

# Highlights from IMW 2019

19-20 novembre 2019  
Bologna  
Royal Hotel Carlton

## **L'insufficienza renale da danno tubulare**

**Alessandro Gozzetti**

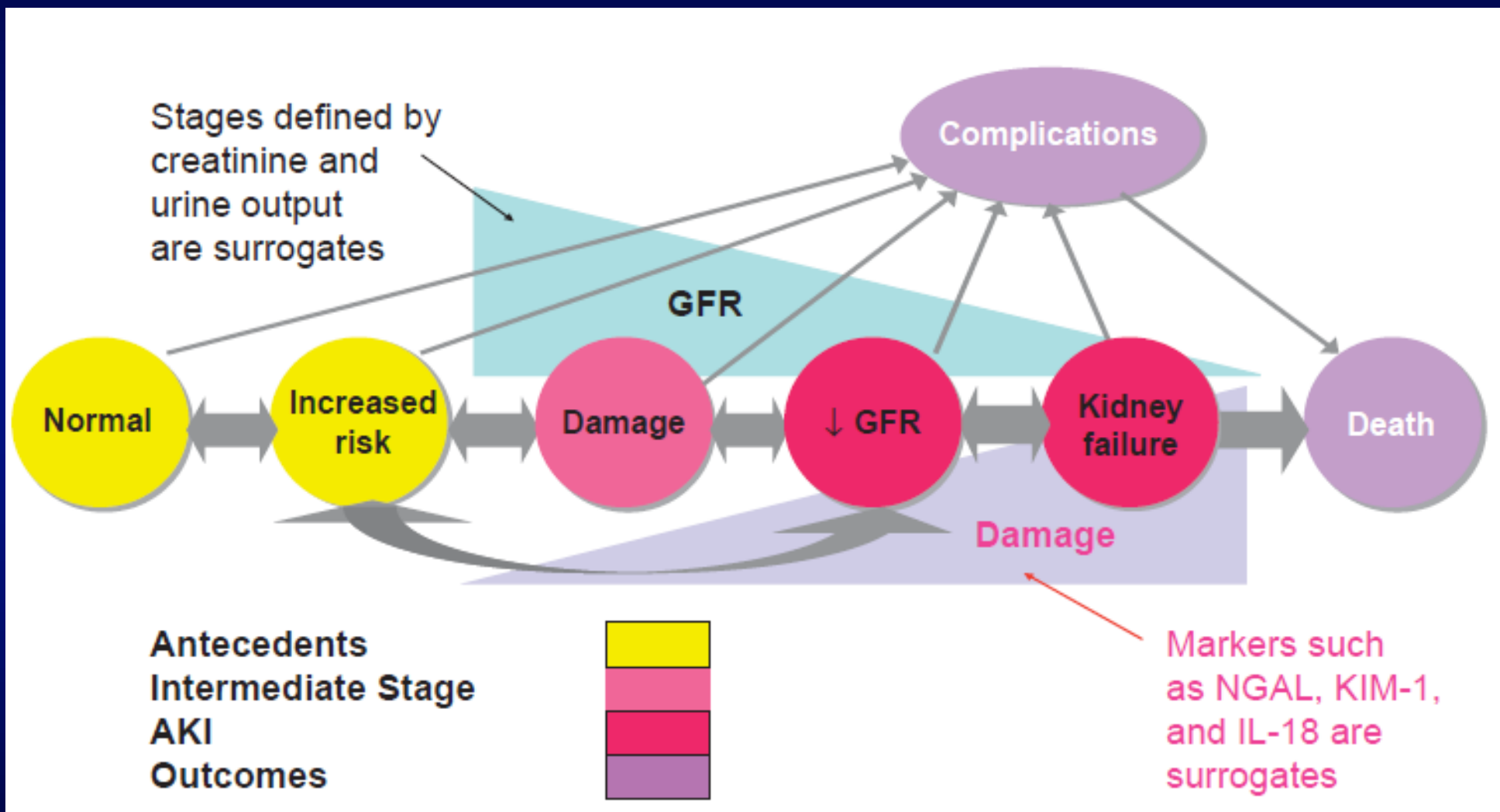
**Ematologia, Siena**



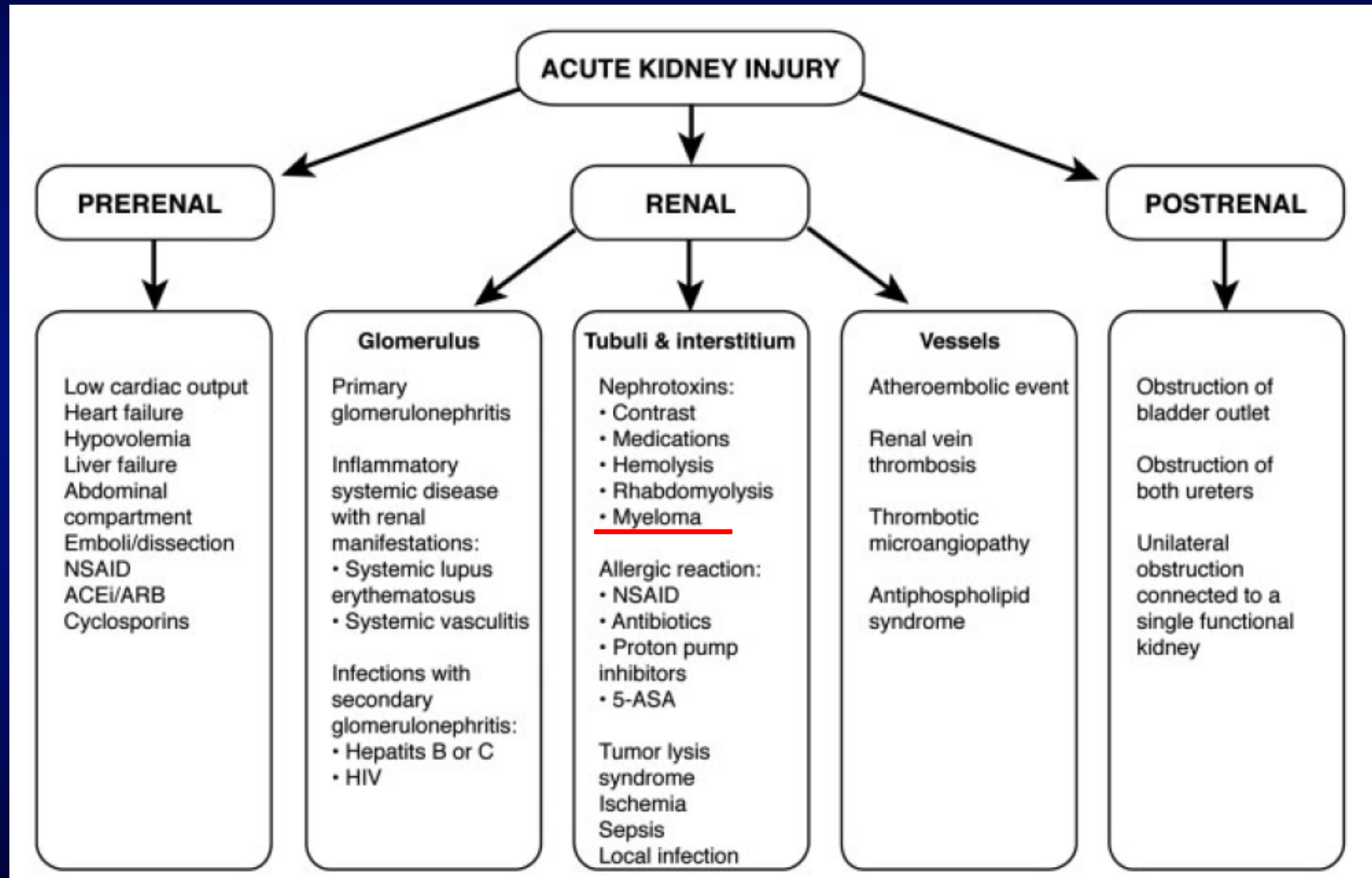
*Coordinatore Scientifico*  
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Michele CAVO  
Maria Teresa PETRUCCI

