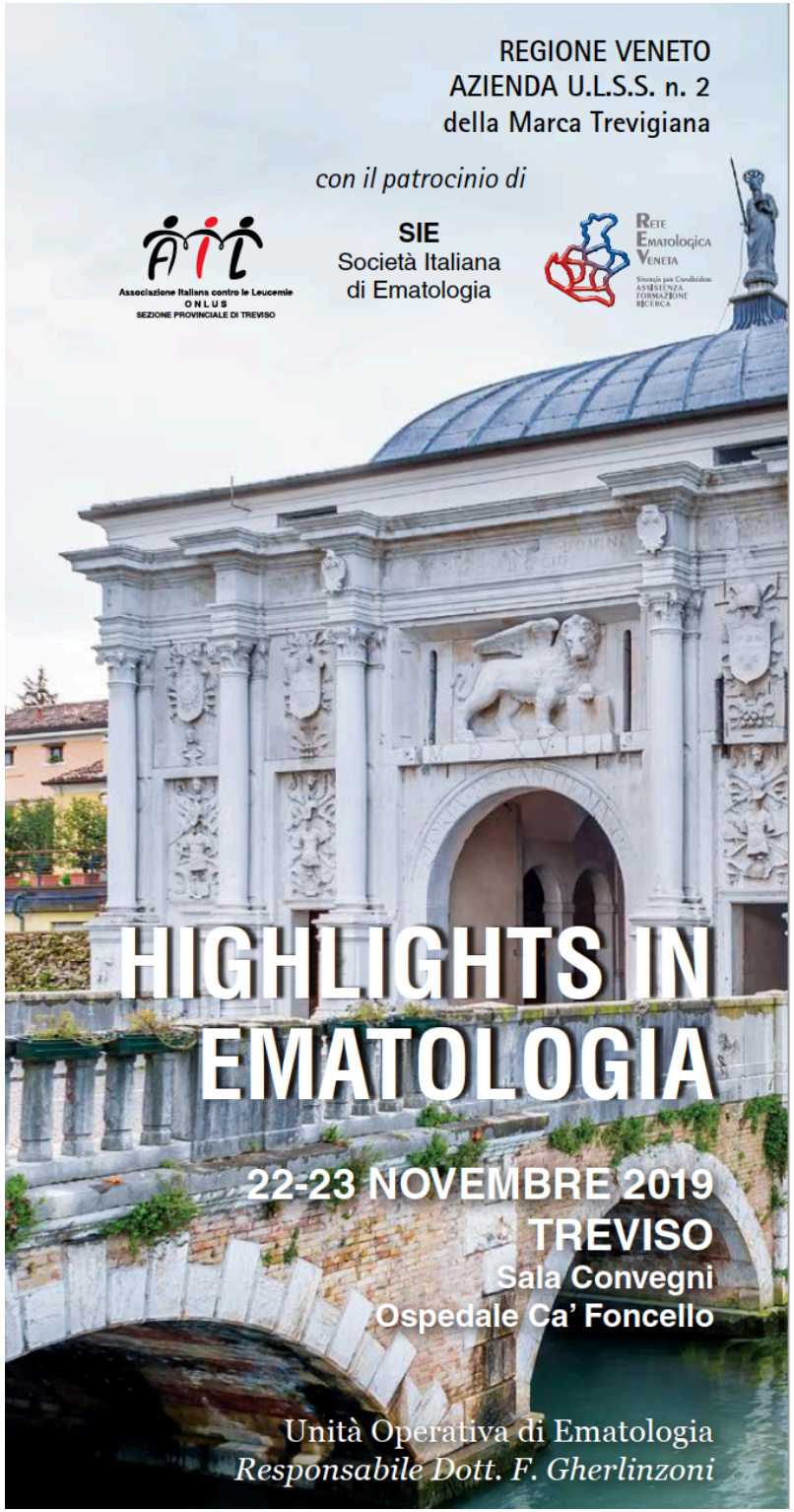


Tossicità renale e nuovi farmaci

Renato Zambello, MD

Dipartimento di Medicina
Università di Padova
Ematologia e Immunologia Clinica

Conflitti di Interesse

Relatore: Renato Zambello

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

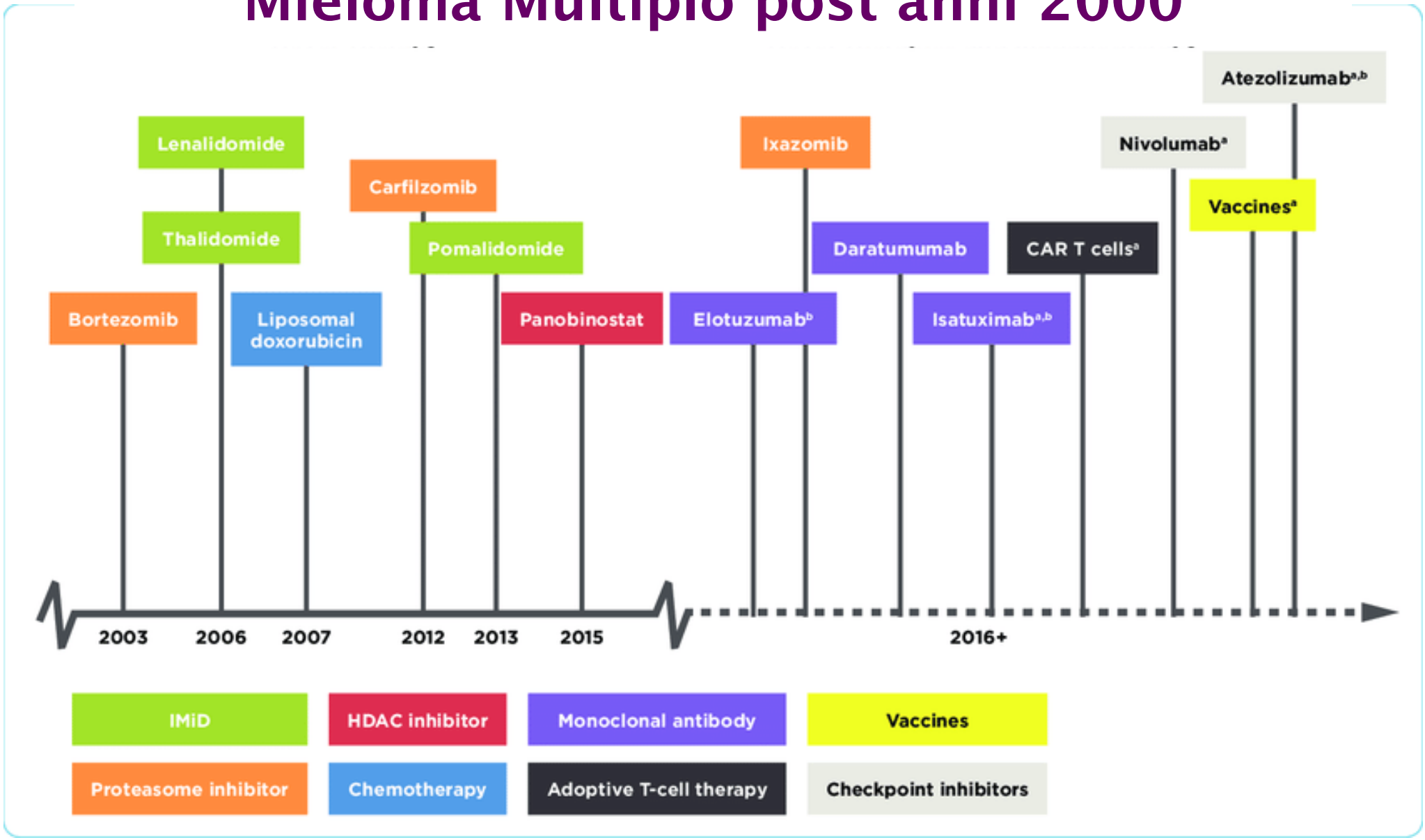
- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(Celgene, Jannsen))**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

Renal Impairment (IR)

- RI reported in 15-40% of MM pts
- *At diagnosis*
  - 30-40% of pts have a serum creatinine above the upper limit of normal
  - 20% have serum creatinine >2 mg/dl
  - 5-10% of pts presents with severe renal failure
- *Causes* = direct tubulo-intestitial damage with typical «myeloma kidney» picture resulting as a direct consequence of (high) FLC excretion
- *Contributing factors* = hypercalcemia, dehydratation, hyperuricemia, amyloid deposition, infections, nephrotoxic medications
- *Impact* = increased risk of complications and early mortality

Dimopoulos MA et al; Leukemia 2008; 22:1485-1193
Dimopoulos MA et al; JCO 2010; 28:4976-4984

Nuovi farmaci nel trattamento del Mieloma Multiplo post anni 2000

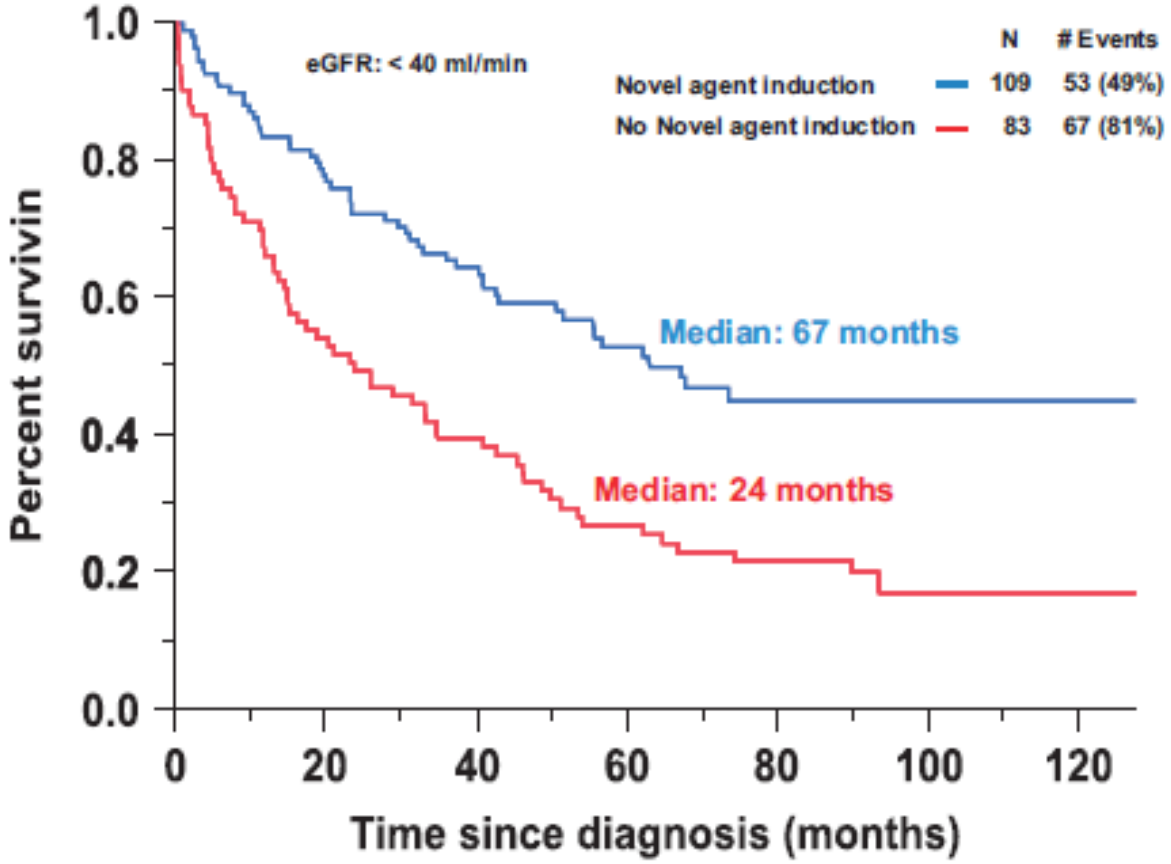


Improvement in renal function and its impact on survival in patients with newly diagnosed multiple myeloma

Blood Cancer Journal 2015

WI Gonsalves, N Leung, SV Rajkumar, A Dispenzieri, MQ Lacy, SR Hayman, FK Buadi, D Dingli, P Kapoor, RS Go, Y Lin, SJ Russell, JA Lust, S Zeldenrust, RA Kyle, MA Gertz and SK Kumar

OS according to novel agents in induction (Thalidomide, Lenalidomide, Bortezomib)



