



Light Chain Cast Nephropathy: Beyond Plex (CAR-T, Bispecific)

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Disclosures

- Consultant: Omeros, Lilly
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- Honoraria:
- Full-time/Part-Time Employee:
- Other:

Learning objectives

- Review the pathogenesis of light chain cast nephropathy
- Examine previous treatments of light chain cast nephropathy
- Discuss the potential of new immunotherapies in myeloma for light chain cast nephropathy

Dr. Henry Bence Jones

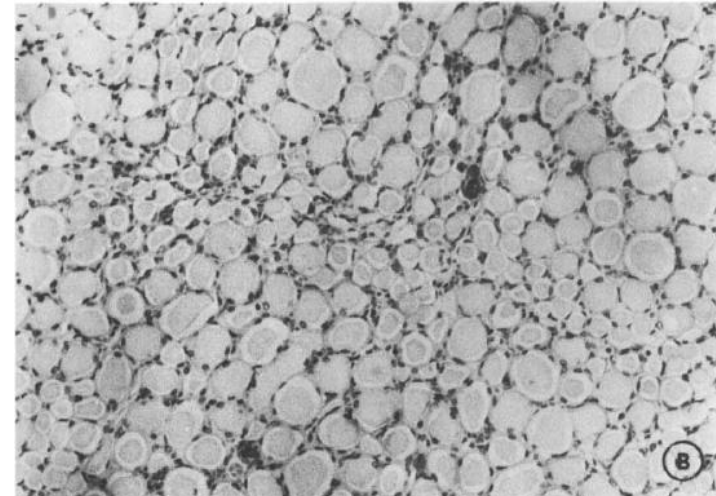
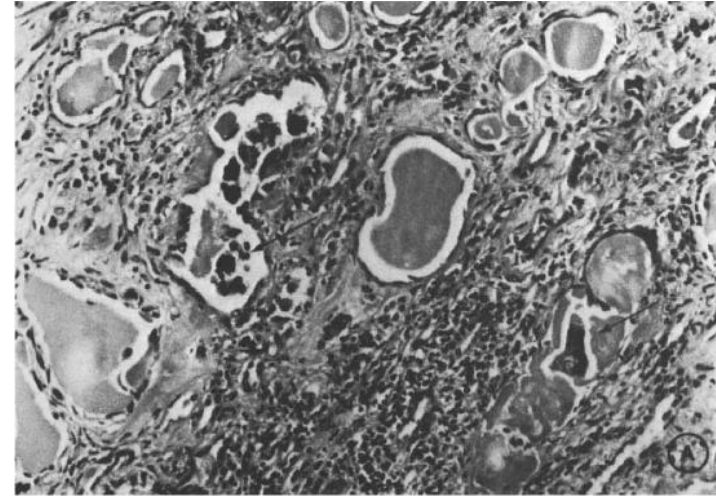
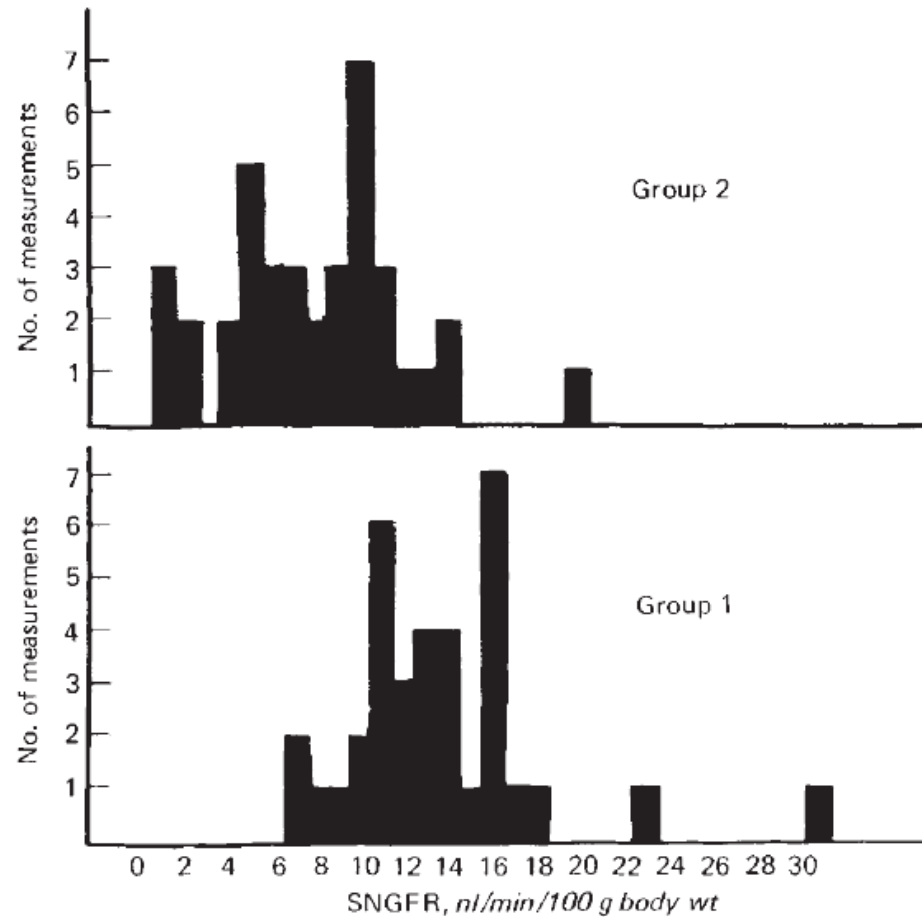


- 1843- Thomas Alexander McBean – age 42
 - Fatigue
 - Body linen was stiffened by his urine
 - Atraumatic severe back pain
 - Dr. William Macintyre – initially saw the patient
 - Dr. Thomas Watson - boiled the urine
 - Dr. Bence Jones
 - hydrated deutoxide of albumin (BJP)
 - 67 g/d

Bence Jones Proteinuria

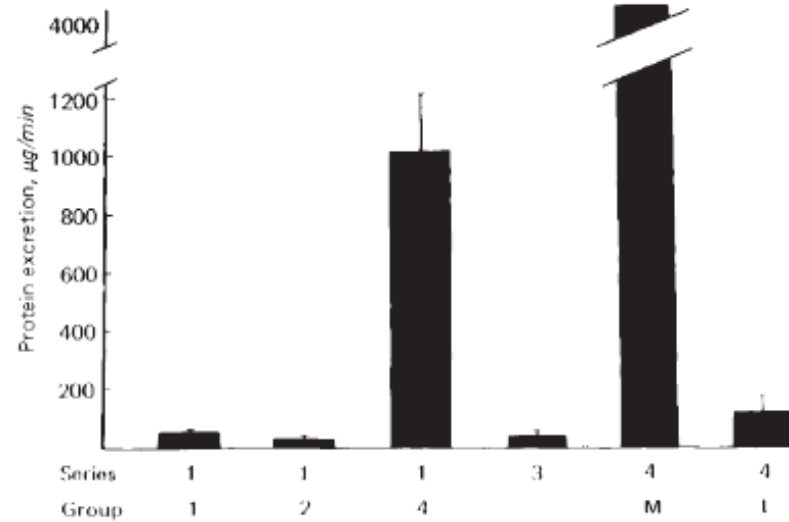
- Initially thought to be benign
- In 1909, Alfred von Decastello described plugging of the kidney by amorphous substance in a multiple myeloma patient
- In 1945, the term cast nephropathy was first used by Oliver and replaced the earlier term myeloma kidney

