

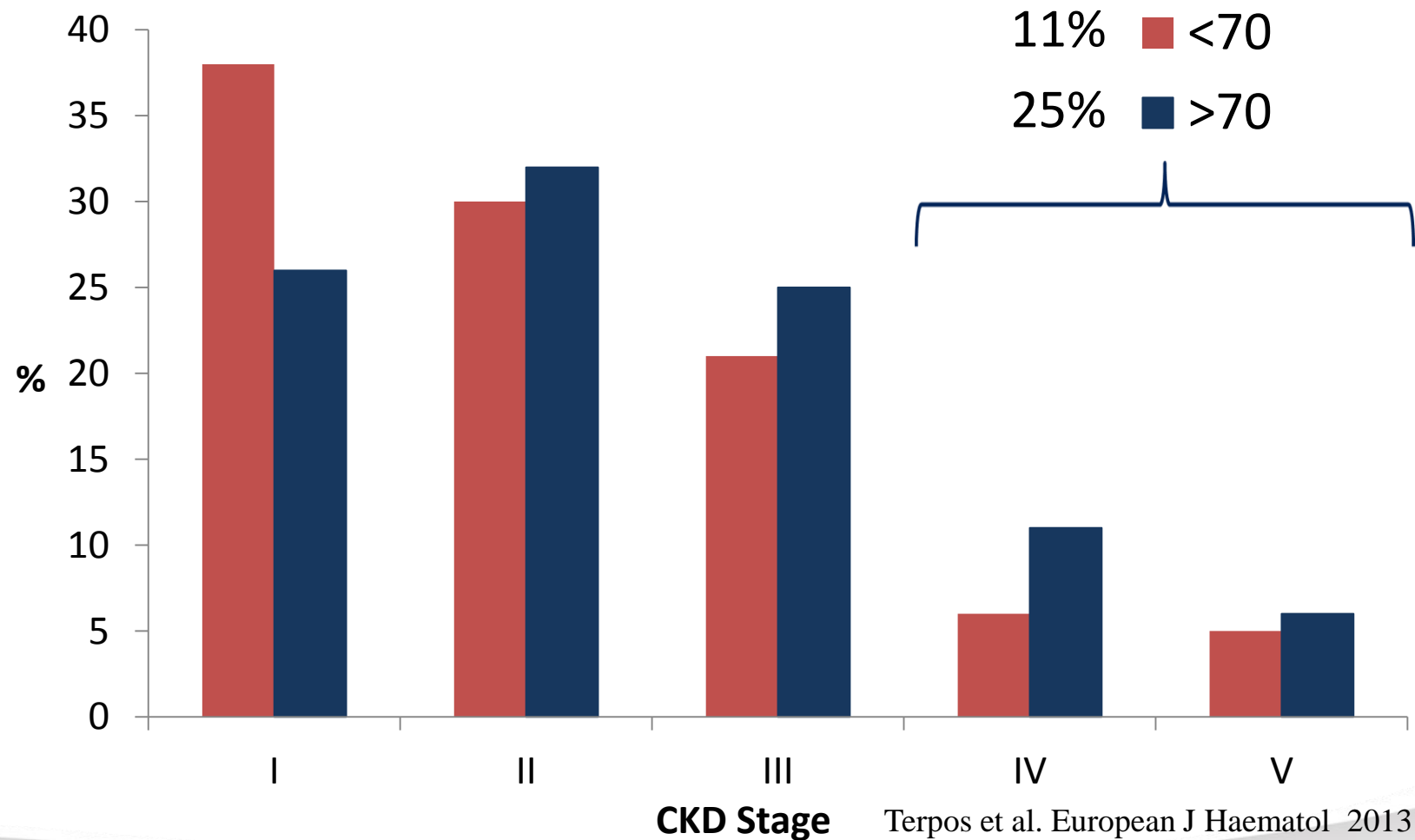
Update on Management of Cast Nephropathy

Nelson Leung

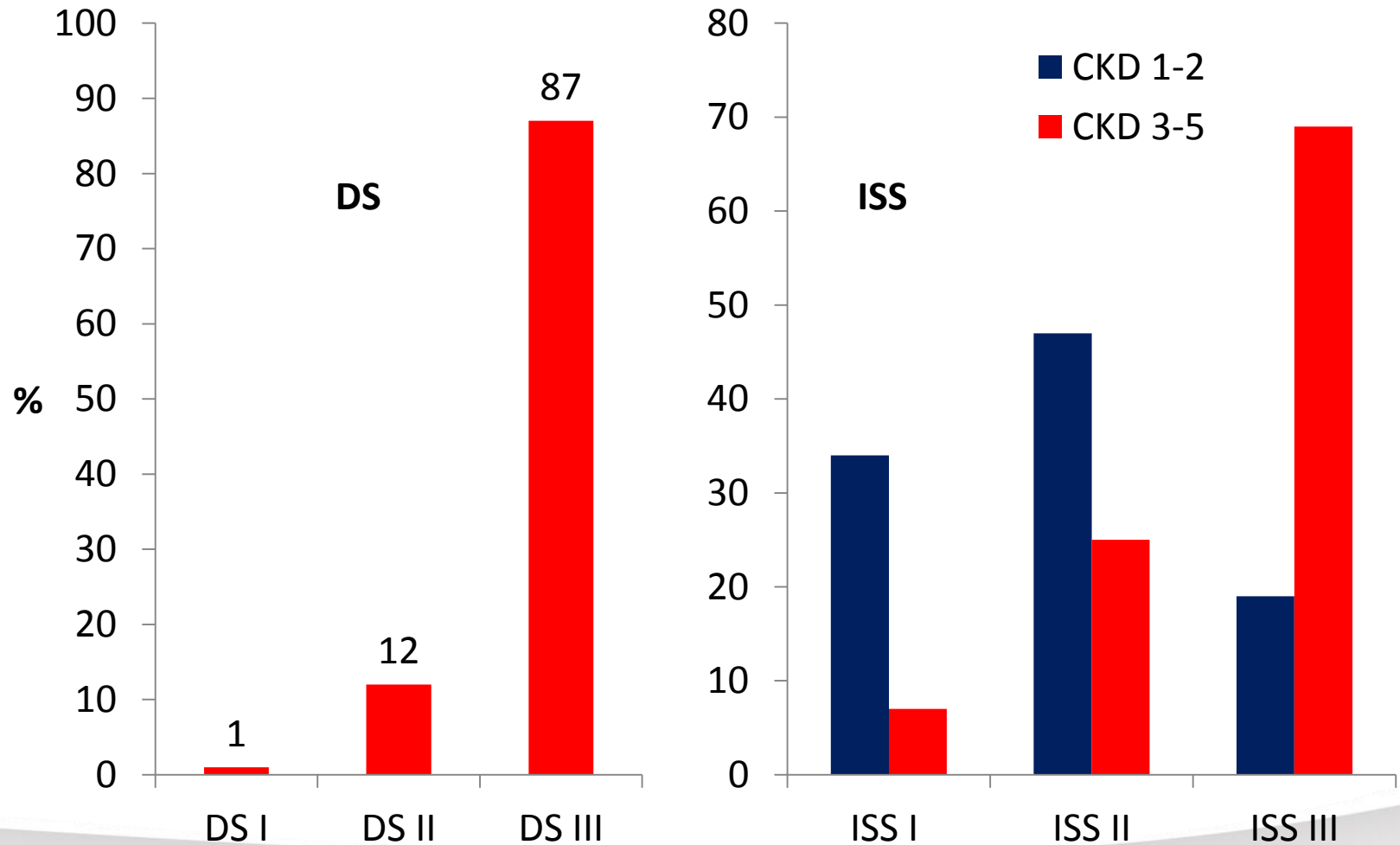
Professor of Medicine

Division of Nephrology and
Hypertension/ Hematology

Renal Function in Newly Diagnosed MM Patients



Renal impairment increases with more advanced disease



Blade et al. Arch Int Med 1998

Eleftherakis-Papapiakovou et al. Leukemia Lymphoma 2011

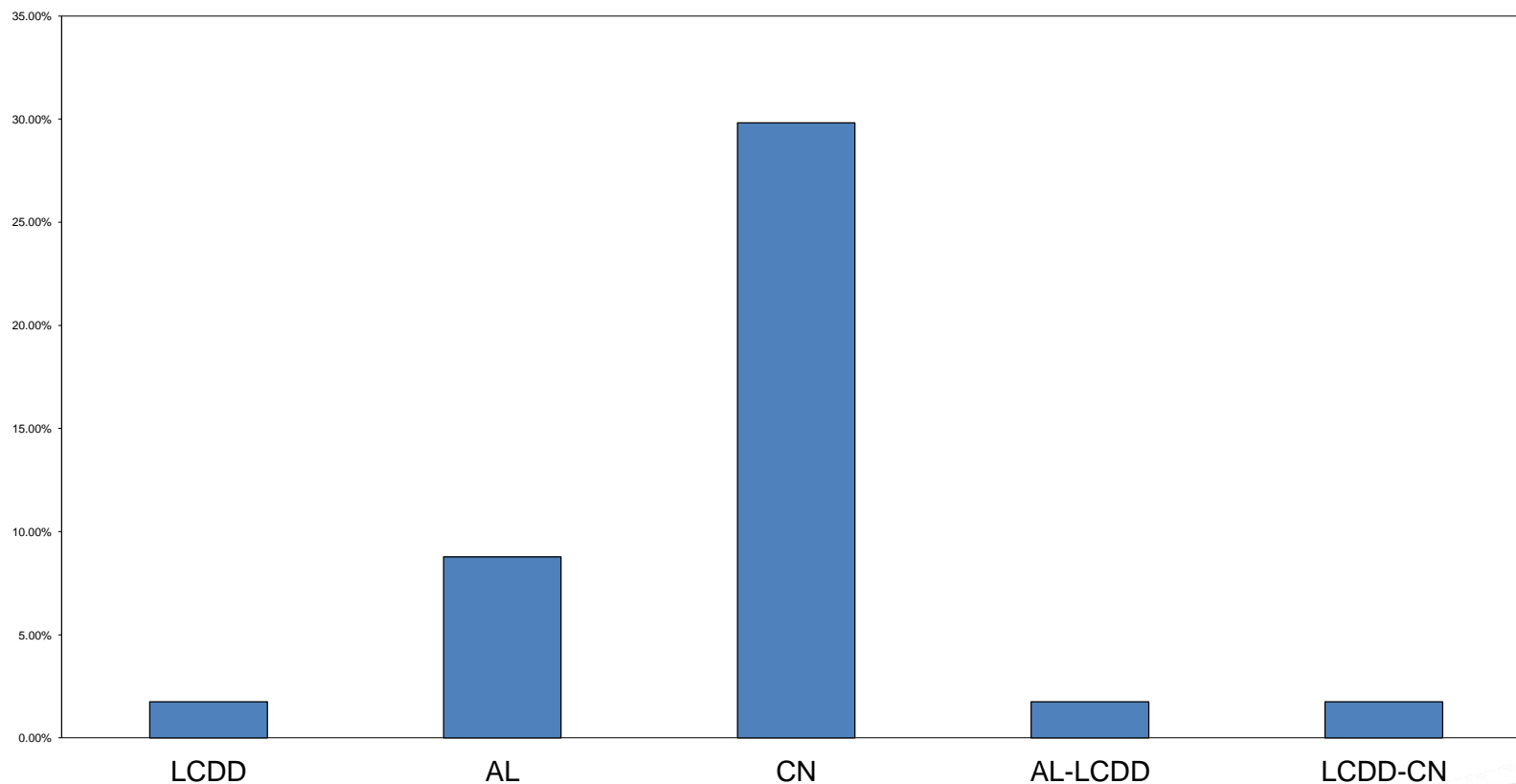
17th

International Congress of Nephrology, Dialysis, and Transplantation

Tabriz, Iran 19-22 November 2019

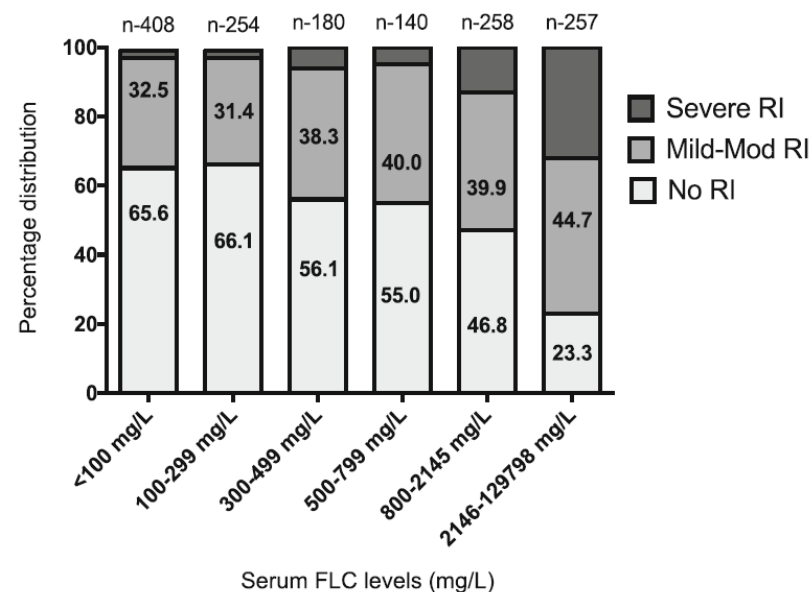
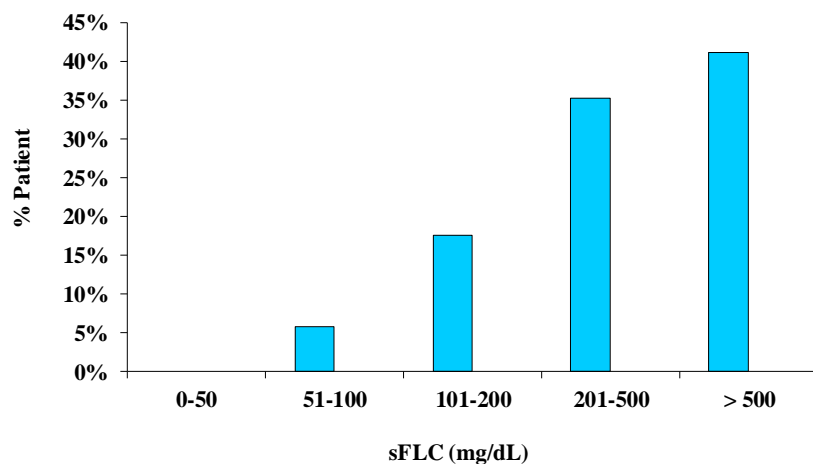


