Management of Bone Disease and Renal Impairment in Patients with Multiple Myeloma

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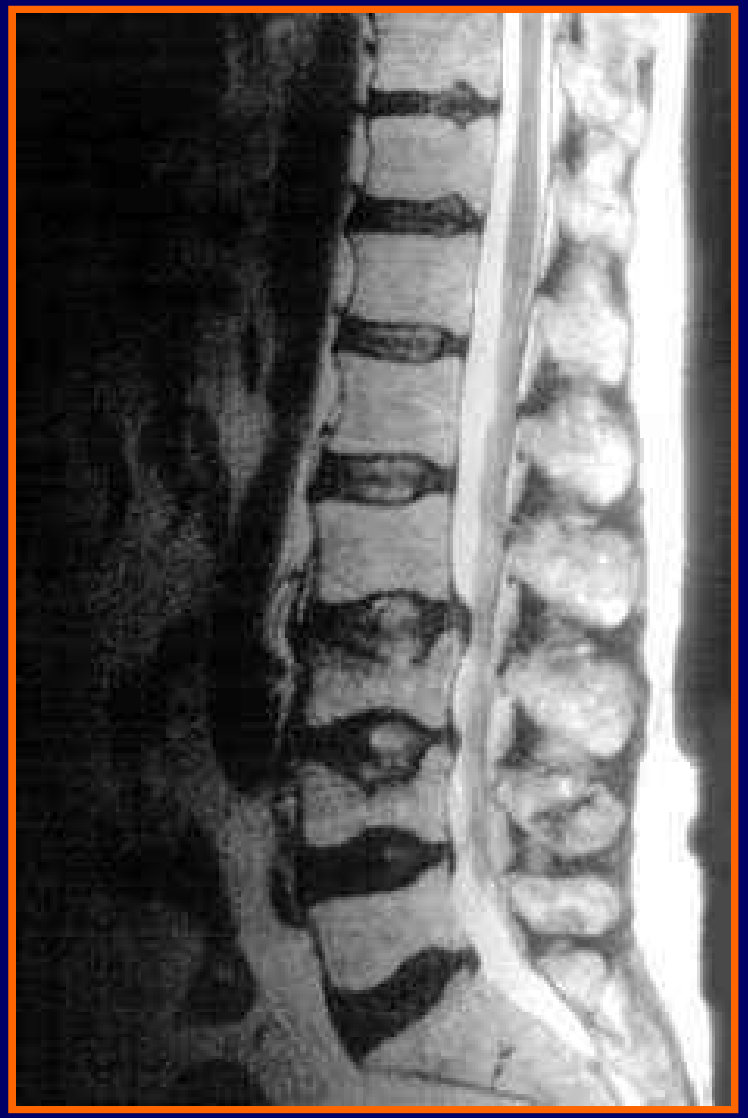
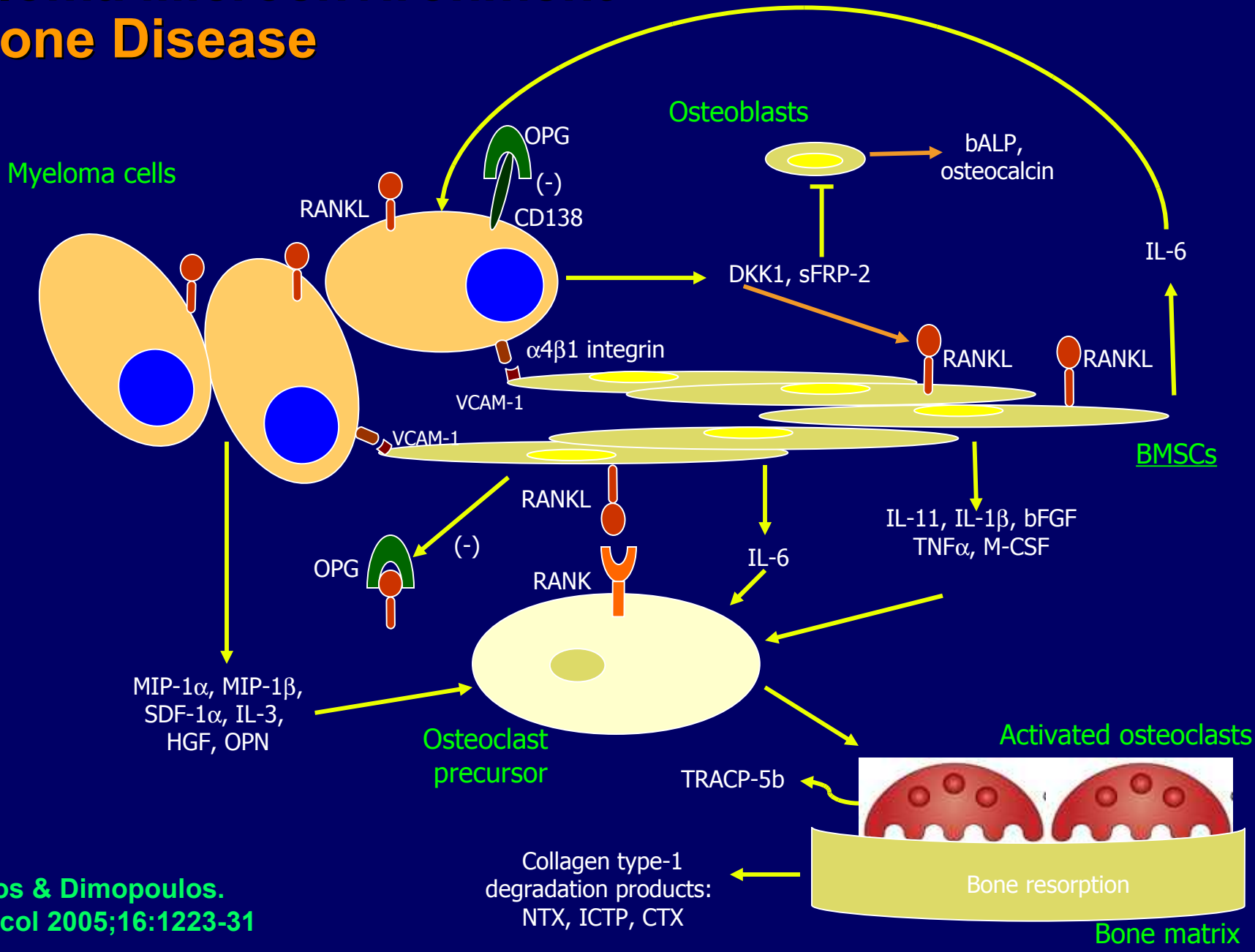
Bone Disease in Multiple Myeloma

- A burdensome and frequent complication in MM
  - Present in up to 80% of patients at diagnosis
- Characterized by osteolytic bone lesions secondary to increased bone resorption and impaired bone formation
- Sequelae
  - Pathological fractures
  - Osteoporosis
  - Hypercalcemia
  - Bone pain
  - Spinal cord compression



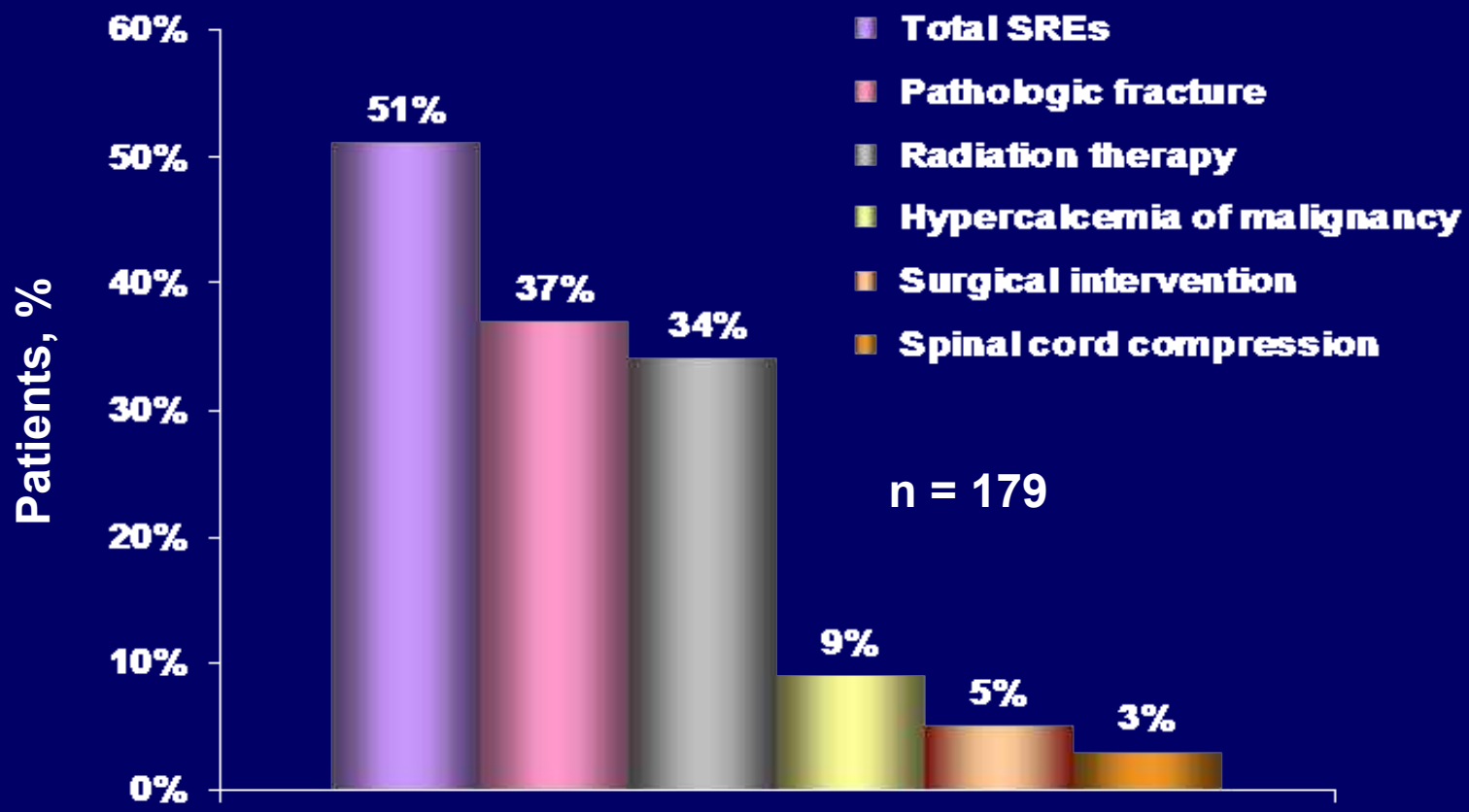
Kyle. Mayo Clin Proc 1975;50:29-40

Myeloma Microenvironment & Bone Disease



Terpos & Dimopoulos.
Ann Oncol 2005;16:1223-31

Skeletal-Related Events (SREs) In Myeloma Patients

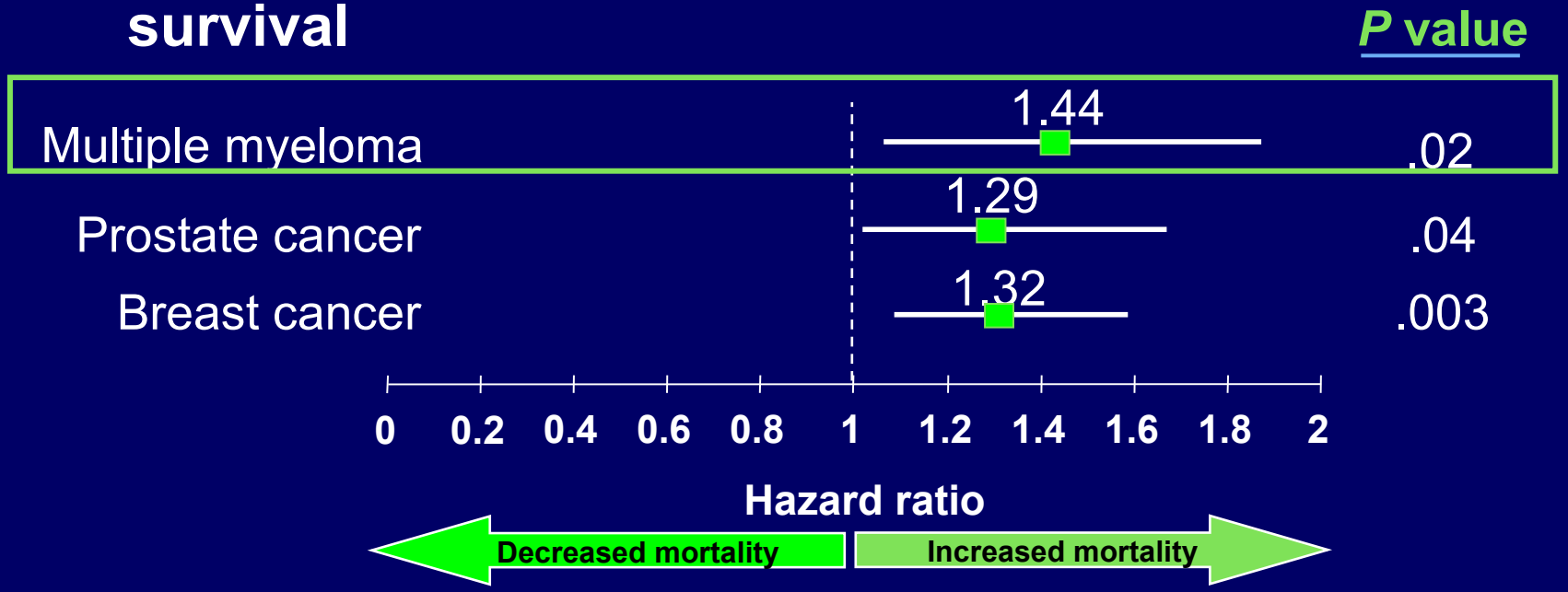


*21-month data (including osteolytic lesions) except for surgical intervention and spinal compression, for which only 9-month data are available from placebo arm of randomized study.

Berenson et al. J Clin Oncol 1998;16:593-602.