Pathophysiology of acute Bence-Jones protein nephrotoxicity in the rat

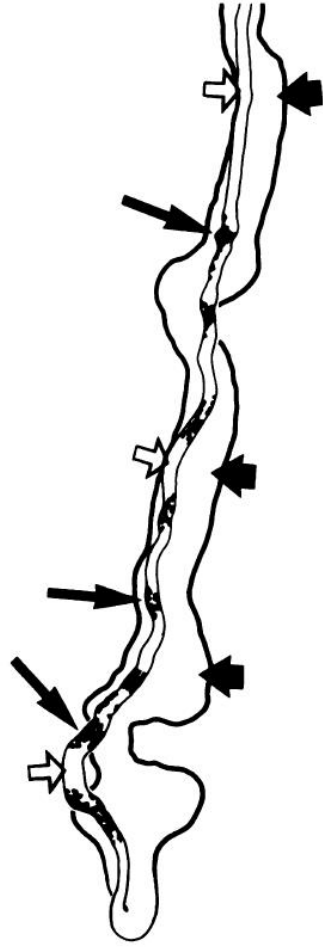


Urinary protein in light chain cast nephropathy

BJP

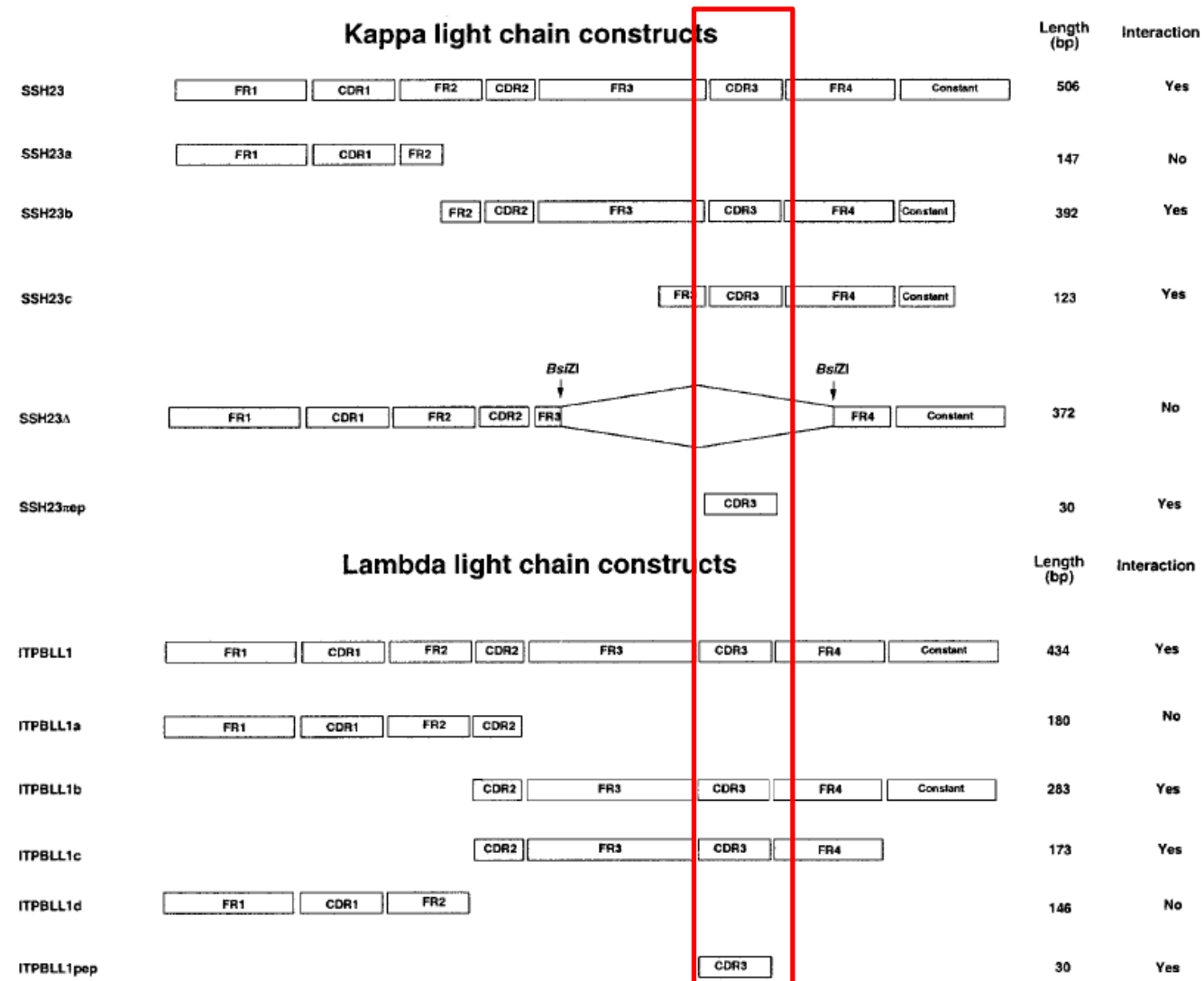


Light chain cast nephropathy

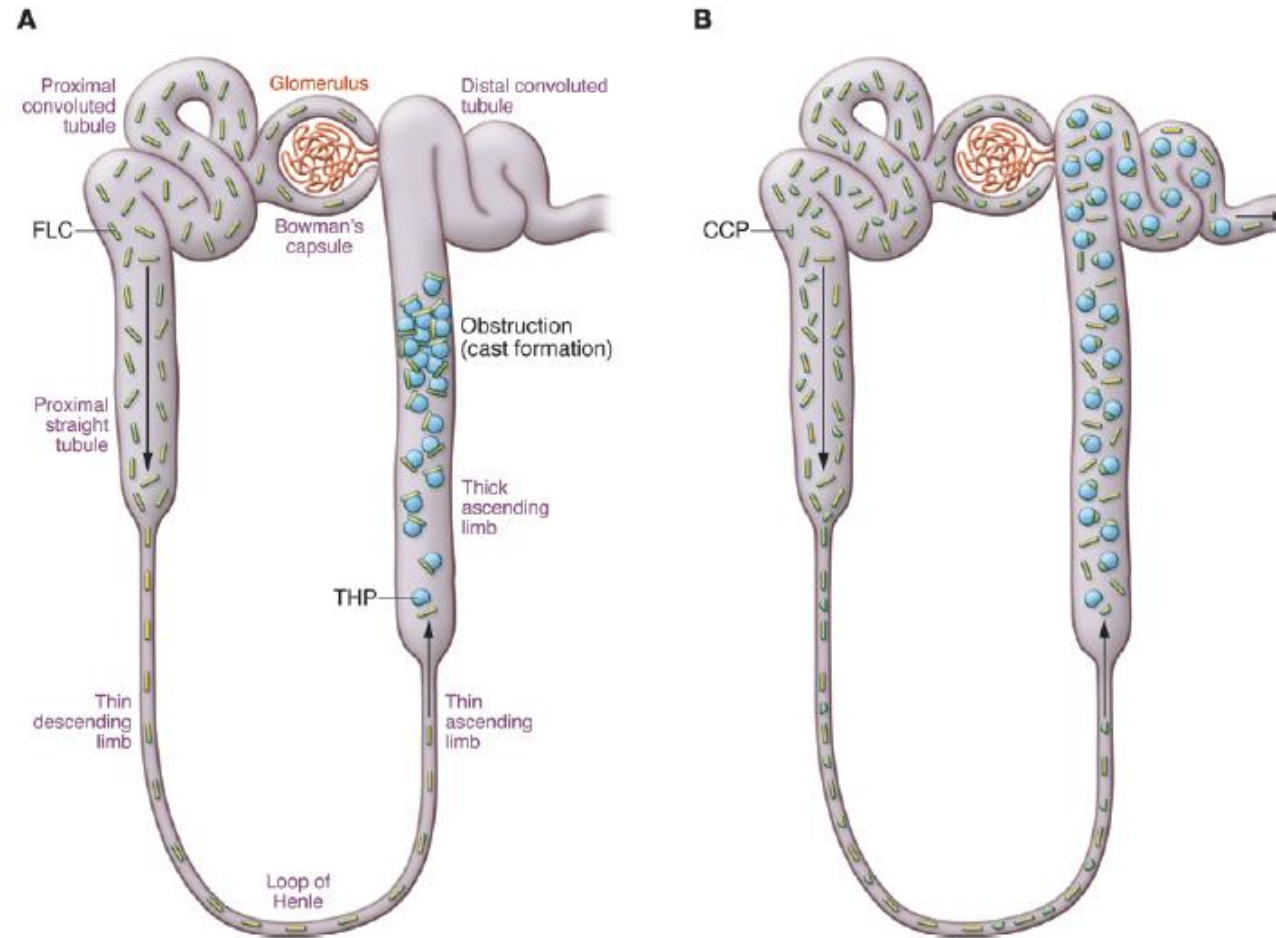


- Distal tubular obstruction at a concentration dependent fashion
- Cast consisted of light chain and Tamm Horsfall protein
- Rate of obstruction was influenced by extracellular fluid status, electrolyte concentrations, enhanced by furosemide and inhibited by colchicine through interaction with Tamm-Horsfall protein

Mapping of the binding site of the immunoglobulin light chain



Cyclic peptide that inhibits light chain cast nephropathy



Incidence of acute kidney injury in NDMM

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

Courant et al. Blood Cancer J.
2015,

Terpos et al. Euro J Haematol
2013,

Gonsalves et al. Blood Cancer
J. 2015

Kleber et al. Euro J Haematol
2009,

Ho et al. Clin Lymph Myeloma
Leuk 2019.

(Scr) > 1.4 mg/dl: 16% - 31%

Scr > 2 mg/dl: 16% - 22%

eGFR < 60 ml/min/1.73 m²: 36% to 45%

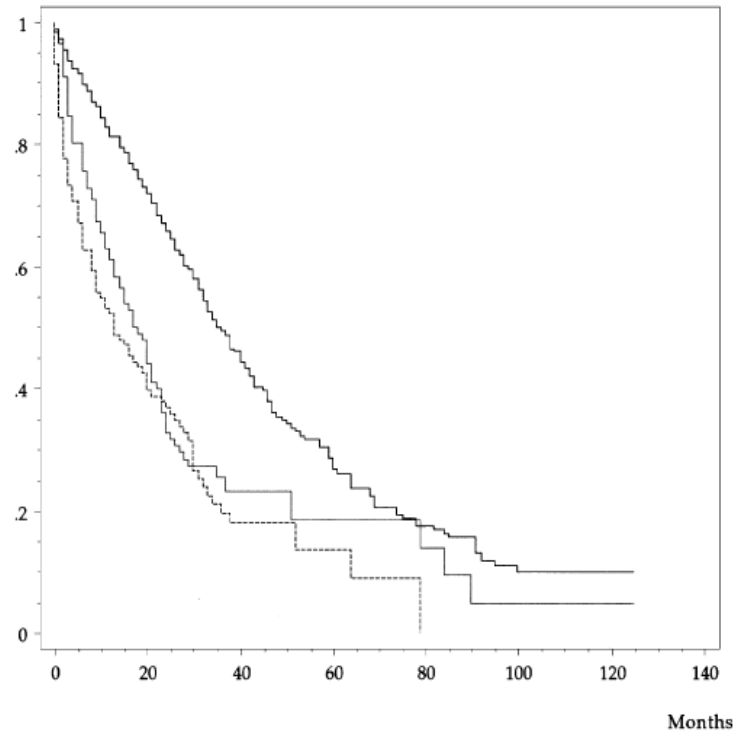
eGFR < 30 ml/min/1.73 m²: 12% to 17%

IMWG criteria (Scr > 2 mg/dl or eGFR < 40):
24.6%

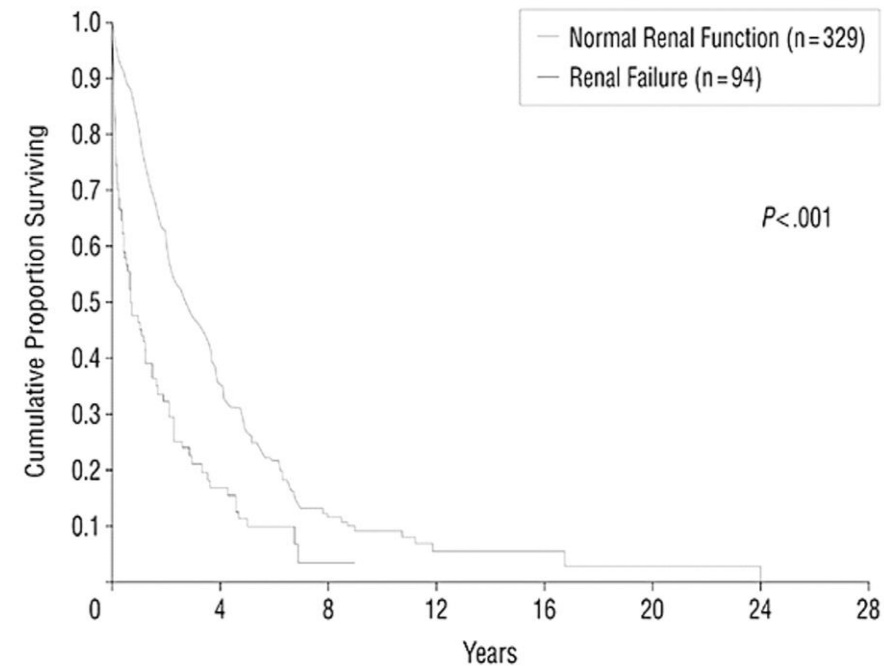
Dialysis: 12.9% (6% - 8%)

Survival of Myeloma Patients by Renal Function

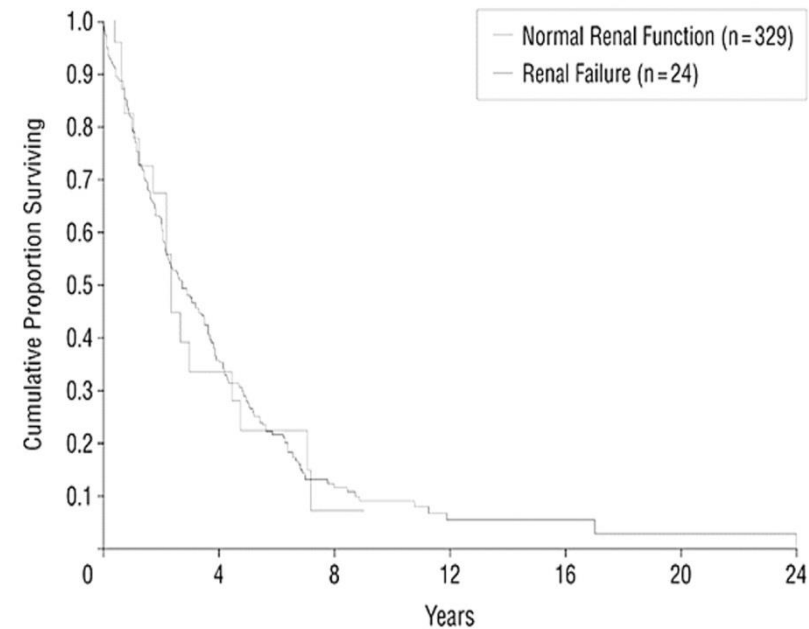
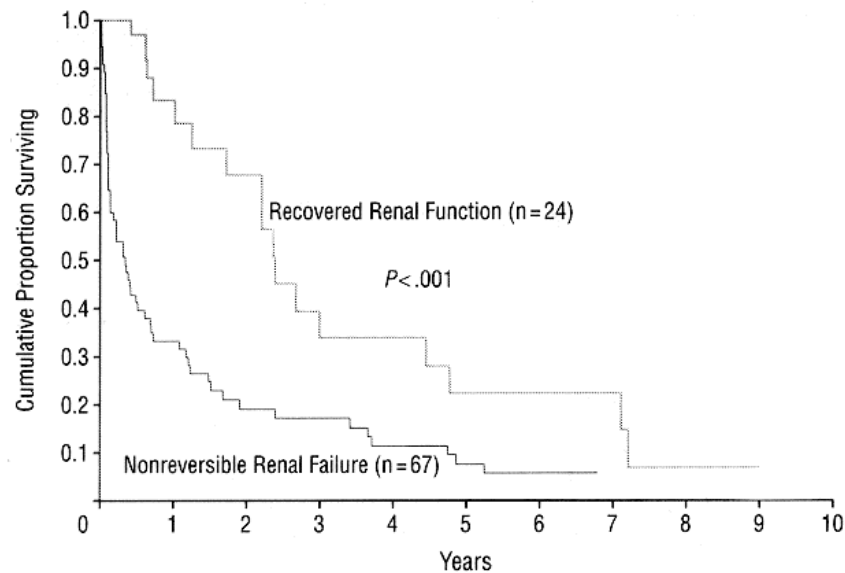
Scr < 1.49, 1.5 – 2.27, >2.27 mg/dL



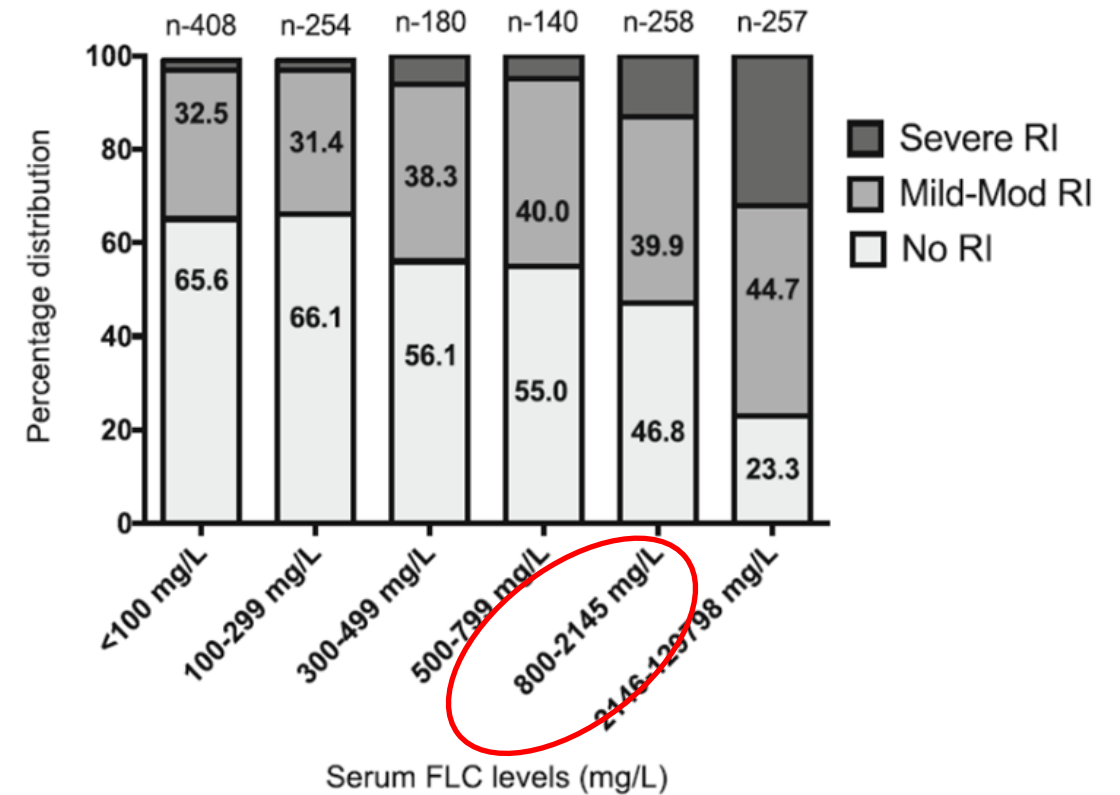
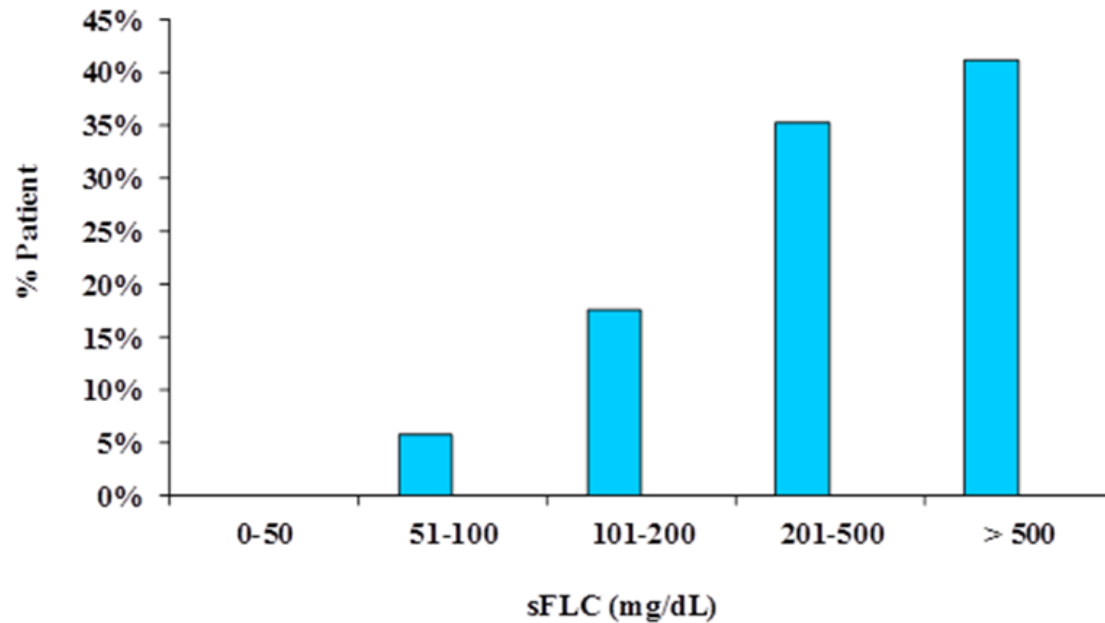
Scr > 2.0 mg/dL