Renal Pathologies in Myeloma Patients



Ivanyi. Arch Pathol Lab Med 1990

Risk of Cast Nephropathy by sFLC level



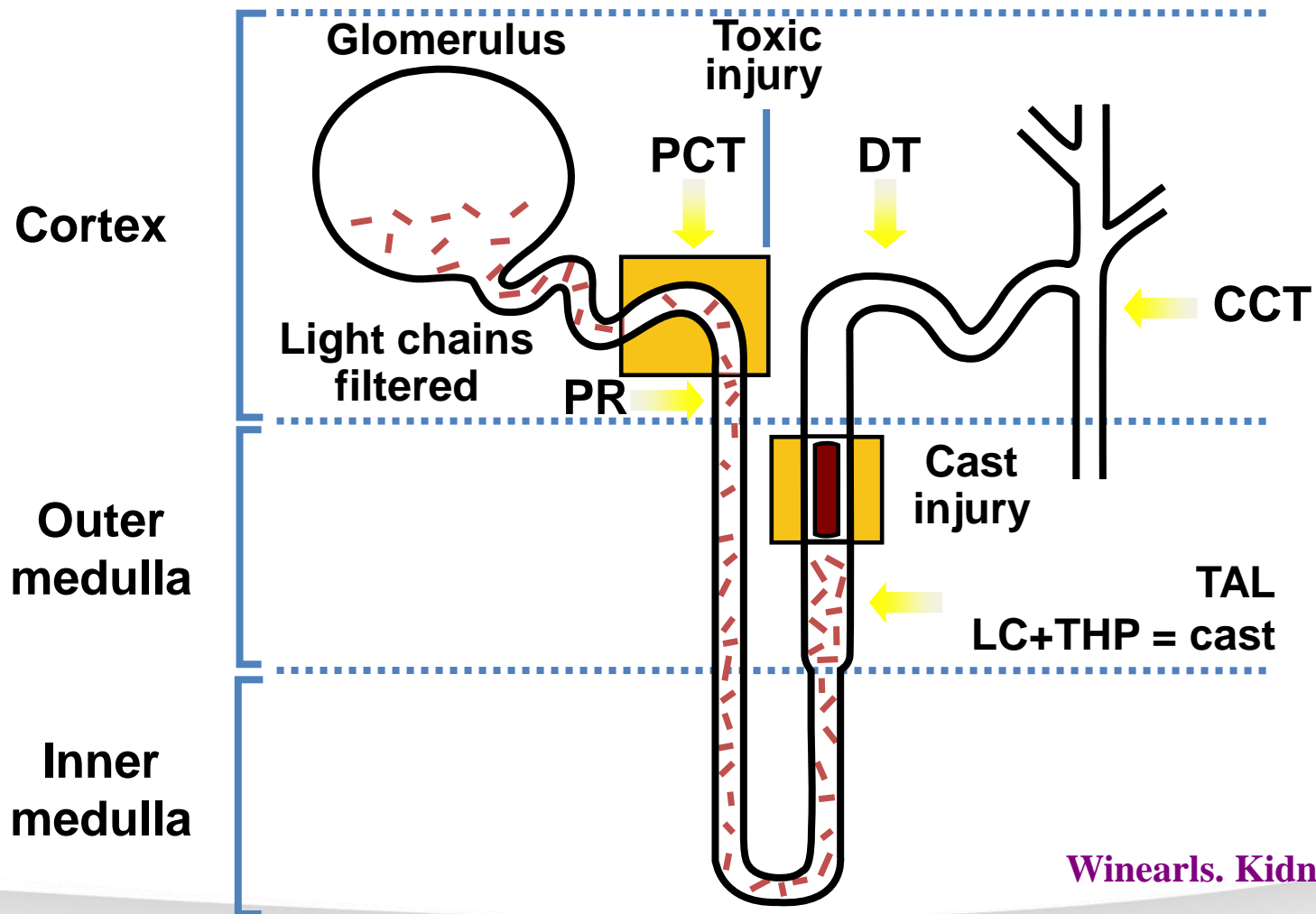
Leung et al. Kidney Int 2008
Yadav et al. BMC Nephrol 2018

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

The criteria have also been updated to clarify that only renal failure caused by light-chain cast nephropathy (based on typical histological changes or presumptive diagnosis based on the presence of high involved FLC levels, typically >1500 mg/L) is regarded as a myeloma-defining events.

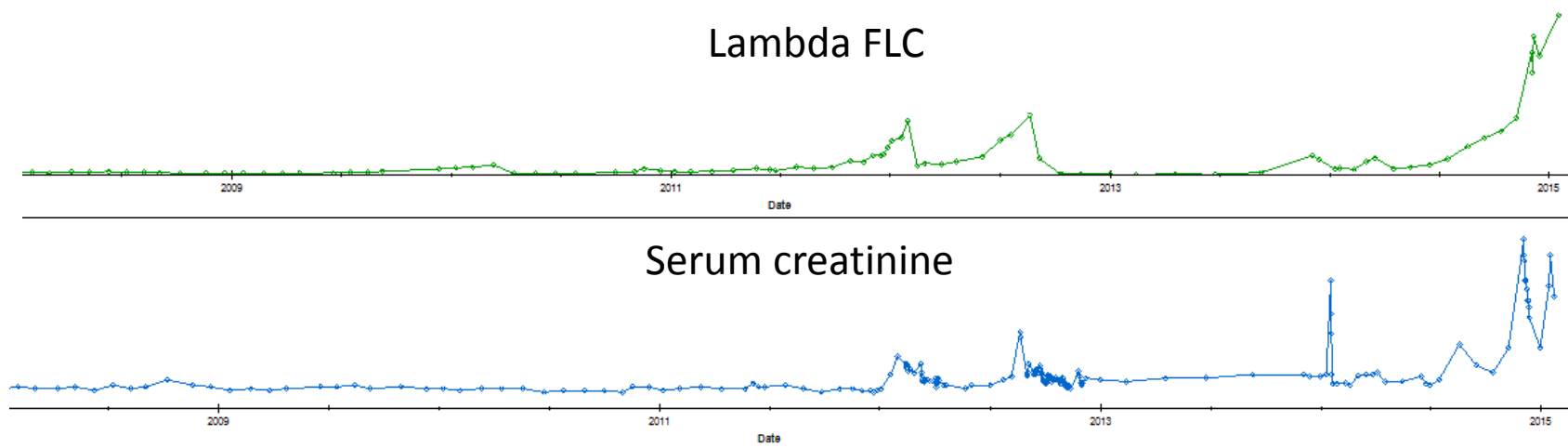
Although other forms of renal damage (eg, AL amyloidosis, monoclonal immunoglobulin deposition disease, light-chain Fanconi syndrome, monoclonal gammopathy-associated membranoproliferative glomerulonephritis) can occur in multiple myeloma, this association is not characteristic of multiple myeloma and can be seen with other types of plasma cell dyscrasias (eg, MGUS) or lymphoproliferative disorders. Although they can occur in conjunction with multiple myeloma, in most patients they occur independently without evidence of other myeloma-defining events. For this reason, these renal disorders are not regarded as myeloma-defining events, and should not lead to multiple myeloma diagnosis, unless they meet criteria for multiple myeloma as listed in the panel. These

Monoclonal FLC and Cast Nephropathy

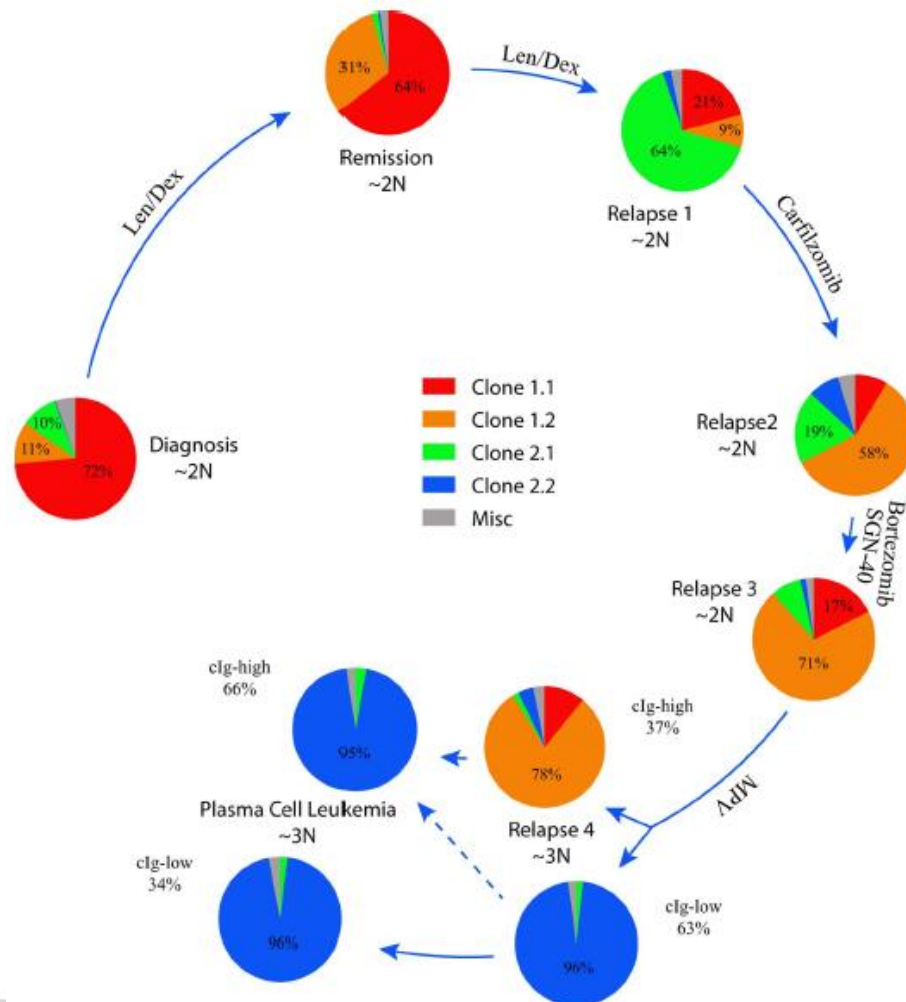


Winearls. Kidney Int, 1995

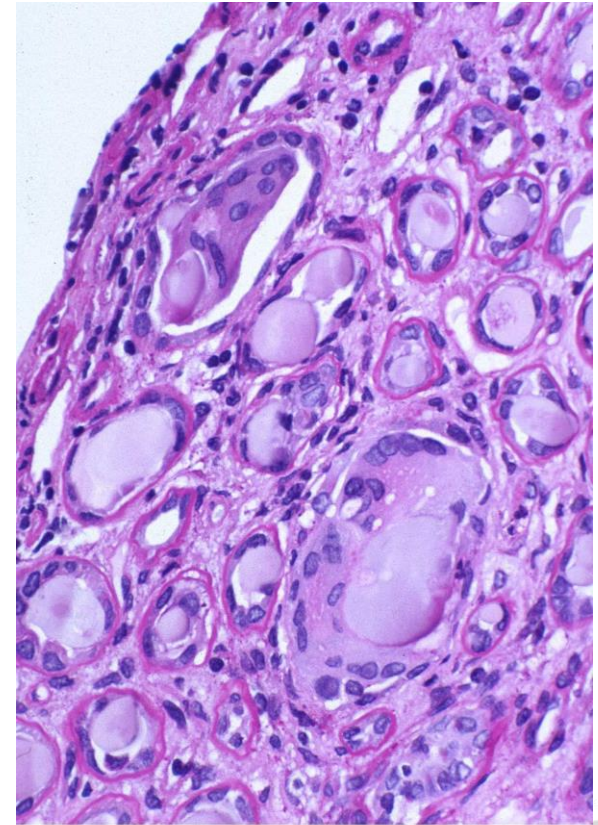
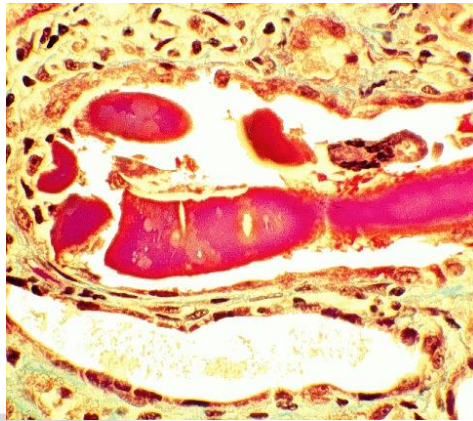
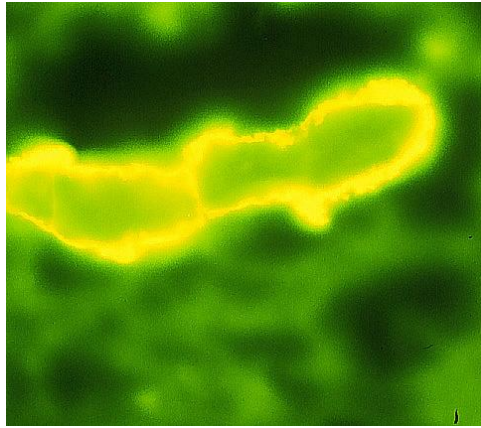
Relationship between serum FLC and serum creatinine



Clonal tiding



Light Chain Cast Nephropathy



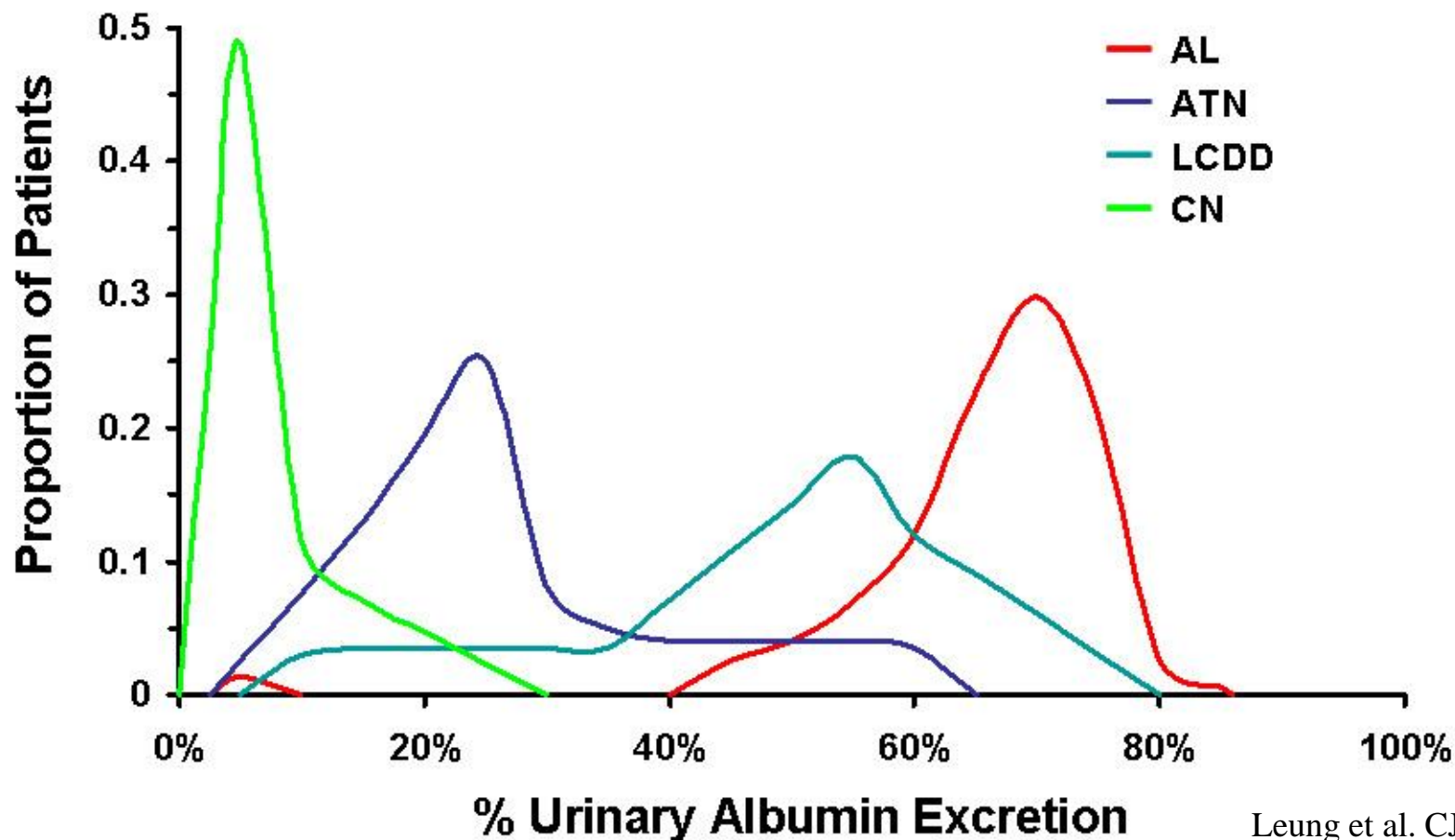
Copyright © 1998 by the National Kidney Foundation