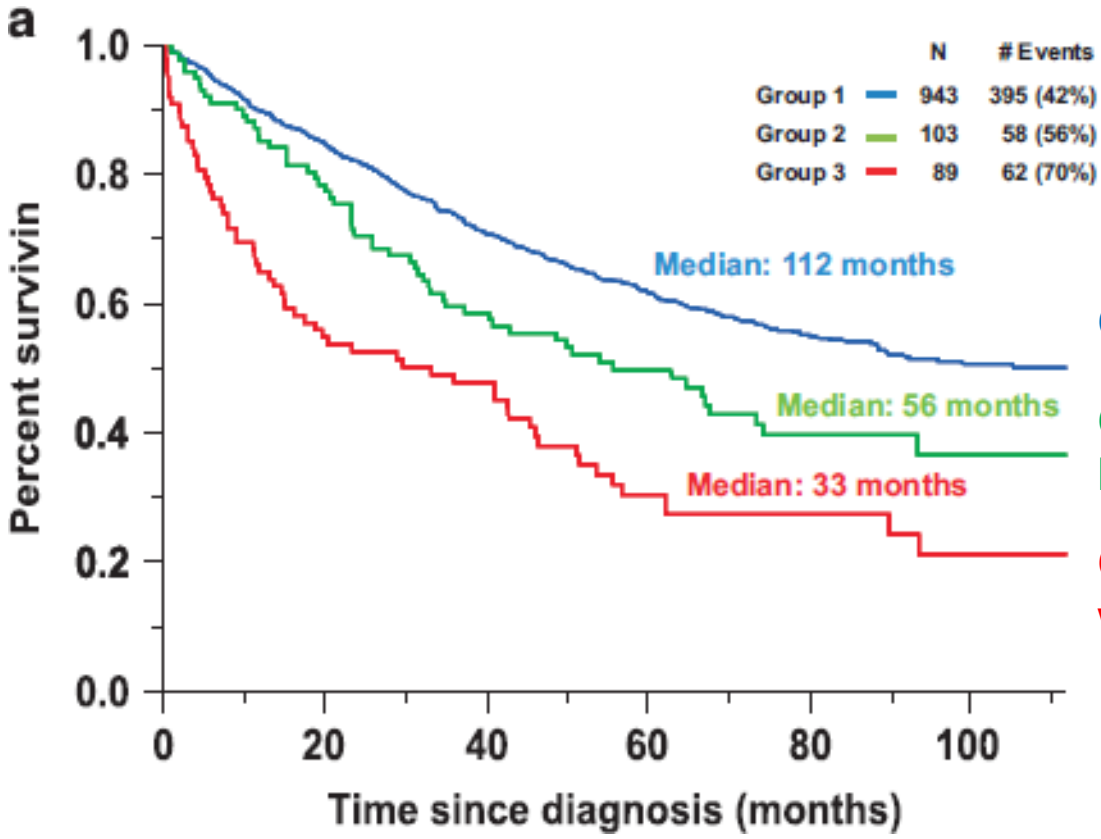
Complete renal response rate:
40% with novel agents
16% without novel agents P < 0.001

Improvement in renal function and its impact on survival in patients with newly diagnosed multiple myeloma

Blood Cancer Journal 2015

WI Gonsalves, N Leung, SV Rajkumar, A Dispenzieri, MQ Lacy, SR Hayman, FK Buadi, D Dingli, P Kapoor, RS Go, Y Lin, SJ Russell, JA Lust, S Zeldenrust, RA Kyle, MA Gertz and SK Kumar

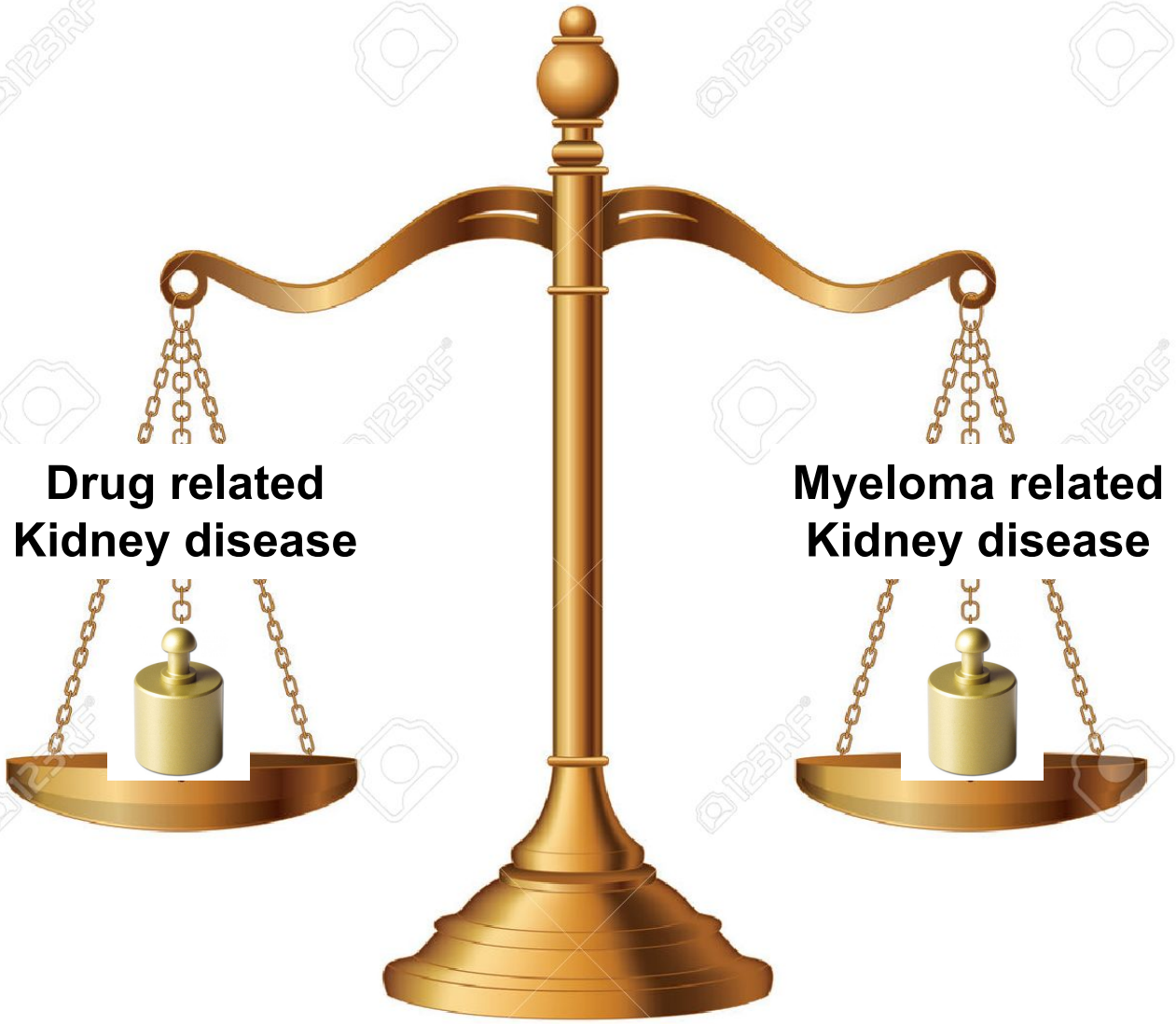
OS according to renal function at diagnosis and response to treatment

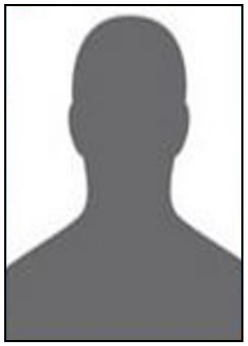


CrCl always ≥ 40 ml/min

CrCl < 40 ml/min at diagnosis but improved after therapy

CrCl < 40 ml/min at diagnosis which did not improve


Drug related
Kidney disease
Myeloma related
Kidney disease



COGNOME E NOME: **B. D.**

Età: **64 anni**

SESSO: **Maschio**

ANAMNESI FISIOLOGICA

- Non tabagismo
- Alcol ai pasti
- Operaio

PATOLOGICA REMOTA

- Nega allergie
- Ipertensione arteriosa
- MGUS IgG/κ in follow up fino al 2013

FARMACI A DOMICILIO

- Lisinopril
- Nifedipina

09/11/16
PADOVA

- Da Agosto calo ponderale di 6 kg ed algie a livello lombo-sacrale
- Nega diatesi infettiva

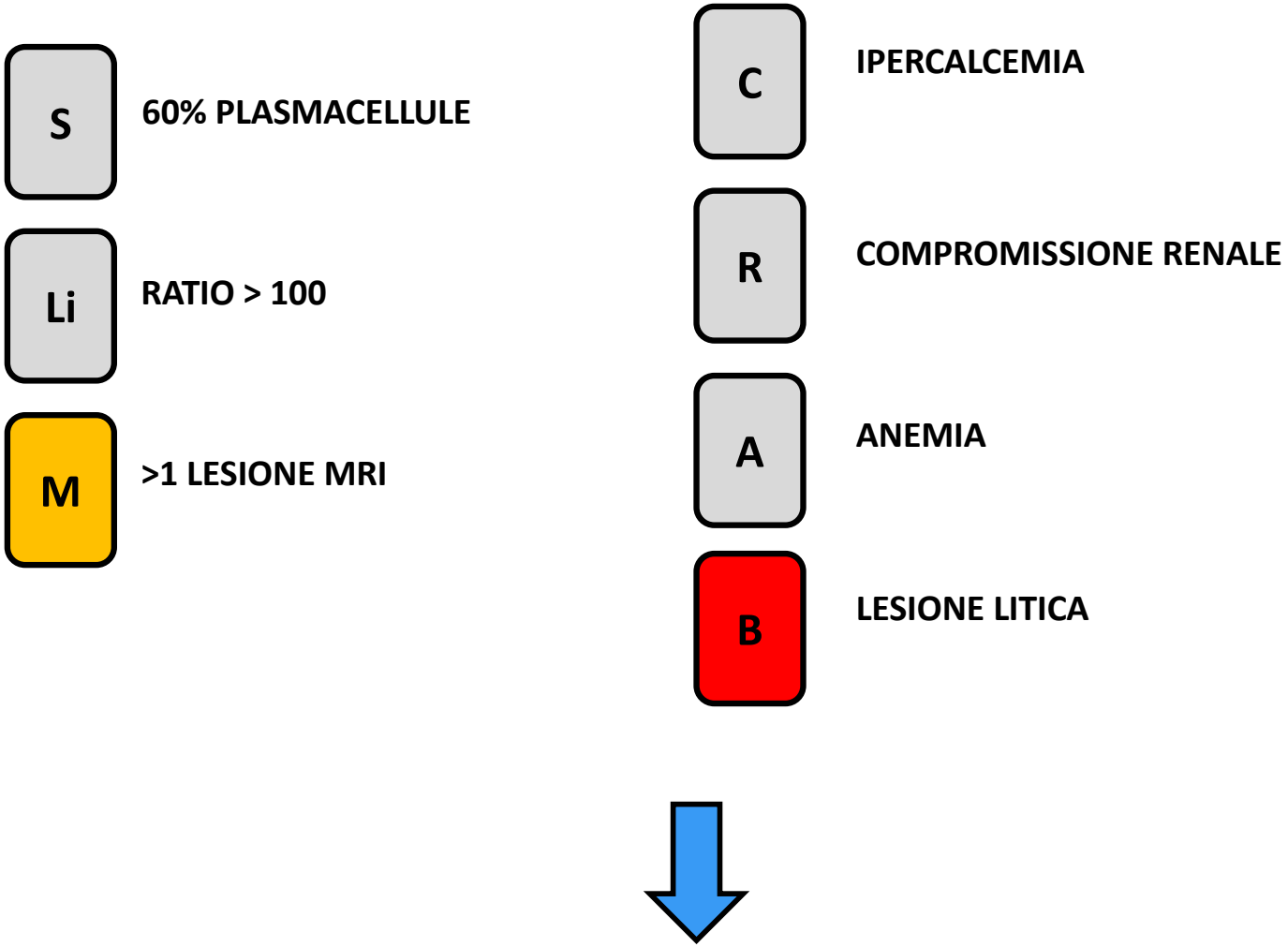
ESAMI EMATOCHIMICI

EMOGLOBINA (g/L)	143
LEUCOCITI (X10^9/L)	8.2
NEUTROFILI (X10^9/L)	6.2
LINFOCITI (X10^9/L)	1,3
PIASTRINE (X10^9/L)	217
β2 microglobulina (mg/L)	**6,2**

CREATININA (UMOL/L)	73
Ca (μMOL/L)	2,3
C.M. g/L	**36**
sFLC	Nei limiti
Immunofissazione urinaria	**Positiva κ**
LAD (fino a 225 U/L)	202

