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Diagnostic Procedures and Management of Renal Impairment in Myeloma

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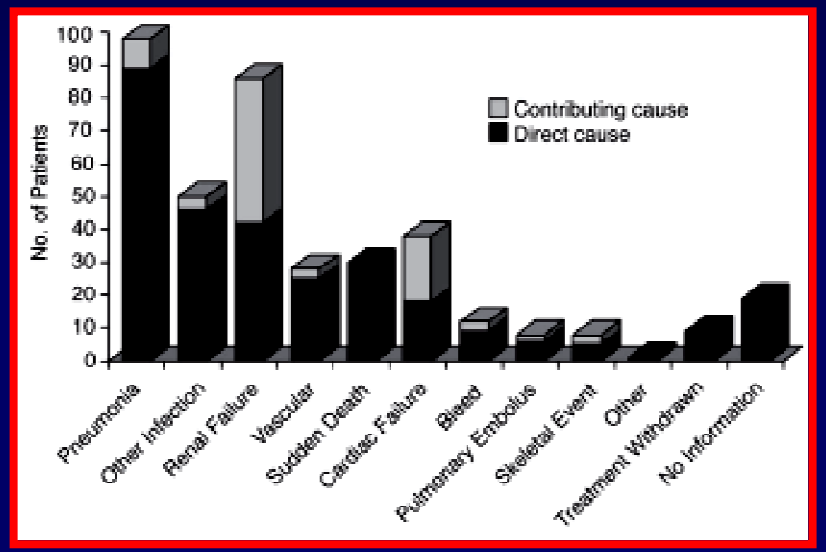
Renal Failure in Multiple Myeloma

- Renal failure is an important complication of myeloma
- Moderate renal impairment in 20-30% at presentation
- Severe renal failure in 3-5%
- Renal impairment in up to 50% during follow up
- 2-5% of myeloma patients require long-term dialysis
- Increased risk of early mortality

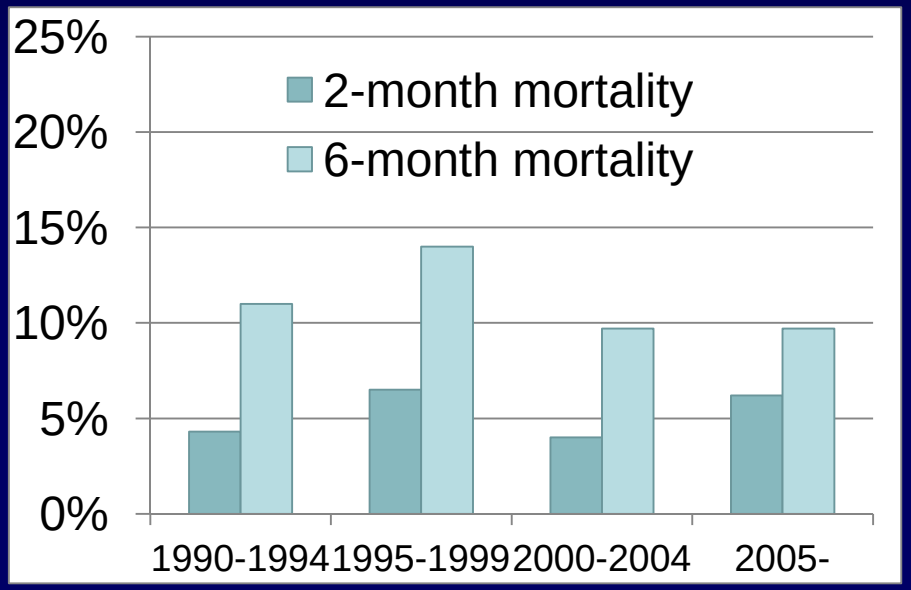
Early mortality before day 60 in MRC trials 1980-2002 (n=3,107)

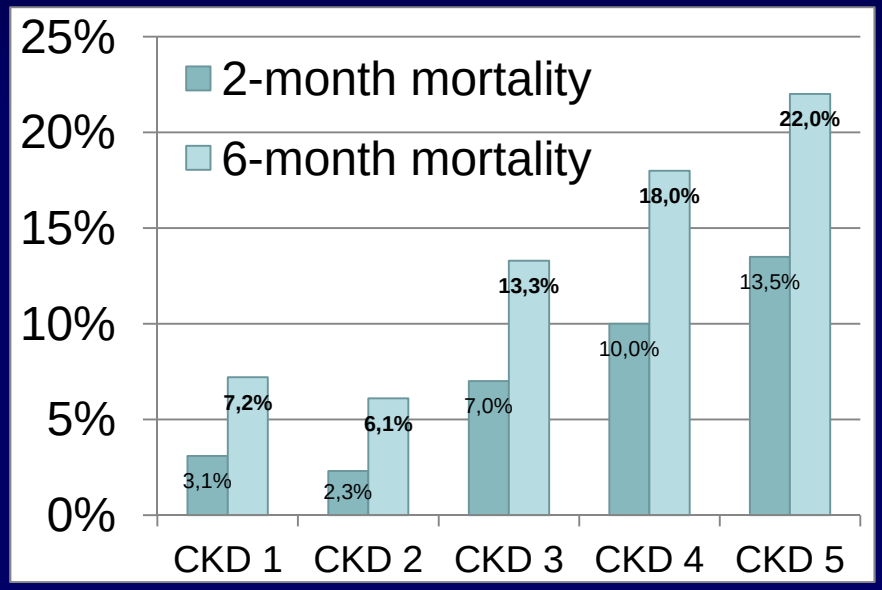


Clark et al. Blood Reviews 1999;13:79-90
Augustson et al. J Clin Oncol 2005;23:9219-26

Early mortality and RI

Severe RI was associated with a substantial increase of early mortality





Dimopoulos et al. ASH 2012;abstract 948

Diagnostic Evaluation of Myeloma Patients Presenting with Renal Impairment

At diagnosis:
sCreatinine, urea, sodium and potassium, calcium and eGFR (MDRD formula)
Measurement of total protein, electrophoresis and immunofixation of a sample from a 24 h urine collection
Serum Free Light Chains

The patient has proteinuria, which consists mainly of light chains[1]

↓

A renal biopsy is probably not necessary but may be helpful in patients in whom other conditions (diabetes, chronic hypertension) are present

The patient has non-selective proteinuria or significant albuminuria

↓

Consider the presence of amyloidosis or MIDD or other comorbid conditions:
• Biopsy of the subcutaneous fat or a rectal biopsy may show amyloidosis (Congo red +)
• Renal biopsy is often necessary

If the patient does not have proteinuria, consider alternative diagnosis for RI

[1]Leung et al. Clin J Am Soc Nephrol 2012;7:1964-8.

Management of Acute Renal Impairment in Myeloma Patients

1. Supportive Care

2. Mechanical Approaches (plasma exchange, conventional hemodialysis, high cut-off hemodialysis)

3. Systemic Antimyeloma Treatment

Management of Renal Impairment/Failure Supportive care

- **Hydration**
  - Salt free saline (Dextrose) may be prefered than normal saline
  - Hydration should be combined with anti-myeloma treatment
- **Urine alkalinization (to reduce cast formation)**
- **Management of hypercalcemia**
  - Bisphosphonates (increased risk of renal toxicity and subsequent hypocalcemia)
  - In mild asymptomatic hypercalcemia conservative measures such as hydration may suffice
  - For moderate or severe hypercalcemia, prompt initiation of antimyeloma therapy.
  - Calcitonin may reduce calcium levels without causing severe hypocalcemia and without the risk of renal toxicity.
  - The use of furosemide to treat hypercalcemia, is discouraged (increases formation of casts in the renal tubule)
- **Treatment of infections**
- **Avoidance of nephrotoxic agents (NSAIDS, aminoglycoside antibiotics and contrast dyes)**

