Myeloma cast nephropathy

Frank Bridoux, Nelson Leung, Colin A. Hutchison

Departments of Nephrology, Poitiers France, Mayo Clinic, Rochester MN, USA, Birmingham, UK

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Conflict of Interest

- Dr Bridoux – Research funding Celgene
- Dr Leung - Travel grant from Binding Site
- Dr Hutchison – Research funding Gambro

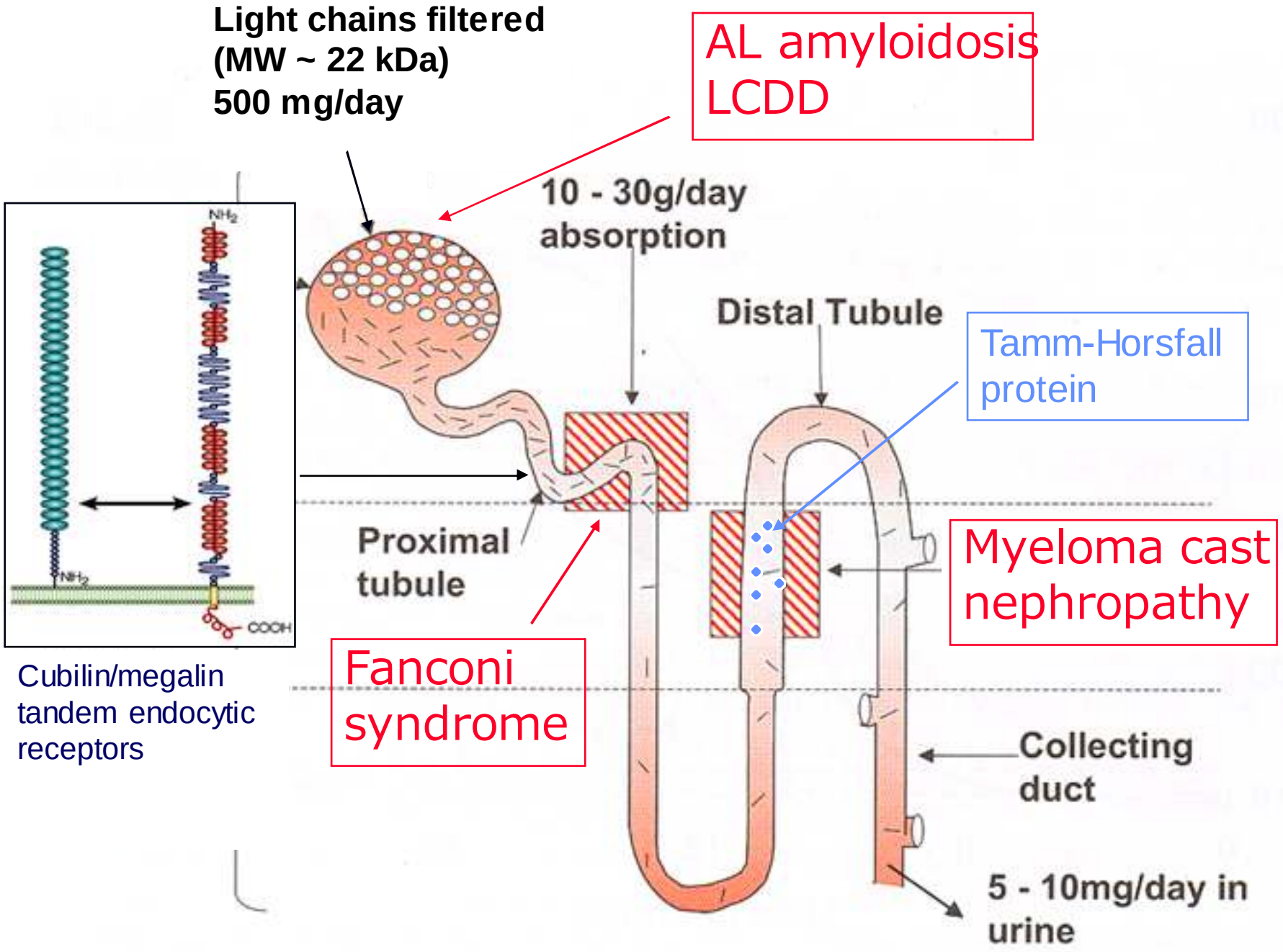
Renal insufficiency in multiple myeloma

- Frequency
  - 25-50% of patients during the course of MM
  - 20-40% at presentation, 10% requiring dialysis
- Causes
  - Mostly-LC related :
    - Myeloma cast nephropathy : ~ 75% of all causes of AKI
    - AL amyloidosis, LCDD (possible associations)
  - Other :
    - Glomerular deposition of monoclonal entire Ig/heavy chain
    - Dehydration, hypercalcemia, infections, nephrotoxic drugs….
- Prognosis
  - Recovery of renal function : ~ 50% of patients (< 20% if dialysis)
  - Persistent RI associated with poor patient survival

Rota S. Medicine (Baltimore) 1987; 66: 126

Alexanian R. Arch Intern Med 1990; 150: 1693

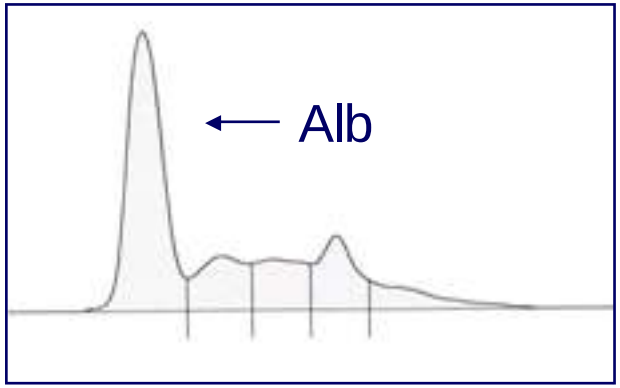
Bladé J. Arch Intern Med 1998; 158: 1889


Light chains filtered
(MW ~ 22 kDa)
500 mg/day
AL amyloidosis
LCDD
10 - 30g/day
absorption
Distal Tubule
Tamm-Horsfall
protein
Proximal
tubule
Myeloma cast
nephropathy
Fanconi
syndrome
Collecting
duct
5 - 10mg/day in
urine
Cubilin/megalin
tandem endocytic
receptors

Renal insufficiency and myeloma: Diagnosis

Urine protein electrophoresis

Albuminuria >40% (>1g/day)

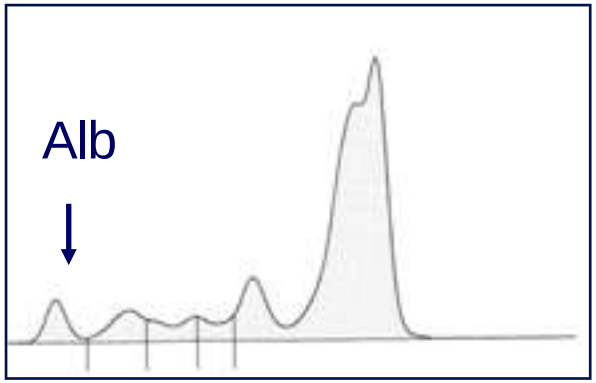


Extra-renal biopsy

Kidney biopsy

Renal insufficiency and myeloma: Diagnosis

Urine protein electrophoresis



Albuminuria < 30-40%
(<1g/day)

Tubulo-interstitial disorders

Fanconi syndrome
Other tubulo-interstitial disorders

Myeloma cast nephropathy

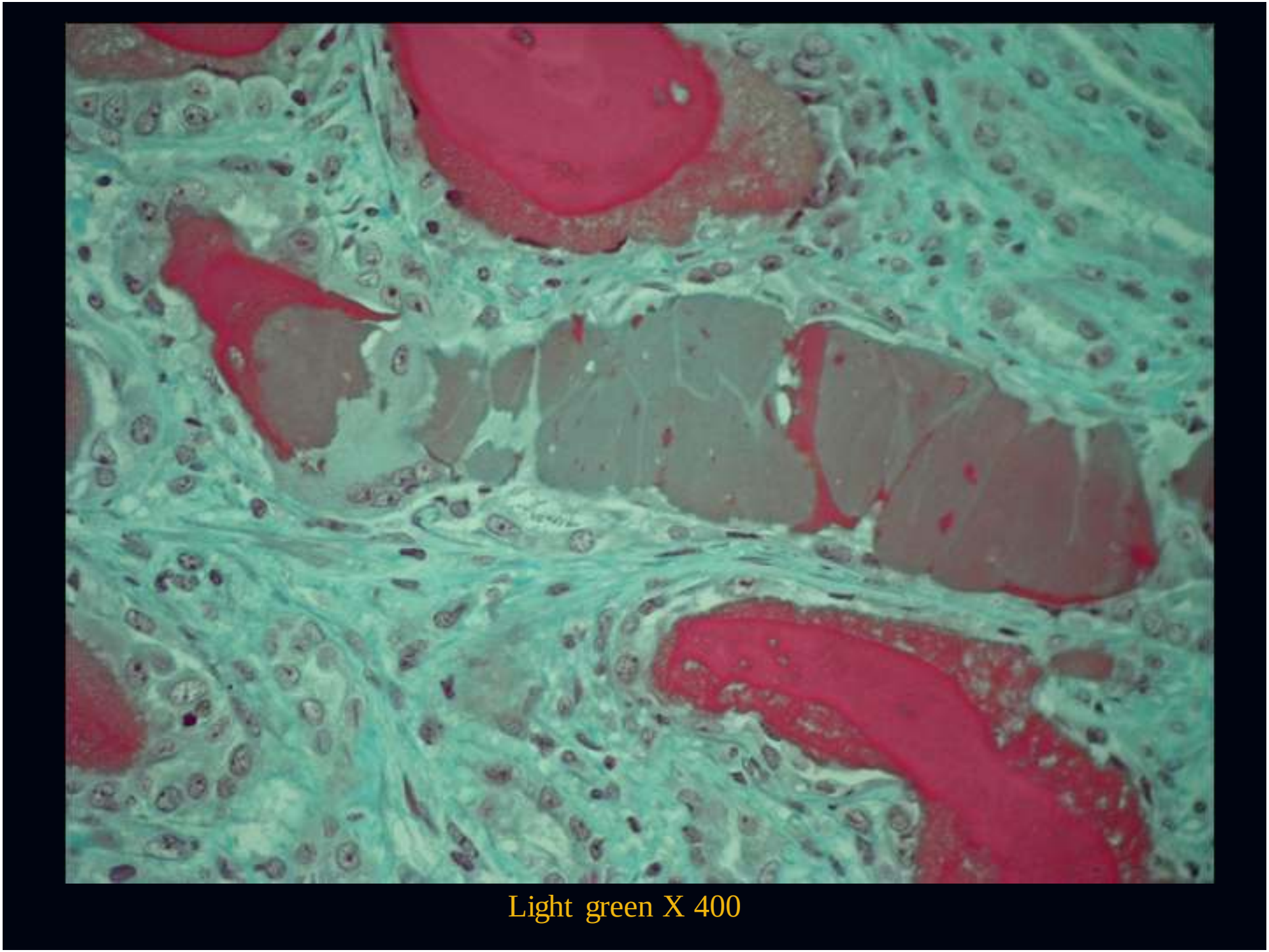
Myeloma cast nephropathy (MCN) : clinical features

- Clinical characteristics
  - High tumor mass MM
  - Light chain MM
  - κ or λ LC (no correlation with LC isotype)
  - Acute RI, often reveals MM
  - Proteinuria : often > 2g/day (> 70% LC, albumin < 1g/d)
  - Negative urine dipsticks

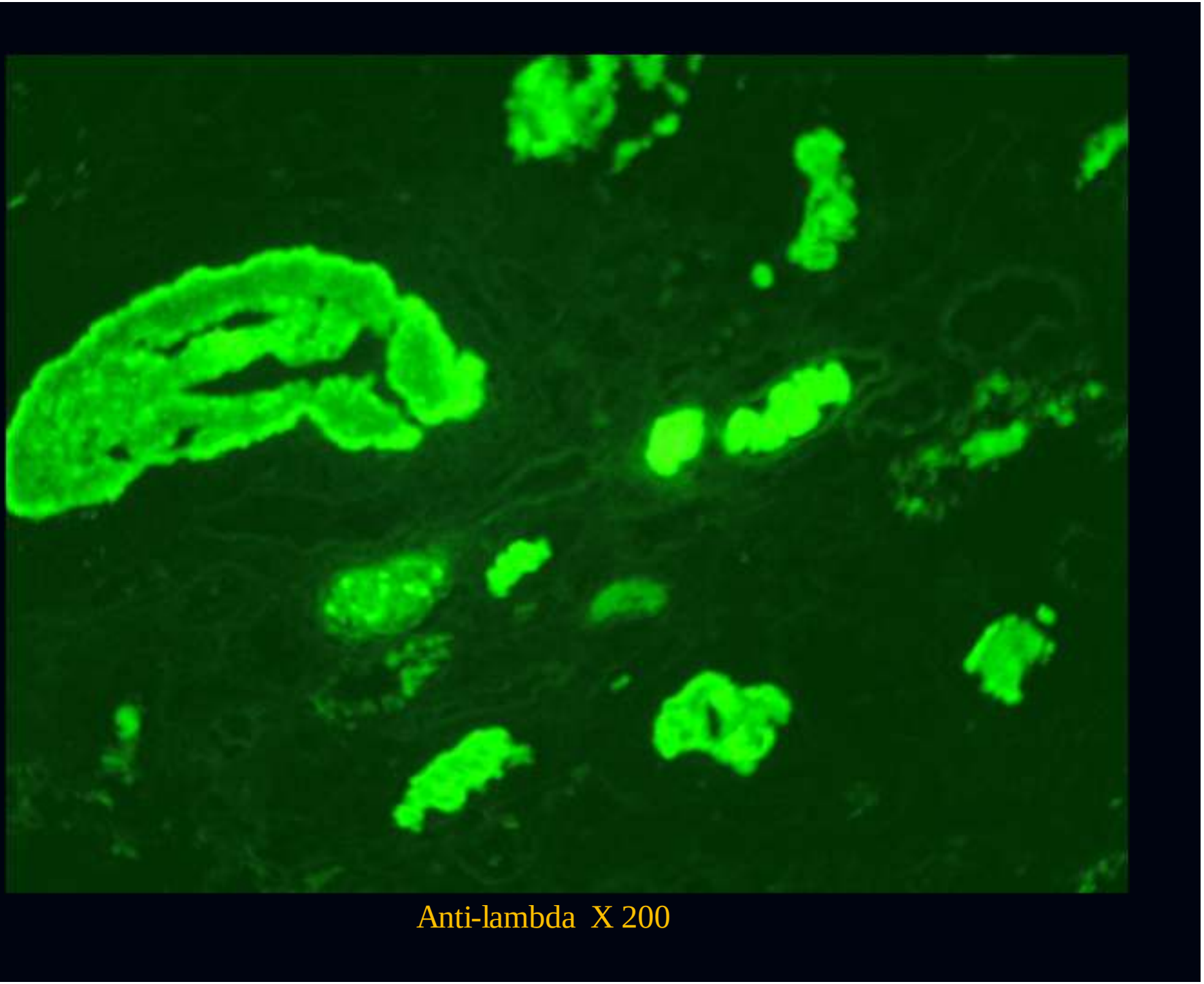
- Precipitating factors
  - Hypercalcemia
  - Dehydration
  - Infection
  - Contrast media
  - Nephrotoxic drugs : NSAIDs, furosemide, aminoglycosides, ACEI, angiotensin 2 receptor antagonists
  - Acidic urine pH