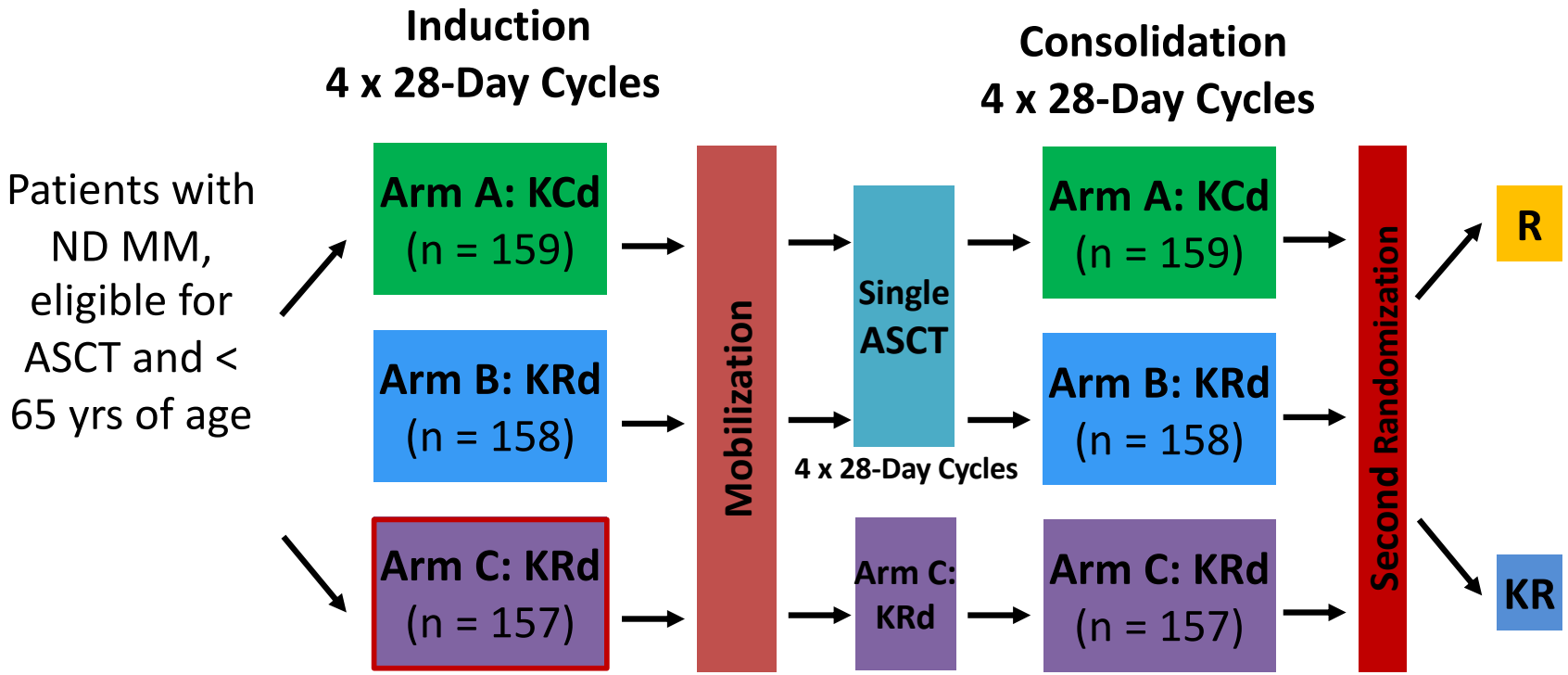
14/11/16
PADOVA

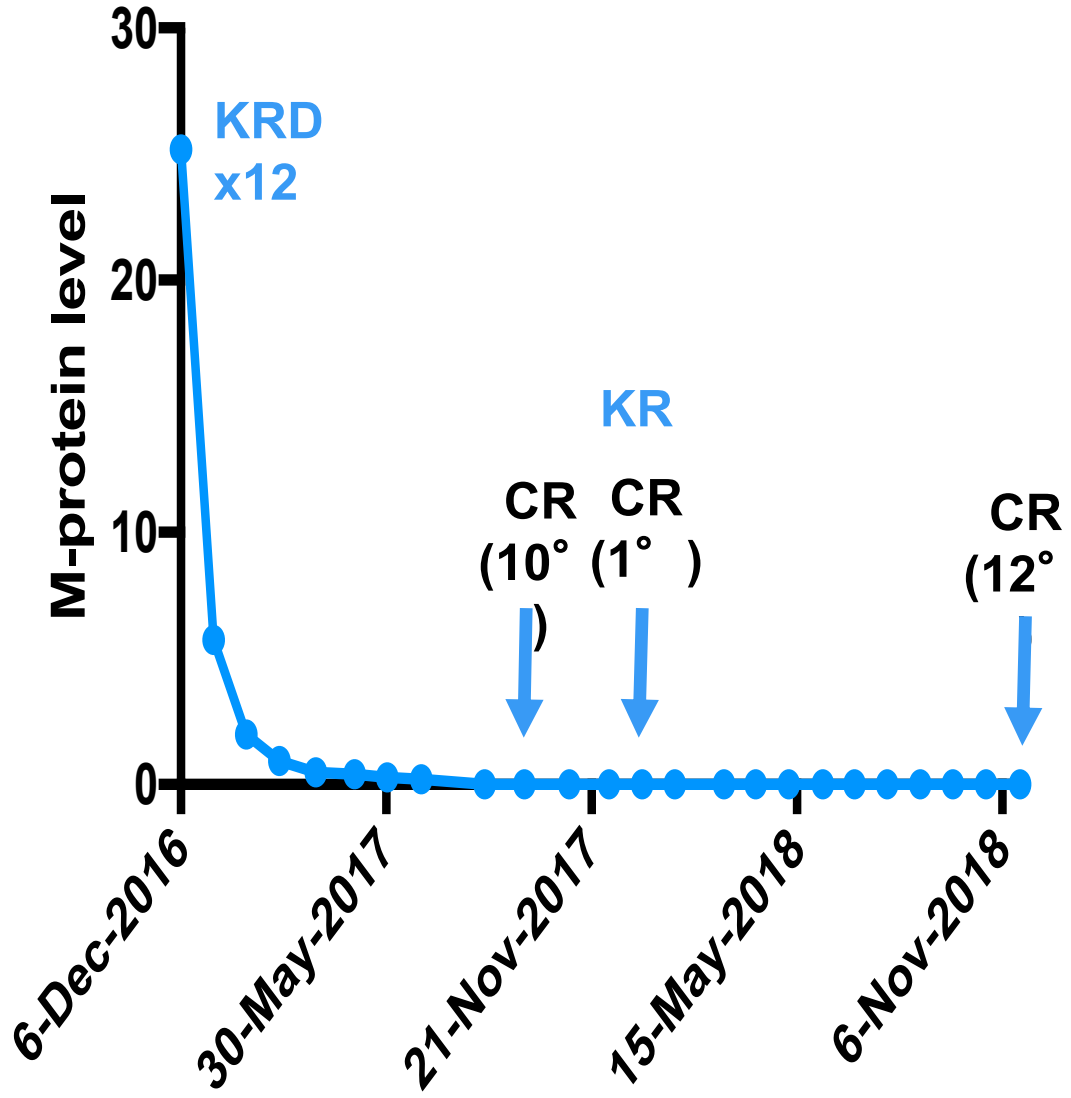
- **BIOPSIA OSTEOMIDOLLARE**: 40% Plasmacellule clonali κ
- **FISH:** assenti t(4;14), t(14;16) e del17p, **presente gain1q**
- **WB MRI DWI: numerose lesioni focali allo scheletro assile e appendicolare**
- **WB LDCT: lesioni osteolitiche diffuse (scheletro assile ed appendicolare), lesione solida a livello di S1-S2 che causa estesa osteolisi (25mm)**



Mieloma Multiplo attivo, ISS II, R-ISS II

FORTE TRIAL


Induction
4 x 28-Day Cycles
Consolidation
4 x 28-Day Cycles
Patients with ND MM, eligible for ASCT and < 65 yrs of age
Arm A: KCd (n = 159)
Arm B: KRd (n = 158)
Arm C: KRd (n = 157)
Mobilization
Single ASCT
4 x 28-Day Cycles
Arm C: KRd
Arm A: KCd (n = 159)
Arm B: KRd (n = 158)
Arm C: KRd (n = 157)
Second Randomization
R
KR


30
20
10
0
M-protein level
KRD
x12
KR
CR
(10°
)
CR
(1°
)
CR
(12°
6-Dec-2016
30-May-2017
21-Nov-2017
15-May-2018
6-Nov-2018

21/11/18
PADOVA

- Iperpiressia e tosse produttiva post infusione di carfilzomib→ stop Lenalidomide, inizia terapia con levofloxacina
- Tentativo fallito di posizionamento di PICC

29/11/18
PADOVA

- Accesso in PS per inappetenza da circa 7 giorni, astenia e contrazione della diuresi→ ricovero in Nefrologia

29/11/18
PADOVA

ESAMI EMATOCHIMICI

EMOGLOBINA (g/L)	70
LEUCOCITI (X10^9/L)	4,34
NEUTROFILI (X10^9/L)	1,98
PIASTRINE (X10^9/L)	59

CREATININA (UMOL/L)	810
Ca (µMOL/L)	2,14
LAD (fino a 225 U/L)	654
AZOTEMIA (UMOL/L)	44

IPOTESI DIAGNOSTICHE?

1. Progressione di malattia?

Esami di rivalutazione compatibili con CR la settimana precedente

2. IRA iatrogena?

Non ha assunto farmaci nefrotossici

1. ???

EMOGLOBINA (g/L)	**70**
LEUCOCITI (X10^9/L)	4,34
NEUTROFILI (X10^9/L)	1,98
PIASTRINE (X10^9/L)	**59**

CREATININA (UMOL/L)	**810**
Ca (µMOL/L)	2,14
LAD (fino a 225 U/L)	**654**
AZOTEMIA (UMOL/L)	**44**

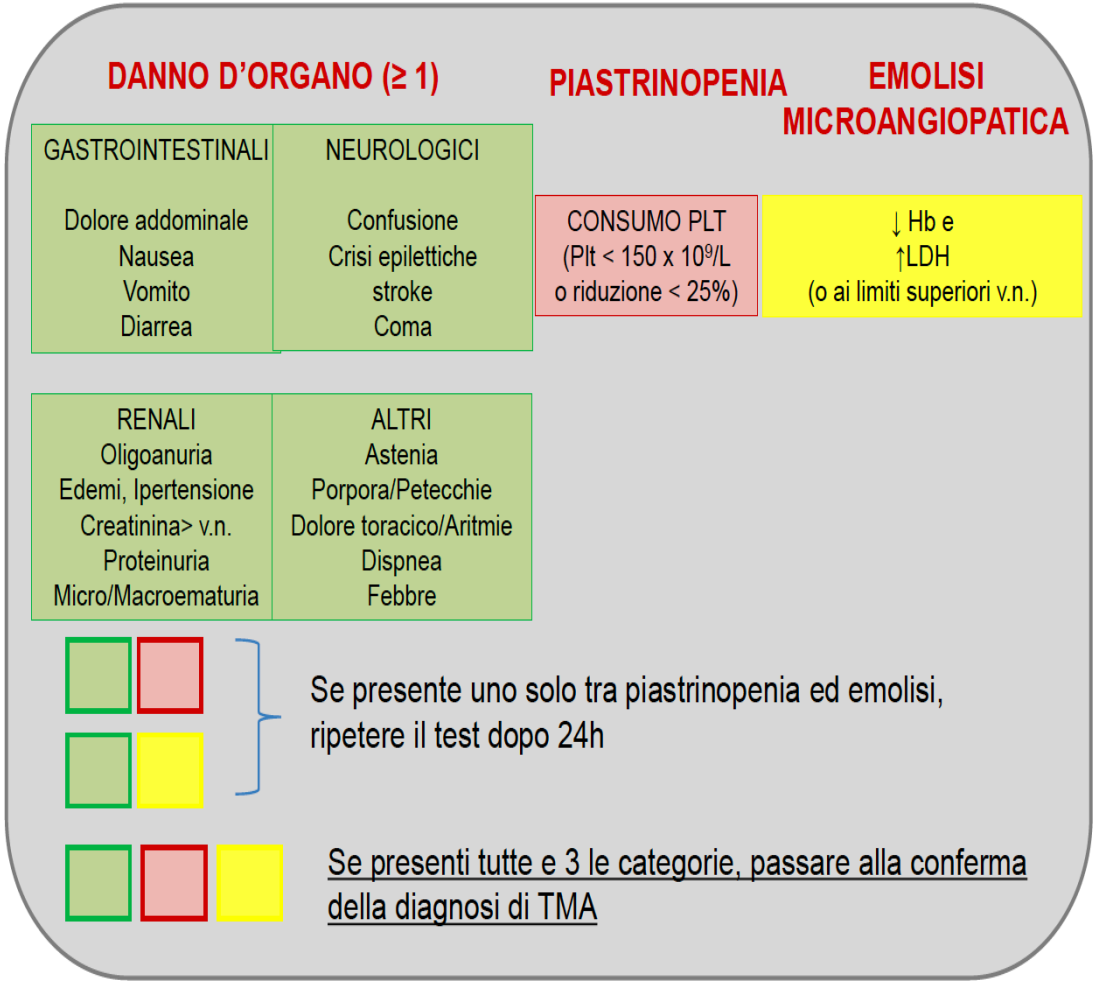
BILIRUBINA TOT (UMOL/L)	**19,2**
BILIRUBINA DIR (µMOL/L)	**7,3**
BILIRUBINA INDIR (µMOL/L	11,9
APTOGLOBINA g/L	**<0,08**

COOMBS DIRETTO	negativo
COOMBS INDIRETTO	negativo
INR	1.1
SCHISTOCITI	**11%**

SOSPETTA MICROANGIOPATIA TROMBOTICA ?

MICROANGIOPATIA TROMBOTICA

Con il termine di **Microangiopatia Trombotica (TMA)** si definisce una patologia caratterizzata da rapida ed ingravescente piastrinopenia e anemia emolitica, secondaria a trombosi delle arteriole e dei capillari.



	TTP (88 pz)	HUS (9 pz)	Other TMA (22 pz)
FEBBRE	36 (41%)	5 (56%)	10 (32%)
SINTOMI NEUROLOGICI	57 (65%)	3 (33%)	7 (32%)
INSUFFICIENZA RENALE	25 (28%)	9 (100%)	11 (50%)
SANGUINAMENTO	68 (77%)	3 (33%)	15 (68%)

G Berti de Marinis et al. *Journal of Thrombosis and Thrombolysis. 2016*

FLOW-CHART APPLICATA AL NOSTRO CASO

Schistociti	Specificare %
Aptoglobina	ridotta
Test di Coombs diretto	negativo
Test coagulazione	Nei range di normalità

SCHISTOCITI	**11%** ✓
APTOGLOBINA	**indosabile** ✓
TEST DI COOMBS DIR.	**negativo** ✓
INR	1.04 ✓

