New Strategies for the Treatment of Plasma Cell-Dyscrasia-Related Kidney Disease

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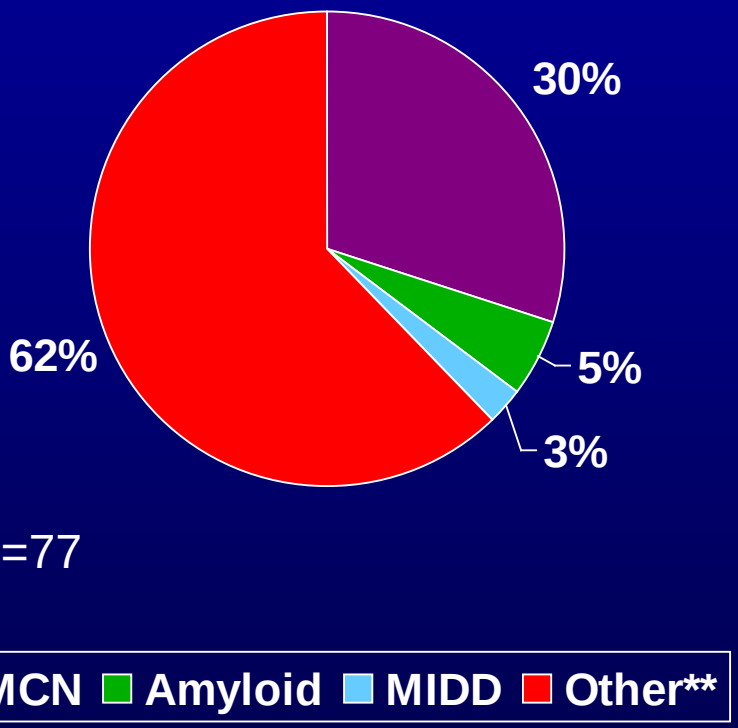
Objectives

- Recognize the adverse prognostic impact of renal failure for patients with multiple myeloma (MM).
- Appreciate novel treatment strategies for MM and their application in the setting of renal failure.
  - Immunomodulatory drugs (lenalidomide)
  - Proteasome Inhibitors (bortezomib)
  - Autologous Stem Cell Transplantation (autoSCT)
- Understand the pharmacology of novel MM agents in the setting of renal failure.
- Understand the use of mechanical means for clearance of free light chains.
  - Plasmapheresis
  - High cut-off HD

Nephropathology in MM*

- Tubular
  - Myeloma cast nephropathy (MCN)
  - Light chain Fanconi syndrome
- Glomerular
  - Amyloidosis
  - Monoclonal immunoglobulin (Ig) deposition disease (MIDD)

Post-mortem Prevalence of Renal Lesions in MM: The UAMS Experience



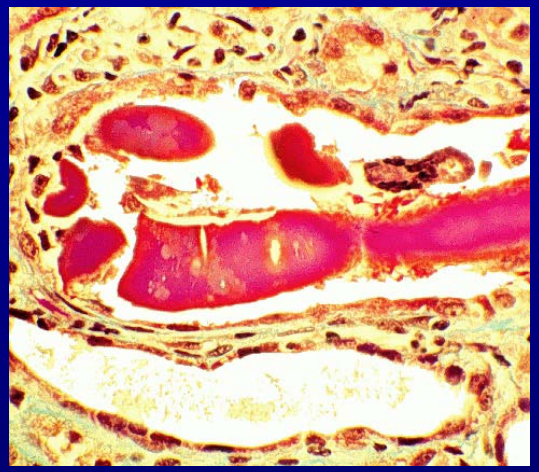
* Cryoglobulinemic GN, immunotactoid GN, and proliferative GN with monoclonal Ig deposits are seen in plasma cell dyscrasias, but rarely or never in MM.

** ATN, autolysis, thrombotic microangiopathy, fungal infection, plasma cell tumor nodules, tubulointerstitial nephritis.

Herrera et al. *Arch Pathol Lab Med.* 2004 Aug; 128(10): 875-9.

Myeloma Cast Nephropathy

- The most common cause of ARF in MM pts.
- Precipitants of cast formation
  - Volume depletion
  - Loop diuretics
  - ↑ urine calcium
  - Radiocontrast media



Adapted from the University of North Carolina Nephropathology Biopsy Cases.

Pathogenesis of Myeloma Cast Nephropathy

Proximal Tubule

Light chains endocytosed

↓

NF-κB- and MAPK-mediated inflammatory response

↓

Production of IL-6, IL-8, MCP-1, TNF-α

↓

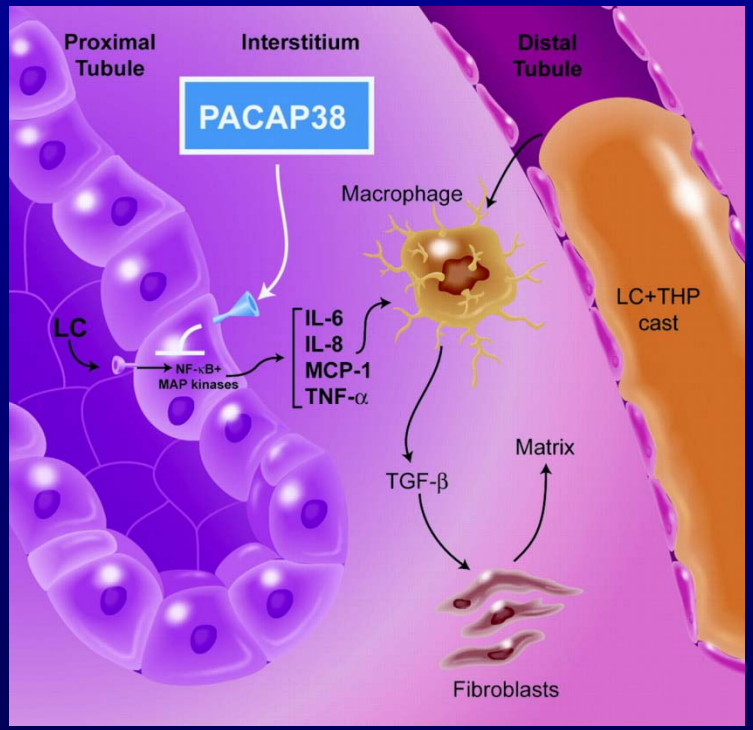
Macrophage activation

↓

TGF-β production

↓

Fibroblast-mediated interstitial matrix deposition



Sanders, P. W. Blood 2006;107:413-414

Distal Tubule

Co-precipitation of free light chains with Tamm-Horsfall protein

↓

Obstruction of tubular fluid flow

↓

Epithelial lining disruption

↓

Tubulointerstital inflammation

Tubulointerstitial fibrosis

Sengul et al. *Kidney Int.* 2002 62: 1977-88.
Sengul et al. *Am J Physiol Renal Physiol.* 2003 284: 1245-54.
Sanders et al. *J Clin Invest.* 1992 89: 630-9.
Huang et al. *J Clin Invest.* 1997 99: 732-6.

Prognosis of Renal Failure in MM

	Normal renal function (N=329)	Renal failure (Cr≥2 mg/dL) (N=94)	Persistent renal failure (N=67)	Renal recovery (N=24)
Median OS (months)	34.5	8.6	3.8	28.3
ORR (%)	56.4	39	--	--

- **Single institution, retrospective analysis from 1969-1994.**
- **22.2% had renal failure at diagnosis.**
- **29% of pts with renal failure died within 2 months of diagnosis.**
- **26% recovered normal renal function with treatment.**

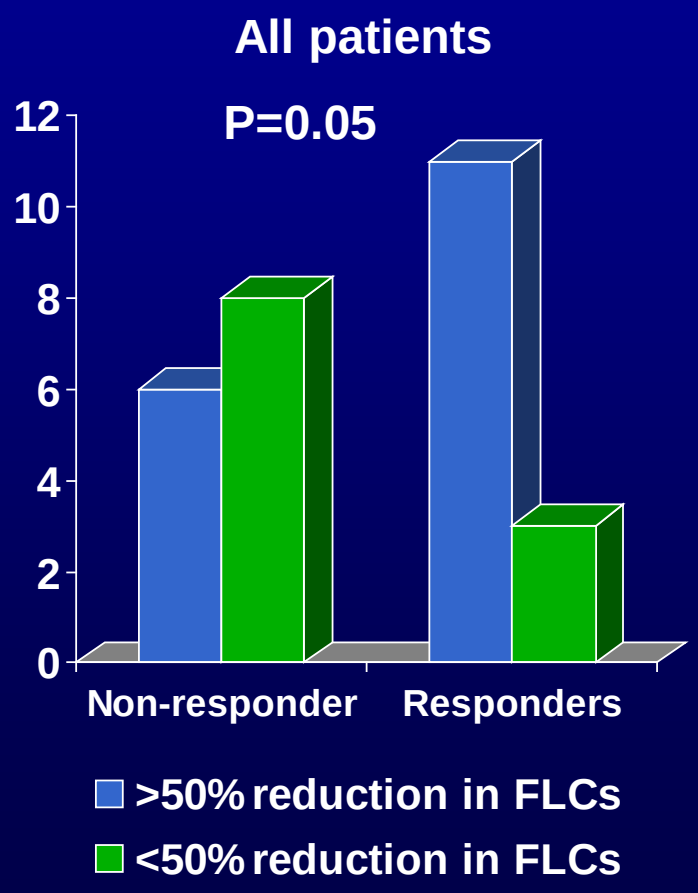
Predictors of Renal Recovery

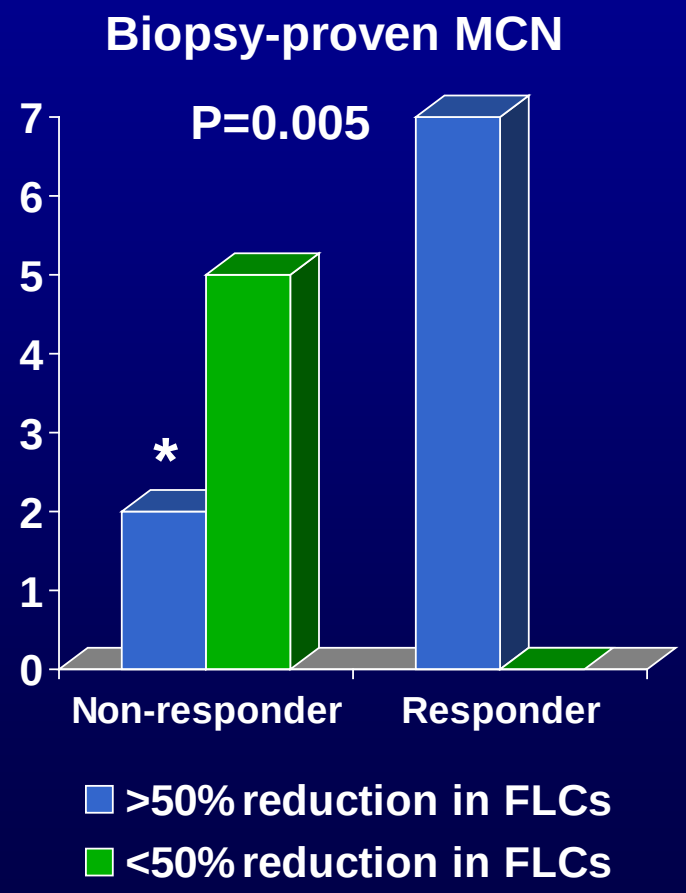
	Relative risk	P value
Cr<4 g/dL	7.5 (2-28)	0.001
Ca>11.5 mg/dL	3.27 (1.1-9.3)	0.02
Proteinuria <1 g/day	2.78 (1.09-7.08)	0.02

Blade et al. *Arch Intern Med.* 1998 Sep; 158(17): 1889-93.