Myeloma cast nephropathy (MCN): diagnosis

- Clinical context
- Urine protein electrophoresis
- Kidney biopsy indicated if:
  - Significant albuminuria
  - None or multiple precipitating factors
  - Dialysis-dependent RI

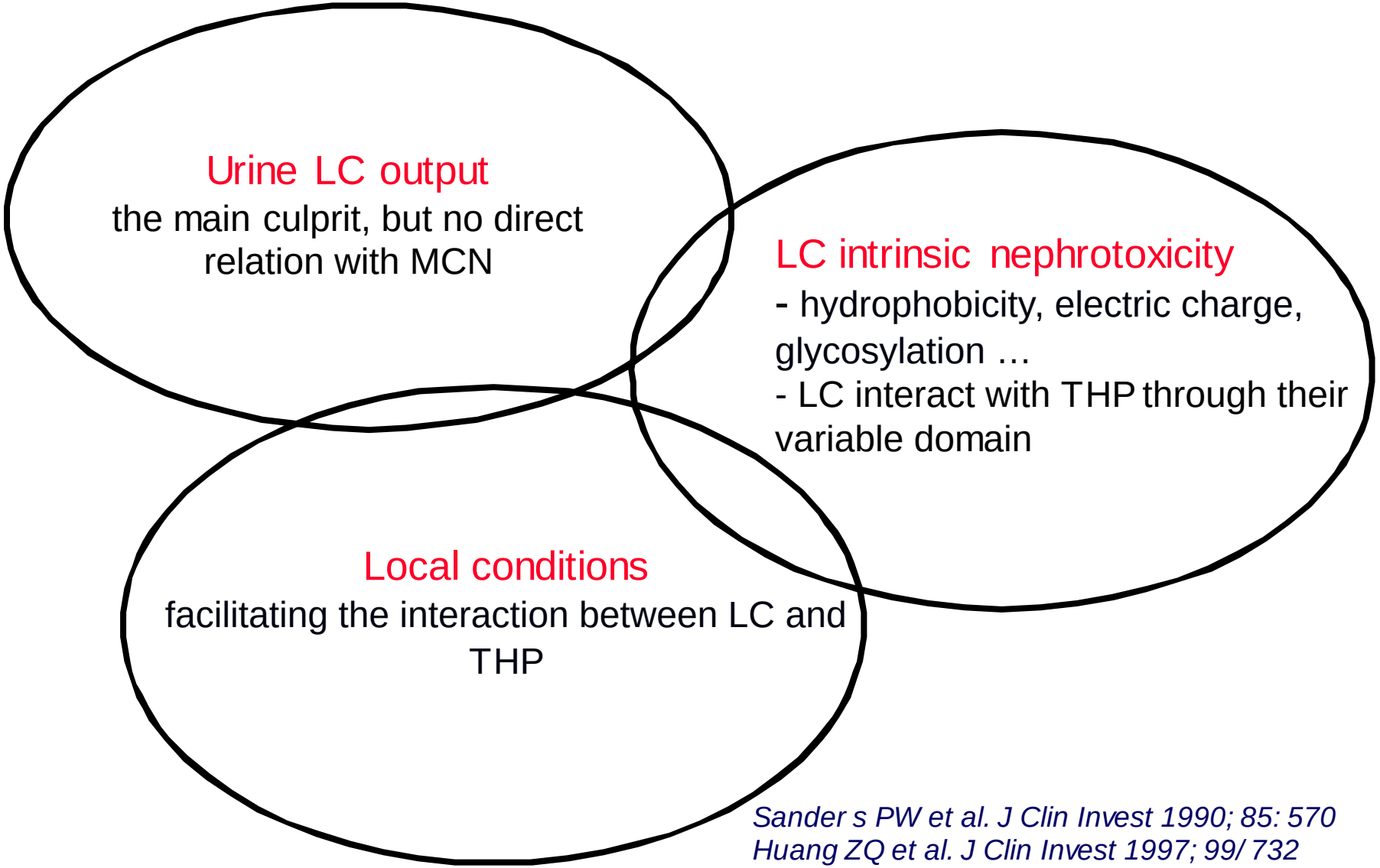


Light green X 400



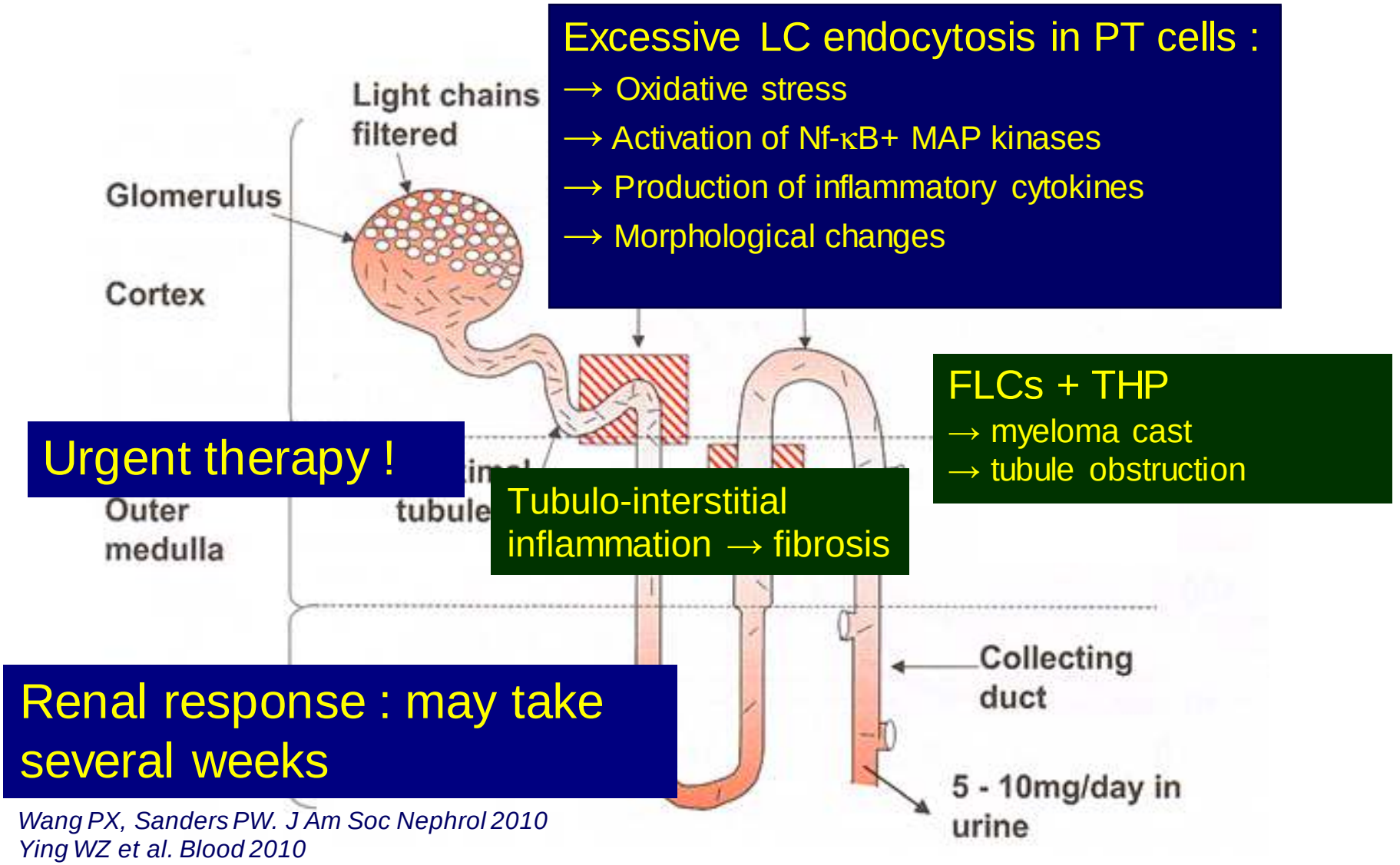
Anti-lambda X 200

Myeloma cast nephropathy : Pathophysiology



Sander s PW et al. J Clin Invest 1990; 85: 570
Huang ZQ et al. J Clin Invest 1997; 99/ 732
Ying WZ et al. Am J Pathol 2001; 2001; 158: 1859

Cast nephropathy : mechanisms of acute kidney injury



Wang PX, Sanders PW. J Am Soc Nephrol 2010
Ying WZ et al. Blood 2010

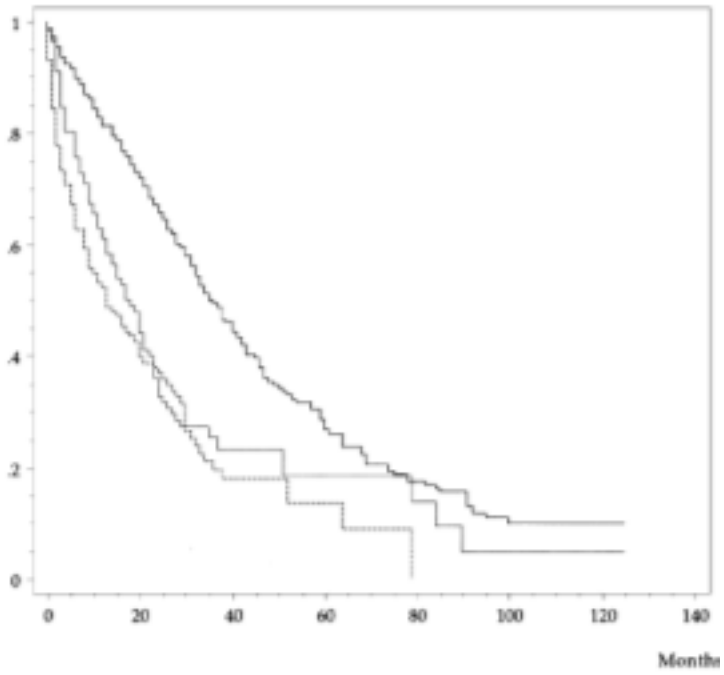
Treatment of myeloma cast nephropathy

- Principles:

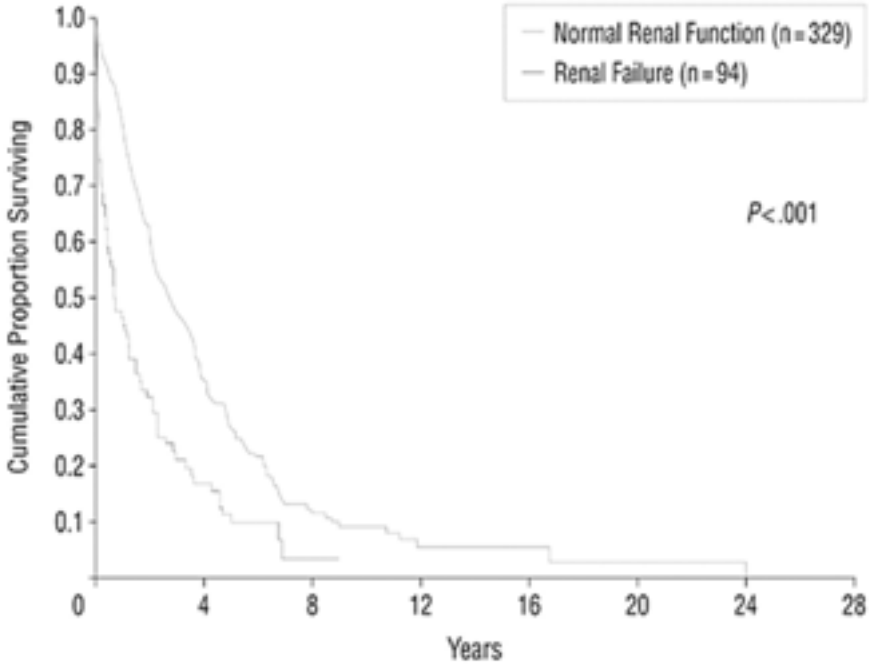
1. **Prevention**
2. **Symptomatic care as an emergency**
3. **Rapid initiation of efficient chemotherapy (tailored to reduced GFR)**
4. **Consider efficient removal of serum FLCs**

Survival of Myeloma Patients by Renal Function

Scr < 130, 130-200, >200 µmol/L



Scr > 177 µmol/L



Knudsen et al. Eur J Haematol. 2000
Blade et al. Arch Int Med 1998

Survival of Dialysis Dependent Myeloma Patients

- USRDS data 2 year mortality rates
  - Myeloma – 58%
  - All others – 31%
- ERA-EDTA (median OS)
  - Myeloma – 0.91 year
  - All others – 4.46 years