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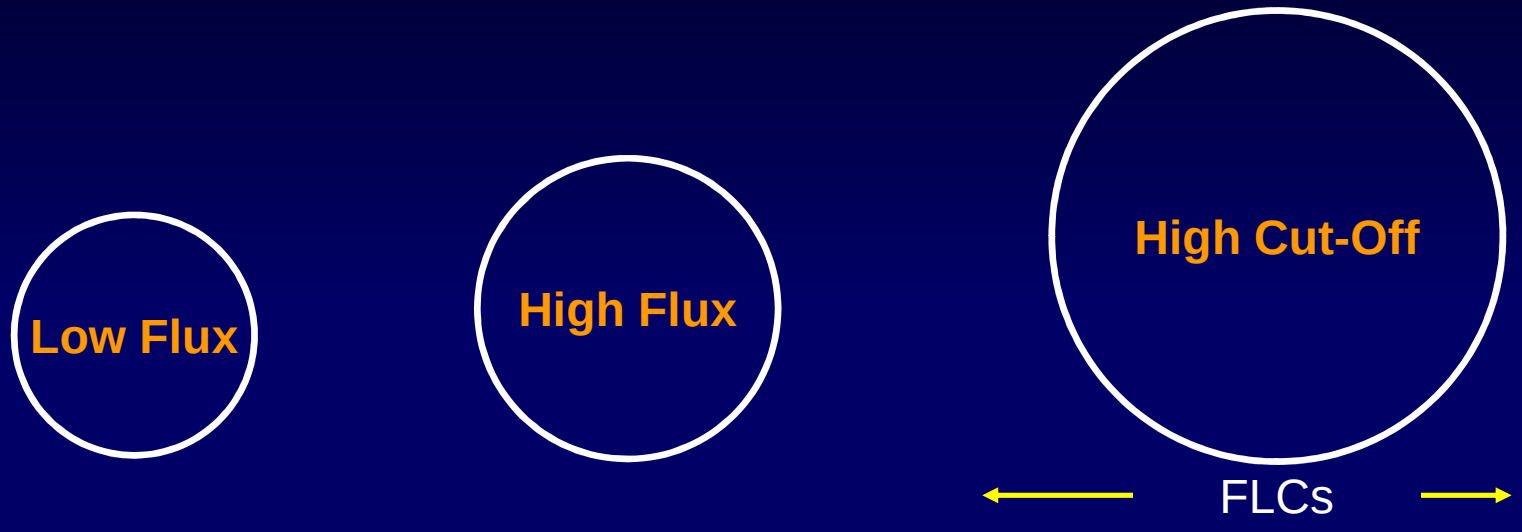
Randomized Trials: Plasma Exchange + Hemodialysis *vs.* Hemodialysis Only

Reference	Number of patients	Off dialysis at the end		*P*
		With plasma exchange	Without plasma exchange	
Zucchelli *et al*[1]	19 newly diagnosed 10 relapsed	11/15	2/14	<0.01
Johnson *et al*[2]	21 newly diagnosed	5/10	4/11	ns
Clark *et al*[3]	97 newly diagnosed	36/58	27/39	ns

Benefit of plasma exchange not established

[1]Zucchelli et al. Kidney Int 1988;33:1175-80
[2]Johnson et al. Arch Intern Med 1990;150:863-9
[3]Clark et al. Ann Intern Med 2005;143:777-84

High Cut-Off Permeability

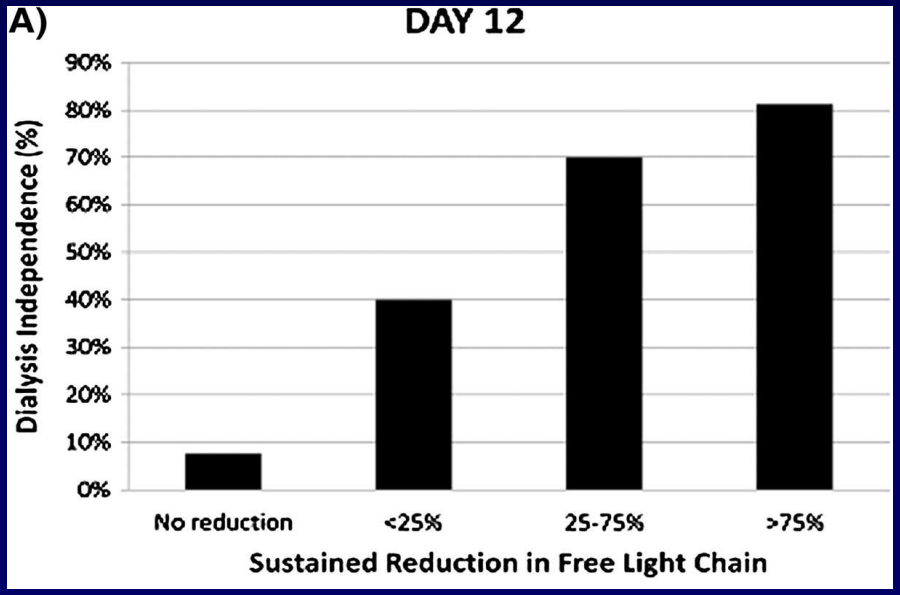


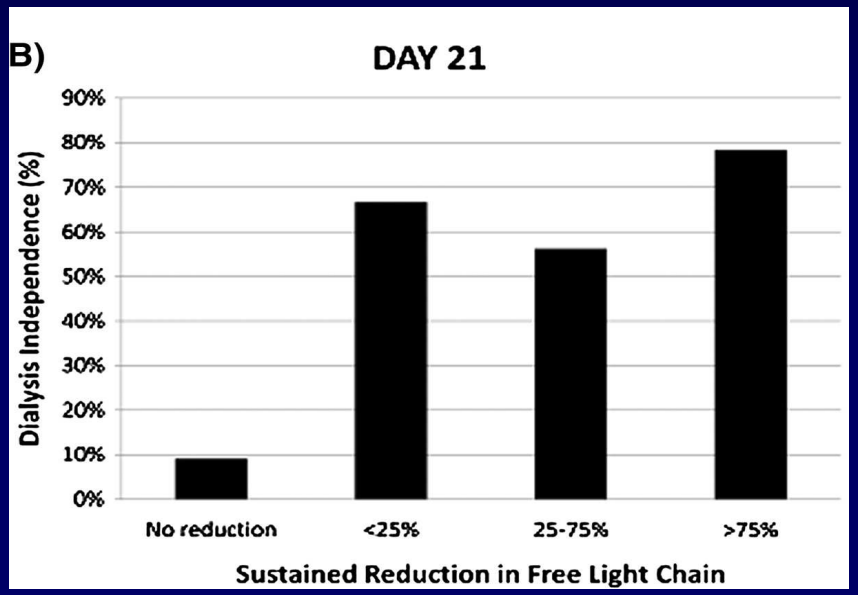
Middle size molecules such as β2m

Small molecular weight uremic toxins e.g. urea, creatinine, phosphate

Treatment of Acute Renal Failure Secondary to MM with Chemotherapy and Extended High Cut-Off Hemodialysis

Patients (n=67) with cast nephropathy and dialysis dependent acute renal failure
85% were treated with dexamethasone in combination bortezomib or thalidomide
the median number of HCO-HD sessions was 11 (range 3–45)