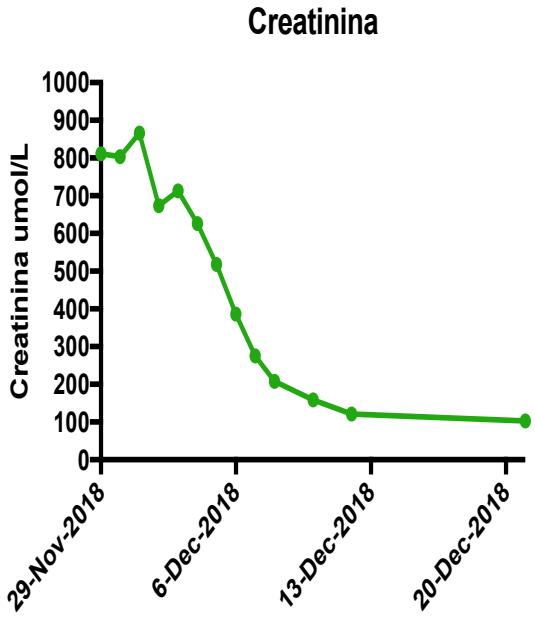
TRATTAMENTO APPLICATO

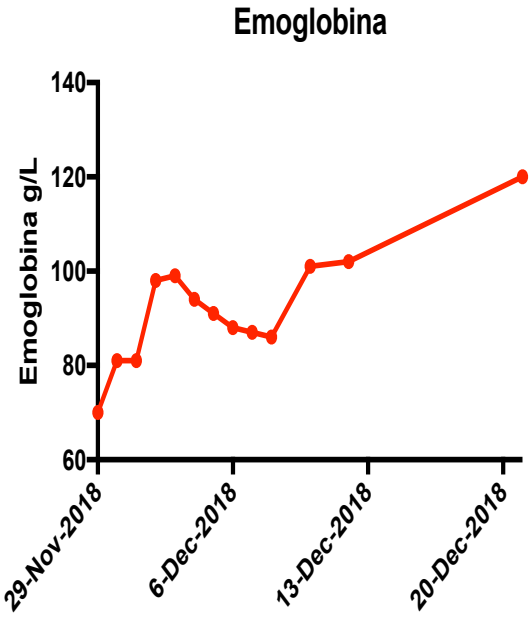
30/11/18
PADOVA

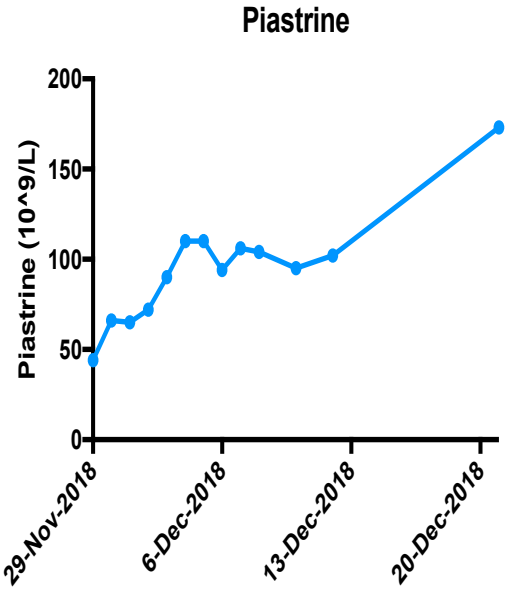
CONSULENZA DI AFERESI TERAPEUTICA: ” …a differenza di altre forme di TMA, nei casi associati al carfilzomib non è indicato lo scambio plasmatico, in quanto **il trattamento elettivo è la sospensione del farmaco e la terapia di supporto**. Si concorda di iniziare scambio plasmatico in assenza di miglioramento del quadro clinico e degli esami correlati alla TMA…”

- **Trasfusione di emazie**
- **Emodialisi**

EVOLUZIONE CLINICA







EPICRISI

18/01/2019
PADOVA

Riprende terapia con sola lenalidomide 10 mg

21/10/2019
PADOVA

Il paziente prosegue terapia di mantenimento
Stato della malattia: CR

Proteasome inhibitor associated thrombotic microangiopathy

Jennifer C. Yui,[1*] Jan Van Keer,[2] Brendan M. Weiss,[3] Adam J. Waxman,[3] Matthew B. Palmer,[4] Vivette D. D'Agati,[5] Efstathios Kastritis,[6] Meletios A. Dimopoulos,[6] Ravi Vij,[7] Dhruv Bansal,[7] David Dingli,[8] Samih H. Nasr,[9] and Nelson Leung[8,10]

American Journal of Hematology, 2016

Thrombotic microangiopathy complicating bortezomib-based therapy for multiple myeloma

Kah-Lok Chan et al*. Leukemia & Lymphoma, 2015*

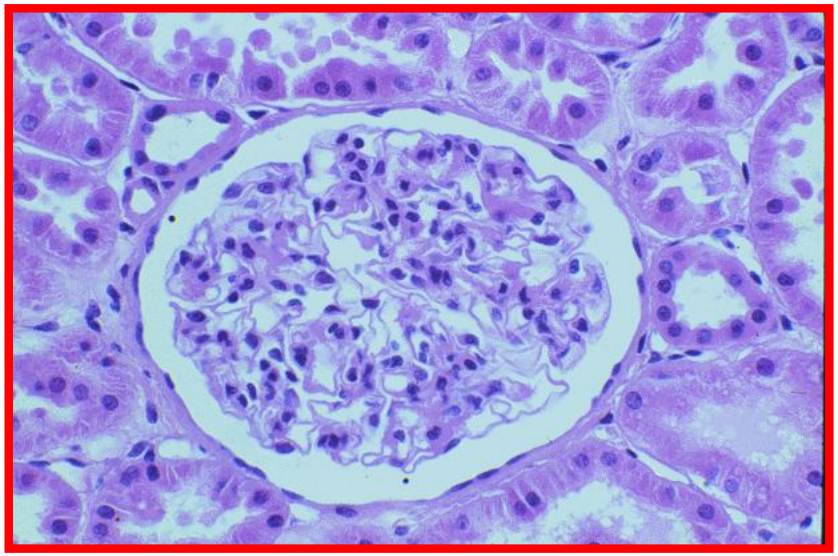
Thrombotic microangiopathy after treatment with bortezomib and dexamethasone in a patient with multiple myeloma

R. Morita et al. *Int J Hematology, 2008*

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

VEGF Inhibition and Renal Thrombotic Microangiopathy



Inibizione produzione VEGF	• Inibitori del proteasoma
Ac anti-VEGF	• Bevacizumab
Inibizione VEGF1-3	• Pazopanib
Inibizione VEGF tirosina kinasi	Sunitinib

Ermina V et al, NEJM 2008

Leukemia (2018) 32:1542–1560
https://doi.org/10.1038/s41375-018-0040-1

REVIEW ARTICLE

Multiple myeloma, gammopathies

Prevention and management of adverse events of novel agents in multiple myeloma: a consensus of the European Myeloma Network

Heinz Ludwig[1] · Michel Delforge[2] · Thierry Facon[3] · Hermann Einsele[4] · Francesca Gay[5] · Philippe Moreau[6] · Hervé Avet-Loiseau[7] · Mario Boccadoro[8] · Roman Hajek[9] · Mohamad Mohty[10] · Michele Cavo[11] · Meletios A Dimopoulos[12] · Jesús F San-Miguel[13] · Evangelos Terpos[12] · Sonja Zweegman[14] · Laurent Garderet[10] · María-Victoria Mateos[15] · Gordon Cook[16] · Xavier Leleu[17] · Hartmut Goldschmidt[18] · Graham Jackson[19] ·

		Teratogenicity	Peripheral neuropathy	Cardiac toxicity	Seizures	Thromboembolic events/DVT	Thrombocytopenia	Hemorrhage	Neutropenia	Anemia	Amenorrhea	Infections	Viral reactivation	Somnolence/drowsiness	Dizziness	Hypotension	Hypertension	Nausea	Vomiting	Diarrhea	Constipation	SPM	Syncope/bradycardia	Infusion reaction	Severe skin reactions	Allergic/hypersensitivity reactions	Hepatic toxicity	Renal toxicity	Edema	Tumor lysis syndrome	Thyroid disorders	Cataract	Pulmonary disorders	Dyspnoea	PML	PRES
IMiDs	Thalidomide	•	•	•	•	•	•		•		•	•	•[a]	•	•							•	•		•	•				•	•					
	Lenalidomide	•	•[b]	•		•	•		•			•										•			•	•				•		•				
	Pomalidomide	•	•[c]	•		•	•		•	•		•			•							•				•	•			•			•			
PIs	Bortezomib	•	•	•	•		•		•	•			•[d]			•		•	•	•	•						•			•			•		•	•
	Carfilzomib	•		•		•[e]	•	•									•							•			•	•		•			•	•		•
	Ixazomib	•	•				•											•	•	•	•				•		•		•							
HDACi	Panobinostat	•		•			•	•	•	•		•						•	•	•	•						•				•					
mABs	Elotuzumab											•										•		•			•									
	Daratumumab						•		•				•											•													

	Published Toxicities	CDK dose adjustement	ESRD dose adjustement
PI			
Bortezomib	TMA, TLS	no	dose after dialysis
Carfilzomib	TMA, TLS, ATN	no	dose after dialysis
Ixazomib	TLS	No in mild to moderate CKD; if <30 ml/min ClCr: 3 mg/week	<30 ml/min ClCr including ESDR: 3 mg/week
IMiDs			
Talidomide	TLS	no	no
Lenalidomide	AKI, AIN, Fanconi Minimal Change Disease , TLS	<30-50 ClCr: 10 mg <30: 7,5 mg o 15 di alt	ESRD: 5 mg after dialysis
Pomalidomide	AKI, cristal nephropaty, TLS	No	dose after dialysis
Mabs			
Elotuzumab	AKI	No	no
Daratumumab	None reported	No	no

TMA: thrombotic microangiopathy; TLS: tumor lysis syndrome; ATN:Acute tubular necrosis; AIN: Acute Intestitial Nephritis; AKI: Acute Kidney Injuries; CKD: chronic kidney disease

	Published Toxicities	CDK dose adjustement	ESRD dose adjustement
PI			
Bortezomib	TMA, TLS	no	dose after dialysis
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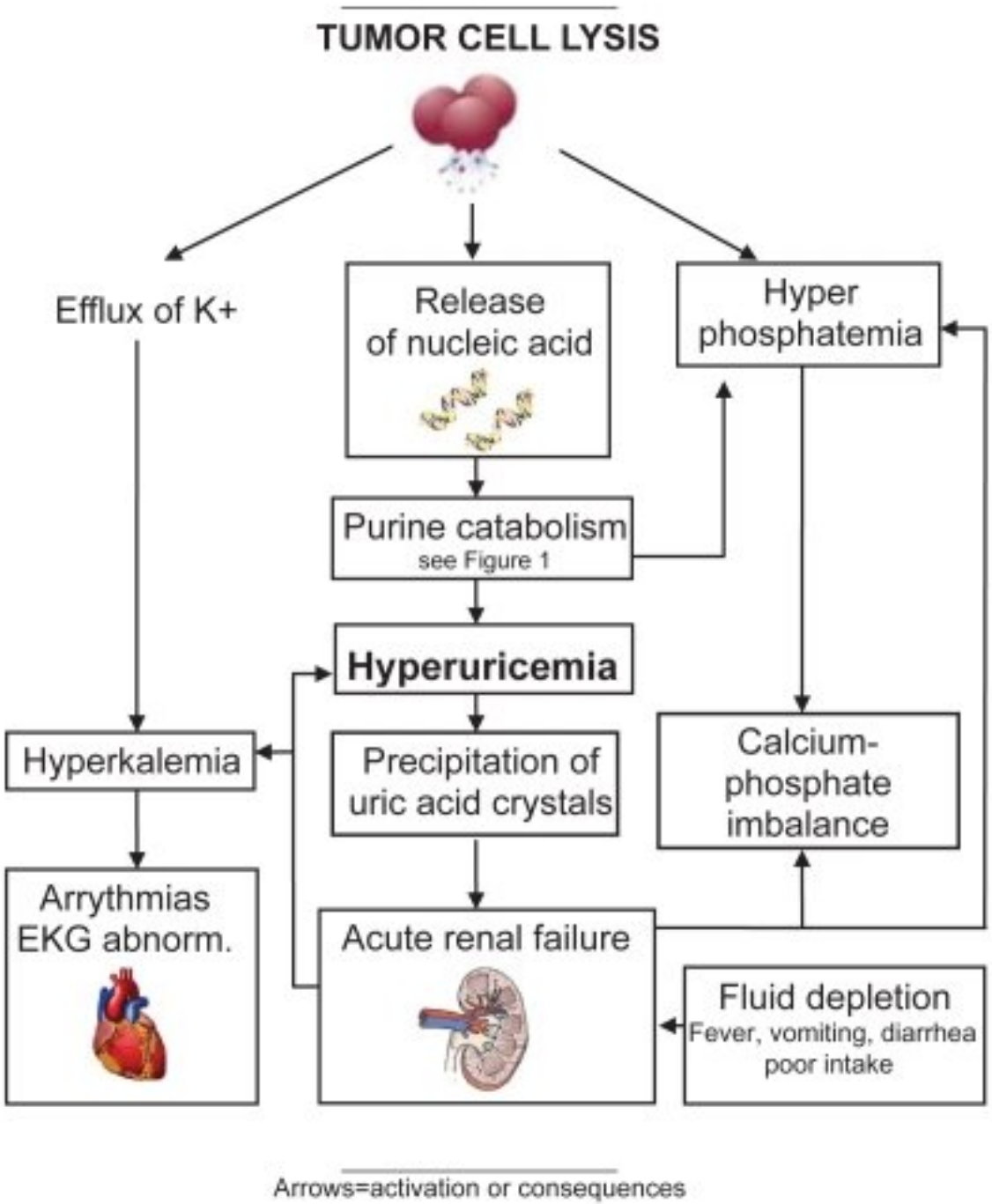
IMiDs			
Talidomide	TLS	no	no
Lenalidomide	AKI, AIN, Fanconi Minimal Change Disease , TLS	<30-50 ClCr: 10 mg <30: 7,5 mg o 15 di alt	ESRD: 5 mg after dialysis
Pomalidomide	AKI, cristal nephropaty, TLS	No	dose after dialysis
Mabs			
Elotuzumab	AKI	No	no
Daratumumab	None reported	No	no

TMA: thrombotic microangiopathy; TLS: tumor lysis syndrome; ATN:Acute tubular necrosis; AIN: Acute Intestitial Nephritis; AKI: Acute Kidney Injuries; CKD: chronic kidney disease


TUMOR CELL LYSIS
Efflux of K+
Release of nucleic acid
Hyper phosphatemia
Purine catabolism
see Figure 1
Hyperuricemia
Hyperkalemia
Precipitation of uric acid crystals
Calcium-phosphate imbalance
Arrythmias EKG abnorm.
Acute renal failure
Fluid depletion
Fever, vomiting, diarrhea poor intake
Arrows=activation or consequences

CARFILZOMIB

Efficacy and safety of carfilzomib in relapsed and/or refractory multiple myeloma: systematic review and meta-analysis of 14 trials