Early Treatment to Prevent SREs Is Important Because…

- **Patients who experience a first SRE are 2-fold more likely to experience subsequent SREs**
- **Pathologic fractures are associated with reduced survival**

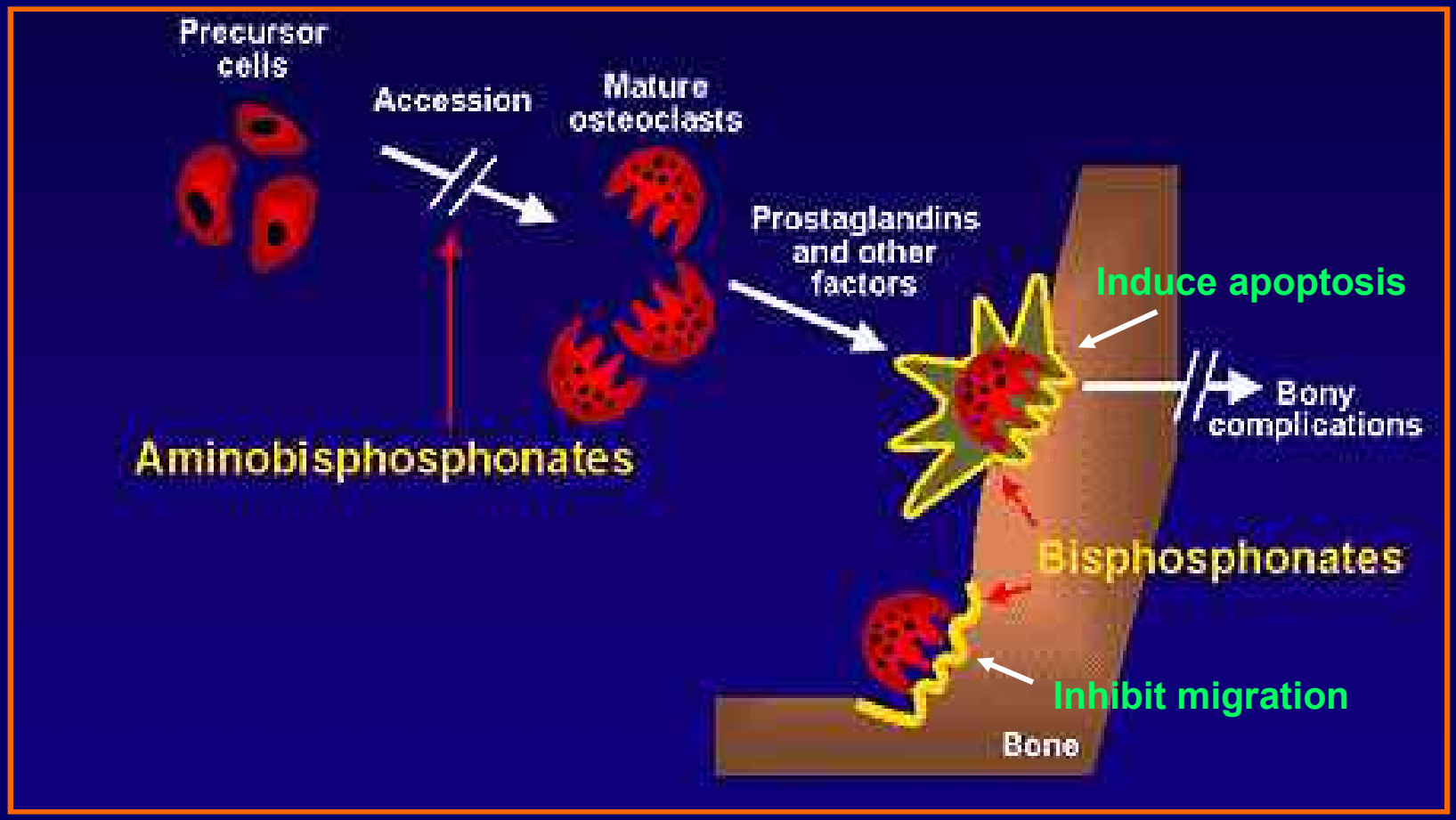


Saad et al. Presented at: ECCO; Oct. 30-Nov. 3, 2005; Paris, France. Abstract 1265.

The Goal of Therapy for Myeloma Bone Disease

- Preserve patient's functional independence and QOL by
  - Preventing skeletal-related events (SREs)
    - Prevent the first SRE
    - Delay the onset of the first SRE
    - Prevent the recurrence of SRE
  - Palliating and controlling bone pain
    - Reduce the need for analgesics and palliative radiotherapy

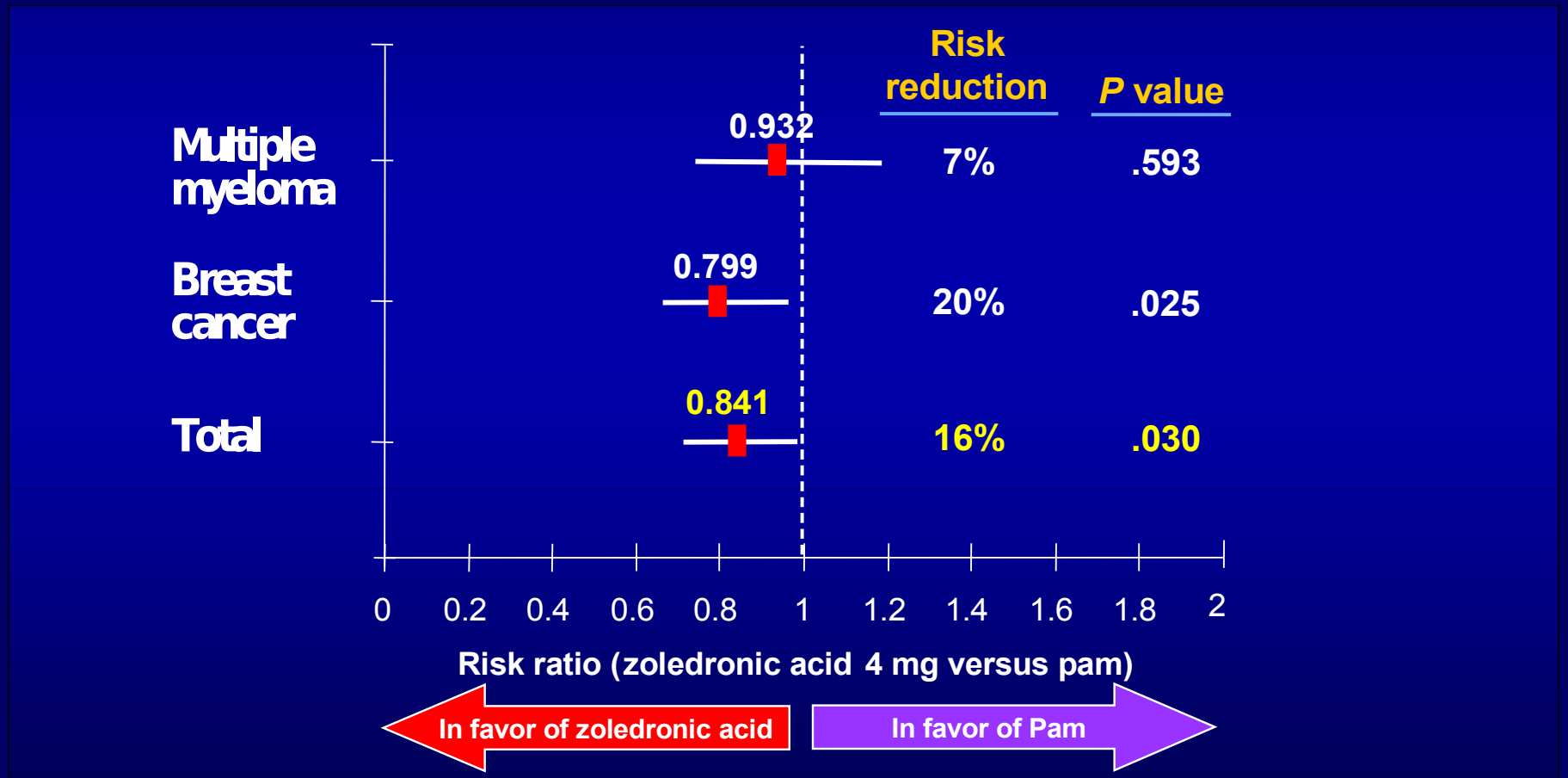
Bisphosphonates



Major Double-Blind, Placebo-Controlled, Trials On Bisphosphonates In MM

Authors/year	Type of BP	No pts	↓ of pain	↓ of SREs	Survival benefit
Belch et al, 1991	Etidronate	173	No	No	No
Daragon et al, '93	Etidronate	94	No	No	No
Lahtinen et al, '92	Clodronate	350	Yes	Yes	NE
McCloskey et al 1998 & 2001	Clodronate	530	Yes	Yes	+/-
Brincker et al, '98	Pamidronate	300	Yes	No	No
Berenson et al, '96	Pamidronate	392	Yes	Yes	+/-
Menssen et al, '02	Ibandronate	198	No	No	No
Berenson et al, '01	Zoledronic acid	108	Yes	Yes	NE
Rosen et al, '01 & '03	Zoledronic acid	513	Yes	Yes	+?

Zoledronic Acid Was at Least as Efficacious as PAM in the Myeloma Stratum



*Hypercalcemia of malignancy is included as an SRE.

Rosen et al. Cancer 2003;98:1735-44

Bisphosphonates: Adverse Events

- Oral
  - GI intolerance (in up to 33% of pts)
    - Especially esophagitis & esophageal ulcers

- Intravenous (PAM or ZOL)
  - Common adverse events
    - Flu-like symptoms
    - Fever/Myalgias/Arthralgias
  - Uncommon adverse events
    - Renal-function effects
    - Osteonecrosis of the jaw

Conte & Guarneri. Oncologist 2004;9(Suppl 4):28-37

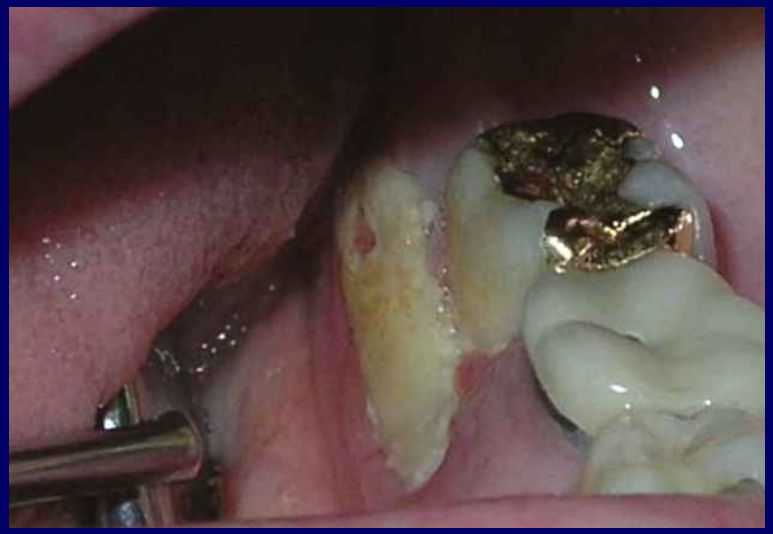
Bisphosphonates and Renal Insufficiency

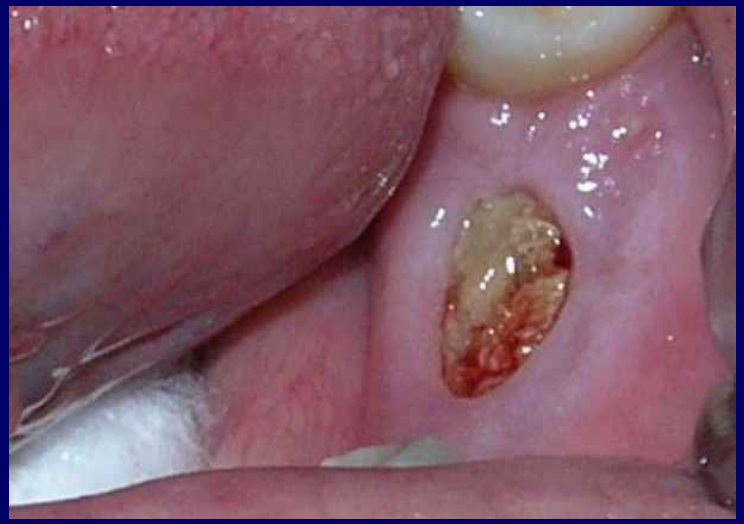
- IV bisphosphonates are cleared almost entirely by the kidneys
- 2007 ASCO Multiple Myeloma Guidelines
  - In patients with pre-existing renal impairment (serum creatinine clearance 30-60 mL/min) should receive reduced dosage of zoledronic acid
  - No change in infusion time or interval of zoledronic acid is required
- Use of these bisphosphonates in patients with more severe renal dysfunction has been minimally assessed

Kyle et al. J Clin Oncol 2007;25:2464-72

ONJ: Novel Complication of Bisphosphonates

- Avascular osteonecrosis of the jaw (ONJ) is a recent complication that has been described in multiple myeloma and other cancer patients who receive potent bisphosphonates.
- ONJ presents as an exposure of the mandible or maxilla that can be either painless or painful.





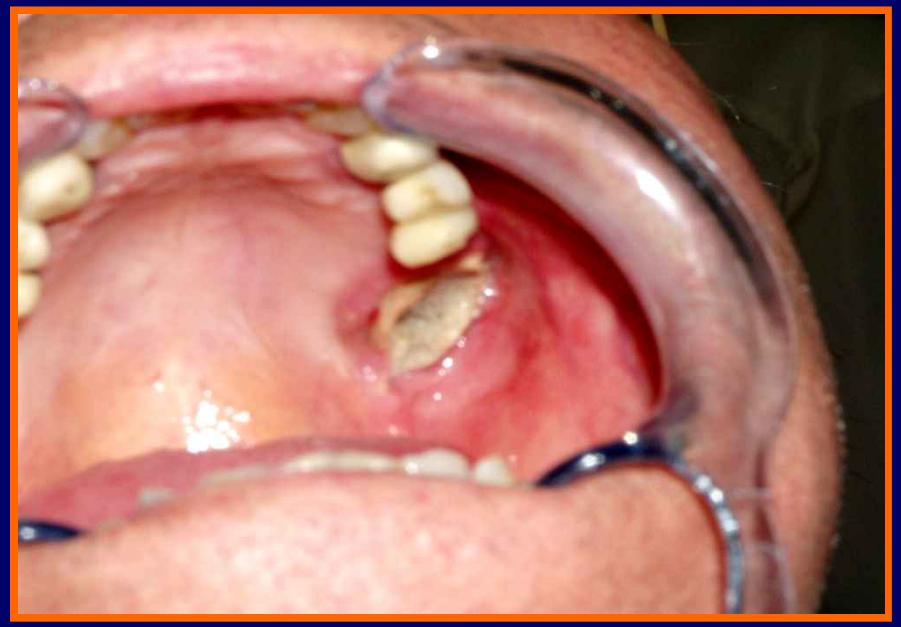
ONJ: characteristics

Symptoms

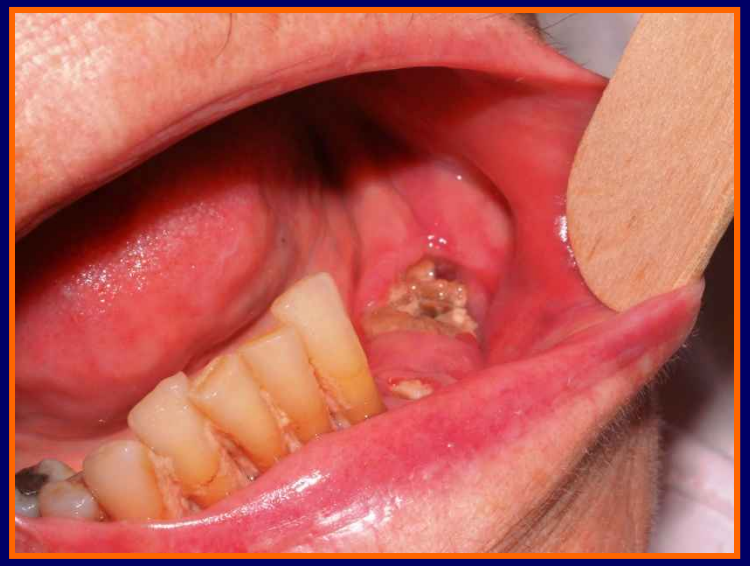
- “heavy jaw”, a dull aching sensation
- numbness/tingling of the jaw
- tooth pain
- undiagnosed oral pain

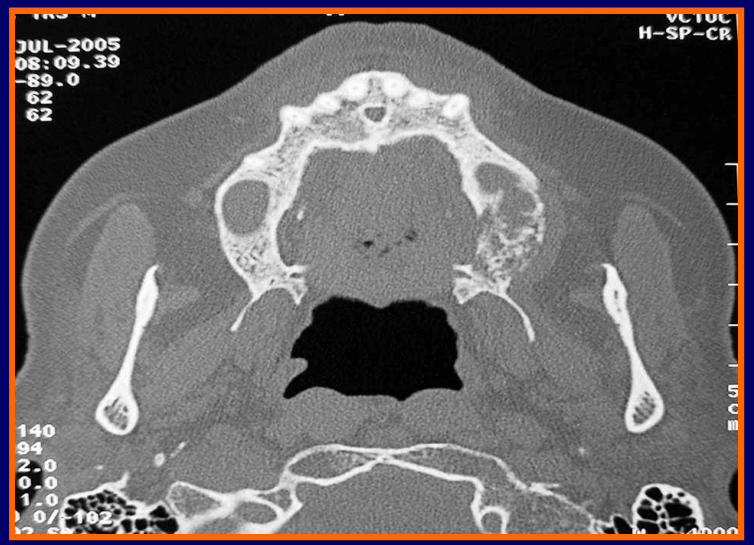
Signs

- rough area on the jawbone
- soft tissue swelling, drainage or infection
- exposed bone in the oral cavity
- sudden change in the health of periodontal tissue
- failure of oral mucosa to heal
- loosening of teeth



