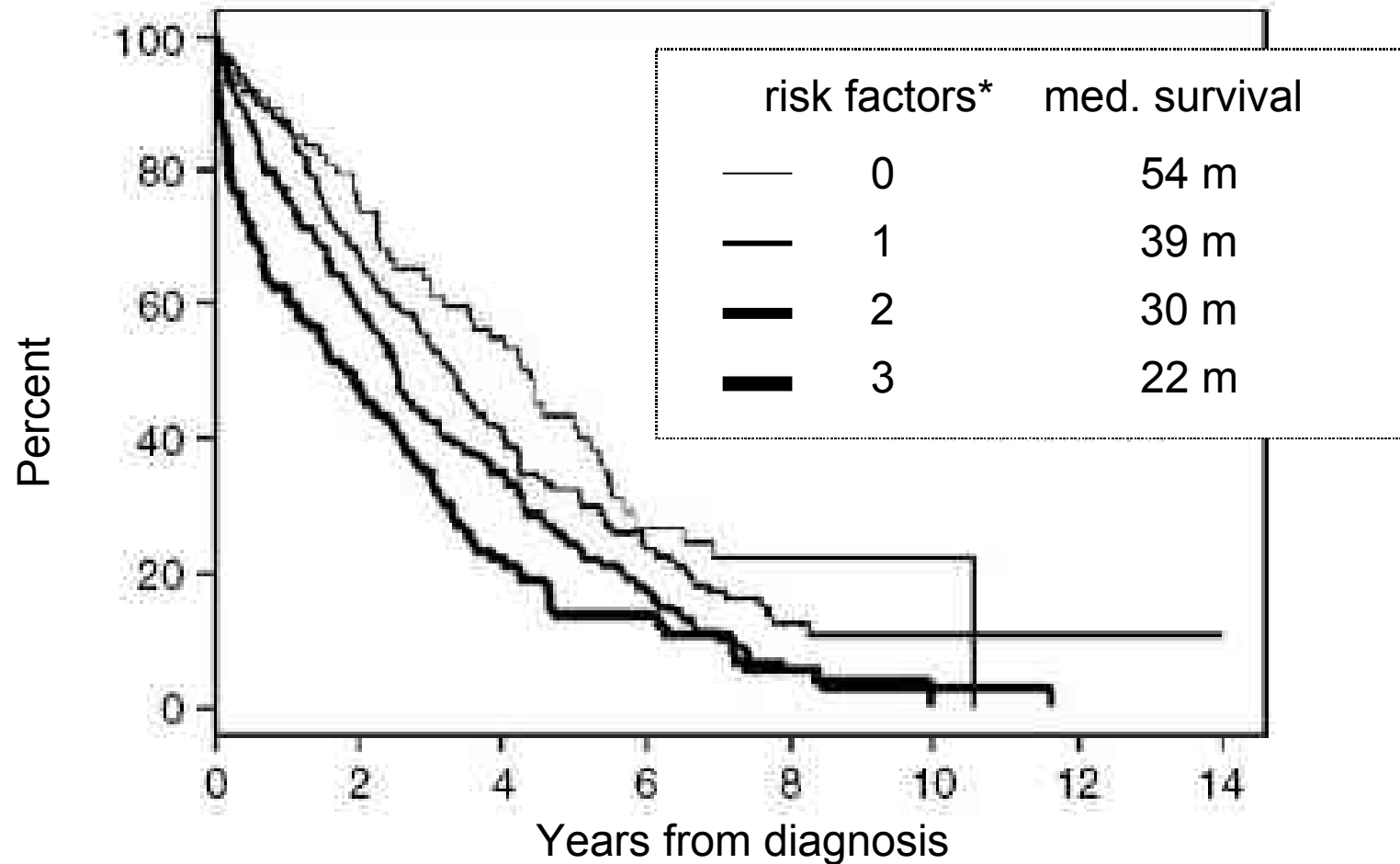
Follow up MGUS patients:

How frequently?