Reduction of Serum FLCs Predictive of Renal Response in MM

- Single center, retrospective analysis of 40 MM pts with RF treated with PLEX (100%) +/- chemotherapy (85%).





Leung et al. *Kidney Int.* 2008 Jun; 73(11): 1282-8.

* 1 pt received IV contrast for a CT

Conclusions

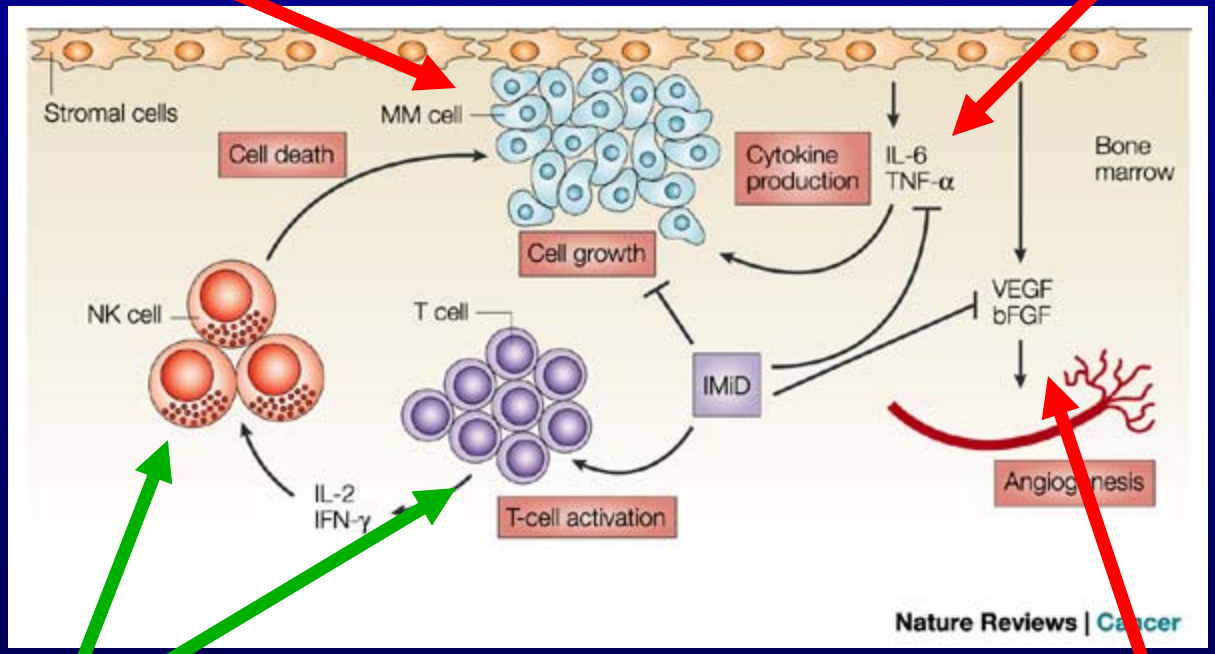
- Renal failure in MM is associated with inferior survival.
- Reversal of renal failure is associated with improved survival.
- Renal failure is most commonly due to myeloma cast nephropathy (MCN).
- Therapy for MCN should produce a rapid, deep, and sustained decrease in Ig production.

Advances in Myeloma Therapy: Lenalidomide

The Immunomodulatory Drug (IMiD) Lenalidomide: Mechanism of Action

1. Direct tumor cell cytotoxicity

2. Inhibits paracrine production of MM cell growth factors



4. Stimulates anti-tumor immunity

3. Anti-angiogenic via inhibition of paracrine production of VEGF, bFGF

Bartlett et al. *Nat Rev Cancer.* 2004 Apr; 4(4): 314-22.

Pharmacokinetics of Lenalidomide

- Time to maximal plasma concentration (T_{max}): 0.5 to 4.0 hours
- $T_{1/2}$: 3.0 to 4.2 hours.
- Linear pharmacokinetics
  - No drug accumulation with repeated dosing
- ~ 2/3 of drug eliminated unchanged in urine
  - Glomerular filtration
  - Tubular secretion
- Plasma protein bound: 30%
- AUC *57% higher in myeloma patients* than normal controls

Chemical structure of lenalidomide

Lenalidomide Package Insert, Celgene Corporation, 1/2009.

Richardson et al. *Blood.* 2002 Nov; 100(9): 3063-7.

MM-009/MM-010: Lenalidomide/Dexamethasone (Len/Dex) vs. Dexamethasone (Dex)

- Two large multi-center, randomized, placebo-controlled phase III studies of dex with or without len for patients with relapsed myeloma.
- Primary end-point: time to disease progression.
- Secondary end-points: overall response, survival, safety.
- *Renal eligibility criterion: Cr<2.5 mg/dL*.

Dimopoulos et al., *N Engl J Med* 2007; 357(21):2123-32.
Weber et al., *N Engl J Med* 2007; 357(21):2133-42.

Len/Dex vs. Dex: Response Rate

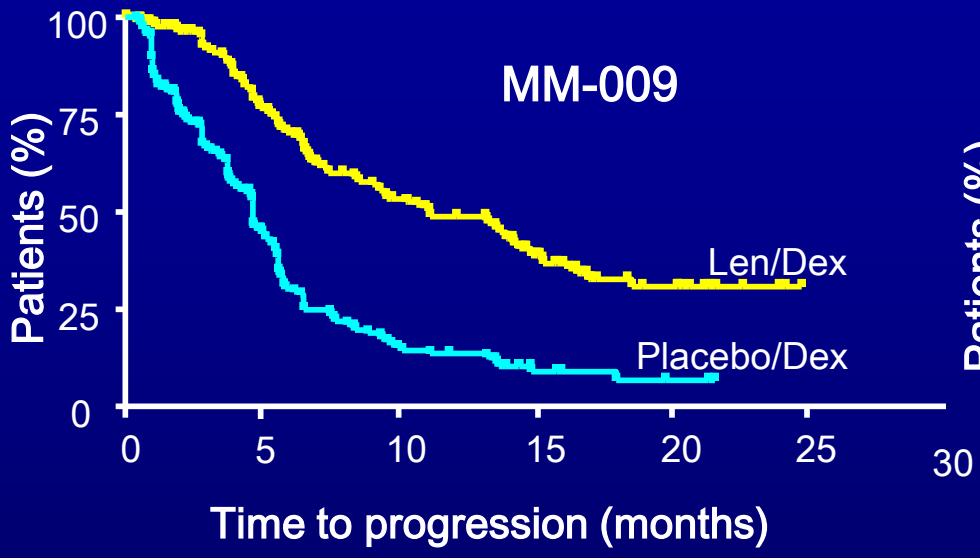
Best response, n (%)	MM-009		MM-010	
	Len/Dex (n=177)	Placebo/Dex (n=176)	Len/Dex (n=176)	Placebo/Dex (n=175)
Overall response	108 (61)*	35 (20)	106 (60)*	42 (24)
CR	25 (14)*	1 (1)	28 (16)*	6 (3)
Near CR	18 (10)	2 (1)	15 (9)	3 (2)
PR	65 (37)	32 (18)	62 (35)	33 (19)
Stable disease	54 (31)	102 (58)	53 (30)	97 (55)
Progressive disease	5 (3)	25 (14)	3 (2)	25 (14)
Not evaluable	10 (6)	14 (8)	14 (8)	11 (6)
Duration of response (months)	16	5	17	8

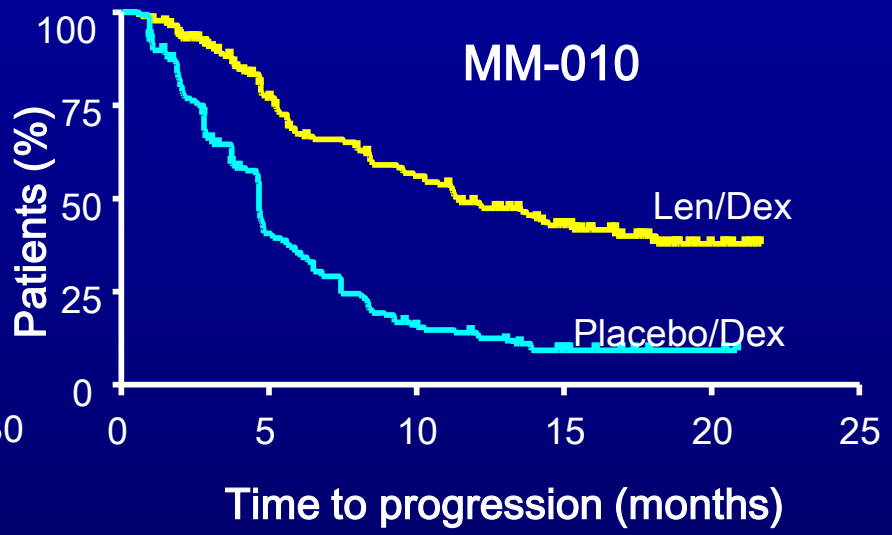
Median time to first response: 2.1 months

*P-value <0.001 for comparison with Placebo/Dex counterpart, as tested with continuity-corrected Pearson chi square test.
CR, complete response; PR, partial response.