Improvement of Renal Recovery is Associated with Better Survival in Myeloma Patients



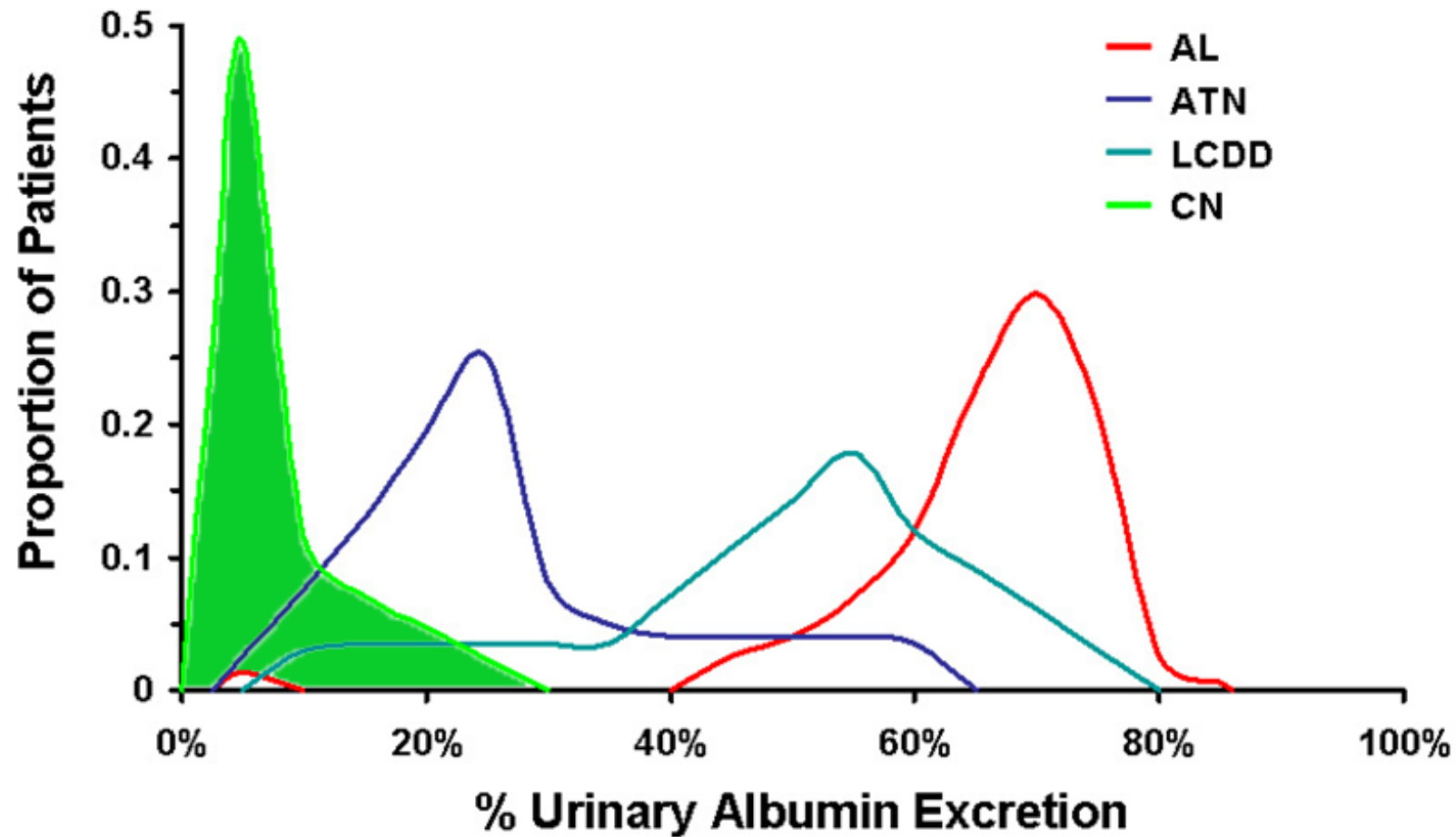
Risk of AKI and Cast Nephrology by sFLC level



Urinary FLC excretion and acute kidney injury

Urinary flc excretion, g/g creatinine	Patients with renal failure, no. (%)		
	IgG	IgA	LCO
0 g/g	28 (2)	29 (3)	0 (0)
Less than 4 g/g	48 (8)	46 (11)	22 (18)
4-12 g/g	13 (29)	12 (28)	18 (38)
More than 12 g/g	11 (48)	13 (48)	60 (54)

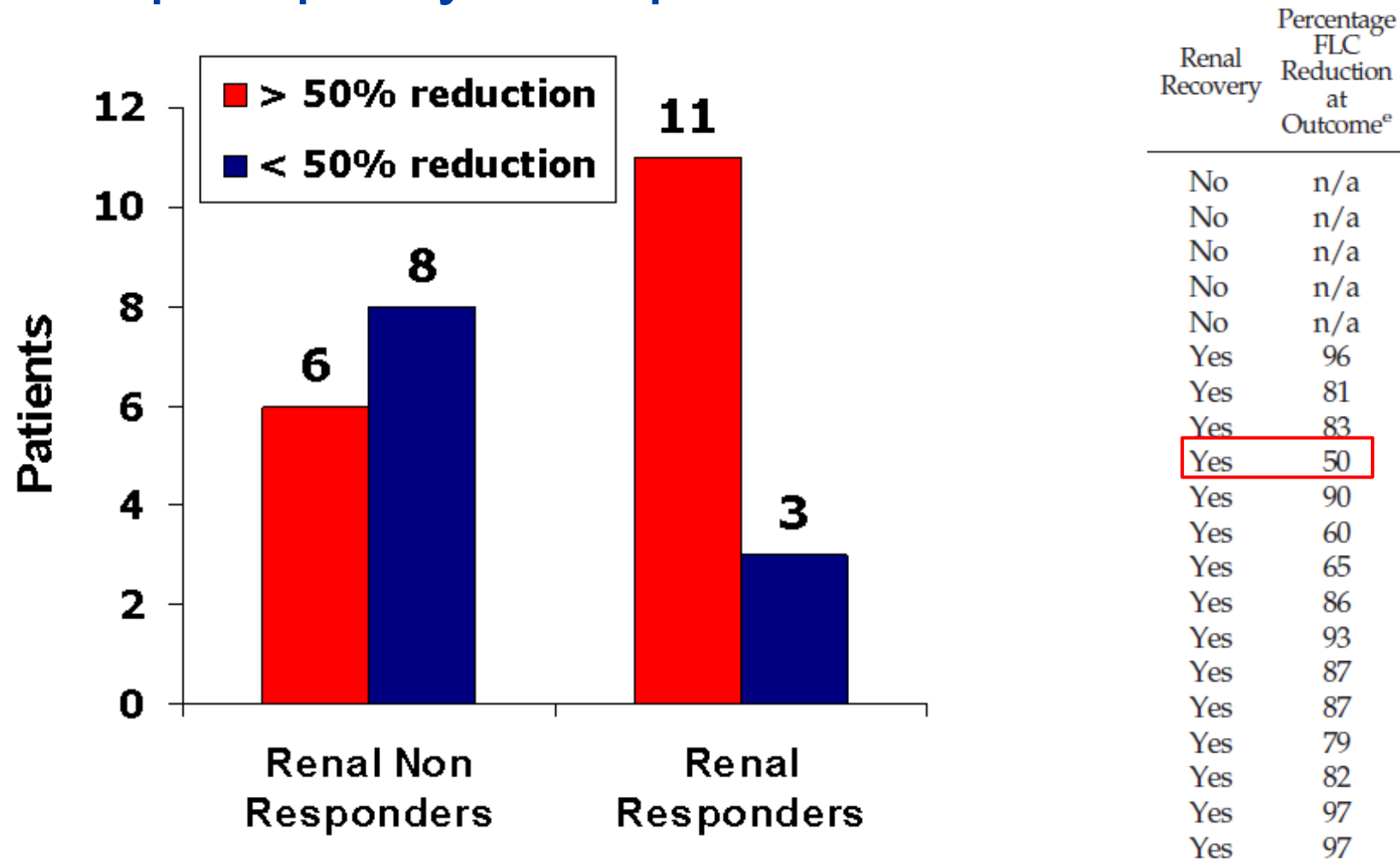
Urinary Albumin Excretion



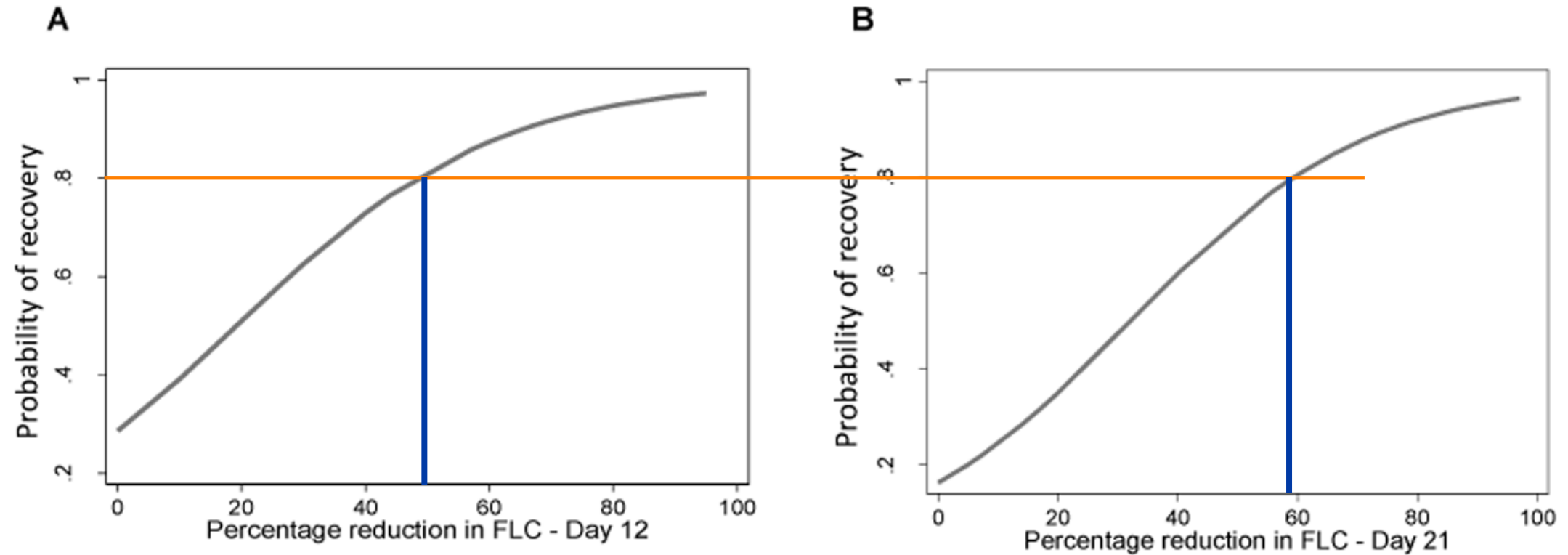
Diagnosis of LCCN

- Gold standard is kidney biopsy
- LCCN can be assumed if
 - Involved FLC > 50
 - $< 10\%$ albuminuria especially with urine M spike if > 200 mg/d

Recovery of renal function in light chain cast nephropathy is dependent on FLC reduction



Probability of Renal Response by Depth and Speed of sFLC Reduction



Factors the predicts renal response

Variable	Univariate Analyses		Multivariate Analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age $\geq$ 65 years	0.43 (0.22 to 0.82)	.011		
Preexisting MGUS	1.57 (0.65 to 3.77)	.31		
Entire Ig-secreting myeloma	1.44 (0.79 to 2.65)	.23		
Precipitating factor	1.82 (0.99 to 3.36)	.055		
Known preexisting CKD ^a	0.08 (0.017 to 0.36)	.001	0.59 (0.47 to 0.75)	< .0001
Serum creatinine at random assignment	1.00 (0.99 to 1.00)	.009		
AKIN stage 3	0.52 (0.28 to 0.97)	.039	0.86 (0.75 to 0.98)	.026
sFLC < 500 mg/L after 1 cycle of chemotherapy	1.52 (0.81 to 2.85)	.19		
sFLC response within 6 months, %				
< 50	1.00 (reference)		1.00 (reference)	
50-90	9.84 (3.02 to 32.1)	.0001	1.44 (1.14 to 1.83)	.0027
> 90	4.20 (1.19 to 14.8)	.026	1.70 (1.37 to 2.10)	< .0001
Random assignment in C-BD group	1.33 (0.73 to 2.43)	.36		

