

# Bortezomib

## In Patients with Renal Failure

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# Renal Impairment in Myeloma

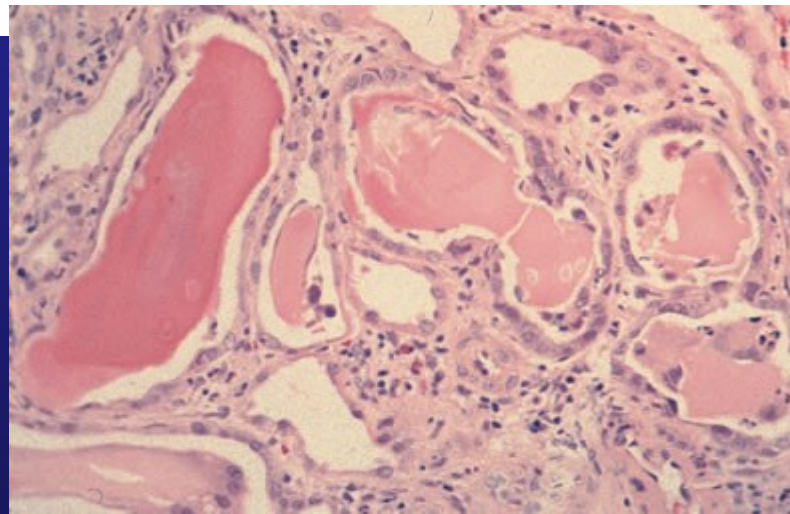
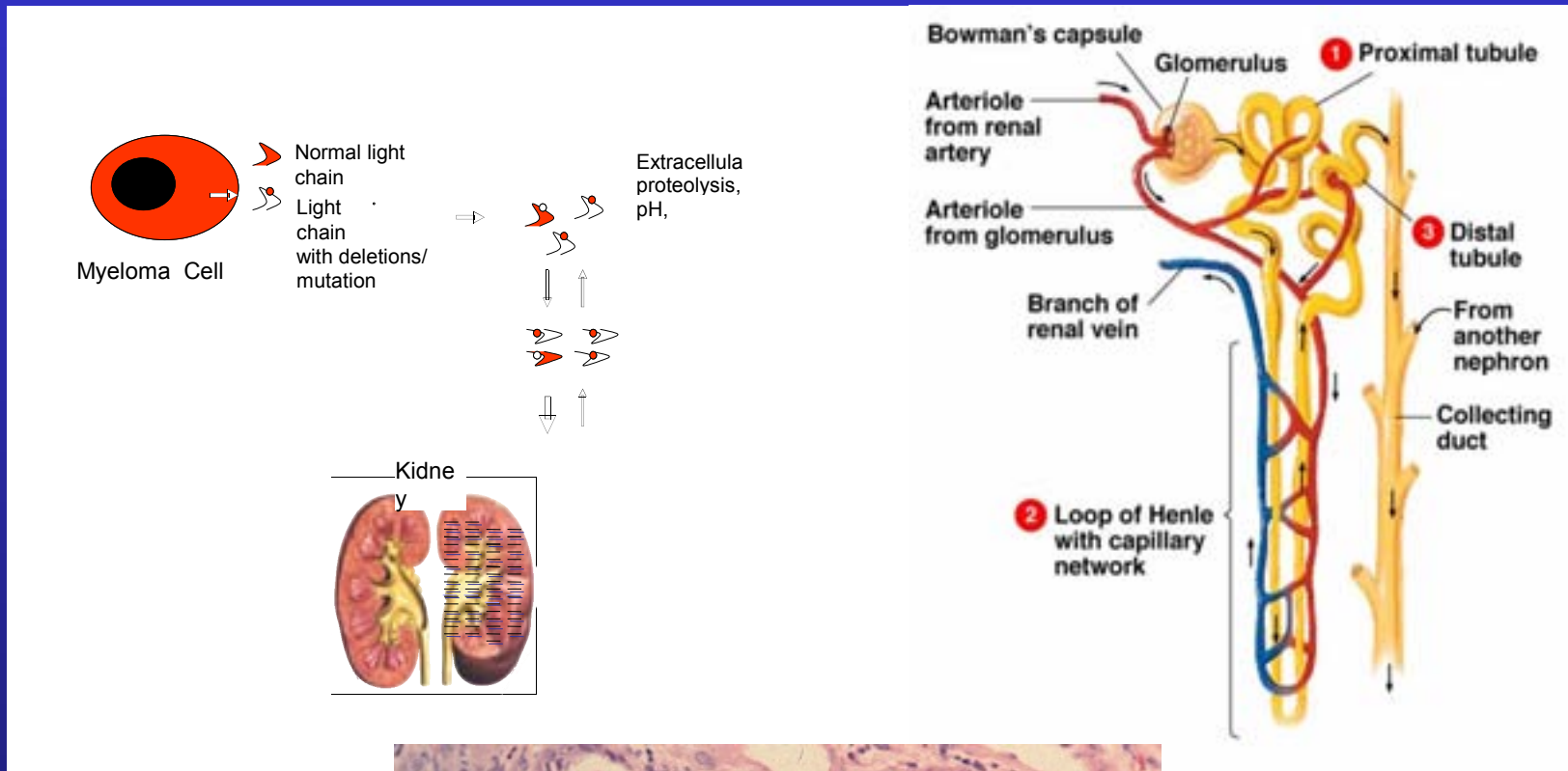
- Severe renal failure is an important complication of myeloma
- 20- 30% of patients have renal impairment at presentation
- 50% of patients at some time
- 2- 5% of patients require long-term dialysis
- Increased mortality