Renal biopsy of patients with multiple myeloma

Pathologic Diagnosis	No. of Patients (%)
Paraprotein-associated renal lesions	
Myeloma cast nephropathy	62 (33)
Monoclonal immunoglobulin deposition disease	41 (22)
Amyloidosis	40 (21)
Fibrillary glomerulonephritis	2 (1)
Immunotactoid glomerulopathy	1 (0.5)
Light chain proximal tubulopathy	1 (0.5)
Interstitial infiltration by malignant plasma cells	2 (1)

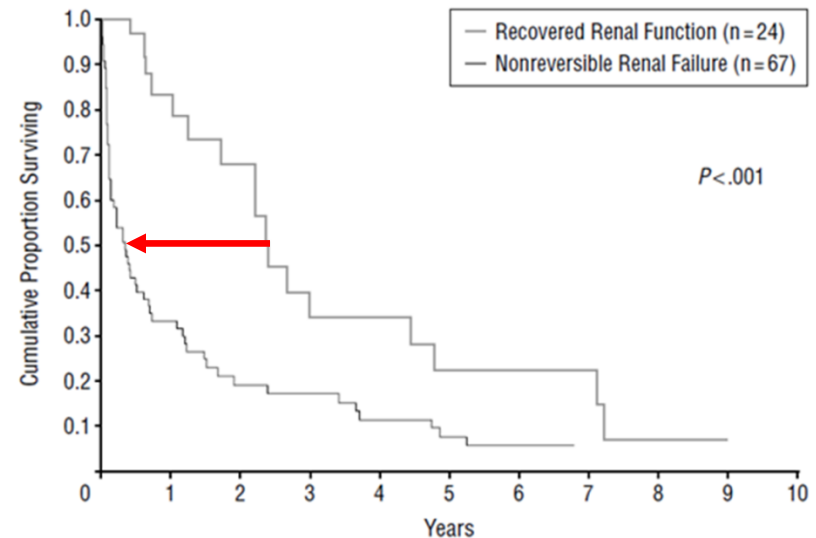
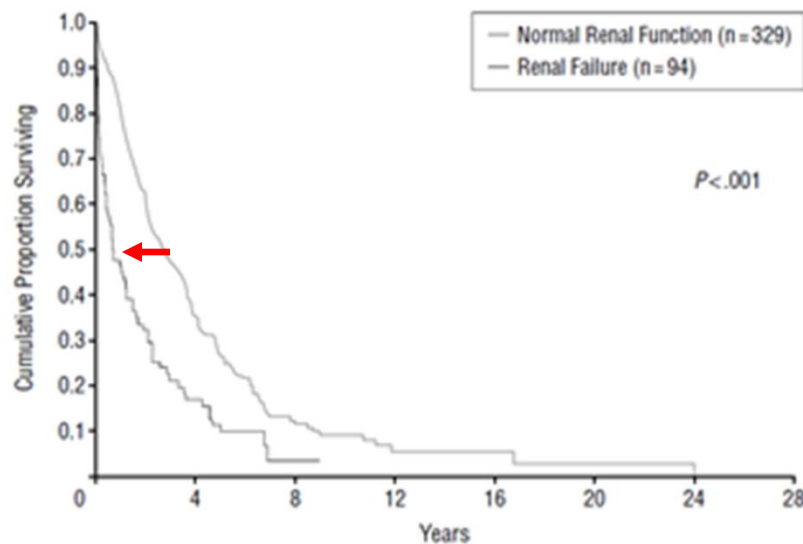
Nasr et al. Am J Kidney Dis 2012

Urinary Albumin Excretion Patterns of Patients with Cast Nephropathy and Other Monoclonal Gammopathy-Related Kidney Diseases



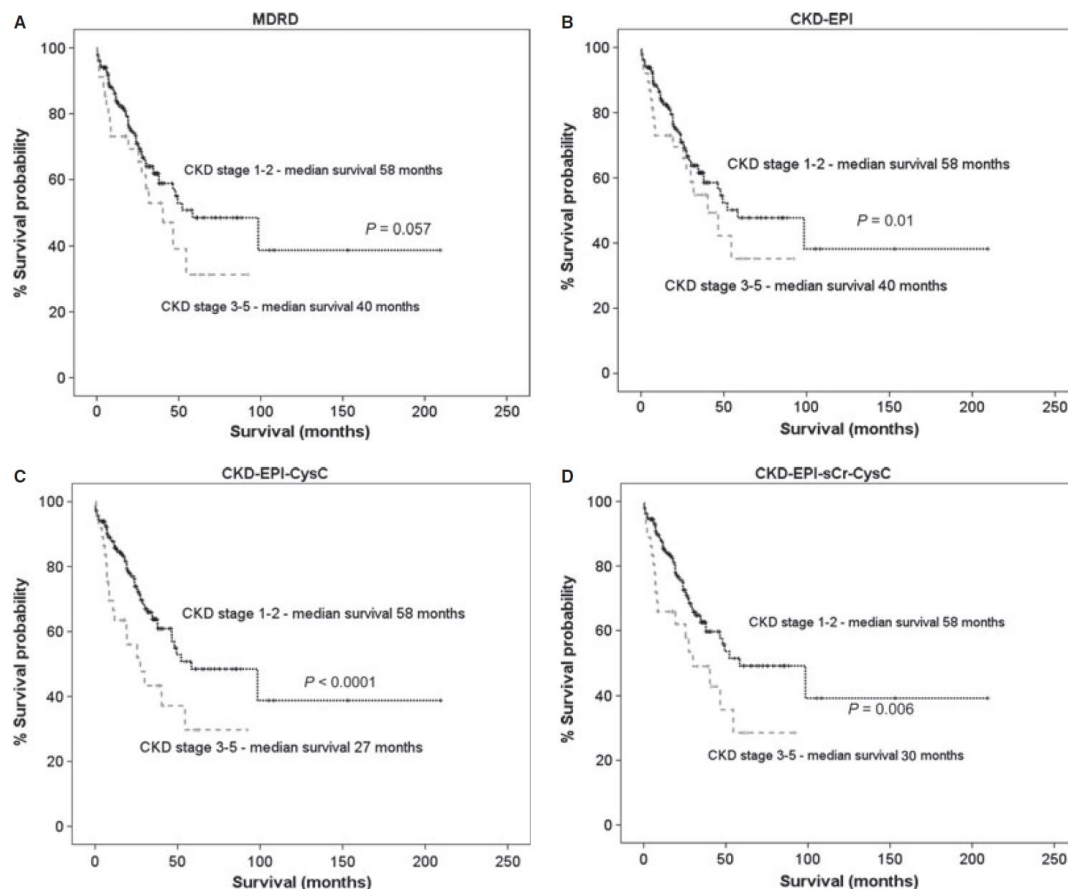
Leung et al. CJASN 2012

Impact of Renal Impairment on Overall Survival



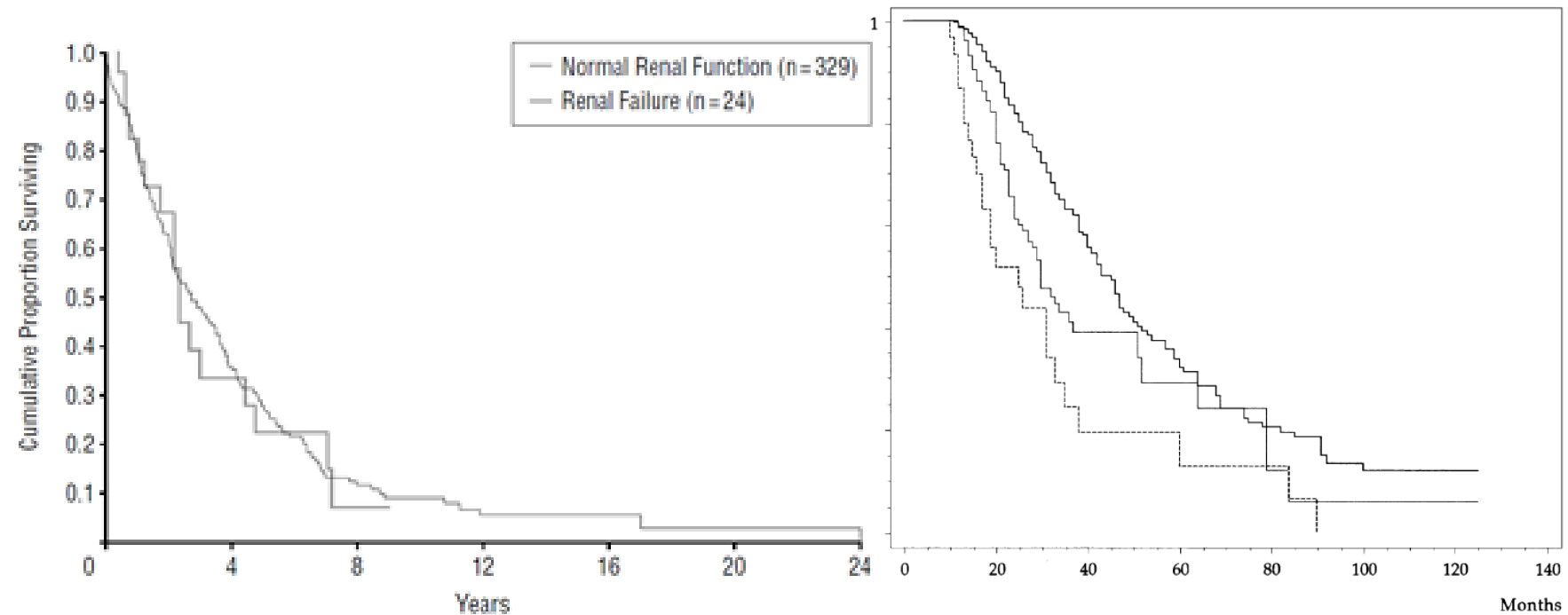
Blade et al. Arch Int Med 1998

The Chronic Kidney Disease Epidemiology Collaboration cystatin C (CKD-EPI-CysC) equation has an independent prognostic value for overall survival in newly diagnosed patients with symptomatic multiple myeloma; is it time to change from MDRD to CKD-EPI-CysC equations?



Terpos et al. Euro J Hematol 2013

Reversing Renal Impairment Improves Overall Survival



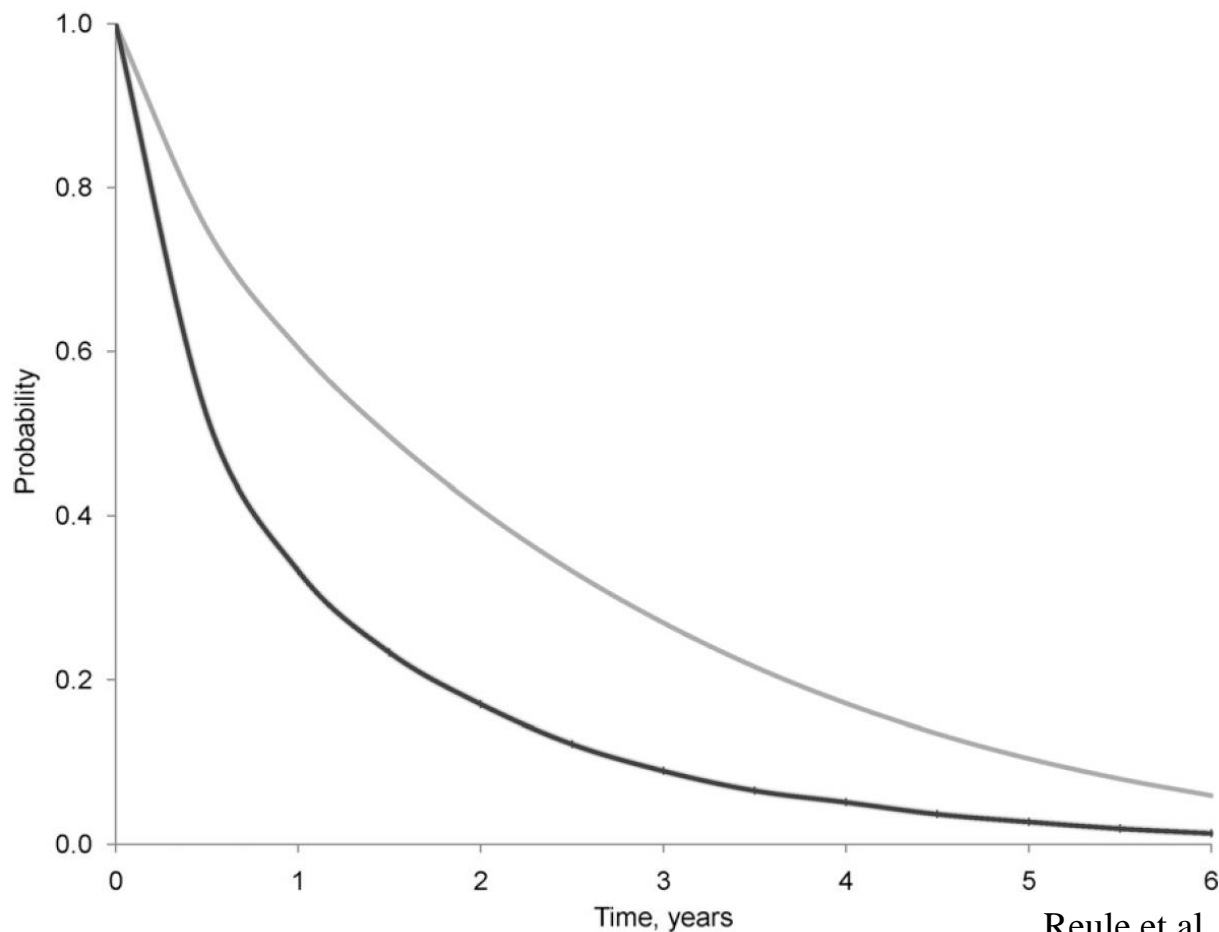
Blade et al. Arch Int Med 1998

Knudsen et al. Eur J Haematol. 2000

ESRD due to Multiple Myeloma in the United States, 2001–2010

Scott Reule,^{*,†} Donal J. Sexton,^{*,†} Craig A. Solid,[†] Shu-Cheng Chen,[†] and Robert N. Foley^{*,†}