MGUS progression



Multiple myeloma survival



* sFLC κ/λ <0.03 or >32 , albumin < 35 g/L, $\beta 2$ MG ≥ 3.5 mg/L

International guidelines for sFLC analysis in MM and related disorders

- Prognosis

- sFLC should be measured at diagnosis for all patients with MGUS, SMM or MM, solitary plasmacytoma and AL amyloidosis

Dispenzieri et al *Leukemia* (2009) 23, 215–224

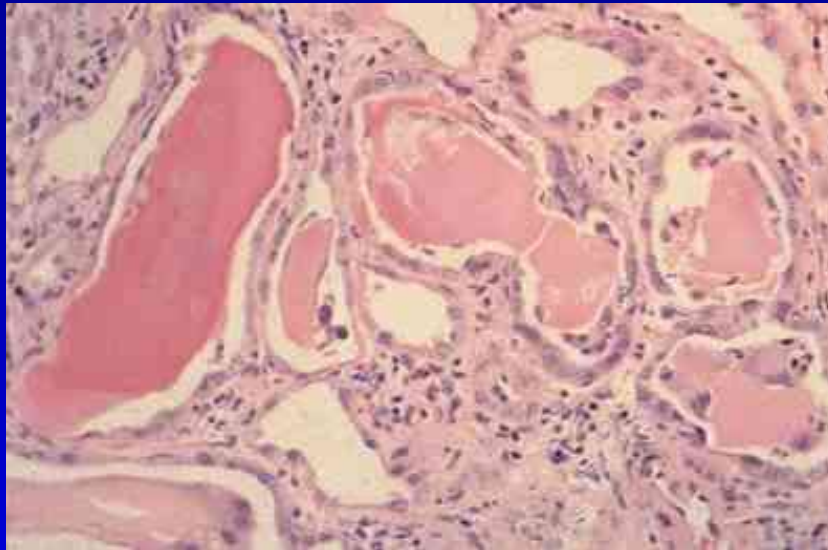
Covered in this talk:

- International guidelines:
 - Monitoring
 - Screening
 - Prognosis
- Serum FLCs and renal impairment
 - Treatment of cast nephropathy
 - EuLITE trial

Myeloma and renal insufficiency

- 10 – 20% myeloma patients present with acute renal failure

Cast
Nephropathy:



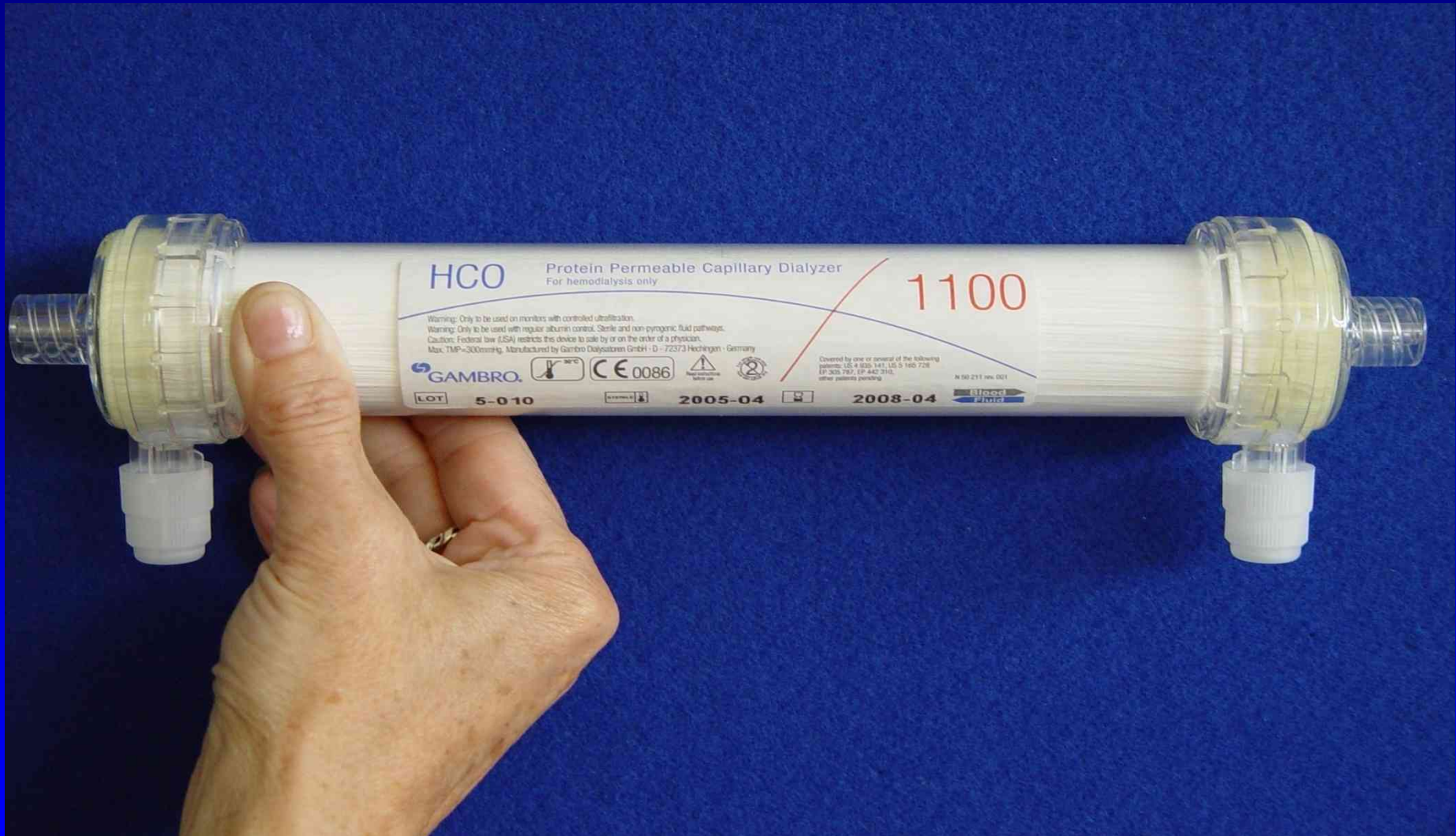
- 10% remain dialysis dependent long term
 - *There is a high mortality rate*
 - *Chemotherapy and transplantation are hazardous*