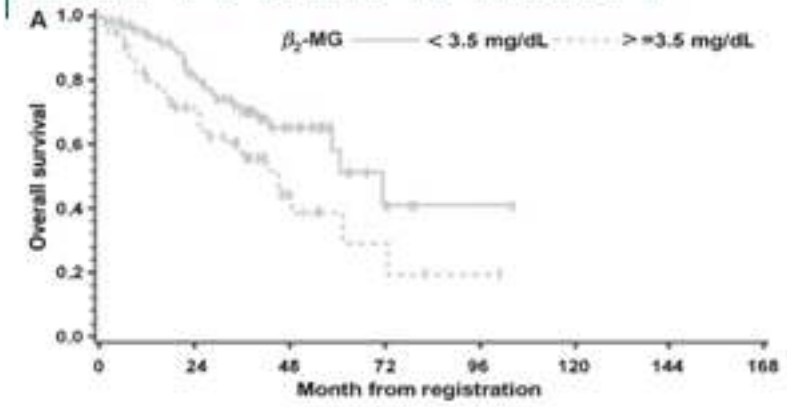
Dimopoulos et al. JCO 2010

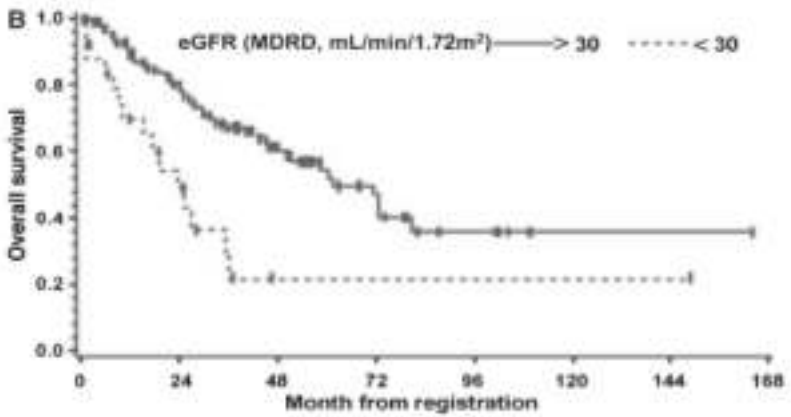
Effects of Renal Impairment on Survival

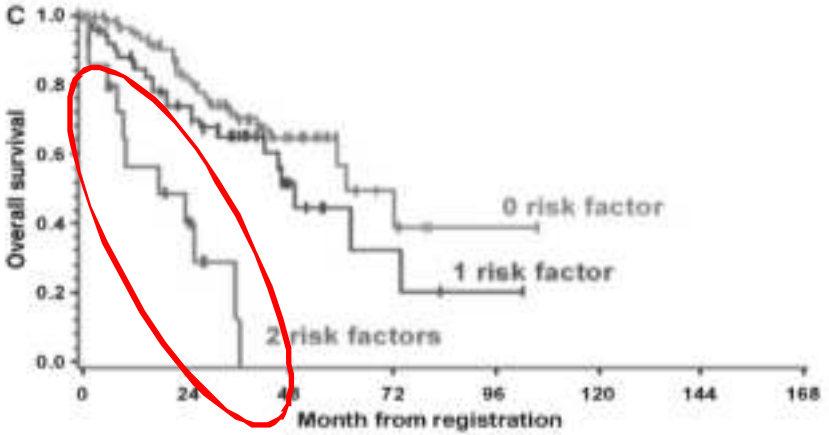
- More advanced disease
  - DS III
    - 44% (normal serum creatinine)
    - 87% (Scr ≥ 2 mg/dl or 177 μmol/L)
- Less chemotherapy responsive
  - 39% vs 56.4%, p <0.01
  - Less chemotherapy (melphalan/prednisone, VAD era)
  - Patients on dialysis had a significantly higher 2 month mortality (29% vs 7.2%)

Blade et al. Arch Int Med 1998

Creatinine is an Independent Predictor of survival from β-2-microglobulin



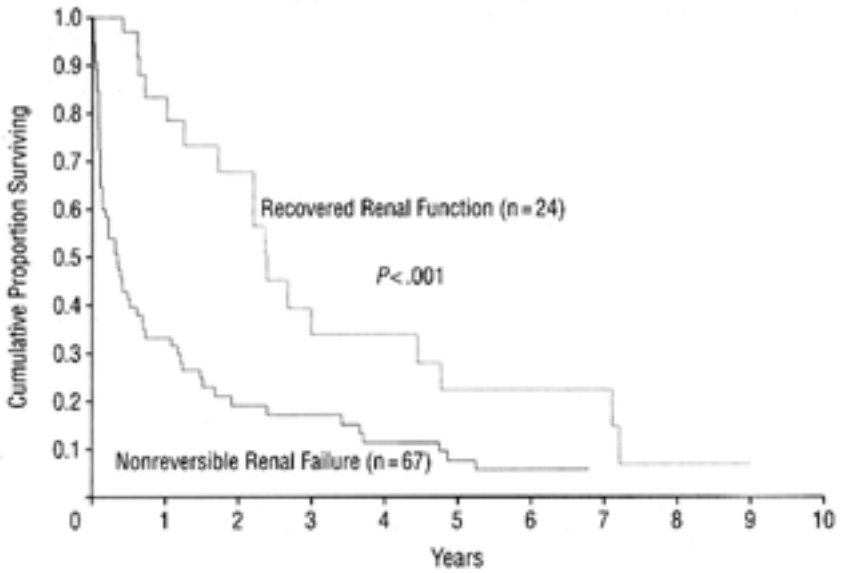


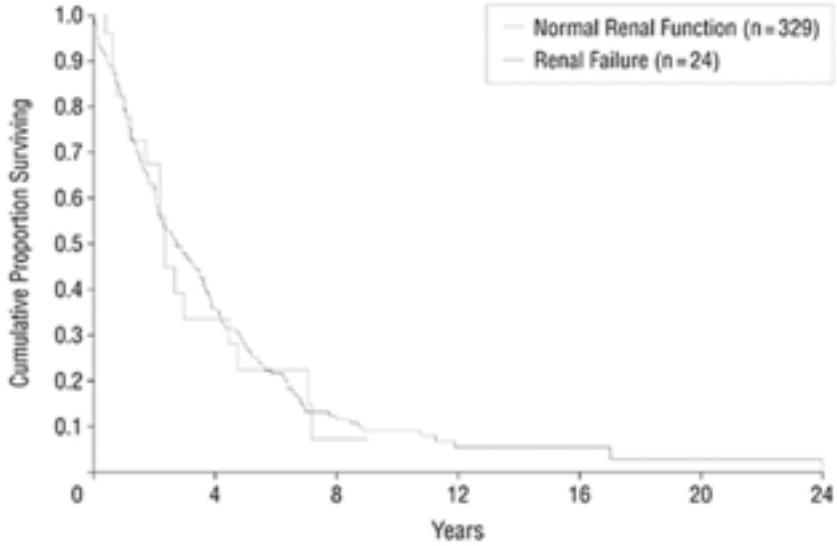


MP/ MPT/ D/ VAD/ ASCT

Kleber et al. Euro J Hematol 2009

Renal Recovery Improves Survival in Myeloma Patients





Blade et al. Arch Int Med 1998

Possible Benefits of Renal Recovery

- Responsiveness to therapy
- Removes limitations on medications
  - Renal dosing
  - Renal toxicity
- Decreases toxicity
  - Immunosuppression
  - Mucositis
- Decreases Infections
- Restores eligibility for clinical trials

Dimopoulos et al. JCO 2009

International Myeloma Working Group Consensus Statement

Renal Response Criteria

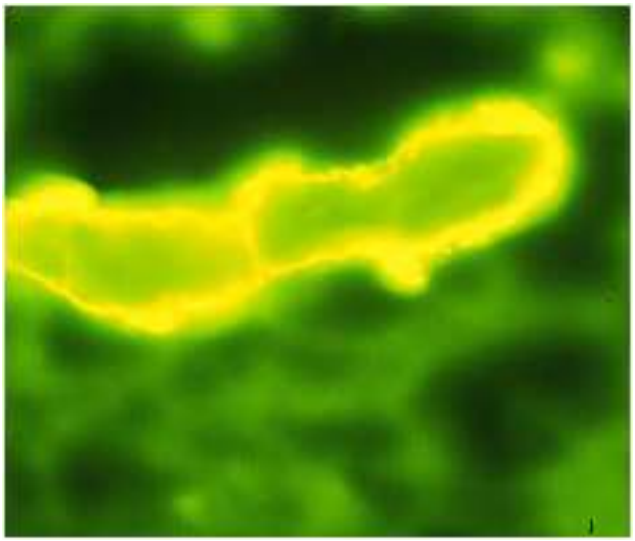
Response	Baseline eGFR*	Best eGFR* Response
CRenal	< 50	>60
PRenal	< 15	30 – 59
MRenal	<15	15 – 29
	15 – 29	30 – 59

*ml/min/1.73m^2 by MDRD

Dimopoulos et al. JCO 2010

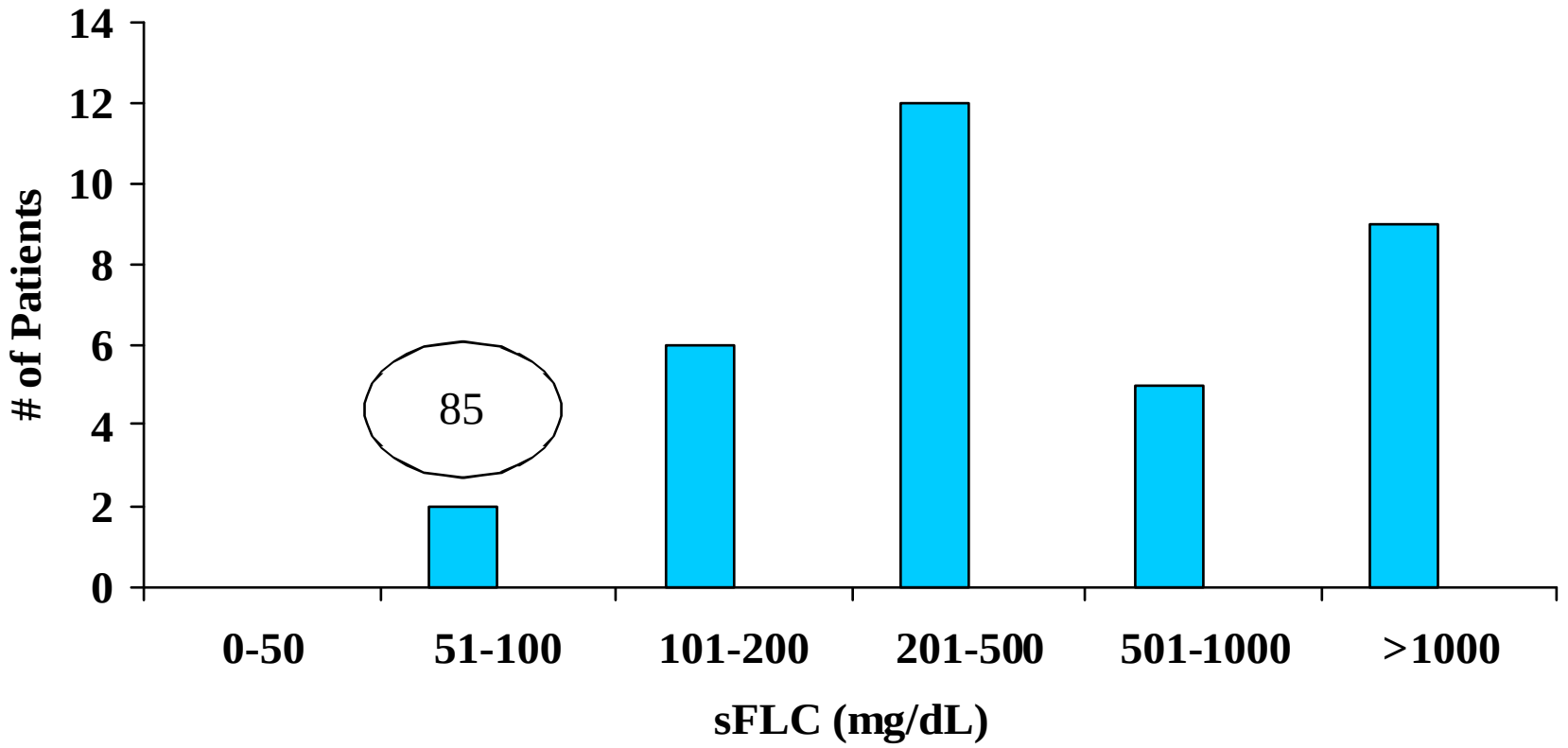
Targeting sFLC for Cast Nephropathy

- sFLC
  - Involved with pathogenesis
    - Freely filtered
    - Ig's are not
  - M-spike may not represent sFLC load
  - Threshold
  - Response