Clinical Presentation and Working Diagnosis of ONJ





Clinical features of suspected ONJ

- Exposed bone in maxillofacial area that occurs in association with dental surgery or occurs spontaneously, with no evidence of healing

Working diagnosis of ONJ

- No evidence of healing after 6 weeks of appropriate evaluation and dental care
- No evidence of metastatic disease in the jaw or osteoradionecrosis

Weitzman et al. Crit Rev Oncol Hematol 2007;62:148-152

Incidence of ONJ in Malignant Bone Disease:

Prior to Implementation of Prevention Strategies

Study	Study type	Pts treated w BP, n	Pts w suspect or proven ONJ, n	Frequency %
Hoff et al. MDACC (JBMR 2008)	Chart review	3,994	29	0.7%
Durie et al (NEJM 2005)	Web-based survey	1,203	152	12.6%
Badros et al (JCO 2005)	Chart review/ observational	340	11	3.2%
Zervas et al (BJH 2006)	Chart review/ prospective after 2001	254	28	11.0%
Dimopoulos et al (Haematologica 2006)	Chart review/ prospective after 2003	202	15	7.4%

Relative Risk for ONJ Development

15/202 developed ONJ (7.4%)	Relative risk							
	12 months		24 m		36 m		48 m	
	%	95%CI	%	95%CI	%	95%CI	%	95%CI
All (n=202)	1	0-2	3	1-4	6	2-10	13	5-21
Zoledronic acid (n=93)	1	0-3	5	0-11	15	3-27	15	3-27
PA (n=33)	0	0	1	0-3	1	0-3	5	0-11

ONJ	Yes	No	p-value
Thalidomide			
Yes	8 (7.5%)	99 (92.5%)	0.977
No	7 (7.4%)	88 (92.6%)	

Dimopoulos et al. Haematologica 2006;91:968-71

ASCO Guidelines

- The Update Committee suggests that bisphosphonate treatment continues for a period of 2 years.
- At 2 years, physicians should seriously consider discontinuing bisphosphonates in patients with responsive or stable disease, but further use is at the discretion of the treating physician.
- Re-initiation at relapse.

Kyle et al. J Clin Oncol 2007;25:2464-72

Update for ONJ and Bisphosphonates in Myeloma (1)

- Appropriate preventative measures, such as a detailed assessment of dental status by experienced specialists, and avoidance of dental procedures during treatment with ZOL have the potential to reduce the number of ONJ cases.
- Group A, with no special precautions (n=38) and Group B, with a detailed dental assessment and preemptive dental care (n=90).
- ONJ occurrence was 0.671/100 person-month for Group A *vs.* 0.230/100 person-month for Group B: 3-fold reduction of ONJ occurrence (p=0.029)

Dimopoulos et al. Ann Oncol 2009;20:117-120

Update for ONJ and Bisphosphonates in Myeloma (2)

- ONJ resolved and did not recur in 60/97 cases (62%)
- resolved and then recurred in 12 patients (12%)
- did not resolve over a follow-up period of at least 9 months in 25 patients (26%)
- ONJ recurrence followed re-initiation of bisphosphonate in 6 of 12 patients

Badros et al. J Clin Oncol 2008;26:5904-9

Update for ONJ and Bisphosphonates in Myeloma (3)

- ONJ recurrence was linked to BP re-challenge, mostly in the setting of relapsed MM

- Patients in whom ONJ was precipitated by dental procedures, were less likely to have recurrence or non-healing lesions, after BP re-initiation following ONJ healing, as compared to those who

Badros et al. J Clin Oncol 2008;26:5904-9

Recommendations by An Expert Panel on behalf of the EMN (1)

- BPs should be given for 2 years; then at the physician's discretion.
- In patients in CR after 12 months the benefit of an additional 12 months of treatment is debatable.
- BP therapy should be resumed upon relapse.
- Comprehensive dental examination & education on dental hygiene. Existing dental conditions should be treated before initiating BPs.
- After therapy initiation, unnecessary invasive dental procedures should be avoided and dental status should be monitored annually.

Terpos et al. Ann Oncol 2009;20:1303-17

Recommendations by An Expert Panel on behalf of the EMN (2)

- Temporary BPs suspension if invasive dental procedures needed.
- Initial ONJ therapy should include discontinuation of BP until healing.
- The decision to restart BP should be individualized, until prospective long-term studies are available.
- The physician has to take into consideration the advantages and disadvantages of BPs mainly in the relapsed/refractory setting.

Terpos et al. Ann Oncol 2009;20:1303-17

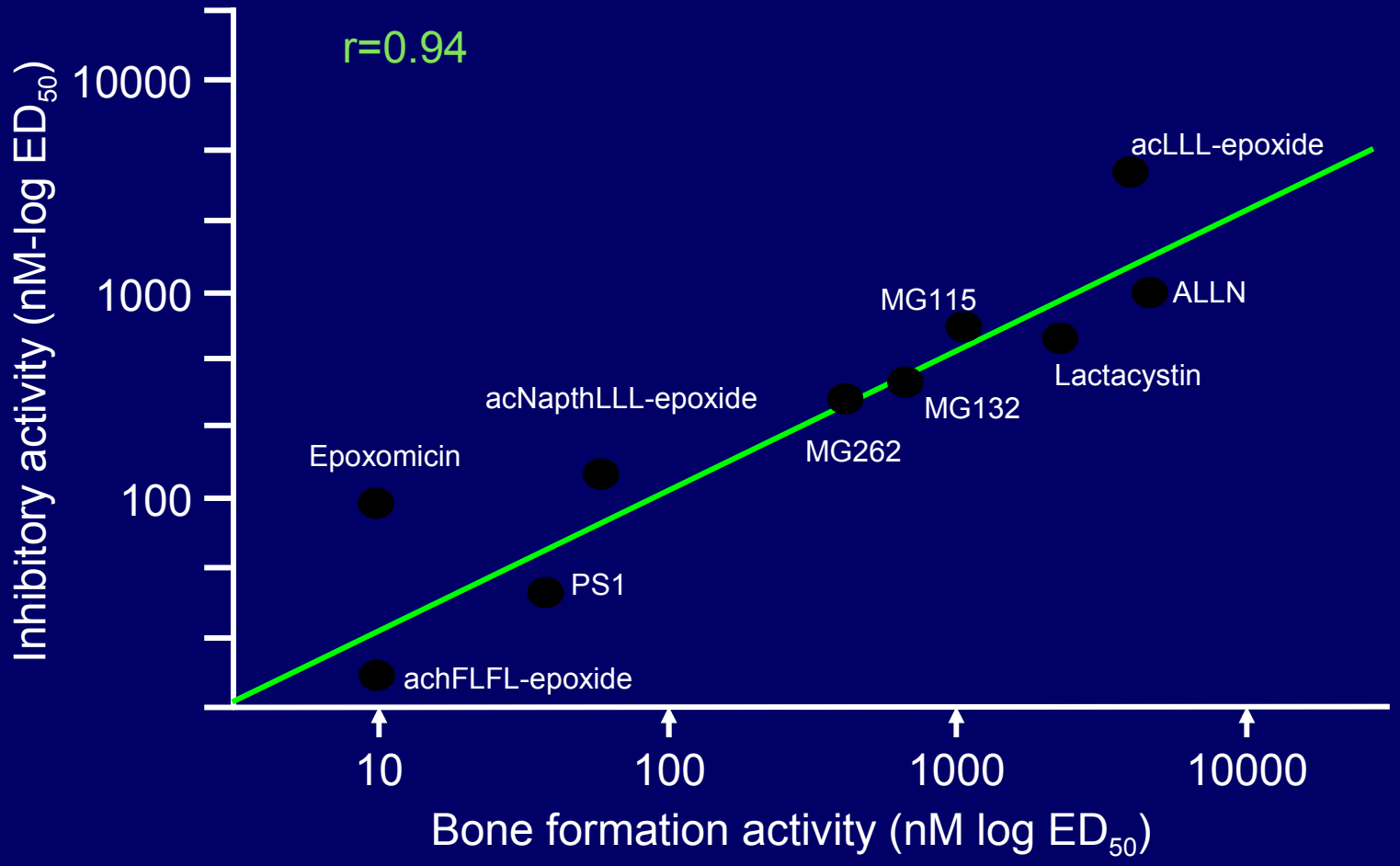
Recommendations by An Expert Panel on behalf of the EMN (3)

Creatinine Clearance rate (mL/min)	Recommended dosage of CLO (1600 mg)
>80	100%
50-80	75%
12-50	50-75%
<12	50% or discontinue

Creatinine Clearance rate (mL/min)	Recommended dosage of ZOL (mg)
> 60	4.0
50-60	3.5
40-49	3.3
30-39	3.0
<30	Not recommended

Creatinine Clearance rate (mL/min)	Recommended infusion time for PAM (90mg)
>30	2-4 hours
<30	Not recommended

Proteasome Inhibition and Bone Formation



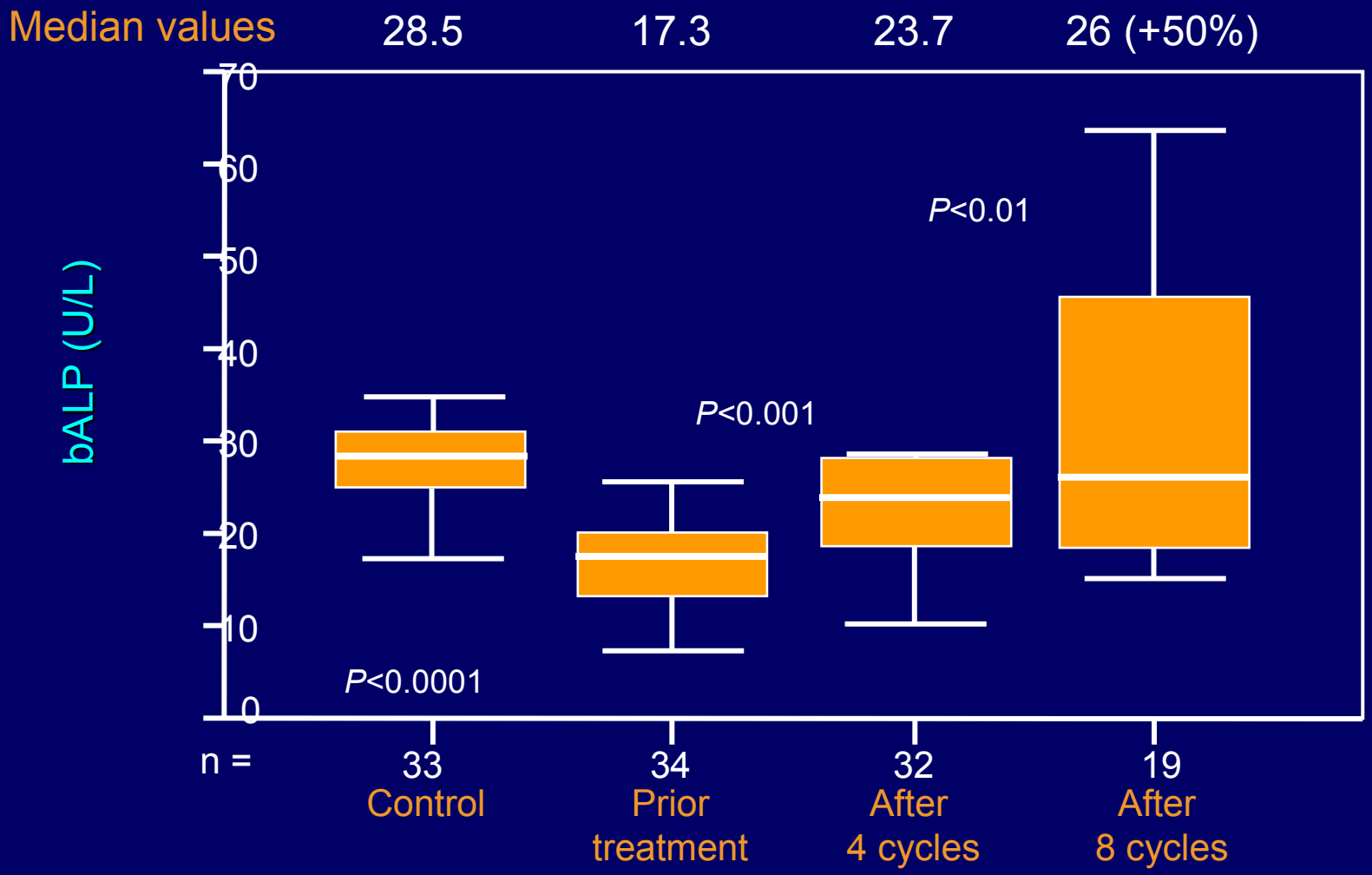
Garrett et al. J Clin Invest 2003;111:1771-8

Effect of Bortezomib on Bone Remodeling in Patients with Relapsed MM

- Aim
  - Evaluate effect of bortezomib on markers of bone remodeling and osteoblast or osteoclast stimulators
    - DKK-1, RANKL, OPG
- 34 patients with relapsed MM
- Treated with bortezomib 1.3 mg/m^2 days 1, 4, 8, 11 of 3-week cycle x 4
  - Responders could receive 4 more cycles
  - Non-responders after 4 cycles could have dex added
- Results
  - Response data
    - 8% CR, 58% PR

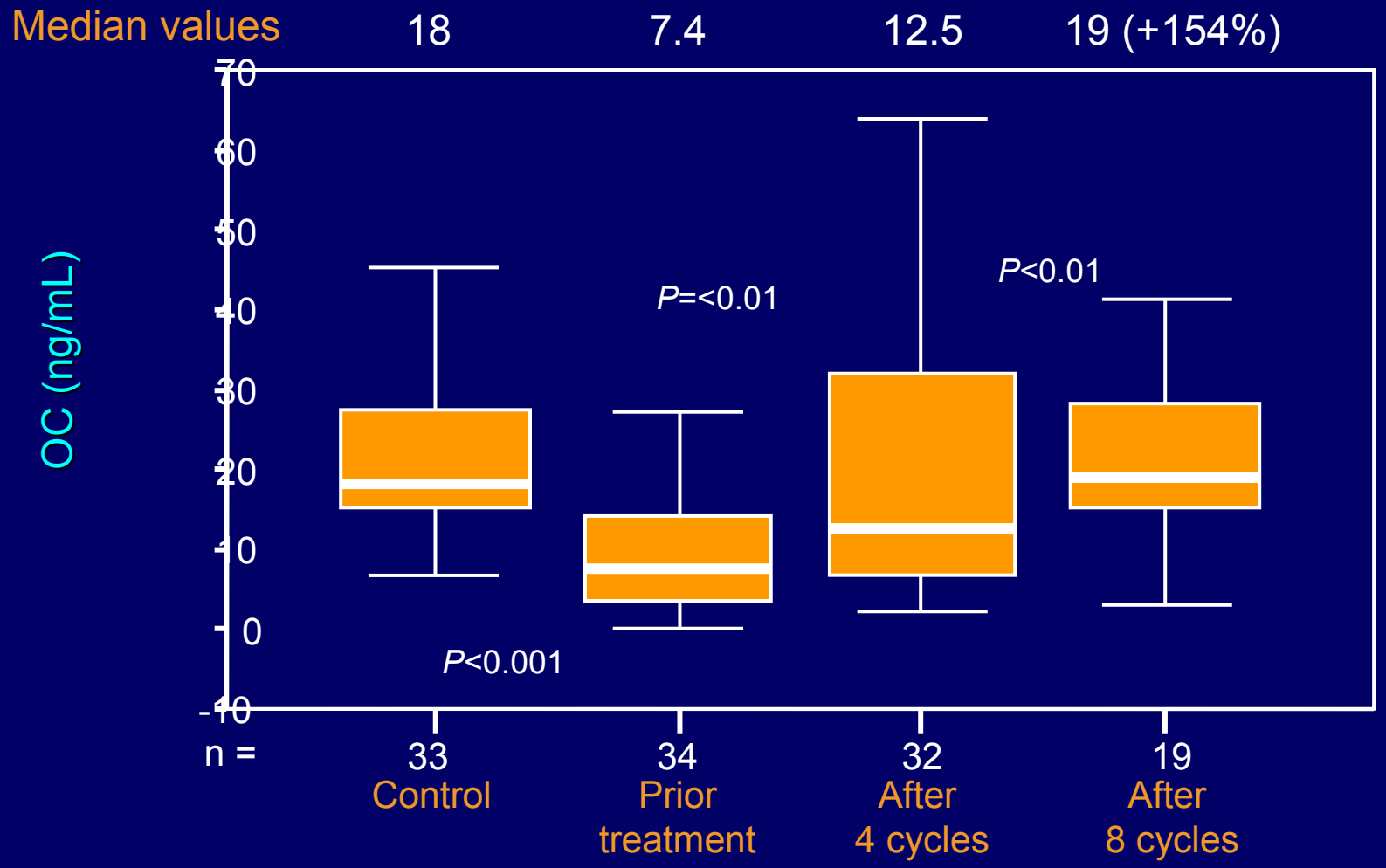
Terpos et al. Br J Haematol 2006;135:688–92