sFLC Removal - Plasma Exchange

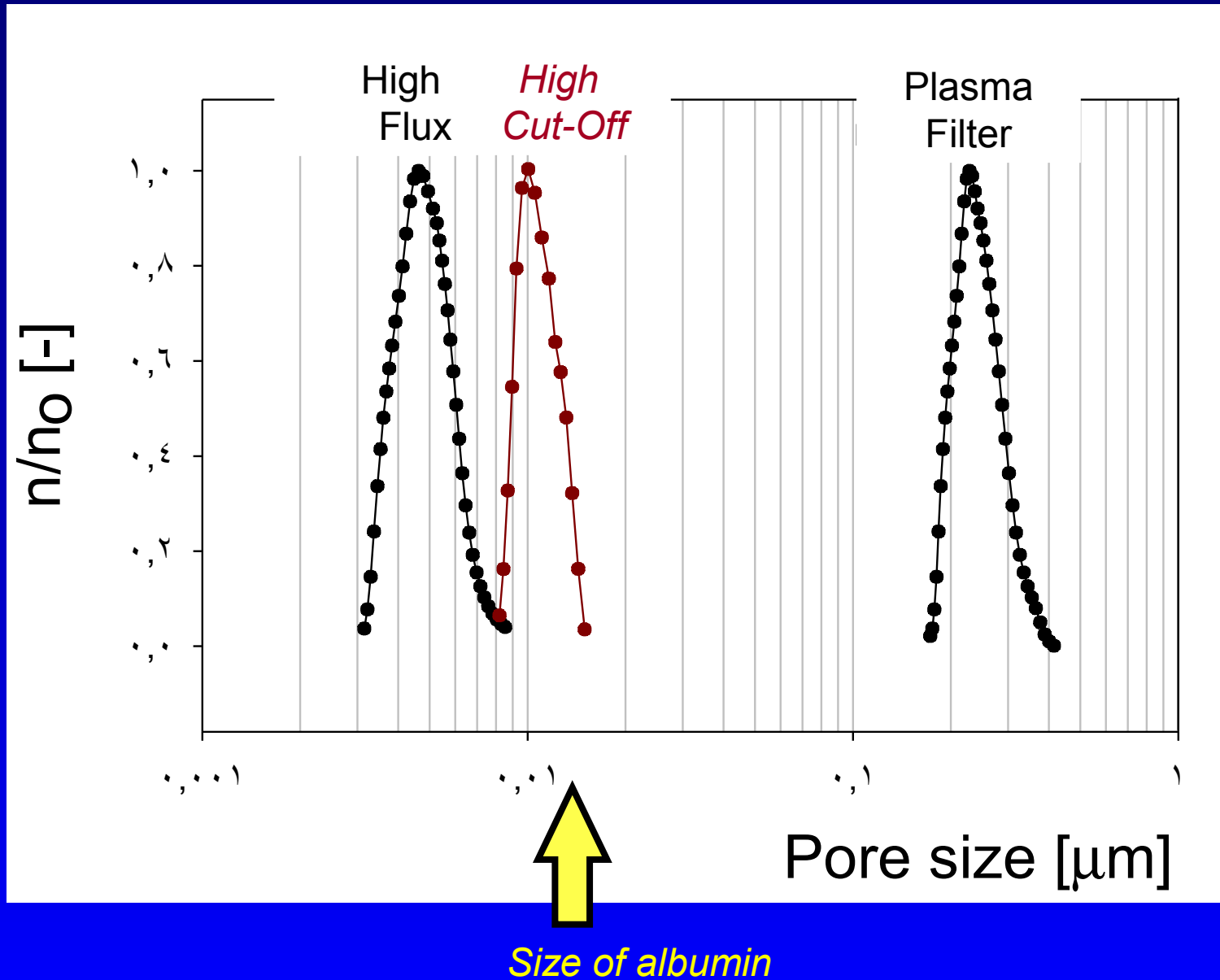
Logical but clinically unsuccessful because:

- Plasma exchange procedures are of limited duration and frequency
- Typical recovery rates: 10 - 20%

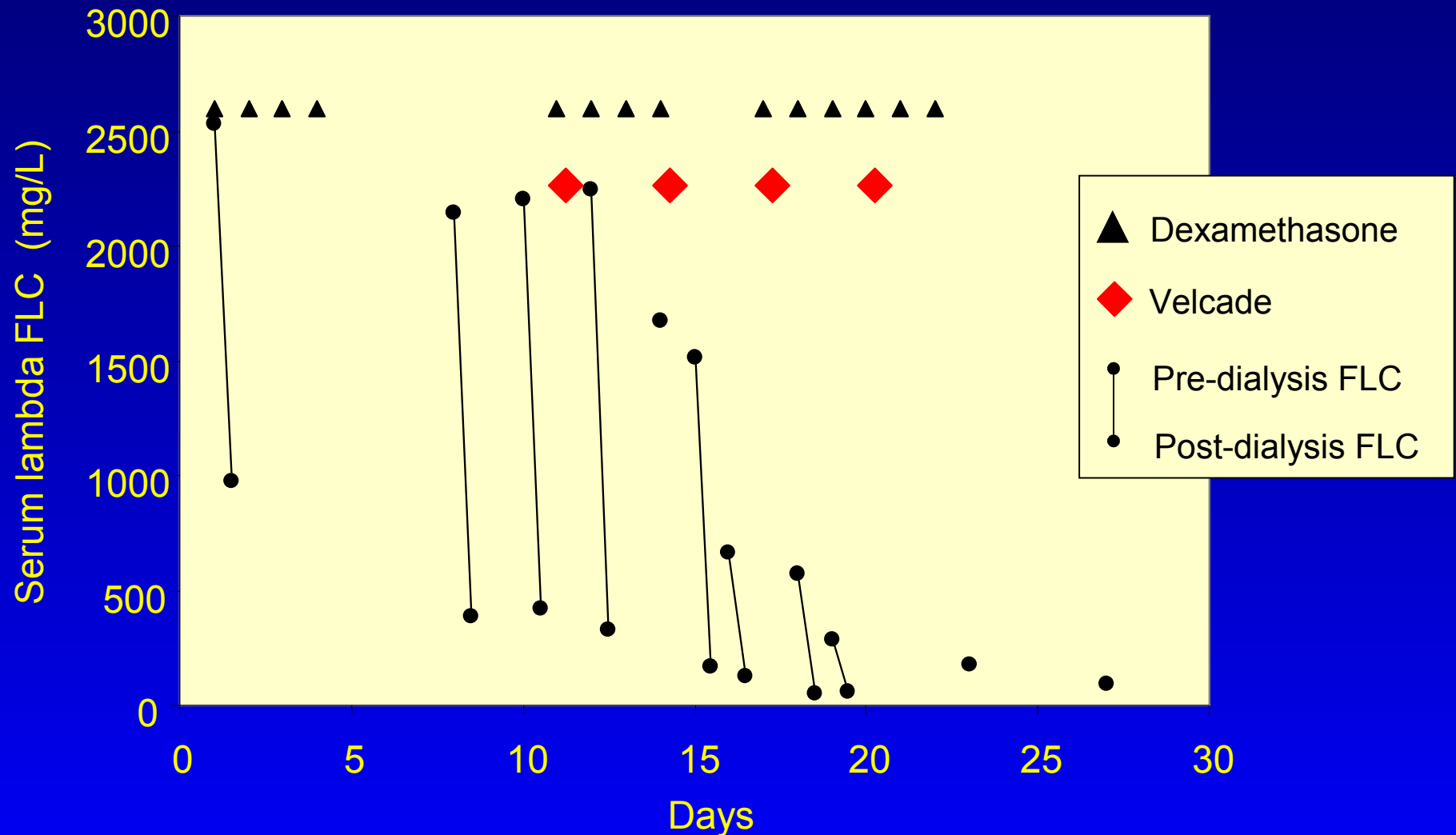
Gambro (high cut-off) protein-leaking dialyser