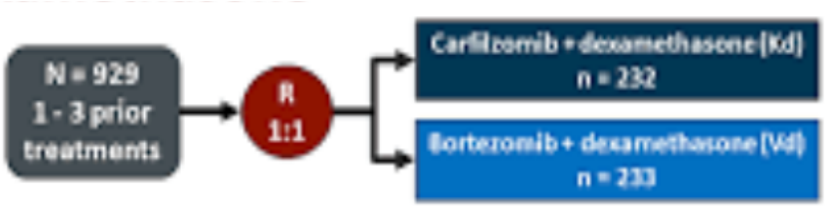
Common Adverse Events

Adverse events	No. of trials	Total events, *N*	Total pts, *N*	I^2 statistics	OR (95% CI)	*P*-value
Hematological						
Anemia	3	336	2036	55.78	1.12 (0.78–1.62)	0.53
Thrombocytopenia	3	267	2036	8.72	1.16 (0.88–1.53)	0.28
Neutropenia	2	250	1107	60.47	0.93 (0.50–1.74)	0.81
Non-hematological						
Neuropathy	3	70	2036	65.46	0.54 (0.18–1.65)	0.28
Renal toxicity	3	90	2036	56.46	1.85 (0.93–3.67)	0.07
Fatigue	2	112	1721	25.82	0.97 (0.62–1.51)	0.87
Diarrhea	2	80	1721	51.76	0.64 (0.33–1.27)	0.20
Nausea	2	13	1244	0	1.60 (0.51–4.99)	0.41
Upper respiratory infection	2	23	1721	0	2.28 (0.93–5.61)	0.07
Pyrexia	3	28	2036	0	4.13 (1.61–10.58)	0.001
Pneumonia	1	29	315	0	0.50 (0.22–1.11)	0.08
Cardiotoxicity	3	61	2036	0	2.04 (1.31–3.17)	0.002
Hypertension	3	64	2036	0	3.33 (1.98–5.60)	<0.0001

Shah et al. Oncotarget 2018

Carfilzomib vs bortezomib in patients with multiple myeloma and renal failure: a subgroup analysis of ENDEAVOR

Meletios Dimopoulos,[1] David Siegel,[2] Darrell J. White,[3,4] Ralph Boccia,[5] Karim S. Iskander,[6] Zhao Yang,[6] Amy S. Kimball,[6] Khalid Mezzi,[6] Heinz Ludwig,[7] and Ruben Niesvizky[8]



KEY POINTS

- **ENDEAVOR reported clinically meaningful PFS and OS improvements with Kd56 vs Vd in RRMM patients with varying degrees of renal impairment.**
- **Patients with complete renal response had superior PFS and OS outcomes compared with nonresponders across treatment groups.**

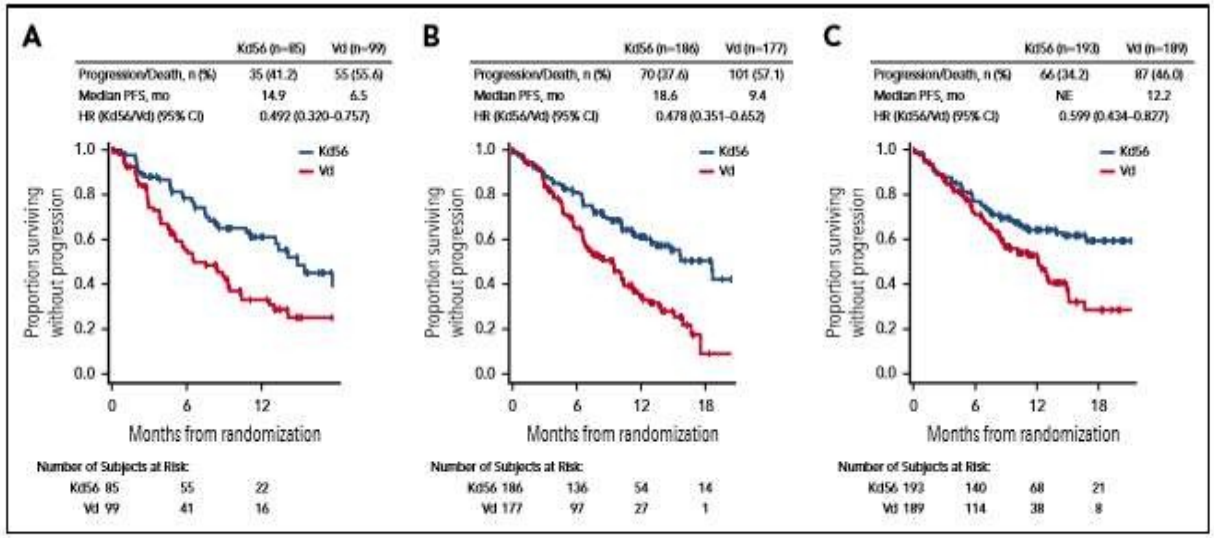


Figure 1. Kaplan-Meier PFS curves for Kd56 and Vd by renal impairment subgroup. CrCL ≥15 to <50 (A), 50 to < 80 (B), and ≥ 80 mL/min (C). Kaplan-Meier curves were displayed until there were ≤10 patients (Kd56 and Vd combined) at risk.

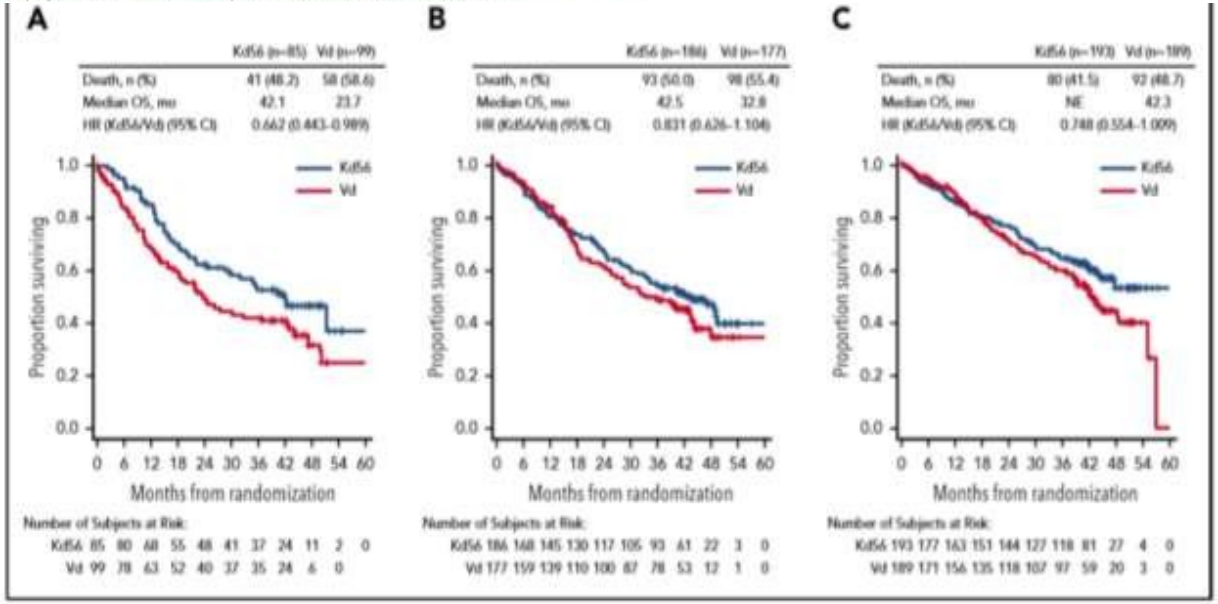


Figure 2. Kaplan-Meier OS curves for Kd56 and Vd by renal impairment subgroup. CrCL ≥15 to <50 (A), 50 to <80 (B), and ≥80 mL/min (C).

Dimopoulos M. et al; Blood 2019, 133(2): 147-155

Pharmacokinetics and safety of carfilzomib in patients with relapsed multiple myeloma and end-stage renal disease (ESRD): an open-label, single-arm, phase I study

Hang Quach[1,2] · Darrell White[3] · Andrew Spencer[4] · P. Joy Ho[5,6] · Divaya Bhutani[7] · Mike White[8] · Sandeep Inamdar[8] · Chris Morris[8] · Ying Ou[8] · Martin Gyger[9]

No clinically meaningful PK differences were observed between patients with normal renal function and patients with ESRD

The 50% ORR in the overall population was similar to those previously reported in trials of carfilzomib 56 mg/m^2 infused for 30 min with or without dexamethasone for relapsed MM (50% in a phase I trial and 55% in a phase II trial)

The observed AE profile in patients with ESRD was similar and generally consistent with the known safety profile of carfilzomib in the treatment of patients with relapsed MM

Based on PK and safety data, no starting dose adjustment of carfilzomib is warranted in patients with MM and ESRD or patients with varying degrees of renal impairment

Cancer Chemother Pharmacol (2017) 79:1067–1076

IXAZOMIB

Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial

*Meletios A Dimopoulos, Francesca Gay, Fredrik Schjesvold, Meral Beksac, Roman Hajek, Katja Christina Weisel, Hartmut Goldschmidt, Vladimir Maisnar, Philippe Moreau, Chang Ki Min, Agnieszka Pluta, Wee-Joo Chng, Martin Kaiser, Sonja Zweegman, Maria-Victoria Mateos, Andrew Spencer, Shinsuke Iida, Gareth Morgan, Kaveri Suryanarayan, Zhaoyang Teng, Tomas Skacel, Antonio Palumbo, Ajeeta B Dash, Neeraj Gupta, Richard Labotka, S Vincent Rajkumar, on behalf of the TOURMALINE-MM3 study group**

Adverse events of Specific Interest

	Ixazomib group (n=394)			Placebo group (n=259)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Common haematological adverse events of any cause						
Other adverse events of clinical interest						
Acute renal failure	11 (3%)	1 (<1%)	0	8 (3%)	1 (<1%)	0
Cardiac arrhythmias	19 (5%)	7 (2%)	0	7 (3%)	2 (1%)	0
Liver impairment	24 (6%)	9 (2%)	0	11 (4%)	3 (1%)	1 (<1%)
Hypotension or orthostatic hypotension	4 (1%)	1 (<1%)	0	1 (<1%)	0	0

Ixazomib Renal Toxicity is limited

The Lancet 2018

	Published Toxicities	CDK dose adjustement	ESRD dose adjustement
PI			
Bortezomib	TMA, TLS	no	dose after dialysis
Carfilzomib	TMA, TLS, ATN	no	dose after dialysis
Ixazomib	TLS	No in mild to moderate CKD; if <30 ml/min ClCr: 3 mg/week	<30 ml/min ClCr including ESDR: 3 mg/week
IMiDs			
Talidomide	TLS	no	no
Lenalidomide	AKI, AIN, Fanconi Minimal Change Disease , TLS	<30-50 ClCr: 10 mg <30: 7,5 mg o 15 di alt	ESRD: 5 mg after dialysis
Pomalidomide	AKI, cristal nephropaty, TLS	No	dose after dialysis
Mabs			
Elotuzumab	AKI	No	no
Daratumumab	None reported	No	no

TMA: thrombotic microangiopathy; TLS: tumor lysis syndrome; ATN:Acute tubular necrosis; AIN: Acute Intestitial Nephritis; AKI: Acute Kidney Injuries; CKD: chronic kidney disease

LENALIDOMIDE

FIRST trial analysis according to Renal Impairment

Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma

Thierry Facon,[1] Meletios A. Dimopoulos,[2] Angela Dispenzieri,[3] John V. Catalano,[4] Andrew Belch,[5] Michele Cavo,[6] Antonello Pinto,[7] Katja Weisel,[8] Heinz Ludwig,[9] Nizar J. Bahlis,[10] Anne Banos,[11] Mourad Tiab,[12] Michel Delforge,[13] Jamie D. Cavenagh,[14] Catarina Geraldes,[15] Je-Jung Lee,[16] Christine Chen,[17] Albert Oriol,[18] Javier De La Rubia,[19] Darrell White,[20] Daniel Binder,[21] Jin Lu,[22] Kenneth C. Anderson,[23] Philippe Moreau,[24] Michel Attal,[25] Aurore Perrot,[26] Bertrand Arnulf,[27] Lugui Qiu,[28] Murielle Roussel,[29] Eileen Boyle,[1] Salomon Manier,[1] Mohamad Mohty,[30] Herve Avet-Loiseau,[31] Xavier Leleu,[32] Annette Ervin-Haynes,[33] Guang Chen,[33] Vanessa Houck,[33] Lotfi Benboubker,[34] and Cyrille Hulin[35]

