

## Renal Impairment in Multiple Myeloma

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## Prevalence of Renal Impairment in Multiple Myeloma

- 20- 30% of patients have renal impairment at presentation<sup>1,2</sup>
- 50% at some time
- Severe renal failure is a serious complication of myeloma
- 2- 5% of myeloma patients require long-term dialysis
- Increased risk of infections and early death<sup>3</sup>

1. Alexanian et al. Arch Intern Med 1990;150:1693-1695.  
 2. Kyle et al. Mayo Clin Proc 2003;78:21-33  
 3. Blade et al. Arch Intern Med 1998;158:1889-1893

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## Causes of Renal Impairment in Patients With Multiple Myeloma

Tubulopathic Light chains	Other causes of renal impairment
Cast nephropathy	Infection
Fanconi Syndrome	Nephrotic drugs – particularly NSAIDS
	Hypercalcaemia/Dehydration
Glomerulopathic Light chains	Hyperuricaemia
Amyloidosis	Myeloma cell infiltration
Light chain deposit disease	Renal vein thrombosis
	Contrast media

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## Resorption and Degradation of FLCs and Formation of FLC – Tam Horsfall Protein Complexes

CDR3 region + Tam Horsfall protein

Proximal renal tubule – site of physiological resorption of FLCs

10-30 g/day  
 3-5 mg FLC/day  
 $\kappa:\lambda$  Ratio 0.63

Light chains are resistant to catabolism and pro-inflammatory ILN-6, -8, and TNF- $\alpha$ , activation of NF- $\kappa$ B and mitogen activated protein kinases

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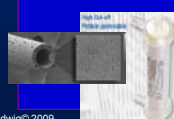
## Management of Light Chain Induced Renal Impairment

- Prompt diagnosis
- Exclude/treat potential additional precipitating factors
- Prompt, effective treatment of myeloma with **fast and complete elimination of nephrotoxic light chains**
  - Conventional CT, autologous transplantation
  - **Thalidomide, Bortezomib, Lenalidomide**
- Accelerated clearance of free light chains
  - Plasmapheresis ?
  - New dialysis membranes ?

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## Symptomatic Management, Plasmapheresis and Dialysis with a new Membrane

- Discontinuation of any nephrotoxic drug
- Fluid replacement
- Alkalinization of urine (sodium bicarbonate)
- Treatment of hypercalcaemia
- Plasmapheresis - *not established*
- Long term dialysis with new membrane – *not established*



Permeable for proteins  $\leq$  45 KD, excludes coagulation factors, not thrombogenic

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### Randomized Trials Comparing Plasmapheresis (exchange) + Hemodialysis with Hemodialysis only

Author	Number of Patients	Off dialysis at the end		P=
		With plasma exchange	Without plasma exchange	
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 composite end-point death, dialysis dependence or crcl <30

**Benefit of Plasmapheresis not established**

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### Thalidomide ± Dexamethasone in Patients with Renal Impairment/Failure

- Pharmacokinetics similar in patients with or without renal failure<sup>1</sup>, only small amount cleared by kidneys<sup>2</sup>
- Tosi et al., 20 patients with in renal failure<sup>3</sup>
  - CR + PR 45%
  - Renal recovery in 12/15 (80%) patients who had myeloma response
- Toxicity
  - Rarely severe hyperkalemia in renal failure<sup>4</sup>
  - ↑nephrotoxicity of aminoglycoside ABs in MM<sup>5</sup>
  - Neuropathy, constipation, lethargy, and bradycardia more frequent when creatinine ≥3 mg/dL<sup>6</sup>

1. Izzedine et al. *Nephrol Dial Transplant* 2005;20:2011-2012  
 2. Eriksson et al. *J Pharm Pharmacol* 2003;55:1701-1706  
 3. Tosi et al. *Contrib Nephrol* 2004;173:95-103  
 4. Harris et al. *Br J Haematol* 2003;122:169-181  
 5. Montgaut et al. *Leuk Lymphoma* 2004;45(8):1711-1712  
 6. Pineda-Roman et al. *Contrib Nephrol* 2007;153:182-194