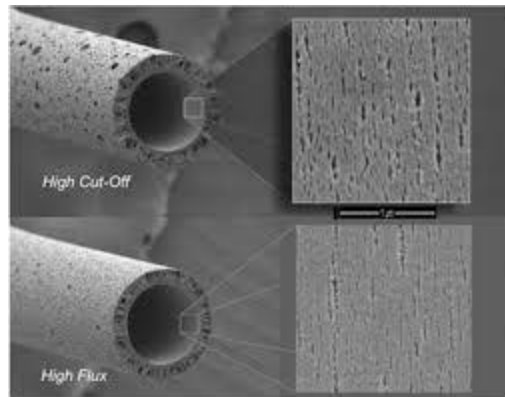
First use of PLEX in MM

- 29 yo male
- Scr = 13.8 mg/dL
- Melphalan alone
- Patient discontinued dialysis and return to work after 9 months

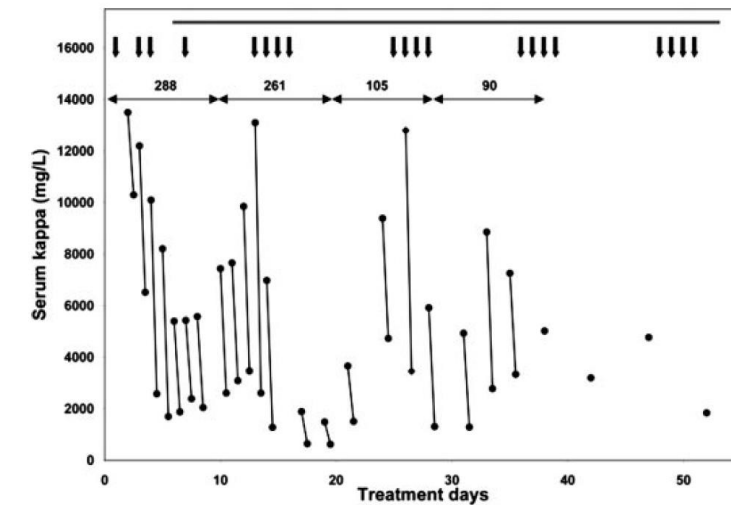
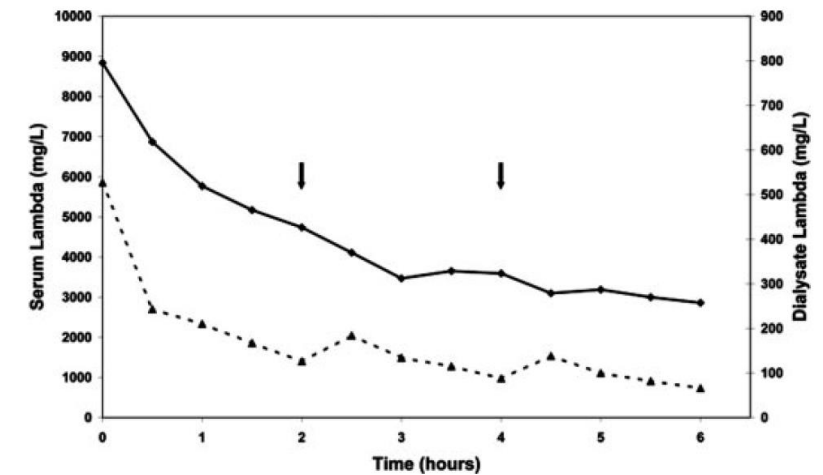
Results of Plasma Exchange Trials

	<u>Zucchelli</u>	<u>Johnson</u>	<u>Clark</u>	<u>Behrens</u>
Patients	29	21	104	78
Biopsy	58.6%	76%	few	unknown
Dialysis	82.8%	57.1%	27.9%	61.5%
PLEX	5 daily, 7, 10	3x/wk	5-7/10 day	7/ 14 days
Chemo	CTX methylpred	MP	VAD	VAD
Renal response	84.6% v 18.2%	63.6% v 50%	57.9% v 69.2%	unknown
Dialysis ind	84.6% v 18.2%	42.8% v 0	66.7% vs 50%	44.7% vs 52.5%
Hem response	decreased BJP	decreased BJP	not mentioned	not mentioned

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

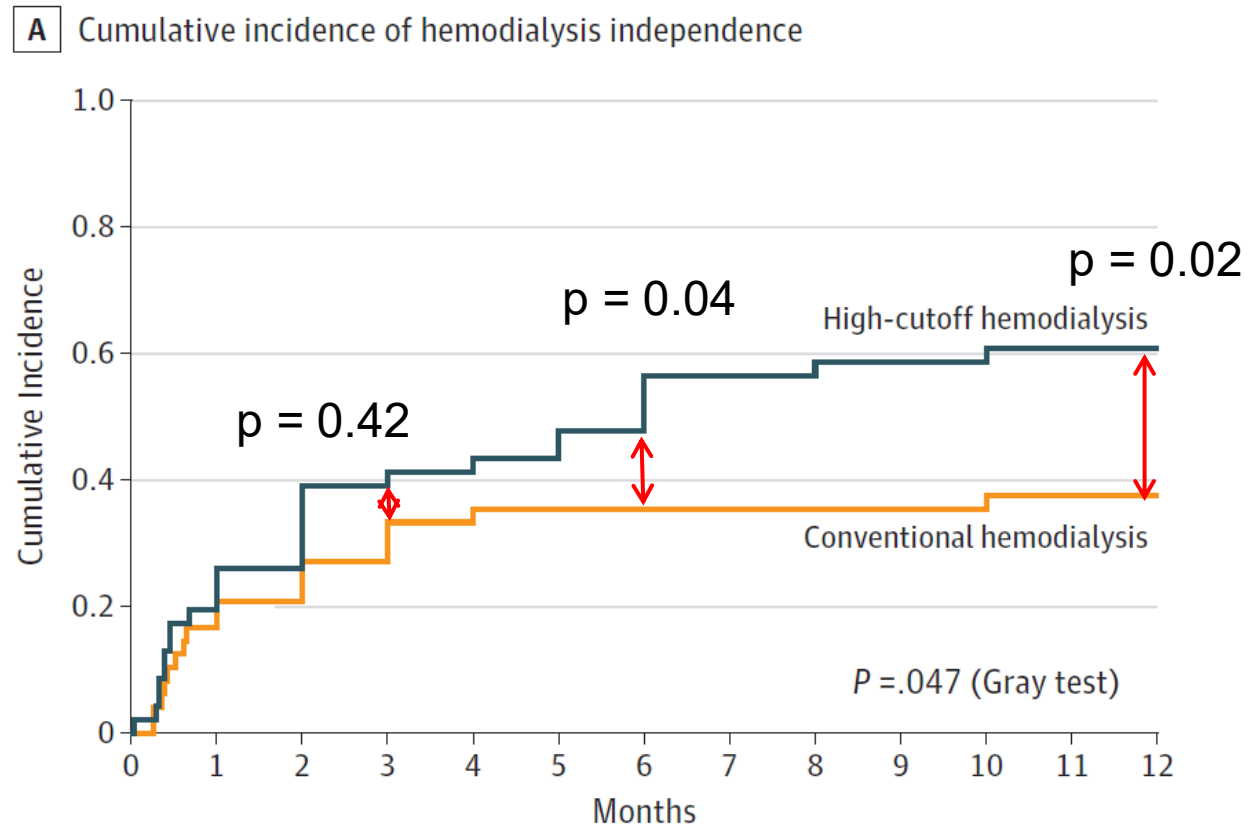


Pore size -
50 kd



Hutchison et al. JASN 2007

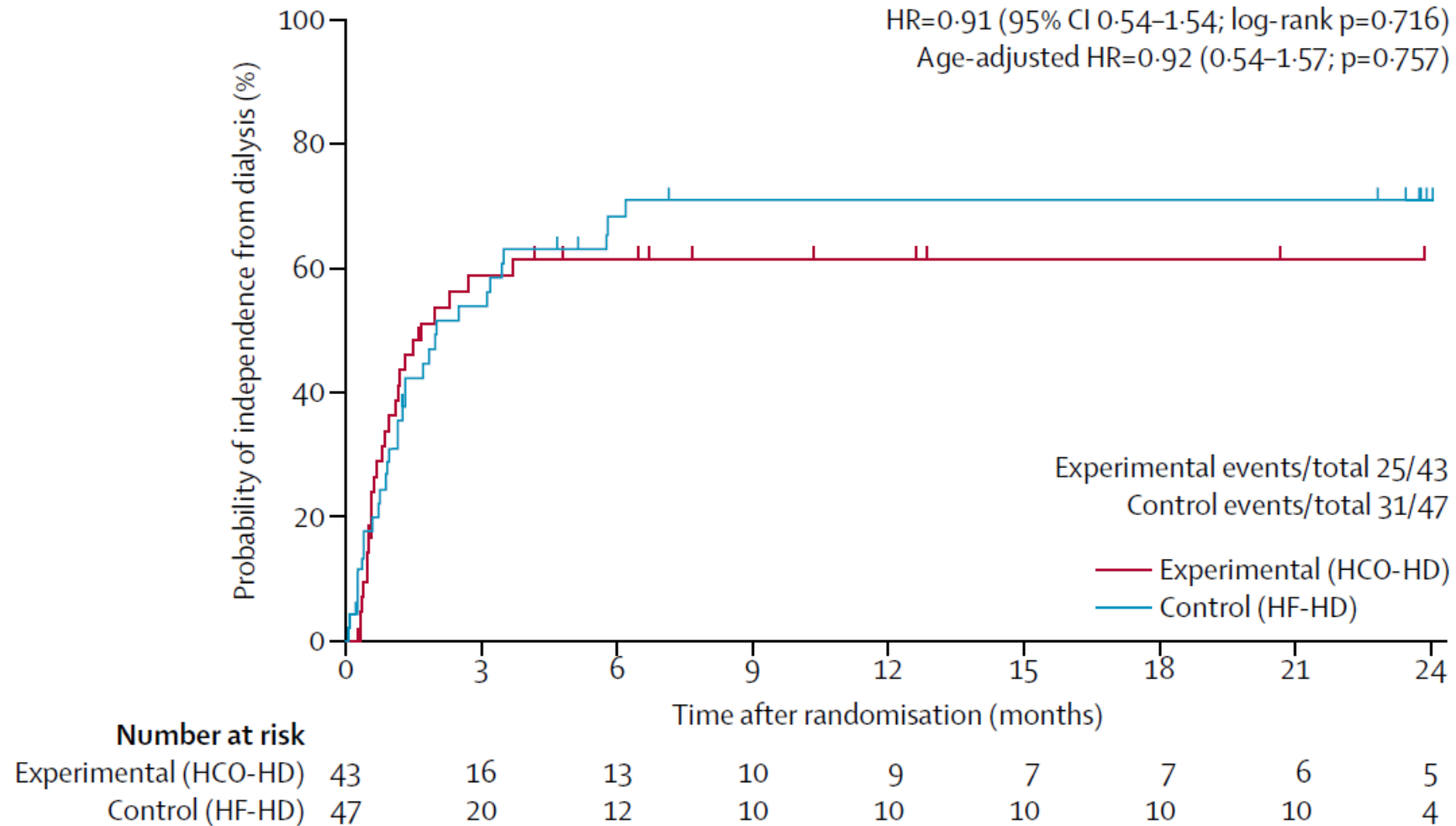
MYRE Trial



No. at risk

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

EuLITE trial



Hematologic responses in the HCO trials

EuLITE

	6 months*		12 months†	
	HCO-HD (n=43)	HF-HD (n=47)	HCO-HD (n=43)	HF-HD (n=47)
Complete response	6 (14%)	14 (30%)	12 (28%)	16 (34%)
Very good partial response	10 (23%)	15 (32%)	3 (7%)	13 (28%)
Partial response	11 (26%)	5 (11%)	3 (7%)	3 (6%)
Stable disease	1 (2%)	0	3 (7%)	1 (2%)
Progressive disease	3 (7%)	3 (6%)	8 (19%)	3 (6%)
Not assessed	3 (7%)	1 (2%)	2 (5%)	2 (4%)
Death or withdrawal	9 (21%)	9 (19%)	12 (28%)	9 (19%)

MYRE

	No. (%) of Patients ^a	
	High-Cutoff Hemodialysis (n = 46)	Conventional Hemodialysis (n = 48)
Primary Outcome		
Cumulative hemodialysis independence within 3 mo	19 (41.3)	16 (33.3)
Secondary Outcomes		
Cumulative hemodialysis independence within 6 mo	26 (56.5)	17 (35.4)
Cumulative hemodialysis independence within 12 mo	28 (60.9)	18 (37.5)
Time to hemodialysis independence, median (IQR), mo	2.0 (0.4 to 5.7)	1.0 (0.4 to 3.0)
Alive without hemodialysis at 12 mo, No./total (%)	24/37 (64.9)	17/38 (44.7)
Hematologic response after first chemotherapy cycle		
Reduction in serum-free light chain, median (IQR), %	89 (61 to 99)	71 (22 to 91)
Serum-free light chain level <500 mg/L	20 (43.5)	15 (31.2)
Hematologic response at 3 mo		
Overall ^b	41 (89.1)	30 (62.5)
Very good partial or complete	28 (60.9)	21 (43.7)
Hematologic response at 6 mo		
Overall ^b	36 (78.3)	29 (60.4)
Very good partial or complete	32 (69.6)	23 (47.9)

Adverse events in EuLITE

	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%)