# Danno Renale Acuto



# Insufficienza renale e MM



# **Insufficienza renale e MM**

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- **25-30% dei pazienti alla diagnosi**
- **50% dei pazienti in vari stadi di malattia**
- **3-12% dei pazienti richiede dialisi  
(solo 30% vivi a >3 anni in dialisi)**

# Insufficienza renale e MM

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JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

## International Myeloma Working Group Recommendations for the Diagnosis and Management of Myeloma-Related Renal Impairment

*Meletios A. Dimopoulos, Pieter Sonneveld, Nelson Leung, Giampaolo Merlini, Heinz Ludwig, Efstathios Kastritis, Hartmut Goldschmidt, Douglas Joshua, Robert Z. Orlowski, Raymond Powles, David H. Vesole, Laurent Garderet, Hermann Einsele, Antonio Palumbo, Michele Cavo, Paul G. Richardson, Philippe Moreau, Jesús San Miguel, S. Vincent Rajkumar, Brian G.M. Durie, and Evangelos Terpos*

**Table 1.** RIFLE and AKIN Definitions of Acute Renal Injury

Creatinine and GFR Criteria		Urine Output Criteria
RIFLE	AKIN	RIFLE and AKIN
Stage R: sCr increase $\geq$ 50%; or GFR decrease $>$ 25%	Stage I: sCr increase $>$ 50%; or $>$ 0.3 mg/dL	$<$ 0.5 mg/kg/h for 6 h
Stage I: sCr increase $\geq$ 100%; or GFR decrease $>$ 50%	Stage II: sCr increase $\geq$ 100%	$<$ 0.5 mg/kg/h for 12 h
Stage F: sCr increase $\geq$ 200%; GFR decrease $>$ 75%; or sCr $\geq$ 4.0 mg/dL with an increase $\geq$ 0.5 mg/dL	Stage III: sCr increase $\geq$ 200%; or sCr $\geq$ 4.0 mg/dL with an increase $\geq$ 0.5 mg/dL	$<$ 0.3 mg/kg/h for 24 h or anuria for 12 h
Stage L: Complete loss of kidney function (need for RRT) $>$ 4 weeks	Stage III: Or RRT	
Stage E: End-stage kidney disease (need for RRT) $>$ 3 months		

Abbreviations: AKIN, Acute Kidney Injury Network classification; GFR, glomerular filtration rate; RIFLE, Risk, Injury, Failure, Loss and End-Stage Kidney Disease criteria; RRT, renal replacement therapy; sCr, serum creatinine.

# Insufficienza renale e MM: Stadiazione IR

**Table A2.** Classification of Chronic Renal Disorders

Stage of Renal Impairment	Description	GFR, mL/min/1.73 m <sup>2</sup>
1	Kidney damage with normal or elevated GFR	≥ 90
2	Kidney damage with mild reduction of GFR	60-89
3	Moderate reduction of GFR	30-59
4	Severe reduction of GFR	15-29
5*	Renal failure	< 15 or on dialysis

Abbreviation: GFR, glomerular filtration rate.

\*Stages 5 is also defined as end-stage renal disease.

# Insufficienza renale e MM

## Glomerular

- Primary amyloidosis (AL or AH)
- Monoclonal immunoglobulin deposition:
  - Light chain deposition disease
  - Heavy chain deposition disease
  - Light and heavy chain deposition disease
- Miscellaneous (cryoglobulinemia, proliferative glomerulonephritis)

## Tubular

- Myeloma kidney (light chain cast nephropathy)
- Distal tubular dysfunction
- Proximal tubule dysfunction or acquired Fanconi syndrome