^{*}Department of Medicine, University of Minnesota, Minneapolis, Minnesota; and [†]Minneapolis Medical Research Foundation, Minneapolis, Minnesota



Reule et al. JASN 2016

Renal Impairment in Patients With Multiple Myeloma: A Consensus Statement on Behalf of the International Myeloma Working Group

Response	Baseline eGFR* (ml/min/1.73 m ²)	Best CrCl Response (mL/min)
CRrenal	< 50	≥ 60
PRrenal	< 15	30-59
MRrenal	< 15	15-29
	15-29	30-59

Dimopoulos et al. JCO 2010

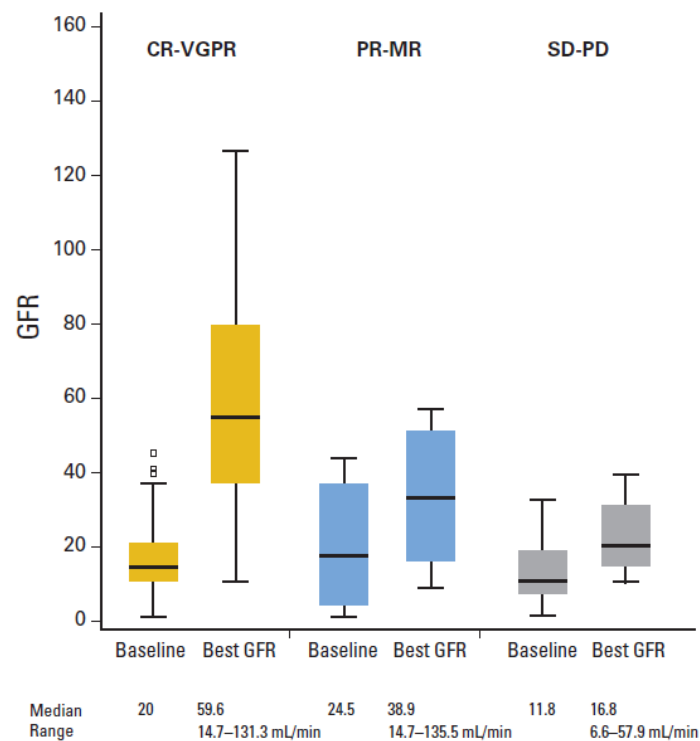
Renal Response by Hematologic Response

Final eGFR by •
hematologic response

>VGPR – 59.5 ml/min/1.73m² –

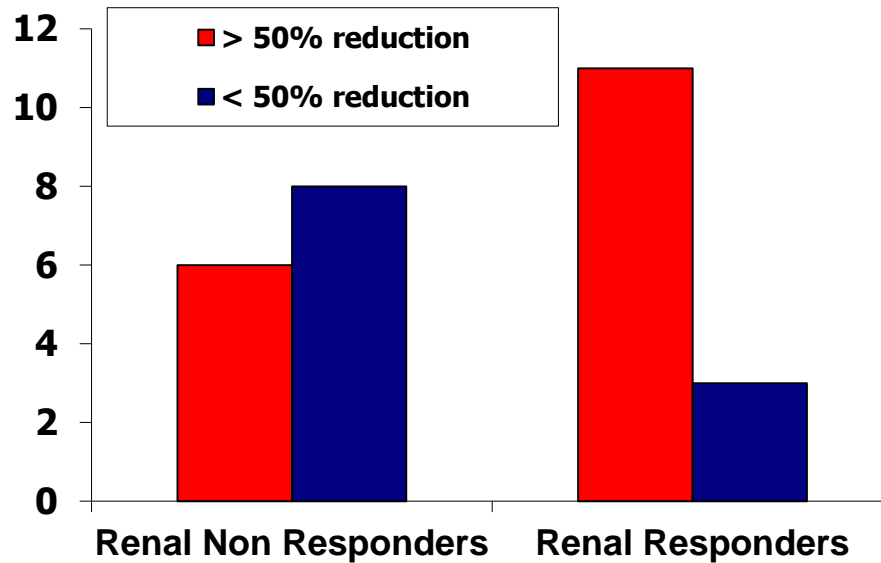
PR/MR – 38.9 ml/min/1.73m² –

SD/PD – 16.8 ml/min/1.73m² –



Ludwig et al. JCO. 2010

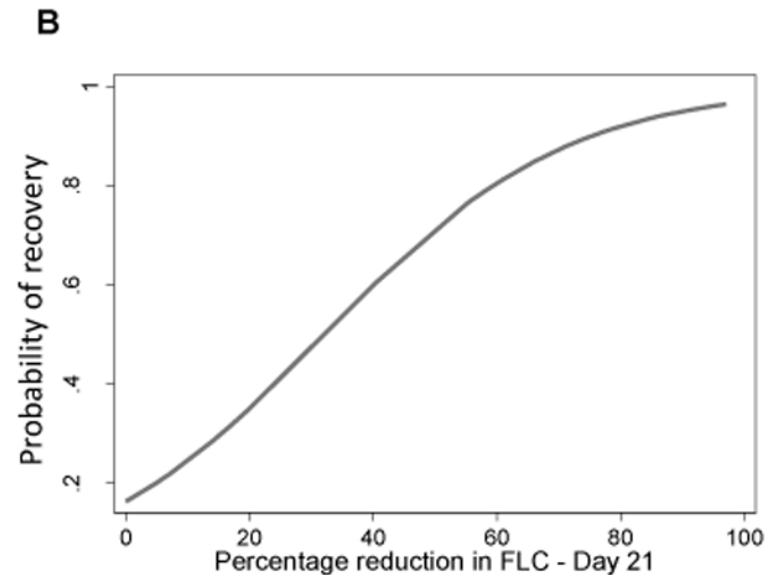
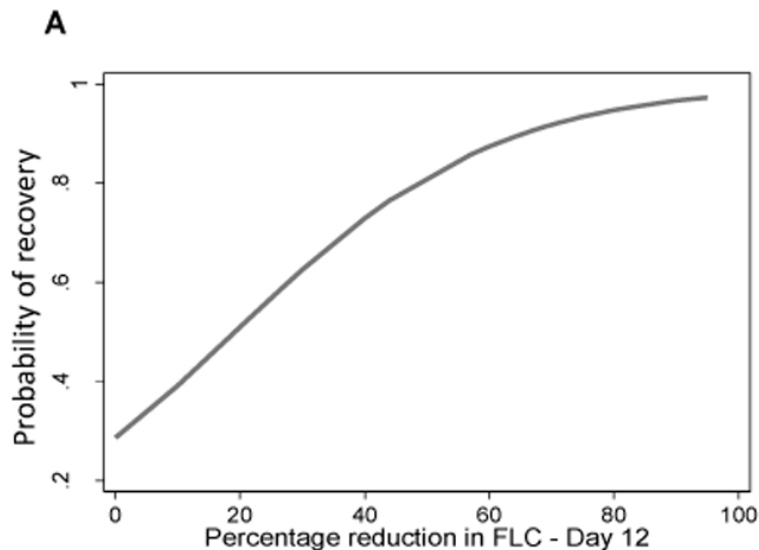
Improvement of acute renal function in patients with MM



> 50% reduction in
the involved sFLC
Cast nephropathy

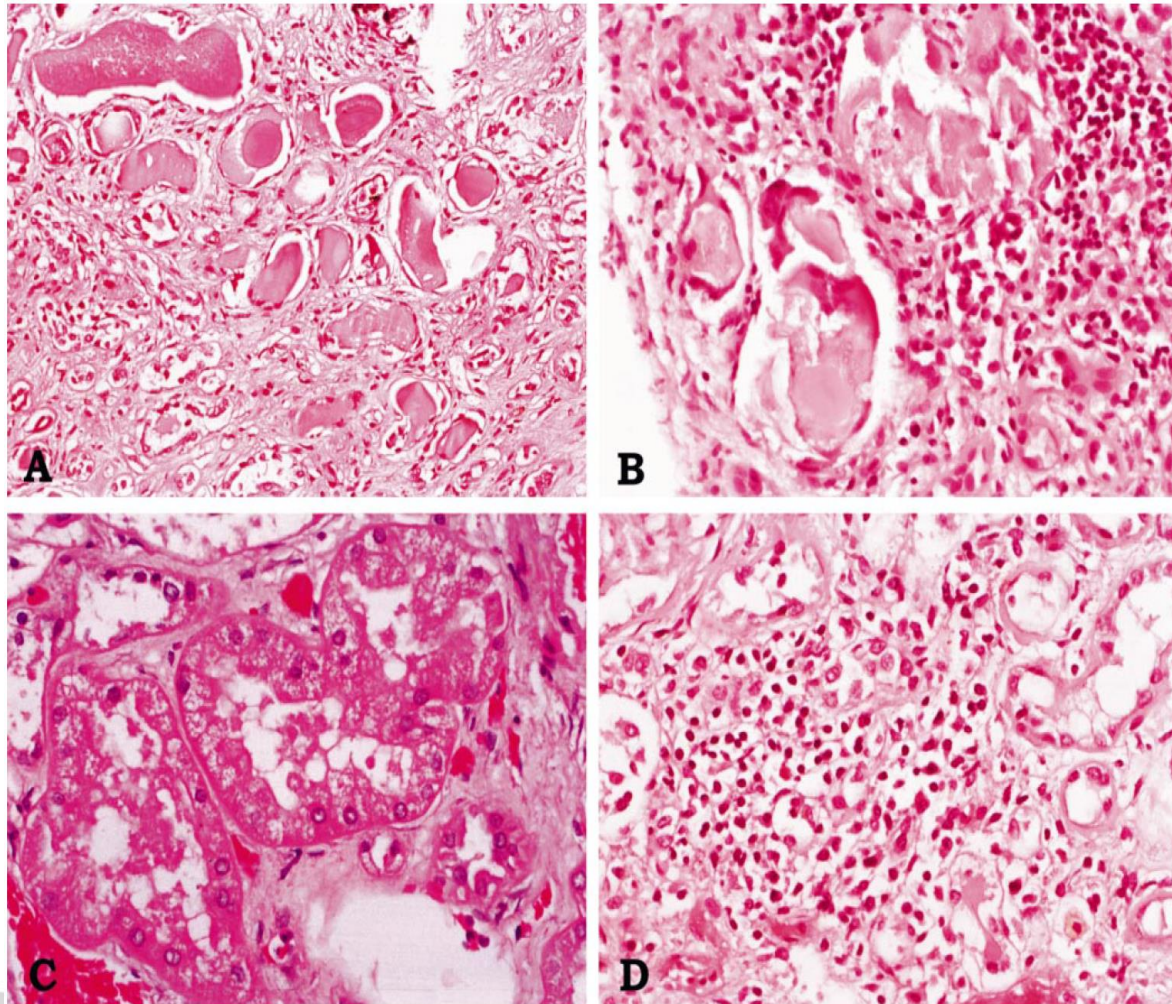
Leung et al. Kidney Int 2008

Probability of Renal Response by Depth and Speed of sFLC Reduction



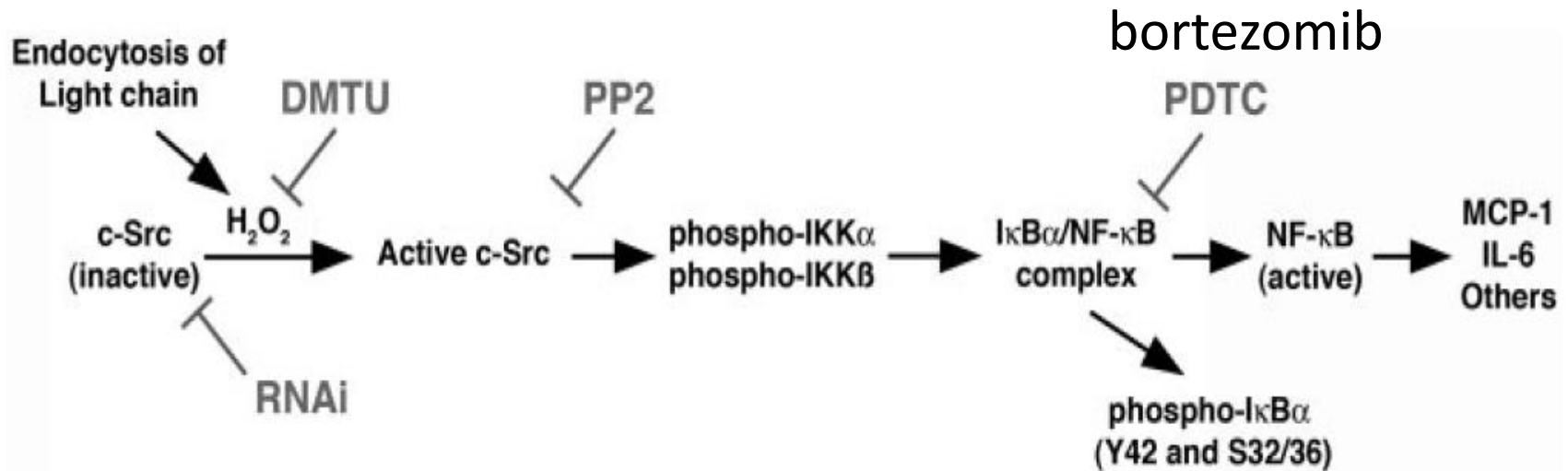
Hutchison et al. J Am Soc Nephrol 2011

Why is early reduction of FLC important for renal recovery?