Osteoblast Markers: Pre- and Post-bortezomib (1)



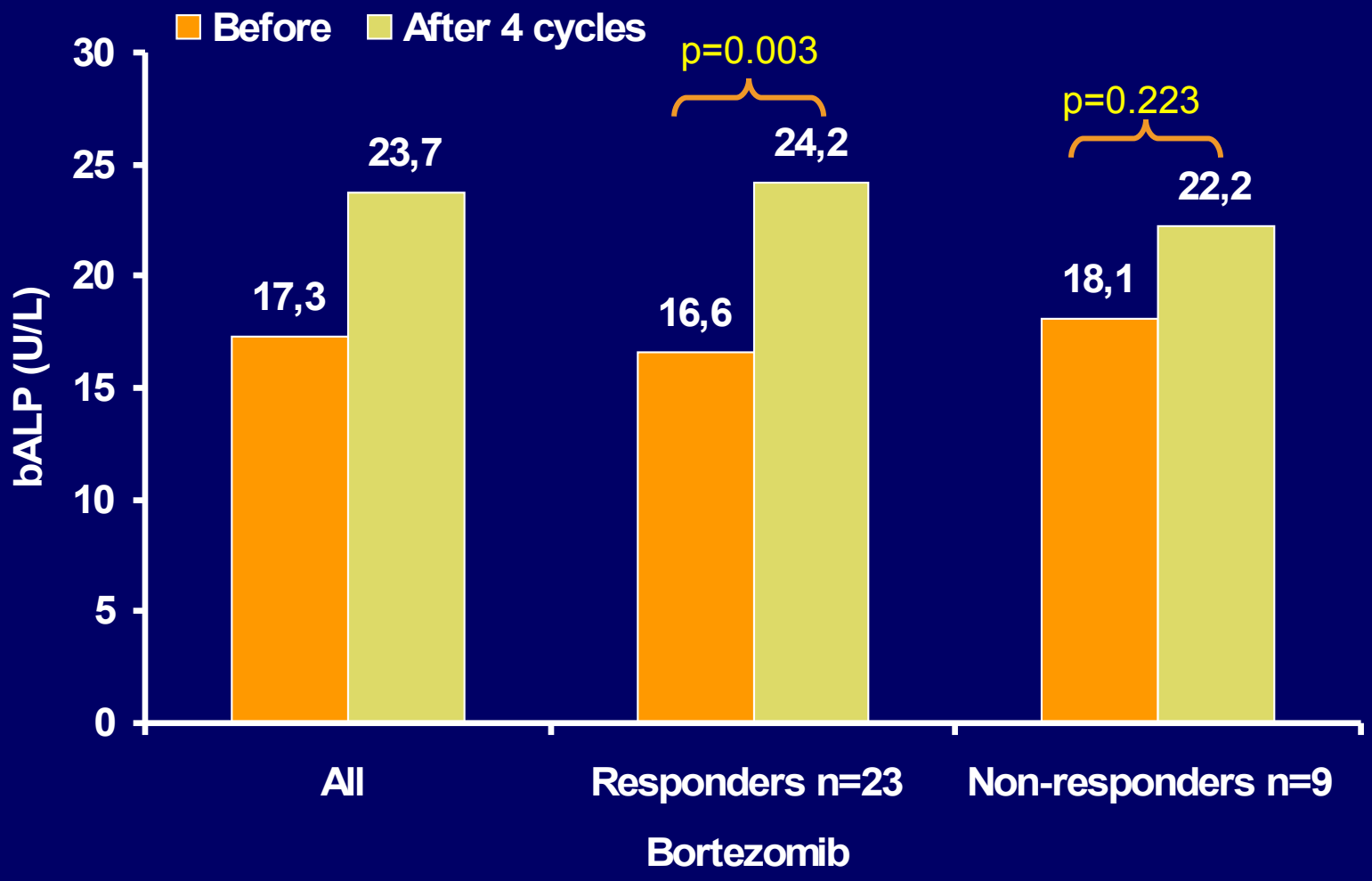
Terpos et al. Br J Haematol 2006;135:688–92

Osteoblast Markers: Pre- and Post-bortezomib (2)



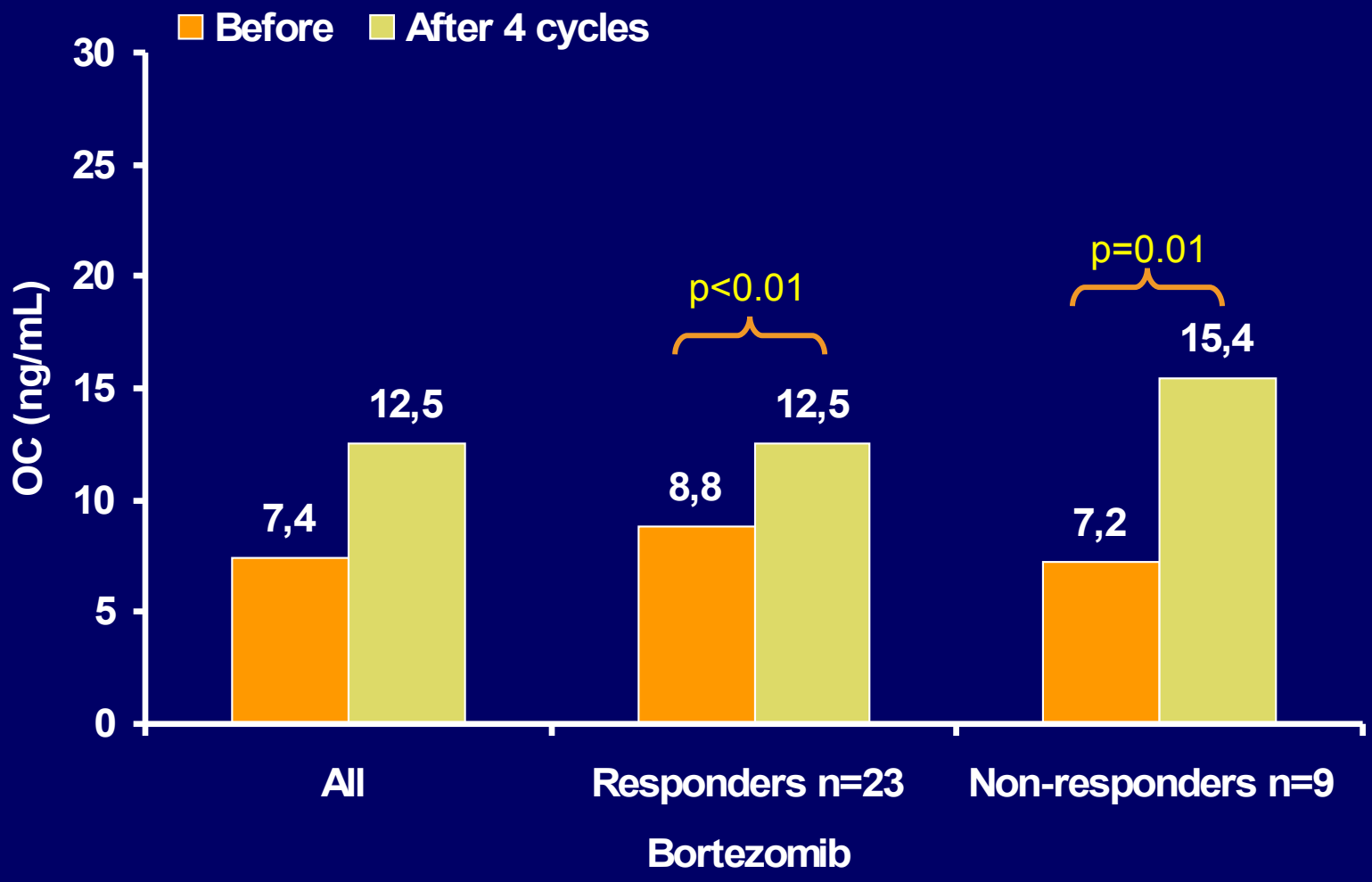
Terpos et al. Br J Haematol 2006;135:688–92

Changes in bALP Levels



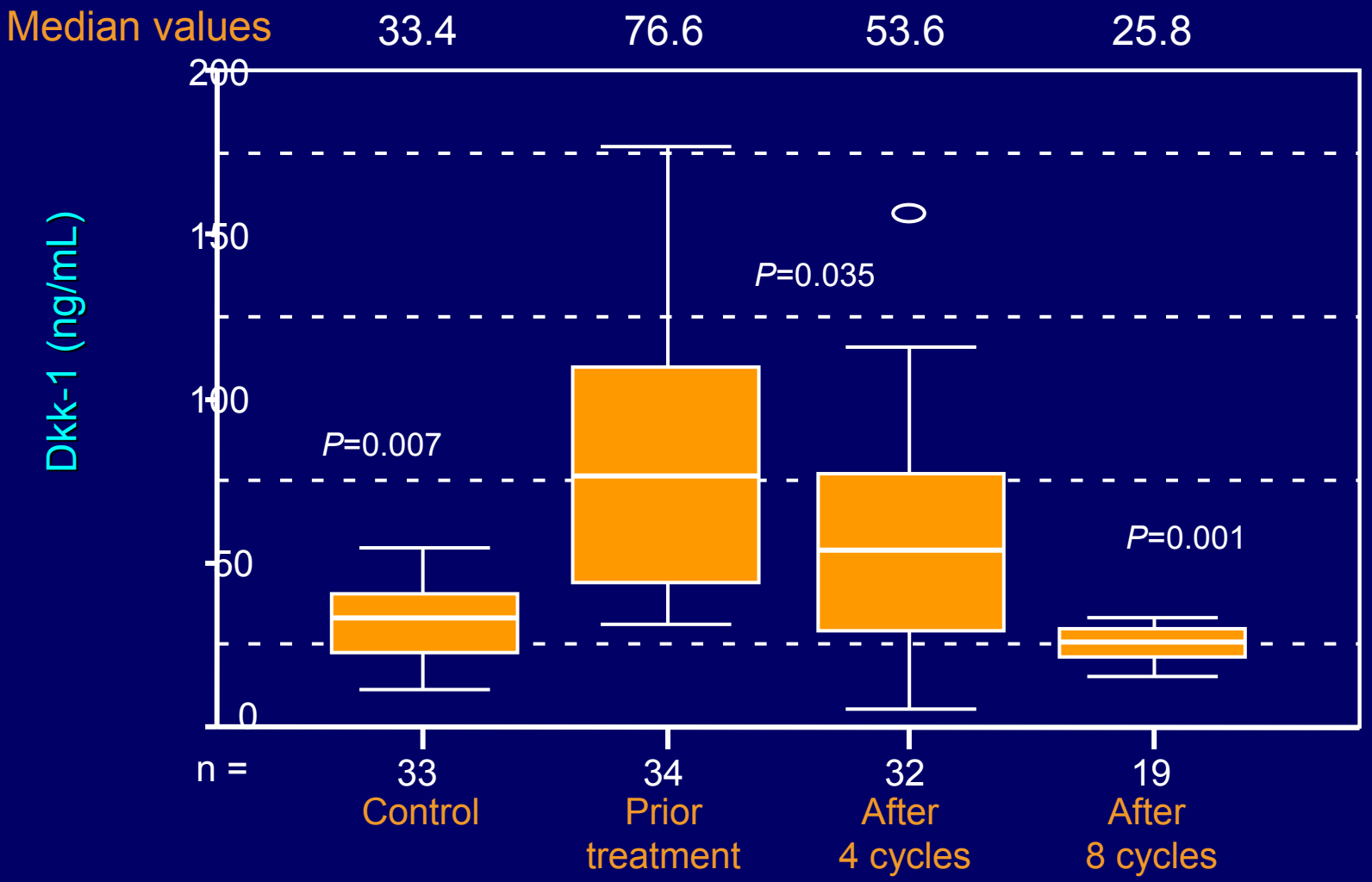
Terpos et al. Br J Haematol 2006;135:688–92

Changes in Osteocalcin Levels



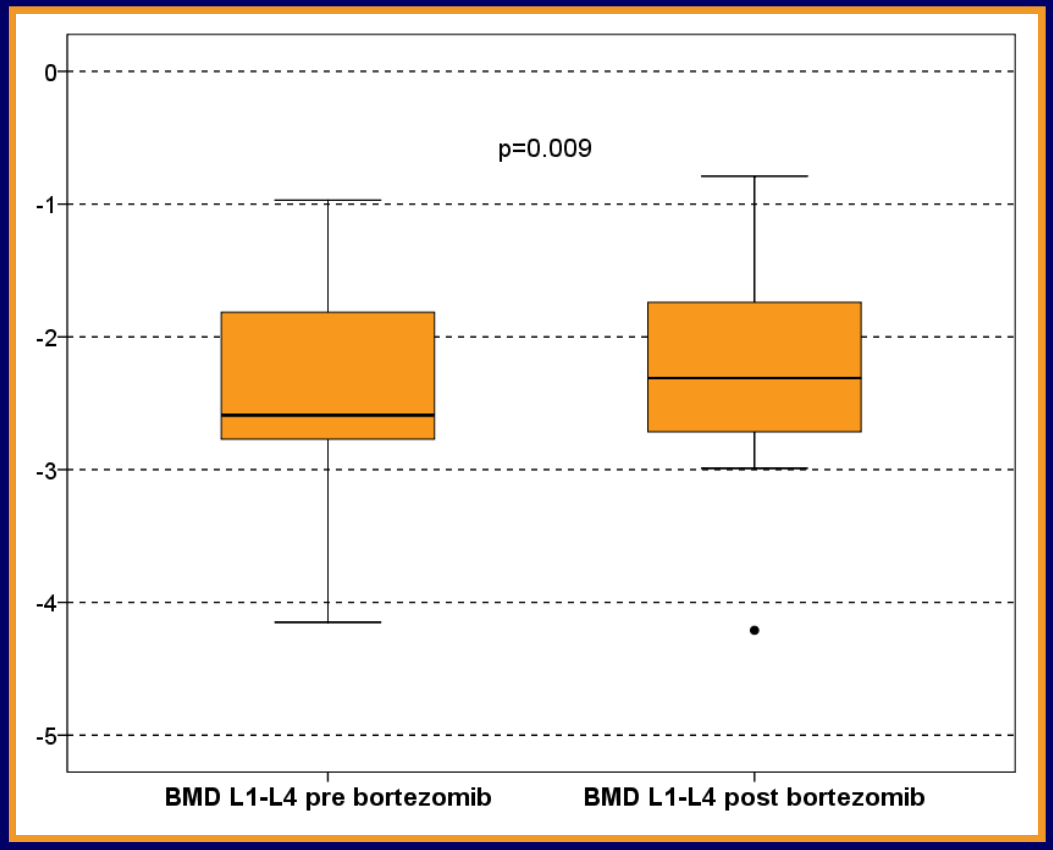
Terpos et al. Br J Haematol 2006;135:688–92