# Frequent Causes of Renal Failure in Multiple Myeloma

1. Hypercalcaemia
3. Light chain damage
4. Dehydration
5. Nephrotic drugs – particularly NSAIDS
5. Infection
6. Hyperuricaemia
7. Plasma cell infiltration
8. Amyloidosis

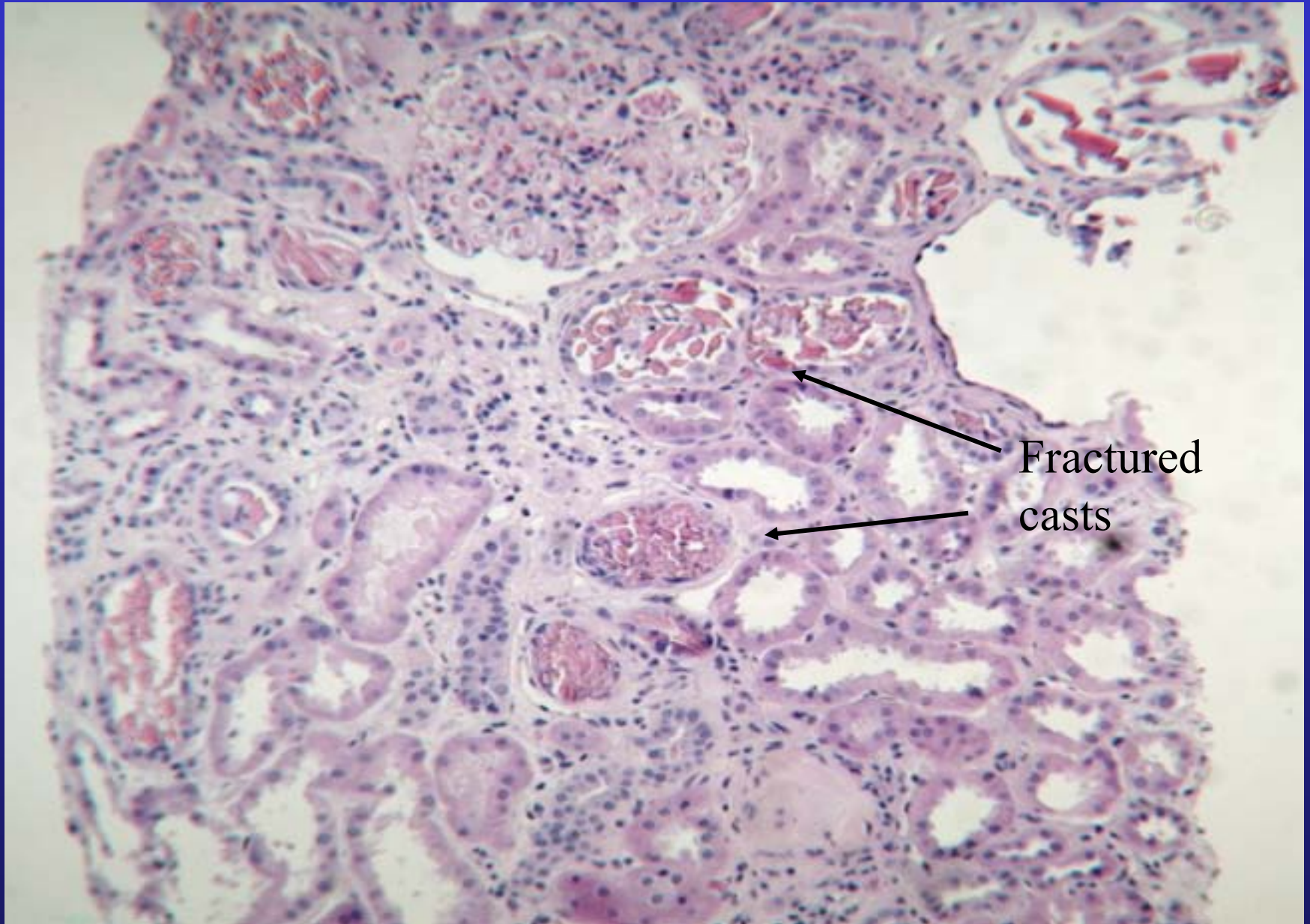
# Mechanism of Light Chain-Induced Renal Damage