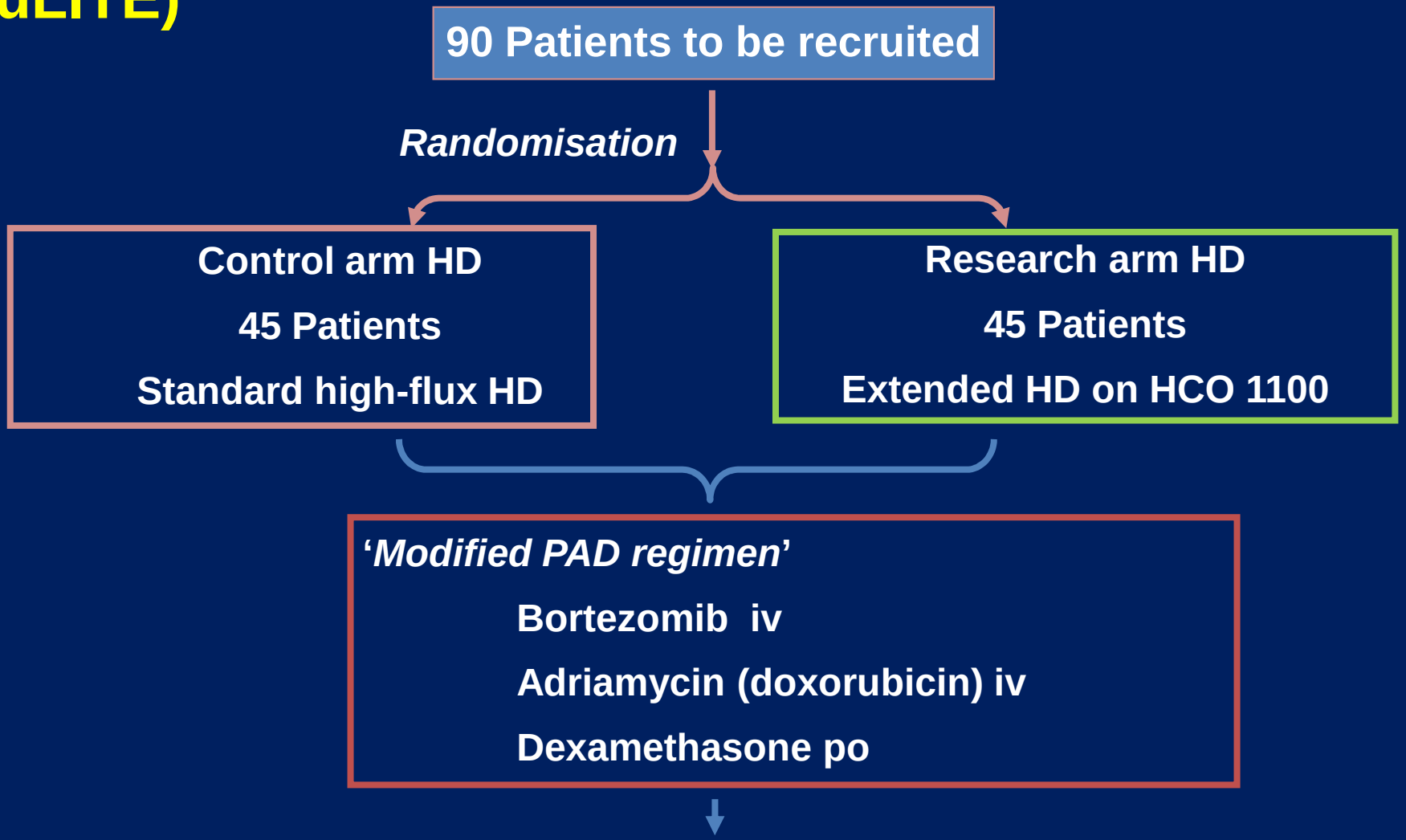




Factors which predicted independence of dialysis were the degree of FLC reduction at Days 12 (P = 0.002) and 21 (P = 0.005) and the time to initiating HCO-HD (P = 0.006).

Hutchison et al. Nephrol Dial Transplant 2012;27:3823-8

European trial of free LIght chain removal by exTENded haemodialysis in cast nephropathy (EuLITE)



http://clinicaltrials.gov (NCT00700531)

Management of Acute Renal Impairment in Myeloma Patients

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Thalidomide Studies in Myeloma Patients with Renal Impairment

Study	MM status	N	Definition of RI	Definition of RF reversal	RI reversal
Tosi et al Eur J Hematol 2004	Rel/ref	**20**	sCr>1.5 mg/dl & CrCl<60 mL/min	sCr<1.5 mg/dl	60%
Kastritis et al Haematologica 2007	Newly diagnosed	**13**	sCr ≥2 mg/dL	sCr<1.5 mg/dl	77%
Tosi et al Eur J Hematol 2010	Newly diagnosed	**31**	CrCl<50 mL/min	CrCl>60 ml/min	55%

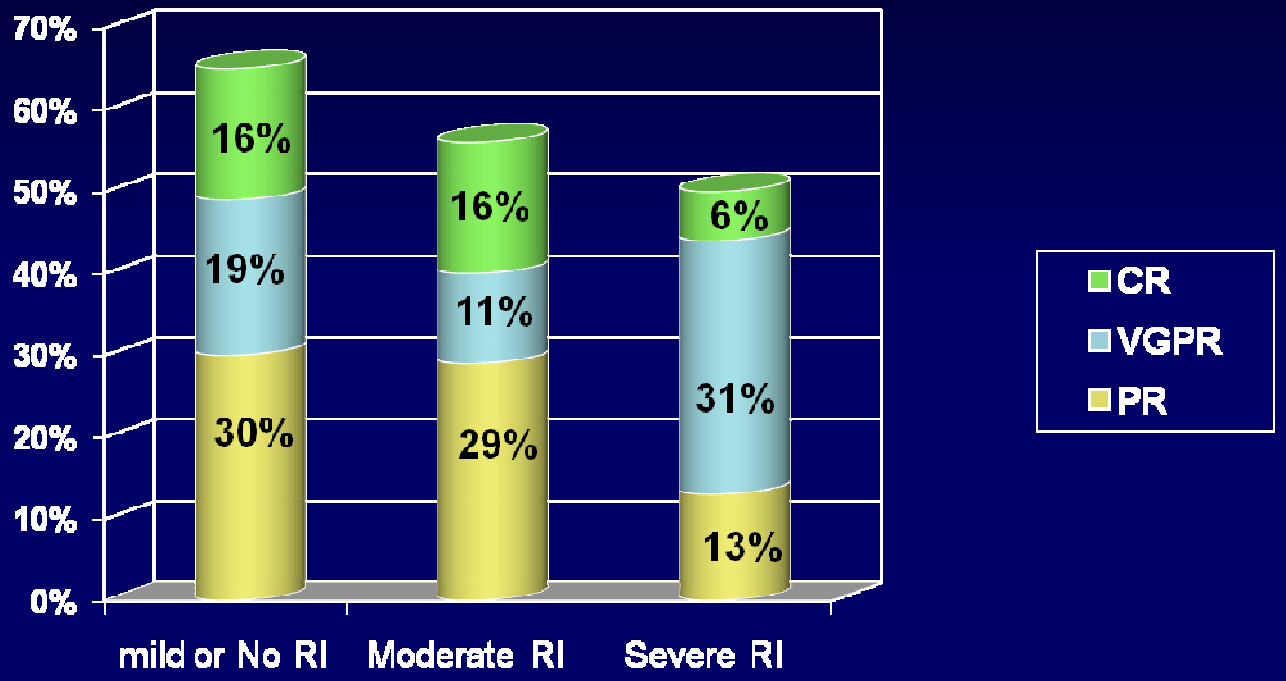
Lenalidomide Studies in Myeloma Patients with Renal Impairment

Study	N	RI definitions	Starting dose of Len adjusted for RI?	Main efficacy outcomes
MM-009 and MM-010[10]	341	No/mild: Cl_{Cr} ⩾60 mL/min (n = 243) Moderate: Cl_{Cr} ⩾30 to < 60 mL/min (n = 82) Severe: Cl_{Cr} <30 mL/min (n = 16)	No	Similar OR, quality of response, median PFS, and median TTP regardless of degree of RI OS was lower in moderate/severe RI versus no/mild RI Improvement in renal function in 72% of patients with moderate/severe RI Restoration of normal renal function in 60% of patients with moderate/severe RI
Dimopoulos et al.[11]	50	No RI: Cl_{Cr} ⩾50 mL/min (n = 38) RI: Cl_{Cr} <50 mL/min (n = 12)	Yes	Similar OR, PFS, and OS regardless of degree of RI Improvement in renal function in 42% of patients with RI
De la Rubia et al.[46]	15	Advanced RI requiring dialysis (n = 15)	NA	OR 60%; CR 29% median PFS 15 mo; median OS 20 mo
Compassionate use study[47]	114	Cl_{Cr} <50 mL/min (n = 8)	Yes	OR 69%; median TTP 9 mo; median OS 22 mo
Compassionate use study (Spain)[48]	111	Serum creatinine >177 μmol/L (n = 14)	Yes	OR 66%; CR 11%; median TTP 13 mo; median OS 17.4 mo
Quach et al.[49]	75	Cl_{Cr} ⩽60 mL/min (n = 28)	Yes[a]	OR in patients with RI (73%) similar to that in patients with normal renal function
Klein et al.[38]	167	No: Cl_{Cr} ⩾80 mL/min (n = 94) Mild: Cl_{Cr} ⩾50 mL/min to <80 mL/min (n = 40) Moderate/severe: Cl_{Cr}<50 mL/min (n = 33)	Yes	OR decreased as degree of RI increased (67% versus 60% versus 49%, respectively) Median TTP lower in patients with any RI versus no RI Median OS similar in patients with any RI versus no RI Renal function improvement in 27%; stabilization in 81%
Ludwig et al.[50]	18	Acute renal failure (n = 18)	Yes	Renal response in 8/13 (62%)

Dimopoulos et al. Cancer Treat Rev 2012;38:1012-9

Len/Dex in RR Myeloma Patients with Renal Impairment

Response according to renal function



- **Incidence of thrombocytopenia was higher in patients with RI**

RI was defined by creatinine clearance (CLCr) level: mild or no RI, CLCr ≥60 mL/min; moderate RI, CLCr ≥30, <60 mL/min; severe RI, CLCr <30 mL/min.

Dimopoulos et al. Cancer 2010;116:3807-14

Pomalidomide + low dose Dexamethasone in RR Myeloma Patients with Renal Impairment

PFS and OS by Renal Function						
RI (CrCl)	**None (≥ 60 mL/min)**			**Moderate (< 60 mL/min)**		
	POM + LoDEX	**HiDEX**	**HR (*P* Value)**	**POM + LoDEX**	**HiDEX**	**HR (*P* Value)**
n (%)	206 (68)	93 (61)	—	94 (31)	59 (39)	—
Median PFS, m	3.6	1.9	0.47 *(< .001)*	3.3	1.7	0.44 *(< .001)*
Median OS, m	Not Reached	9.2	0.57 *(.021)*	10.4	4.5	0.51 *(.008)*

CrCl, creatinine clearance; HiDEX, high-dose dexamethasone; HR, hazard ratio; LoDEX, low-dose dexamethasone; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; RI, renal impairment.