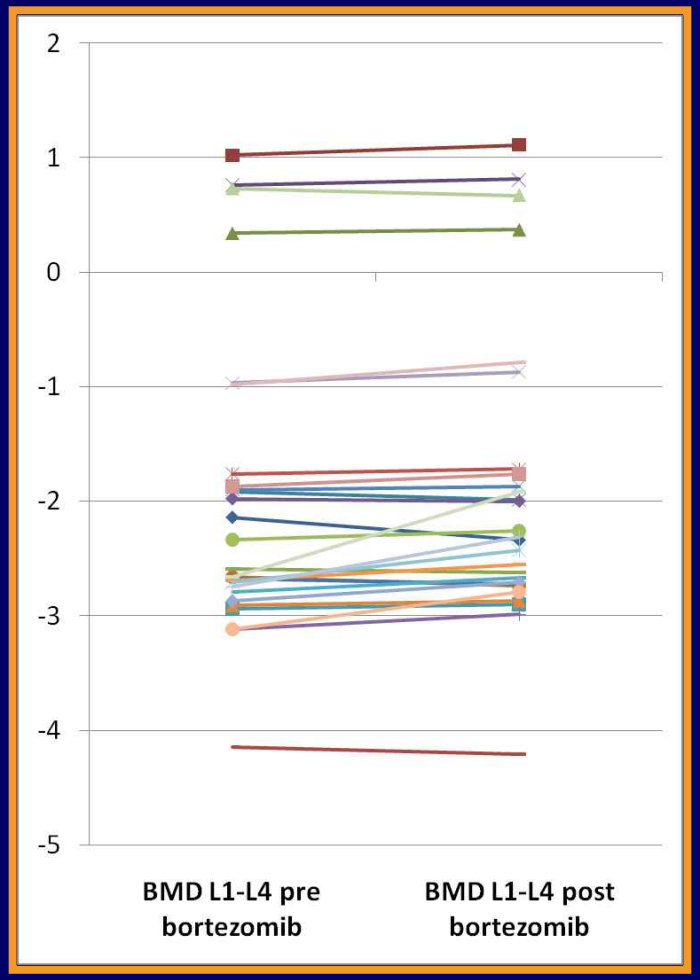
Dkk-1: Pre- and Post-bortezomib



Terpos et al. Br J Haematol 2006;135:688–92

BMD: Pre- and Post-bortezomib

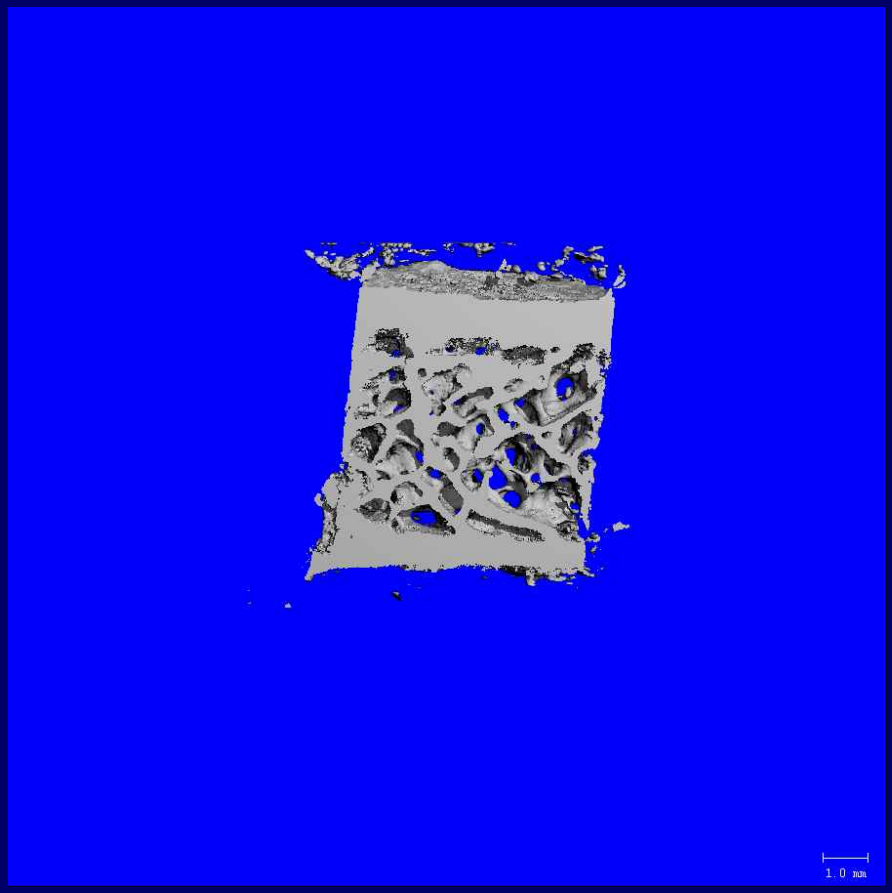




4/27 patients (14%) showed at least 10% of increase in L1-L4 BMD; all these patients had osteoporosis according to DXA, had responded to VD therapy (3 PR and one CR), and had received VD as second line treatment

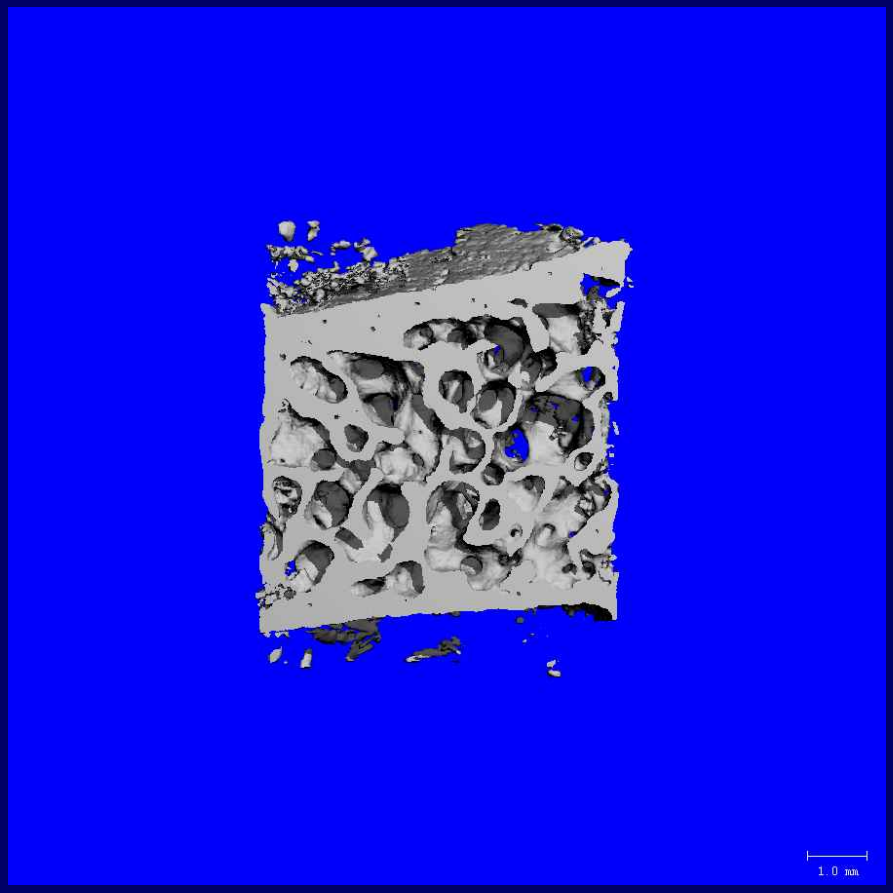
Terpos et al; presented at EHA 2009/Berlin abstract No 958

Pre-Bor



BV/TV = 12.85%
Tb.Th = 0.1
Tb.Sp. = 0.7
Tb.N. = 1.5

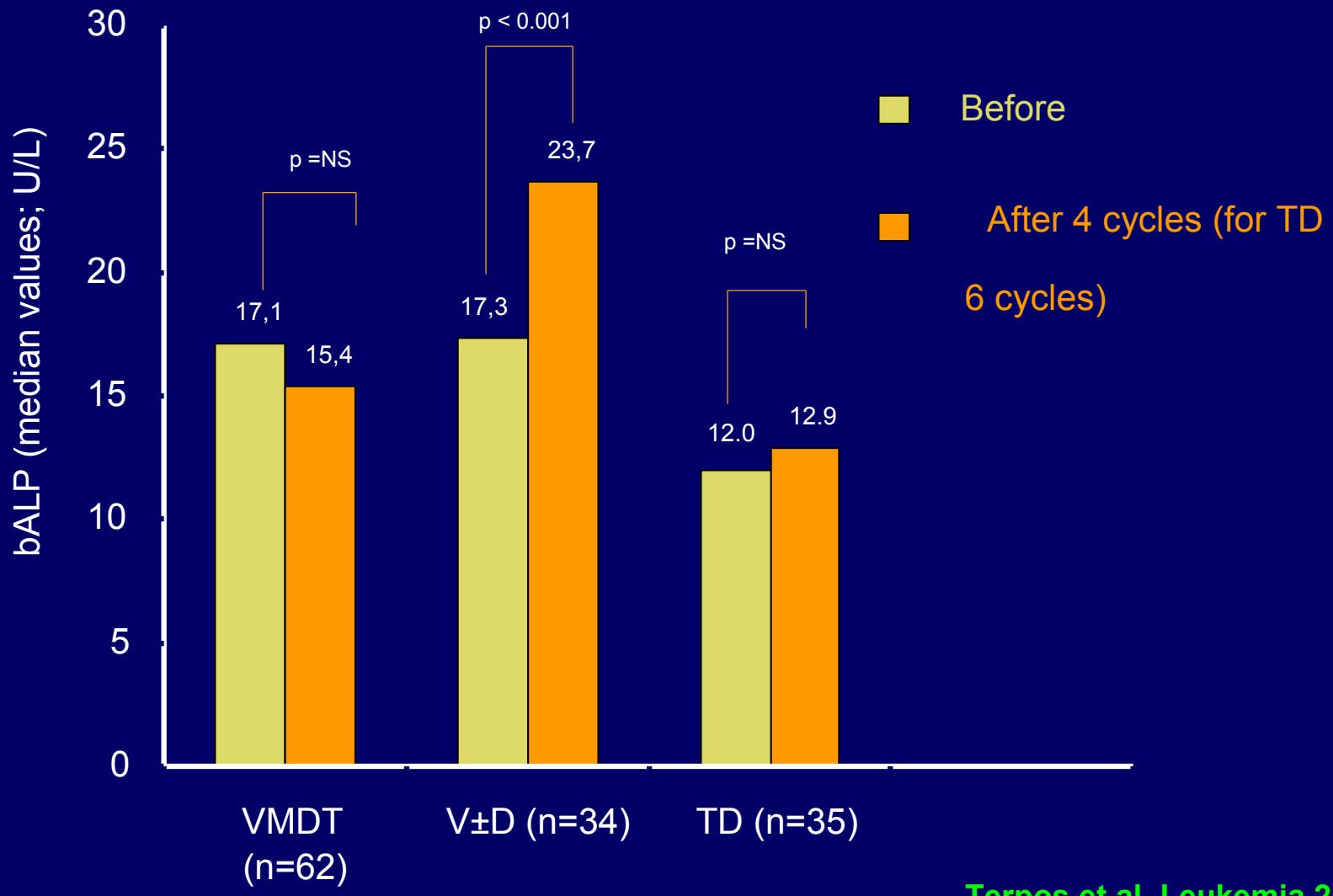
Post-Bor



BV/TV = 90%
Tb.Th = 0.7
Tb.Sp. = 0.2
Tb.N. = 2.8

Zangari et al.
EHA 2007 (abstract 695)

Bone Formation in Bortezomib Combinations



Terpos et al. Leukemia 2008;22:2247

RD *vs.* VDR in Relapsed/Refractory Myeloma: Patient Eligibility & Treatment Schedule

- Relapsed/Refractory Myeloma
- No prior treatment with lenalidomide
- Peripheral neuropathy

< grade 2

V 1 mg/m^2 on days 1, 4, 8 and 11

R 15 mg days 1-14 (or at a lower dose if CrCl < 30 ml/min)

D 40 mg PO on days 1-4 Courses are repeated every 21d

N=40

≥ grade 2

R on days 1 to 21 according to CrCl

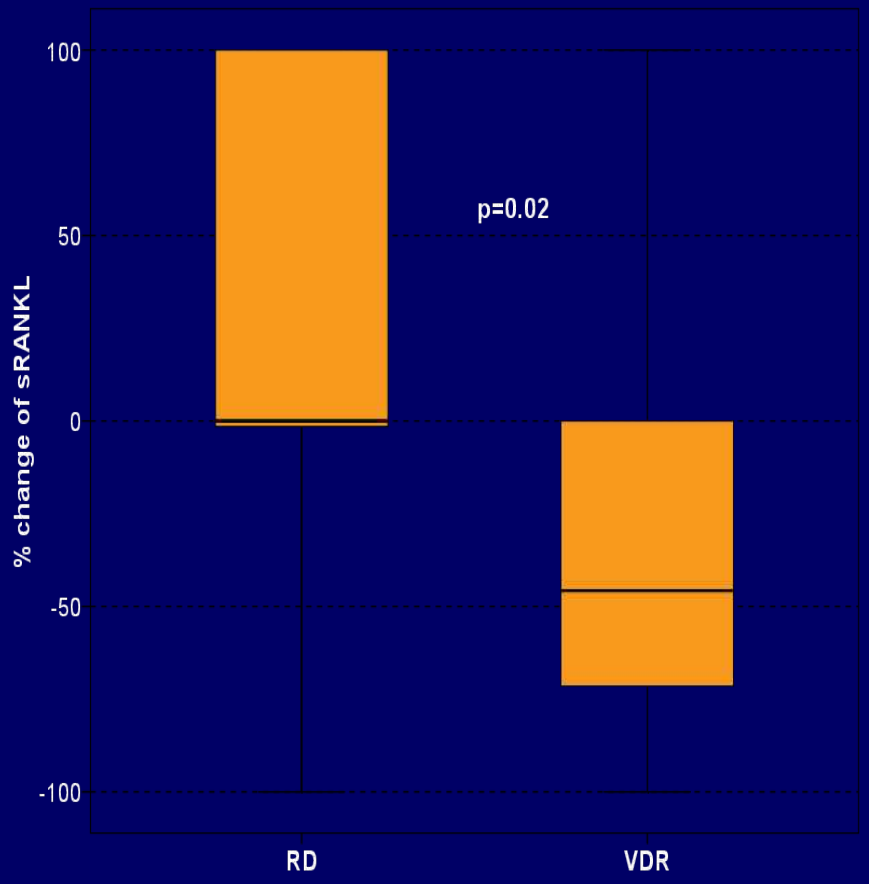
D 40 mg PO on days 1-4 and 15-28 for the first 4 cycles and only days 1-4 thereafter