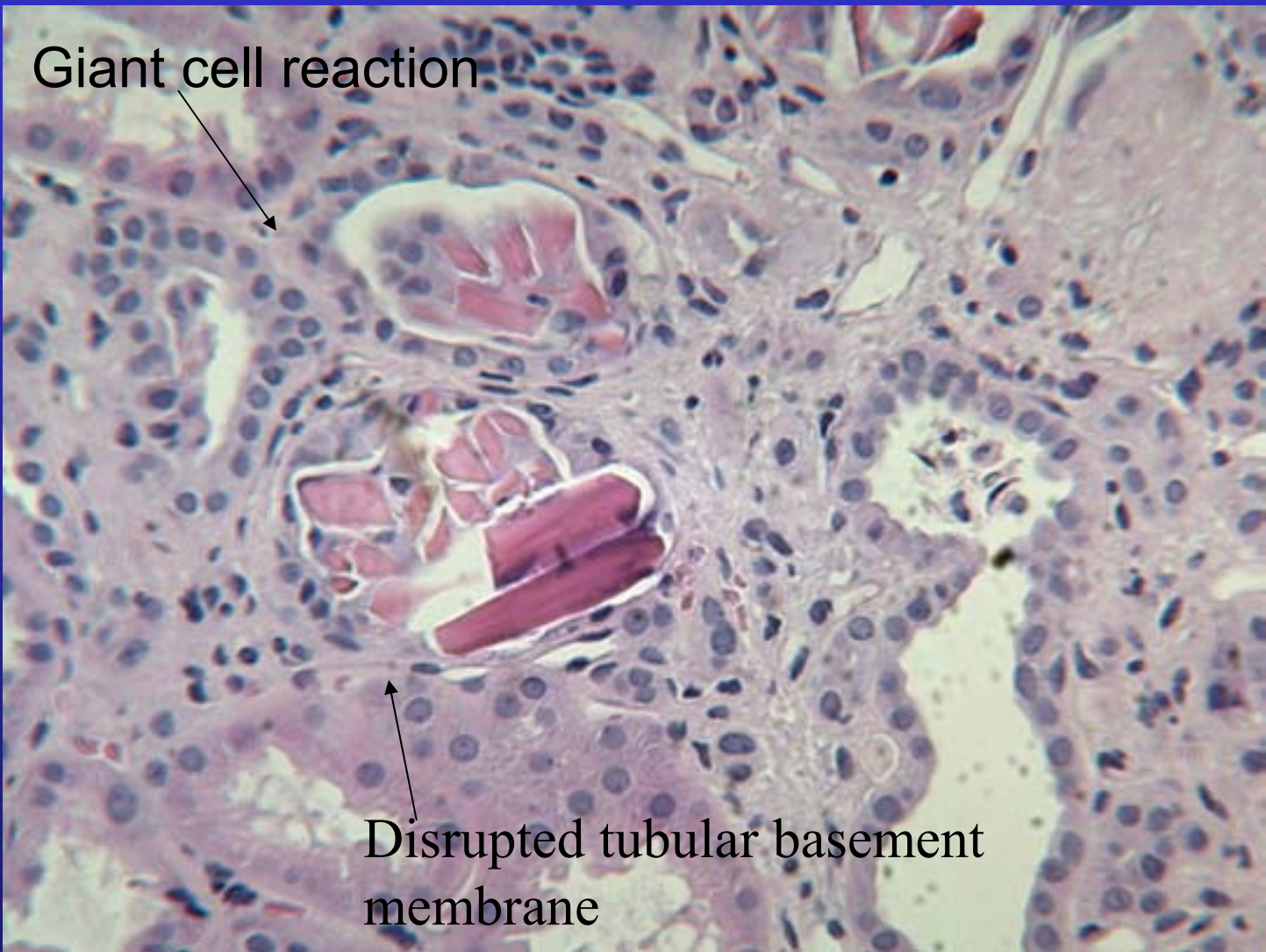


Proximal renal tubule –  
site of physiological resorption

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

# Myeloma Kidney



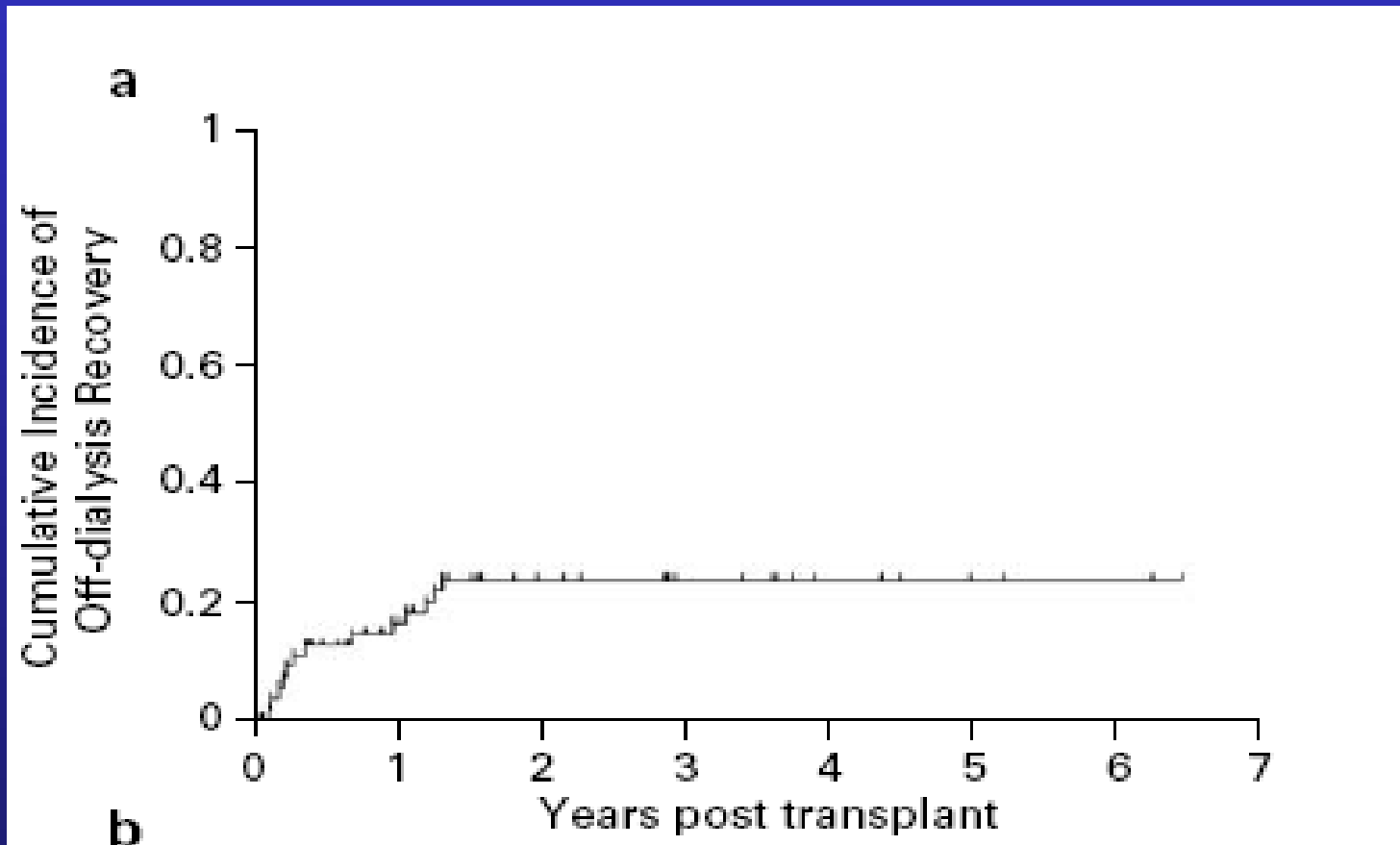


# Prospective Randomized Trials Comparing Plasmapheresis (exchange) + Hemodialysis with Hemodialysis only

Author	# Pts	Off dialysis at the end		P=
		With plasma exchange	Without plasma exchange	
Zucchelli 1988	19/29 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