Dimopoulos et al. IMW 2013;abstract 311

Bortezomib Studies in Patients with Renal Impairment/Failure

Study details	Patients with renal impairment (n)	Dialysis pts (n)	Outcome	Reference
Phase II (SUMMIT, CREST subanalysis)	151		• Bortezomib effective • Manageable toxicities	Jagannath *et al. Cancer* 2005;103:1195–2000
Phase III (APEX subanalysis)	62		• Efficacy, safety, TTP, OS not substantially affected in moderate- to- severe renal impairment	San Miguel et al. Leukemia 2008;22:842-9
Retrospective analysis	24	24	• High response rate • Manageable AEs	Chanan-Khan *et al. Blood* 2007; 109:2604–2606
Phase I	34	9	• Bortezomib clearance independent of renal function	Mulkerin *et al. Blood* 2007;110:(Abstract 3477)
Phase II	54	3	• No significant association between renal function and response to treatment	Ailawadhi *et al. Blood* 2007;110:(Abstract 1477)
Retrospective analysis	46	9	• Reversal of renal failure in 59% • 2 / 9 became dialysis independent	Dimopoulos et al. Clin Lymphoma Myeloma 2009;9:302-6.
Phase II	68	9	• 3 / 9 became dialysis independent • 62% had a renal response	Ludwig et al. J Clin Oncol 2010;28:4635-41
Retrospective analysis	117	14	• >80 ml/min in 41% • 3 / 14 discontinued dialysis	Morabito et al Eur J Haematol 2010; 84:223–228

Bortezomib: Dialysis Patients

- Retrospective case analysis from 5 US cancer centers
- 24 patients with MM and advanced RF receiving or scheduled for dialysis
- Bortezomib 1.3 mg/m^2 alone or in combination before (n = 2), during* (n = 1) or after (n = 19) dialysis

Response rates (%)	
ORR	75
CR	25
nCR	5
PR	45

- 1 patient responded rapidly (spared dialysis)
- 3 patients became dialysis-independent
- Median DOR: 12.5 months

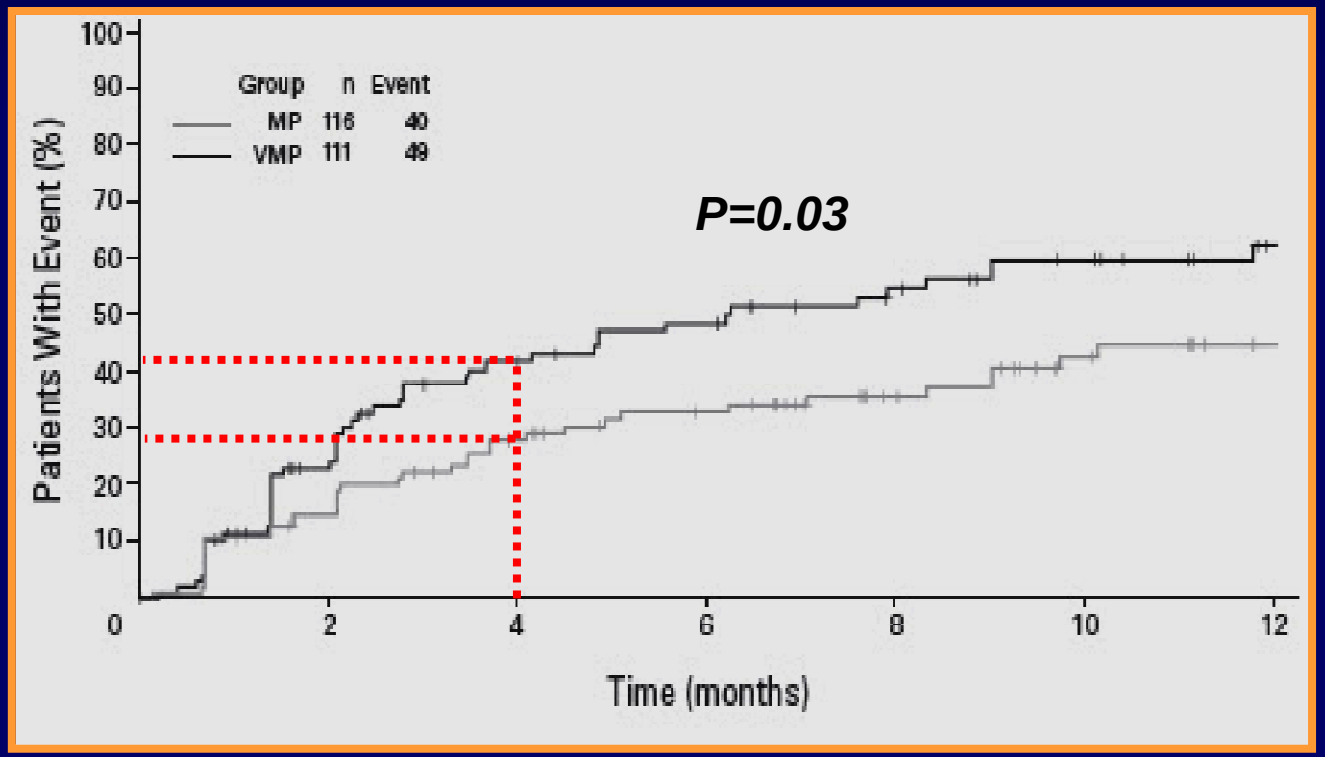
Adverse event (all grades,>10%)	Patients (n=18)
Thrombocytopenia	39%
Peripheral neuropathy	11%
Infection	11%
Serious AEs	6%
Progressive disease	33%

*during peritoneal dialysis, all other cases hemodialysis

Chanan-Khan et al. Blood 2007;109:2604-6

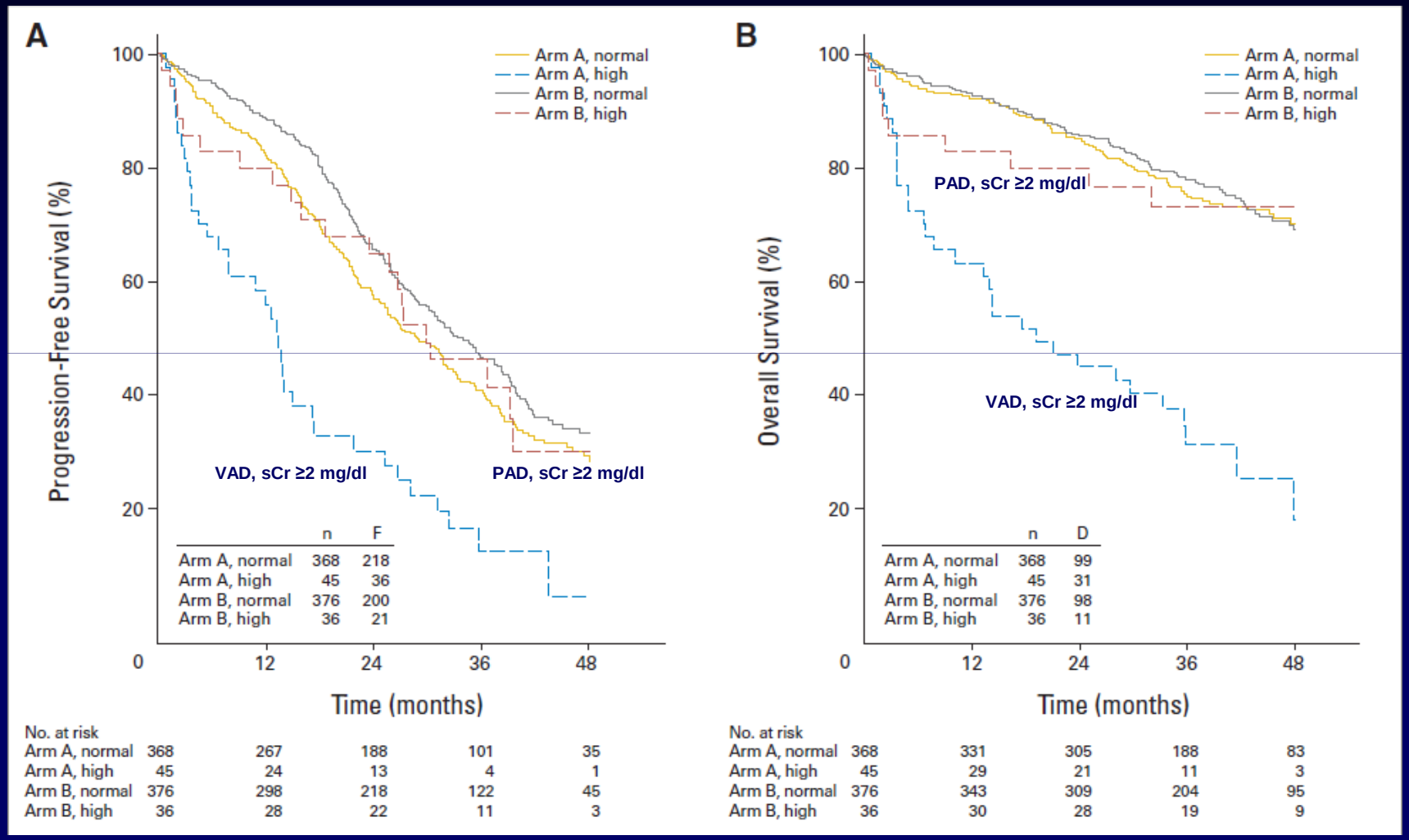
VISTA: Time to Reversal of Renal Impairment