Courses are repeated every 28d

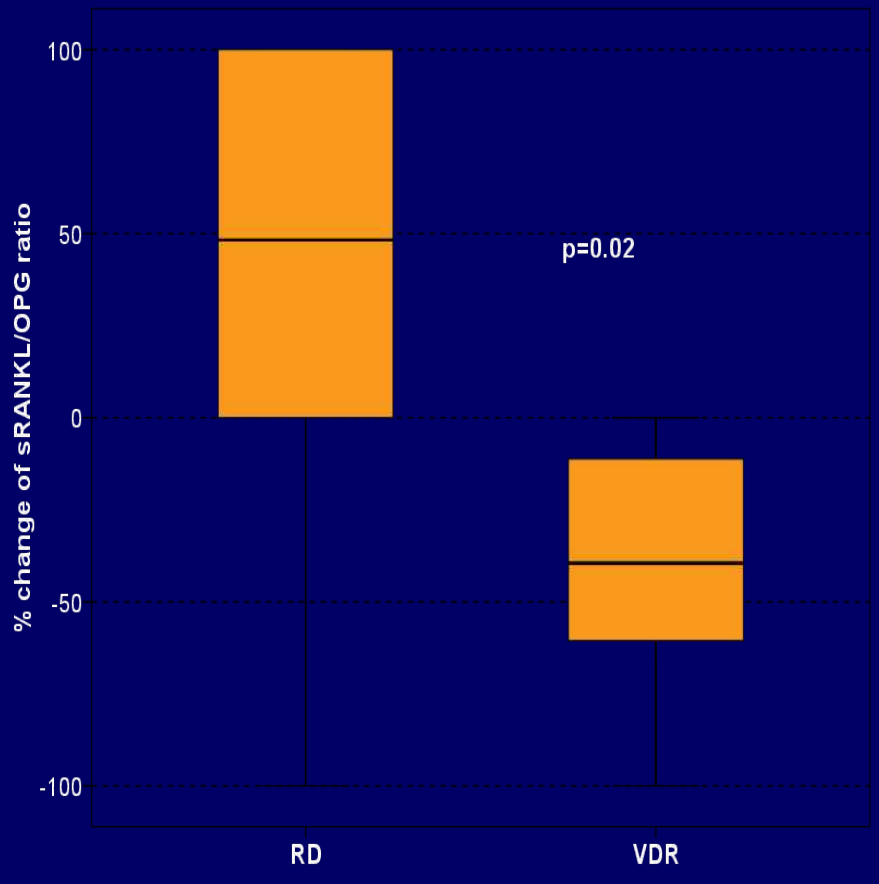
N=41

Dimopoulos et al. IMW 2009

Effect of RD and VRD on RANKL in Patients with Relapsed/Refractory MM: RANKL



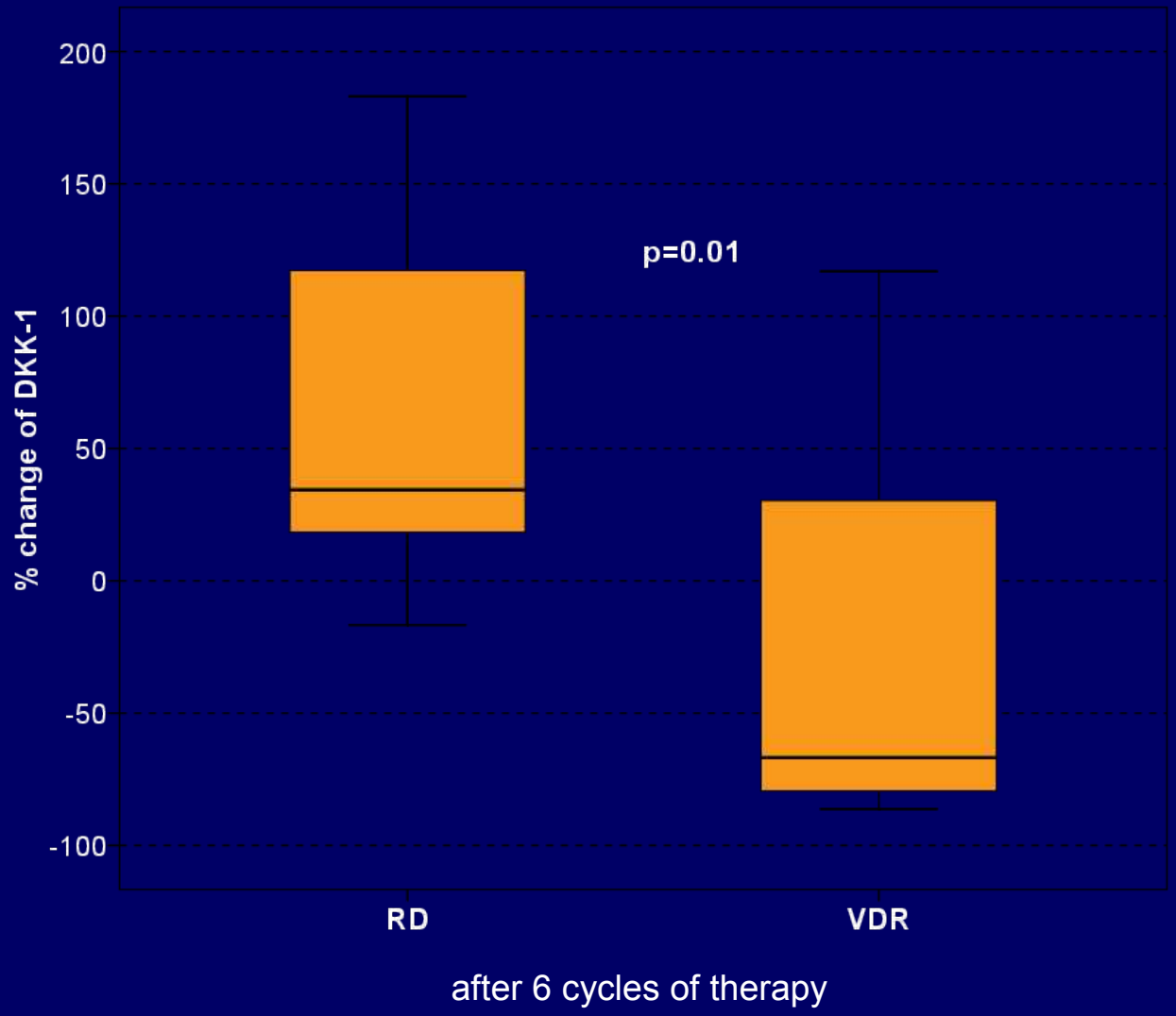
after 6 cycles of therapy



after 6 cycles of therapy

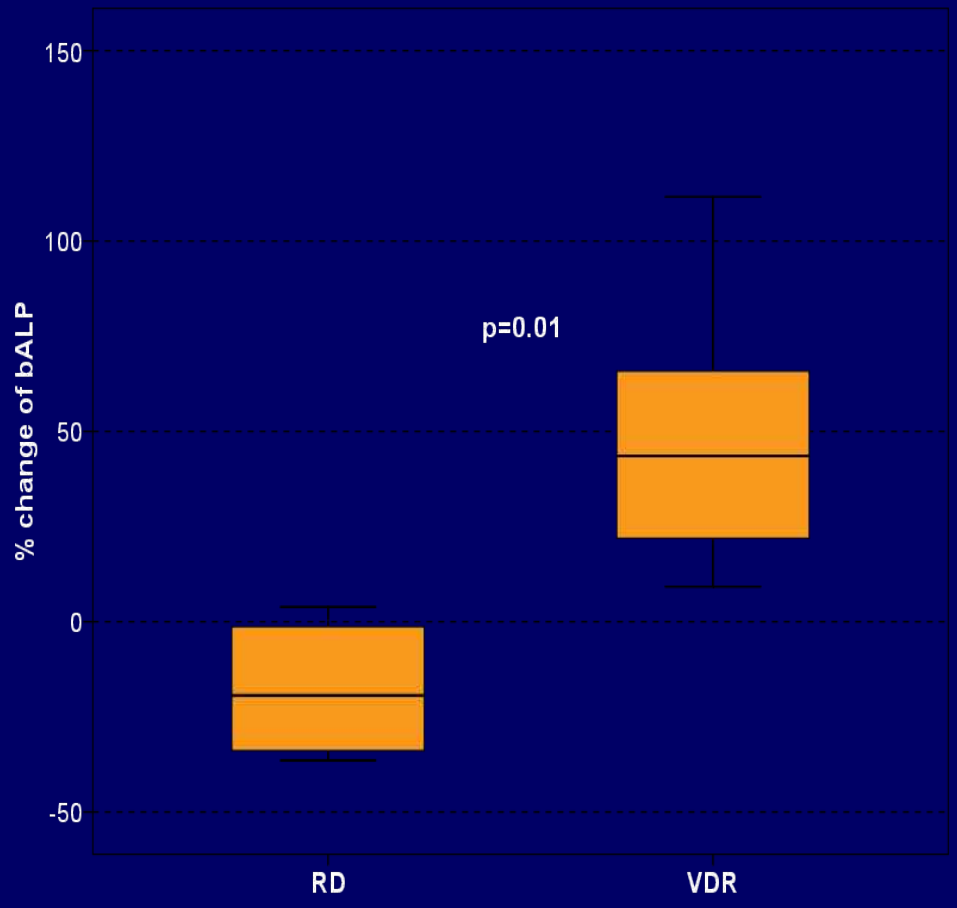
Terpos et al. ASH 2009

Effect of RD and VRD on Dickkopf-1

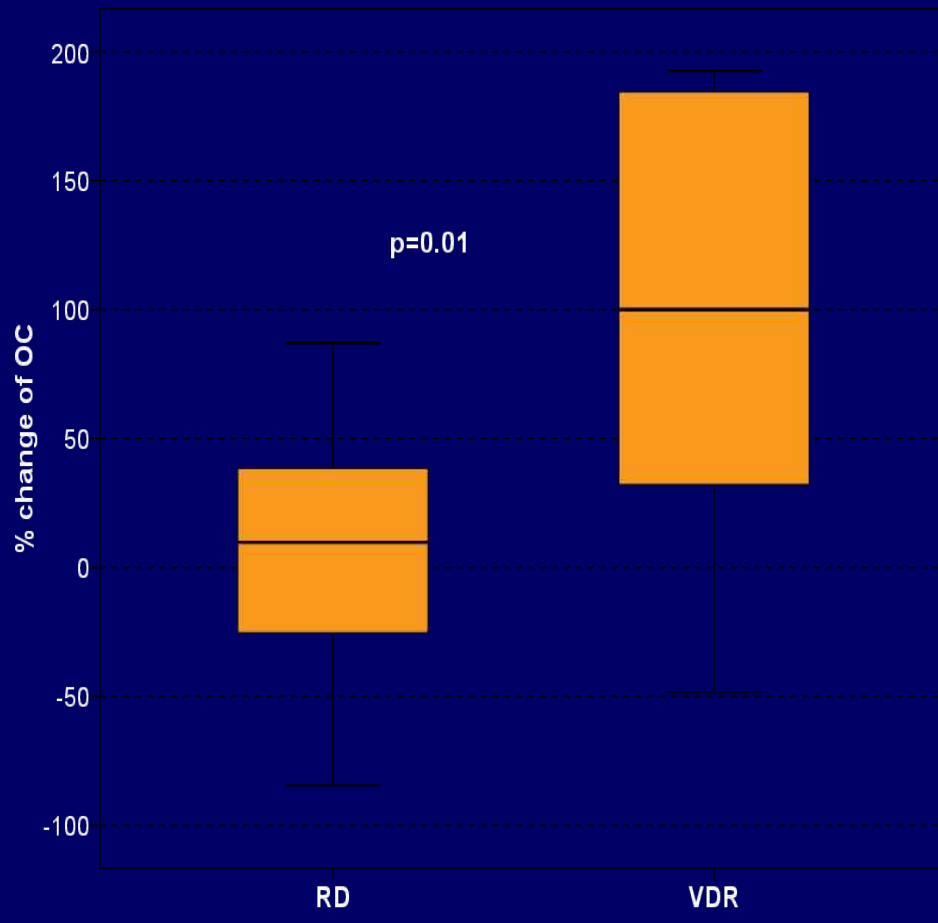


Terpos et al. ASH 2009

Effect of RD and VRD on Bone Formation



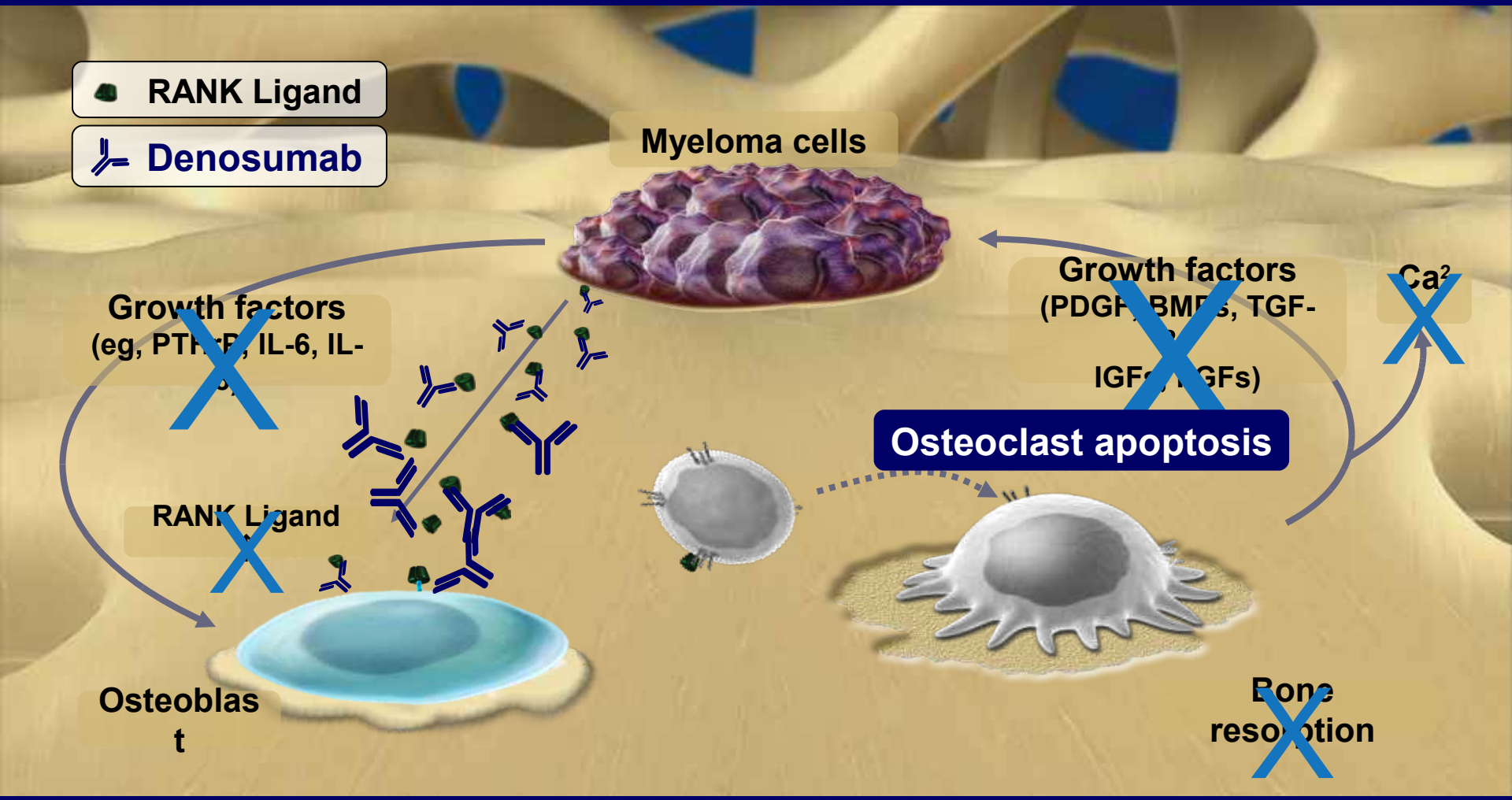
after 6 cycles of therapy



after 6 cycles of therapy

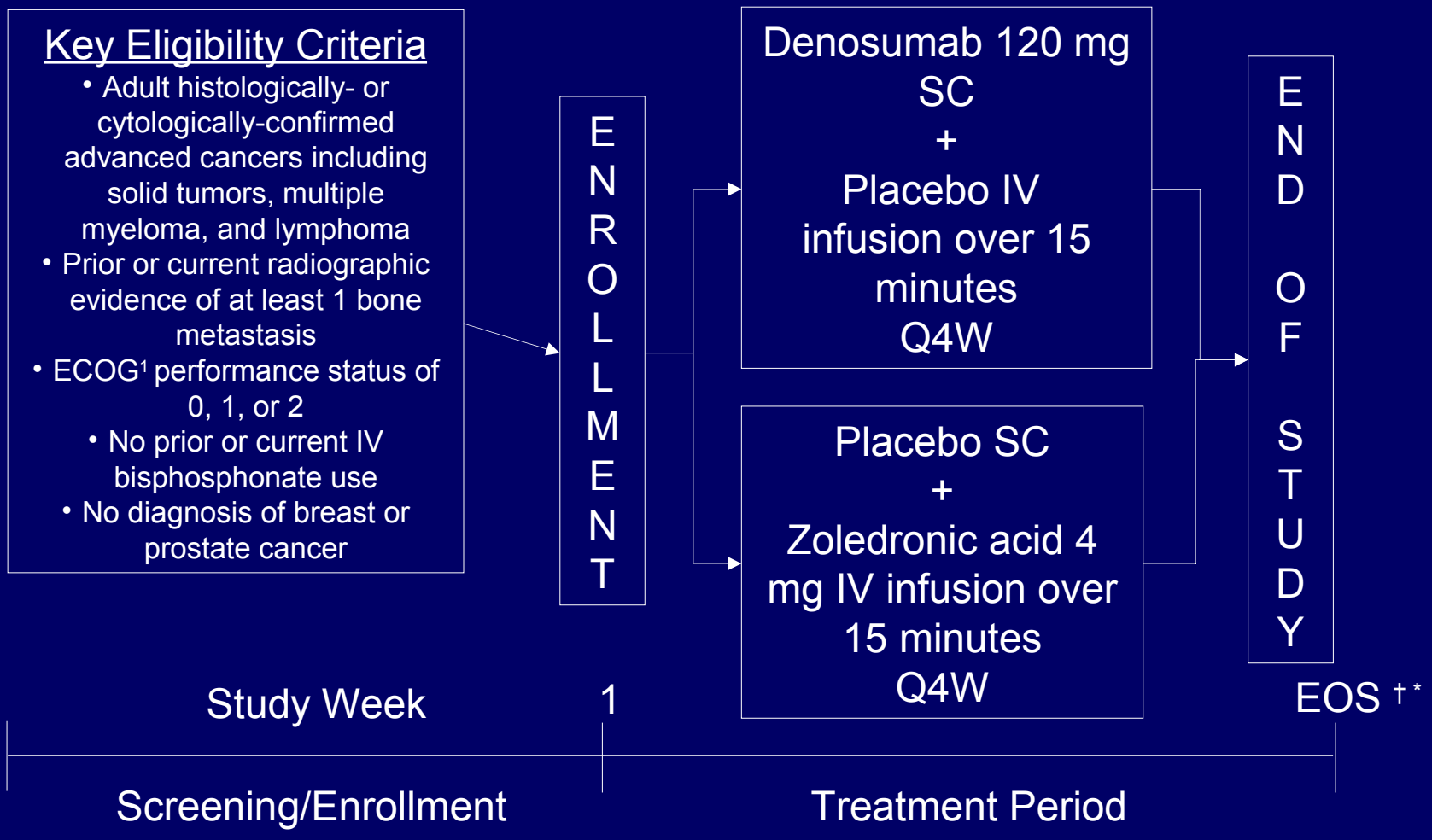
Terpos et al. ASH 2009

Denosumab in multiple myeloma



Adapted from: Boyle et al. Nature 2003;423:337-42;
Roodman GD. N Engl J Med 2004;350:1655-64

Study Schema
Denosumab 20050244



[1]Eastern Cooperative Oncology Group

† Event Driven

* End Of Study

Results of denosumab 20050244

- Similar time to first SRE (fracture, radiation to bone, surgery to bone, or spinal cord compression) compared to zoredronic acid (hazard ratio 0.84, 95 percent CI: 0.71-0.98), which is statistically significant for non-inferiority ($p<0.0007$).
- The delay in the time to first SRE associated with denosumab treatment was not statistically superior compared to zoledronic acid (adjusted $p=0.06$) (secondary endpoint).
- The time to first-and-subsequent SRE was also not statistically superior compared to zoledronic acid (hazard ratio 0.90, 95 percent CI: 0.77-1.04) (secondary endpoint).