# Reversal of Renal Function by High Dose Melphalan and Autologous Transplantation



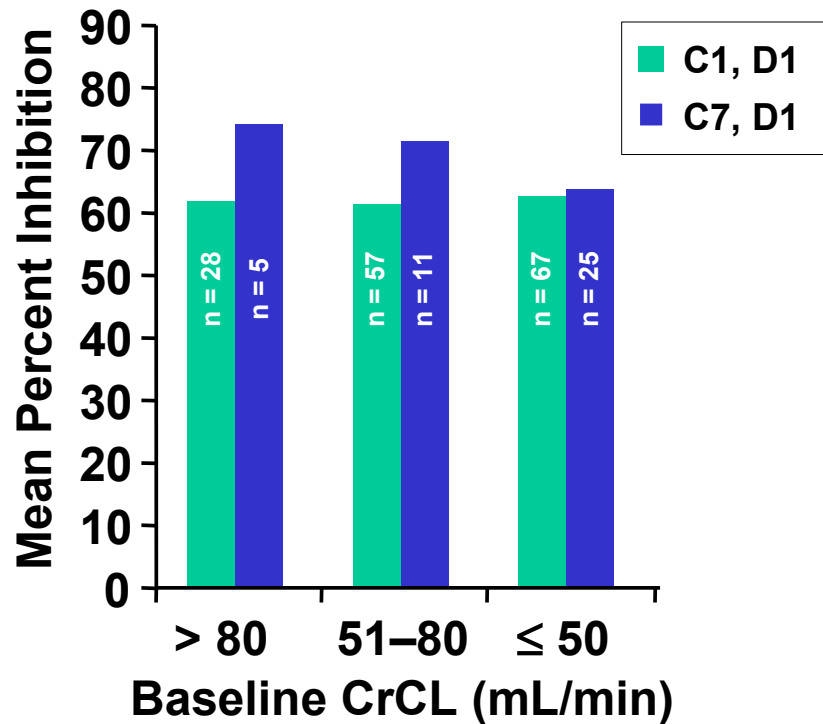
Duration of Dialysis and Pre Transplant GFR (>10ml/min)  
Predictors for Recovery

# Rationale for Use of Bortezomib Combination Therapy in Patients with Renal Failure

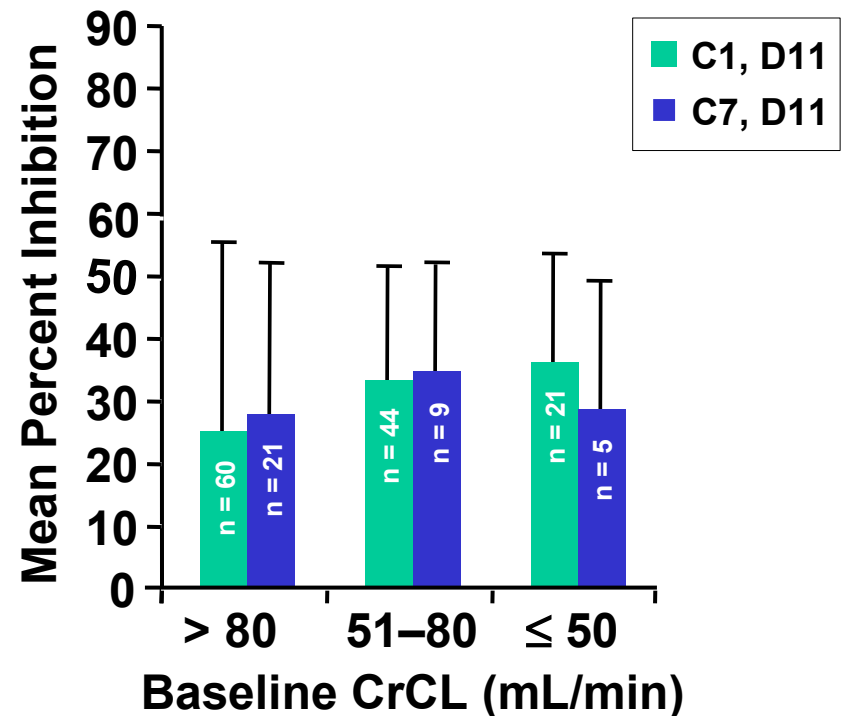
1. Significant activity in patient with relapsed MM
2. Increased efficacy with addition of dexamethasone
3. Synergy with other myeloma treatments
4. Inhibition of NF $\kappa$  B reduces peritubular inflammation
5. All of above
6. None of above