## Interstitial

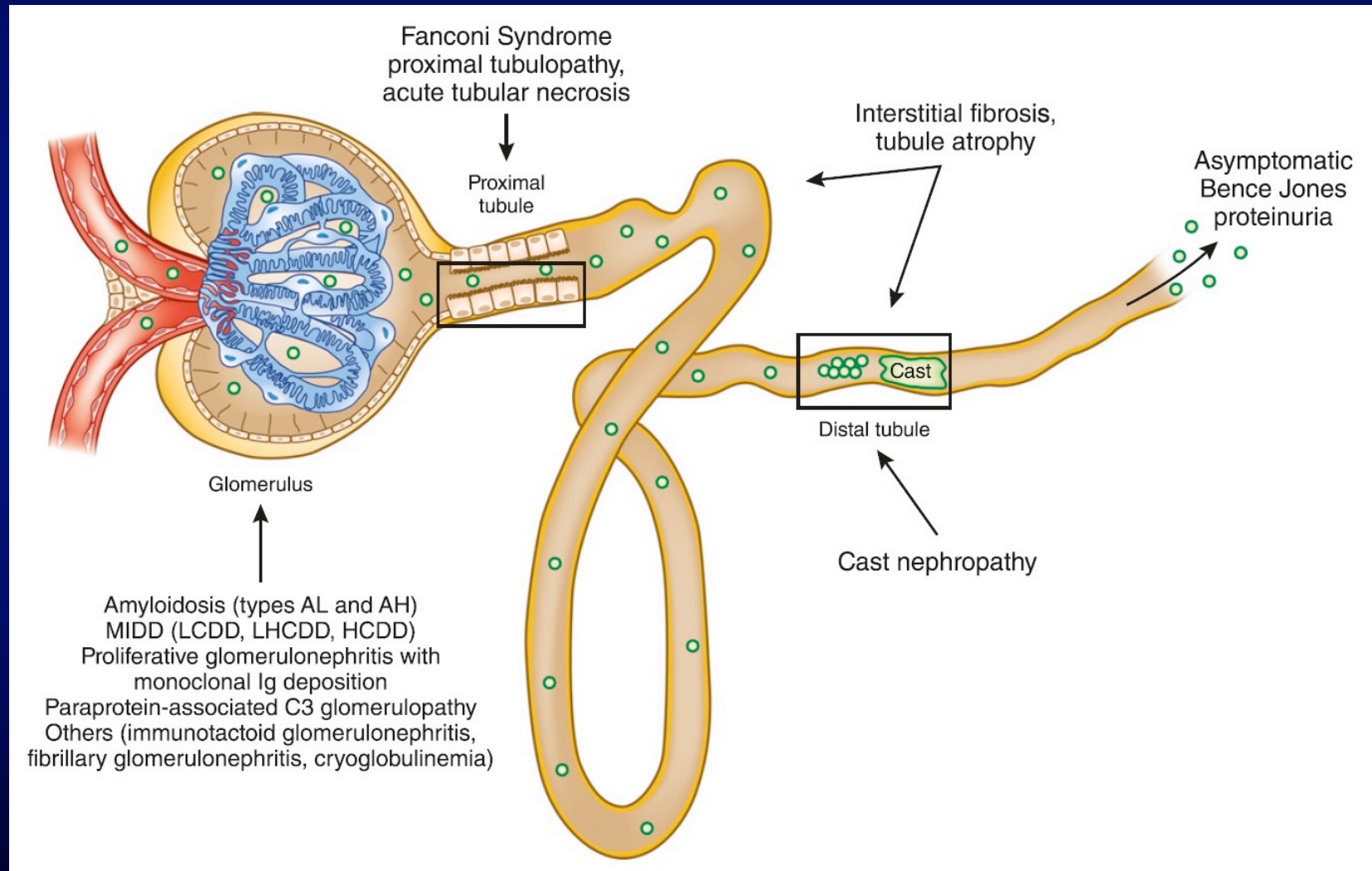
- Plasma cell infiltration
- Interstitial nephritis

## Other causes

- Hyperuricemia
- Hypercalcemia
- Drugs (e.g., NSAIDs)

*Expert Rev. Hematol.* 5(1), 51–68 (2012)

# Insufficienza renale e MM





## **Insufficienza renale e MM**

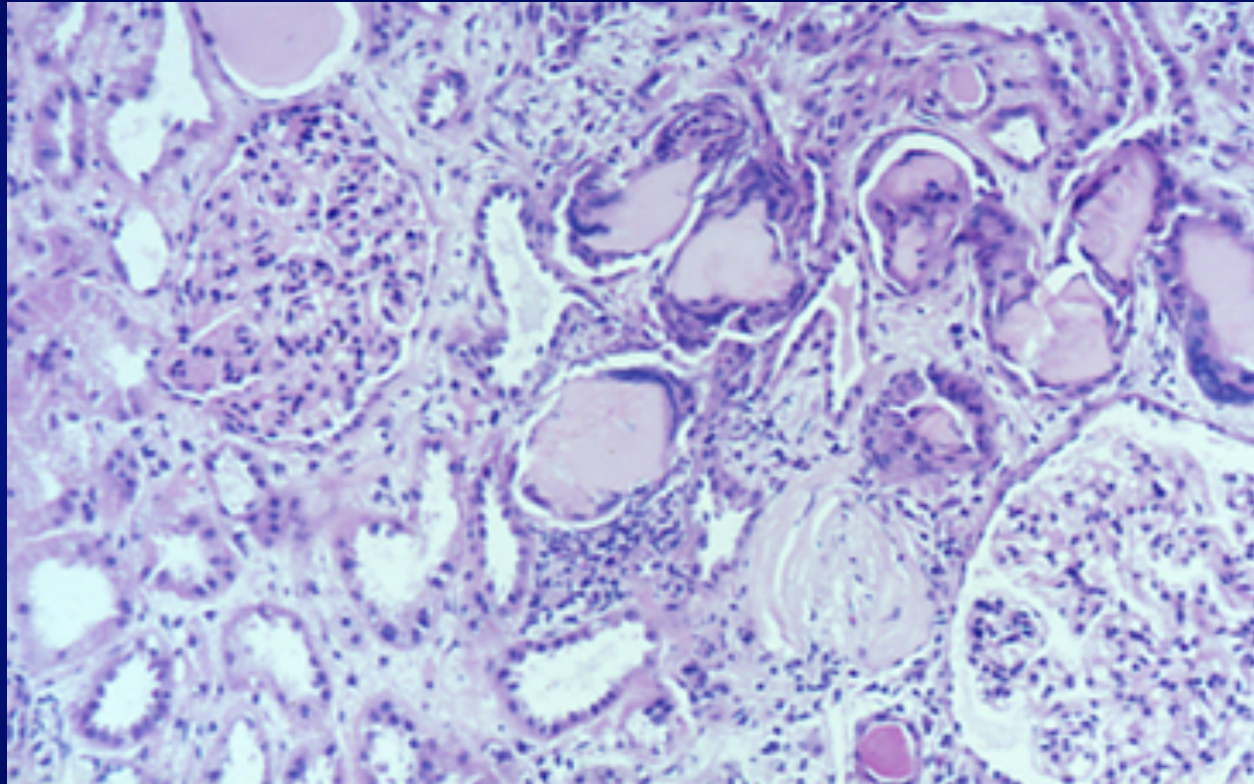
# **CAST NEPHROPATHY**

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- **La cast nephropathy si verifica soprattutto in presenza di elevata escrezione di catene leggere (> 1 g/die) per:**
  - **Formazione di cilindri e ostruzione tubulare;**
  - **Tossicità tubulare diretta**
  - **interazione fra catene leggere e proteina di Tamm-Horsfall**
  - **Le catene leggere riassorbite interferiscono con la funzione lisosomiale delle cellule tubulari prossimali**