VISTA MP vs VMP

VMP

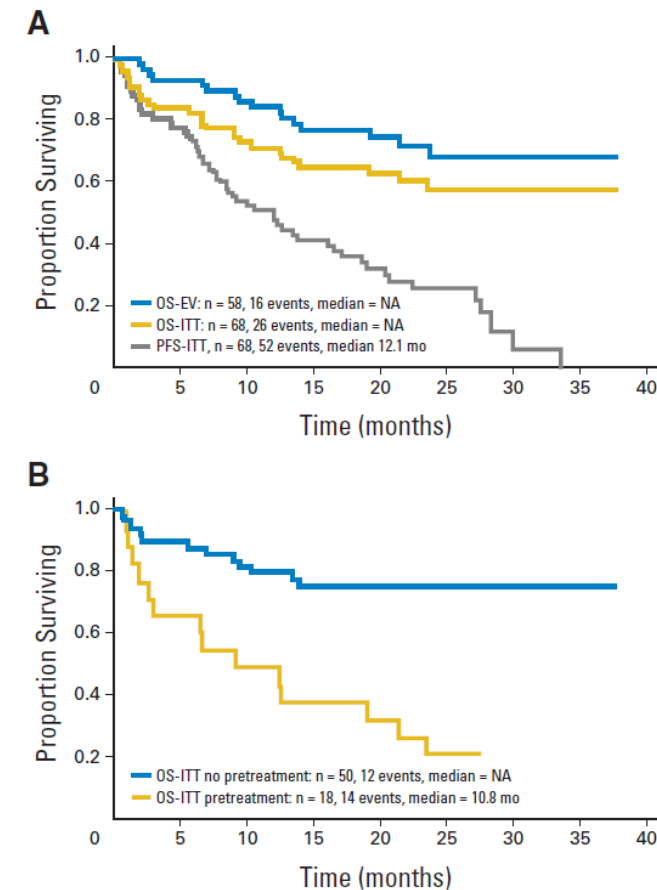
MP

	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

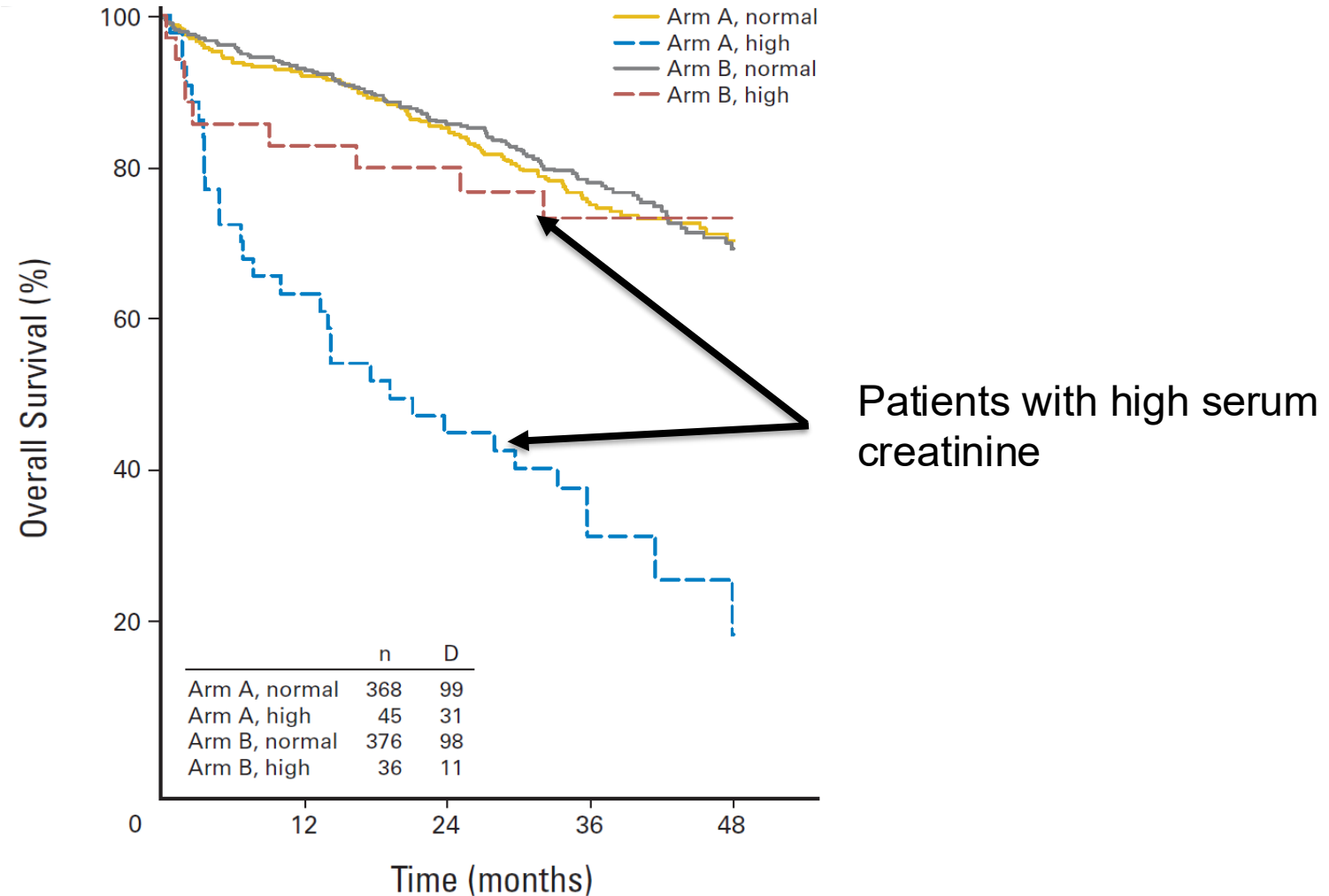
Phase II Trial with bortezomib doxorubicin dexamethasone in patients with acute renal failure

- Inclusion criteria
 - eGFR < 60 ml/min/1.73m²
 - ARF must occurred <4 weeks
- Treatment
 - Bortezomib 1.3 mg/m² on Day 1,4,8,11
 - Doxorubicin 9 mg/m² 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/m²

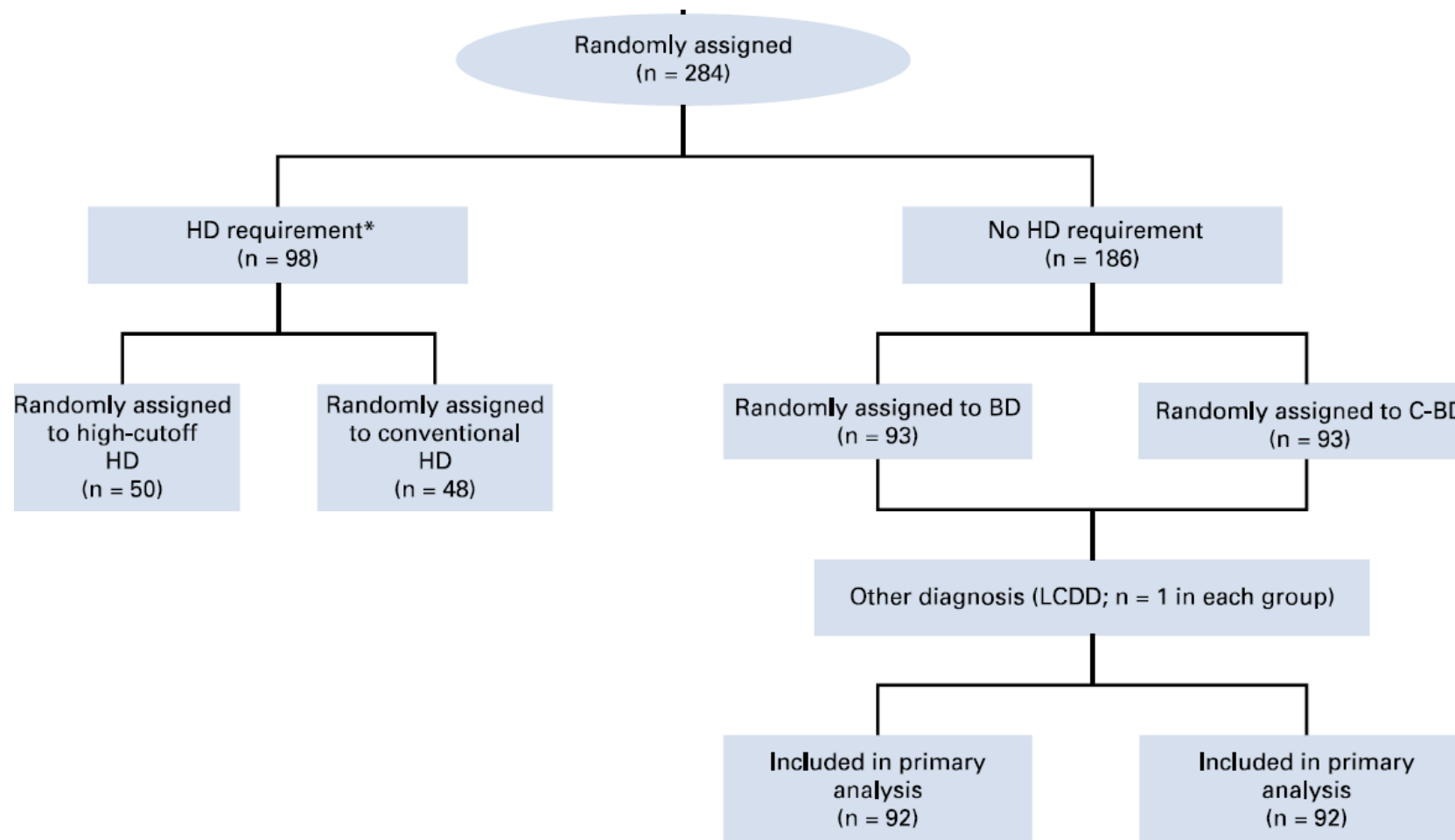


Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a subgroup analysis from the HOVON-65/GMMG-HD4 trial

Bortezomib Adriamycin
dexamethasone (PAD)
vs Vincristine Adriamycin
dexamethasone (VAD)



Randomized Trial Comparing Double Versus Triple Bortezomib-Based Regimen in Patients With Multiple Myeloma and Acute Kidney Injury Due to Cast Nephropathy



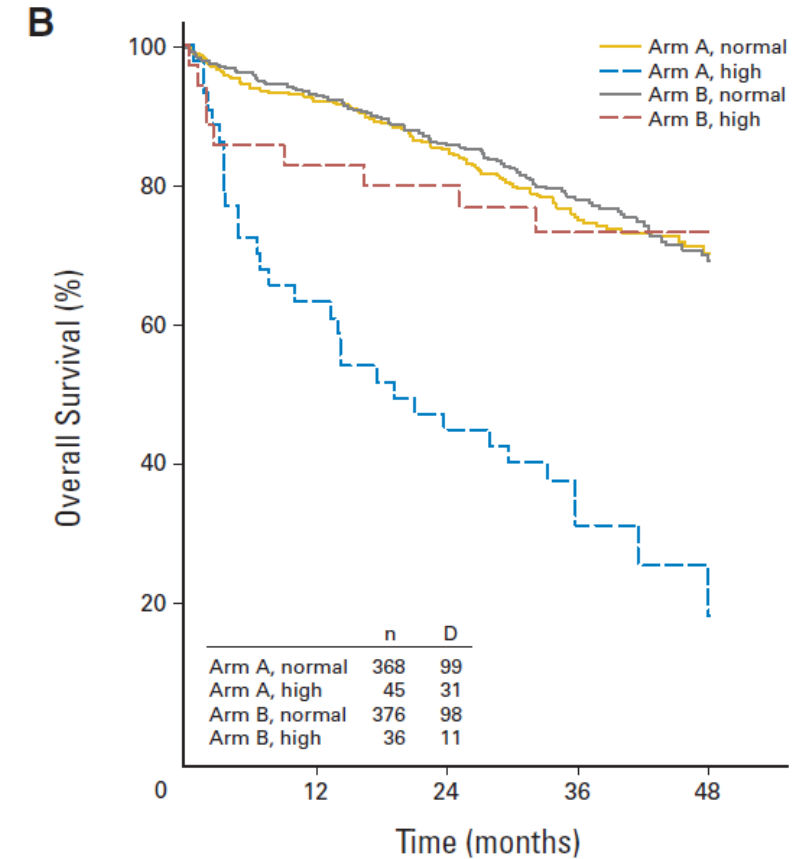
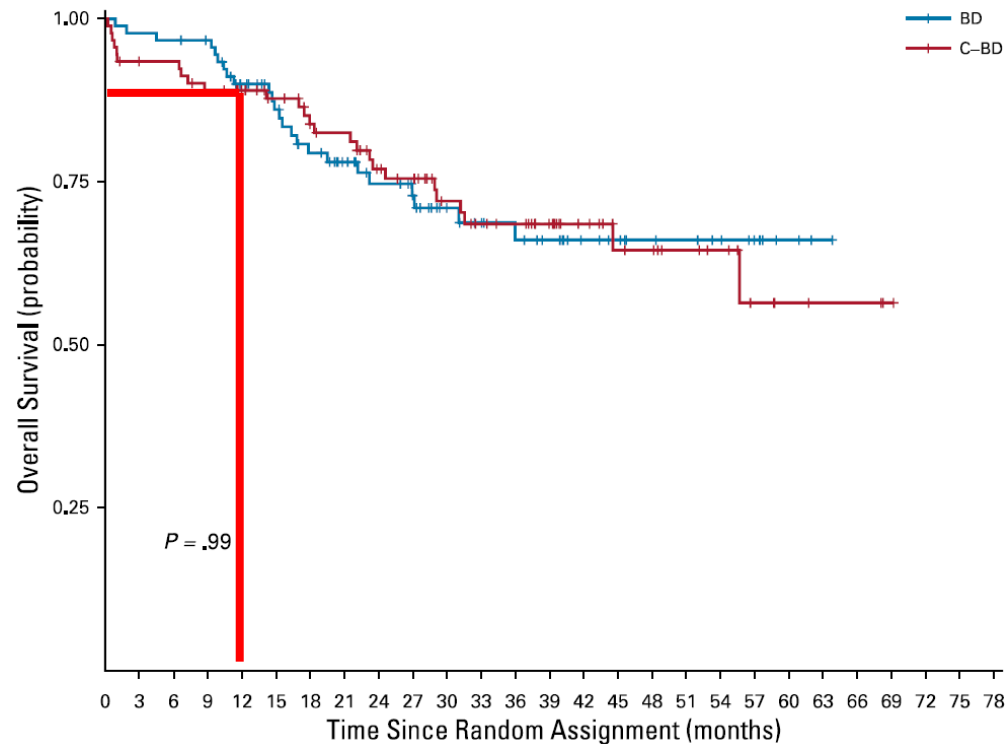
Hematologic and renal response