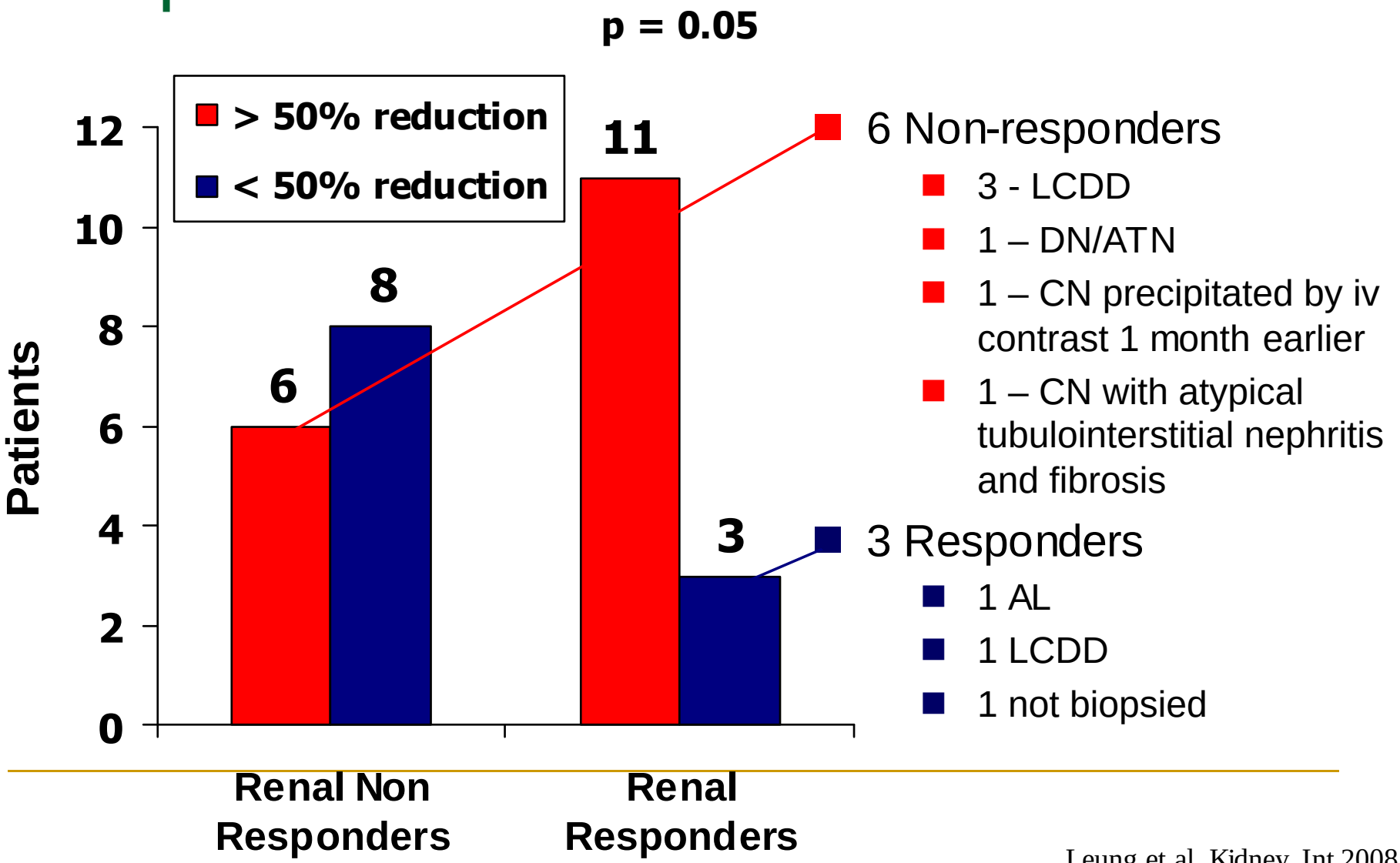
Sanders and Booker J Clin Invest 1992
Leung et al. Kidney Int 2005
Hutchison et al. Clin JASN 2009

sFLC and Cast Nephropathy



Leung et al. Kidney Int 2005
Hutchison et al. Clin JASN 2009

Reduction of FLC vs. Renal Response



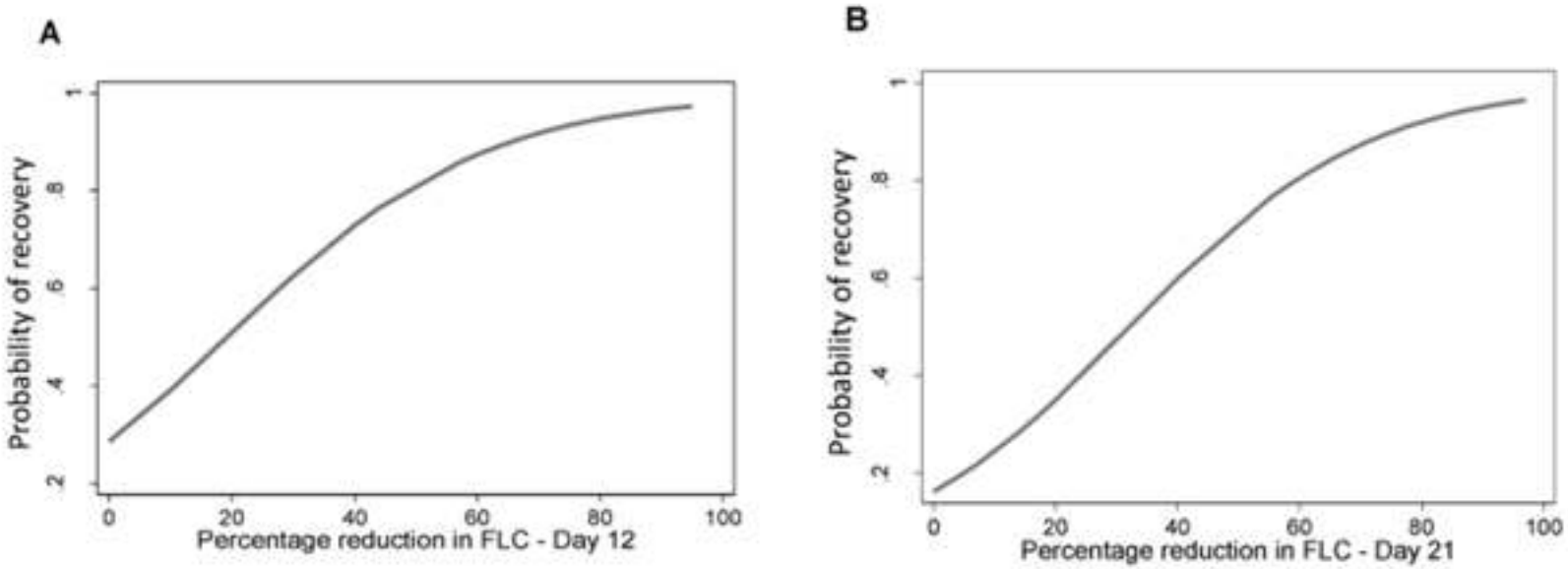
Leung et al. Kidney Int 2008

HCO Dialyzer

Patient	Age	Gender	Ethnicity	Myeloma		Previous GFR[a]	GFR at Presentation	Oligo-anuric[b]	Hyper-calcaemia	NSAID[c]	Presenting FLC Concentration (mg/L)	Interruption to Chemotherapy[d]	Renal Recovery	Percentage FLC Reduction at Outcome[e]	Duration of HCO-HD (days)	GFR at 3 months[f]
				Presentation	Type											
1	51	Male	Ca	New	IgA K	n/a	11	No	Yes	No	42,000	Yes	No	n/a	27	n/a
2	68	Female	Ca	New	IgG L	n/a	5	No	No	No	1120	Yes	No	n/a	39	n/a
3	58	Male	Ca	New	IgG L	58	13	No	No	No	855	Yes	No	n/a	32	n/a
4	64	Female	Ca	New	IgA L	n/a	5	Yes	Yes	Yes	1740	Yes	No	n/a	5	n/a
5	52	Male	Ca	Relapsing	Free L	23	9	No	No	No	69,430	Yes	No	n/a	29	n/a
6[g]	59	Male	Ca	New	Free L	n/a	4	No	No	No	26,382	No	Yes	96	14	83
7	68	Female	Ca	New	Free K	30	8	No	No	No	18,500	No	Yes	81	8	45
8	62	Male	AC	MGUS	IgG K	n/a	6	No	No	Yes	1030	No	Yes	83	18	45
9	53	Male	IA	New	IgA K	>60	13	No	No	No	13,500	No	Yes	50	34	48
10	81	Male	Ca	New	IgG L	n/a	7	Yes	No	No	2110	No	Yes	90	29	34
11	61	Male	IA	Relapsing	IgG K	>60	3	No	No	No	2520	No	Yes	60	18	76
12	71	Male	Ca	New	IgA L	49	3	No	No	No	4200	No	Yes	65	22	34
13	46	Male	Ca	New	IgG K	n/a	9	No	No	No	1780	No	Yes	86	26	29
14	64	Male	IA	Relapsing	IgG L	31	9	No	No	No	2530	No	Yes	93	19	37
15	61	Female	Ca	New	Free K	n/a	5	No	No	No	3000	No	Yes	87	45	11[h]
16	38	Male	Ca	New	Free K	n/a	7	No	No	No	27,000	No	Yes	87	28	27
17	60	Male	Ca	New	IgG K	n/a	12	No	No	No	2254	No	Yes	79	12	67
18	67	Male	Ca	CLL	IgM L	>60	4	No	No	No	2585	No	Yes	82	39	43
19	55	Female	Ca	New	Free K	n/a	8	No	No	No	8076	Yes	Yes	97	105	17[h]
20	56	Male	Ca	New	IgA L	n/a	6	No	No	No	9918	No	Yes	97	56	27

Hutchison et al. Clin JASN 2009

Probability of Renal Response by Depth and Speed of sFLC Reduction



Hutchison et al. J Am Soc Nephrol In Press

chemotherapy

- Not renally cleared
- Not nephrotoxic
  - Bortezomib
  - Thalidomide
  - Steroids

Bortezomib

SUMMIT and CREST

10/256 had CrCl ≤ 30 ml/min

- Overall response
  - PR- 2
  - MR - 1
  - SD - 1
- ≥ Grade 3 Toxicity
  - Thrombocytopenia - 4
  - Neutropenia – 3
  - Peripheral neuropathy - 3
  - Fracture – 2
  - Arthralgia - 2

Jagannath et al. Cancer 2005

VISTA

	VMP		MP	
	Normal	RI	Normal	RI
ISS III	21%	62%	22%	54%
≤ 30 ml/min		84%		80%
Overall Response	72%	68%	29%	46%
CR	30%	31%	3%	5%
≤ 30 ml/min		37%		13%
First response	1.4m	1.0m	4.9m	3.4m
Median TTP	NE	19.9m	18.0m	16.1m
Median OS	NE	NE	NE	31.9m

* Serum Cr ≤ 2.0 mg/dL

Dimopoulos et al. JCO 2009

Renal Response

	VMP	MP
Overall Response	51%	44%
CRenal	44%	34%
PRenal		50%
MRenal	42%	67%
GFR 30 – < 50 ml/min	46%	39%
GFR ≤ 30 ml/min	37%	7%
Time to RR	2.1m	2.4m
< 50% reduction in M-protein	26%	17%
≥ 50% reduction in M-protein	48%	42%

Dimopoulos et al. JCO 2009

Safety

- AE's, SAE's and discontinuation were lower in patients with reversible renal impairment
  - VMP
    - AE's (8% reversible vs 15% irreversible)
    - SAE's (43% reversible vs 60% irreversible)
    - Discontinuation (6% reversible vs 24% irreversible)
  - MP
    - AE's (10% reversible vs 13% irreversible)
    - Discontinuation (8% reversible vs 24% irreversible)

Dimopoulos et al. JCO 2009

Phase II Trial with bortezomib doxorubicin dexamethasone (BDD) in patients with acute renal failure

- Inclusion criteria
  - eGFR < 60 ml/min/1.73m^2
  - ARF must occurred <4 weeks
- Excluded
  - 2 - AL
  - 1 – elevated liver function tests
  - 1 – eGFR
- Not evaluated
  - 7 – died < 2 cycles
  - 1 – discontinued after 1 cycle due to toxicity
  - 1 – progression
  - 1 – incomplete data

- Treatment
  - Bortezomib 1.3 mg/m^2 on Day 1,4,8,11
  - Doxorubicin 9 mg/m^2 Day 1,4,8,11
  - Dexamethasone 40 mg on Day 1,4,8,11
  - After first 5 patients, doxorubicin was given only on Day 1 and 4 and bortezomib was reduced to 1.0 mg/m^2

Ludwig et al. JCO. 2010

Responses of 58 patients to BDD

Hematologic

- CR/nCR - 38%
- VGPR - 15%
- PR - 13%
- MR - 6%
- Overall - 72%

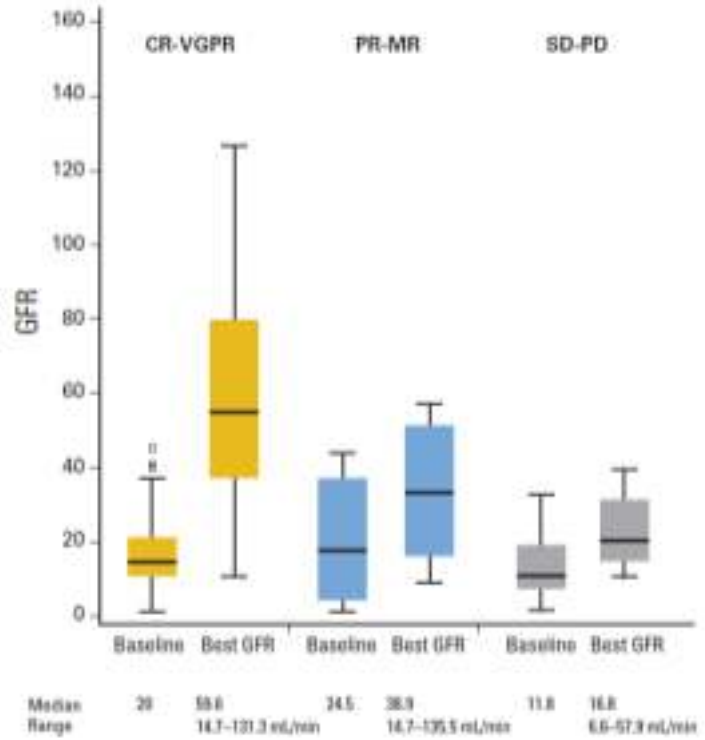
Renal

- CRenal – 31%
- PRenal – 7%
- MRenal – 24%
- Overall – 62%

Ludwig et al. JCO. 2010

Renal Response by Hematologic Response

- Final eGFR by hematologic response
  - >VGPR – 59.5 ml/min/1.73m^2
  - PR/MR – 38.9 ml/min/1.73m^2
  - SD/PD – 16.8 ml/min/1.73m^2



Ludwig et al. JCO. 2010

Upfront Thalidomide Dexamethasone Induction Before Double ASCT

- 31 patients
- Renal impairment = CrCl < 50 ml/min by Cockcroft Gault
  - 52% < 30 ml/min
  - 23% were dialysis dependent