Median time to renal impairment reversal in all patients with baseline GFR <50 mL/min was significantly shorter with VMP *vs*. MP



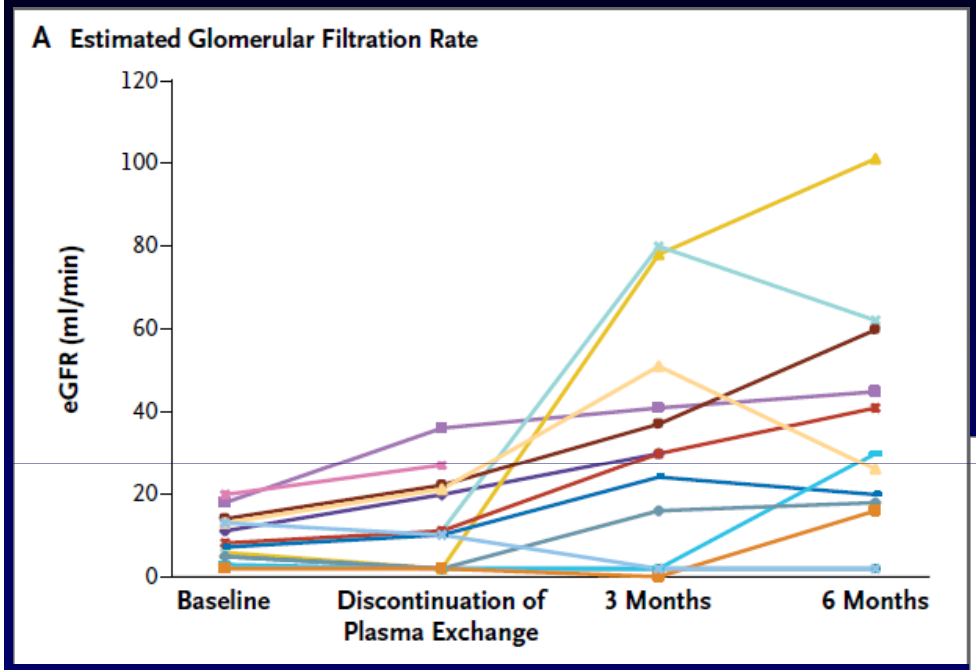
Dimopoulos et al. J Clin Oncol 2009;27:6086-93

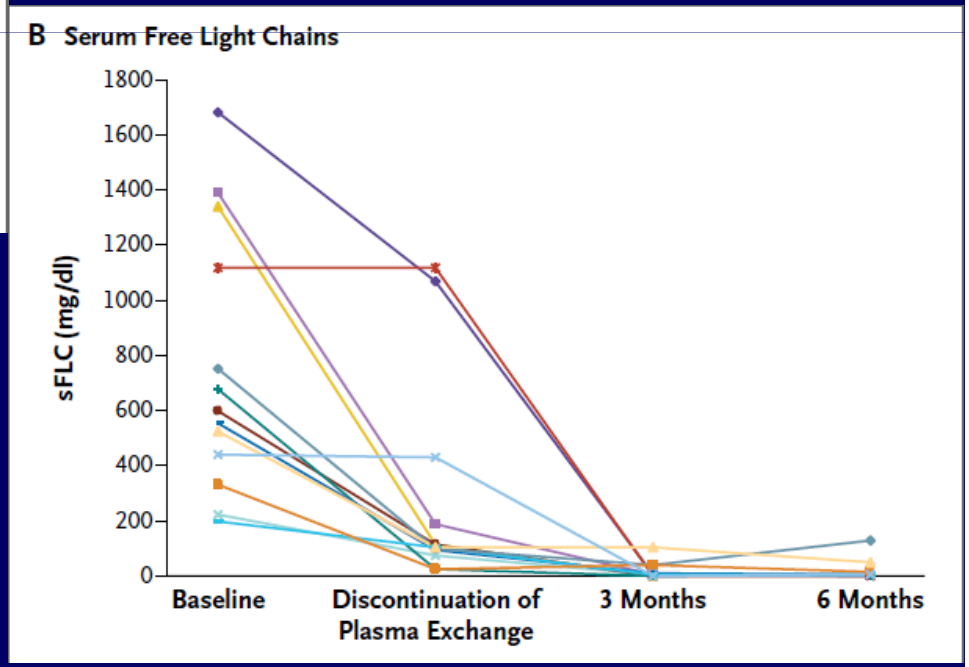
PAD vs. VAD: PFS and OS according to Renal Function



Sonneveld et al. J Clin Oncol 2012;30:2946-55

Bortezomib + Plasma Exchange in Patients with Renal Impairment

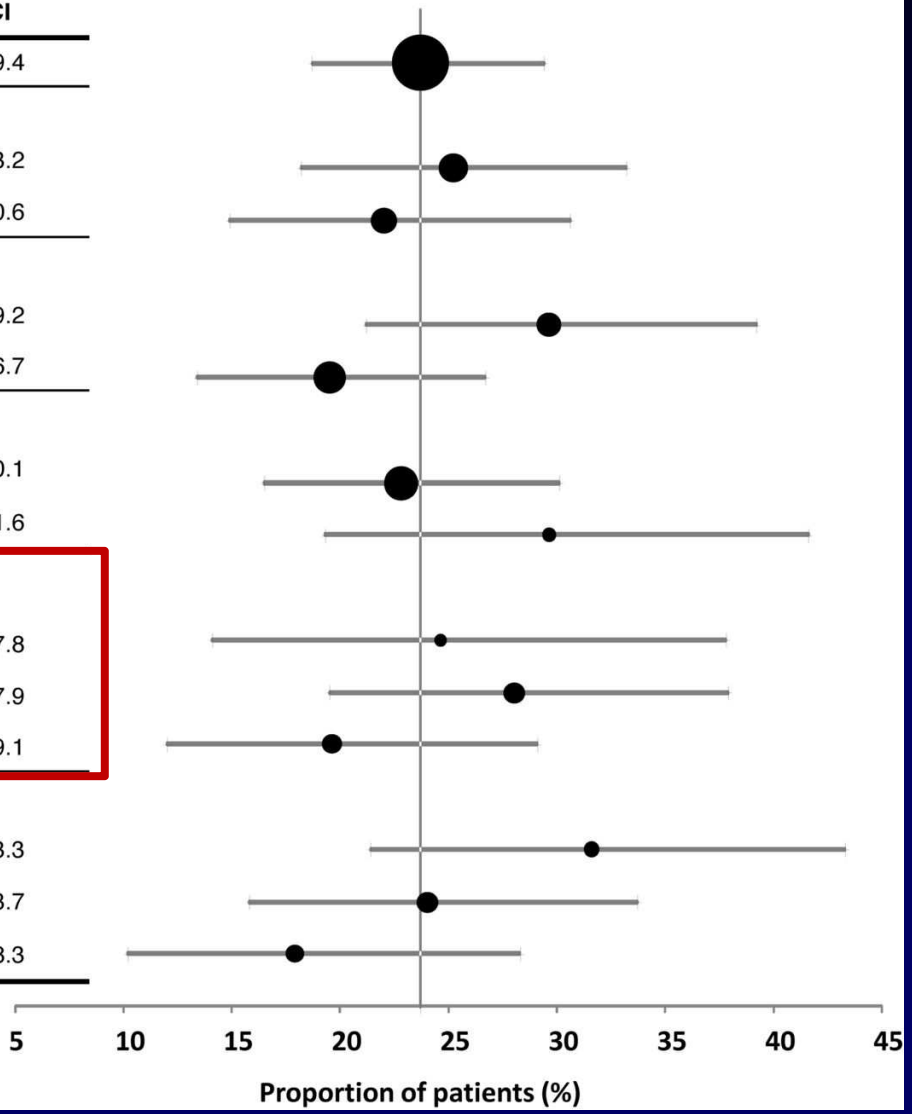




Burnette et al. N Engl J Med 2011;364:2365-6

Carfilzomib in Patients with Renal Impairment (1)