### Lenalidomide in Patients with Renal Impairment/Failure (Subanalysis of Phase 3 Len/Dex trials<sup>1</sup>)

- Primarily excreted by kidneys

	No RI CrCl >80 mL/min (n=158)	Mild RI CrCl 50 <sub>2</sub> - <80 mL/min (n=125)	Moderate RI CrCl 30 <sub>2</sub> - <50 mL/min (n=42)	Severe RI CrCl <30 mL/min (n=16)
ORR	64%	64%	62%	50%
OS	Not reached	34.7 months	30.4 months	18.6 months*
Lenalidomide dose reductions for AEs	17%	34%	40%	38%

\*P<0.01 vs no RI

**Dose reduction of Lenalidomide in patients with impaired renal function is mandatory<sup>3,4</sup>**

1. Weber et al. ASCO 2008 (Abstract 8542)  
 2. *Haematologica* 2006;108 (abstract 3548)  
 3. Revlimid SmPC June 2007  
 4. Chen et al. *J Clin Pharmacol* 2007;47:1466-1475

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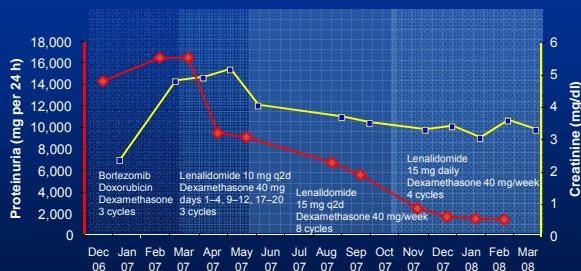
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**Dose reduction of Lenalidomide in patients with impaired renal function is mandatory<sup>3,4</sup>**

**Of 174 patients with renal insufficiency, 68% had improvement in their renal function by at least one level within 4 months.**

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### Patient with λ Light Chain Induced Renal Failure Resistant to Bortezomib and Rescued with Lenalidomide Dexamethasone



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Ludwig et al. 2008

### Ongoing Phase II Study: Lenalidomide and Dexamethasone for Patients with Acute Myeloma (light chain)-induced Renal Failure



- Primary goals:** Reversal of renal failure  
Myeloma response rate
- Secondary goals:**  
 PFS, OS  
 Relationship - myeloma response and improvement in GFR  
 Proportion of patients spared of hemodialysis

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### Rationale for the use of Bortezomib in Patients with Myeloma-induced Renal Impairment

- Short time to response<sup>1</sup>
  - Median time to initial response: 1.2 months
  - First response within 4 cycles: 86%
- High overall and complete responses
- Well tolerated; toxicity similar in patients with and without renal impairment<sup>4,5</sup>
- Half-life independent of renal clearance<sup>3</sup>
- Reduces inflammation in myeloma kidney disease<sup>2</sup>

1. Richardson P *et al. Blood* 2005;106:(Abstract 2547)  
 2. Ludwig *et al. Haematologica* 2007;92:1411-1414  
 3. Mulkering *et al. Blood* 2007;110:(Abstract 3477)  
 4. Jagannath S *et al. Cancer* 2005;103:1195-2000  
 5. Chanan-Khan *et al. Blood* 2007;109:2604-2606

### Phase II: Recovery of Renal Impairment by Bortezomib-Doxorubicin-Dexamethasone in Acute LC-Induced Renal failure

Number of patients/evaluable patients (≥2 cycles)	71/58
Age median (range)	66.0 (40.7 – 79.1)
Newly diagnosed MM, n=	47
Previously diagnosed	11
ISS Stage I	2
ISS Stage II	6
ISS Stage III	50
Number of prior treatment lines	
1	4
2	6
>3	1
Serum baseline paraprotein	
IgG (g/l), median (range), n=18	46.3 (3.1-106.0)
IgA (g/l), median (range), n=10	20.8 (3.2-48.4)
IgD (g/l), median (range), n=3	16.4 (8.1-49.6)
Kappa light chain (mg/l), median (range), n=14	6.360 (1.690-18.000)
Lambda light chain (mg/l), median (range), n=13	6.143 (755-51.000)
Urine baseline 24 hrs LC excretion mg (median)	4.500 (247 – 47.700)