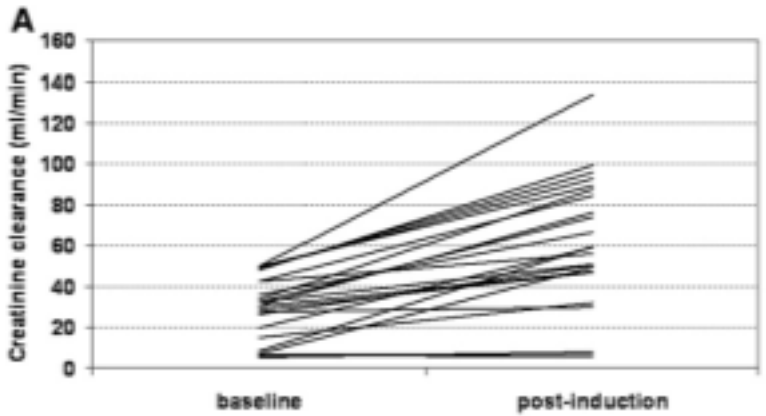
Tosi et al. Biol Blood Marrow Transplant. 2010

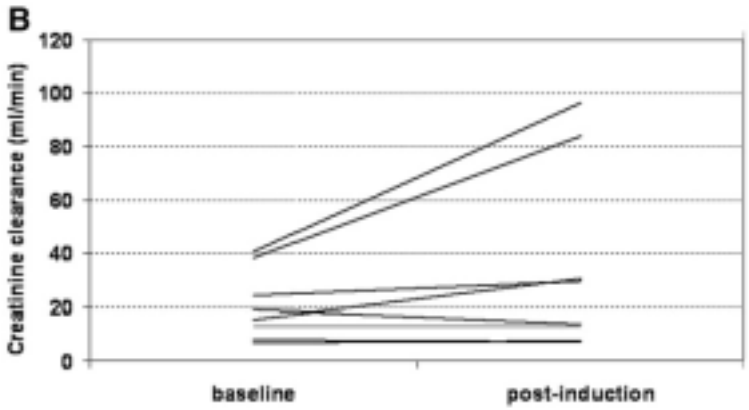
Response and Adverse Events

- Hematologic response
  - CR – 29%
  - > VGPR – 42%
- AE
  - DVT – 9.6%
  - Skin – 1
  - PN – 1
  - Constipation – 2
  - Lethargy - 1

Tosi et al. Biol Blood Marrow Transplant. 2010

Renal Response





	Improved RF	> 50 ml/min
<PR	37.5%	25%
>PR	82.6%	65%
VGPR (69% CR)		84.6%

Overall renal response rate 74%

Tosi et al. Biol Blood Marrow Transplant. 2010

Lenalidomide and Dexamethasone in Patients with Renal Impairment

- MM-009 and MM-010
  - RD vs D
  - 353 patients randomized to RD
  - Renal function calculated by Cockcroft Gault equation
  - Scr cutoff for the studies was < 2.5 mg/dl
  - Treatment
    - Median dose for patient with CrCl > 30 ml/min = 25 mg/d
    - Median dose for patient with CrCl < 30 ml/min = 15 mg/d

Dimopoulos et al. Cancer 2010

Outcome

Outcome	No. of Patients (%)		
	Mild or No RI: CL_{Cr} ≥60 mL/min	Moderate RI: CL_{Cr} ≥30 mL/min to <60 mL/min	Severe RI: CL_{Cr} <30 mL/min
Total no. of patients	243	82	16
Response			
Overall response	156 (64)	46 (56)	8 (50)
Complete response	38 (16)	13 (16)	1 (6)
Very good partial response	45 (19)	9 (11)	5 (31)
Partial response	73 (30)	24 (29)	2 (13)
Stable disease	69 (28)	28 (34)	5 (31)
Progressive disease	5 (2)	3 (4)	0
Response not evaluable[a]	13 (5)	5 (6)	3 (19)
Efficacy, mo			
Median time to progression	12.0	11.1	7.8
Median PFS	11.1	9.5	7.8
Median OS	38.9	29.0[b]	18.4[b]

Dimopoulos et al. Cancer 2010

Toxicity of RD in Renally Impaired Patients

Adverse Event	Mild or No RI: CL_{Cr} ≥60 mL/min	Moderate RI: CL_{Cr} ≥30 mL/min to <60 mL/min	Severe RI: CL_{Cr} <30 mL/min
Total no. of patients	243	82	16
Hematologic toxicities, %			
Neutropenia	32	48[a]	38
Thrombocytopenia	9	23[a]	38[a]
Anemia	5	21[a]	44[a]
Nonhematologic toxicities, %			
Thrombotic events[b]	13	15	6
Hypertension NOS	0.8	2	13
Atrial fibrillation	3	4	13
Fatigue	5	12[a]	0
Asthenia	4	5	13
Constipation	2	1	13
Hypocalcemia	3	6	19
Dehydration	0.8	2[a]	13[a]
Pneumonia NOS	7	9	25[a]
Clinically important adverse events, %			
Febrile neutropenia	3	2	0
Neuropathy	2	2	0
Peripheral neuropathy	2	1	0

RI indicates renal impairment; CL_{Cr}, creatinine clearance; NOS, not otherwise specified.

[a] $P < .05$ versus patients with mild or no RI.

[b] Thrombotic events included pulmonary embolism, deep vein thrombosis, and venous thrombosis NOS.

Dimopoulos et al. Cancer 2010

Improvement in Renal Function

Renal Function at Baseline	No. of Patients (%)		
	Mild or No RI: CL_{Cr} ≥60 mL/min	Moderate RI: CL_{Cr} ≥30 mL/min to <60 mL/min	Severe RI: CL_{Cr} <30 mL/min
Mild or no RI, n=238	235 (99)	1 (0.5)	2 (1)
Moderate RI, n=80	56 (70)[a]	24 (30)	0 (0)
Severe RI, n=14	0 (0)	12 (86)[a]	2 (14)
Total, N=332	291 (88)	37 (11)	4 (1)

RI indicates renal impairment; CL_{Cr}, creatinine clearance.
[a] These patients improved with treatment. The best postbaseline renal responses were used.

Overall renal response rate – 72%

Dimopoulos et al. Cancer 2010

Hematologic and Renal Response by Therapy

	Hematologic OR/> VGPR	Renal
MP/VAD/VCMP	39%	26%
MP	35%/4%	34%
VMP	71%/30%	44%
BDD	72%/53%	62%
RD	55%/29%	72%
TD + ASCT	74%*/42%	74%

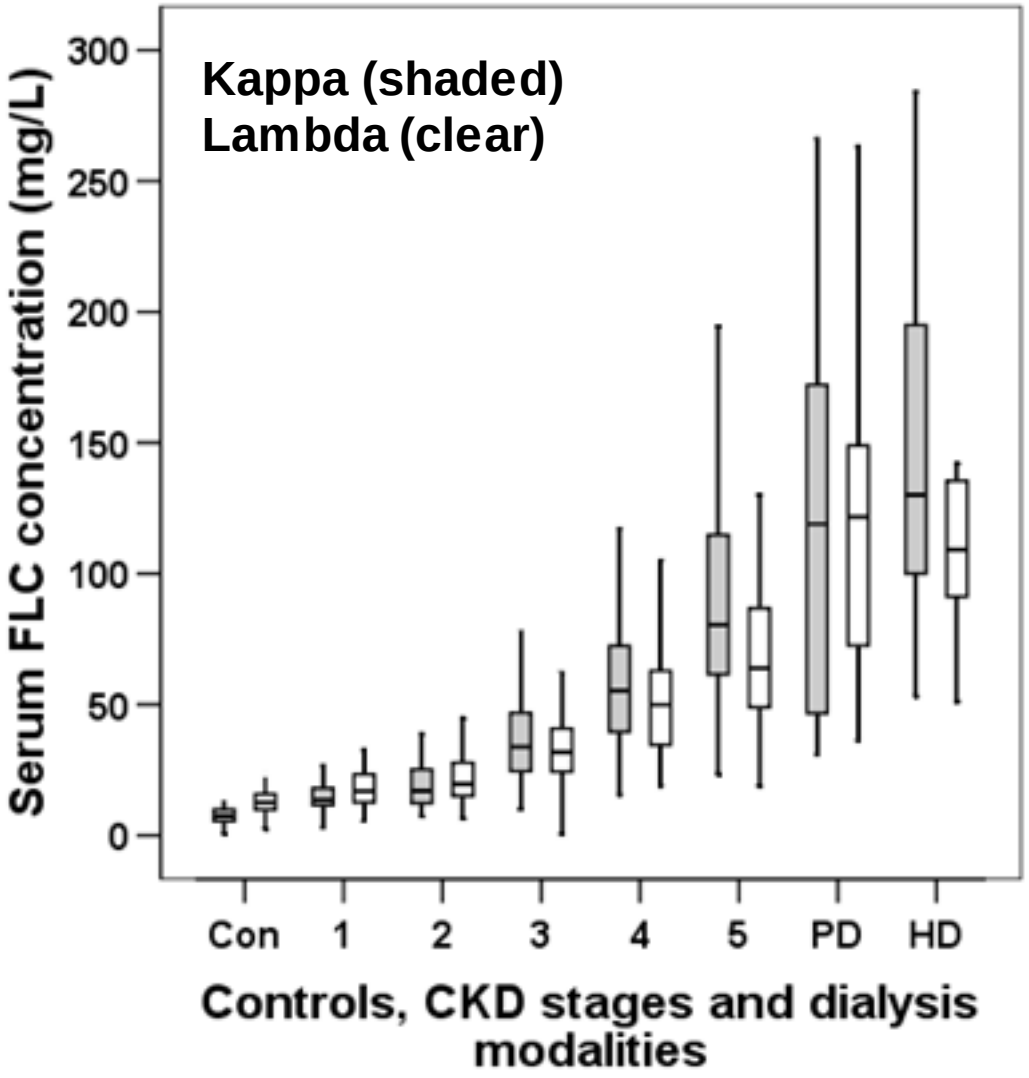
Management of myeloma kidney: reducing FLCs

How do we reduce serum FLC levels?

Two components:

- Effective chemotherapy – novel agents
- Direct removal of FLCs from the serum

Why remove FLCs - kinetics in renal failure

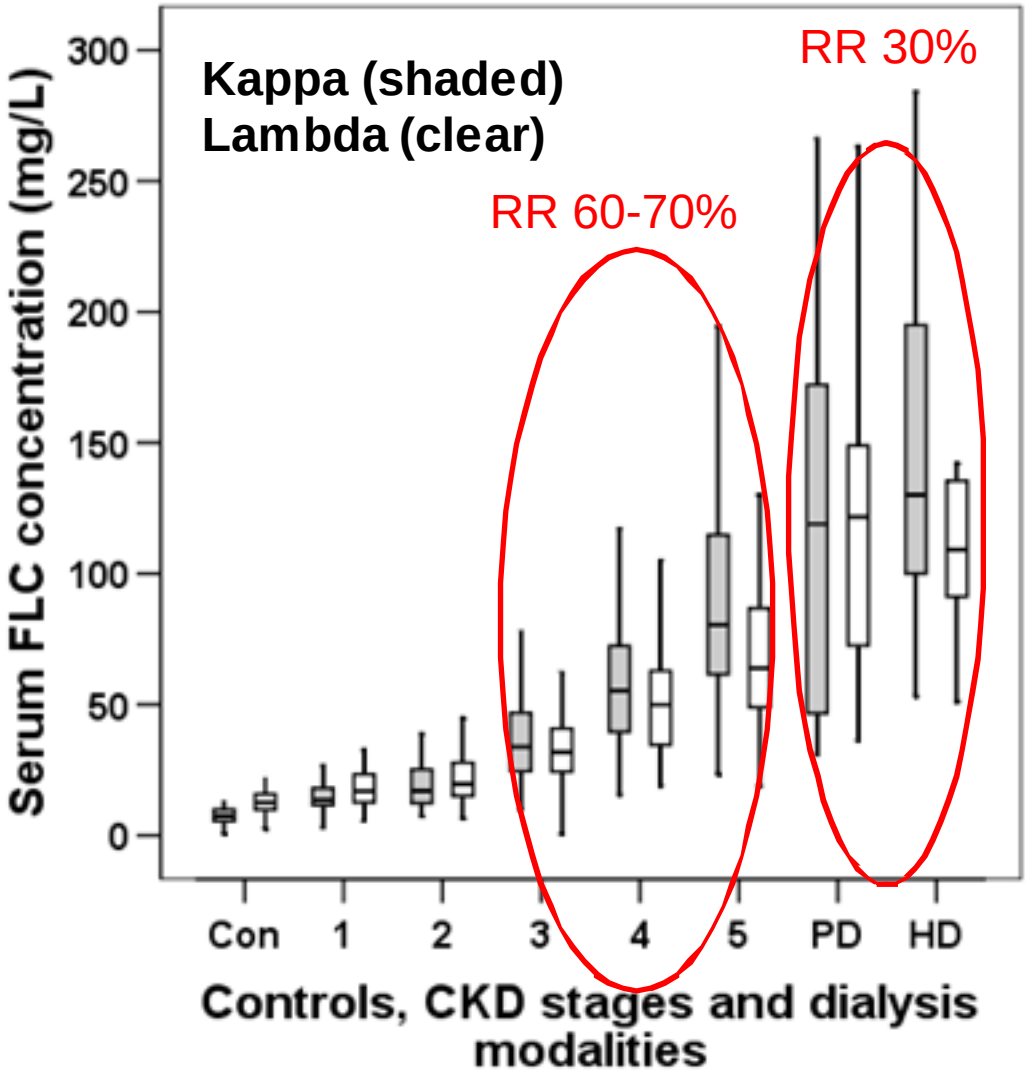


As kidneys fail serum half-lives increase

Both: P<0.01

Hutchison et al, cJASN 2008

Why remove FLCs - kinetics in renal failure



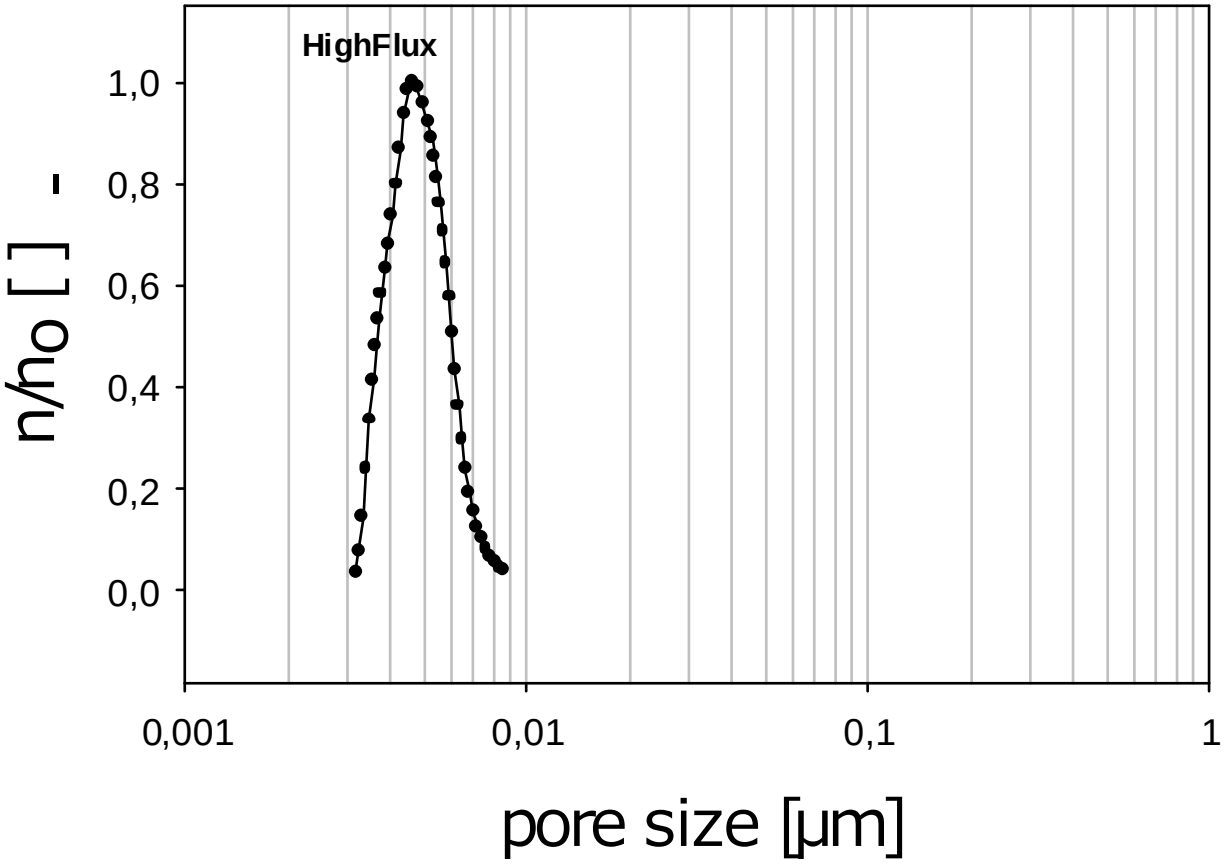
Dimopoulos MA, Clin Lymph + Myeloma 2009

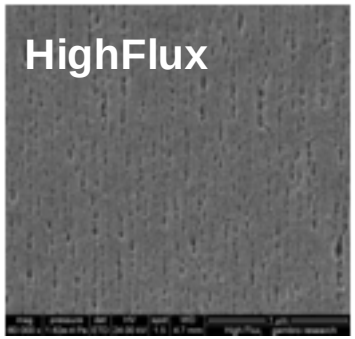
Ludwig H, J Clin Onc 2010

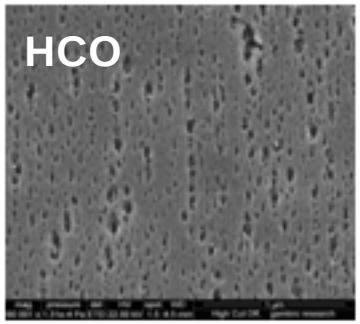
Both: P<0.01

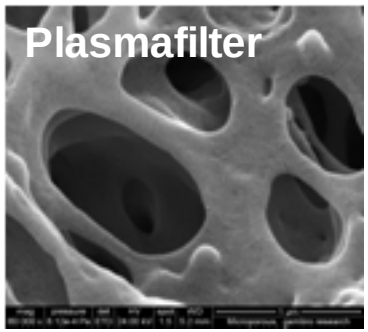
Hutchison et al, cJASN 2008

Pore Sizes of High Cut-Off (HCO) Membranes in comparison to HighFlux and plasmafiltration membranes



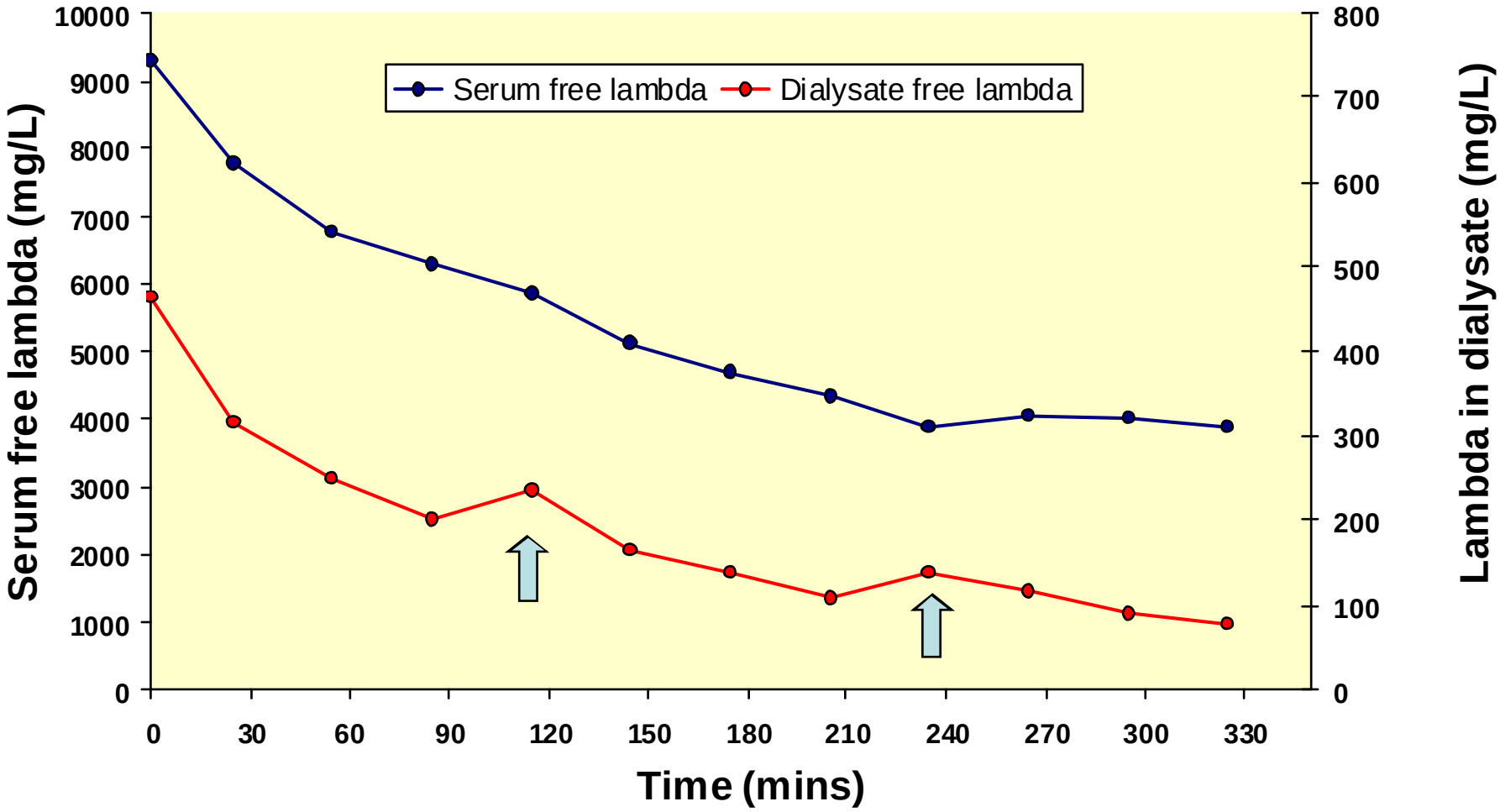






Courtesy of Dr Storr, Hechingen, Germany

Gambro HCO 1100 – 6 hour dialysis

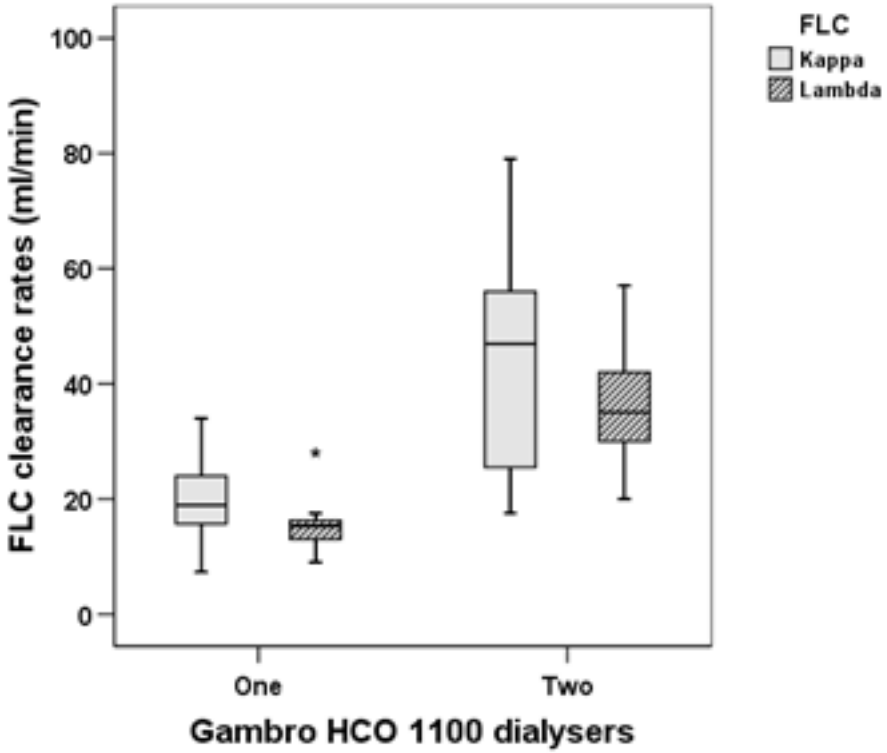


Hutchison et al. JASN March 2007

Serum Free-Light Chain Removal by High Cutoff Hemodialysis: Optimizing Removal and Supportive Care

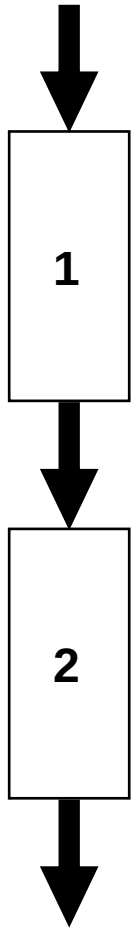
*†Colin A. Hutchison, ‡Stephen Harding, ‡Graham Mead, §Hermann Goehl, §Markus Storr, ¶Arthur Bradwell, and *†Paul Cockwell

Artificial Organs
32(12):910–917, Wiley Periodicals, Inc.

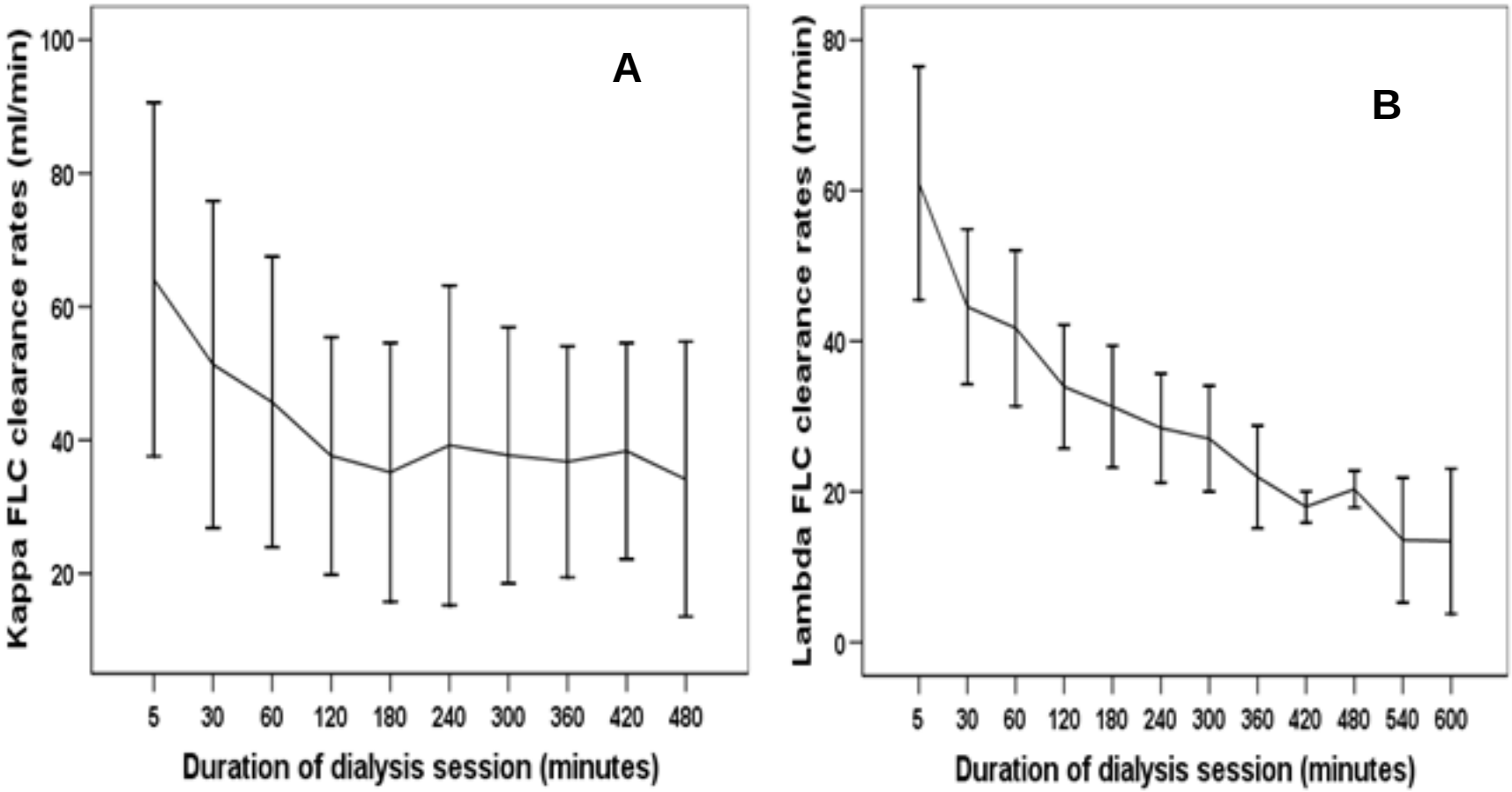


Key points:

- Clearance of κ and λ FLCs are comparable
- Clearance rates dramatically increased when 2 dialysers are used in series



Clearance remains effective over extended dialysis sessions (8 hours)



Pilot Study of FLC removal by HCO-HD

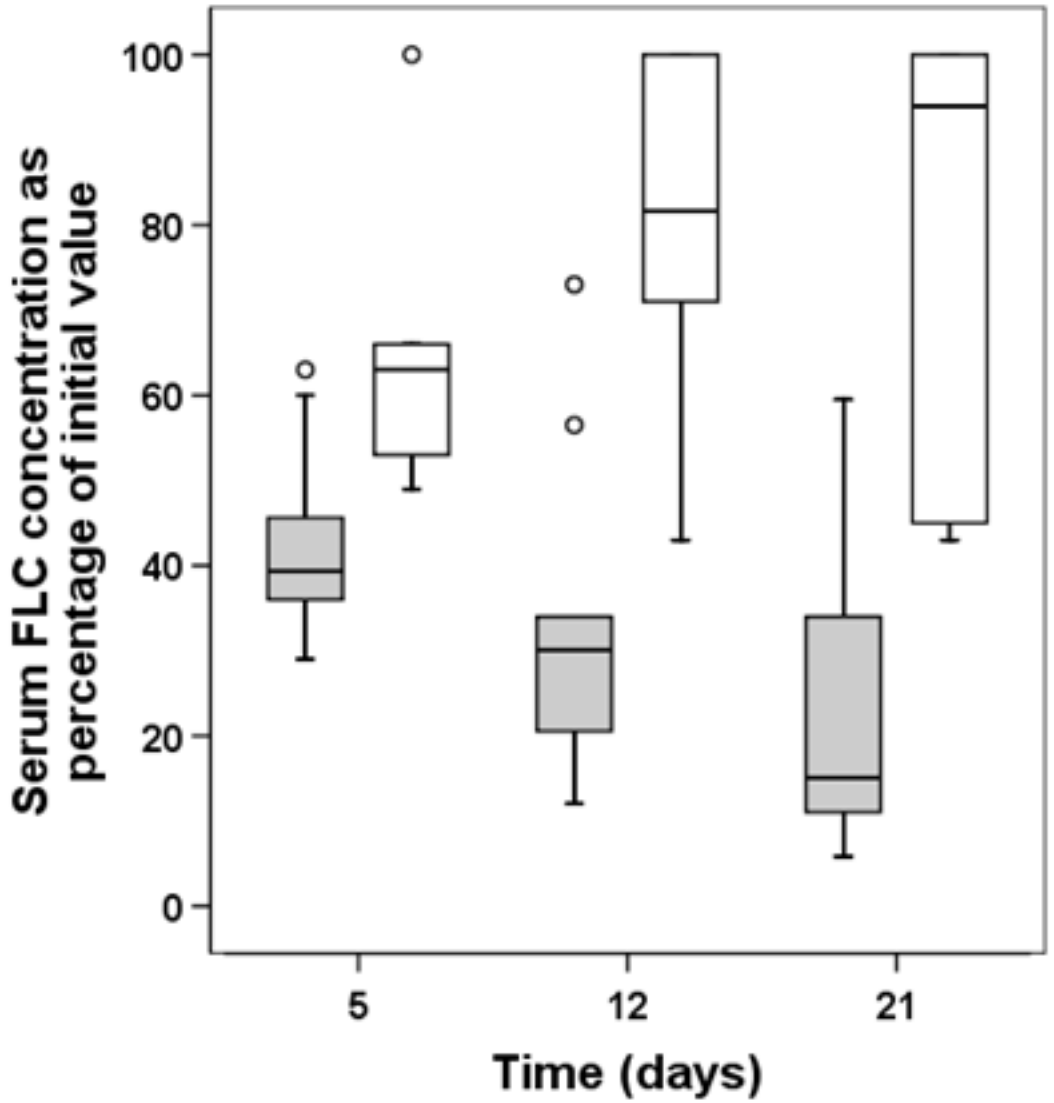
Aim: Evaluate the removal of FLCs by extended HD in patients with biopsy proven cast nephropathy + dialysis dependent acute renal failure

Combination of chemotherapy and HCO-HD:

- Chemotherapy: high dose dexamethasone and thalidomide for *de novo;* bortezomib for relapsing
- Daily extended (8 hours) HD using the Gambro HCO 1100 – 5 days
- HD then reduced to alternate days for next 21 days or until FLC concentrations <500mg/L

Hutchison et al. cJASN 2009

Primary outcome: FLC reductions



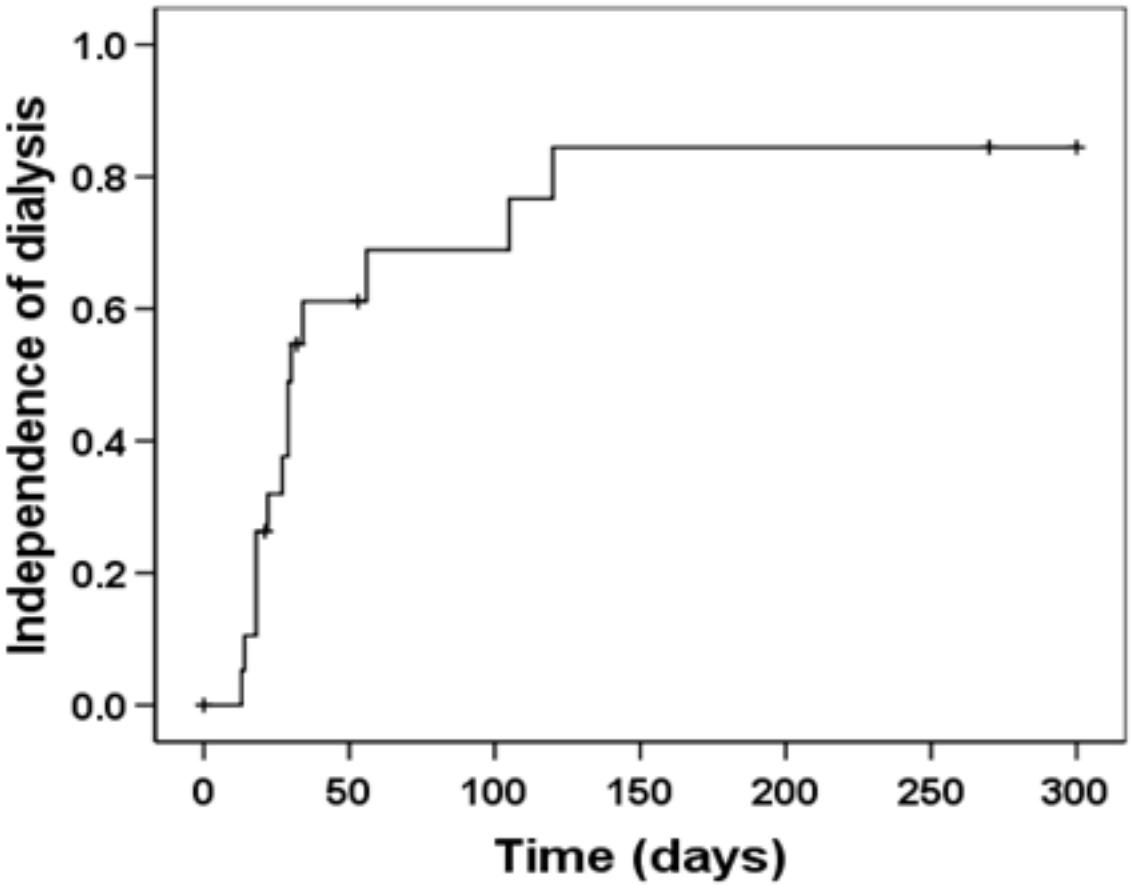
6 Patients
Chemotherapy stopped

13 Patients continuous combined HD and chemotherapy

P<0.01

Hutchison et al cJASN 2009

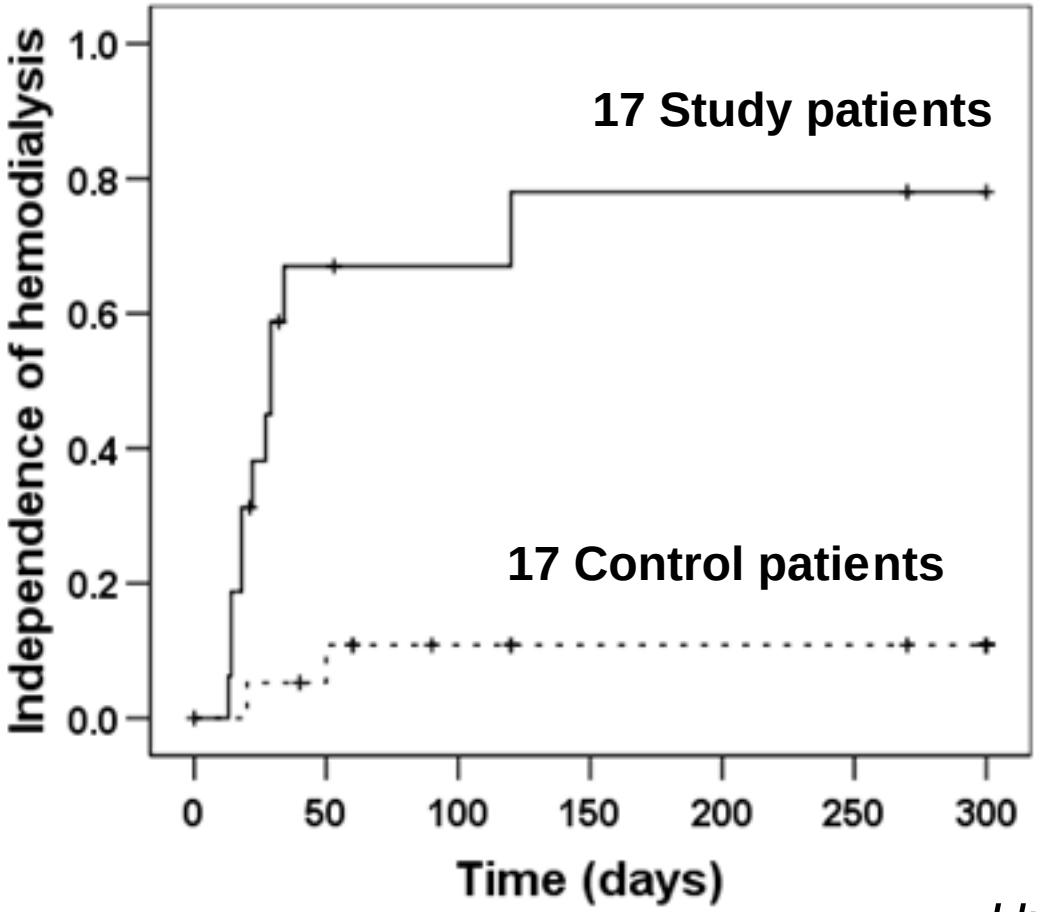
Recovery of renal function



14 of 19 patients

Hutchison et al cJASN 2009

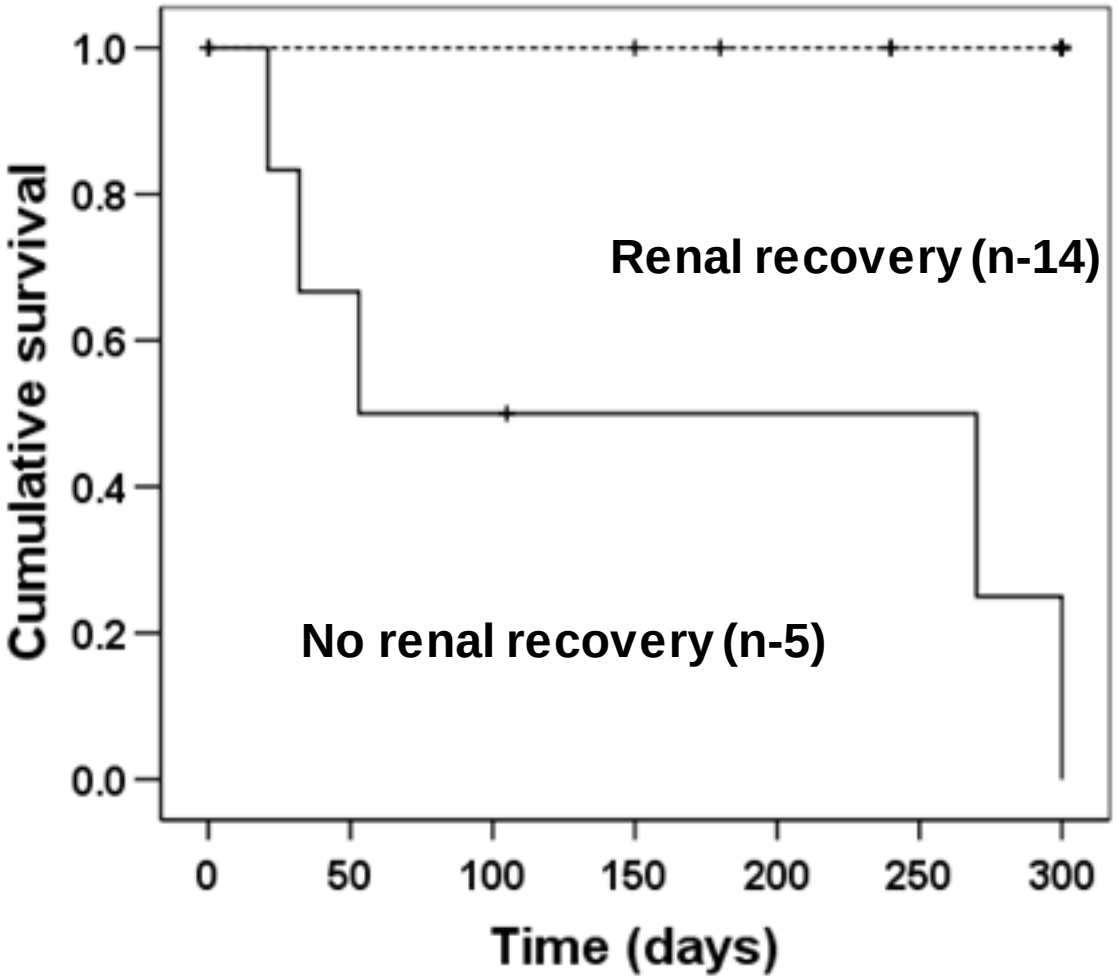
Renal recovery rates in study population and a case matched control population



P<0.001

Hutchison et al, EDTA 2008.