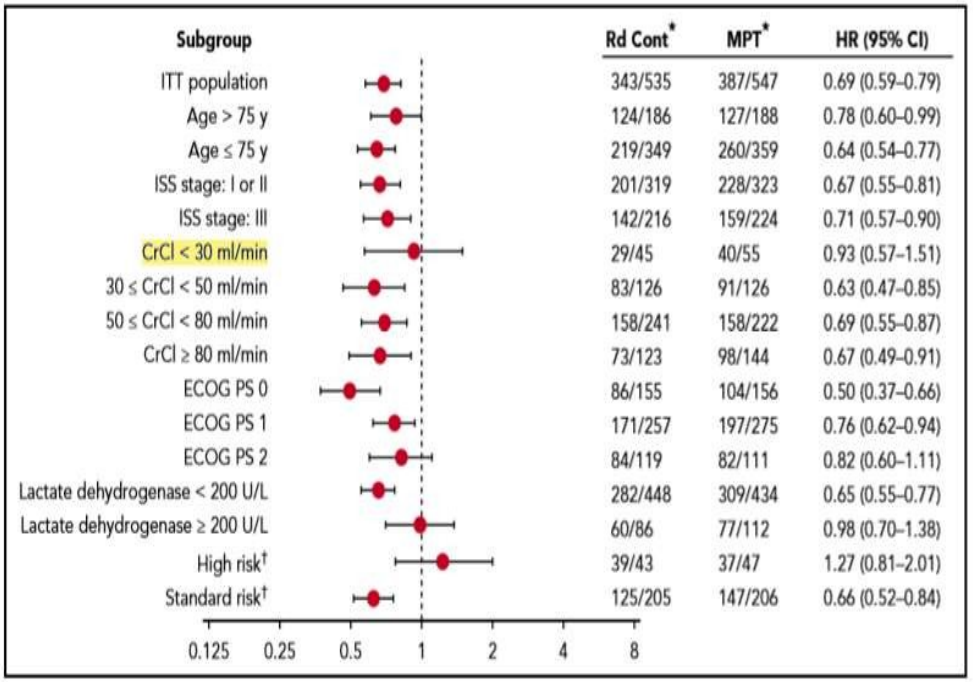


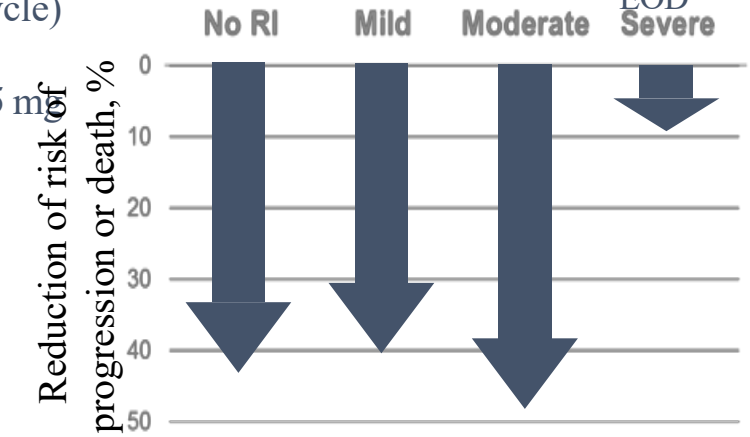
Figure 2. Effect of patient subgroup on PFS. *Number of events per number of patients. †Complete cytogenetics profile for 501 patients (248 in Rd continuous and 253 in MPT); high-risk cytogenetics included t(4;14), t(14;16), and del(17p). cont, continuous; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System.

Rd vs MPT

Dosing (d1-21/28d cycle)

25 mg

25 mg 10 mg 15 mg EOD



More than twice as many patients with mild or moderate renal impairment remained alive and progression-free after 4 years (34.3% vs 12.7% and 26.9% vs 11.8% repectively) (Dimopoulos et al., Haematologica 2016)

Dimopoulos MA et al. Haematologica 2016; 101(3)363-370
Facon T et al. Blood 2018; 131(3):301-310

ARTICLE Open Access

Lenalidomide and dexamethasone in patients with relapsed multiple myeloma and impaired renal function: PrE1003, a PrECOG study

Joseph Mikhael[1,2], Judith Manola[3], Amylou C. Dueck[1], Suzanne Hayman[4], Kurt Oettel[5], Abraham S. Kanate[6], Sagar Lonial[7] and S. Vincent Rajkumar[4]

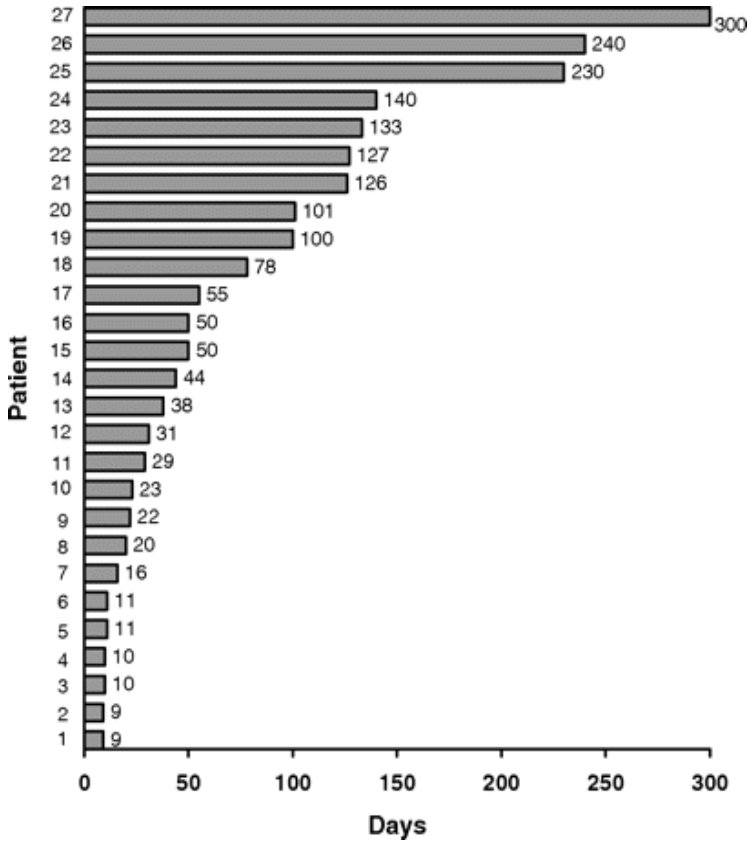
REVLIMID dosing instructions for renal impairment		
Renal Function in MM	**Dose**	**Frequency**
CrCl >60 mL/min		Once daily
CrCl 30-60 mL/min		Once daily
CrCl <30 mL/min (not requiring dialysis)		Every other day
CrCl <30 mL/min (requiring dialysis)		Once daily. On dialysis days, administer the dose following dialysis

Mikhael J. et al; Blood Cancer Journal 2018, 8(86):1-8

Kidney dysfunction during lenalidomide treatment for AL amyloidosis

Richard Specter[1], Vaishali Sanchorawala[2,3], David C. Seldin[2,3], Anthony Shelton[2,3], Salli Fennessey[2,3], Kathleen T. Finn[2,3], Jerome B. Zeldis[4] and Laura M. Dember[1,2]

Days from initiation of lenalidomide to kidney dysfunction (≥ 50% increase in serum creatinine) for each of the 27 patients



Nephrology Dialysis Transplantation, Volume 26, Issue 3, March 2011, Pages 881–886, https://doi.org/10.1093/ndt/gfq482

POMALIDOMIDE

Pharmacokinetic properties of Pomalidomide and Lenalidomide are different

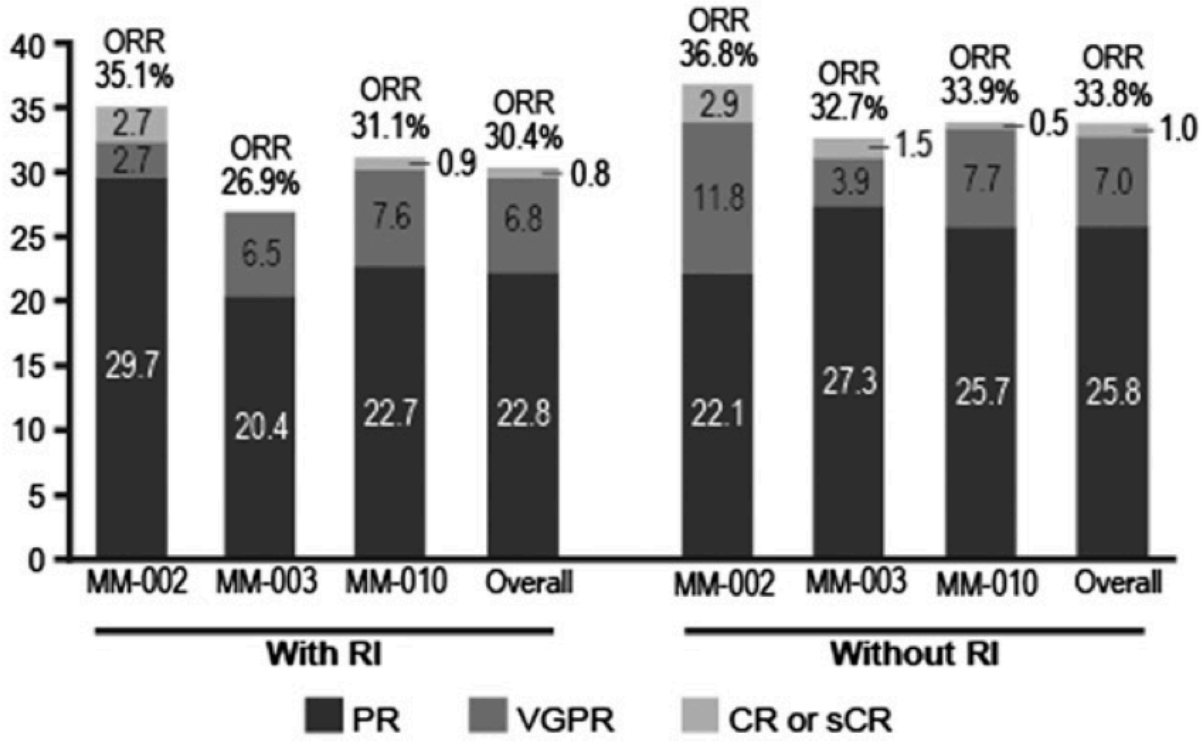
Pharmacokinetic property	LEN[1,2]	POM[1,3]
Absorption, time to C_{max}, h	0.5–2	2–3
Elimination, median plasma half-life, h		
Healthy volunteers	~3	~9.5
Myeloma patients	~3–5	~7.5
Excretion, % excreted unchanged in urine	**82**	**2**

C_{max}, maximum concentration

1. Dimopoulos MA, et al. Leukemia. 2014 Feb 5 [Epub ahead of print].
2. [redacted]
3. [redacted]

Pomalidomide plus low-dose dexamethasone in patients with relapsed/refractory multiple myeloma and moderate renal impairment: a pooled analysis of three clinical trials

David S. Siegel[a], Katja C. Weisel[b], Meletios A. Dimopoulos[c], Rachid Baz[d], Paul Richardson[e], Michel Delforge[f], Kevin W. Song[g], Jesus F. San Miguel[h], Philippe Moreau[i], Hartmut Goldschmidt[j], Michele Cavo[k], Sundar Jagannath[l], Xin Yu[m], Kevin Hong[m], Lars Sternas[m], Mohamed Zaki[m] and Antonio Palumbo[n]



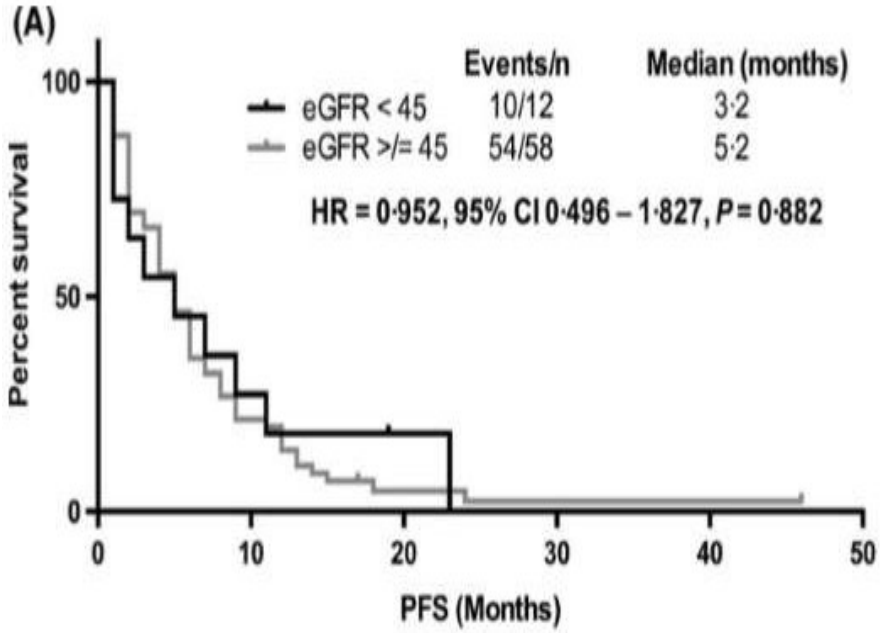
Overall response rate (ORR) in patients with baseline renal impairment (RI; creatinine clearance [CrCl] > 30 and <60mL/min) and without baseline RI (>60mL/min).