# Proteasome Inhibition and Recovery Independent of Renal Function

**A. Maximal proteasome inhibition (1 hr)**

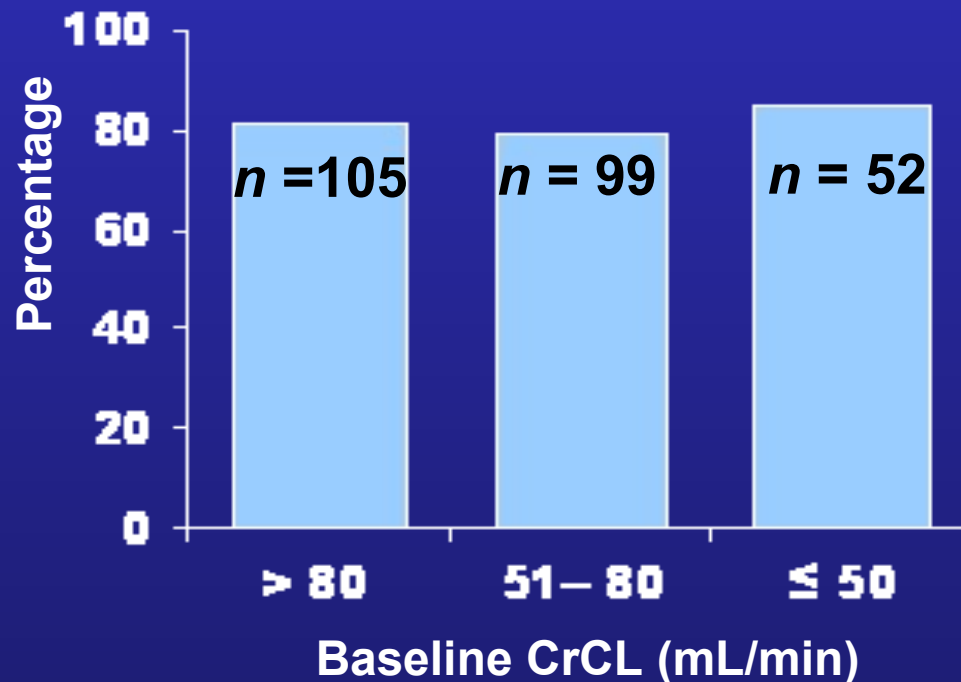


**B. Proteasome inhibition (predose)**



## SUMMIT & CREST:

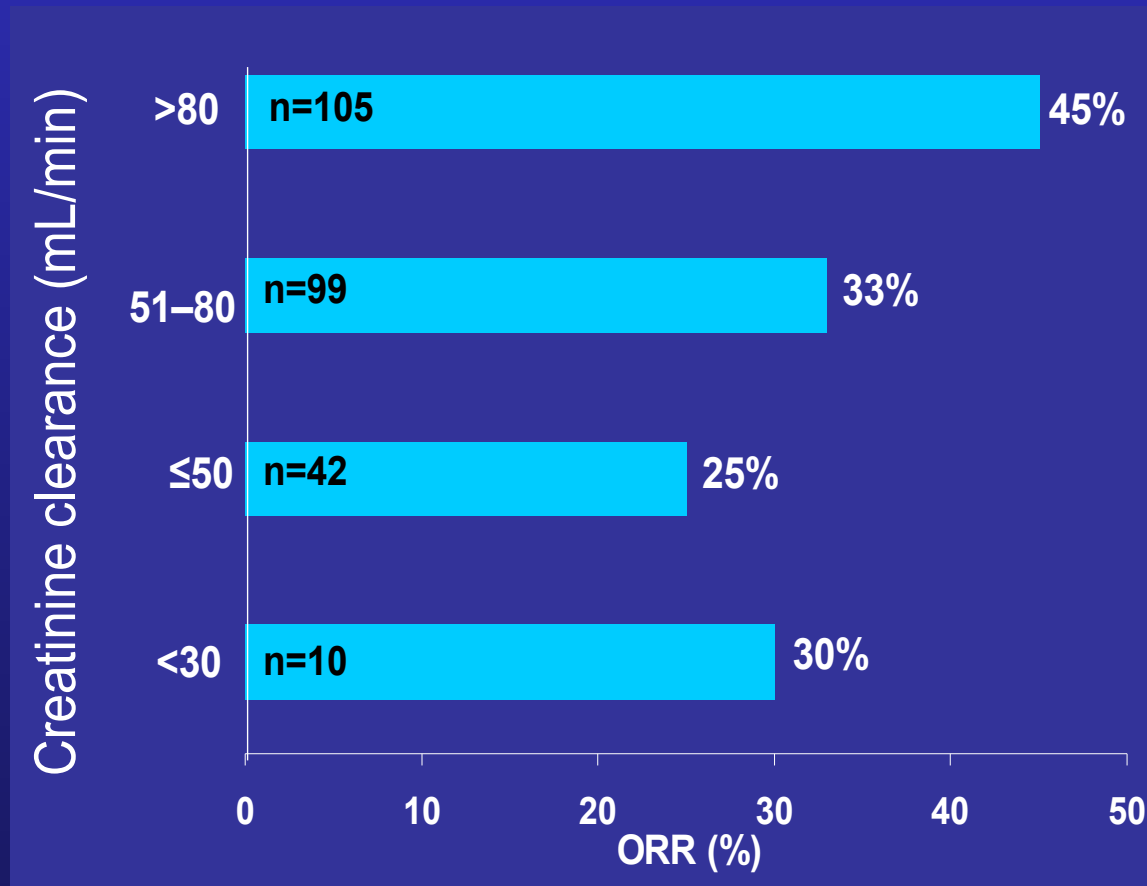
Incidence of Grade 3/4 Adverse Events was Similar Across all Creatinine Clearance (CrCL) Groups ( $n = 256$ )