	BD	CBD
3m Hem Response	78.3%	77.2%
VGPR/CR (3m)	39.1%	51.1%
VGPR/CR (6m)	46.8%	53.3%
After cycle 1		
iFLC reduction	86%	88%
<500 mg/L	75.0%	72.8%
TTNT	7m	11.5m
Renal response (3m)	44.6%	51.1%
Renal response (6m)	55.4%	60.9%
Renal response (12m)	53.9%	57.3%

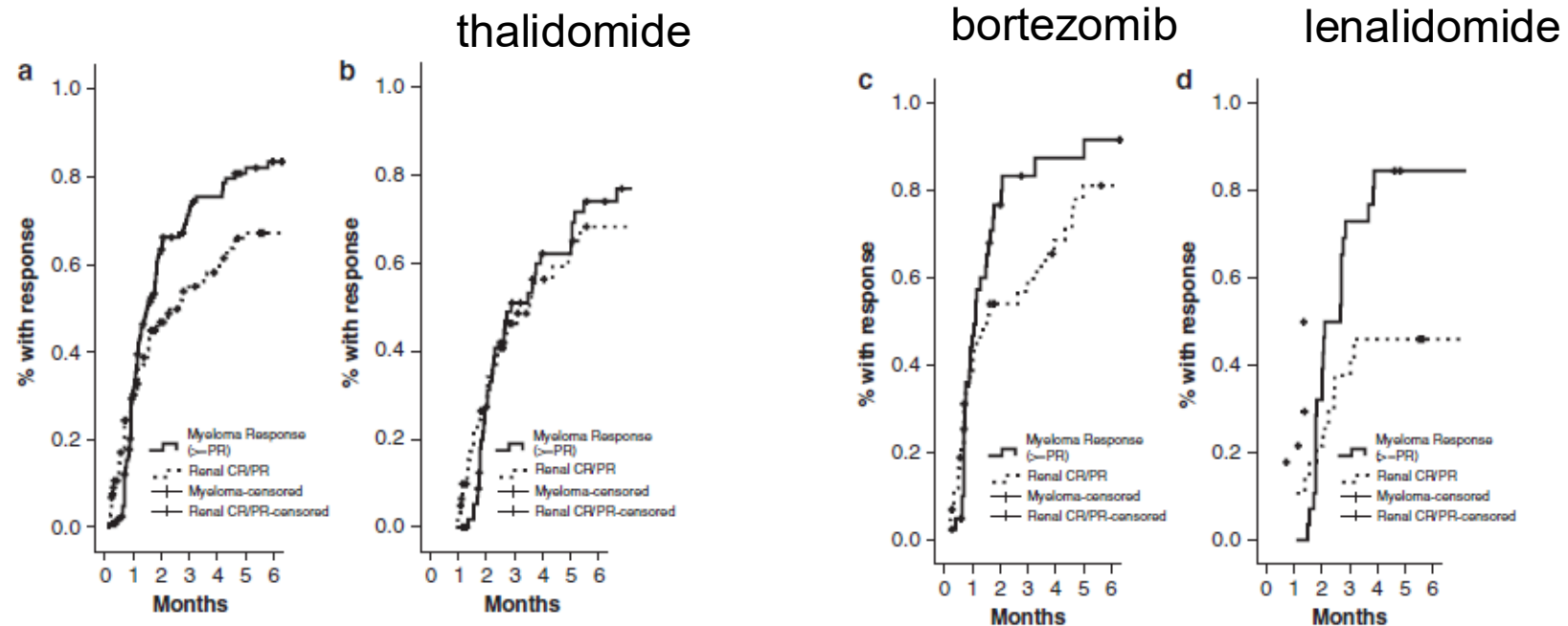
Studies	Pts	OR	≥VGPR	early deaths
Moreau	≤65			
VCD		83.4%	56.2%	1.7%
VTD		92.3%	66.3%	1.2%
Moreau	≤65			
VD		77%	36%	0%
vtD		90%	49%	0%
Mai	≤70			
VCD		78.1% (79.5%)	37.0% (59%)	0.4%
BDD		72.1% (59.5%)	34.3% (43.2%)	2.4%
HOVON 65	≤65			
VAD		54% (64%)	14% (40%)	8.8%
BDD		78% (86%)	42% (78%)	5.6%
Bridoux	AKI (60 – 74)			
VD		78.3%	39.1%	2.2%/9.8%
VCD		77.2%	51.1%	6.5%/10.9%

Bridoux et al. JCO 2020; Mai et al. Leukemia 2015; Moreau et al. Blood 2011; Moreau et al. Blood 2016;
Scheid et al. Haematologica 2014; Sonneveld et al. JCO 2012

Survival of myeloma with renal impairment remains inferior despite novel agents

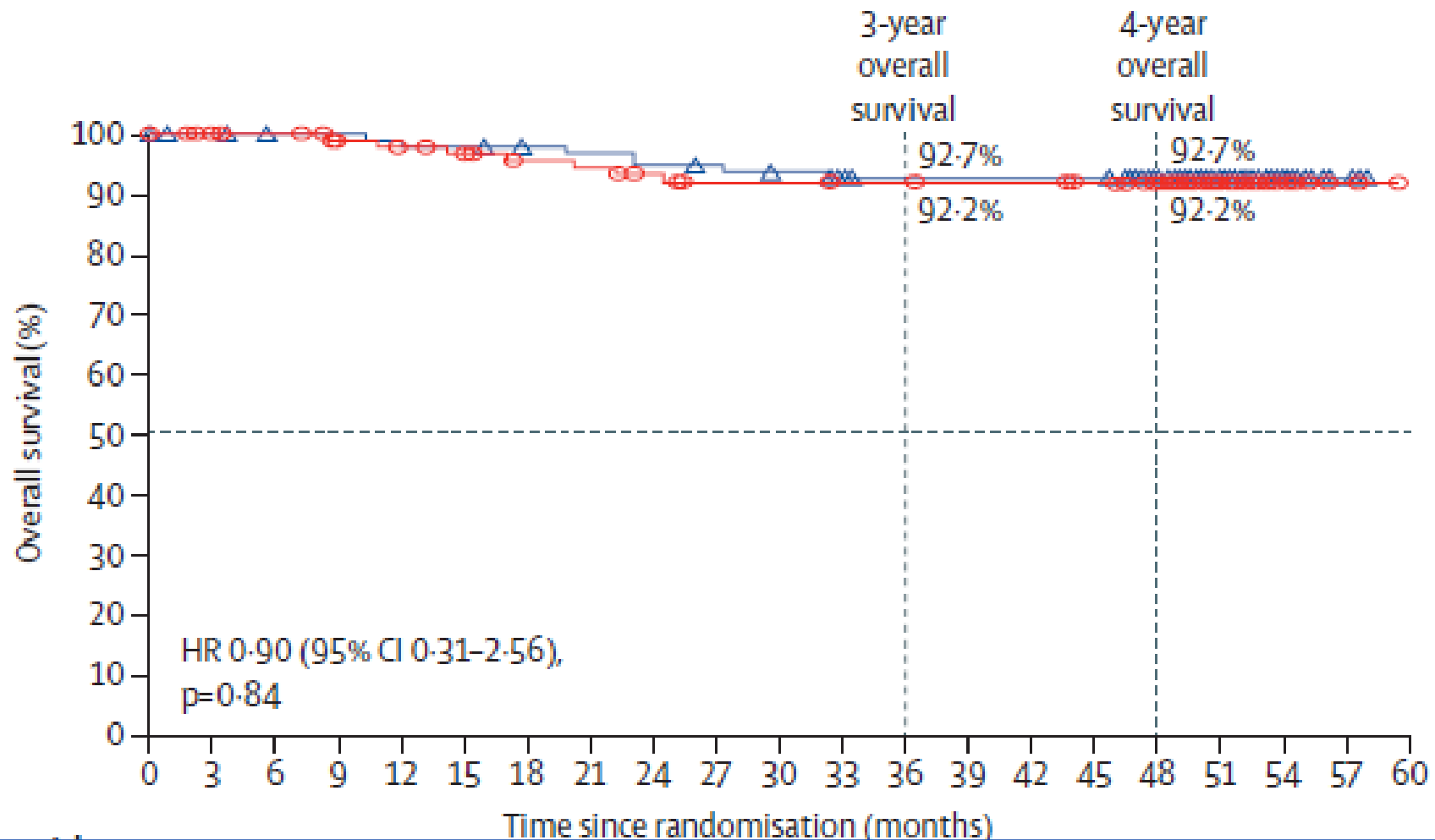


Not all novel agents are the same when it comes to renally impaired patients

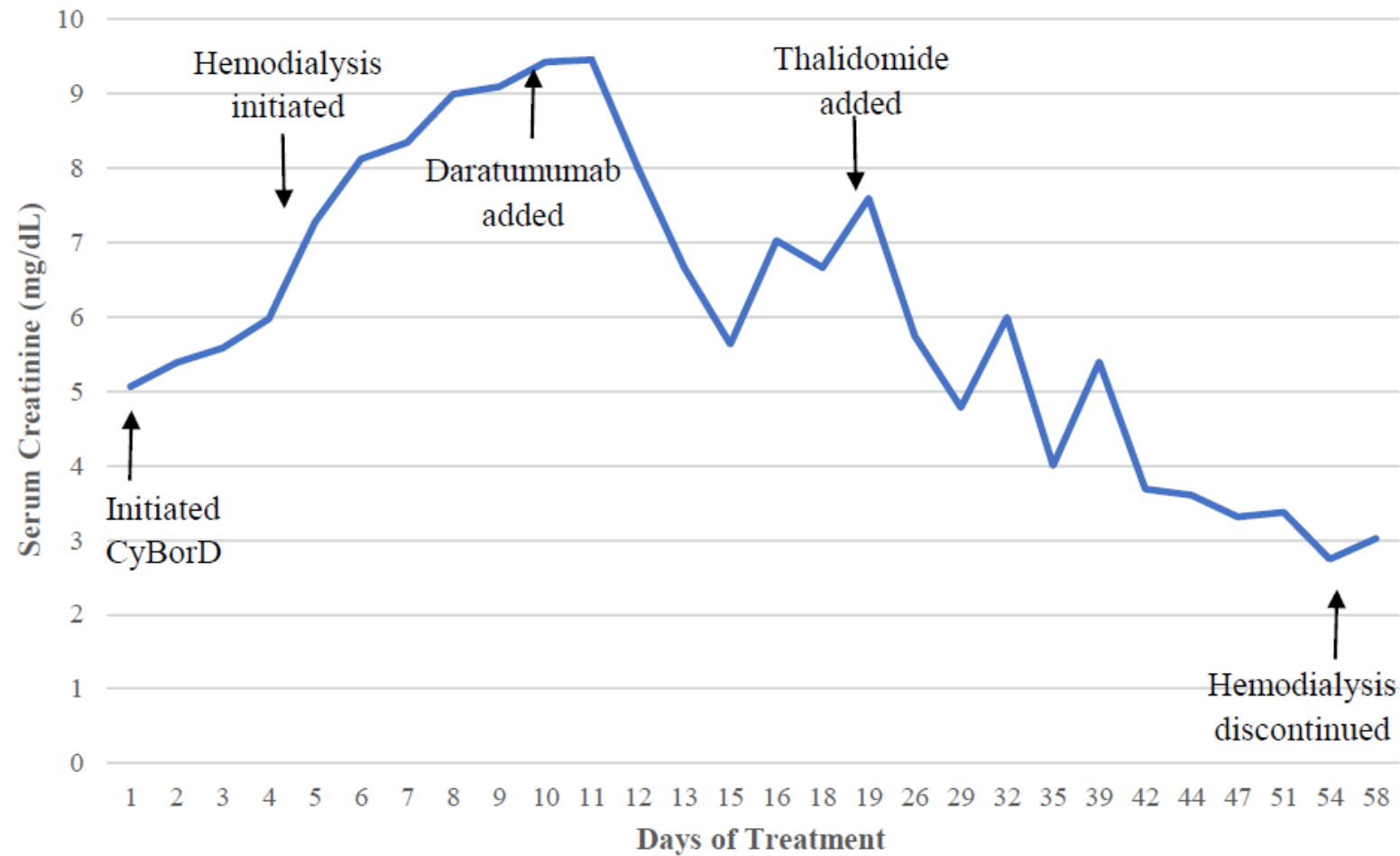


	Thalidomide	Bortezomib	Lenalidomide	P-value
Baseline eGFR (ml/min/1.73 m ²), median(range)	38 (6–59)	21 (4–59)	37 (6–58)	0.037
Best eGFR (ml/min/1.73 m ²), median(range)	69 (16–140)	77 (5–175)	45 (15–106)	0.2
Renal response (≥renalMR)	46 (74%)	35 (81%)	17 (61%)	0.153
Major renal response (≥renalPR)	34 (55%)	33 (77%)	12 (43%)	0.011
RenalCR	33 (53%)	29 (67%)	10 (36%)	0.032
Baseline eGFR (ml/min/1.73 m ²) for patients who achieved renalCR, median (range)	44 (6–58)	27 (5–59)	49 (15–58)	
Best eGFR (ml/min/1.73 m ²) for patients who achieved renalCR, median (range)	86 (64–139)	91 (61–175)	85 (65–106)	

GRIFFIN (VRD vs DaraVRD)



Dialysis Independence Following Combination Daratumumab, Thalidomide, Bortezomib, Cyclophosphamide, and Dexamethasone in Multiple Myeloma With Severe Renal Failure



Effect of daratumumab on light chain reduction in newly diagnosed multiple myeloma with light chain cast nephropathy.