Dimopoulos et al., *N Engl J Med* 2007; 357(21):2123-32.
Weber et al., *N Engl J Med* 2007; 357(21):2133-42.

Len/Dex vs. Dex: Time to Progression





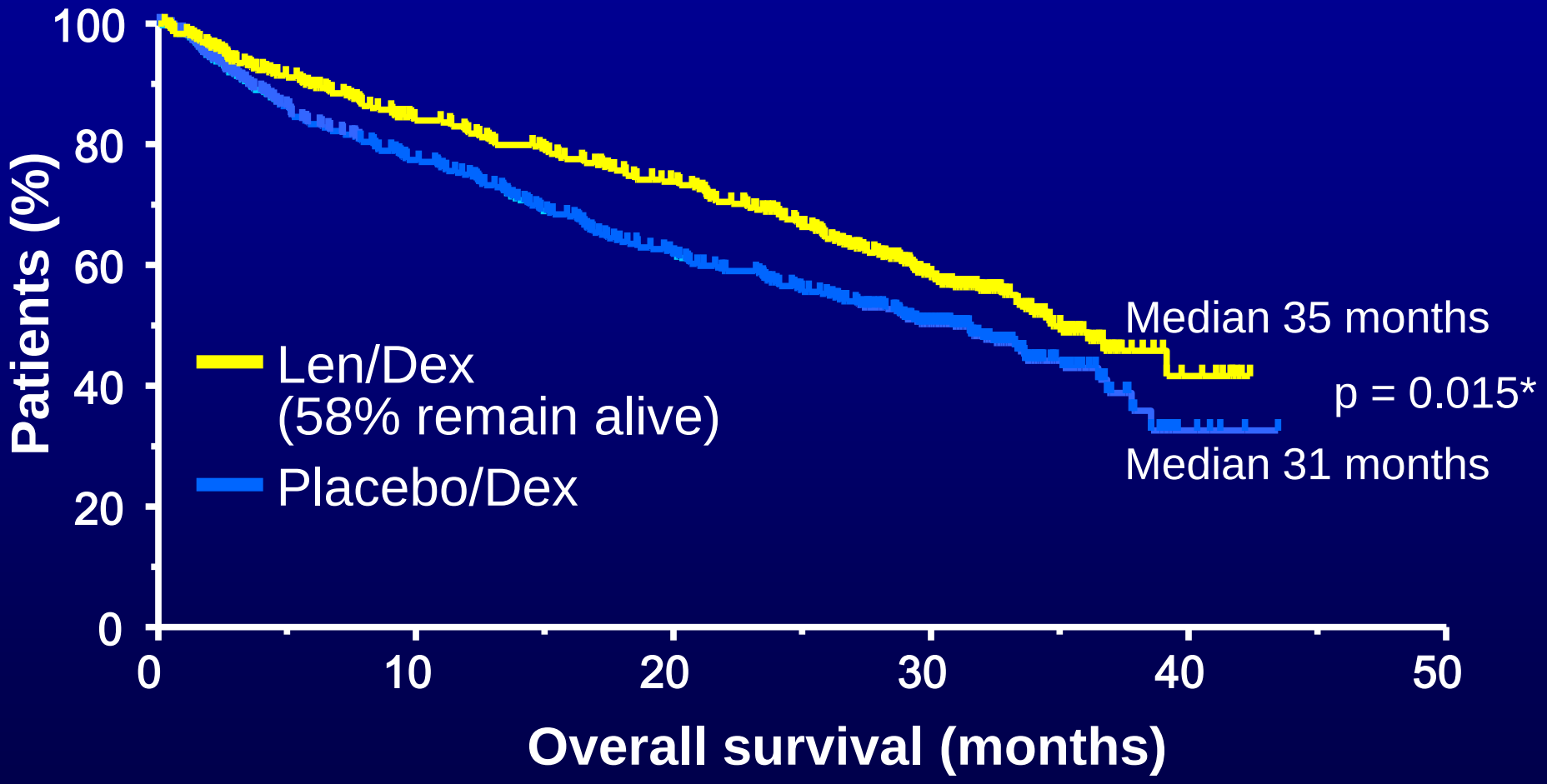
Median time to progression (months)			
	Len/Dex	Placebo/Dex	*P**
MM-009	11.1	4.7	<0.001
MM-010	11.3	4.7	<0.001

*`P-value from log-rank test.

Dimopoulos et al., *N Engl J Med* 2007; 357(21):2123-32.
Weber et al., *N Engl J Med* 2007; 357(21):2133-42.

Len/Dex vs. Dex: 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).

Weber et al. *Blood* 2007;110(11)[Abstract 412].

Pharmacokinetics of Lenalidomide in Renal Failure

A pharmacokinetic study of single-dose lenalidomide in subjects with varying levels of renal impairment (5 to 7 subjects per cohort).

PK Parameter	Normal	Mild	Moderate	Severe	ESRD off HD	ESRD on HD**
C_{max} (ng/mL)	568	684	568	761	538	370
V/F (L)	56	50	60	40	51	--
AUC (ng x h/mL)	**2091**	**2627**	**5964***	**8088***	**10,958***	**6778**
CL/F (mL/min)	**199**	**159**	**70***	**52***	**38***	**--**
$t_{1/2}$ (hours)	**3.26**	**3.61**	**9.97***	**8.93***	**15.5***	**16.0**
Urine excretion (% dose)	**84**	**69**	**38***	**43***	**--**	**--**

*p<0.05 vs. normal group; **Dose administered 3 hours prior to a 4-hour HD session.

C_{max}=maximal plasma [ ]; V/F=volume of distribution; AUC=area under the plasma concentration-time curve; CL/F=total body clearance; $t_{1/2}$=terminal half-life

Normal:CrCl>80 mL/min; Mild:50-80 mL/min; Moderate:30-49 mL/min; Severe:<30 mL/min

Chen et al. *J Clin Pharmacol.* 2007 Dec; 47(12): 1466-75.

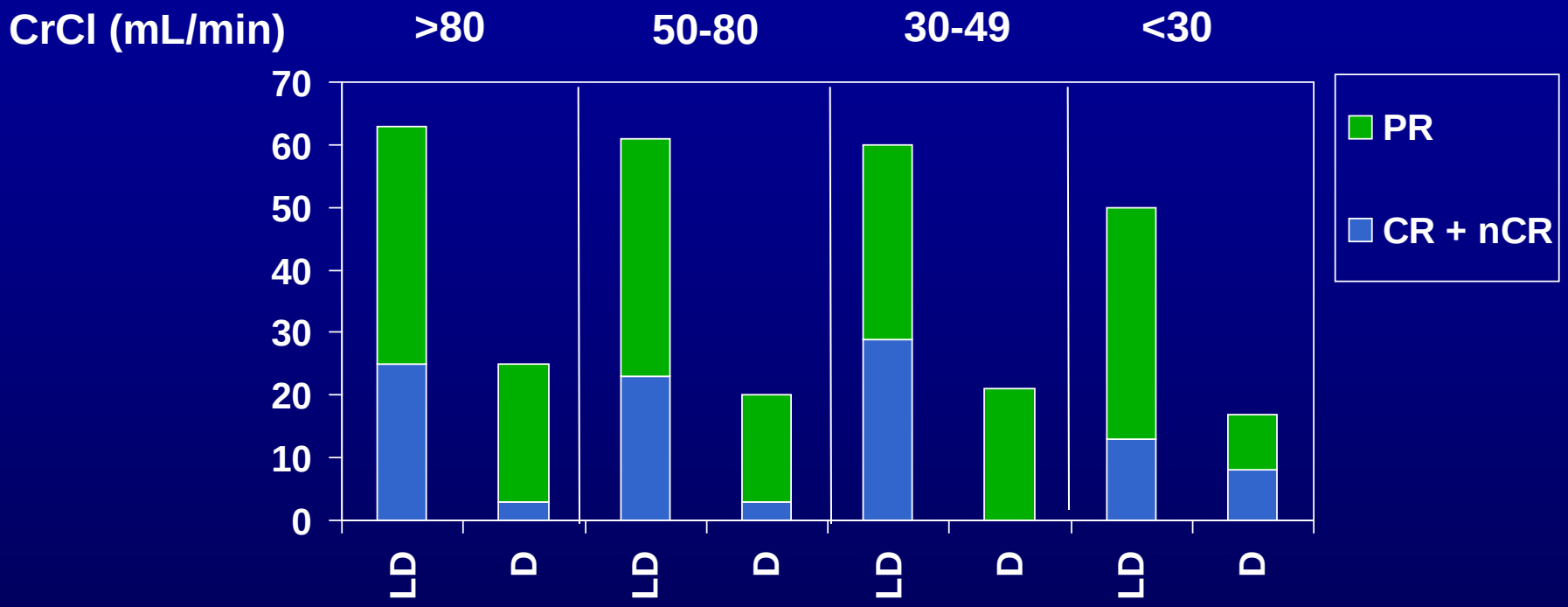
Lenalidomide Dosing Guidelines in Renal Failure

Level of Renal Impairment	Multiple Myeloma	Myelodysplastic Syndrome
Moderate	10 mg every 24 hours	5 mg every 24 hours
Severe	15 mg every 48 hours	5 mg every 48 hours
ESRD on HD	5 mg daily. Dose after dialysis on dialysis days	5 mg 3x/week after HD

Moderate:CrCl≥30-59 mL/min; Severe:CrCl<30 mL/min

Chen et al. *J Clin Pharmacol.* 2007 Dec; 47(12): 1466-75.
Lenalidomide prescribing information. http://www.revlimid.com/pdf/Revlimid_PI.pdf

Lenalidomide and Dexamethasone: Efficacy and Safety in Renal Dysfunction



Median TTP (mo)	11.2	4.7	12.1	4.7	11.4	2.8	7.9	4.7
Neutropenia (%)	31.0	4.3	39.2	1.5	42.9	5.9	37.5	8.3
Low Platelets (%)	7.0	5.5	16.0	5.3	19.0	17.6	**37.5**	0.0
Infection (%)	22.2	15.3	20.0	14.5	31.0	17.6	**56.3**	33.3

LD=Lenalidomide/dexamethasone; D=dexamethasone

Weber et al. *Blood* 2007;110(11)[Abstract 412].