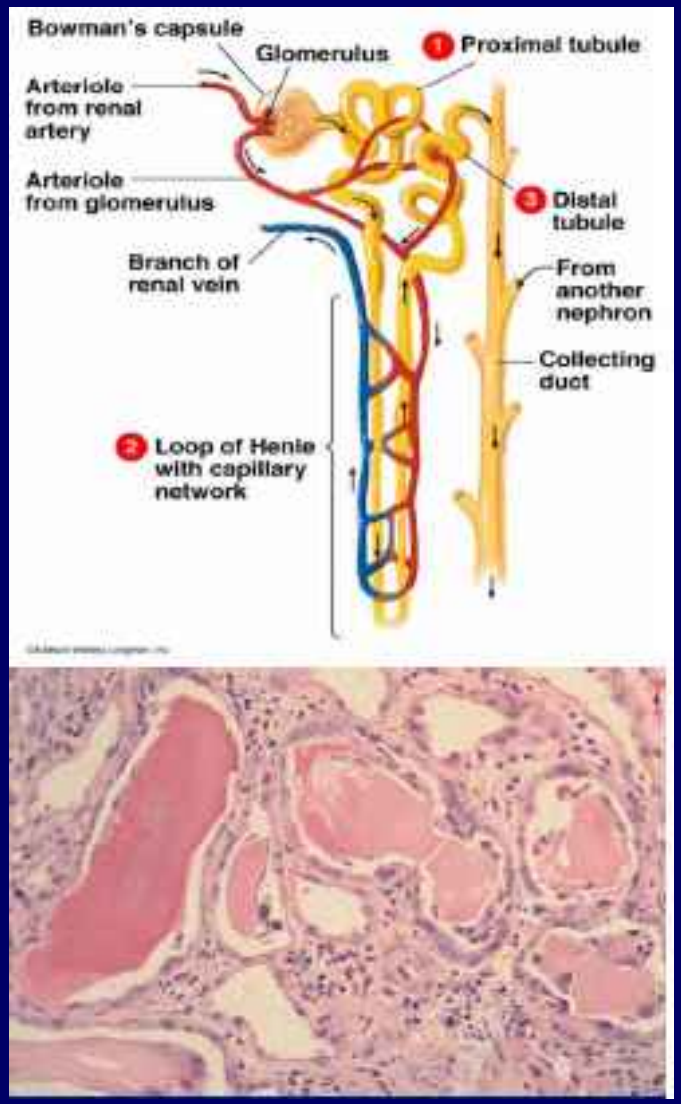
CONCLUSIONS

- Bisphosphonates are useful and remain the cornerstone of the management of bone destruction in MM.
- However many questions have not been answered yet. What is the maximum duration for their use? What is the long-term safety profile? Be careful in renal dysfunction and be aware of ONJ.
- Novel agents (bortezomib, denosumab) in combination with or without bisphosphonates may help in the better management of myeloma bone disease.

Myeloma and Renal impairment

Renal Failure

- 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



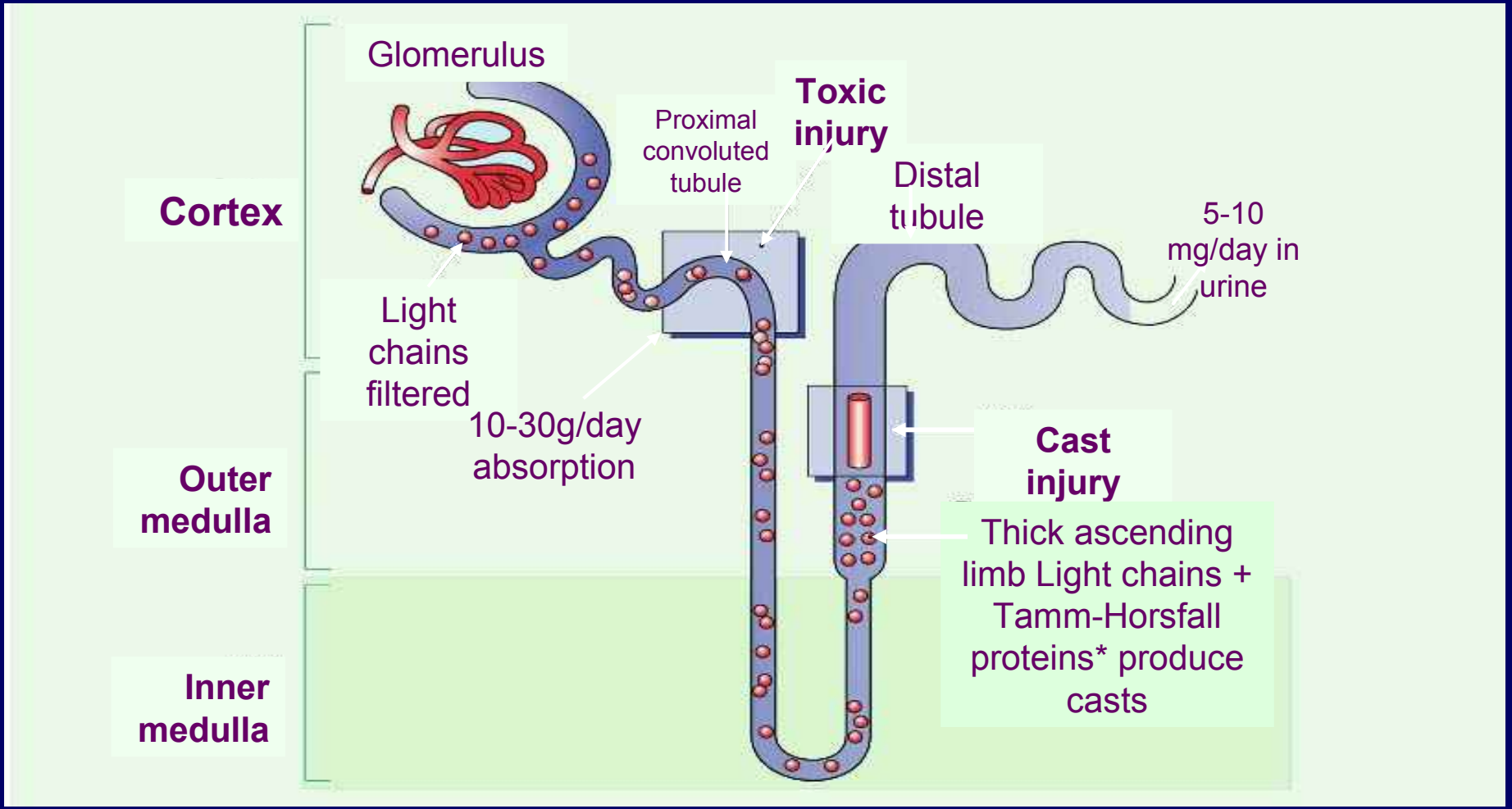
Clark et al. Blood Reviews 1999;13:79-90

Renal Impairment and Myeloma

- Pathogenesis is multifactorial[1]
  - Toxic effect of light chains
    - Myeloma kidney (light chain cast neuropathy)
    - Light chain deposition disease
    - Amyloidosis
    - Tubular dysfunction
  - Dehydration
  - Hypercalcemia
  - Non-steroidal anti-inflammatory drugs
- Urinary light chain excretion and/or hypercalcemia are the most important factors and are present in 90% of cases[2]

1. Dimopoulos et al, Leukemia 2008;22:1485-93
2. San Miguel et al. Haematologica 1999;84:36-58

Cast nephropathy

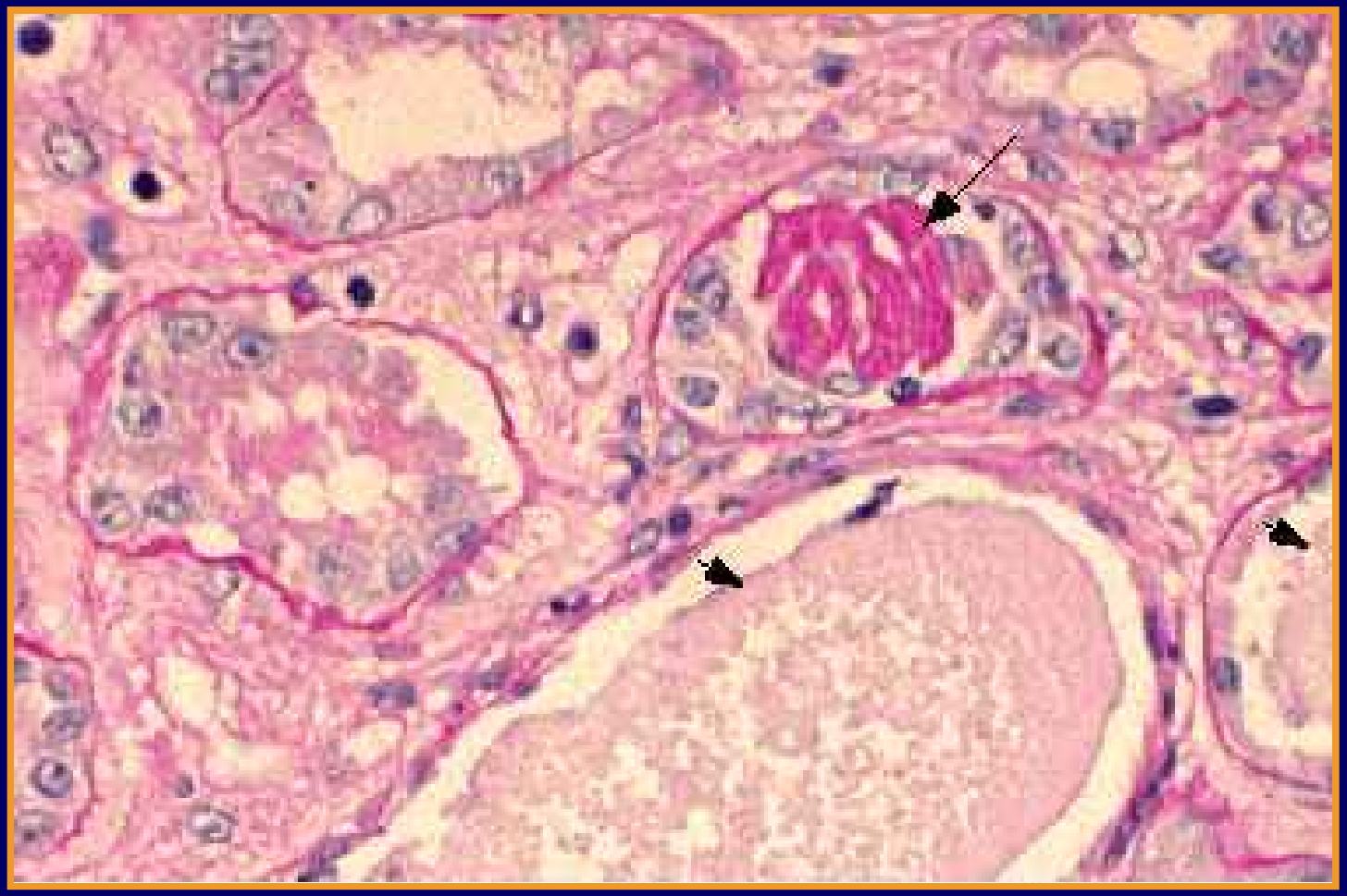


*uromodulin, a glycoprotein synthesized by the cells in the medullary thick ascending limb of the loop of Henle with affinity for monoclonal light chains