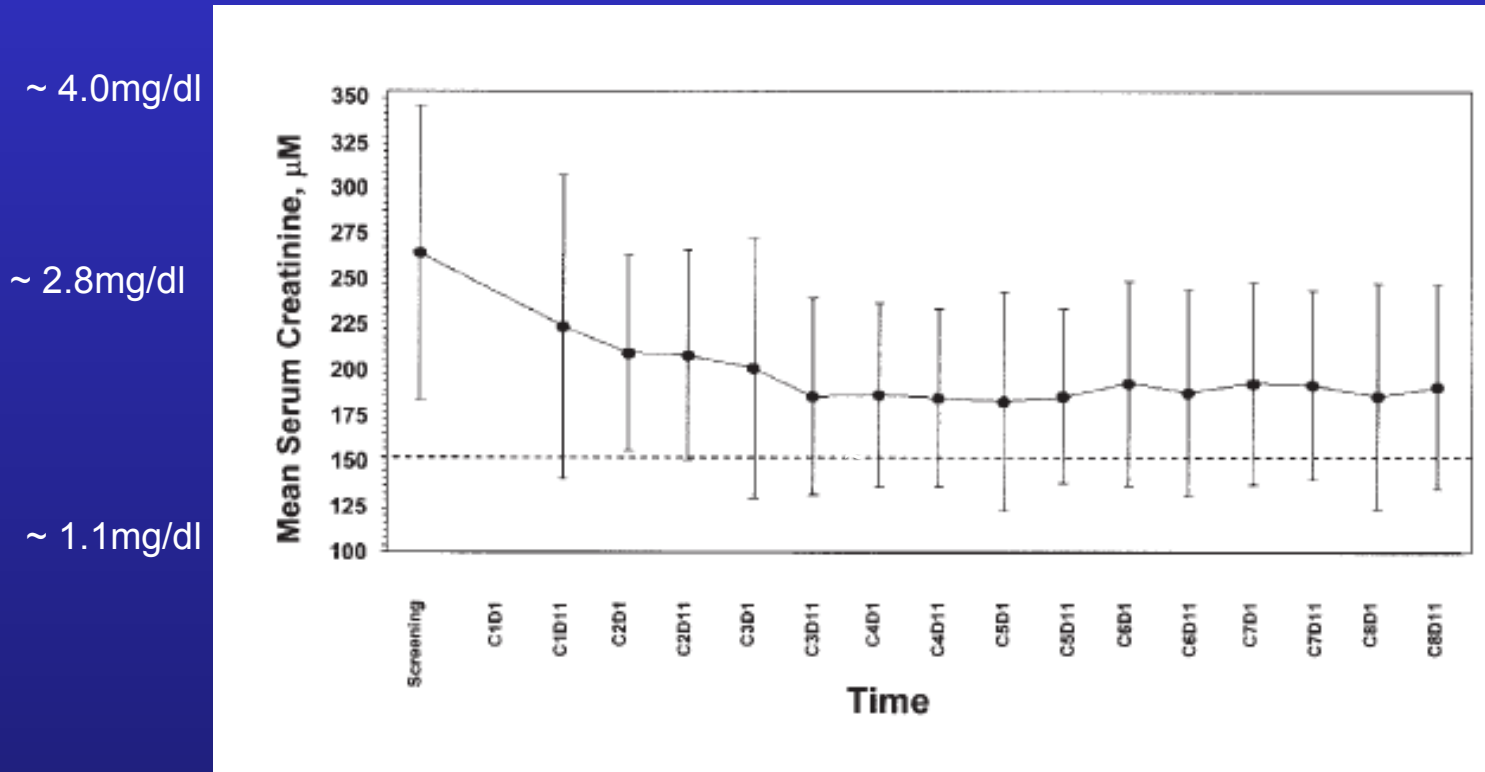
# Tolerability and Efficacy of Bortezomib in Patients with Renal Impairment