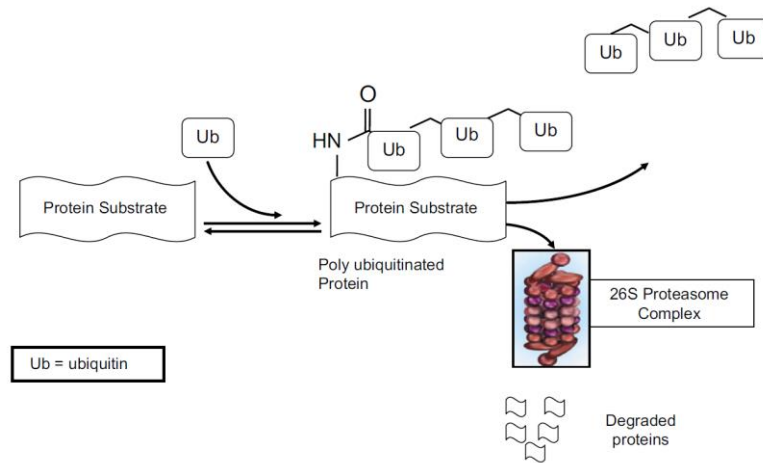
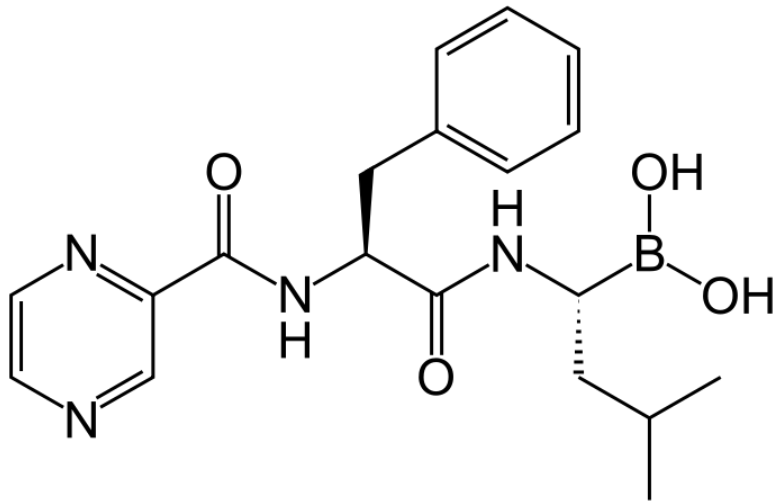
MCP-1

Signal Pathway induced by Free Light Chains



Sanders et al. Blood 2011

Bortezomib



VISTA

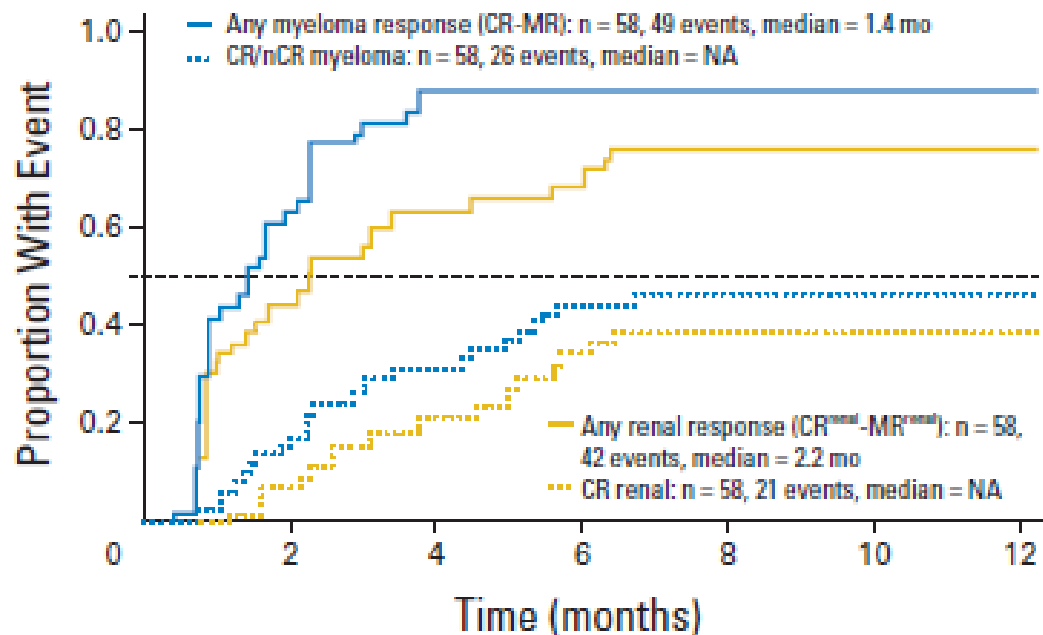
MP vs VMP

	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

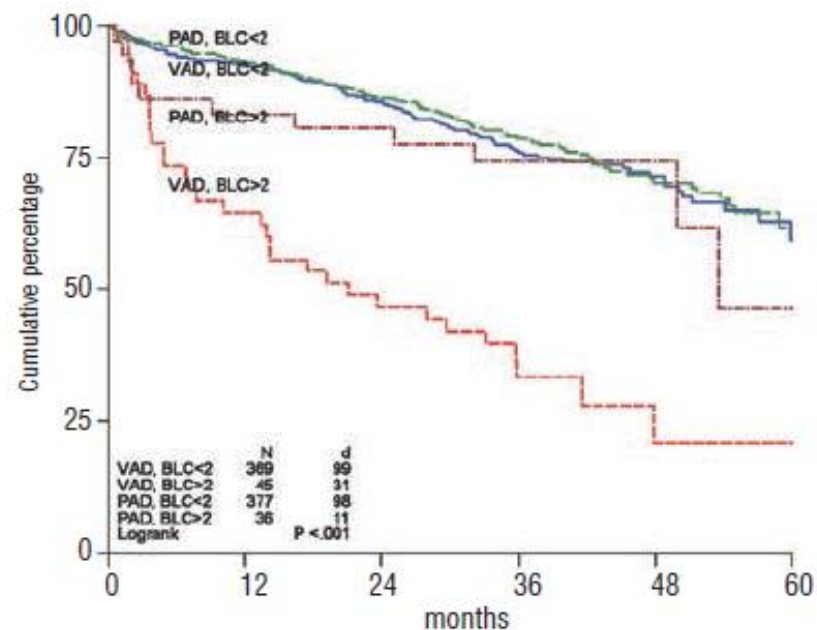
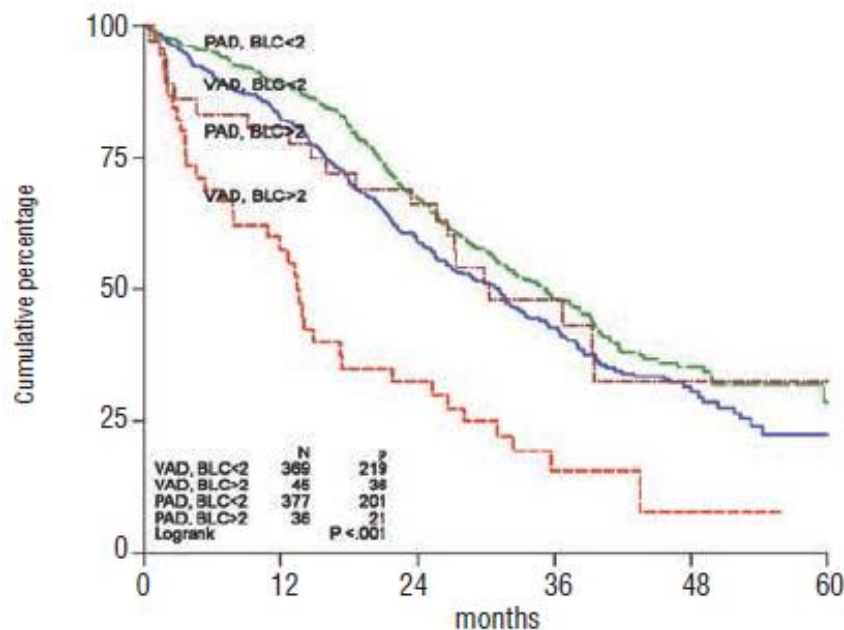
Light Chain–Induced Acute Renal Failure Can Be Reversed by Bortezomib-Doxorubicin-Dexamethasone in Multiple Myeloma: Results of a Phase II Study

Heinz Ludwig, Zdenek Adam, Roman Hajek, Richard Greil, Elena Tóthová, Felix Keil, Eva Maria Autzinger, Josef Thaler, Heinz Gisslinger, Alois Lang, Miklós Egyed, Irene Womastek, and Niklas Zojer



Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a subgroup analysis from the HOVON-65/GMMG-HD4 trial

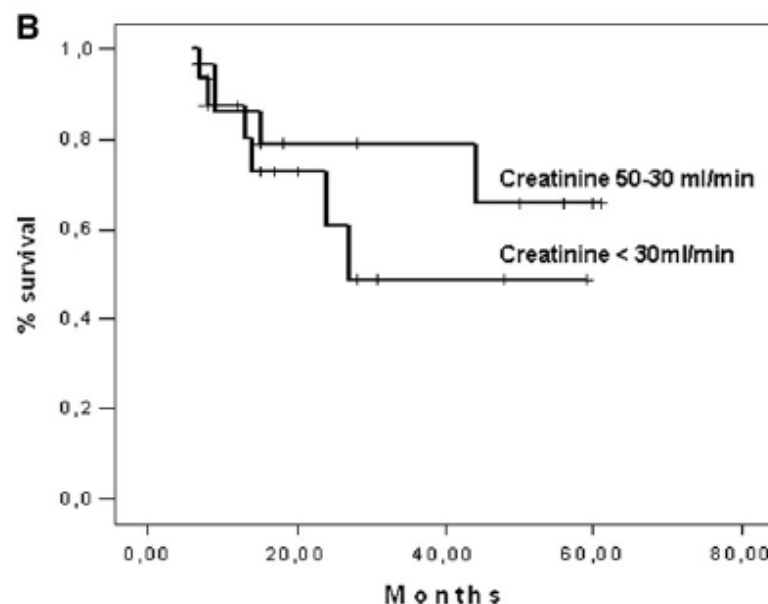
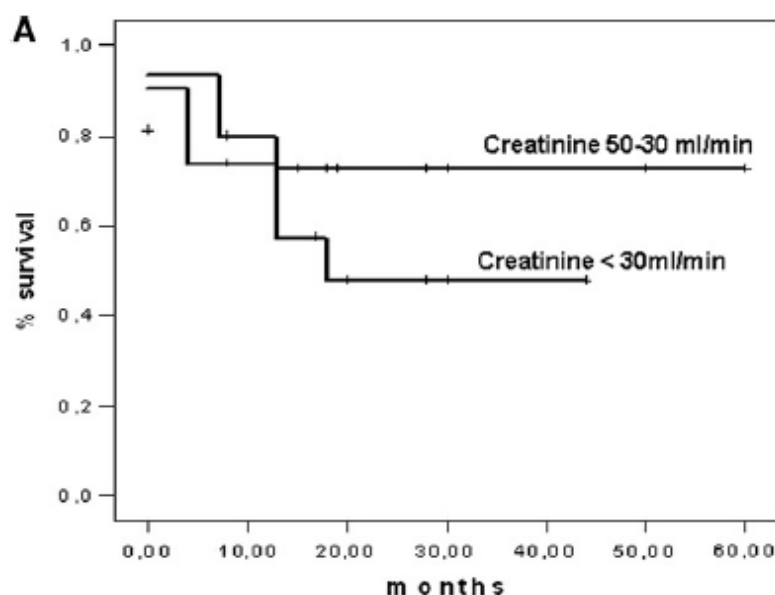
Christof Scheid,¹ Pieter Sonneveld,² Ingo G.H. Schmidt-Wolf,³ Bronno van der Holt,² Laila el Jarari,² Uta Bertsch,⁴ Hans Salwender,³ Sonja Zweegman,² Igor Wolfgang Blau,³ Edo Vellenga,² Katja Weisel,³ Michael Pfreundschuh,³ Kon-Siong Jie,² Kai Neben,⁴ Helgi van de Velde,⁵ Ulrich Diehrsen,³ M. Ron Schaafsma,² Walter Lindemann,³ Marie José Kersten,² Norma Peter,³ Mathias Hänel,³ Sandra Croockewit,² Hans Martin,³ Shulamiet Wittebol,² Gerard MJ Bos,² Marinus van Marwijk-Kooy,² Pierre Wijermans,² Hartmut Goldschmidt,⁴ and Henk M. Lokhorst²



Scheid et al. Haematologic 2014

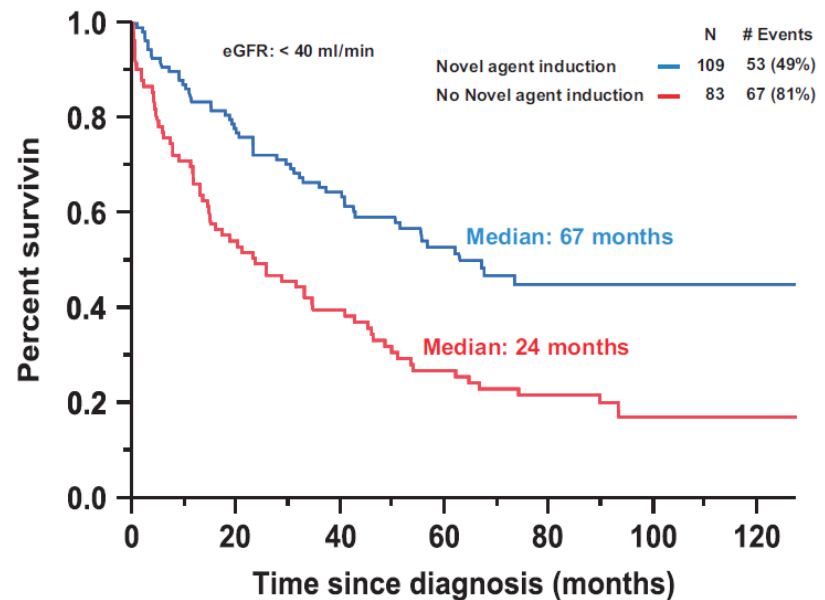
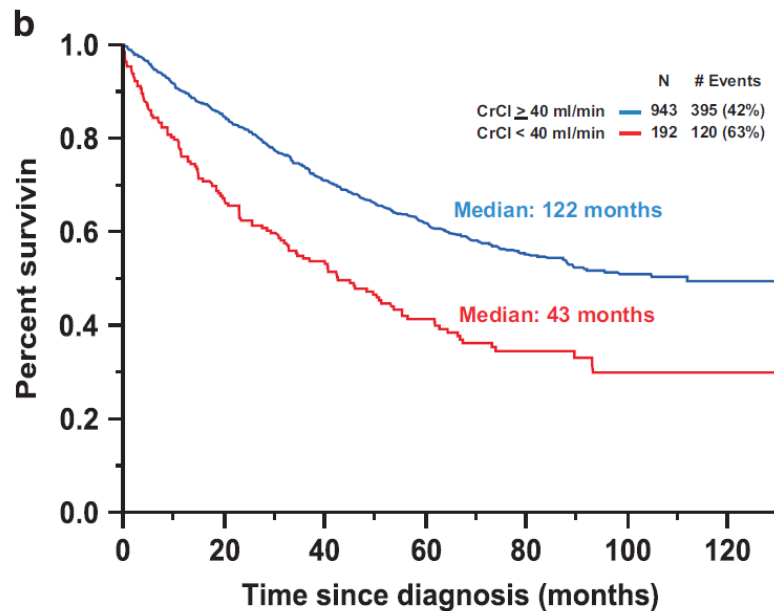
Thalidomide-Dexamethasone as Induction Therapy before Autologous Stem Cell Transplantation in Patients with Newly Diagnosed Multiple Myeloma and Renal Insufficiency

Patrizia Tosi, Elena Zamagni, Paola Tacchetti, Michela Ceccolini, Giulia Perrone, Annamaria Brioli, Maria Caterina Pallotti, Lucia Pantani, Alessandro Petrucci, Michele Baccarani, Michele Cavo



Improvement in renal function and its impact on survival in patients with newly diagnosed multiple myeloma

WI Gonsalves, N Leung, SV Rajkumar, A Dispenzieri, MQ Lacy, SR Hayman, FK Buadi, D Dingli, P Kapoor, RS Go, Y Lin, SJ Russell, JA Lust, S Zeldenrust, RA Kyle, MA Gertz and SK Kumar