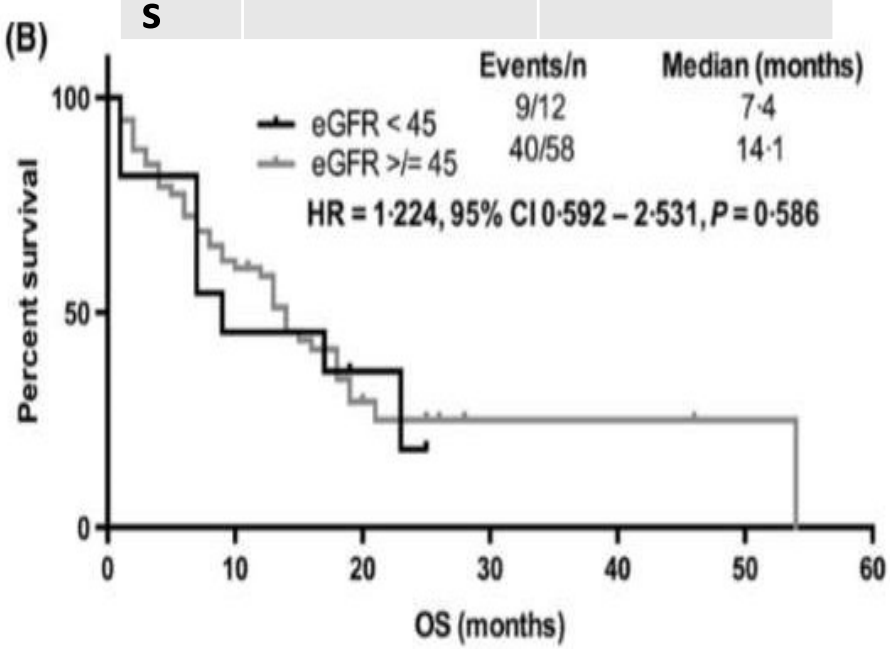
LEUKEMIA & LYMPHOMA, 2016

Real-world use of pomalidomide and dexamethasone in double refractory multiple myeloma suggests benefit in renal impairment and adverse genetics: a multi-centre UK experience

Nicola Maciocia,[1] Andrew Melville,[1] Simon Cheesman,[2] Faye Sharpley,[3] Karthik Ramasamy,[3] Matthew Streetly,[4] Matthew Jenner,[5] Reuben Benjamin,[6] Steve Schey,[6] Paul Maciocia,[1] Rakesh Popat,[1] Shirley D'sa,[1] Ali Rismani,[7] Aviva Cerner,[1] Kwee Yong[1] and Neil Rabin[1]

Effect of renal impairment		
	GFR <45 ml/min	GFR >45 ml/min
ORRs	50%	53,4%

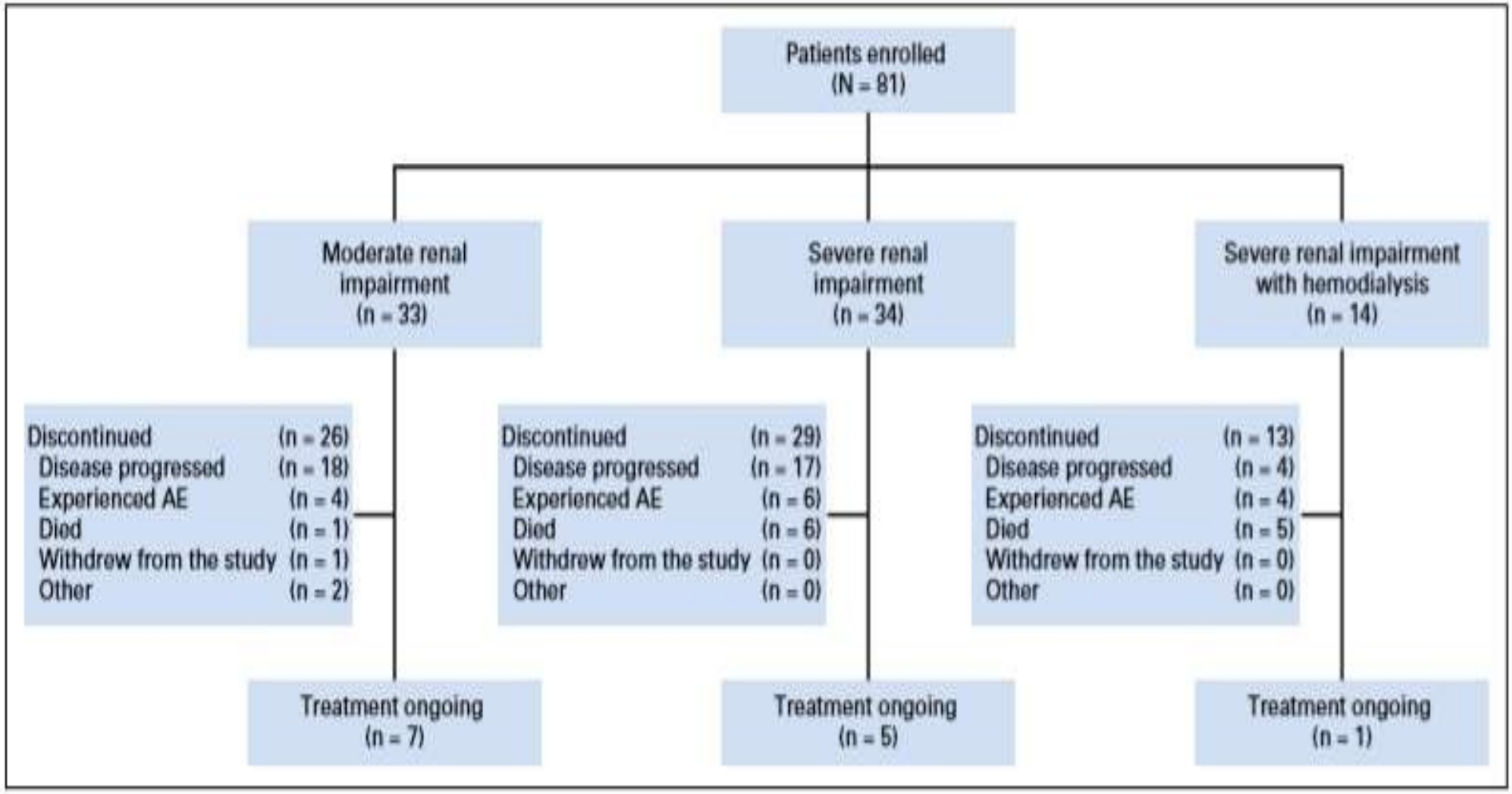




Maciocia N. et al; BJH 2017; 176: 908-917

Pomalidomide Plus Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma and Renal Impairment: Results From a Phase II Trial

Meletios Dimopoulos, Katja Weisel, Niels W.C.J. van de Donk, Karthik Ramasamy, Barbara Gamberi, Matthew Streetly, Massimo Offidani, Frank Bridoux, Javier de la Rubia, Maria-Victoria Mateos, Antonio Ardizzoia, Elisabeth Kueenburg, Shona Collins, Antonia Di Micco, Barbara Rosettani, Yan Li, Pamela Bacon, and Pieter Sonneveld



Dimopoulos MA et al; JCO 2018, 36(20): 2035-2043

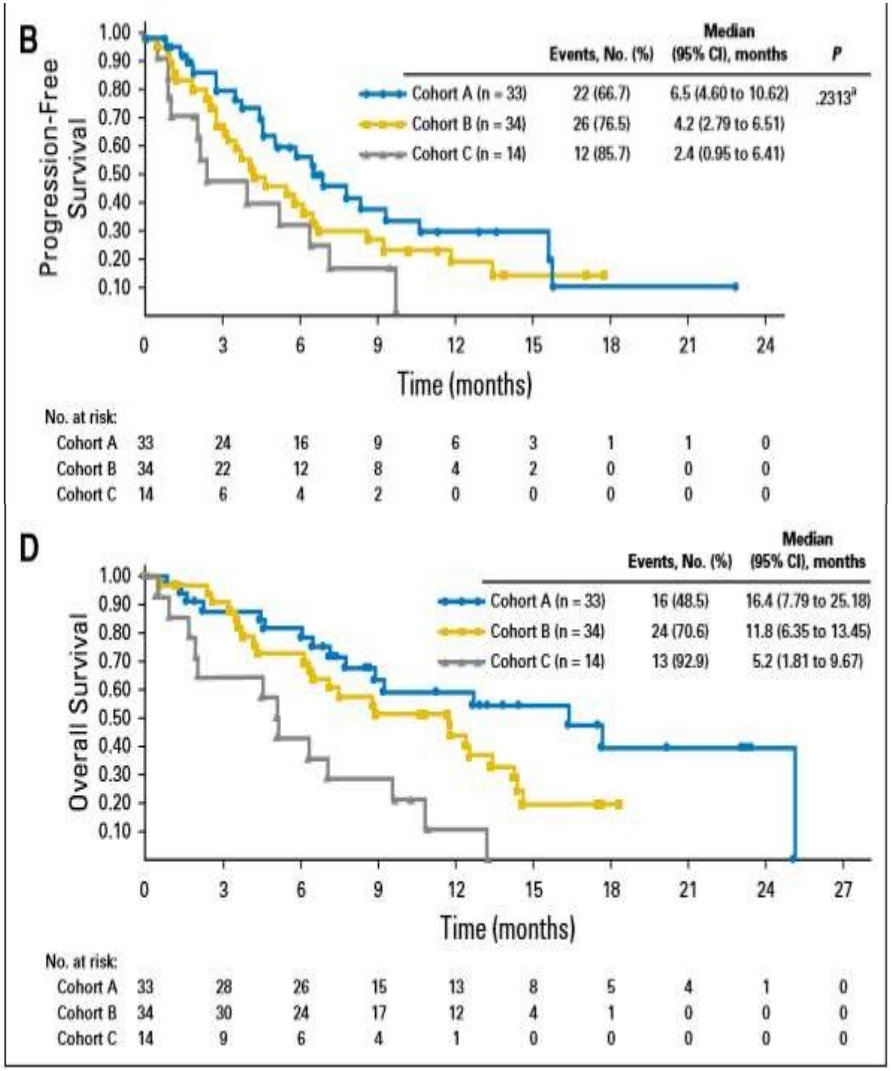
Pomalidomide + LoDex

- ha determinato un beneficio clinico in termini di OS e ORR in tutte le coorti

Myeloma Response			
	Cohort A (moderate RI)	Cohort B (severe RI)	Cohort C (HD)
ORRs (mos)	39,4	32,4	14,3
DoR (mos)	14,7	4,6	NE
OS (mos)	16,4	11,8	5,2
PFS (mos)	6,5	4,2	2,4

Pomalidomide Plus Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma and Renal Impairment: Results From a Phase II Trial

Meletios Dimopoulos, Katja Weisel, Niels W.C.J. van de Donk, Karthik Ramasamy, Barbara Gamberi, Matthew Streetly, Massimo Offidani, Frank Bridoux, Javier de la Rubia, Maria-Victoria Mateos, Antonio Ardizzoia, Elisabeth Kueenburg, Shona Collins, Antonia Di Micco, Barbara Rosettani, Yan Li, Pamela Bacon, and Pieter Sonneveld



	Published Toxicities	CDK dose adjustement	ESRD dose adjustement
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Talidomide	TLS	no	no
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Elotuzumab	AKI	No	no
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TMA: thrombotic microangiopathy; TLS: tumor lysis syndrome; ATN:Acute tubular necrosis; AIN: Acute Intestitial Nephritis; AKI: Acute Kidney Injuries; CKD: chronic kidney disease

ELOTUZUMAB

Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma

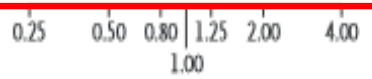
Sagar Lonial, M.D., Meletios Dimopoulos, M.D., Antonio Palumbo, M.D., Darrell White, M.D., Sebastian Grosicki, M.D., Ph.D., Ivan Spicka, M.D., Adam Walter-Croneck, M.D., Philippe Moreau, M.D., Maria-Victoria Mateos, M.D., Ph.D., Hila Magen, M.D., Andrew Belch, M.D., Donna Reece, M.D., Meral Beksac, M.D., Andrew Spencer, M.D., Heather Oakervee, M.D., Robert Z. Orlowski, M.D., Masafumi Taniwaki, M.D., Christoph Röllig, M.D., Hermann Einsele, M.D., Ka Lung Wu, M.D., Anil Singhal, Ph.D., Jesus San-Miguel, M.D., Morio Matsumoto, M.D., Jessica Katz, M.D., Ph.D., Eric Bleickardt, M.D., Valerie Poulart, M.Sc., Kenneth C. Anderson, M.D., and Paul Richardson, M.D., for the ELOQUENT-2 Investigators

PATIENTS

Eligible patients were 18 years of age or older and had multiple myeloma and measurable disease. All patients had received one to three previous therapies and had documented disease progression after their most recent therapy. All patients had a creatinine clearance of 30 ml per minute or higher. Previous treatment with lenalidomide was permitted, subject to restrictions (see the Supplementary Appendix, available at NEJM.org).

B Subgroup Analyses

Subgroup	Elotuzumab	Control	Hazard Ratio (95% CI)
	no. of events (total no. of patients)		
Age			
<65 yr	78 (134)	87 (142)	0.75 (0.55–1.02)
≥65 yr	101 (187)	118 (183)	0.65 (0.50–0.85)
Baseline β_2-microglobulin			
<3.5 mg/liter	82 (173)	107 (179)	0.61 (0.46–0.81)
≥3.5 mg/liter	97 (147)	98 (146)	0.79 (0.60–1.05)
ISS stage at enrollment			
I	68 (141)	80 (138)	0.63 (0.46–0.87)
II	60 (102)	67 (105)	0.86 (0.61–1.22)
III	48 (66)	50 (68)	0.70 (0.47–1.04)
Response to most recent line of therapy			
Resistance	67 (113)	77 (114)	0.56 (0.40–0.78)
Relapse	112 (207)	128 (211)	0.77 (0.60–1.00)
No. of lines of previous therapy			
1	85 (151)	101 (159)	0.75 (0.56–1.00)
2 or 3	94 (170)	104 (166)	0.65 (0.49–0.87)
Previous IMiD therapy			
None	85 (155)	91 (151)	0.78 (0.58–1.05)
Thalidomide only	85 (150)	101 (153)	0.64 (0.48–0.85)
Other	9 (16)	13 (21)	0.59 (0.25–1.40)
Previous bortezomib			
Yes	132 (219)	150 (231)	0.68 (0.54–0.86)
No	47 (102)	55 (94)	0.72 (0.49–1.07)
Previous lenalidomide			
Yes	9 (16)	13 (21)	0.59 (0.25–1.40)
No	170 (305)	192 (304)	0.70 (0.57–0.87)
Previous stem-cell transplantation			
Yes	102 (167)	117 (185)	0.75 (0.58–0.99)
No	77 (154)	88 (140)	0.63 (0.46–0.86)
Mutations			
del(17p)	50 (102)	61 (104)	0.65 (0.45–0.94)
1q21	88 (147)	105 (163)	0.75 (0.56–0.99)
t(4;14)	21 (30)	25 (31)	0.53 (0.29–0.95)
Baseline creatinine clearance			
<60 ml/min	53 (96)	55 (75)	0.56 (0.39–0.82)
≥60 ml/min	126 (225)	150 (250)	0.74 (0.58–0.94)