Juan Esteban Velez-Hernandez, Mateo Mejia Saldarriaga, Mark Bustoros, Roger Niles Pearse, Ruben Niesvizky, Jorge Monge Urrea; Weill Cornell Medicine, New York, NY

	Dara (n = 19)	Non-Dara (n = 32)	Total (n = 51)
Age, median (IQR)	70 (60-80)	68 (54-75)	68 (56-77)
Female, n (%)	7 (37%)	14 (44%)	21 (41%)
ISS 3, n (%)	19 (100%)	25 (78%)	44 (86%)
eGFR at diagnosis, median (IQR)	16.3 (10.6-22.8)	18.6 (6.4-25.1)	17.3 (8.3-24.7)
iFLC, median (IQR)	869 (356-1258)	1200 (743-1456)	1155 (490-1435)
Cyclophosphamide-containing regimens, n (%)	6 (32%)	26 (81%)	32 (63%)
Hematologic response at d30, n (%)	17 (89%)	23 (72%)	40 (78%)
FLC-R at d30, n (%)	11 (58%)	10 (31%)	21 (41%)
RR at d90*, n (%)	11 (69%)	15 (58%)	26 (62%)

Early daratumumab therapy improves renal outcomes in newly diagnosed patients with myeloma admitted with kidney injury

Characteristics	N = 20
Age at diagnosis, y	
Median (range)	65 (44-87)
Subgroup, n (%)	
18 to <65	10 (50)
≥65 to <75	7 (35)
≥75	3 (15)
Male, n (%)	9 (45)
Peak SCr at admission, median (range), mg/dL	6.5 (3.1-17.8)
eGFR (CKD-EPI), median (range), mL/min per 1.73 m ²	8 (2-16)
Requiring dialysis during hospitalization, n (%)	9 (45)
Peak involved sFLC at diagnosis, median (range), mg/L	6603 (1839-26 023)
HRCAs*, n (%)	
0	9 (45)
1	9 (45)
≥2	2 (10)
Extramedullary disease, n (%)	2 (10)

- DaraVCD – 11, DaraVD – 9
- All patients had $\geq 50\%$ FLC reduction with a median of 3 days
- Median time to FLC ≤ 500 mg/L was 14.5 days
- $\geq \geq$ VGPR – 90%
- Renal response at 3m = 85%
- At 3m 4 of 9 and at 12m 6 of 9 achieved dialysis independence

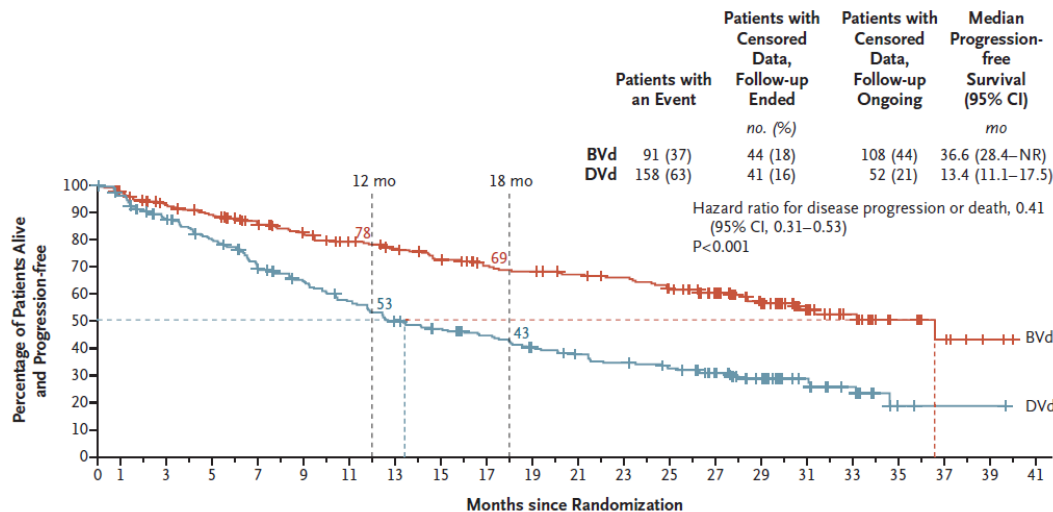
Beyond Novel Agents

1. Antibody conjugate
2. CAR-T cell therapy
3. Bispecific antibodies

Antibody conjugate: Belantamab



- Targets BCMA
- FDA approved in 2025 for RRMM with bortezomib dexamethasone
 - DREAMM-7 BeVd vs DVd
 - PFS – 31.3m vs 10.4m
- Toxicity
 - Ocular toxicity (keratopathy) – 92%
 - Grade 3/4 – 77% requiring dosing reduction



Belantamab in Renal Impairment or LCCN

- Renal impairment
 - DREAMM-2
 - Patients with eGFR > 30 ml/min/1.73 m² were allowed
 - 5 patients had eGFR between 15 and 30
 - No differences in response or AE
 - Lower eGFR is being explored in DREAMM-12
- LCCN
 - No data

Bispecific antibodies



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- BCMA
 - Teclistamab
 - Elranatamab
 - Linvoseltamab
- GPRC5D
 - Talquetamab
- FcRL5
 - Cevostamab (in trial)
- Trispecific antibodies
 - In development

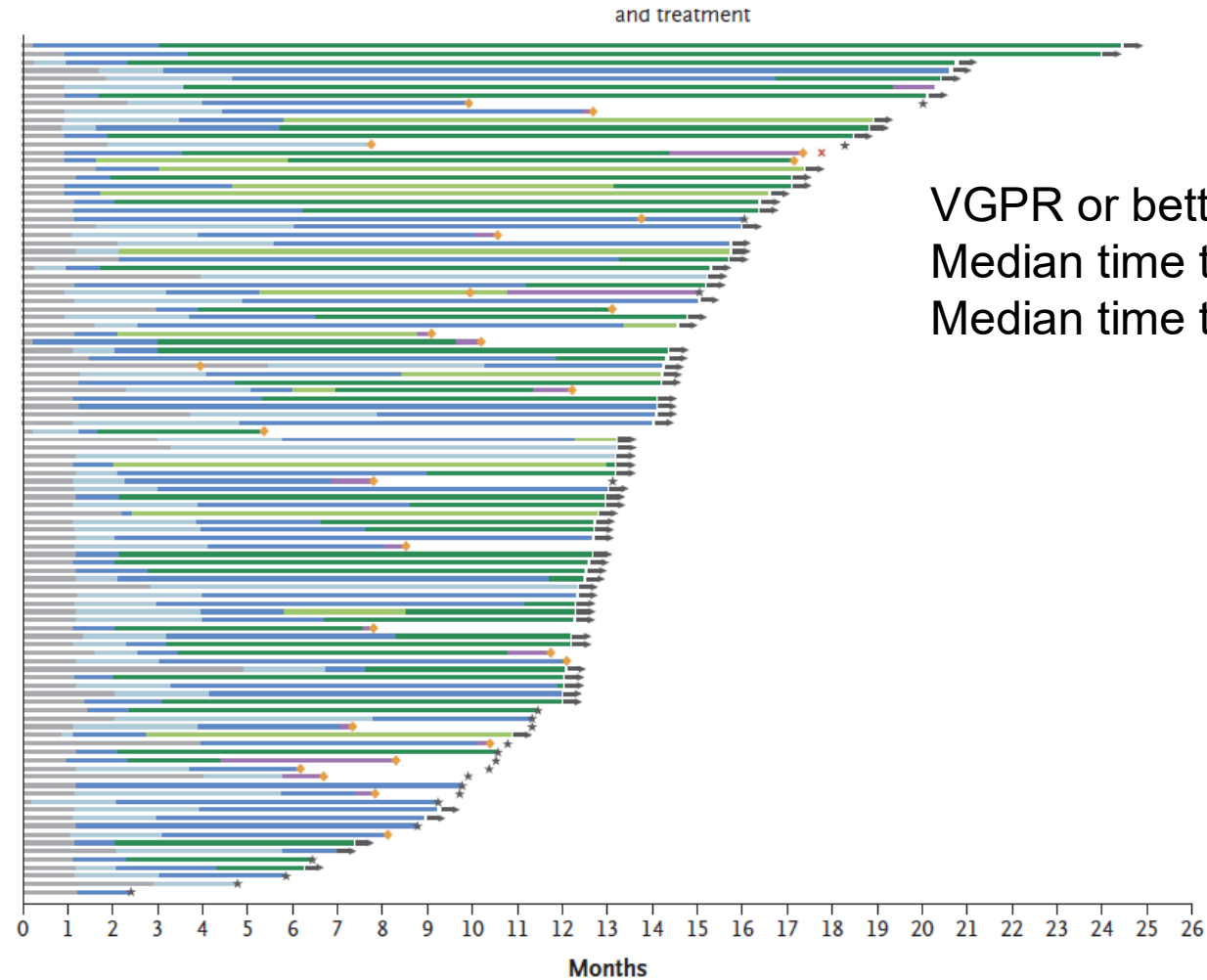
Renal impairment and LCCN (BCMA)

- Teclistamab
 - 384 patients with CrCl < 40
 - 5% were dialysis dependent
 - Adverse events
 - CRS: 51% v 59%, p = NS
 - ICANS: 16% v 15%, NS
 - Infections: 33% v 46%, p = 0.06
 - Dialysis
 - CRS – 56%
 - ICANS – 17%
- Elranatamab
 - Safe in dialysis (case reports)
 - Ogiya et al. Ann of Hem 2025
 - Van de Wyngaert et al. Clin Hem Int 2024
- Linvoseltamab
 - No information
- LCCN
 - No data

AKI with Teclistamab

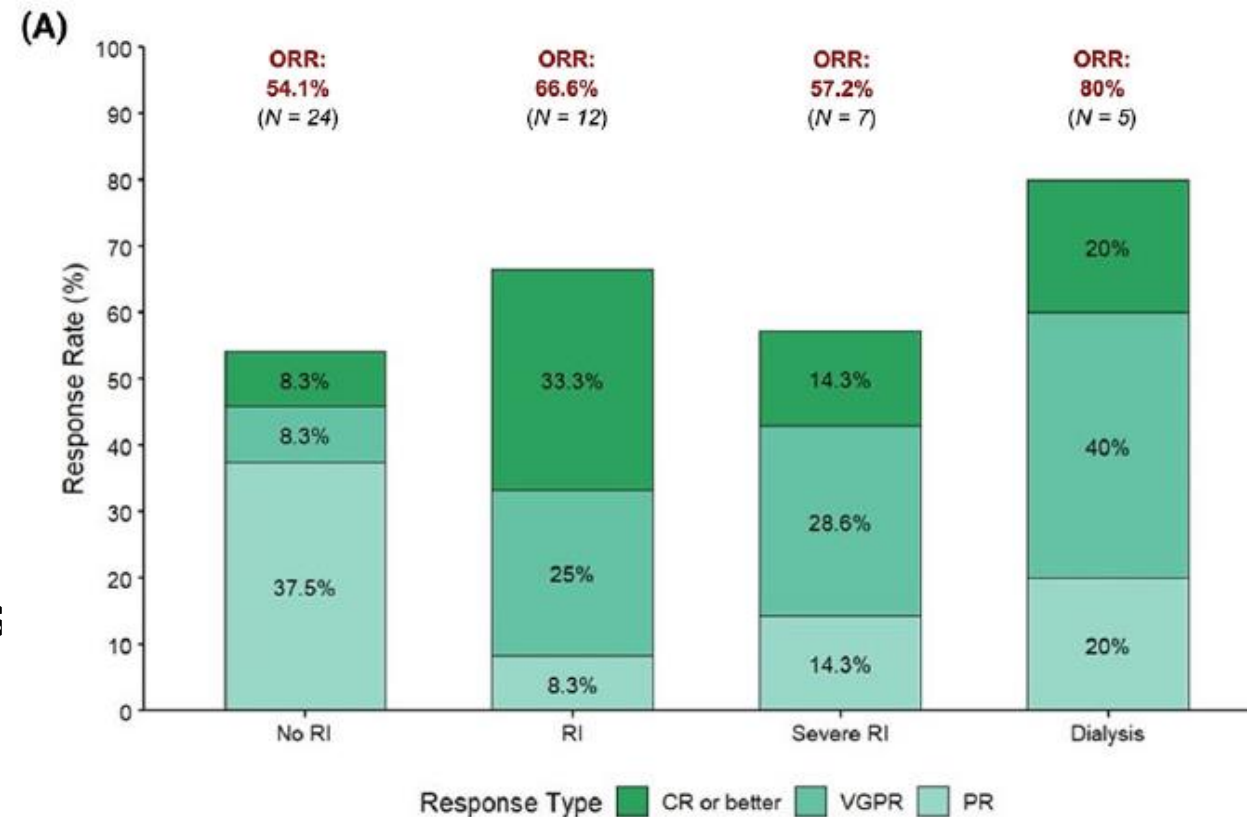
- 34 patients treated with Teclistamab vs 30 with CAR T
- AKI
 - Teclistamab – 22%
 - CAR T – 13%
 - AKI stages
 - 1 – n = 6
 - 2 – n = 3
 - 3 – n = 1
 - No association with CRS

Rapid response with Teclistamab



Renal impairment (GPRC5D)

- Single center study
 - No RI = 24
 - RI = 12 patients, 5 were on dialysis
- AE
 - CRS – 66.7% both groups
 - $\geq$ grade 3 – 8.3% both groups
 - ICANS – 16.7% RI vs 20.8%
 - Bacterial infections – 8.3% RI vs 16.7%
 - Dysgeusia – 83% both groups
 - Skin – 75% RI vs 58.3%
 - Nail – 83.3% RI vs 54.2%



CAR T cell therapy approved for relapsed or refractory MM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma

P. Rodriguez-Otero, S. Ailawadhi, B. Arnulf, K. Patel, M. Cavo, A.K. Nooka, S. Manier, N. Callander, L.J. Costa, R. Vij, N.J. Bahlis, P. Moreau, S.R. Solomon, M. Delforge, J. Berdeja, A. Truppel-Hartmann, Z. Yang, L. Favre-Kontula, F. Wu, J. Piasecki, M. Cook, and S. Giralt