Characteristic	n	ORR	95% CI
All patients	257	23.7	18.7–29.4
Age			
<65 years	139	25.2	18.2–33.2
≥65 years	118	22.0	14.9–30.6
Gender			
Female	108	29.6	21.2–39.2
Male	149	19.5	13.4–26.7
Cytogenetics or FISH			
Normal/favorable	158	22.8	16.5–30.1
Unfavorable	71	29.6	19.3–41.6
Baseline CrCl (mL/min)			
30 to <50	57	24.6	14.1–37.8
50 to <80	100	28.0	19.5–37.9
≥80	92	19.6	12.0–29.1
ISS stage			
I	76	31.6	21.4–43.3
II	96	24.0	15.8–33.7
III	78	17.9	10.2–28.3



Siegel D S et al. Blood 2012;120:2817-25

Carfilzomib in Patients with Renal Impairment (2)

	Group 1	Group 2	Group 3	Group 4	Group 5	All patients
All patients with response assessment						
Response category, *n* (%)	*n* = 11	*n* = 11	*n* = 9	*n* = 8	*n* = 8	*n* = 47
Complete response	0	0	0	0	0	0
Very good PR	0	0	0	0	0	0
PR	2 (18.2)	3 (27.3)	2 (22.2)	2 (25.0)	3 (37.5)	12 (25.5)
Minimal response	1 (9.1)	1 (9.1)	0	1 (12.5)	0	3 (6.4)
Stable disease	7 (63.6)	3 (27.3)	4 (44.4)	3 (37.5)	4 (50.0)	21 (44.7)
Progressive disease	1 (9.1)	4 (36.4)	3 (33.3)	2 (25.0)	0	10 (21.3)
Not evaluable	0	0	0	0	1 (12.5)	1
Overall response rate, *n* (%)	2 (18.2)	3 (27.3)	2 (22.2)	2 (25.0)	3 (37.5)	12 (25.5)
Duration of response, median (95% CI), months	NE (2.0–NE)	NE (4.2–NE)	NE (2.3–NE)	NE (7.9–NE)	7.9 (6.5–8.5)	7.9 (6.5–NE)
Response assessment in patients who received dexamethasone ⩾20 mg before carfilzomib doses[a]						
Response category, *n* (%)	*n* = 7	*n* = 8	*n* = 4	*n* = 5	*n* = 4	*n* = 28
Complete response	0	0	0	0	0	0
Very good PR	0	0	0	0	0	0
PR	3 (42.9)	3 (37.5)	1 (25.0)	0	3 (75.0)	10 (35.7)
Minimal response	1	1 (12.5)	0	1 (20.0)	0	3 (10.7)
Stable disease	3 (42.9)	1 (12.5)	3 (75.0)	2 (40.0)	1 (25.0)	10 (35.7)
Progressive disease	0	3 (37.5)	0	2 (40.0)	0	5 (17.9)
Not evaluable	0	0	0	0	0	0

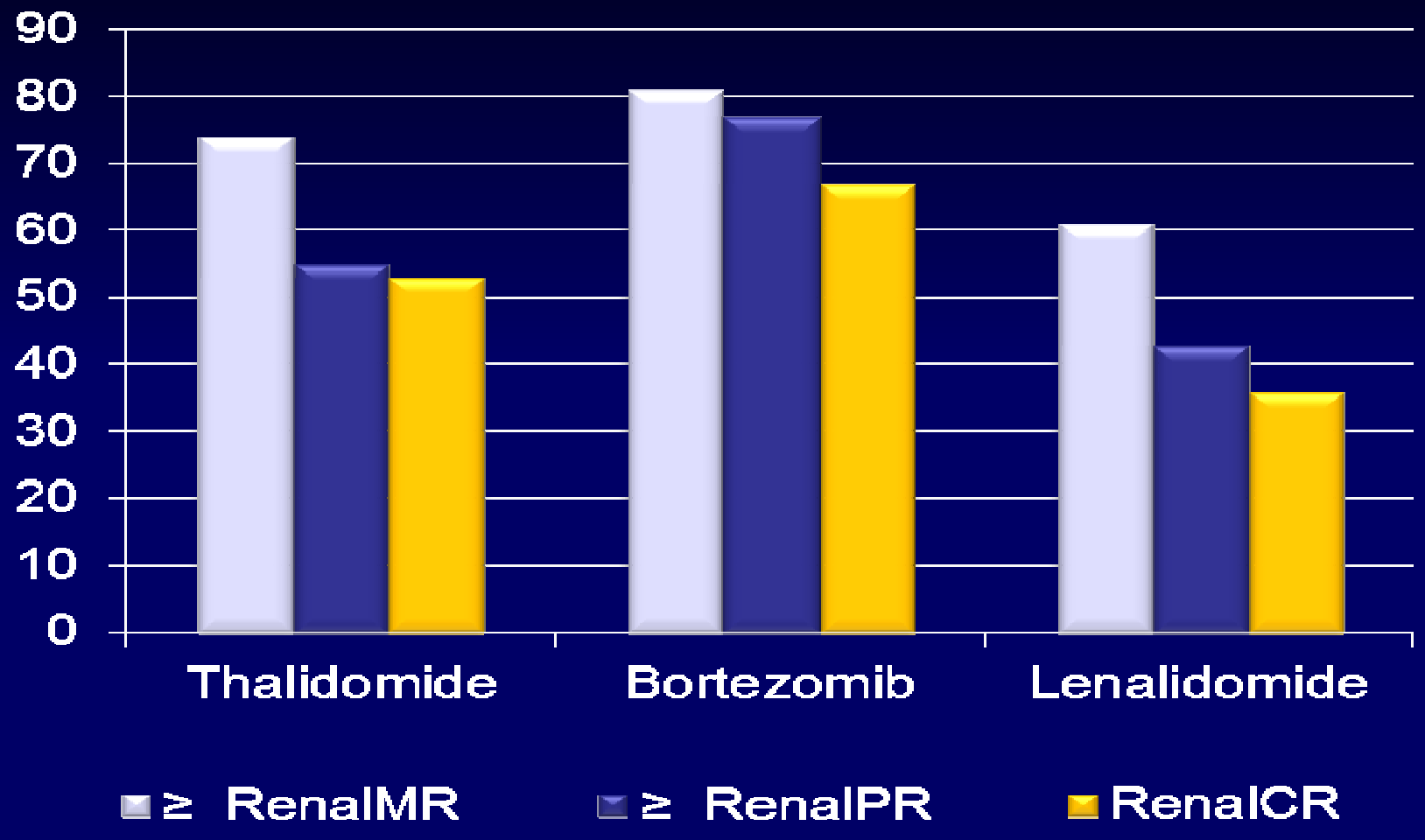
Badros et al. Leukemia 2013; in press

Novel Agents and the Reversibility of Renal Impairment in Newly Diagnosed Myeloma Patients

- N=133 consecutive previously untreated patients
  - Group T: 62 patients received thalidomide-based regimens (TD, T-VAD, MDT, MPT)
  - Group B: 43 patients received bortezomib-based regimens (VD, VCD, VTD)
  - Group L: 28 patients received lenalidomide-based regimens (Rd, MPR)