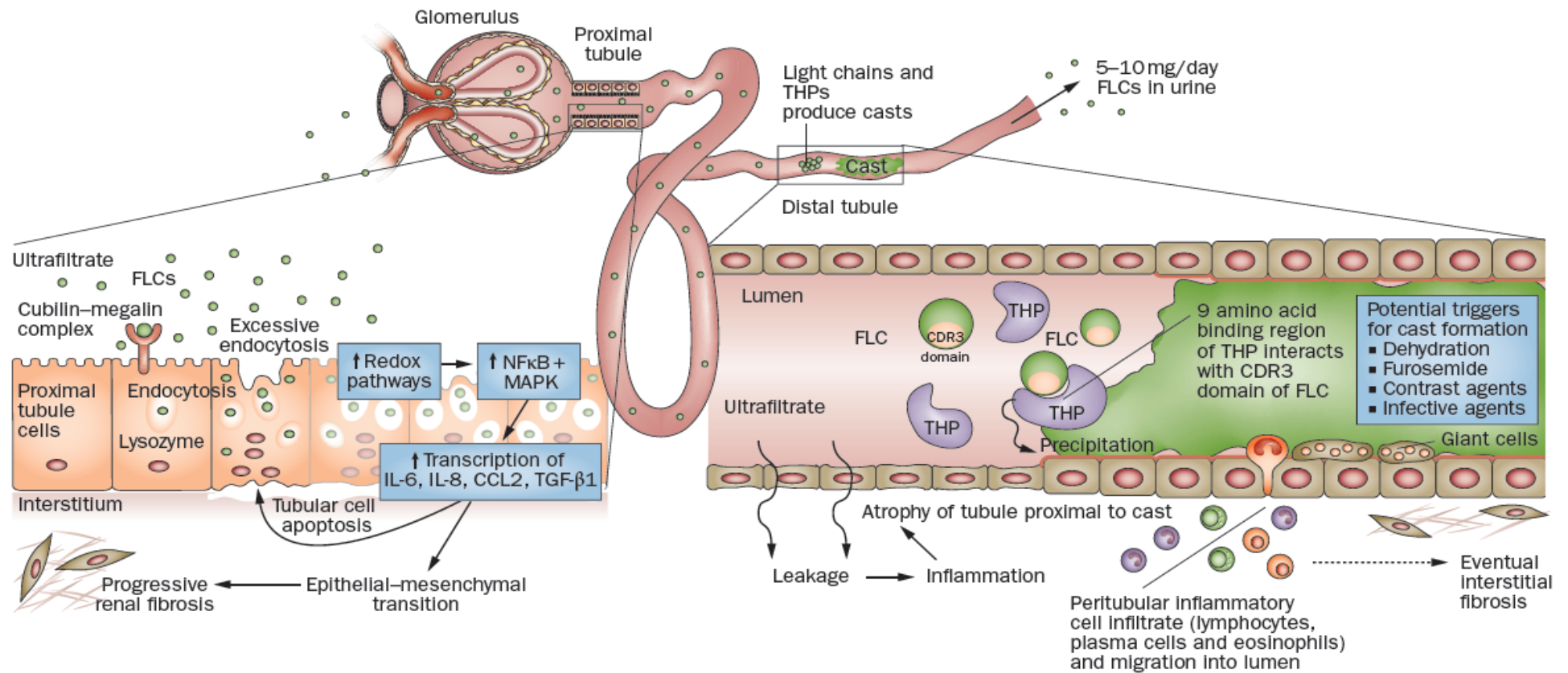
# **Insufficienza renale e MM**

## **CAST NEPHROPATHY**



**Larghi cilindri intratubulari circondati da reazione cellulare**

# Insufficienza renale e MM



# **Insufficienza renale e MM**

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**Nel 15% dei mielomi e IRA (biopsiati su rene) la causa non è da gammapatia:**

**Arterioneftrosclerosi (6%)**

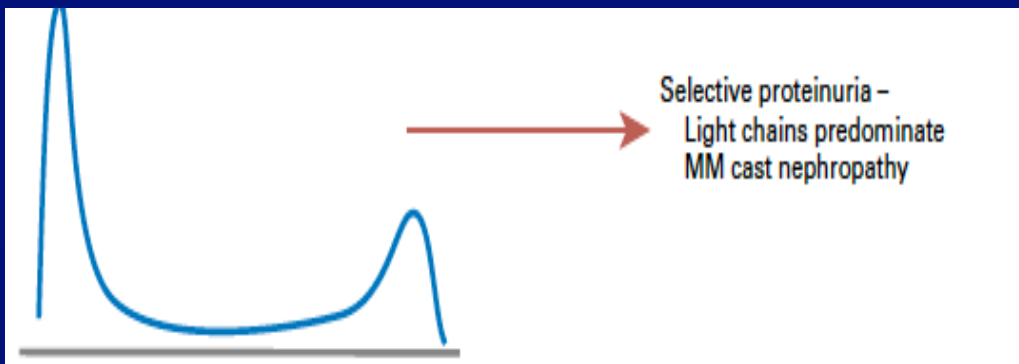
**Glomerulosclerosi diabetica (5%)**

**Glomerulonefrite post-infettiva (2%)**

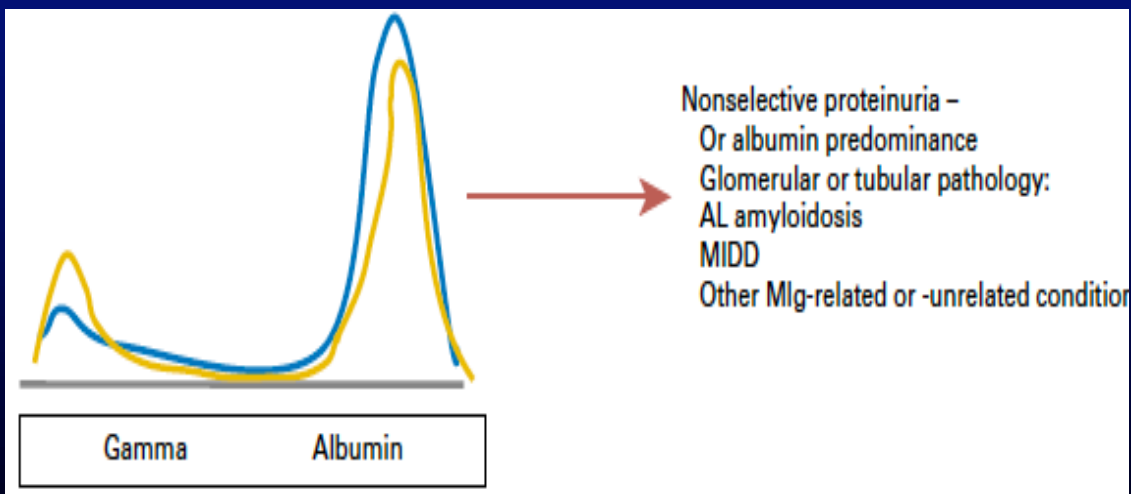
**Glomerulopatia correlata al fumo (0.5%).**