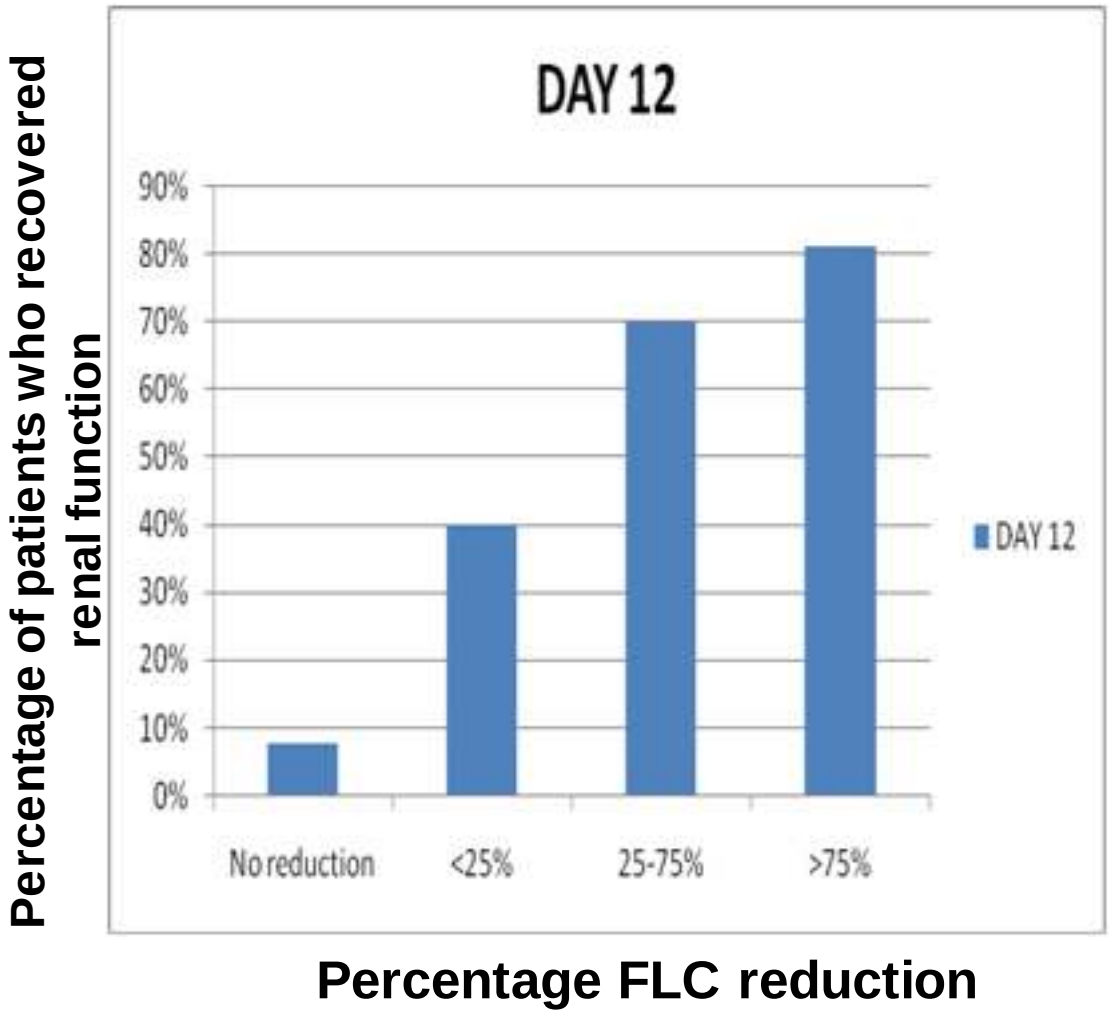
Study population's survival relates to recovery of renal function



P<0.001

Hutchison et al, EDTA 2008.

International experience with HCO-HD Chart Audit of Renal Recovery in Multiple Myeloma



- 67 patients treated across Europe and Australia
- Median 12 sessions
- 63% had renal recovery

Trials

BioMed Central

Study protocol

Open Access

European trial of free light chain removal by extended haemodialysis in cast nephropathy (EuLITE): A randomised control trial

Colin A Hutchison*[1,2], Mark Cook[3], Nils Heyne[4], Katja Weisel[5], Lucinda Billingham[6], Arthur Bradwell[7] and Paul Cockwell[1,2]

Hypothesis

The EuLITE trial examines the hypothesis that FLC removal haemodialysis will increase the rate of renal recovery in patients with cast nephropathy, severe renal failure and *de novo* multiple myeloma.

EuLITE

A randomized control trial of FLC removal HD versus standard care

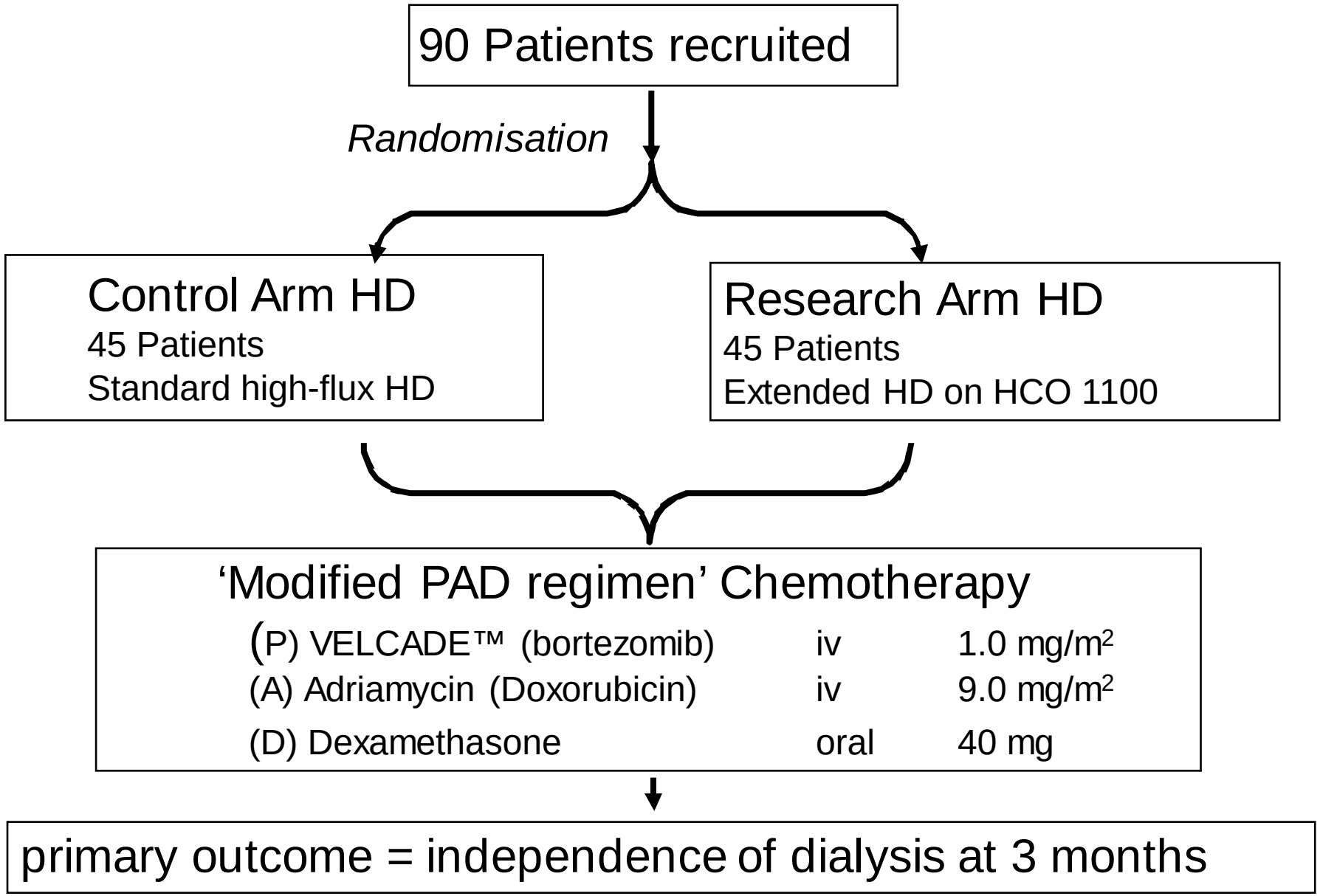
Inclusion criteria:

- *De novo* multiple myeloma
- New dialysis dependent renal failure (eGFR<15)
- Cast nephropathy on renal biopsy

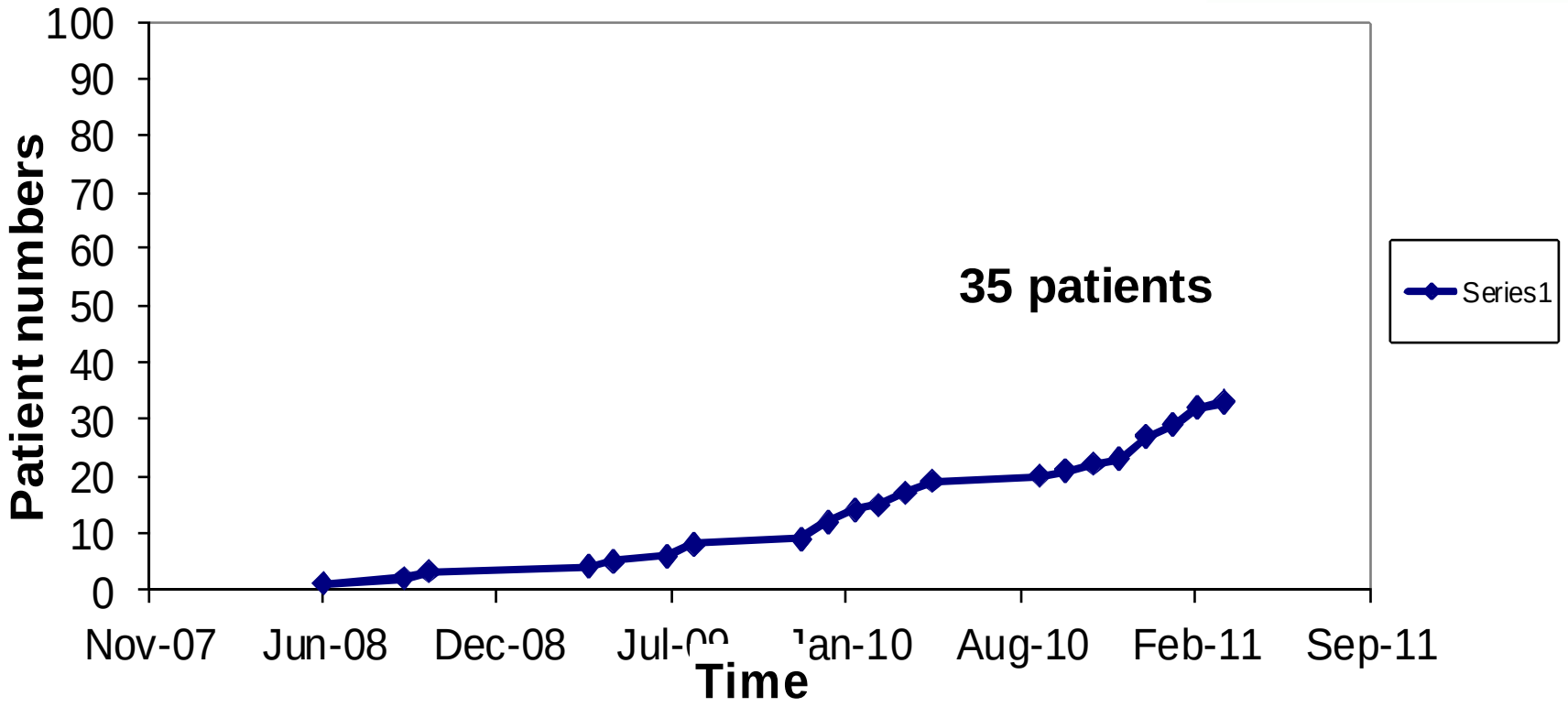
Exclusion criteria:

- Chronic renal failure
- Contra-indication to chemotherapy

Randomised and controlled



EuLITE recruitment



- In total 20 UK centres will participate (15 active)
- 6 German centres will participate (2 active)

MYRE – A French RCT

How to manage renal impairment in MM:

Part 1 – Moderate renal impairment and new MM:

- 200 patients randomized to CBD or BD

Part 2 – Severe renal impairment and new MM:

- 90 patients with biopsy proven myeloma kidney randomized to FLC removal HD or standard care

Frank Bridoux + Jean Paul Fermand

Improving Outcomes in Myeloma Kidney - Summary

1. Rapid diagnosis is essential
2. Early initiation of disease specific treatment
    1. High dose dexamethasone
    2. Bortezomib
3. In severe kidney failure – direct removal of FLCs may be indicated
    1. EuLITE – 2012
    2. MYRE – 2012/3