Gonsalves et al. Blood Cancer J 2015

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 —

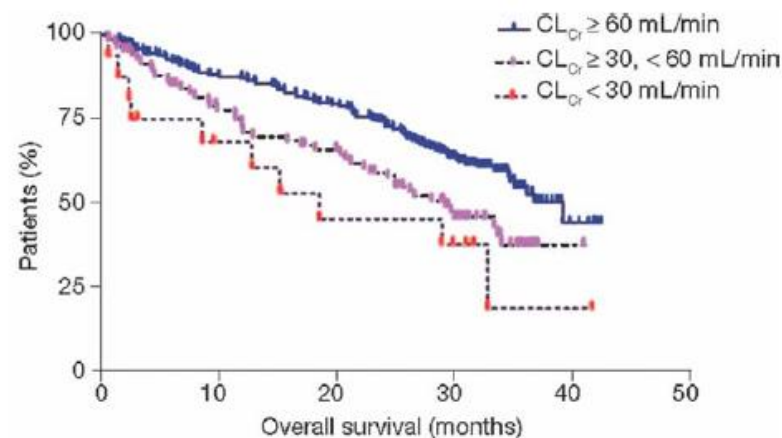
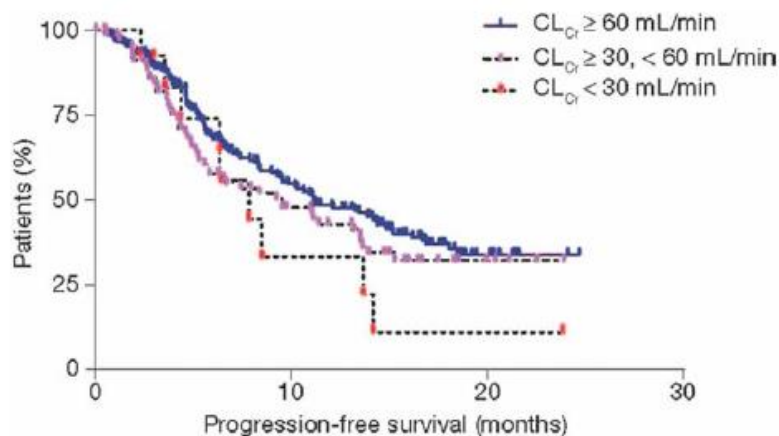
Treatment —

Median dose for patient with $\text{CrCl} > 30$ ml/min = 25 mg/d •

Median dose for patient with $\text{CrCl} < 30$ ml/min = 15 mg/d •

The Efficacy and Safety of Lenalidomide Plus Dexamethasone in Relapsed and/or Refractory Multiple Myeloma Patients With Impaired Renal Function

Meletios Dimopoulos, MD¹; Adrian Alegre, MD²; Edward A. Stadtmauer, MD³; Hartmut Goldschmidt, MD⁴; Jeffrey A. Zonder, MD⁵; Carlos M. de Castro, MD⁶; Zvenyslava Masliak, MD⁷; Donna Reece, MD⁸; Marta Olesnyckyj, RN⁹; Zhinuan Yu, PhD⁹; and Donna M. Weber, MD¹⁰



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	22 ^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.

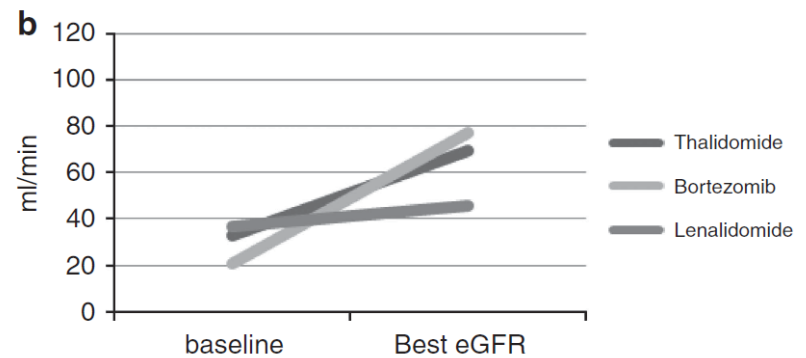
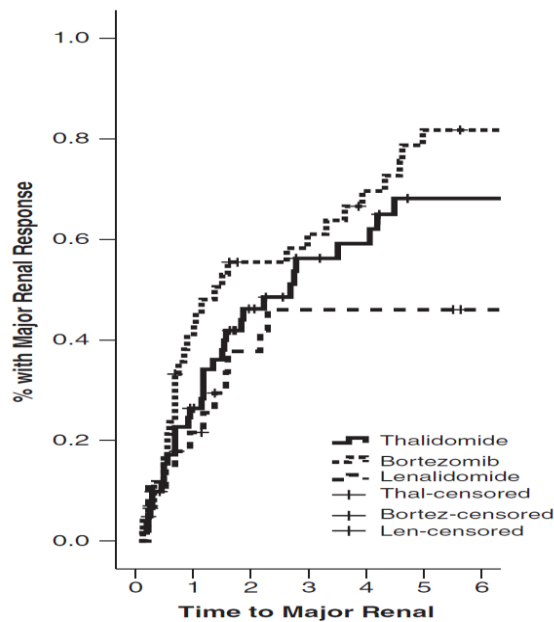
^a*P* < .05 versus patients with mild or no RI.

^bThrombotic events included pulmonary embolism, deep vein thrombosis, and venous thrombosis NOS.

ORIGINAL ARTICLE

The role of novel agents on the reversibility of renal impairment in newly diagnosed symptomatic patients with multiple myeloma

MA Dimopoulos, M Roussou, M Gkatzamanidou, N Nikitas, E Psimenou, D Mparmparoussi, C Matsouka, M Spyropoulou-Vlachou, E Terpos and E Kastritis



Baseline eGFR (ml/min/1.73 m²), median(range)
 Best eGFR (ml/min/1.73 m²), median(range)
 Renal response (\geq renalMR)
 Major renal response (\geq renalPR)
 RenalCR
 Baseline eGFR (ml/min/1.73 m²) for patients who achieved renalCR, median (range)
 Best eGFR (ml/min/1.73 m²) for patients who achieved renalCR, median (range)

Thalidomide	Bortezomib	Lenalidomide	P-value
38 (6–59)	21 (4–59)	37 (6–58)	0.037
69 (16–140)	77 (5–175)	45 (15–106)	0.2
46 (74%)	35 (81%)	17 (61%)	0.153
34 (55%)	33 (77%)	12 (43%)	0.011
33 (53%)	29 (67%)	10 (36%)	0.032
44 (6–58)	27 (5–59)	49 (15–58)	
86 (64–139)	91 (61–175)	85 (65–106)	

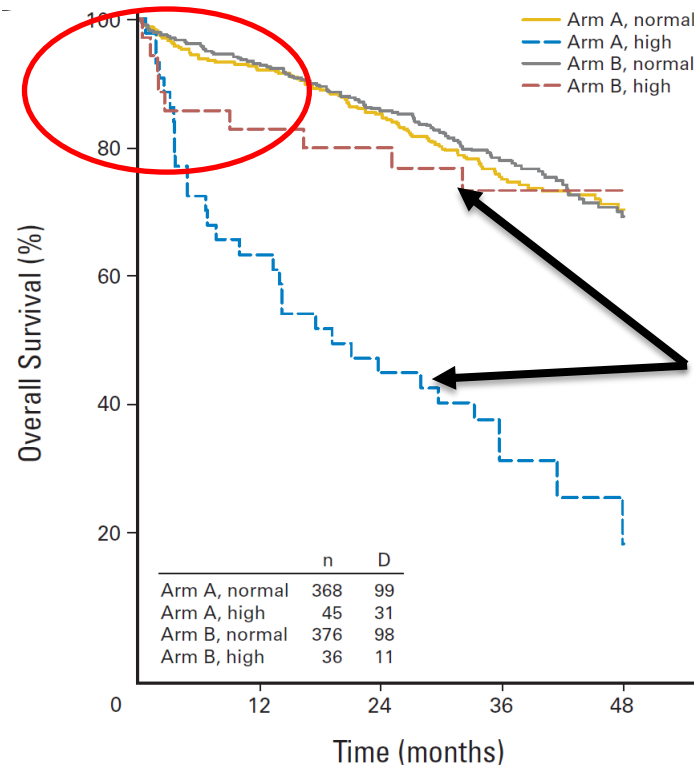
Dimopoulos et al. Leukemia 2103

Factors associated with a major renal response

	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age < 65 years	5.08 (1.93–25.7)	0.001	3.39 (1.070–10.75)	0.038
eGFR ≥ 30 ml/min	2.3 (1.024–4.123)	0.043	2.93 (1.28–6.7)	0.011
24-h Urine (Bence Jones Protein) ≥ 2 g	0.892 (0.387–1.8)	0.639	NA	
Light chain only myeloma	1.393 (0.59–3.289)	0.449	NA	
Myeloma response (≥ PR)	3.05 (1.37–6.8)	0.006	2.65 (1.08–6.49)	0.033
Dexamethasone dose ≥ 160 mg	3.072 (1.36–6.93)	0.007	1.74 (0.64–4.5)	0.256
Lenalidomide	1		1	
Thalidomide	1.62 (0.66–3.98)	0.294	2.36 (0.868–6.405)	0.092
Bortezomib	4.4 (1.571–12.324)	0.005	4.25 (1.3–13.94)	0.017

Dimopoulos et al. Leukemia 2103

Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a subgroup analysis from the HOVON-65/GMMG-HD4 trial



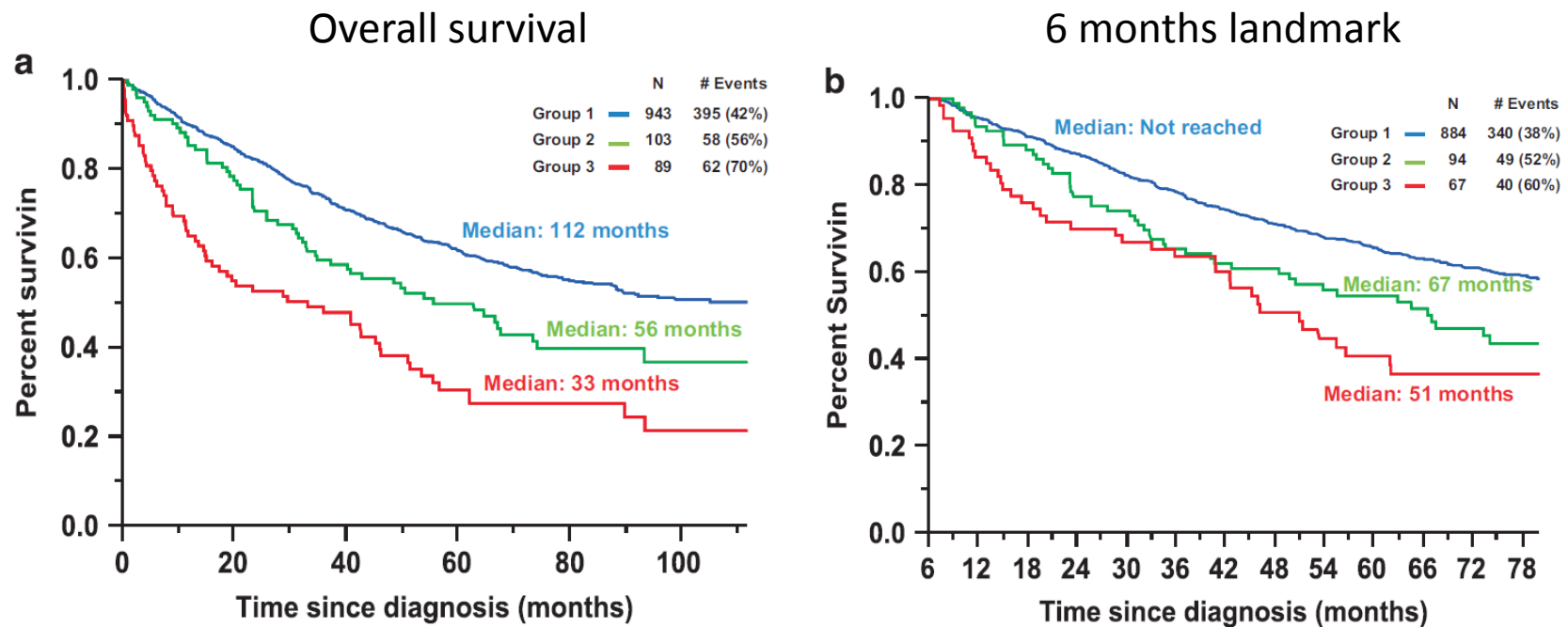
PAD vs VAD

Patients with high serum creatinine

Scheid et al. Haematologica 2014

Improvement in renal function and its impact on survival in patients with newly diagnosed multiple myeloma

WI Gonsalves, N Leung, SV Rajkumar, A Dispenzieri, MQ Lacy, SR Hayman, FK Buadi, D Dingli, P Kapoor, RS Go, Y Lin, SJ Russell, JA Lust, S Zeldenrust, RA Kyle, MA Gertz and SK Kumar



Gonsalves et al. Blood Cancer J 2015

Plasmapheresis

3 randomized trials

Zucchelli Study

Randomized Trial •

- 29 patients
- Methylprednisolone and cyclophosphamide
- 2 to 5 L/d of NS or sodium bicarbonate
- 500 mg to 1500 mg of furosemide
- 17 patients had renal biopsies
- 15 received 5 PLEX (more if necessary)
- 14 dialysis dependent

Results

Control Group

2 recovered enough renal function to stop dialysis

3 died within the first month of study

2 more died during the second month

PLEX

11/13 dialysis dependent patients recovered renal function

Renal recovery period ranged from 9 to 34 days

1 died within 2 months of study

Johnson's Study

21 patients

Melphalan & Prednisone

½ NS with HCO_3^-

Furosemide to achieve urine output of 100 cc/h

Renal biopsy was performed on 16 patients

Randomization

Control – 10

PLEX – 11

Results

Improvement in renal function

Control – 5

PLEX – 7

Patients who were chemo-responsive were more likely to have improvement in renal function

Of the 12 patients on HD, only patients (3) who received PLEX were able to discontinue dialysis

Patients with lower histologic score were more likely to recover renal function

No differences in survival was noted between the 2 groups

Plasma Exchange When Myeloma Presents as Acute Renal Failure

A Randomized, Controlled Trial

William F. Clark, MD; A. Keith Stewart, MD; Gail A. Rock, MD; Marion Sternbach, MD; David M. Sutton, MD; Brendan J. Barrett, MD; A. Paul Heidenhelm, MA; Amit X. Garg, MD; David N. Churchill, MD; and the Canadian Apheresis Group

Ann Intern Med. 2005;143:777-784.