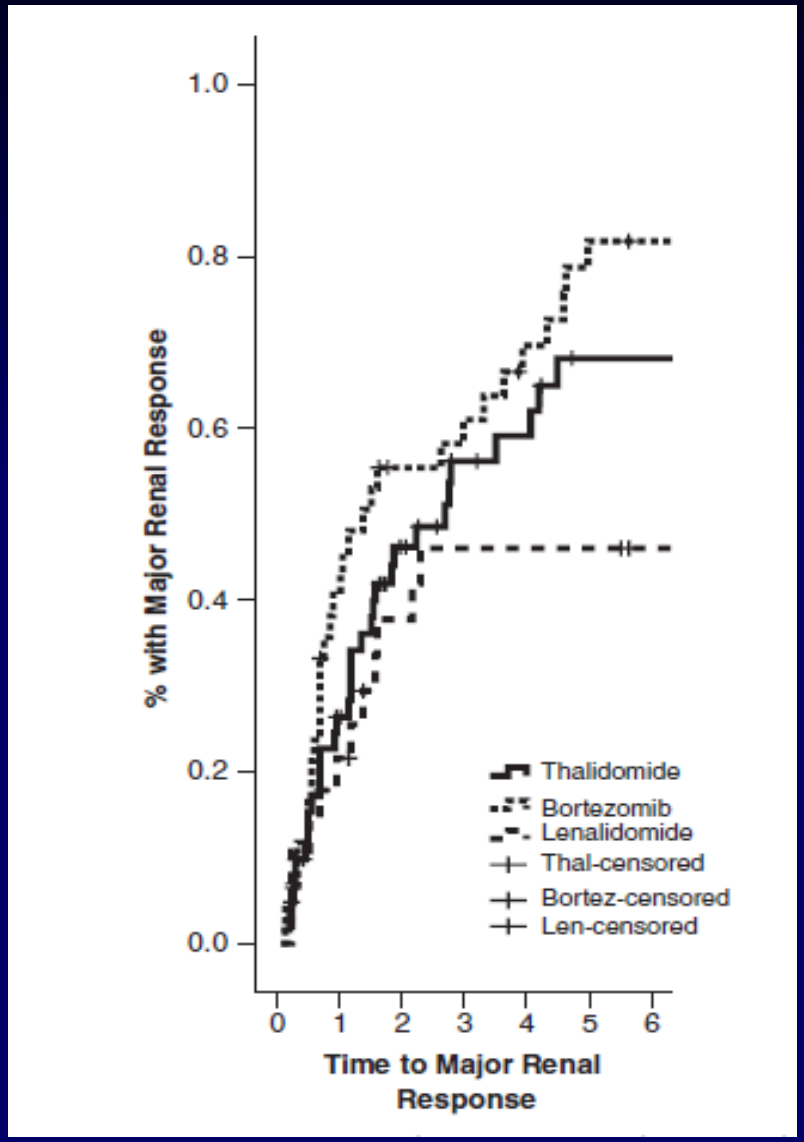
Dimopoulos et al. Leukemia 2013;27:423-9

Impact of Novel Agents on Renal Impairment

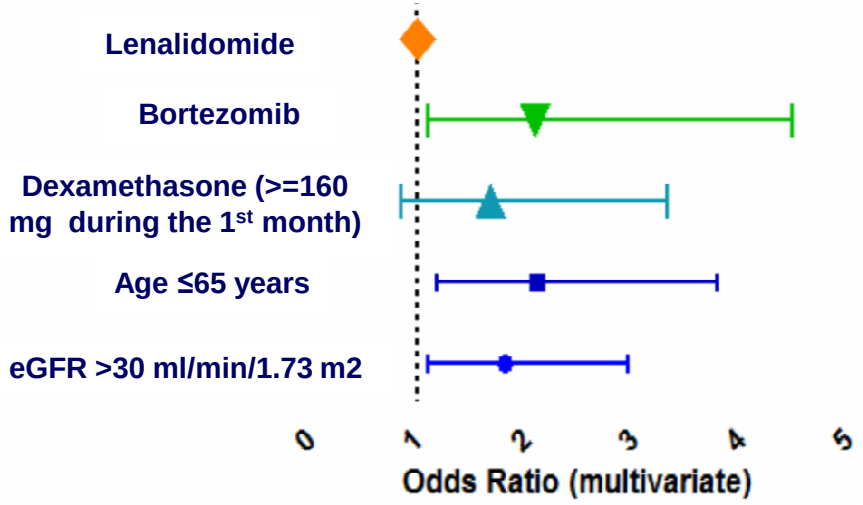


Dimopoulos et al. Leukemia 2013;27:423-9

Impact of Novel Agents on the Reversibility of Renal Impairment



Multivariate analysis for factors associated with time to renalPR



Dimopoulos et al. Leukemia 2013;27:423-9

High Dose Melphalan and Autologous Stem Cell Transplant in patients with RI

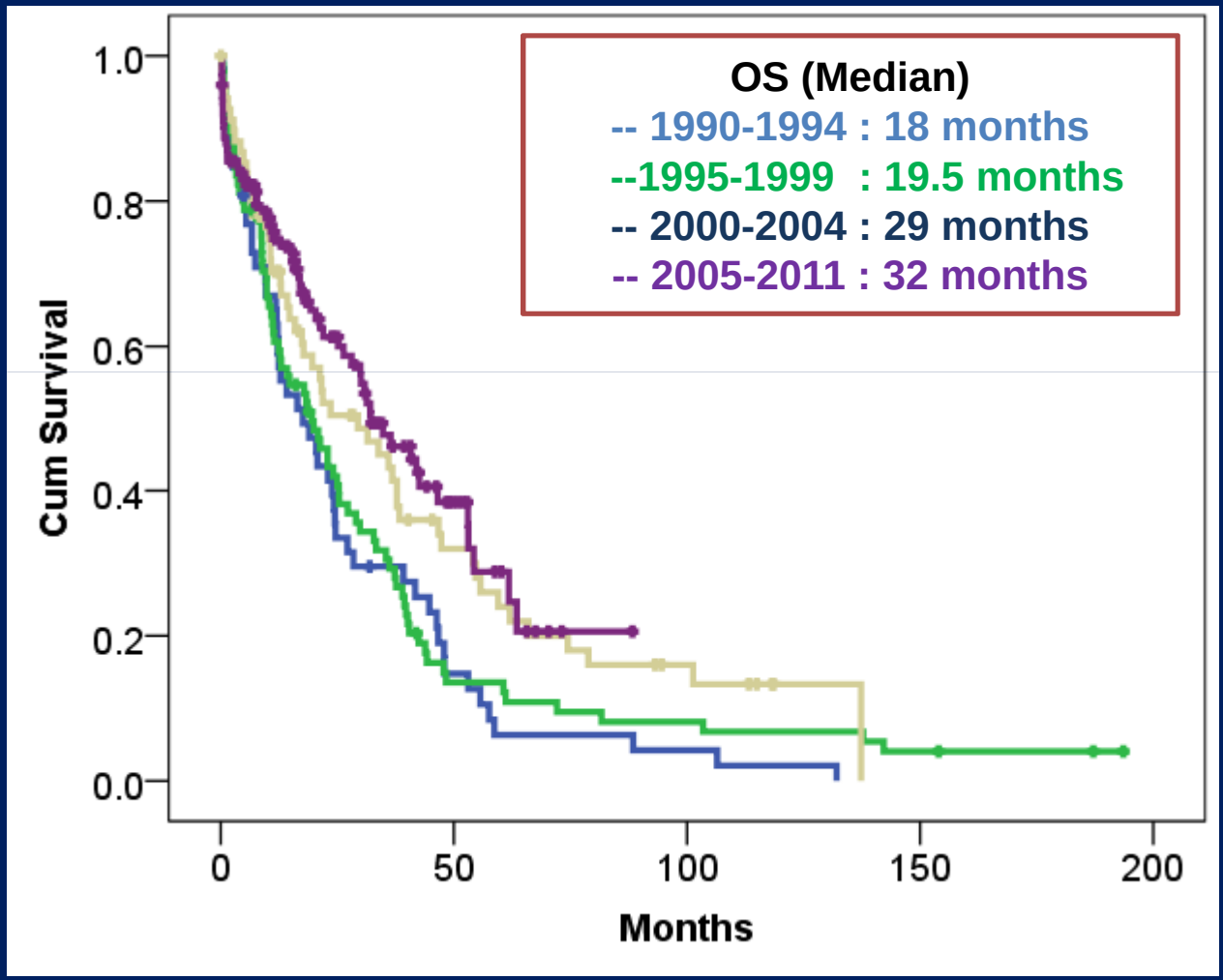
- Renal impairment does not affect the quality of stem cell collection or engraftment[1-3] .

- A reduced dose of melphalan (140 mg/m^2) is used in patients with severe RI or those undergoing dialysis; the reduced dose does appear to be as effective as the standard 200 mg/m^2 but it has not been tested in a randomized study[1]

- HDM in patients with RI is associated with increased risk of toxicity, which seems to increase with the degree of renal dysfunction[4,5].