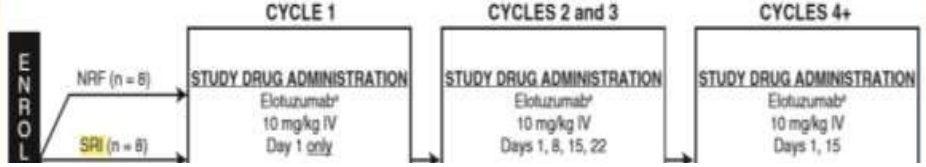


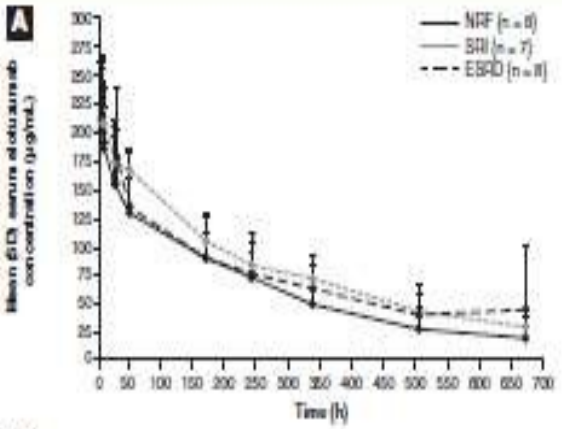
Lonial S. et al; NEJM 2015, 373(7): 621-631

Pharmacokinetics and Safety of Elotuzumab Combined With Lenalidomide and Dexamethasone in Patients With Multiple Myeloma and Various Levels of Renal Impairment: Results of a Phase Ib Study

Jesus Berdeja,[1] Sundar Jagannath,[2] Jeffrey Zonder,[3] Ashraf Badros,[4] Jonathan L. Kaufman,[5] Robert Manges,[6] Manish Gupta,[7] Amol Tendolkar,[7] Mark Lynch,[8] Eric Bleickardt,[8] Prashni Paliwal,[8] Ravi Vij[9]

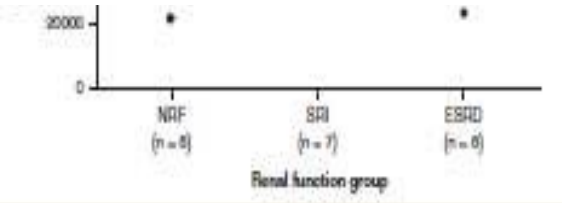
Figure 1 Study Design Showing the Number of Patients Planned for Enrollment. [a]Premedication With an H1 Blocker (Diphenhydramine, 25-50 mg, or Equivalent), an H2 Blocker (Ranitidine, 50 mg, Adjusted for Renal Failure, or Equivalent), and Acetaminophen (650-1000 mg) Was Required 30-90 Minutes Before Elotuzumab Administration. [b]In All Patients, Lenalidomide Was Given Daily for 21 Days of a 28-day Cycle: Normal Renal Function (NRF), 25 mg Orally (p.o.) Once Daily; Severe Renal Impairment (SRI), 15 mg p.o. Every 48 Hours; End-Stage Renal Disease (ESRD), 5 mg p.o. Once Daily. [c]Weeks Without Elotuzumab: 40 mg p.o.; Weeks With Elotuzumab 8 mg Intravenously (I.V.) Plus 28 mg p.o.





Preferred Term	NRF (n = 8)		SRI (n = 9)		ESRD (n = 9)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Injury, poisoning, and procedural complications	1 (13)	0	4 (44)	0	2 (22)	0
Renal and urinary disorders	1 (13)	0	3 (33)	1 (11)	0	0
Vascular disorders	1 (13)	0	4 (44)	3 (33)	2 (22)	1 (11)

Elotuzumab Pharmacokinetics (PK) Values Stratified by Renal Function[a]: (A) Elotuzumab Serum Concentration Profiles Over Time From Initial Elotuzumab Dose[b]; (B) Maximum Observed Serum Concentration (C_{max}); (C) Area Under the Concentration–Time Curve From Time 0 to Infinity [$AUC_{0\infty}$]. [a]Three Patients Were Excluded From the PK Summary Statistics Because of a Dosing Error (End-Stage Renal Disease [ESRD] Group, n = 1), Estimated Glomerular Filtration Rate (eGFR) Outside the Value Limit Range (Severe Renal Impairment [SRI] Group, n = 1), and Limited Samples or Biologically Implausible Time Corresponding to C_{max} (T_{max}) at 672 Hours (SRI Group, n = 1). [b]Mean 48-hour Dialysis Values Were Excluded in 1 Patient



DARATUMUMAB

Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma

Saad Z. Usmani,[1] Brendan M. Weiss,[2] Torben Plesner,[3] Nizar J. Bahlis,[4] Andrew Belch,[5] Sagar Lonial,[6] Henk M. Lokhorst,[7] Peter M. Voorhees,[8] Paul G. Richardson,[9] Ajai Chari,[10] A. Kate Sasser,[11] Amy Axel,[11] Huaibao Feng,[12] Clarissa M. Uhlar,[11] Jianping Wang,[11] Imran Khan,[12] Tahamtan Ahmadi,[11] and Hareth Nahi[13]

Subgroup analyses revealed that responses were observed across all subgroups regardless of the number or type of prior lines of therapy, refractory status, renal function, or baseline percentage of plasma cells in the bone marrow (Figure 2). The ORRs in patients with heavy chain (31.8% [107 patients]) and light chain (29.3% [41 patients]) disease were consistent with those in the total population. Cytogenetic data were not collected for GEN501 part 2. ORRs for high-, standard-, and low-risk patients in SIRIUS were reported previously.[12] Importantly, the ORR in patients with impaired renal function (ie, creatinine clearance of >30 to ≤60 mL/min) was consistent with that observed in the overall population.

	GEN501 (n = 42)		SIRIUS (n = 106)		Combined studies (N = 148)	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**
Age, y						
Median (range)	64.0 (44-76)		63.5 (31-84)		64.0 (31-84)	
65 to <75	16	38	36	34	52	35
≥75	4	10	12	11	16	11
Sex						
Female	15	36	54	51	69	47
Male	27	64	52	49	79	53
ECOG performance score						
0	12	29	29	27	41	28
1	28	67	69	65	97	66
2	2	5	8	8	10	7
Renal function at baseline (creatinine clearance), mL/min						
≥60	29	69	60	57	89	60
≥30 to <60	12	29	42	40	54	37
<30	1	2	4	4	5	3

Usmani SZ. et al; Blood 2016; 128(1):37-44

Safety and efficacy of daratumumab in dialysis-dependent renal failure secondary to multiple myeloma

Serena Rocchi, Paola Tacchetti, Lucia Pantani, Katia Mancuso, Beatrice Zannetti, Michele Cavo and Elena Zamagni

[1]"Seràgnoli" Institute of Hematology, Bologna University School of Medicine, Italy

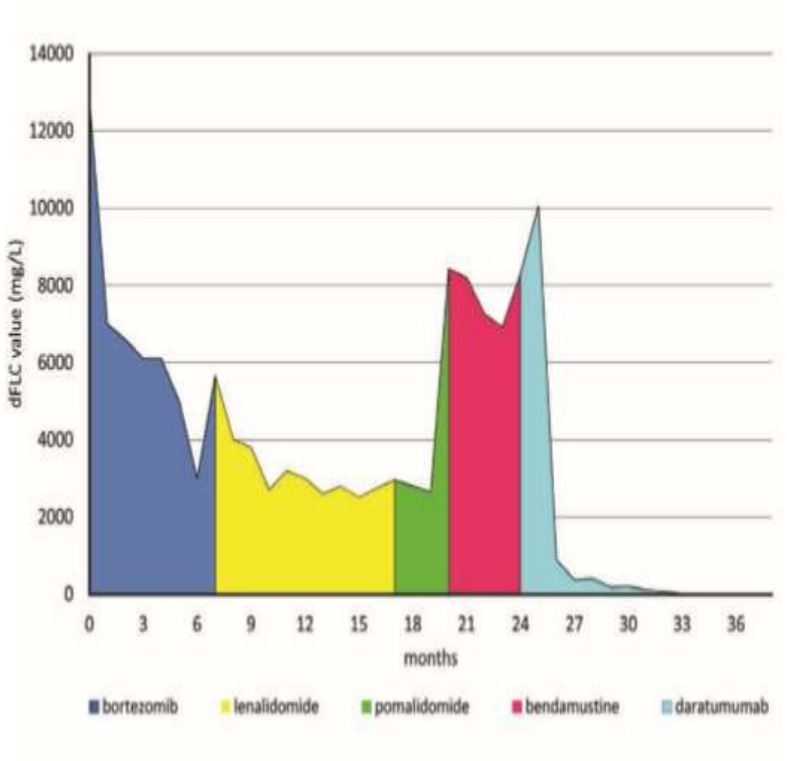


Figure 1. Trend of dFLC from first to fifth line of treatment. The main vertical axis shows the dFLC values (mg/L) at diagnosis and during treatment. The horizontal axis shows the sequential lines of treatment over time (months). dFLC: difference between involved and uninvolved serum-free light chains.

Rocchi S. et al; Haematol 2018, 103:e278

Dialysis independence following single-agent daratumumab in refractory myeloma with renal failure

Irish Journal of Medical Science (1971 -)
https://doi.org/10.1007/s11845-018-1951-6

Elizabeth Smyth[1] · Siobhan Glavey[1] · Dario Melotti[1] · Patrick Thornton[1] · Jeremy Sargent[1] · Peter Conlon[2] · Philip Murphy[1] · John Quinn[1]

Received: 19 November 2018 / Accepted: 10 December 2018

Dear Editor,

Although outcomes for multiple myeloma (MM) patients have improved dramatically, MM patients with dialysis-dependent renal failure (DDRF) are a subgroup with an adverse prognosis [1]. In particular, patients with MM not achieving independence from dialysis (DI) despite intensive therapy fare very poorly [2]. Thus, providing treatments that induce rapid disease responses and result in DI is essential if outcomes are to be improved [3, 4]. Here, we report a MM patient with refractory MM with DDRF who achieved DI with single-agent daratumumab, an anti-CD38 monoclonal antibody that has shown significant single-agent activity in relapsed/refractory myeloma [5].

A 67-year-old male was diagnosed with IgA-kappa MM at another institution in 2016. There was widespread lytic-bone disease, serum IgA-kappa paraprotein 15 g/L, and 80% kappa-restricted plasma cells in the bone marrow (BM). Baseline parameters are as follows: beta-2-microglobulin 2.3 mg/L, albumin 31 g/L, creatinine 66 µmol/L serum free-light chain ratio (SFLCr): kappa 58 mg/L:lambda 6.6 mg/L (ratio 8.8). Unfortunately, fluorescence in situ hybridization (FISH) was not performed. He received 6 cycles of bortezomib, lenalidomide, and dexamethasone (RVD) after which no paraprotein was detectable and SFLCr was 3.8. Fourteen months later, he presented to our center with acute kidney injury (AKI) with creatinine 468 µmol/L, calcium 2.33 mmol/L, paraprotein 30 g/L, kappa > 1800 mg/dl, lambda 0.9 mg/L (SFLCr > 2000). BM again showed 80% plasma cells (renal biopsy not undertaken). He commenced hemodialysis three times a week with high-dose dexamethasone (D 40 mg OD days 1–4) and bortezomib (Bz) 1.3 mg/m^2 on days 1, 4, 8, and 11 every 21 days. Weekly oral cyclophosphamide was added to BzD after 2 cycles; however, after 3 cycles of Bz-based therapy, renal function was unchanged and he remained DD with paraprotein 21 g/L, kappa > 8000 mg/L, lambda 0.9 mg/L and imaging showing progressive bony disease. Given the refractory disease and dialysis-requirement, daratumumab (alone) was commenced at 16 mg/kg/week post-dialysis. Infusion commenced at 50 mls/h, titrated per protocol with standard dilution volumes with no infusion-related reactions. Four weeks later, renal function had dramatically improved and he discontinued dialysis completely just 27 days post-commencing daratumumab with repeat assessment showing creatinine 114 µmol/L, paraprotein < 2 g/L, kappa 56.9 g/L, and lambda 12.9 mg/L. He has now completed 19 weeks of treatment and remains DI.

Dose Modifications

Creatinina Clearence

	Clearence by kidneys	>60 ml/min	30-59 ml/min	15-29 ml/min	<15ml/min	On dialysis
Melphalan	yes	200 mg/m^2	140 mg/m^2	140 mg/m^2	140 mg/m^2	140 mg/m^2
Bortezomib	no	1,3 mg/m^2	no modification	no modification	no modification	no modification
Thalidomide	no	100 mg/d	no modification	no modification	no modification	no modification
Lenalidomide	yes	25 mg/d	10 mg/die	15 mg once every other d	5 mg/d	5 mg/die
Pomalidomide	no	4 mg/d	no modification	no modification	no modification	no modification
Carfilzomib	no	20-27 mg/m^2	no modification	no modification	no modification	no modification
Ixazomib	no	4 mg/d	?	?	?	?
Elotuzumab	no	10 mg/kg	no modification	no modification	no modification	no modification
Daratumumab	no	16/kg	no modification	no modification	no modification	no modification
Zoledronic Ac.	yes	4 mg	dose modification	/	/	/
Pamidronate	yes	60/90 mg	dose modification	/	/	/

Conclusioni

L’utilizzo di nuovi farmaci ha comportato un significativo miglioramento della prognosi dei pazienti con mieloma multiplo

Gli PI rappresentano la classe di farmaci che è maggiormente correlata allo sviluppo di tossicità renale (in particolare TMA)

Con l’incremento di nuove terapie (selinexor, venetoclax) e nuove combinazioni, ematologi e nefrologi devono prestare particolare attenzione alla tossicità renale di questi farmaci

Grazie per l’attenzione