Multicenter prospective trial

Chemo: VAD vs M&P

104 Patients

7 patients withdrew from the study

3 withdrew from the study

2 patients in each arm were lost to F/U

58 PLEX :39 Control

Composite outcome

Death, Dialysis, eGFR < 30 ml/min/1.73m²

Results

<u>PLEX</u>	<u>Control</u>	
65.2	61.3	Age
4.78	5.21	Initial Scr (mg/dL)
41.4%	43.6%	Durie-Salmon IIIb
57.9%	69.2%	Composite outcome
32.8%	33.3%	Death at 6 months
41.6%	38.6%	Discontinued dialysis
31.4	30.2	eGFR at 6 months (ml/min/1.73m ²)

Conclusion

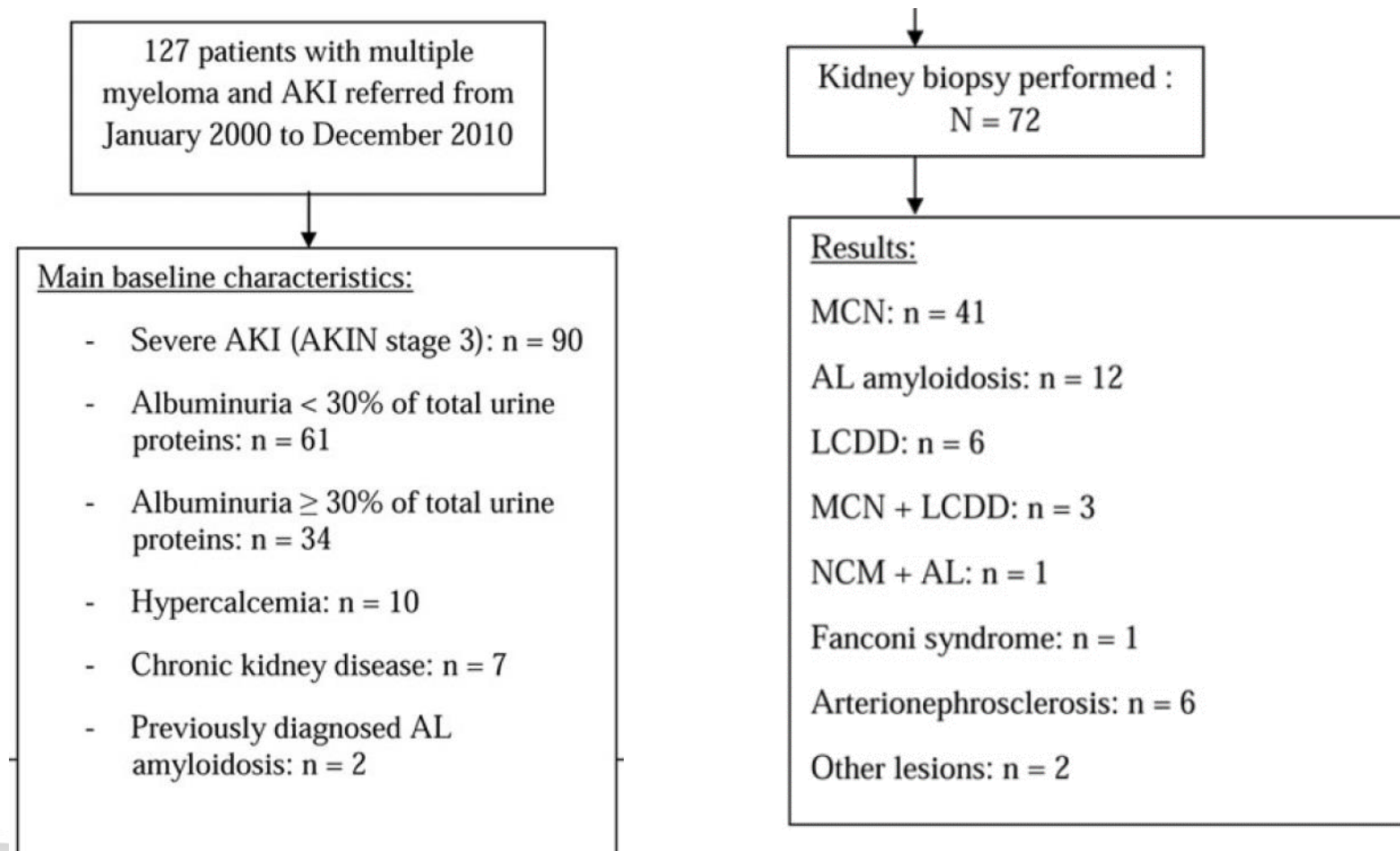
In our randomized, multicenter clinical trial of 97 participants from 14 centers in Canada, plasma exchange in myeloma-associated acute kidney failure showed no clinically meaningful difference for the primary composite outcome of death, dialysis dependence, or GFR less than $0.29 \text{ mL} \cdot \text{s}^{-2} \cdot \text{m}^{-2}$ ($<30 \text{ mL/min per } 1.73 \text{ m}^2$) at 6 months,

Problems with Clark's study

Renal biopsy rate was low

Serum free light chain was not used to measure response

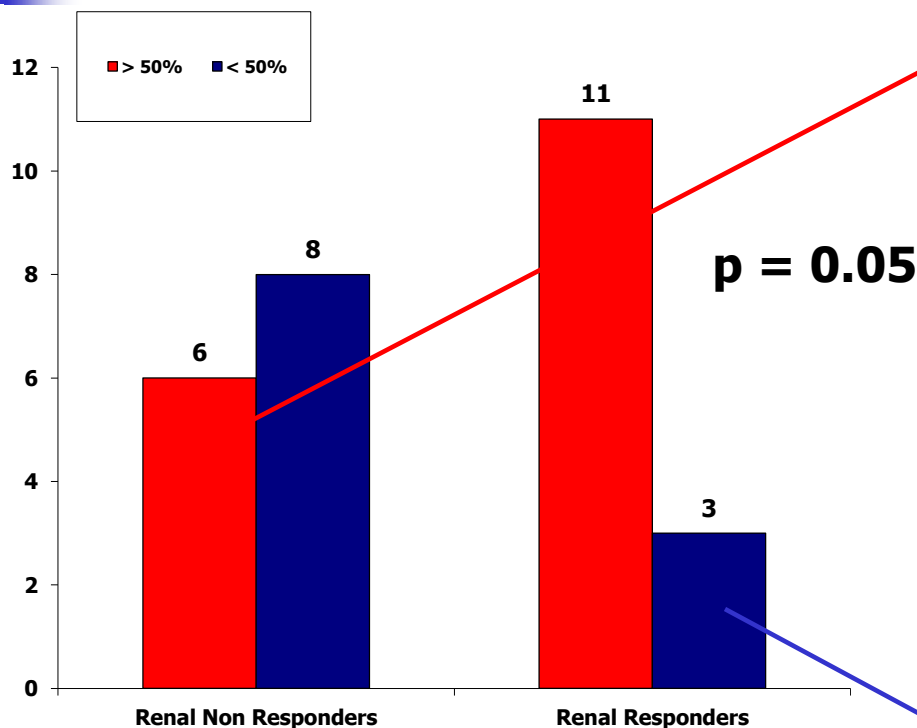
Prognostic value of kidney biopsy in myeloma cast nephropathy: a retrospective study of 70 patients



Ecotiere et al. NDT 2016

see commentary on page 1211

Improvement of cast nephropathy with plasma exchange depends on the diagnosis and on reduction of serum free light chains



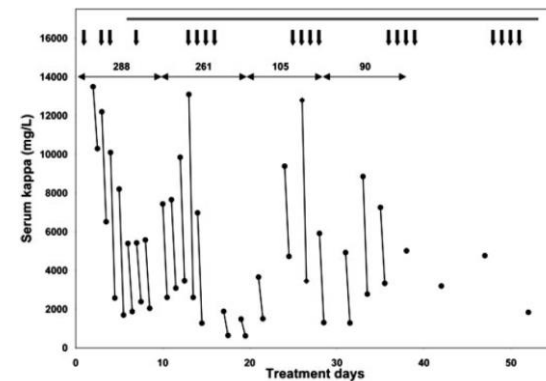
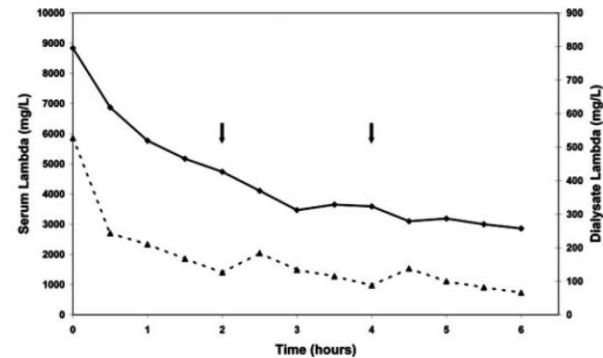
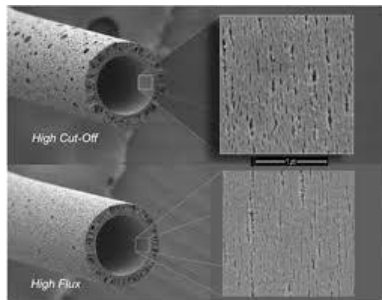
6 Non-responders

- 3 - LCDD
- 1 - DN/ATN
- 1 - CN precipitated by iv contrast 1 month earlier
- 1 - CN with atypical tubulointerstitial nephritis and fibrosis

3 Responders

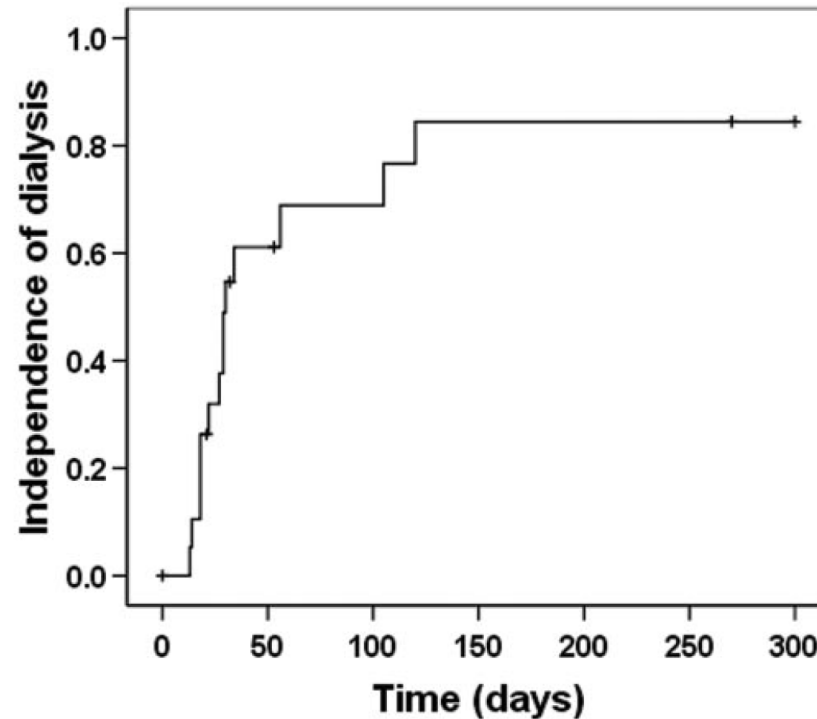
- 1 AL
- 1 LCDD
- 1 not biopsied

Efficient Removal of Immunoglobulin Free Light Chains by Hemodialysis for Multiple Myeloma: *In Vitro* and *In Vivo* Studies



Hutchison et al. JASN 2007

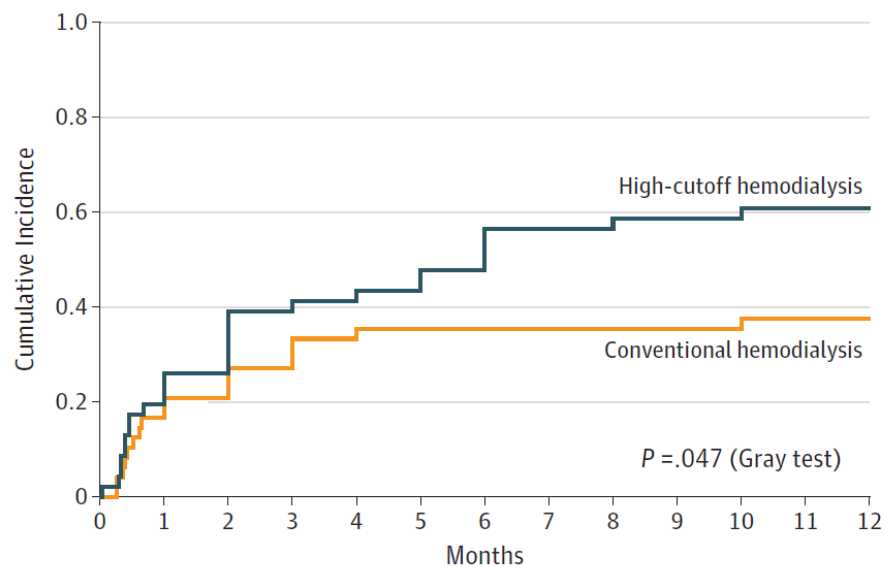
Treatment of Acute Renal Failure Secondary to Multiple Myeloma with Chemotherapy and Extended High Cut-Off Hemodialysis