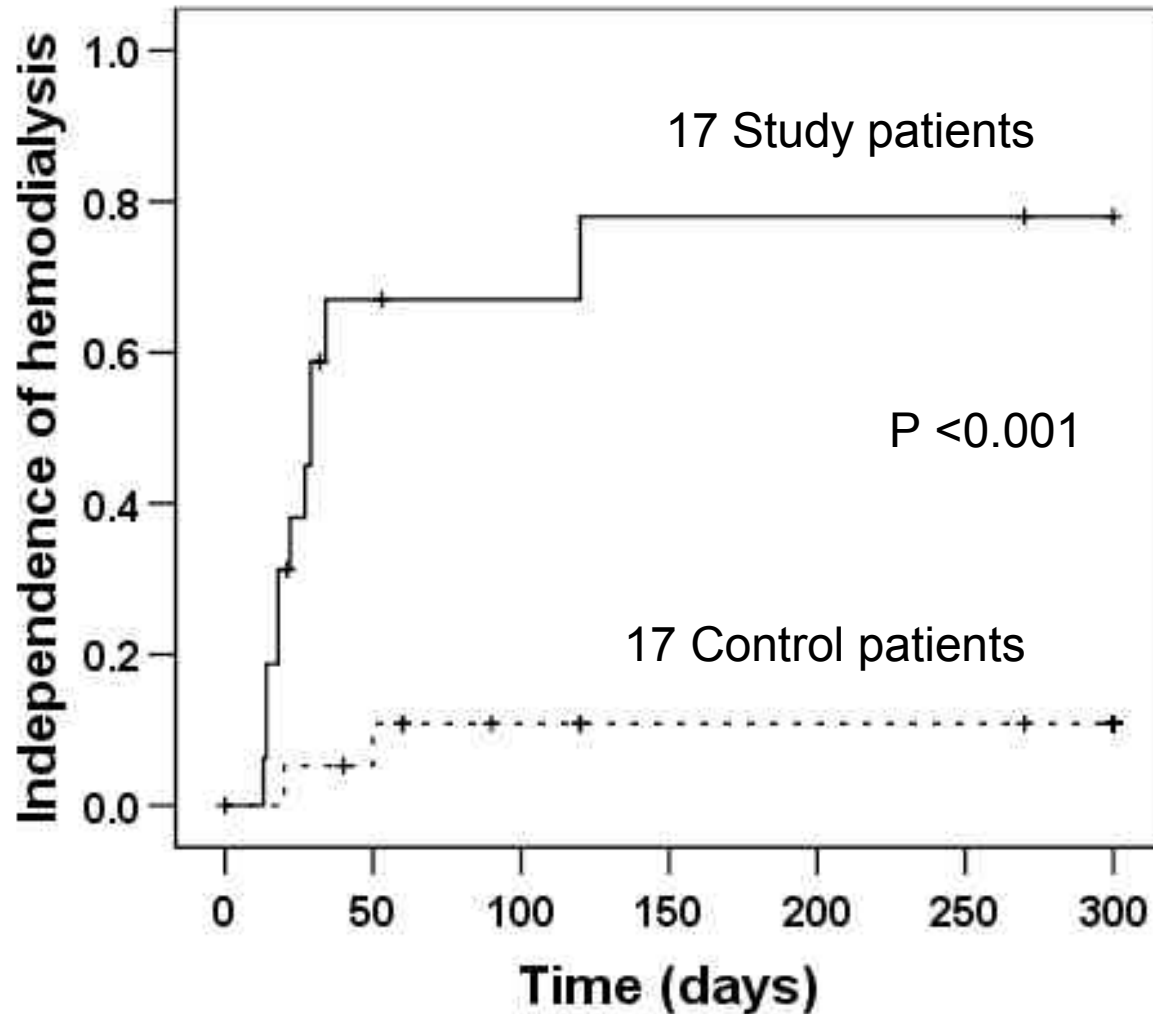
Distribution of filter pore sizes



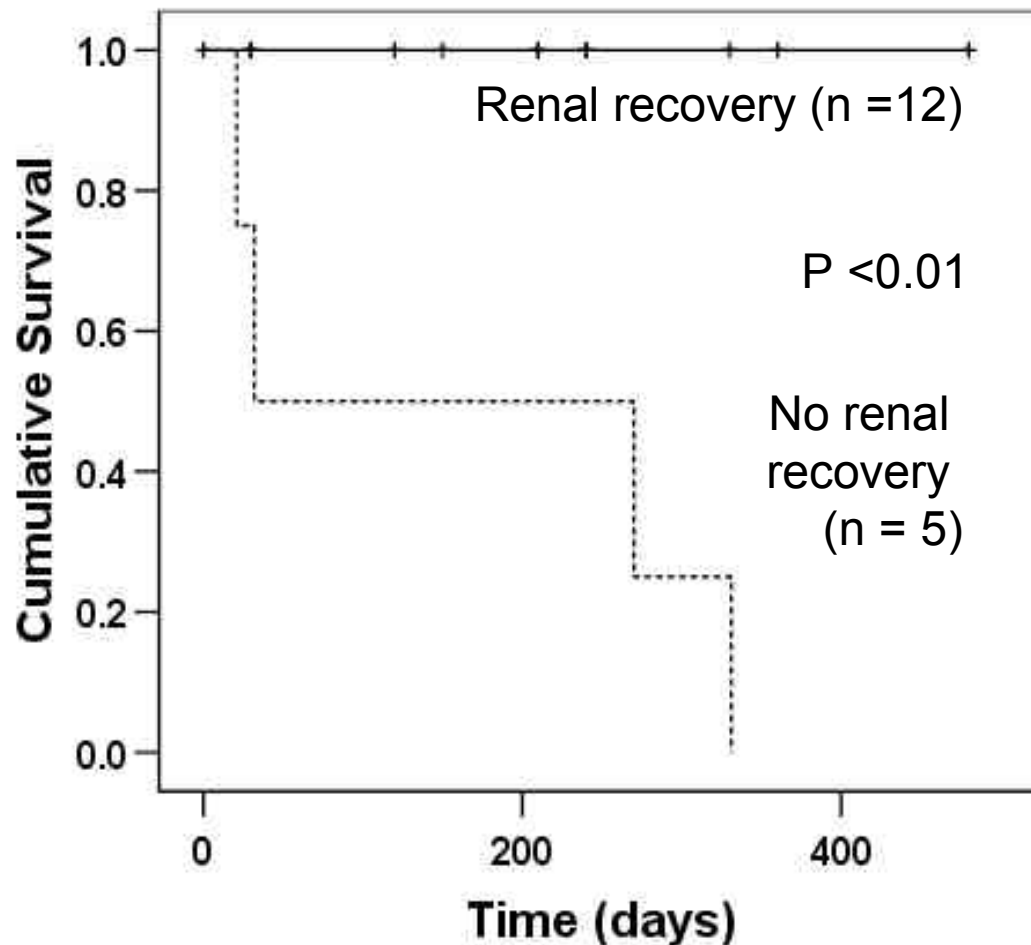
Patient 3:



Pilot study: Renal recovery rates



Pilot study: survival relates to recovery of renal function



European Trial of Free Light Chain Removal by Extended Haemodialysis in Cast Nephropathy



Contact:

Dr Colin Hutchison
cah692@bham.ac.uk

Summary

International serum FLC guidelines from IMWG:

Screening

- sFLC in combination with SPE/sIFE
- Eliminates need for 24 hour urine
(with exception of AL amyloidosis)

Prognosis

Measure sFLC at diagnosis:

- MGUS, SMM
- Solitary plasmacytoma, MM
- AL amyloidosis

Monitoring

Routine serial sFLC measurements:

- AL amyloidosis
 - Oligosecretory MM
 - All MM patients to define a *stringent CR*