Subanalysis of SUMMIT and CREST

Comparable response rates in patients with compromised renal function



# Creatinine During Bortezomib Based Treatment in 10 Patients with CrCl < 30ml/min



Response rate similar to that seen in overall population

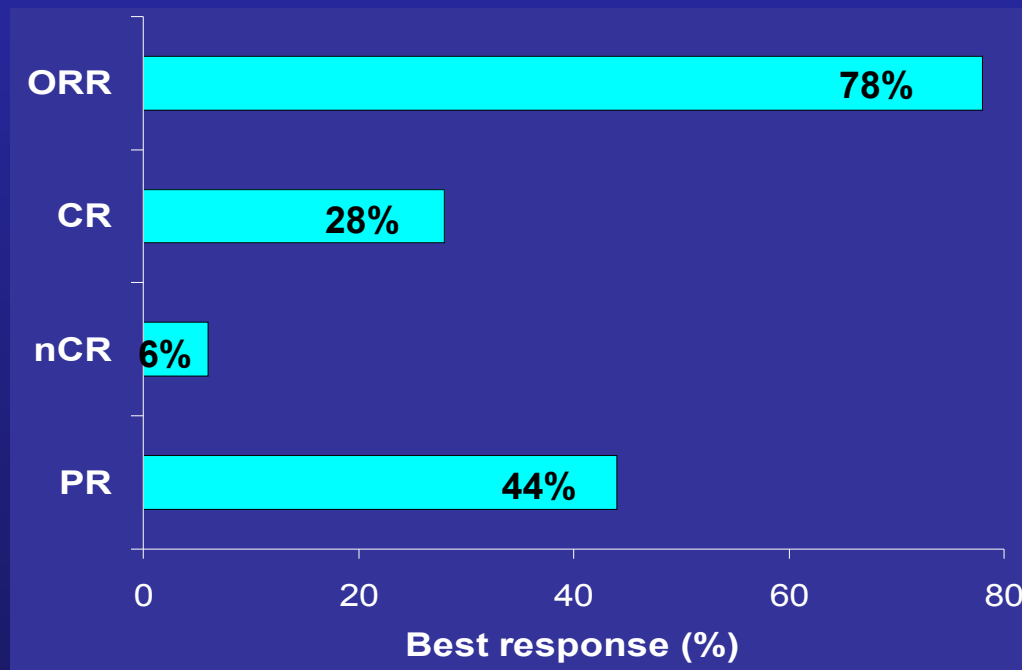
2/10 PR

1/10 MR

Results suggest that bortezomib can be administered safely to patients with renal impairment associated with MM.

# Bortezomib in patients with renal failure requiring dialysis

- Retrospective analysis of 24 patients treated with
  - single-agent bortezomib
  - bortezomib combinations (+ dex + thal/dex + thal/doxorubicin)
- Number of therapies prior to bortezomib: median 2 (range 0–6)
  - 1 patient with no prior therapy



# Bortezomib in patients with renal failure requiring dialysis

- High response rates
- Most adverse events were mild to moderate and manageable
- Incidence and severity of adverse events comparable to those of patients with normal renal function

## Participating Investigators/Institutions

Prof. Dr. H. Graf	Rudolfstiftung
Prof. Dr. F. Keil	KH Leoben
OA Dr. A. Lang	KH Feldkirch
Prof. Dr. JG. Meran	Barmherzige Brüder Wien
Prof. Dr. H. Ludwig	Wilhelminenspital

# Bortezomib–Doxorubicin–Dexamethasone (BDD ) for Reversal of Acute Renal Failure in Patients with MM

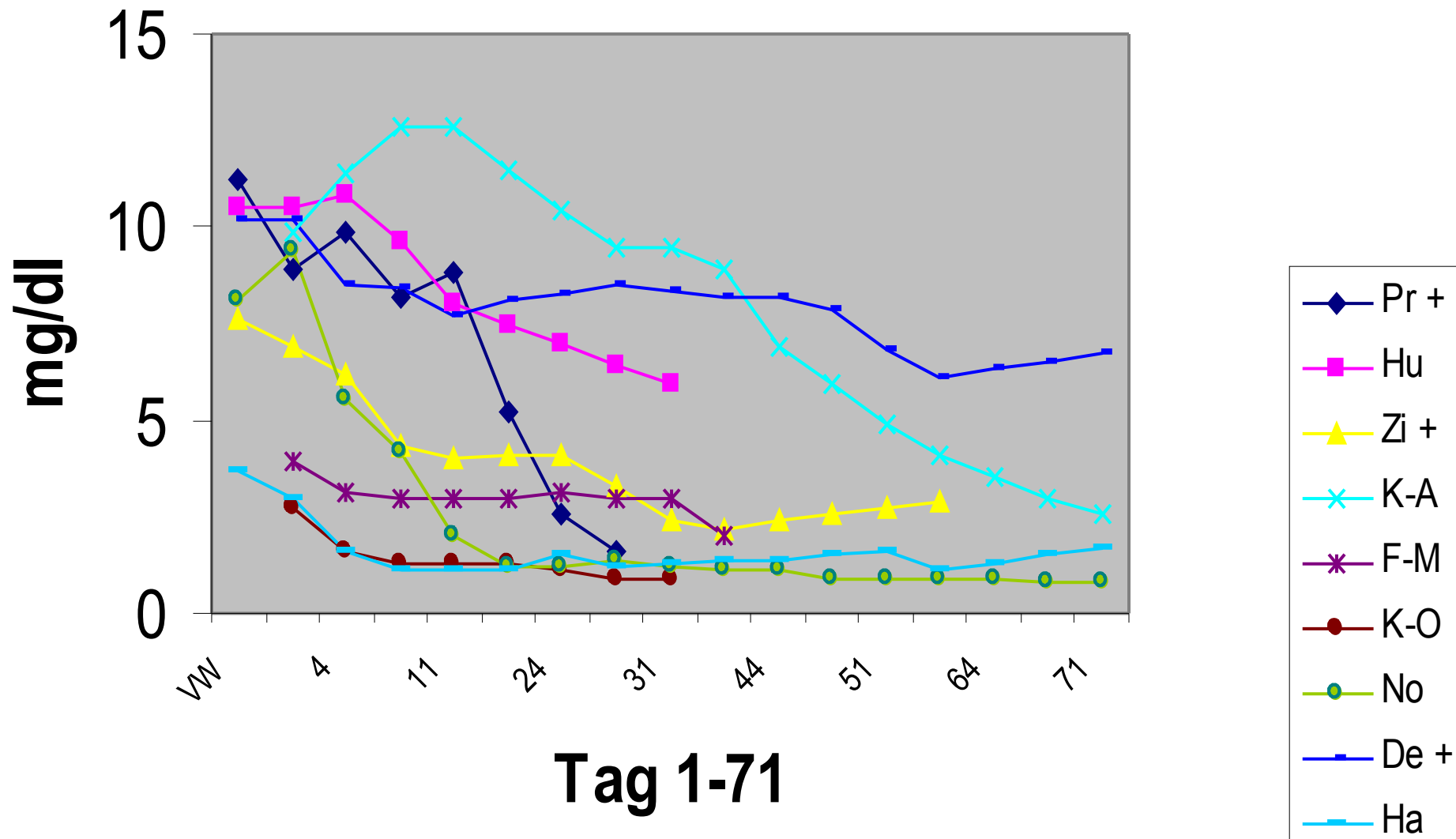
Drugs should be administrated on Days 1, 4, 8, 11 in the following order.