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Ludwig *et al. ASH* 2008 (Abstract 3682)

### Recovery of Renal Function by Bortezomib-Doxorubicin-Dexamethasone: Tumor and GFR Response

#### Results

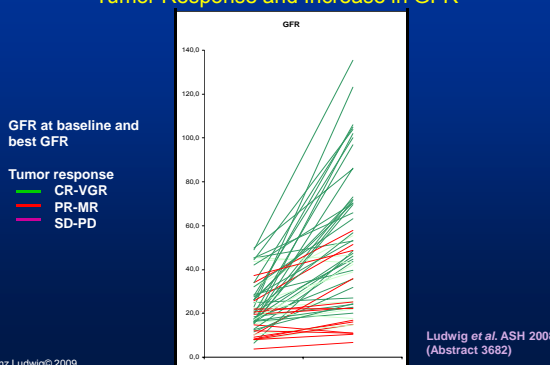
- ORR (including MR): 76%, ≥VGPR 58%
- Time to response (median): 4.2 months
- Number of cycles (median): 8 (range 2-8)
- Myeloma responses correlated with renal response

Tumor response	n	N total (%)	Best GFR Median (range)
CR	16	34 (58.6%)	64.6 ml/min (20.2-135.5)
nCR	11		
VGPR	7		
PR	5	10 (17.2%)	30.7 ml/min (14.7-55.3)
MR	5		
SD	12	14 (24.1%)	19.6 ml/min (6.7-57.9)
PD	2		

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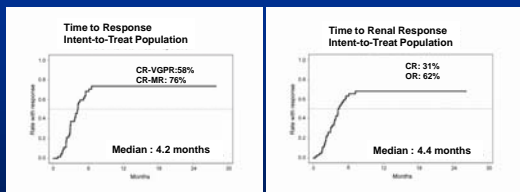
Ludwig *et al. ASH* 2008 (Abstract 3682)

### Recovery of Renal Impairment by Bortezomib-Doxorubicin-Dexamethasone: Correlation Between Tumor Response and Increase in GFR



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### Time to Myeloma and Time to Renal Response with Bortezomib-Doxorubicin-Dexamethasone

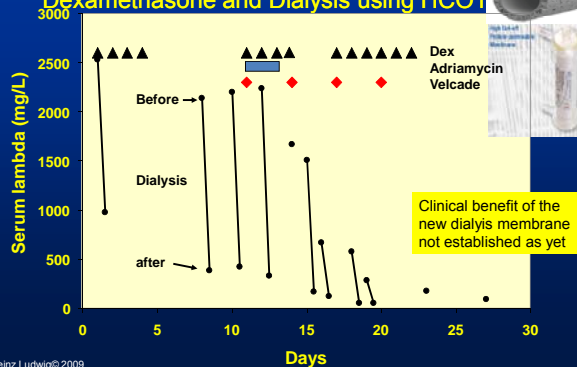


The better the myeloma response – the higher the chance for recovery of renal function  
 Patients with GFR <15ml/min – less likely to achieve a renal response

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Ludwig *et al. ASH* 2008 (Abstract 3682)

### Light Chain Concentration after Dexamethasone TX followed by Bortezomib-Doxorubicin-Dexamethasone and Dialysis using HCO<sub>3</sub>



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### Conclusion

- Light-chain induced renal failure – a frequent complication of progressive myeloma – often an emergency situation
- Cast nephropathy most common complication
- Rapid reduction of nephrotoxic light chains essential
- Management has been improved lately
- Tumor response correlates with renal recovery
- Impact of new dialysis membrane and prolonged dialysis time unclear
- Novel drugs highly effective
- Further studies ongoing



Greetings from Vienna



Thank you for your attention