# Biopsia renale: quando?

**Creatinina, FLC sieriche, proteinuria 24 ore, elettroforesi urine**



**FLC alte >500 mg/L  
Probabile Cast nephropathy  
No biopsia renale**



**FLC basse <500 mg/L  
albuminuria  
Si biopsia renale**

# Risposta renale

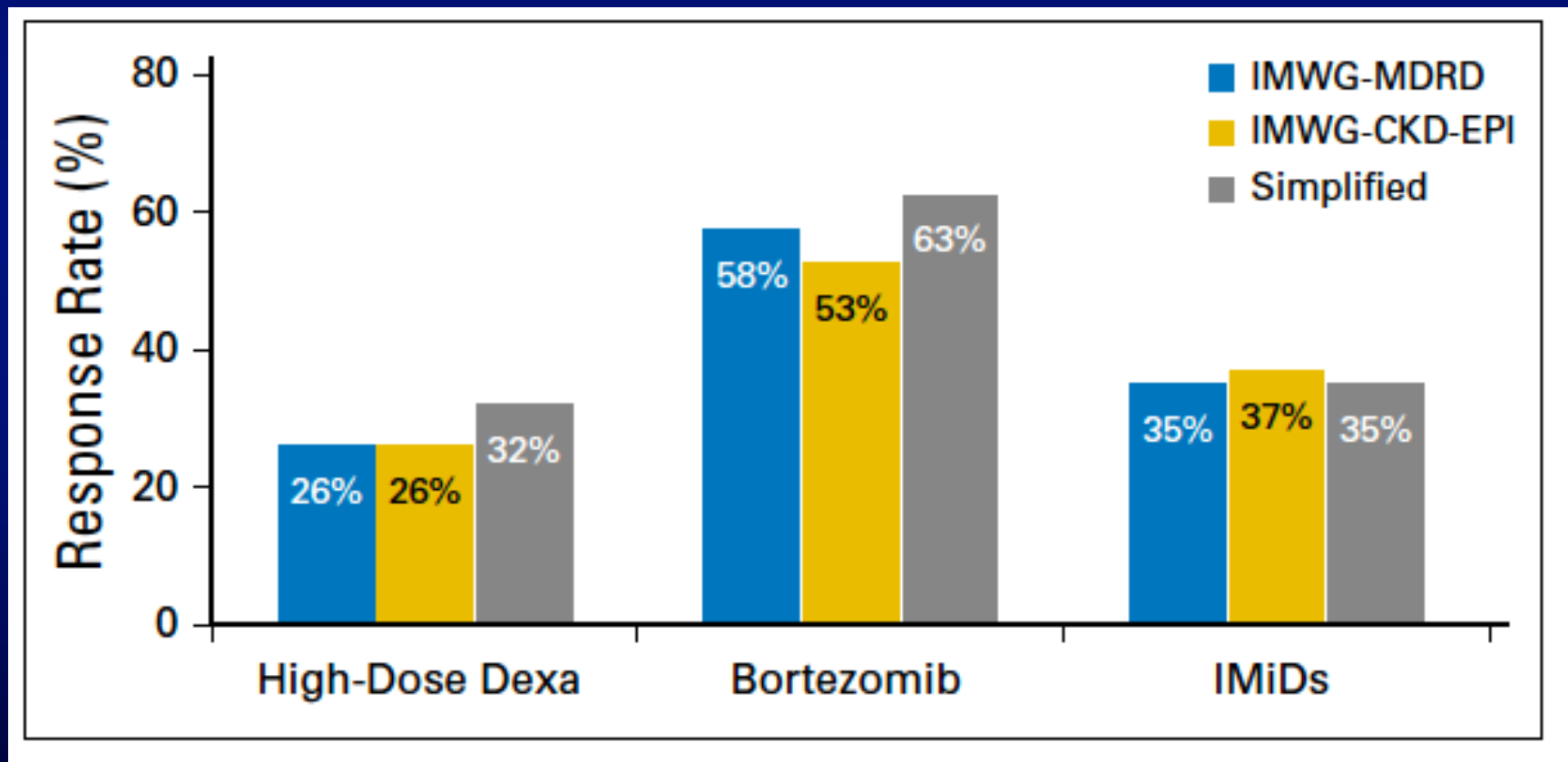
**Table 3.** Criteria for the Definition of Renal Response to Antimyeloma Therapy

Renal Response	Baseline eGFR, mL/min/1.73 m <sup>2</sup> *	Best CrCl Response
Complete response	< 50	≥60 mL/min
Partial response	< 15	30-59 mL/min
Minor response	< 15	15-29 mL/min
	15-29	30-59 mL/min

Abbreviations: CrCl, creatinine clearance; eGFR, estimate glomerular filtration rate.

\*eGFR is based on the Modification of Diet in Renal Disease formula, or the Chronic Kidney Disease Epidemiology Collaboration equation.

# Risposta renale alla diagnosi Bortezomib e IMiD'S (N= 105)



# **Insufficienza renale e MM**

## **Supporto**

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- **Idratazione >3 L/giorno (2L/m<sup>2</sup> giorno)**
- **No diuretico**
- **Non serve alcalinizzare urine**
- **No difosfonati in IRA severa (<30 ml/min)**
- **No farmaci nefrotossici (aminoglicosidici), né contrasto radiologico**



# **Insufficienza renale e MM Plasmaferesi (PF)**

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**Trial randomizzato su 104 pazienti  
Nessuna differenza in indipendenza da  
dialisi<sup>1</sup>**

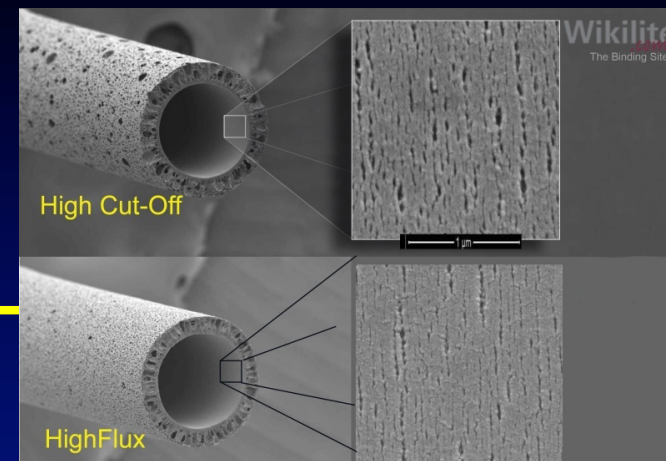
**Meta-analisi 63 vs 84 paz. CHT vs CHT+ PF;  
no differenze<sup>2</sup>**