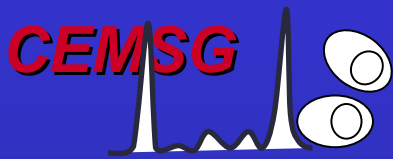
1. Dexamethasone 40 mg i.v.
2. Doxorubicin 9 mg/m<sup>2</sup>/d i.v.
3. Bortezomib 1.0 or 1.3 mg/m<sup>2</sup> i.v.

Restart next cycle on Day 22.

The Bortezomib dose is planed to be 1.3 mg/m<sup>2</sup>. Nevertheless for the safety reasons, the first 3 patients are going to be treated by 1.0 mg/m<sup>2</sup> Bortezomib.

# Creatinine Levels During Treatment with BD±D in Acute Renal Failure in Patients with MM





## Clinical Trial

# BDD for Reversal of Acute Renal Failure

### Primary objective:

Reversal of acute renal failure

### Secondary objectives:

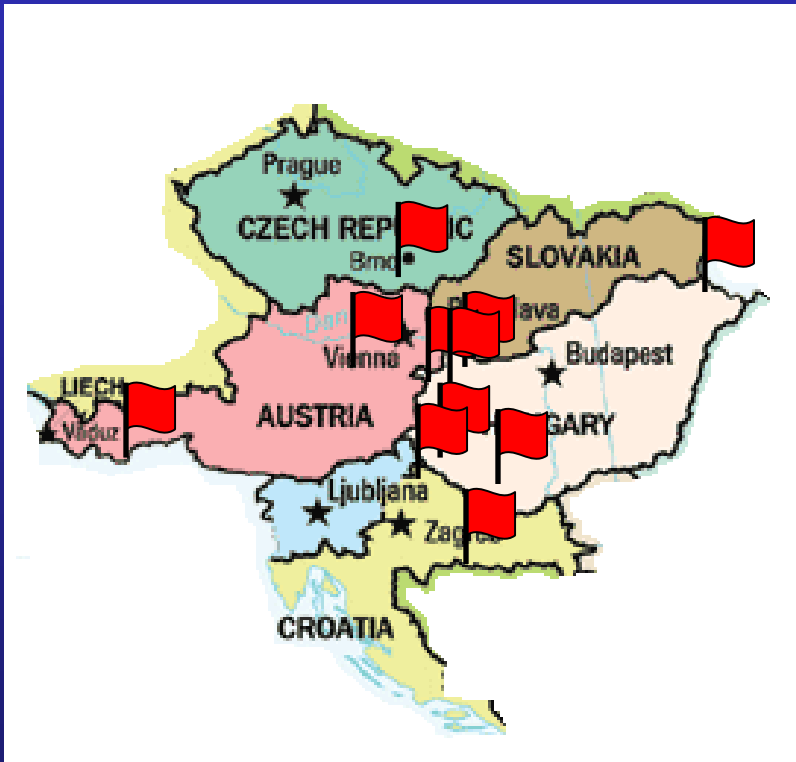
Tumor response (complete and partial response)

Safety of BDD in this patient population

Progression free survival

Overall survival

## Participating Study Centers



Univ. Prof. Dr. Heinz Gisslinger, Vienna, Austria

Univ. Prof. Dr. Johannes Drach, Vienna, Austria

Univ. Prof. Dr. Richard Greil, Salzburg, Austria

OA Dr. Alois Lang, Feldkirch, Austria

Univ. Prof. Dr. Felix Keil, Leoben, Austria

Univ. -Prof. Dr. Werner Linkesch, Graz, Austria

Univ. Prof. Dr. Heinz Ludwig, Vienna, Austria

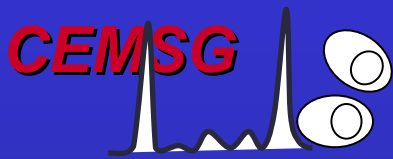
Dr. Miklós Egyed, Kaposvár, Hungary

Prof. MU Dr. CSc. Elena Tóthová, Košice, Slovakia

Univ. Prof. PhD. M.D. Zdenek Adam, Brno, Czech Republic

PhD M.D. Roman Hajek, Brno, Czech Republic

Univ. Prof. Dr. Boris Labar, Zagreb, Croatia



# Response Criteria

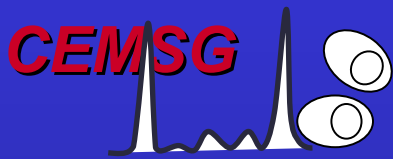
## Reversal of renal failure

### ➤ Complete response

- Reversal of renal failure to  $\text{GFR} > 60\text{ml/min}$

### ➤ Partial response

- Improvement of GFR by  $> 50\%$  but to  $< 60\text{ml/min}$



## Contact Details

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