Advances in Myeloma Therapy: Bortezomib

Bortezomib: Mechanism of Action

Inhibition of NF-κB
- **Direct cytotoxicity**
- **↓ MM cell adhesion to bone marrow stroma**
- **↓ production of MM cell growth factors (e.g. IL-6)**

Bortezomib: a reversible inhibitor of the chymotryptic-like activity of the proteasome

26S Proteasome

↑ proteotoxic stress
- **Direct cytotoxicity**
- **ER stress and induction of UPR play a role**

Inhibition of angiogenesis
- **↓ production of VEGF**

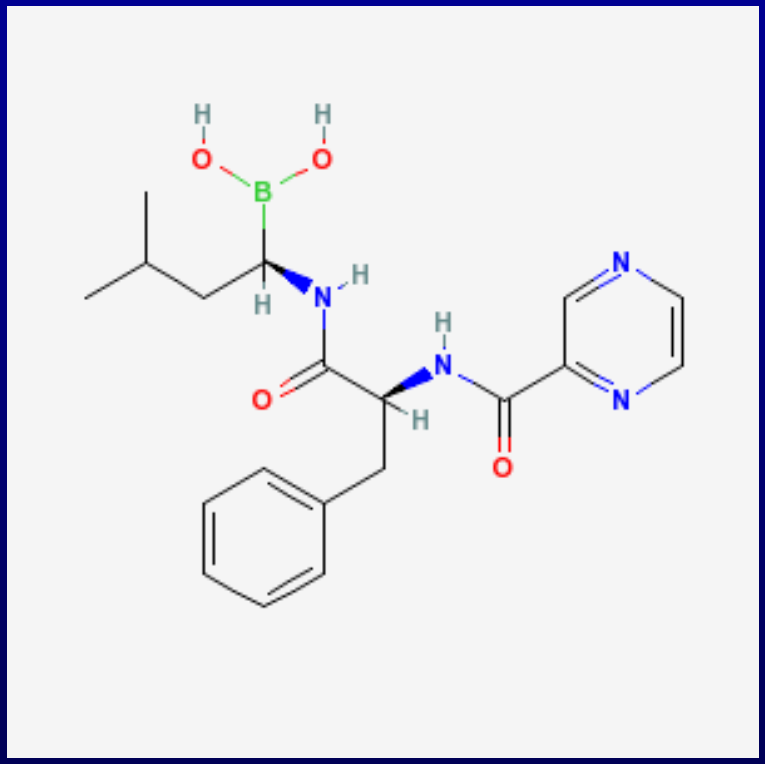
Osteoblast activation
- **Activation of β-catenin/TCF signaling**

Chemosensitization
- **↓ NF-κB activity**
- **↓ DNA repair**

Enhanced cellular immunity to MM cells

Bortezomib: Pharmacokinetics

- Hepatic metabolism: cytochrome P450-mediated oxidative deboronation.
  - CYP3A4, CYP2C19, CYP1A2.
- Elimination not well characterized in humans.



Chemical structure of bortezomib

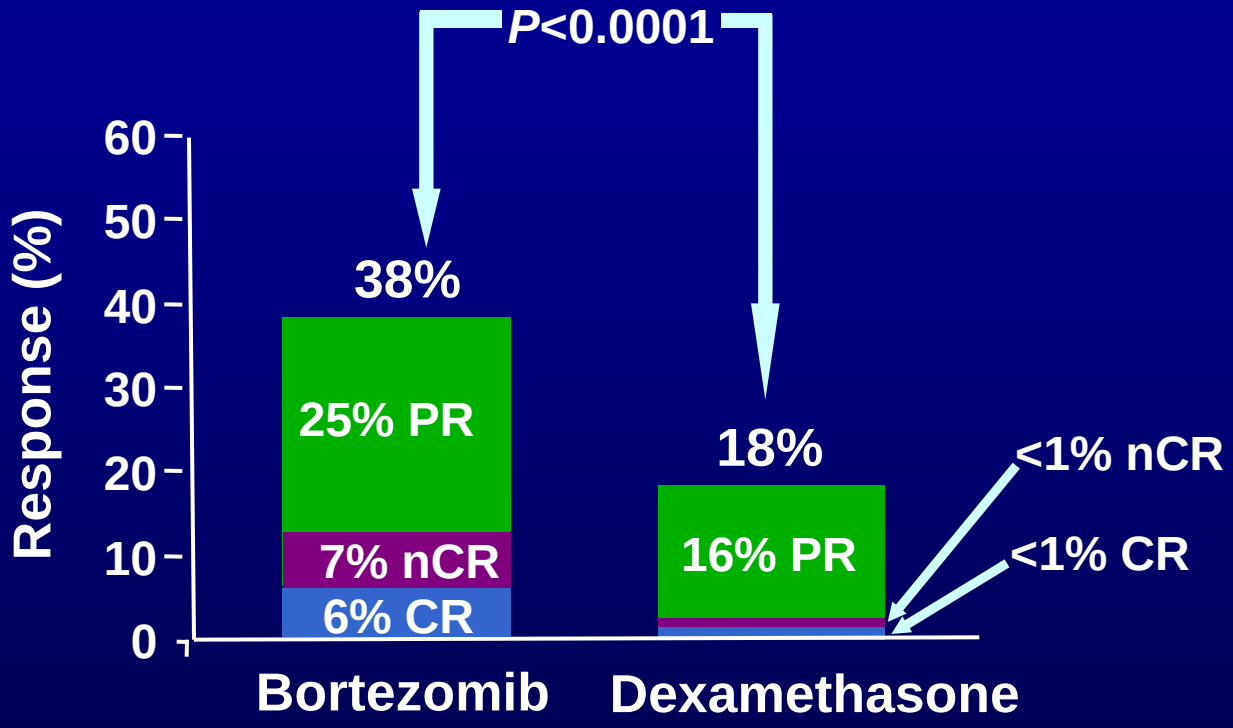
Labutti et al. *Chem Res Toxicol.* 2006 Apr; 19(4): 539-46.

APEX: Assessment of Proteasome inhibition for EXtending remissions

- A multi-center, randomized phase III study of bortezomib vs. dexamethasone for the treatment of relapsed MM
- Primary outcome: Time to disease progression
- Secondary outcome: Response rate, overall survival, safety
- *Renal eligibility criterion: CrCl>20 mL/min*

Richardson et al. *N Engl J Med.* 2005 Jun; 352(24): 2487-98.

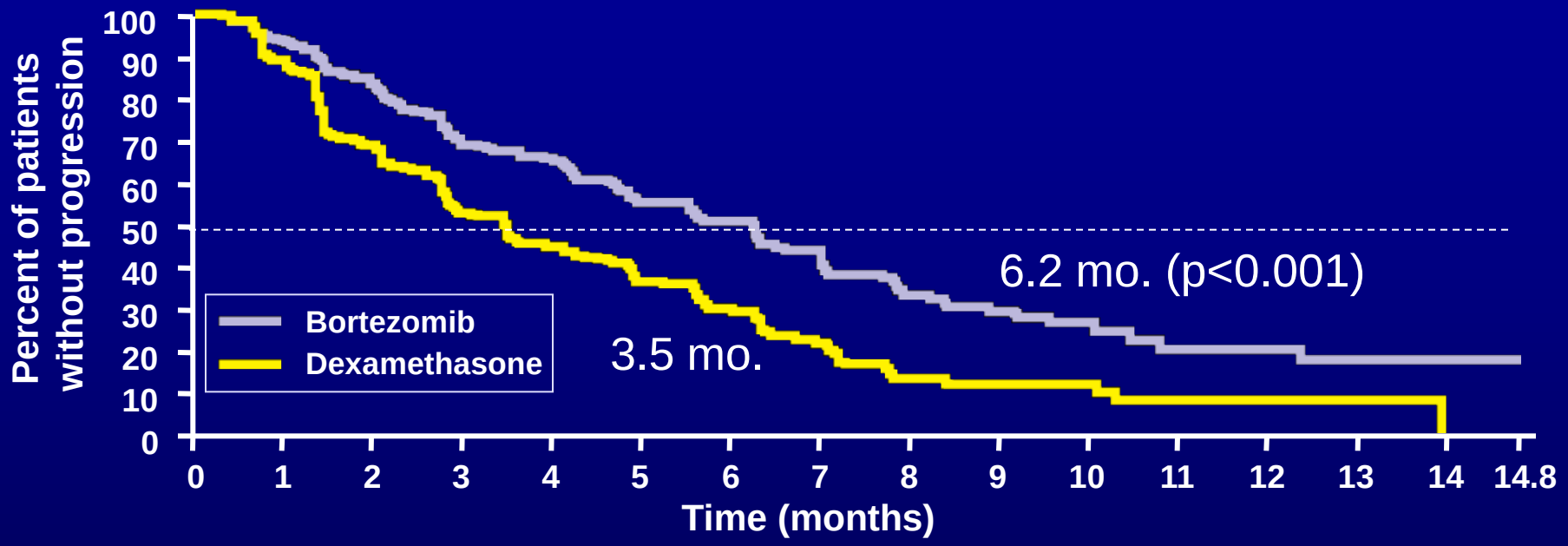
APEX: Response Data



- Median time to first response: 43 days.

Richardson et al. *N Engl J Med.* 2005 Jun; 352(24): 2487-98.

APEX: Clinical Efficacy



- Median OS: 29.8 mo. for bortezomib arm vs. 23.7 mo. despite >62% cross-over (p=0.0272).
- One-year OS: 80% vs. 67% in favor of bortezomib (p=0.0002).

Richardson et al. *N Engl J Med.* 2005 Jun; 352(24): 2487-98.