1.Clark WF, Stewart AK, Rock GA, et al: Ann Intern Med 143:777-784, 2005

2.Yu X, Gan L,Wang Z, et al.: Int J Clin Pharmacol Ther 53:391-397,2015

# Insufficienza renale e MM

## Dialisi HCO



Study	EuLITE	MYRE
Patient number	90	98
Study population	Newly diagnosed myeloma Biopsy confirmed Light chains >500 mg/L Requires acute dialysis	New or untreated myeloma Biopsy confirmed Requires acute dialysis
Chemotherapy regimen	Bortezomib Doxorubicin Dexamethasone	Bortezomib Dexamethasone Cyclophosphamide (if no response after third cycle)
HF-HD protocol	Minimum 4-hour treatments thrice weekly Nephrologists' discretion	5-hour treatments 8 sessions over first 10 days 3 sessions per week thereafter
HCO-HD protocol	Two 1.1 m <sup>2</sup> filters in series 6 hours day 0 8 hours days 2, 3, 5-7, 9, 10 8 hours QOD after day 12	Single 2.1 m <sup>2</sup> filter 5-hour treatments 8 sessions over first 10 days 3 sessions per week thereafter
Primary outcome	Dialysis independence day 30 51.5% HF-HD vs. 55.8% HCO-HD p = NS	Dialysis independence day 30 33% HF-HD vs. 41% HCO-HD p = NS
Secondary outcome	Overall renal recovery 66% HF-HD vs. 58.1% HCO-HD p = NS	Dialysis independence 6 months 35% HF-HD vs. 57% HCO-HD p = 0.04

# Farmaci e riduzioni di dose

patients with renal dysfunction

	Clearance by the kidneys	Dose adjustment in RI	Potential of renal toxicity	Data for use in patients on dialysis
Dexamethasone	Yes	No	Low	Yes, safe
Melphalan	Yes	Yes	Low	Yes, with adjustments
Bortezomib	No	No	Low	Yes, safe
Thalidomide	No	No	Low	Yes, safe
Lenalidomide	Yes	Yes	Moderate	Yes, dose adjustment required
Pomalidomide [94]	Yes	No	Moderate	No, adjustment dose not requires
Doxorubicin	No	No	No	Yes
Daratumumab	No	No	Low	No, but probably no dose adjustment required
Elotuzumab	No	No	Low	No, but probably no dose adjustment required
Panobinostat	No	Yes	Low	No
Ixazomib	Yes	Yes	Low	No
Carfilzomib	Yes	No	Moderate	Yes
Zoledronic acid	Yes	Yes	Yes	No
Pamidronate	Yes	Yes	Yes	No

# PI's e IMID's trials MM e IR

Trials	Fase	Terapia	N	Dialisi	Risposta (>PR)	PFS/OS (mesi)	Renal Response
<b>Thalidomide-based</b>							
Tosi (2004)	RR	Thal /dex	20	3	45%	7/7	60% (PR)
Kastritis (2007)	Dx	Thal /dex	13	4	65%	NA/23	73%( PR)
Tosi (2010)	Dx	Thal/dex+ASCT	31	5	74% (10% CR)	30/Not Reached	55% (PR)
Bringhen (2013)	Dx	MPT	34	0	NA	NA/38% at 3 years	NR
<b>Lenalidomide-based</b>							
Dimopoulos (2010)	RR	Len-dex	98 (16 with CRCl<30)	0	65% (14 CR)	9/29 (18 for CrCl<30)	72%
De la Rubia (2010)	RR	Len-dex	15	15	60% (4 CR)	15/20	10% (1 CR)
Klein (2011)	RR	Len-dex	33	5	49% (3 CR)	6/25	27% (PR)
Tosi (2013)	RR	Len-dex	20	4	40%	9/9	20% (PR)
Oerlein (2012)	RR	Len-dex	26	3	84% (1CR)	11.8/33	42% (6CR)
<b>Bortezomib-based</b>							
Jagannath (2005)	RR	Vel-dex	52	0	25%	NA	30%
San-Miguel (2008)	RR	Vel	58	0	40%	4.9/22.8	NR
Dimopoulos (2009)	RR	Vel-dex (+CHT)	46	9	76%	NA	59%
Ludwig (2010)	Dx+RR	PAD	68 (50 Dx +18 RR)	9	72% (38% CR)	12.1/Not reached	62%
Morabito (2010)	Dx+RR	Vel-dex (+CHT)	117 (27 Dx+90 RR)	14	73% (19% CR)	51% /71% at 2 years	41%
Dimopoulos (2009)	Dx	VMP	111	0	68% (31% CR)	19.9/ 70% at 2 years	44%
Bladé (2008)	RR	Vel/ PAD	193	0	49% (PAD); 42% Vel- dex	10.9 (PAD); 6.5 Vel	NA
Morabito (2011)	Dx	VMPT-VT	63	0	93% (41%CR)	Not Reached	25%
<b>Carfilzomib</b>							
Badros (2013)	RR	Car-dex	50	8	25%	7.8 /NA	NA