Hutchison et al. CJASN 2009

MYRE Trial

A Cumulative incidence of hemodialysis independence

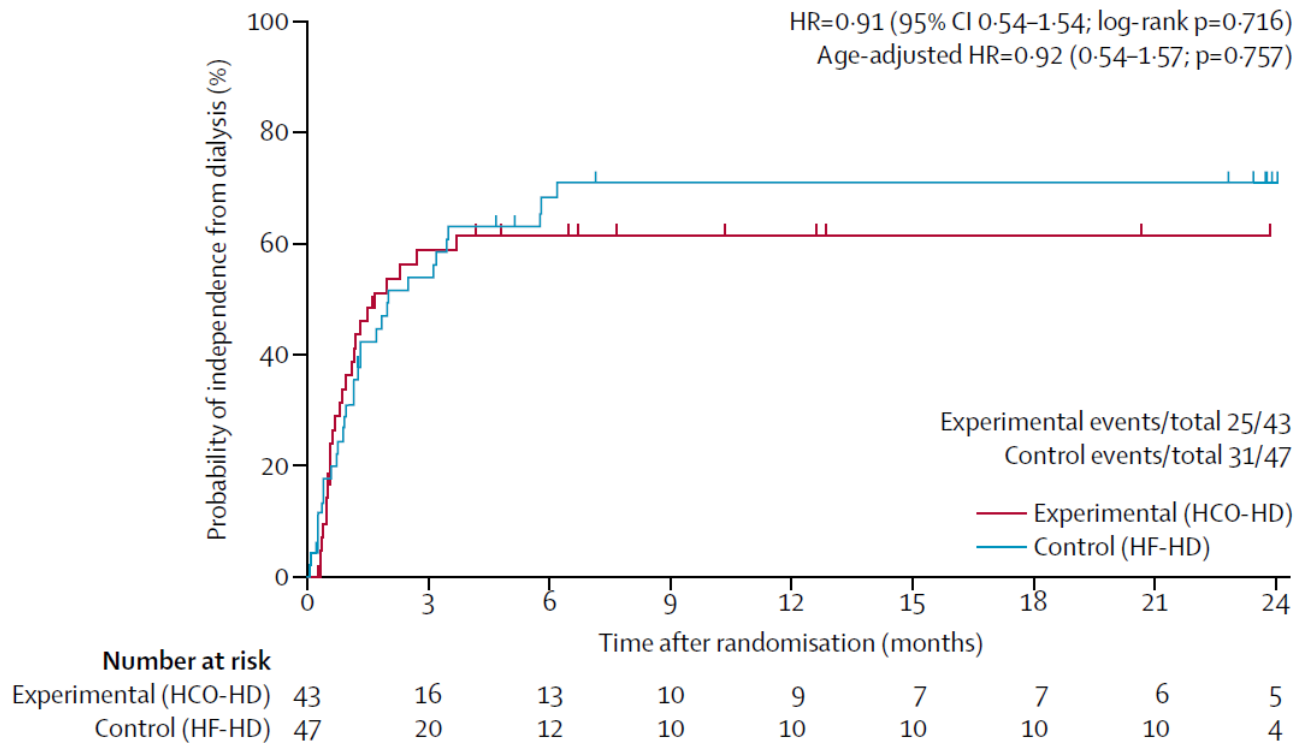


No. at risk

High-cutoff hemodialysis	46	28	22	14
Conventional hemodialysis	48	31	26	21

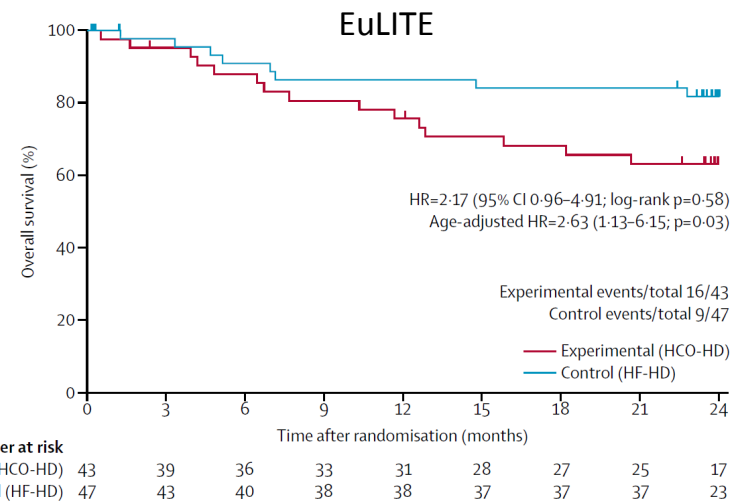
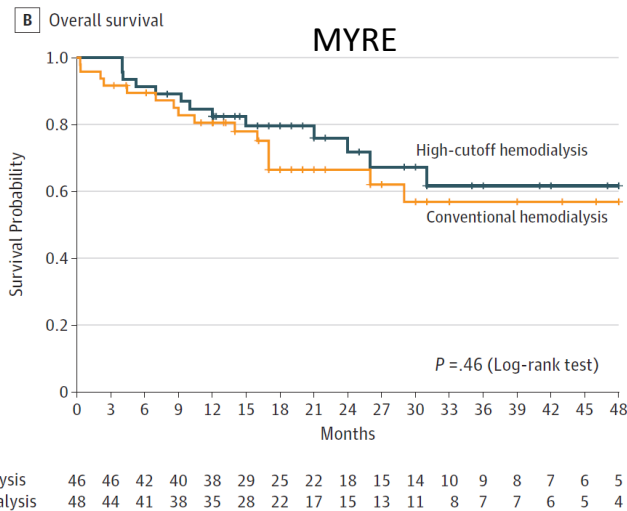
Bridoux et al. JAMA 2017

EuLITE trial



Hutchison et al. Lancet Haematol 2019

Difference in Overall Survival between MYRE and EuLITE



Hutchison et al. Lancet Haematol 2019

Bridoux et al. JAMA 2017

Hematologic Responses between EuLITE and MYRE

≥VGPR	EuLITE	MYRE
3 months		
HCO		60.9%
Conventional		43.7%
6 months		
HCO	37%	69.6%*
Conventional	62%	47.9%
12 months		
HCO	35%	
Conventional	62%*	

* P < 0.05

Hutchison et al. Lancet Haematol 2019

Bridoux et al. JAMA 2017

Prescription of the Therapy

	MYRE	EuLITE
Chemotherapy	VD*/VCD	BDD
HCO Dialyzer	2.1 m ² Theralite Gambro	Two 1.1 m ² Baxter Gambro HCO 1100
Frequency of dialysis	5h x 8 sessions first 10 days then 3x/ week	6h day 0 8h days 2,3, 5-7, 9, 10 then 6 h 3x/week
Penicillin	Prophylaxis	No
Cotrimazole	Prophylaxis	480 mg 3x/week
Albumin	20 g	60 g

* First 3 cycles

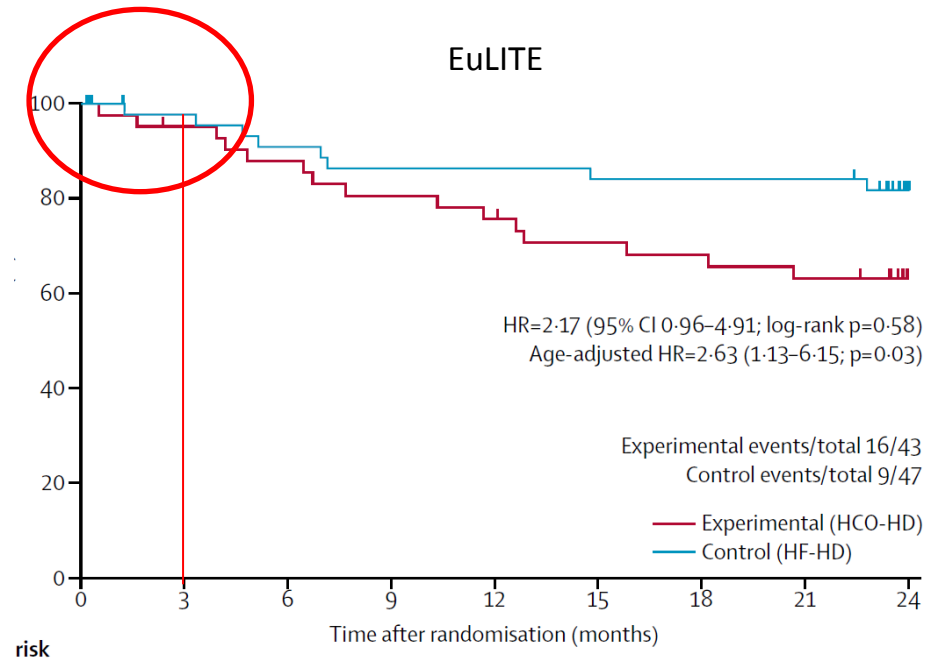
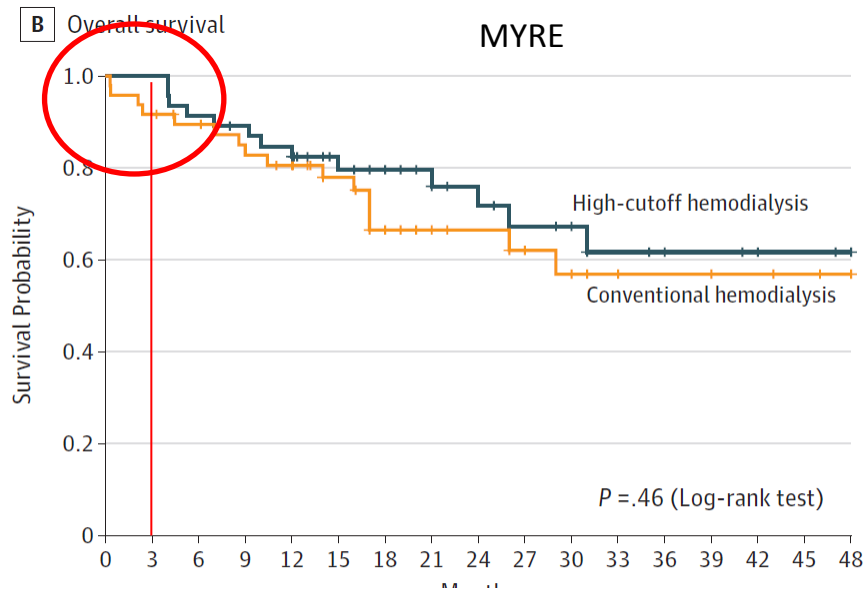
Adverse events between EuLITE and MYRE

RR – 4.64
95% CI 1.42 – 15.20
P = 0.008

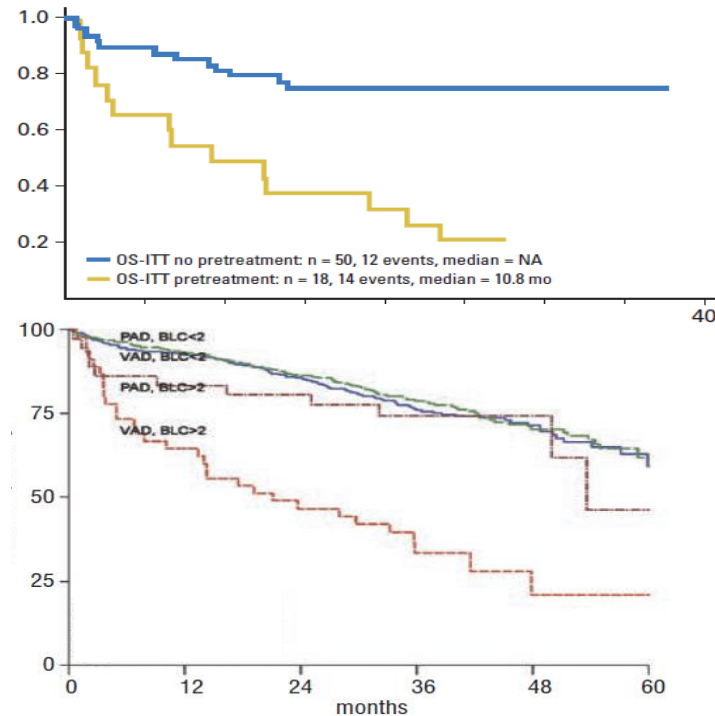
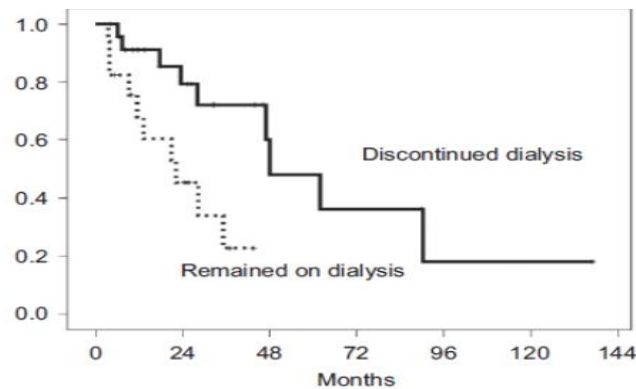
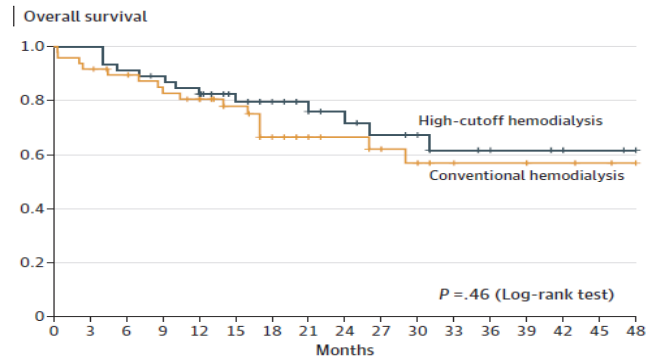
	HCO-HD	HF-HD	Total
Between 0 and 90 days*			
Infections	26 (58%)	13 (39%)	39 (50%)
Catheter-related	5 (11%)	3 (9%)	8 (10%)
Lung	14 (31%)	3 (9%)	17 (22%)
Sepsis	1 (2%)	2 (6%)	3 (4%)
Other	6 (13%)	5 (15%)	11 (14%)
Not infections	19 (42%)	20 (61%)	39 (50%)
Cardiovascular and thrombotic	3 (7%)	3 (9%)	6 (8%)
Gastrointestinal	3 (7%)	1 (3%)	4 (5%)
Haematological	0	0	0
Musculoskeletal	5 (11%)	3 (9%)	8 (10%)
Neurological	1 (2%)	1 (3%)	2 (3%)
Other organ systems	7 (16%)	12 (36%)	19 (24%)

Chemotherapy was prematurely discontinued because of toxic effects in 5 patients (3 in the high-cutoff hemodialysis group and 2 in the conventional hemodialysis group). The incidence of grade 3 or greater cytopenia and infectious complications was not significantly different. Grade 3 or greater peripheral neuropathy was observed in 1 patient in the high-cutoff hemodialysis group and in 4 patients in the conventional hemodialysis group. At least 1 serious adverse event was recorded in 39% of the patients in the high-cutoff hemodialysis group and in 37% of the patients in the conventional hemodialysis group.

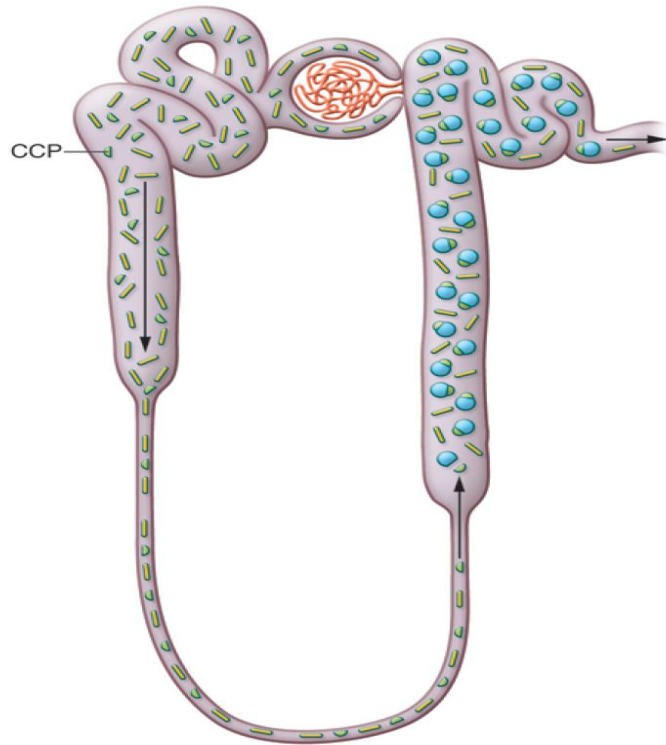
Difference in Early Survival between MYRE and EuLITE



Early Mortality in Myeloma Patients with Renal Failure



Potential Future Therapy



Cyclized Peptide •

Targets the binding site —
on THP

Coadministration of CCP —
with FLC prevents the
development of acute
kidney injury

Reversal of kidney injury —
with CCP is observed up
to 4 hours after injection
of FLC

Thank you for your attention

Welcome to mSMART: The Risk Adapted Approach to Management of Multiple Myeloma and Related Disorders

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MISSION

Our MISSION is to present the state of the art approach to management of these plasma cells disorders including Myeloma, Amyloidosis, and Waldenstrom's Macroglobulinemia. Views expressed here are opinions of a group of experts, based on best available evidence

Questions



Scottsdale, Arizona



Rochester, Minnesota



Jacksonville, Florida