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

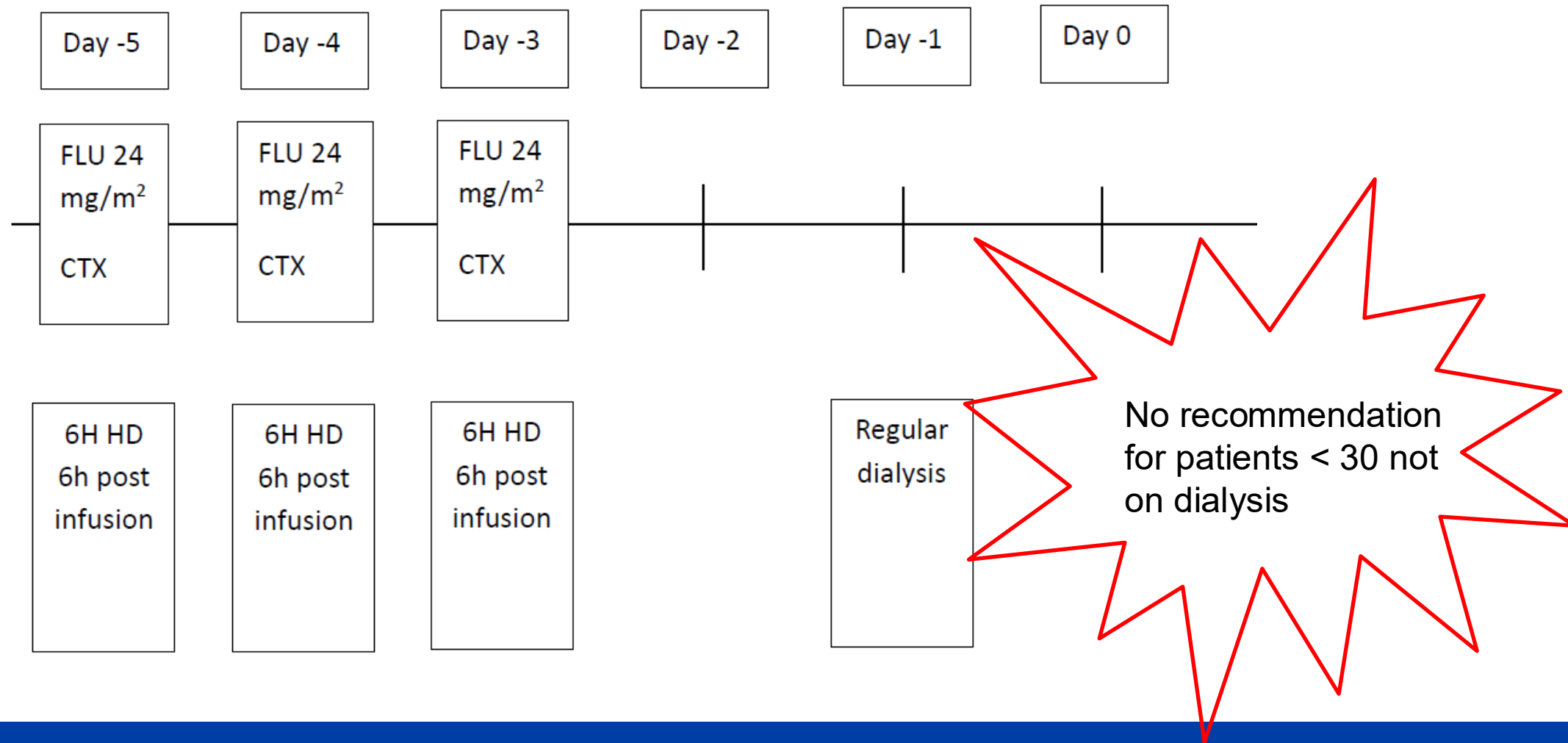
Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma

J. San-Miguel, B. Dhakal, K. Yong, A. Spencer, S. Anguille, M.-V. Mateos, C. Fernández de Larrea, J. Martínez-López, P. Moreau, C. Touzeau, X. Leleu, I. Avivi, M. Cavo, T. Ishida, S.J. Kim, W. Roeloffzen, N.W.C.J. van de Donk, D. Dytfeld, S. Sidana, L.J. Costa, A. Oriol, R. Popat, A.M. Khan, Y.C. Cohen, P.J. Ho, J. Griffin, N. Lendvai, C. Lonardi, A. Slaughter, J.M. Schecter, C.C. Jackson, K. Connors, K. Li, E. Zudaire, D. Chen, J. Gilbert, T. Yeh, S. Nagle, E. Florendo, L. Pacaud, N. Patel, S.J. Harrison, and H. Einsele

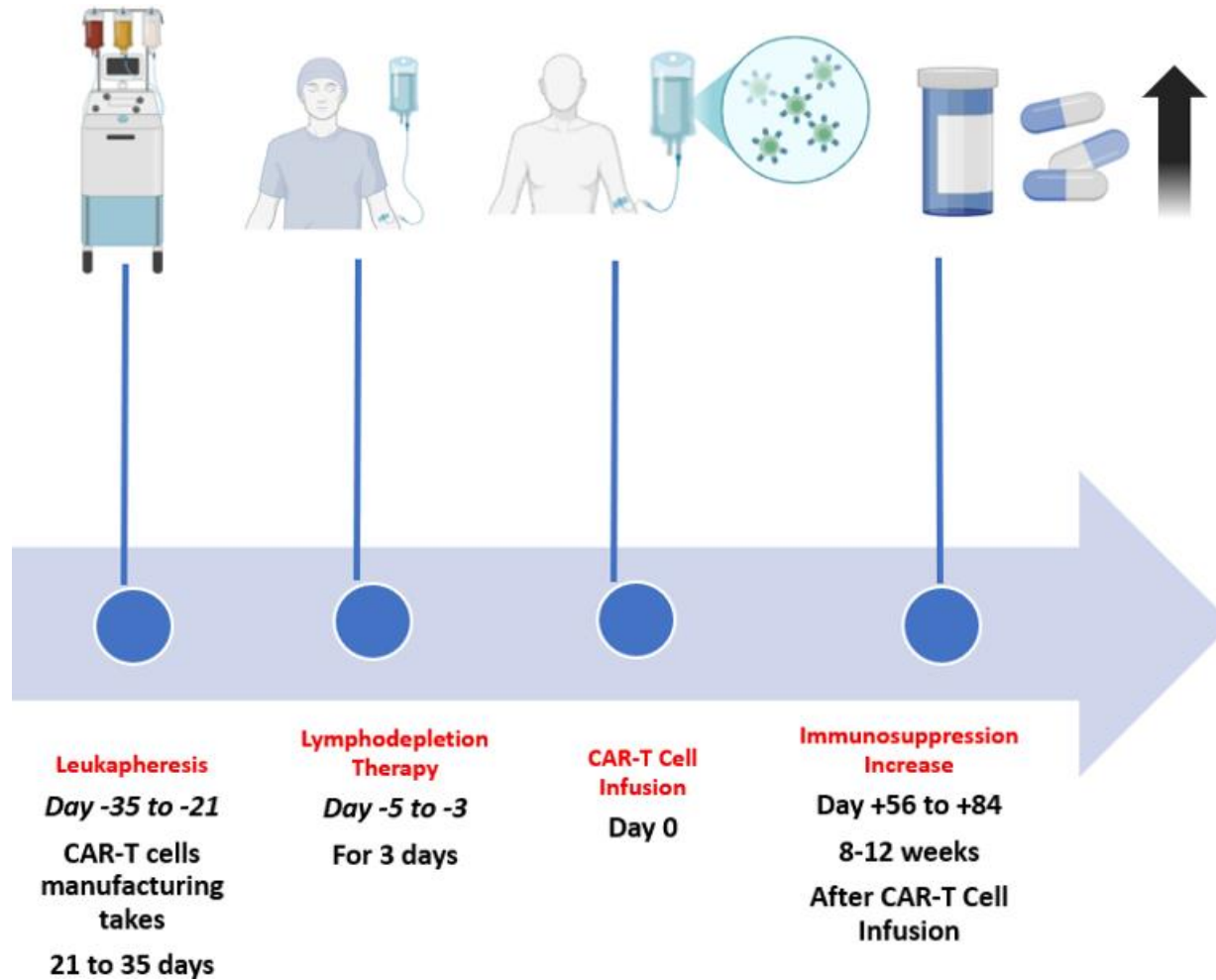
Fludarabine

- Required for lymphodepletion
- No dosing recommendation for patients with eGFR < 30
- No patients were enrolled in the clinical trial with poor kidney function or dialysis dependent

Lymphodepletion Protocol for Dialysis Dependent Patients Undergoing CAR T



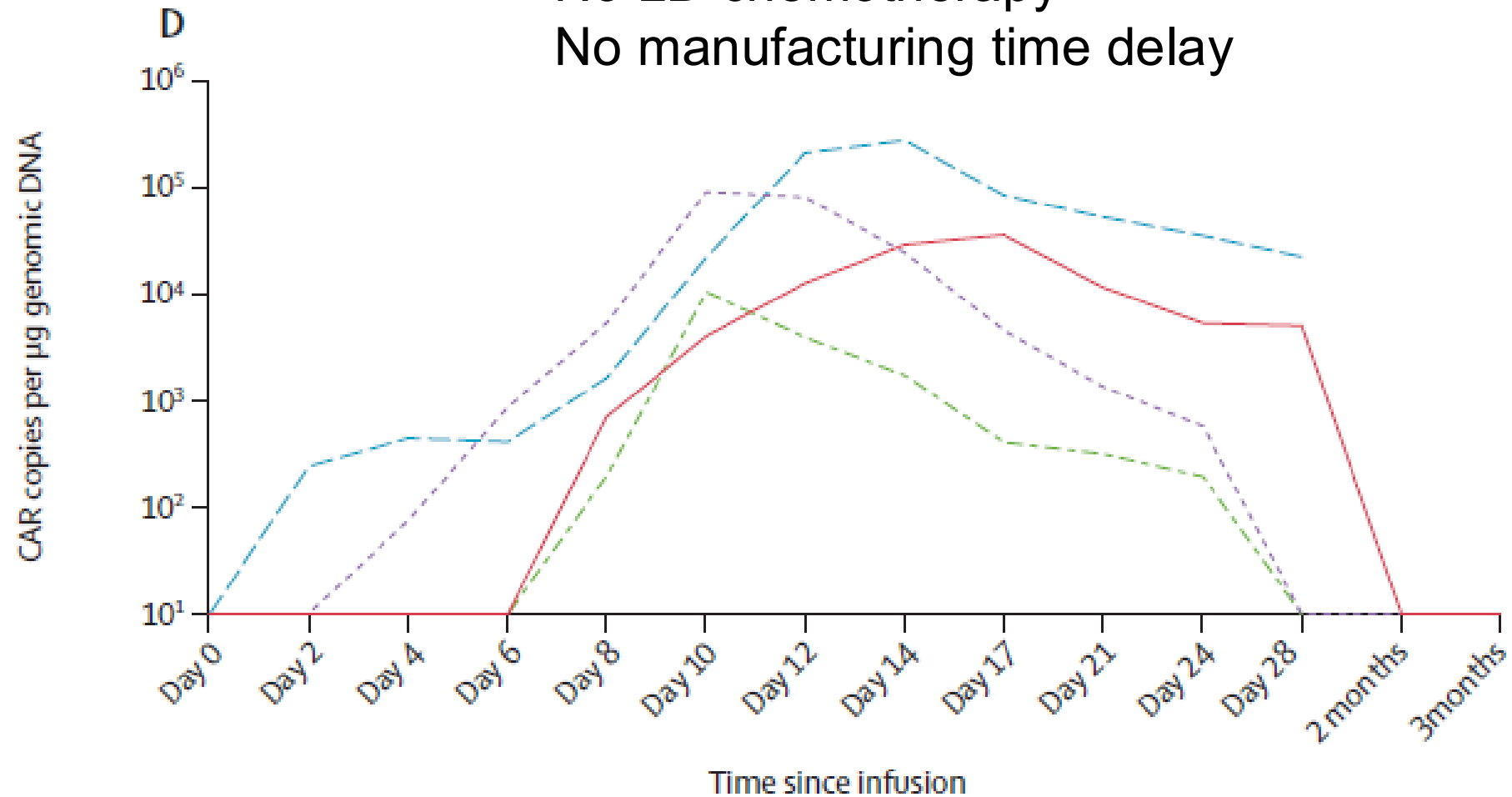
Timeline for CAR T therapy



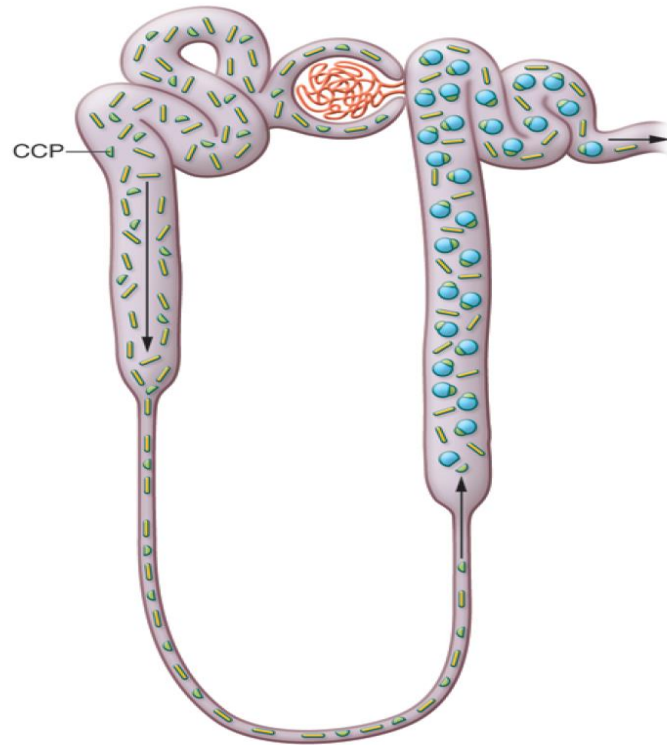
CAR –T cell therapy currently is not a good option for LCCN

In Vivo CAR-T

No LD chemotherapy
No manufacturing time delay



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

Take home messages

- Light chain cast nephropathy is a consequence of high tumor burden from multiple myeloma
- Rapid and sustained reduction of the involved free light chain is essential for recovery of kidney function from light chain cast nephropathy
- Despite extremely effective therapies for multiple myeloma, treatment for light chain cast nephropathy remains an unmet need.

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Leticia Rolon



Aleksandra Kukla