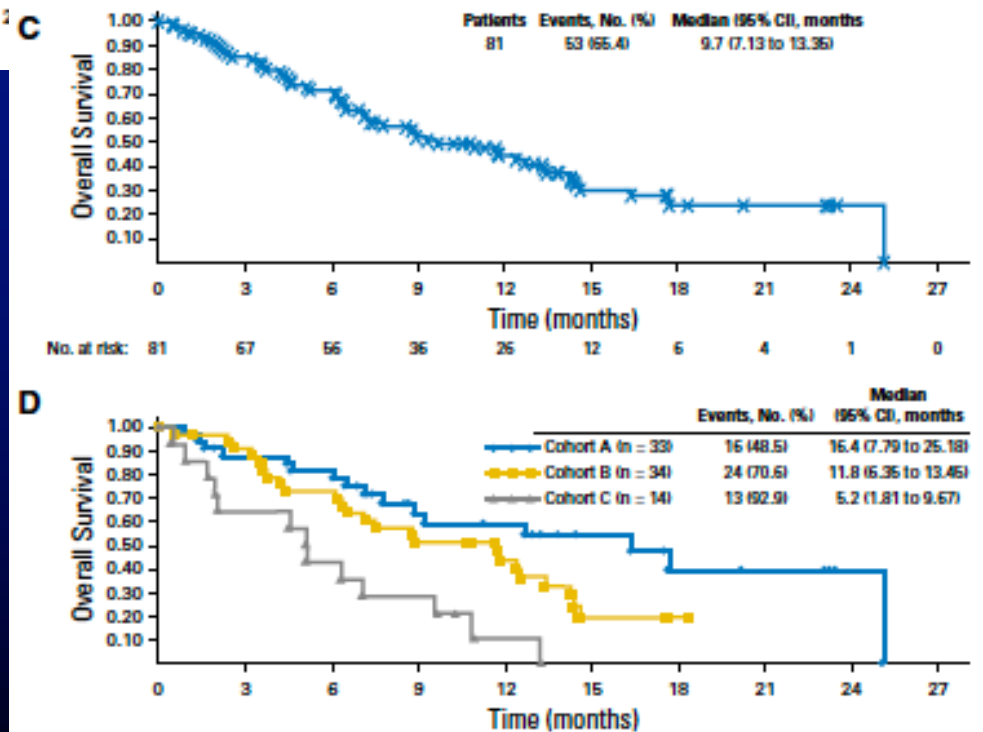
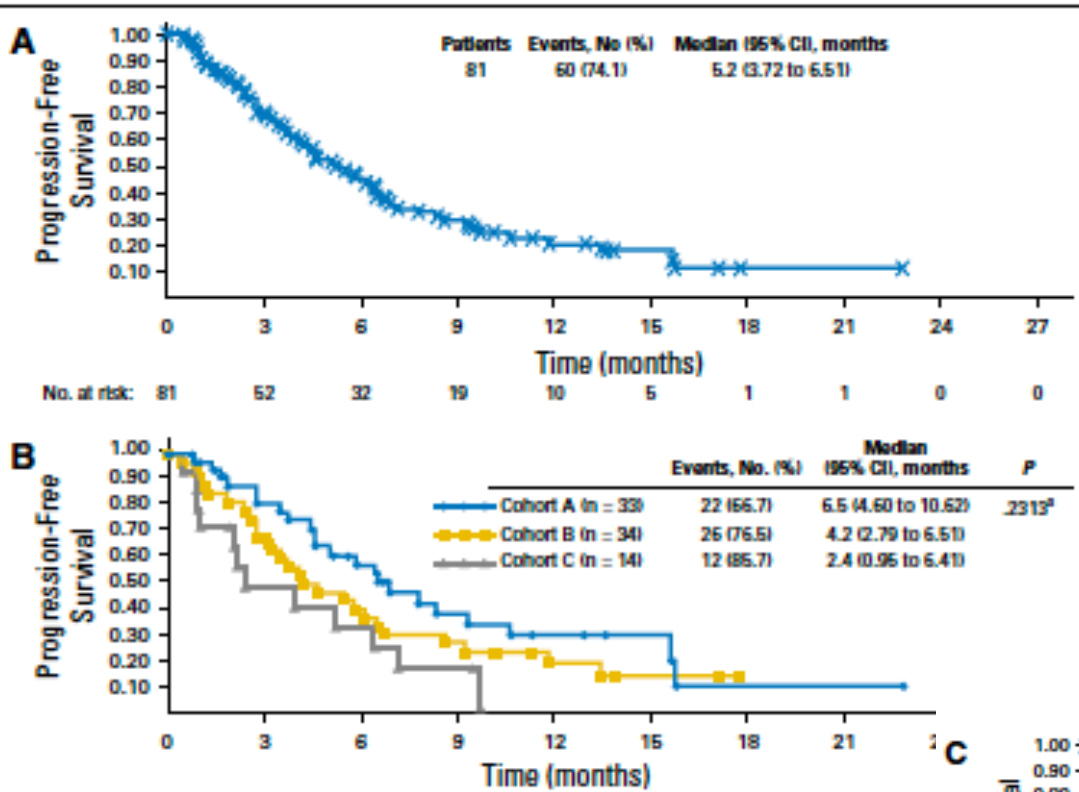
# Pomalidomide

**Pomalidomide IMiD di 3 generazione**  
**Solo il 2% di poma è escreto immodificato a livello renale, il resto è metabolizzato precedentemente**

Siegel et al 2012 [54] Pomalidomide (POM) with low-dose dexamethasone (LoDEX) in patients with relapsed and refractory multiple myeloma (RRMM): impact of renal function on patient outcomes	113	61% CrCl >60 mL/min 12% CrCl 45-60 mL/min 23% CrCl <45 mL/min 4% CrCl ≤30 mL/min	Comparable AEs across all renal groups but caution with small numbers
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# Poma

81 paz. con IR



Dimopoulos et al. JCO 2018

# Daratumumab e IR

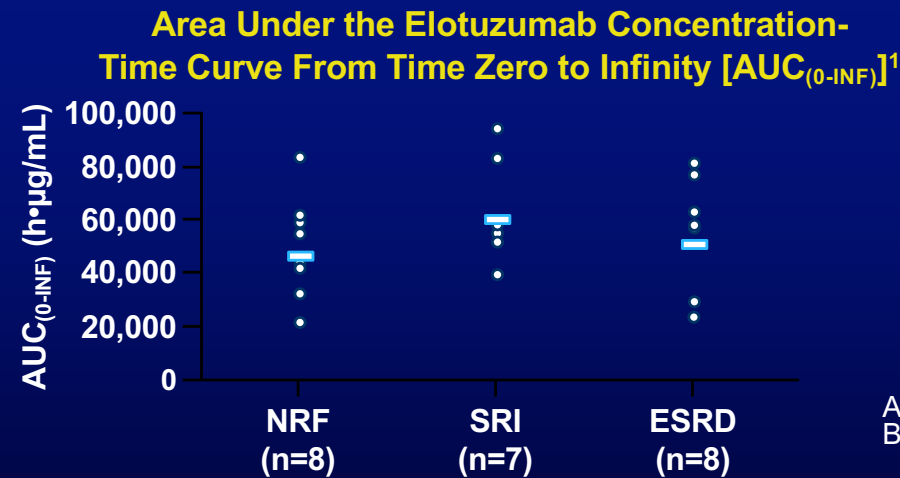
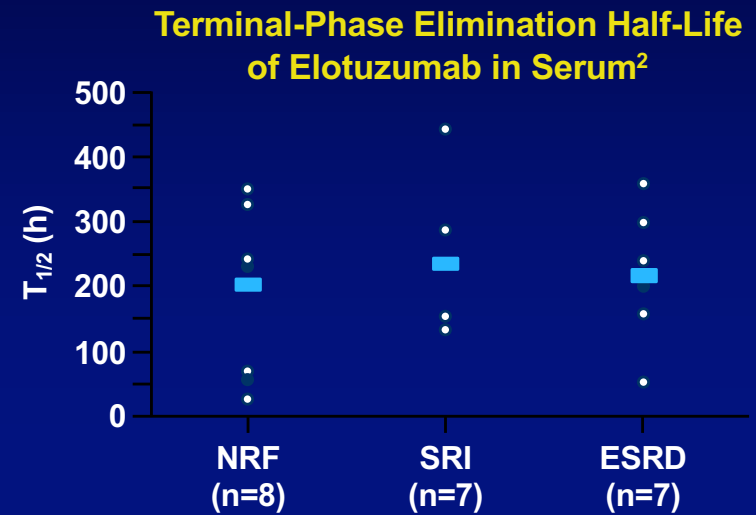
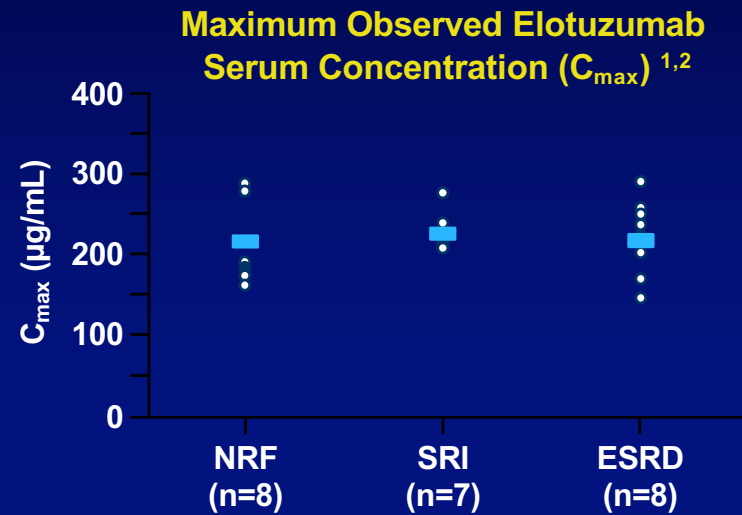
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**Nel Fase 2 MMY2002 (SIRIUS) i pazienti hanno ricevuto Dara in monoterapia**