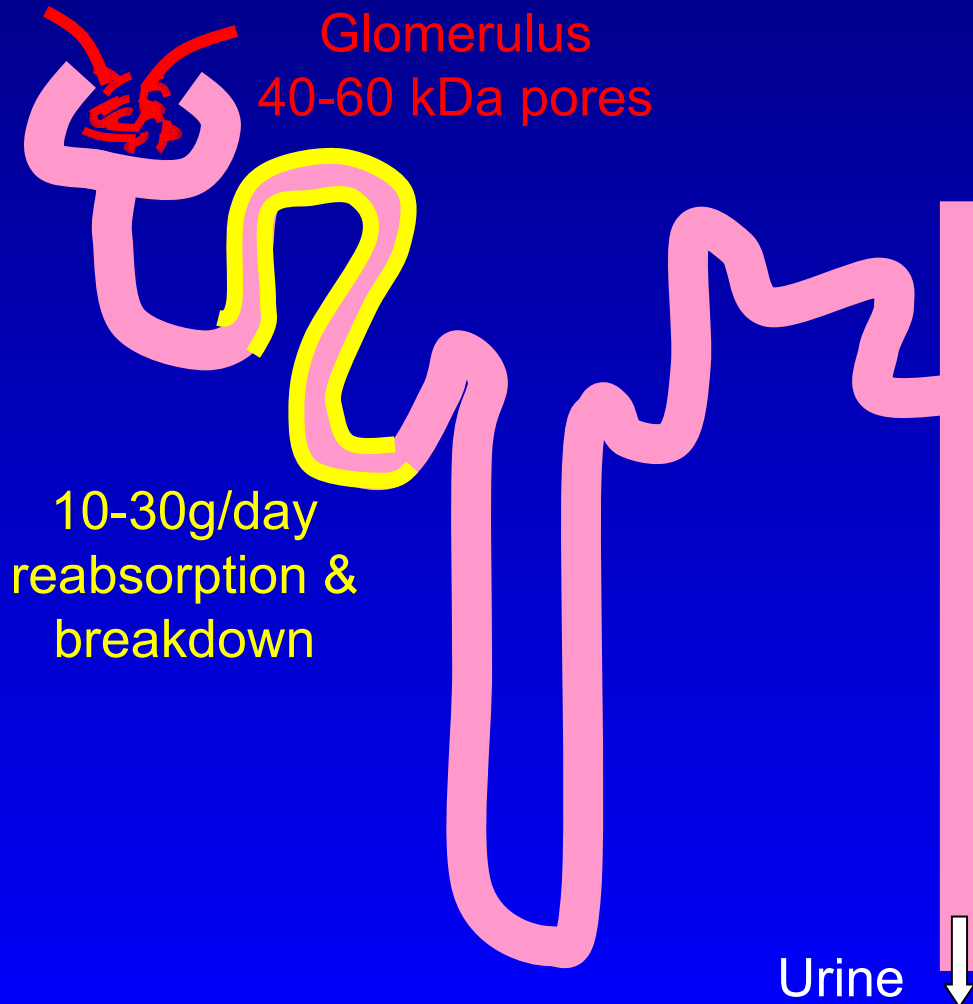
Any Questions?

- ***alex.legg@bindingsite.com***

Renal Metabolism of FLC

κ FLC - 25 kDa

λ FLC - 50 kDa



Serum free light chain immunoassay platforms

BECKMAN COULTER	IMAGE, IMAGE 800
BINDING SITE	SPA _{PLUS}
OLYMPUS	AU400 / 640 / 2700 / 5400
ROCHE	MODULAR P Cobas Integra 400 / 800 Cobas c501
ROCHE (Hitachi)	911, 912 , 917
SIEMENS (Bayer)	ADVIA 1650 / 1800 / 2400
SIEMENS (Dade Behring)	BNII, Prospec