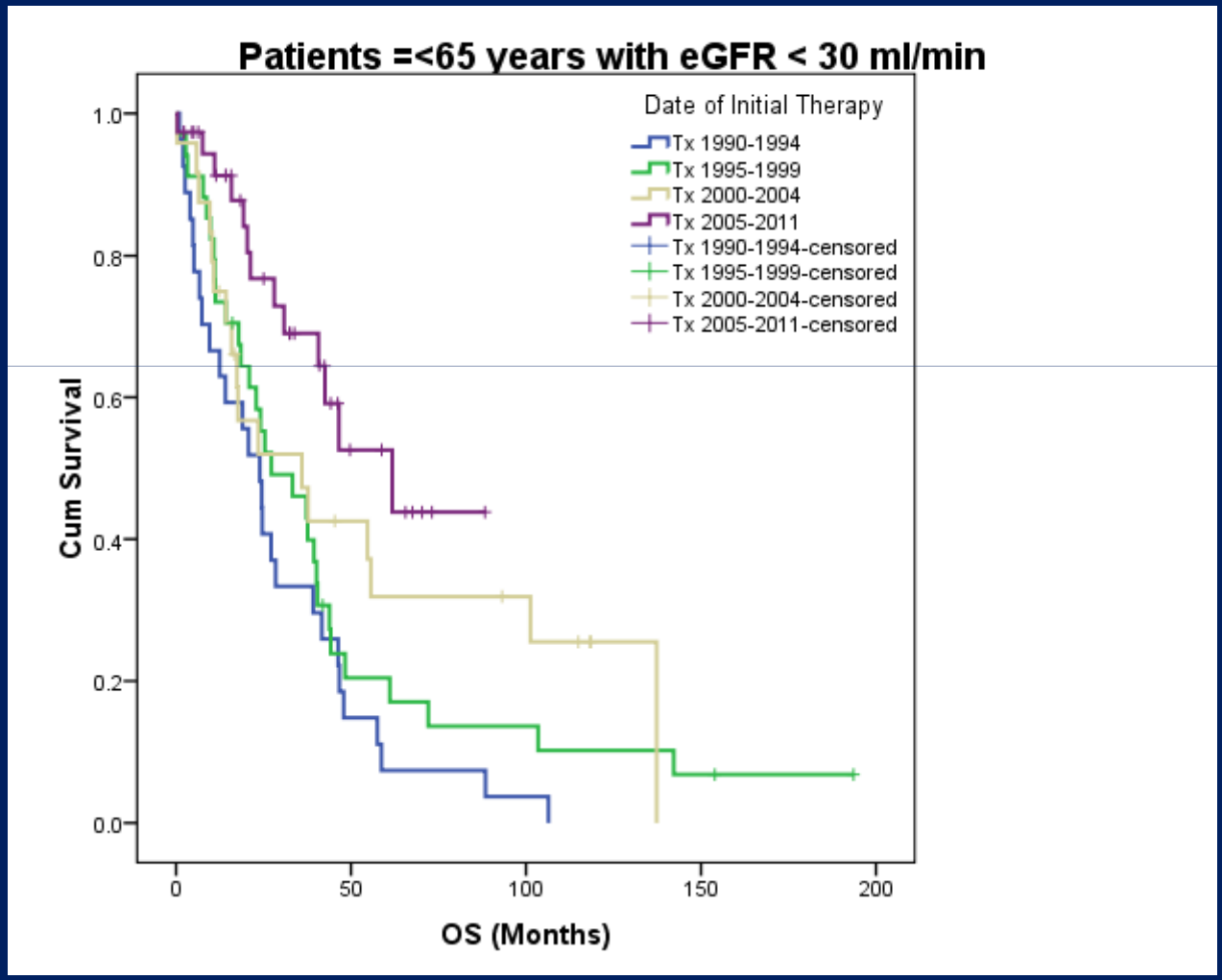
1 Badros A et al. Br J Haematol 2001;114:822-9; 2. San Miguel JF et al. Hematol J 2000;1:28-36;
3. Lee CK et al. Bone Marrow Transplant 2004;33:823-8;
4. Tricot G et al. Clin Cancer Res 1996;2:947-52; 5.Carlson K. Bone Marrow Transplant 2005;35:985-90.

Survival of patients with severe RI (CKD 4-5)



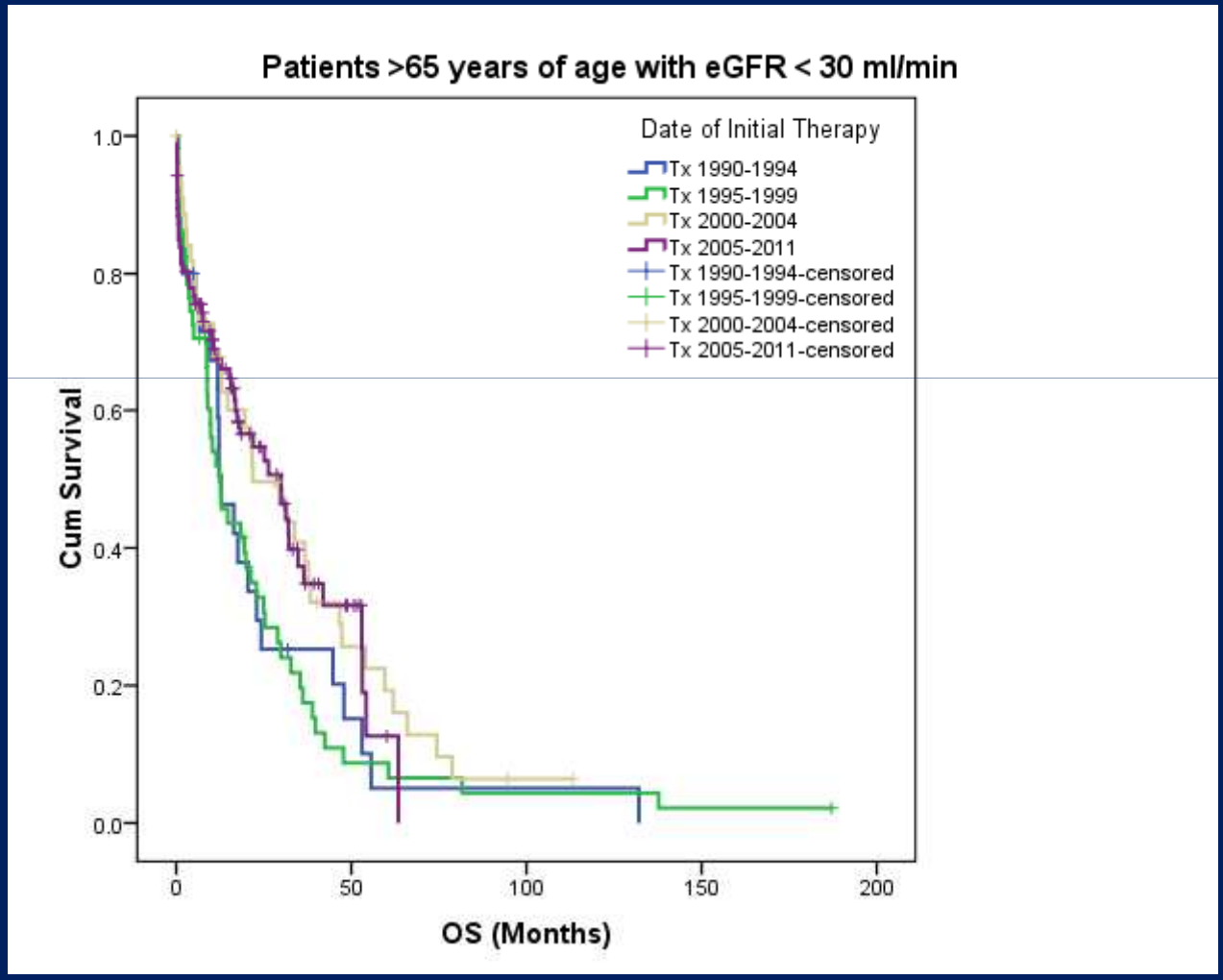
Dimopoulos et al. ASH 2012;abstract 948

The Use of Novel Agents Have Increased Survival of Myeloma Patients with Severe Renal Impairment mainly in Patients ≤65 Years (1)



Dimopoulos et al. ASH 2012; abstract 948

The Use of Novel Agents Has Increased Survival of Myeloma Patients with Severe Renal Impairment also in Patients > 65 Years (2)



Dimopoulos et al. ASH 2012; abstract 948

Renal Impairment Summary
IMWG Guidelines

In Myeloma Patients with Renal Impairment

- Available data support the safety and efficacy of bortezomib-based therapies in this setting and thus bortezomib plus high dexamethasone (maybe with thalidomide, cyclophosphamide or doxorubicin?) is the recommended treatment for myeloma patients with renal impairment of any grade.
- Thalidomide is also an option for patients with severe renal impairment, although data are less extensive.
- Lenalidomide is a feasible and effective treatment option for patients with mild-to-moderate renal impairment, if it is used at the recommended reduced dose based on renal function.

Dimopoulos et al. J Clin Oncol 2010;28:4976-84 (IMWG consensus statment)

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