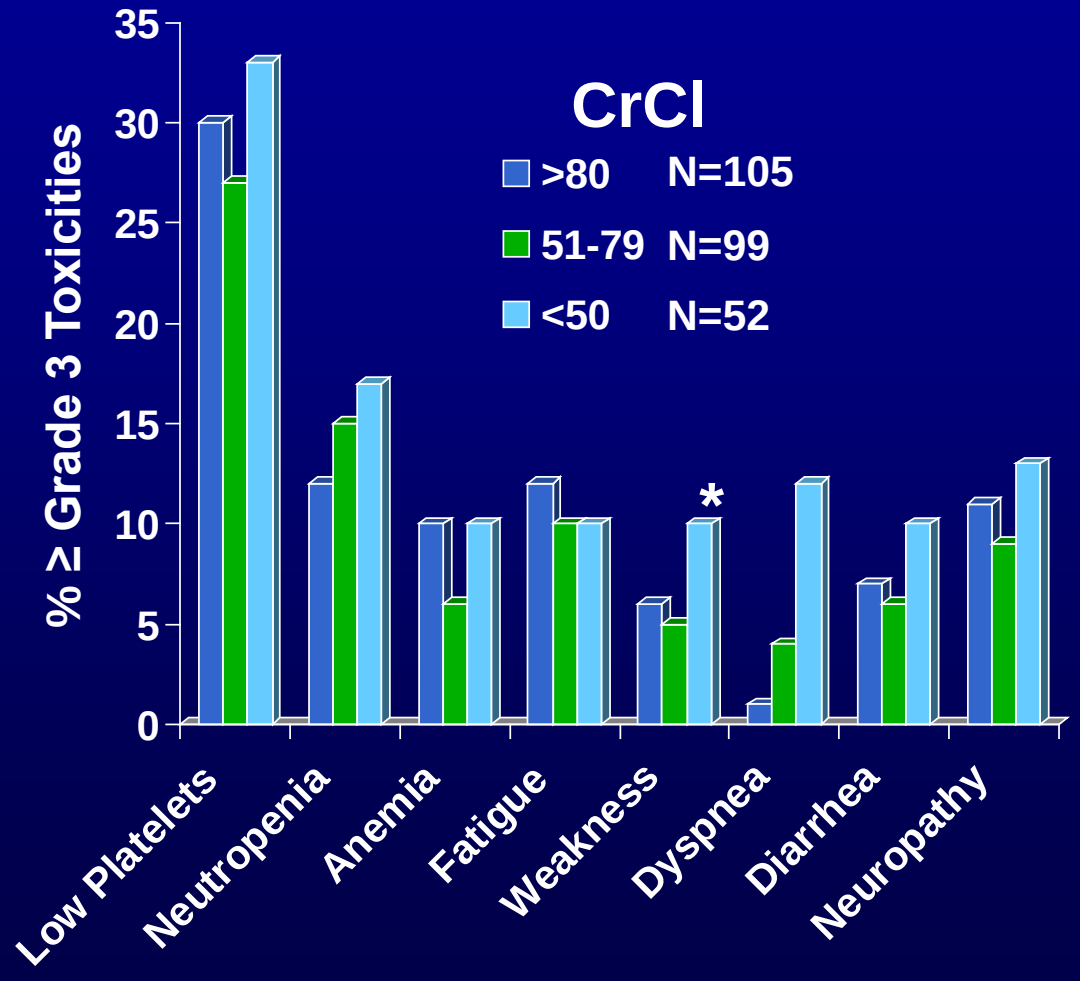
Bortezomib Pharmacokinetics in Renal Failure

- Phase I dose-escalation study of bortezomib in cancer patients with mild to severe renal impairment
  - 5 dose cohorts: CrCl≥60, 40-59, 20-39, <20 mL/min, and dialysis-dependent
- 59 pts treated
  - 9 dialysis patients
- No difference in toxicity profile across cohorts
- Pharmacokinetic parameters comparable across cohorts
- No dose modifications necessary for pts with renal failure of any degree

Mulkerin et al. *ASH Annual Meeting Abstracts*. 2007;110:abstract 3477.

Safety of Bortezomib in Renal Failure

Retrospective analysis of 256 patients with relapsed and/or refractory MM treated with bortezomib +/- dexamethasone in two large phase II studies



- **Mean serum creatinine unaffected by bortezomib**
- **Discontinuations: 28%, 22%, 38% for CrCl of >80, 51-79, <50 mL/min**
- **SAEs: 41%, 51%, 60%, respectively**

*** p=0.01; Fisher exact test; SAEs=Serious adverse events**

Jagannath et al. *Cancer*. 2005;103:1195.

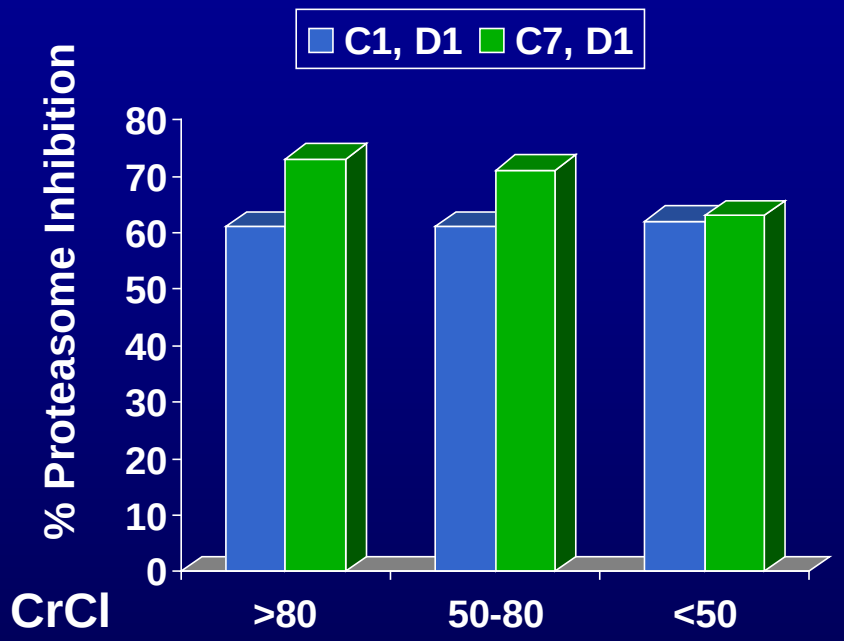
Bortezomib in Renal Failure

Efficacy

Creatinine Clearance	No. of Pts	ORR (%)
>80 mL/min	105	45
51-80 mL/min	99	33
≤50 mL/min	42	25
<30 mL/min	10	30

Comparable response rates in patients with compromised renal function.

Pharmacodynamics

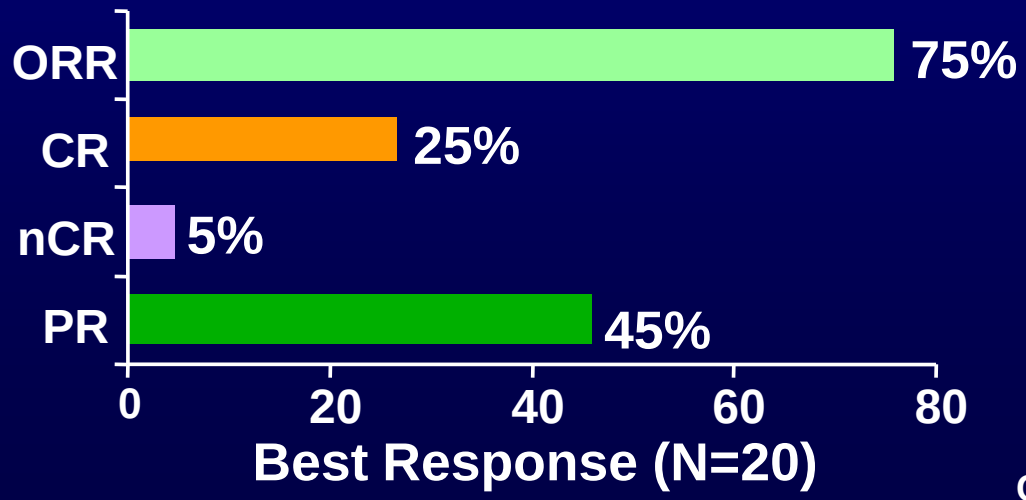


Whole blood proteasome activity assay unaffected by renal function.

Jagannath et al. *Cancer*. 2005;103:1195.

Bortezomib in Dialysis-Dependent Renal Failure

- Retrospective analysis of 24 dialysis-dependent patients treated with single-agent bortezomib (8%) or bortezomib-based combinations (92%)
- Median number of prior therapies: 2 (range, 0-6)
  - 1 newly-diagnosed patient
- Patients received a median of 5 cycles of bortezomib-based therapy
- Acceptable toxicity profile
  - No treatment-related deaths (1 from disease progression)
  - Thrombocytopenia 39%, neuropathy 17%, infection 11%

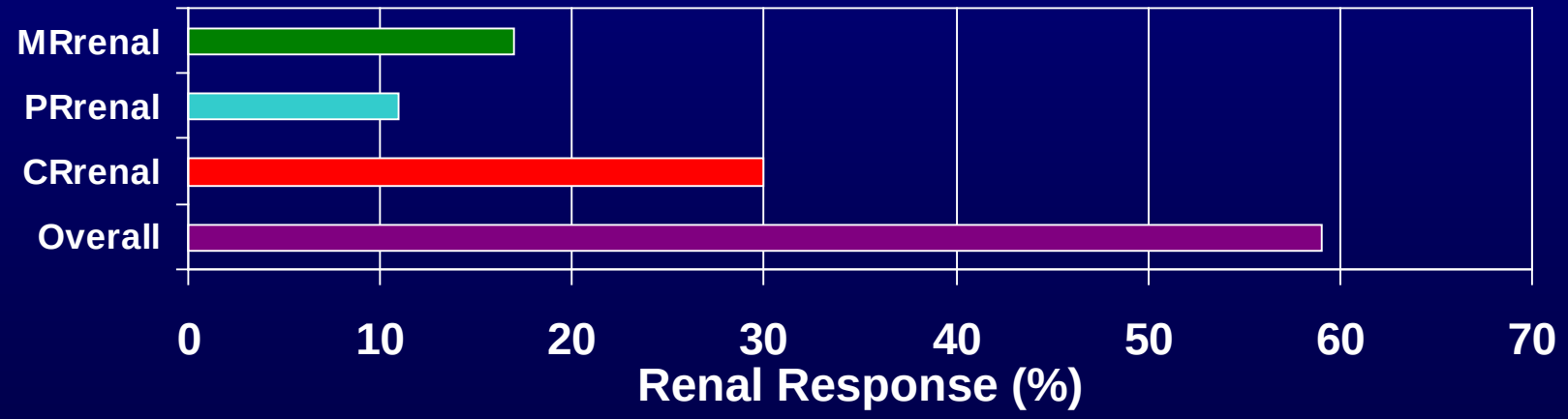


4 patients became dialysis independent, 3 of which were attributable to treatment response.

Chanan-Khan et al. *Blood.* 2007;109:2604.