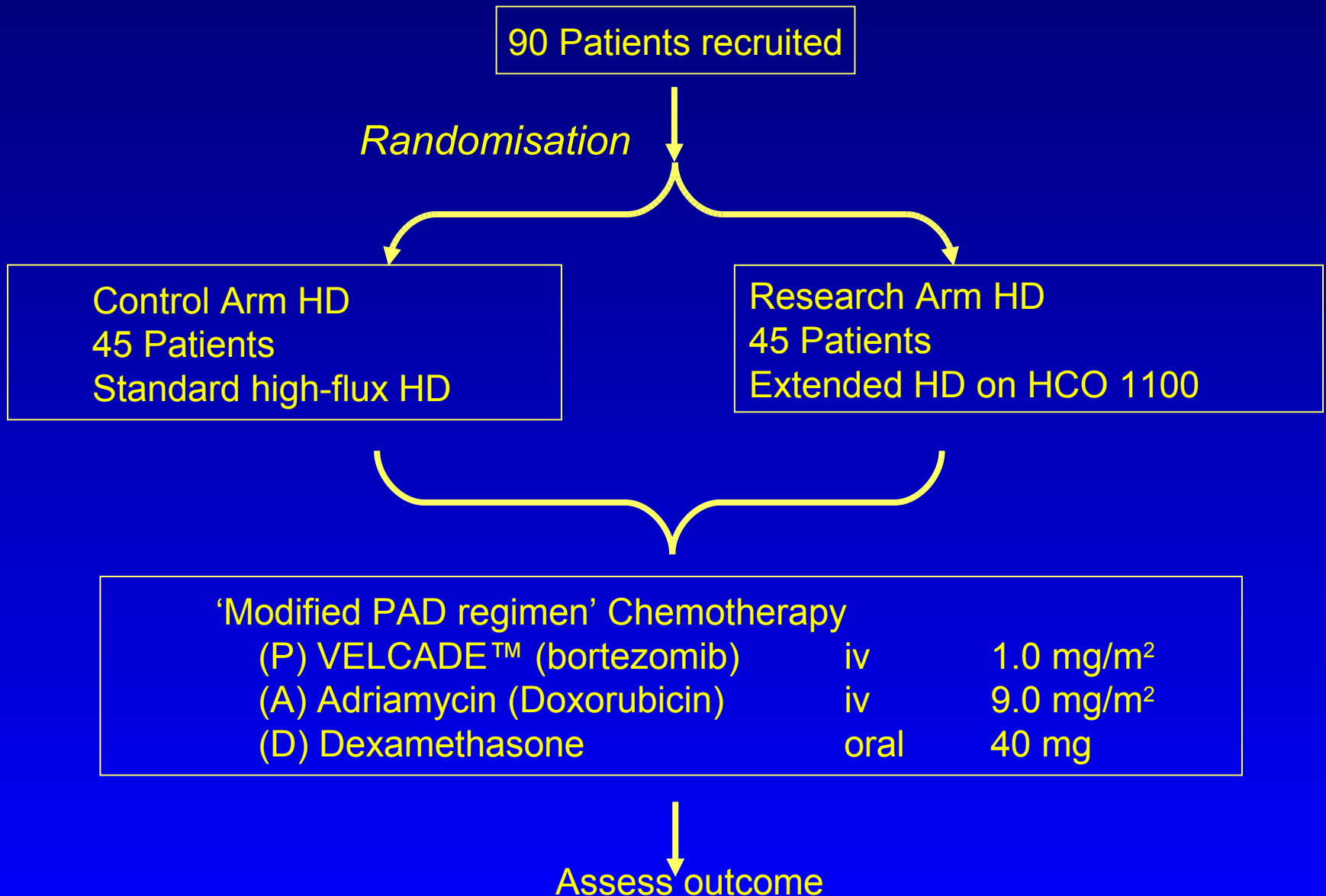
Risk stratification summary:

	Risk Factors		
	No.	Serum FLC ratio	Other risk factors
MGUS	3	<0.26 or >1.65	M-protein size M-protein type
SPB	2	<0.26 or >1.65	M-protein size
SMM	3	<0.125 or >8	% BM plasma cells M-protein size
MM	3	<0.03 or >32	Albumin β2-microglobulin

Patient inclusion criteria

- Dialysis dependent renal failure, renal biopsy proven cast nephropathy
- Fulfills diagnostic criteria for the diagnosis of symptomatic de novo MM
- Abnormal sFLC ratio and sFLC > 500 mg/L
- Informed consent
- Commencement of study within 10 days of presentation

Randomised and controlled



Trial time course

Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22 onwards
Research arm HD (Hours)	√ (6)		√ (8)	√ (8)		√ (8)	√ (8)	√ (8)		√ (8)	√ (8)		√ (8)		√ (8)		√ (8)		√ (8)		√ (8)		Accord. to clin need (6)
Chemo		V A D	A D	A D	V A D				V D*	D*	D*	D*				D*	D*	D*	D*				As per PAD protocol
sFLC measured	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

sFLC measured

- at assessment
- pre dialysis
- post dialysis
- non-dialysis

Run within 24 hours

Run once /week