**L'analisi PK non ha evidenziato differenze per vari gradi di IR**

**57% dei pazienti aveva eGFR  $\geq 60$ ml/min, 40% 30-60ml/min e 3%  $< 30$ ml/min**

# Elotuzumab



Adapted from Berdeja J et al. 2016<sup>1</sup> and Berdeja J et al. 2014.<sup>2</sup>

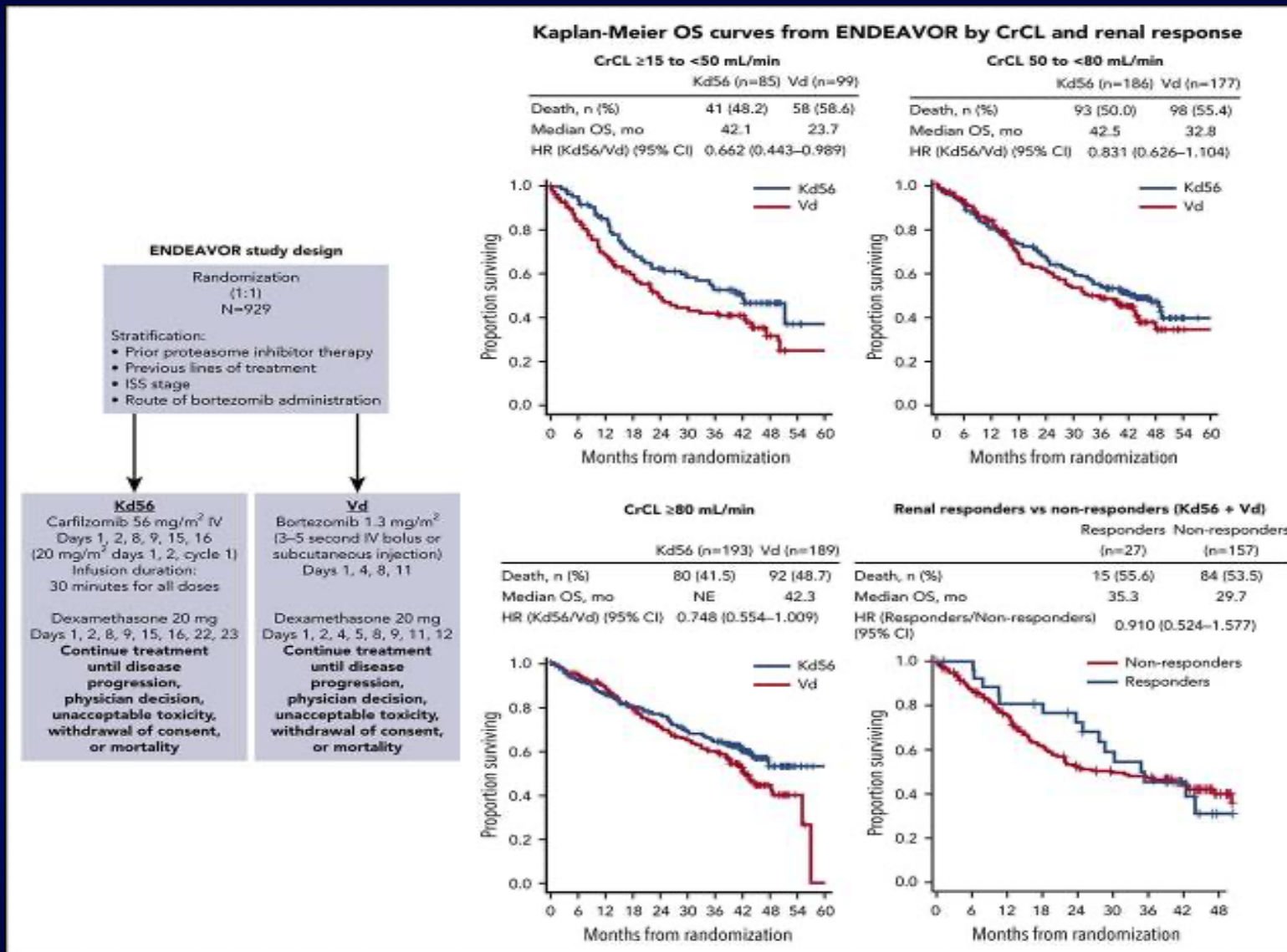


# Elotuzumab

Treatment Response	NRF (n=8)	SRI (n=9)	ESRD (n=9)
<b>ORR,*</b> <b>n (%) [95% CI]</b>	6 (75 [35–97])	6 (67 [30–93])	5 (56 [21–86])
<b>Best overall response, n (%)</b>			
<b>sCR</b>	0	1 (11)	0
<b>CR</b>	2 (25)	0	0
<b>VGPR</b>	1 (13)	4 (44)	1 (11)
<b>PR</b>	3 (38)	1 (11)	4 (44)
<b>SD</b>	1 (13)	0	1 (11)
<b>PD</b>	0	0	0
<b>NE</b>	1 (13)	0	1 (11)

\*1. Berdeja J et al. *Clin Lymphoma Myeloma Leuk*. 2016;16:129-138.

# Carfilzomib (Endeavor)



# ASCT

**IR e dialisi non sono criteri di esclusione assoluti**

**IR non ostacola la mobilizzazione di CD34 né l'engraftment**

**Nei pazienti con IR severa o dialisi sono raccomandate ridotte dosi di melphalan (140mg/m<sup>2</sup>)**

# CONCLUSIONI

- **IR è comune nel paziente con MM (Cast N la più comune)**
- **Un recupero della funzione renale è associato con outcome migliore**
- **I regimi bor-based sono raccomandati**
- **Imid's possono essere utilizzati nei pazienti che non possono ricevere bor**
- **I nuovi farmaci sembrano avere efficacia e non escrezione renale**
- **POCHI TRIALS CON PAZIENTI IN IR SEVERA O DIALISI!!!! REAL LIFE**