Reversal of Renal Failure with Bortezomib-based Therapy

- **Retrospective analysis of 46 consecutive patients treated with bortezimib-based therapy**
- **Median age 72 (43-88), median eGFR 18.5 mL/min (4.7-47.8)**
- **79% of patients previously treated**
- **Overall renal response rate 59%**
  - **2 of 9 patients achieved dialysis independence**
- **Light chain disease associated with higher likelihood of renal response** in multivariate analysis (HR 4.4; CI, 1.1-19)
- **Renal response in MM responders** (≥PR) vs. non-responders (<PR): **76% vs. 29%**
- **Landmark analysis** of survivors beyond one month: **82% 1-year survival for renal responders vs. 54% for renal non-responders**



MRrenal=GFR from <15 mL/min to 15-29 mL/min or from 15-29 mL/min to 30-59 mL/min

PRrenal=GFR from <15 mL/min to 30-59 mL/min

CRrenal=GFR from <50 mL/min to ≥60 mL/min

Dimopoulos et al. *Clin Lymphoma Myeloma.* 2009 Aug; 9(4): 302-6.

Reversal of Renal Failure with Bortezomib-based Therapy

- Prospective phase II study of bortezomib, doxorubicin, and dexamethasone in MM pts with renal failure
  - Newly-diagnosed pts: GFR<50 mL/min
  - Relapsed and/or refractory pts: ↓ in GFR by >25% to <60mL/min in pts with previous baseline GFR >60 mL/min
- MCN had to be the established etiology of the ARF
- 72 pts enrolled
  - 58 evaluable for response
- Median age: 66 (40.7-82), median GFR 16.8 mL/min (4-48)
- 81% with newly-diagnosed MM

Ludwig et al. *ASH Annual Meeting Abstracts*. 2009;114:abstract 3862.

Reversal of Renal Failure with Bortezomib-based Therapy

- Overall myeloma response rate: 78%
  - Time to best response: 88 days
- Overall renal response: 69%
  - Median GFR increased from 20.0 to 48.4 mL/min
  - Complete renal response: 36%
  - Time to renal response: 4.4 months
- Myeloma response correlated with renal response
- Overall survival at 2 years: 60%

Tumor Response	N (%)	Best GFR Median (mL/min)
CR/nCR/VGPR	36 (62%)	60.0
PR	9 (16%)	38.9
SD/PD	9 (15%)	16.8

CR=complete response; VGPR=very good partial response; PR=partial response; MR=minor response; SD=stable disease; PD=progressive disease

Ludwig et al. *ASH Annual Meeting Abstracts*. 2009;114:abstract 3862.

Advances in Myeloma Therapy: Autologous Stem Cell Transplantation

AutoSCT in Renal Failure: The UAMS Experience

- 81 pts with RF treated at the University of Arkansas for Medical Sciences (UAMS) from 10/1996 through 10/2000.
  - Renal failure defined as a Cr>2.0 mg/dL.
  - 38 pts dialysis-dependent.
- Median age: 53 (median age at diagnosis for MM pts: 70)
- 78% Durie-Salmon stage IIIB disease, 47% light chain disease
- The first 60 pts received melphalan 200 mg/m^2 (100 mg/m^2/d x 2d)
  - The last 21 pts received 140 mg/m^2 (single dose) due to toxicity with the 200 mg/m^2 dose.
- 31 pts received a second transplant
  - Dose 140 mg/m^2 – 200 mg/m^2.

Badros et al. *Br J Haematol.* 2001 Sep; 114(4): 822-9.

AutoSCT in Renal Failure: Efficacy

- Median EFS and OS: 23 mos and >52 mos
- Dialysis dependence and melphalan dose had no impact on outcome.
- No difference between single vs. tandem SCT
- Older age and low albumin were associated with worse outcome.

	MEL-140 (N=21)	MEL-200 (N=60)	HD (N=38)	No HD (N=43)
CR rate	35%	33%	37%	33%
Median EFS	>21 mos	20 mos	20 mos	24 mos
Median OS	>21 mos	>52 mos	>51 mos	>52 mos

Badros et al. *Br J Haematol.* 2001 Sep; 114(4): 822-9.

AutoSCT in Renal Failure: Renal Recovery

- 59 pts with dialysis-dependent RF underwent autoSCT at UAMS
  - 23 underwent tandem transplantation
  - Nephropathology (N=28): 15 MCN, 10 LCDD, 2 LHCDD, 1 amyloidosis
- 24% became dialysis-independent
  - 5 of 10 with LCDD, 6 of 15 with MCN
- Transplant-related mortality (TRM): 19%

Predictors of Renal Recovery: Univariate Analysis

Factor	Renal Recovery	*P* Value
Dialysis duration: ≤6 mos vs. >6 mos	33% vs. 6%	0.03
CrCl at SCT: >10 mL/min vs. ≤10 mL/min	38% vs. 11%	0.04
CR/nCR vs. ≤PR	39% vs. 5%	0.04

Lee et al. *Bone Marrow Transpl.* 2004; 33 823-8.

AutoSCT in Renal Failure: Toxicity

Incidence of Adverse Events in Patients with Cr>2.0 mg/dL (%)

≥ Grade 2 Toxicities	MEL-140 (N=18)	MEL-200 (N=28)	*P* Value	HD (N=30)	No HD (N=16)	*P* Value
Vomiting	72	79	0.7	70	88	0.3
Mucositis	67	93	0.04	77	94	0.2
Diarrhea	44	68	0.1	53	69	0.3
Infection	56	43	0.4	40	62	0.15
Pulmonary	17	57	0.007	53	19	0.02
Hypotension	5	25	0.12	20	12	0.7
Dysrhythmia	0	21	0.07	17	6	0.6
Neurologic	27	36	0.6	47	6	0.005
Rash	27	36	0.6	10	75	<0.0001
TRM	5 (N=21)	6 (N=60)	0.4	5 (N=38)	16 (N=43)	0.2

- Stem cell mobilization and engraftment kinetics not affected by RF

Badros et al. *Br J Haematol.* 2001 Sep; 114(4): 822-9.

AutoSCT in Renal Failure: Transplant-Related Mortality (TRM)

Study	N	RF Defined	TRM	Predictors of TRM
Badros et al, 2001	81	Cr>2.0 mg/dL	1st SCT: 6% 2nd SCT: 13%	
San Miguel et al, 2000	Cr (diagnosis→ pre-transplant) Nl→nl (479) Abn→nl (73) Abn→abn (14)	Cr≥2.0 mg/dL	 3.3% 4.1% 29.0%	ECOG PS≥3, Hb<9.5 g/dL, Cr≥5 mg/dL
Knudsen et al, 2005	Cr (diagnosis→ pre-transplant) Nl→nl (78) Abn→nl (30) Abn→abn (29)	CrCl<60 mL/min	 1.0% 0.0% 17% (4 of 8 on dialysis)	
Bird et al, 2006	27 (23 with MM, 4 with AL amyloid)	Dialysis dependent or CrCl<20 mL/min	18.5%	

- The most common reported causes of TRM in these studies were sepsis, pneumonia, and multi-system organ failure NOS.

Efficacy of Emerging Lenalidomide- and Bortezomib-based Regimens for Newly-Diagnosed MM

Regimen	Trial	Phase	No. of Pts	ORR*	VGPR	CR/nCR
RVD	Richardson, 2008	II	68	100%	30%	44%
VRCD	Kumar, 2008	II	26	100%	32%	36%†
CyBorD	Reeder, 2008	II	33	97%	21%	39%
VTD	Cavo, 2008	III	226	94%	30%	32%
VDD	Jakubowiak, 2008	II	30	93%	23%	40%
PAD	Sonneveld, 2008	III	150	83%	37%	5%
VD	Harousseau, 2008	III	223	82.5%	27.3%	19.3%
MPV	San Miguel, 2008	III	337	71%	--	30%†
Rd	Rajkumar, 2008	III	222	70%	26%	14%

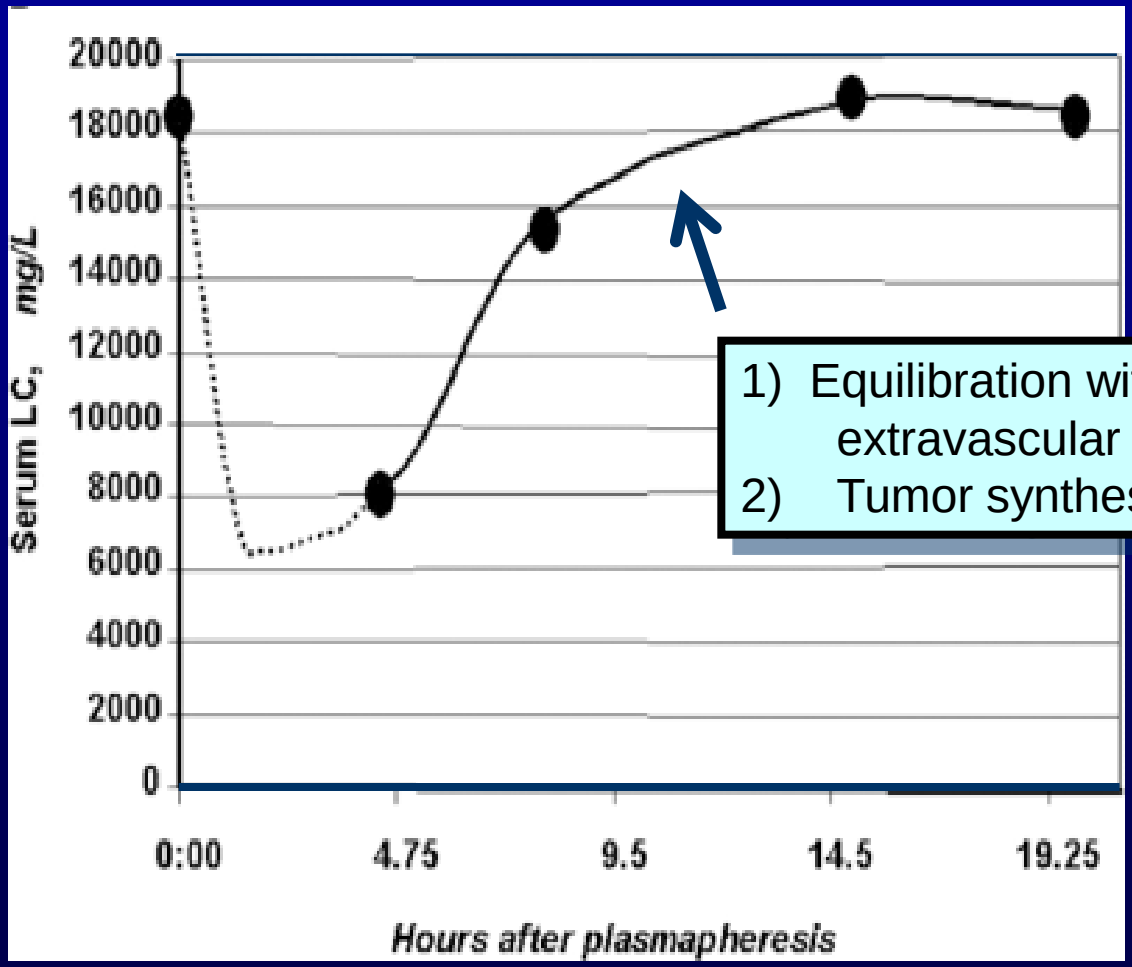
*ORR=PR or better. †CR only

A=doxorubicin; Bor=bortezomib; C=cyclophosphamide; Cy=cyclophosphamide; D=dexamethasone; P=bortezomib; R=lenalidomide; T=thalidomide; V=bortezomib; M=melphalan; P=prednisone; VDD=bortezomib/liposomal doxorubicin/dexamethasone, Vel=bortezomib.

Richardson. *ASH*. 2008 (abstr 92); Kumar. *ASH*. 2008 (abstr 93); Knop. *ASH*. 2008 (abstr 2776); Sonneveld. *ASH*. 2008 (abstr 653); Reeder. *ASCO*. 2008 (abstr 8517); Jakubowiak. *ASH*. 2008 (abstr 3713); Cavo. *ASH* 2008 (abstr 158); Harousseau. *ASCO* 2008 (abstr 8505), San Miguel. *ASH* 2008 (abstr 650); Rajkumar. *ASH* 2008. Joint ASH/ASCO Symposium.

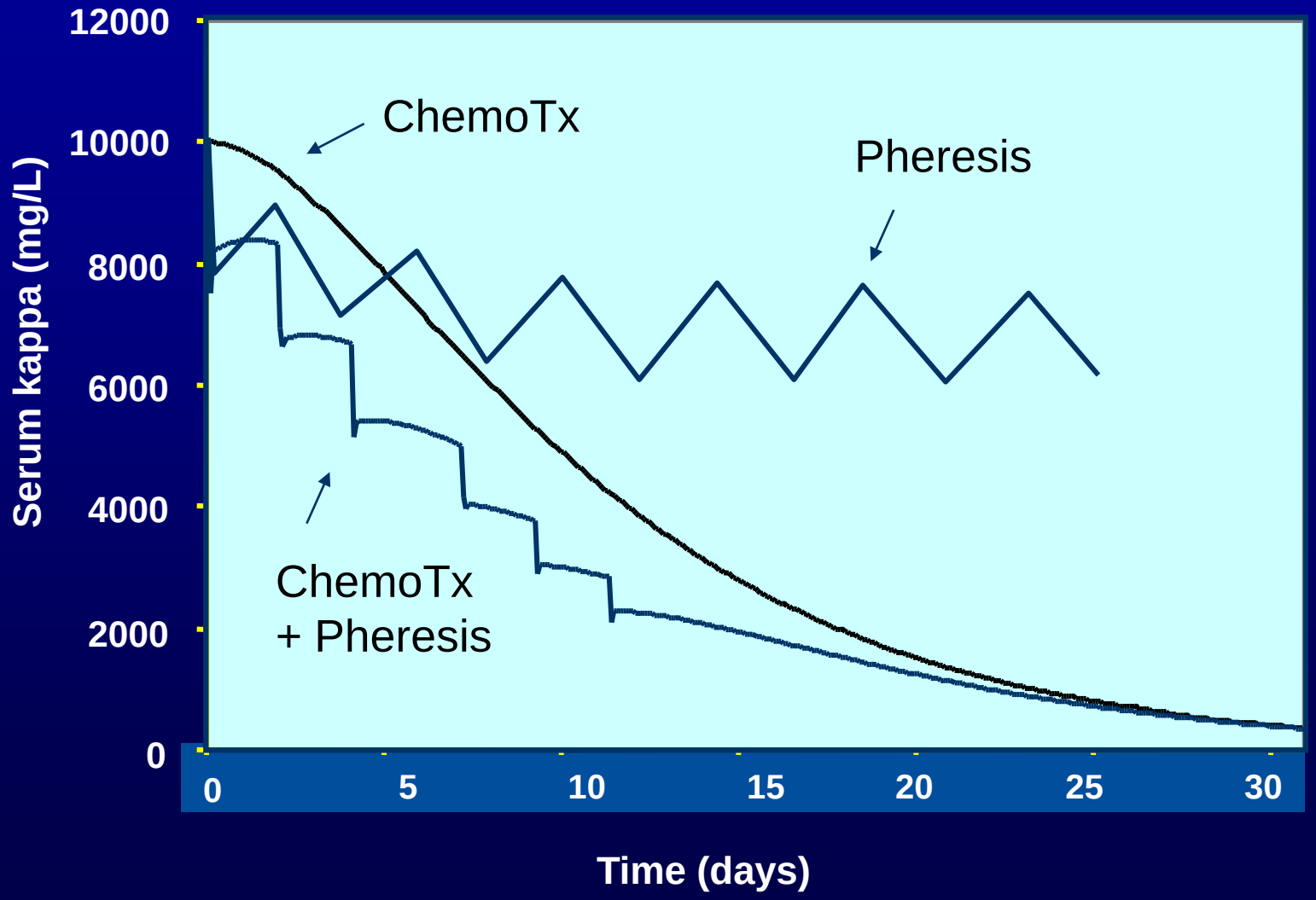
Advances in Myeloma Therapy: Mechanical Clearance of Free Light Chains

Free light chain (FLC) removal with plasmapheresis



Adapted from: Cserti, C. et al. Transfusion. 47:511-514, 2007

FLC removal with plasmapheresis



Adapted from: Hutchison, CA. et al. CJASN. 18:886-895, 2006

The Role of PLEX in MCN

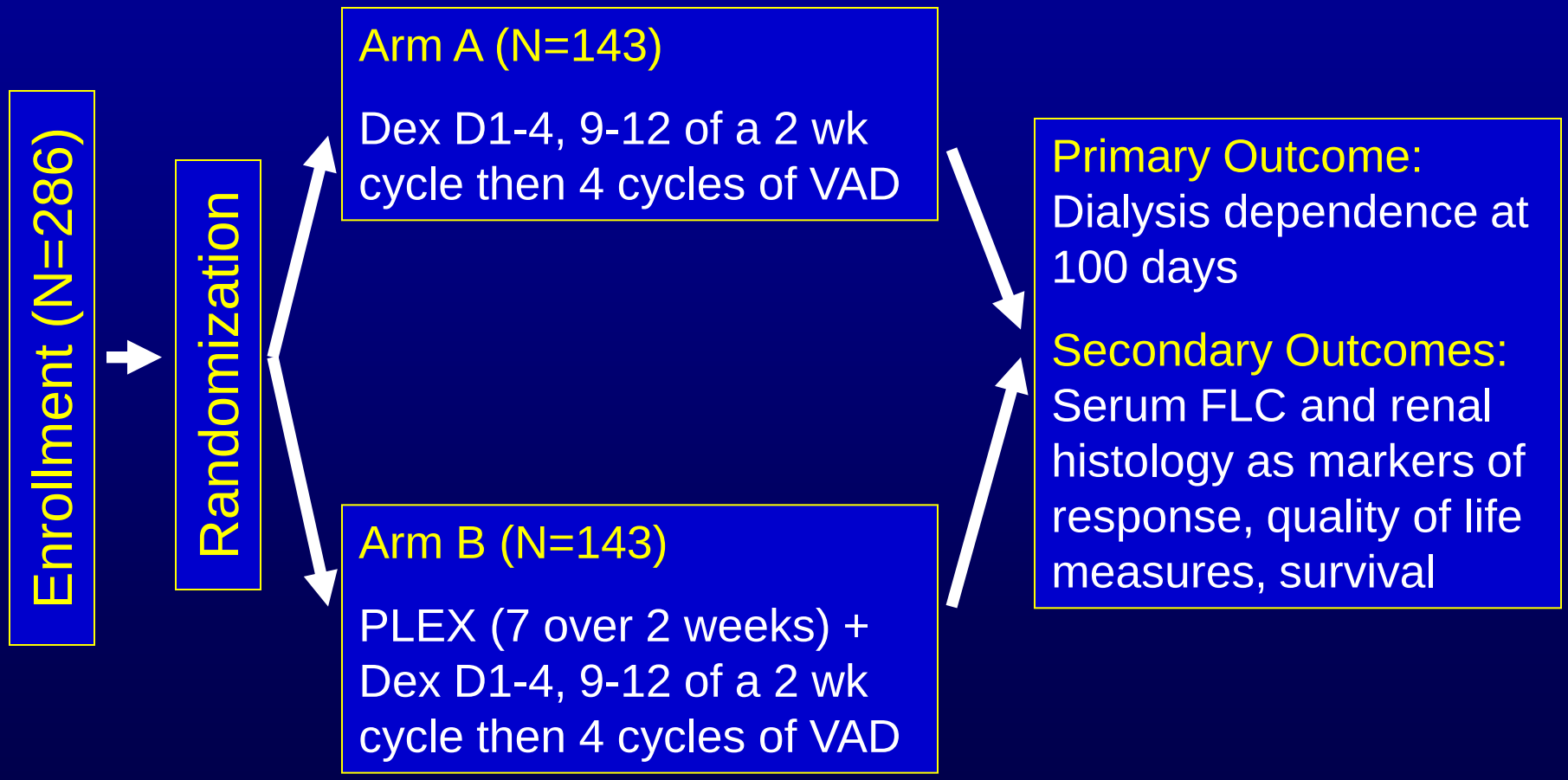
Author	N	Dialysis Independence		P Value
		PLEX	No Plex	
Zucchelli 1988	29 (19 newly diagnosed)	11/15	2/14	<0.01
Johnson 1990	21 newly diagnosed	5/10	4/11	NS
Clark 2005	97 newly diagnosed	36/58*	27/39*	NS

* Primary end-point a composite measure of death, dialysis dependence, or glomerular filtration rate less than 30 mL/min per 1.73 m^2

- Small samples sizes, rigor of restricting eligibility to MCN, and lack of serial LC measurements to assess efficacy of intervention make interpretation of these studies difficult.
- The role of PLEX in MCN remains uncertain.

MERIT: MyEloma Renal Impairment Trial

• A multicenter, phase III study of dexamethasone-based chemotherapy +/- PLEX for pts with newly-diagnosed MM and ARF.



• Patient recruitment complete.

High Cut-Off HD (HCO-HD) in MM

- Light chains are low molecular weight proteins
  - κ light chain 25 kD, λ light chain 50kD
  - Comparable levels in intra- and extravascular compartments
  - Predicts for inefficient clearance of FLCs via PLEX.
- Extended HD using protein-leaking dialyzers an attractive alternative approach to FLC clearance.

The Gambro HCO 1100 dialyzer. Surface area: 1.1 m^2, molecular cut-off in blood: 45 kD.

HCO-HD in MM Patients

- The Gambro HCO 1100 dialyzer outperformed the Toray BK-F 2.1 and the B. Braun Hi-Pes 18 in *in vitro* ultrafiltration studies and in vivo studies in MM pts.
- Two dialyzers in series was better than one.
- Longer sessions led to greater ↓ in serum FLC [ ].

Extended HCO-HD and chemotx in 5 pts with newly-diagnosed MCN

Age	Myeloma Type	Baseline FLC [ ] (mg/L)	Mean % ↓ in FLC [ ]*	Mean Dialysate FLC [ ] mg/L*	Outcome
68	IgGκ	1030	45	18.1	eGFR 49 mL/min at 9 mo
51	IgAκ	42,000	36-75	439-515	ESRD
61	IgAκ	13,500	35.1-81	193-307	eGFR 29 mL/min at 4 mo
68	IgGλ	1120	66.4-80.4	34-46	ESRD
81	IgGλ	110	58-74	13.7-28.9	eGFR 36 mL/min at 3 mo

* Mean expressed as a range for those subjects who underwent HD with different numbers of dialyzers in series.

Hutchison et al. *J Am Soc Nephrol.* 2007 Mar; 18(3): 886-95.

Modeling Extended High Cut-Off HD in MCN

FLC Clearance Efficiency
Percentage of FLC Removed by Intervention with Different Daily Chemotherapeutic Tumor Killing Rates

Intervention	100%	10%	5%	2%	0%
None	--(14)	--(30)	--(52)	--(114)	--(10 g/L)
PEx6 in 10 days	29(10)	24(29)	17(52)	9(121)	3(10 g/L)
HD 4 h 3d/wk	60(7)	54(19)	53(31)	51(73)	50(3.6 g/L)
HD 4 h/d	76(4)	73(13)	72(23)	71(55)	70(1.9 g/L)
HD 8 h/d	87(3)	85(7)	84(14)	83(29)	82(1.0 g/L)
HD 12 h/d	91(2)	89(5)	89(8)	88(16)	88(0.7 g/L)

Days needed to reduce the serum FLC [ ] from 10 g/L to 0.5 g/L indicated in parentheses.

A two-compartment mathematical model of FLC homeostasis in multiple myeloma demonstrates that HCO-HD (HD) is more effective at clearing FLCs than PLEX (PE).

Hutchison et al. *J Am Soc Nephrol.* 2007 Mar; 18(3): 886-95.

HCO-HD in MM Patients: A Pilot Study

- April 2006-May 2008: A single center, prospective pilot study of HCO-HD + chemotx for pts with MCN requiring HD
- 19 pts with biopsy-proven MCN included
- 2 HCO 1100 dialyzers used in series
- Schedule: 8 h daily for 5 d, 8 h every other day for 12 d, 6 h 3x/wk thereafter

Patient Demographics

Age, years	60 (38-81)
Male, %	74%
Cr µmol/L	714 (427-1508)
eGFR	7 (3-13)
K FLCs	50%
Serum FLC [ ], g/L	2.6 (0.8-69)

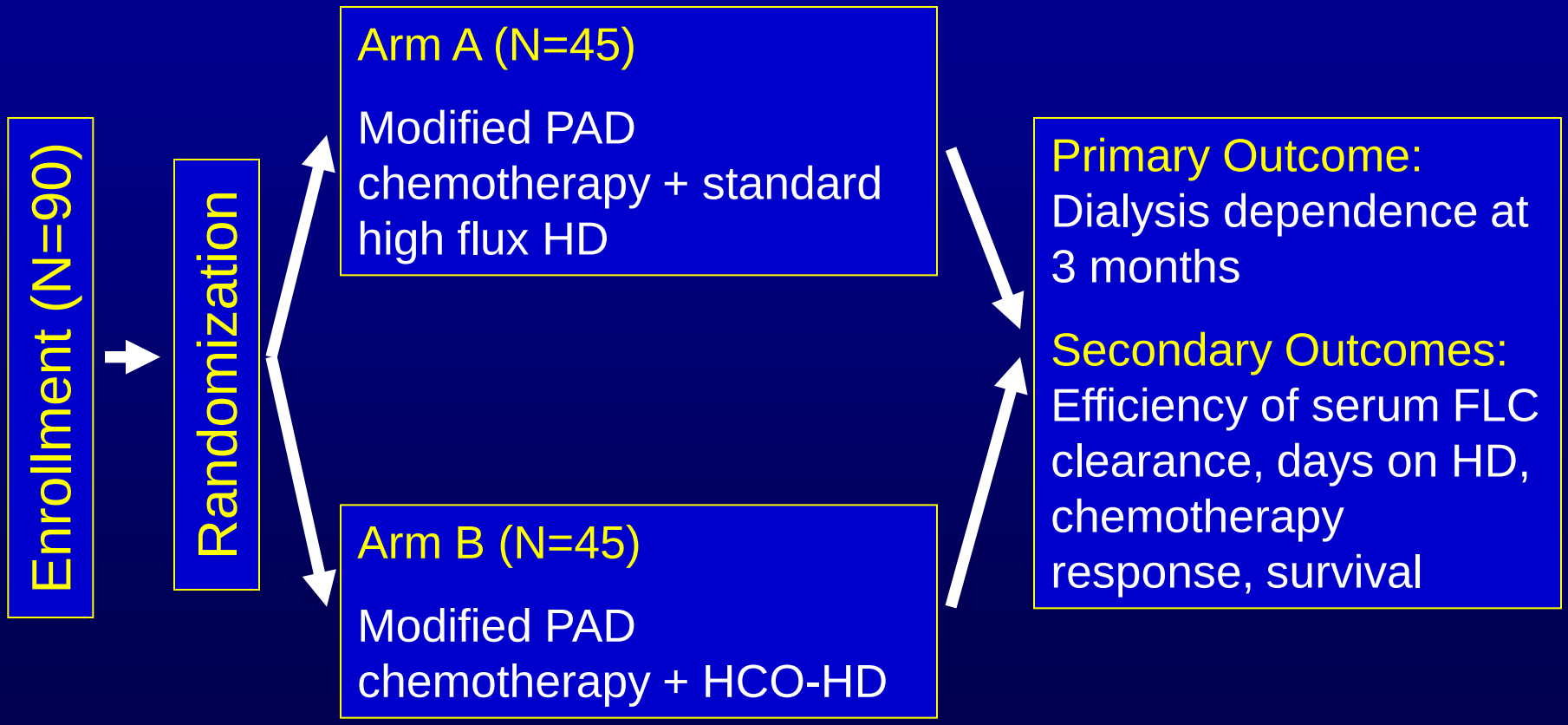
Results

- 14 of 19 pts became HD independent
- Early interruption of chemotherapy associated with worse renal outcome ($p<0.002$)
- HCO-HD well tolerated
  - Albumin, Ca, and Mg supplementation required for 19, 12, and 15 pts, respectively.

Hutchison et al. *Clin J Am Soc Nephrol.* 2009 Apr; 4(4): 745-54.

The EuLite Study

• A multicenter, phase III study of bortezomib-based chemotherapy +/- HCO-HD for pts with newly-diagnosed MM and biopsy-proven MCN.



PAD=Bortezomib 1.0 mg/m^2 D1, 4, 8, 11; doxorubicin 9 mg/m^2 D1, 4; dexamethasone 40 mg D1-4, 8-11, 15-18 on cycle 1, D1-4 only thereafter. 1 cycle=3 weeks.

Hutchison et al. *Trials.* 2008 Sep; 28: 55.

Novel Agents for the Treatment of AL Amyloidosis

Regimen	Study Design	N	New Dx vs. Rel/Ref	ORR (CR)	Time to response	Organ Response Rate
Bort +/- Dex	Retro	94	19%/81%	71% (25%)	1.7 mo.	30%*
Bort	Prosp Phase I	31	0%/100%	50% (20%)	1.2 mo.	NR
Bort +/- Dex	Retro	20	0%/100%	80% (15%)	3 cycles (9 wks)	38%
Len +/- Dex	Prosp Phase II	34	9%/91%	67% (29%) 47% ORR by ITT	6 cycles (24 wks)	NR
Len +/- Dex	Prosp Phase II	23	43%/57%	75% (41% ORR by ITT)	6.2 mo.	42% (23% by ITT)

* Organ response based on hematologic response (HR) vs. no HR: 44% vs. 0% ($p<0.0001$); CR vs. PR: 64% vs. 32% ($p=0.001$)

Kastritis et al. *J Clin Oncol.* 2010; 28(6): 1031-7.
Reece et al. *Blood.* 2009 ; 114: 1489-97.
Wechalekar et al. *Haematologica.* 2008; 93(2): 295-8.
Dispenzieri et al. *Blood* 2007; 109(2): 465-70.
Sanchorawala et al. *Blood* 2007; 109(2): 402-6.

Concluding Remarks

- The novel agents lenalidomide and bortezomib have led to the development of combination therapies with unprecedented activity in MM.
  - Efficacy profile approaching that of autologous stem cell transplantation.
  - Responses are rapid and deep.
- Dose modifications of bortezomib are not necessary in renal failure.
  - Safety in renal failure comparable to those with normal renal function.
- Dose modifications of lenalidomide are necessary in renal failure.
  - Preliminary safety data of dose-adjusted lenalidomide encouraging but limited.

Concluding Remarks

- The role of autologous SCT in the setting of renal failure remains poorly defined.
  - Renal failure alone should not be used as an exclusion to SCT
  - Proceed with caution in those patients with advanced renal failure and poor performance status
  - Lower doses of melphalan appear to be better tolerated
- The role of clearing light chains via PLEX or HCO HD in the era of modern MM therapy remains to be determined.
  - PLEX may have a role as an adjunct to effective tumor burden reduction
    - Target ≥50% light chain reduction
  - HCO HD + chemotherapy highly promising.

Concluding Remarks

- Clinical trials targeting patients with renal failure needed
  - Uniform definition of renal failure and renal improvement
  - Rigorous identification of the cause of renal failure
- Further studies refining the role of newer MM therapies in the treatment of other plasma cell dyscrasias are eagerly awaited.
  - Preliminary data with bortezomib in AL Amyloidosis encouraging.