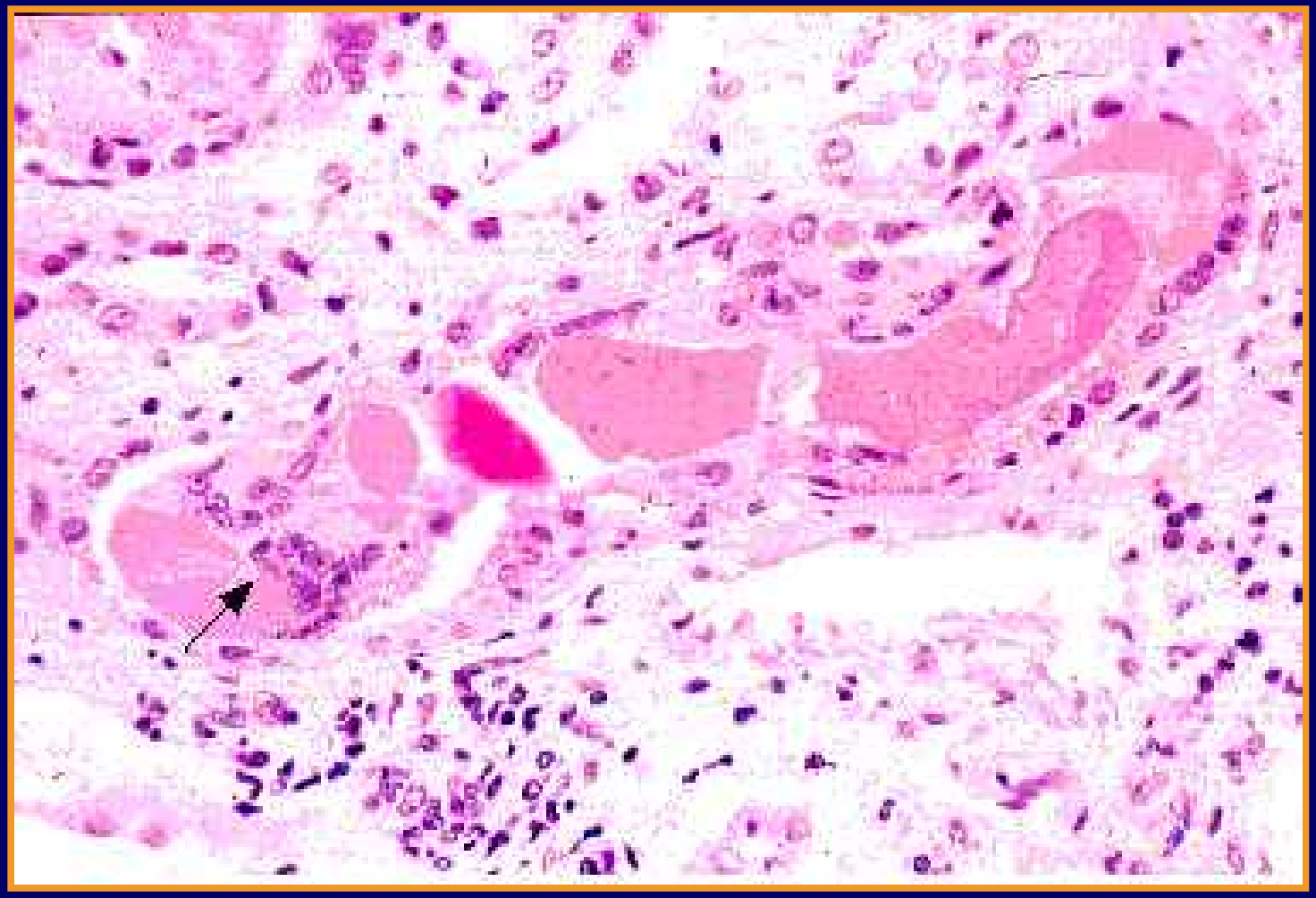
What biochemical factors favour cast formation?

- Concentration FLC
- Concentration and -CHO content of Tamm Horsfall protein
- Distal nephron NaCl
- Distal nephron Calcium
- Tubular flow rate
- Presence of furosemide
- Acidic pH

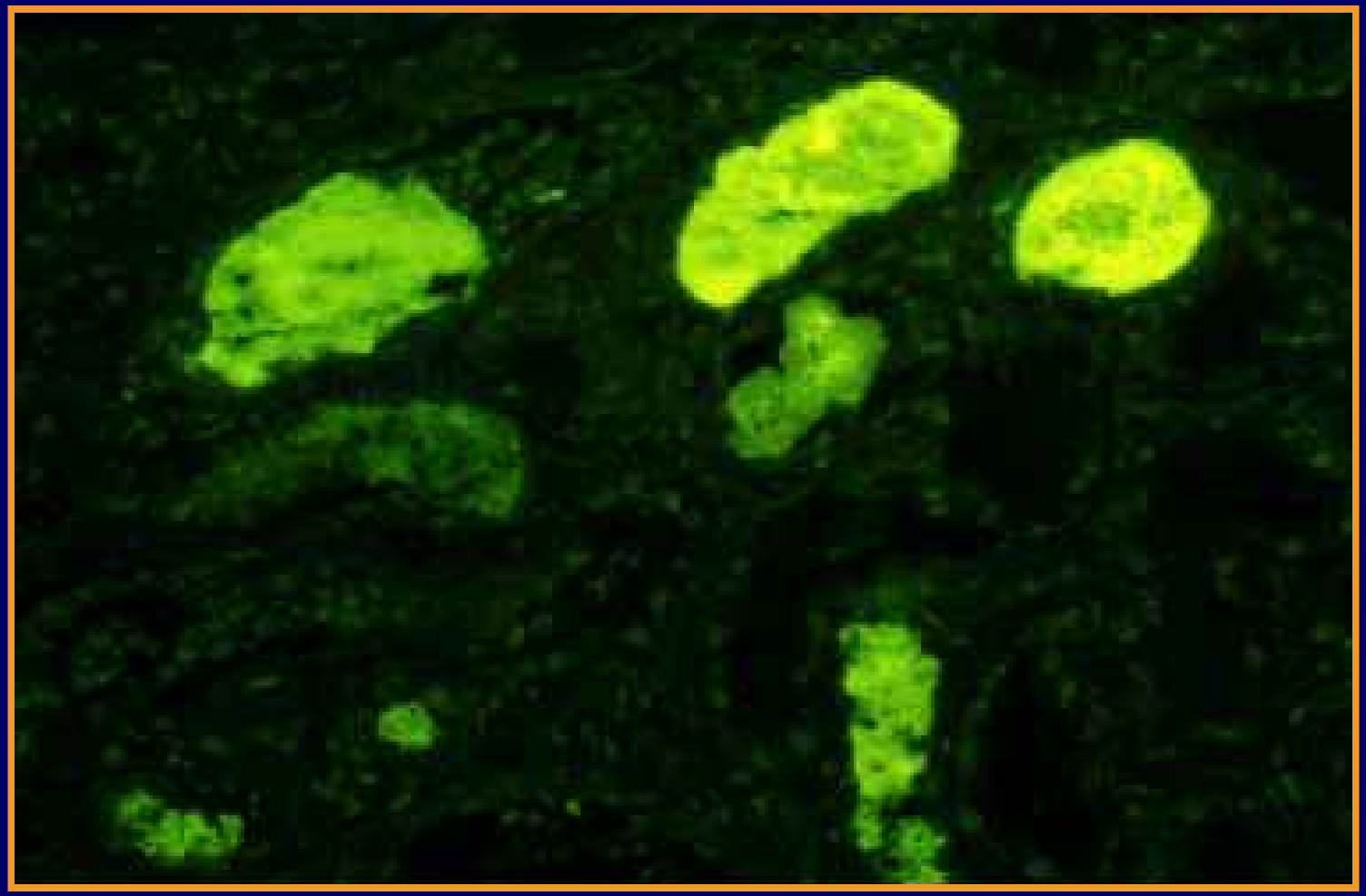
Cast Nephropathy



Cast Nephropathy



Cast Nephropathy



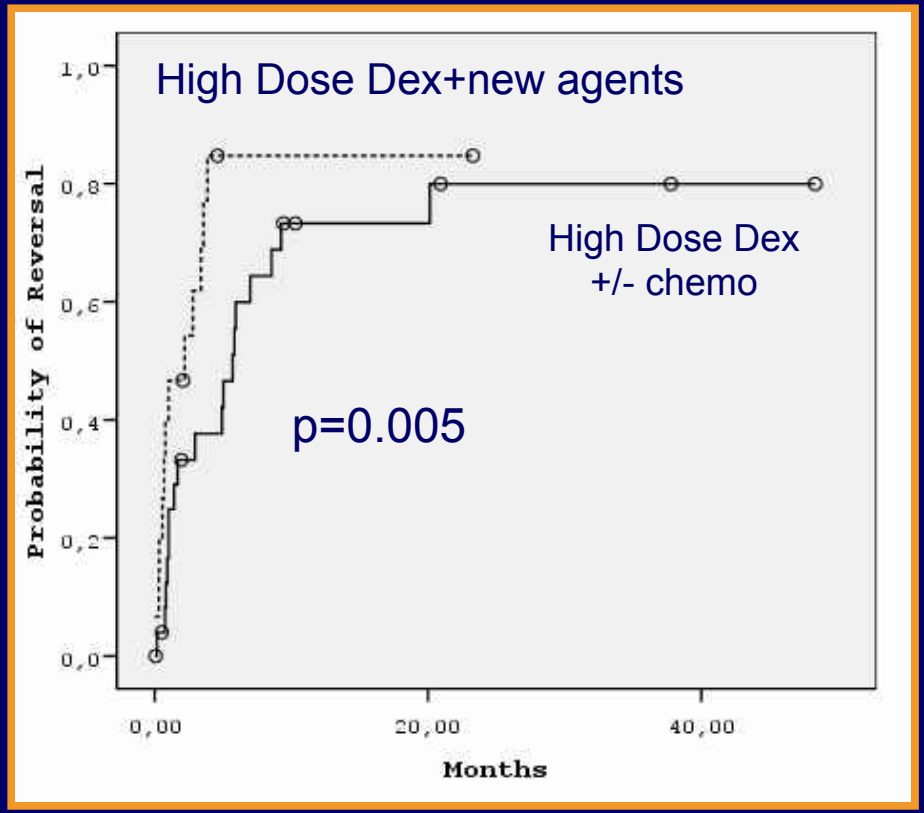
Treatment of Renal Impairment in MM

- Treat precipitants of renal failure
  - adequate hydration
- Maintain as much residual kidney function as is possible
  - Start dialysis if required
  - Plasma exchange/free light chain removal with dialysis filters
  - Use with caution: Melphalan, prednisone
  - Suitable therapies: high dose dexamethasone, bortezomib, ASCT, lenalidomide (?)

Dimopoulos et al, Leukemia 2008;22:1485-93

Management of renal failure with high dose dexamethasone and new agents

- High rates of RF reversal (~80%)
- Median time to RF reversal (sustained creatinine <1.5 mg/dl) → 0.9 months
- More rapid improvement of renal function with high dose dexamethasone combinations with novel agents (0.9 vs 2 months)
- Similar toxicity profile



Kastritis et al, Haematologica 2007;92:546-9

Rationale for use of Bortezomib in patients with renal impairment

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

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

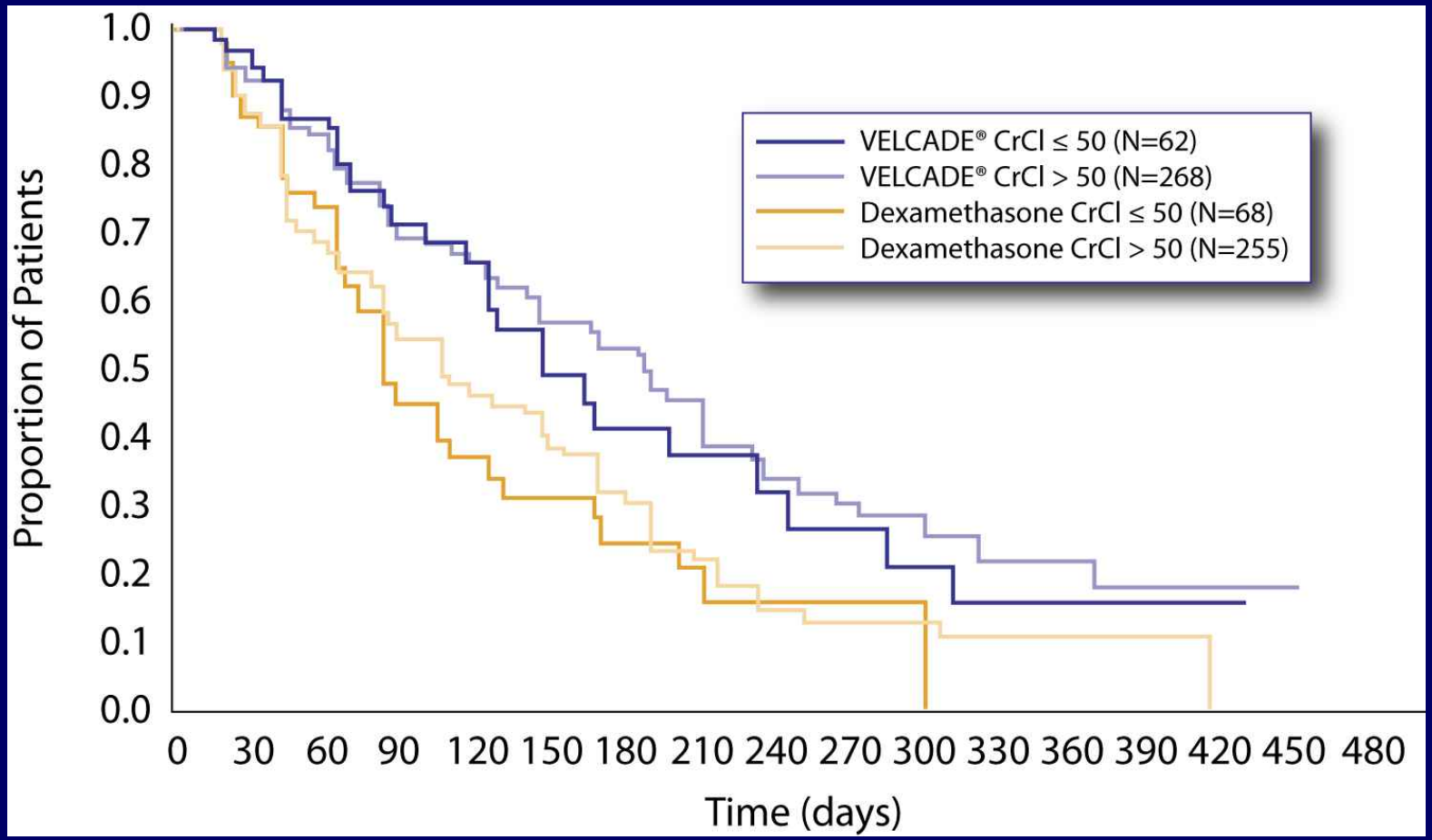
APEX: Renal Impairment

- Subgroup analysis of the Phase III APEX study assessing the safety and efficacy of MM patients with renal impairment.
- Bortezomib had significantly higher TTP and OS compared to dexamethasone irrespective of whether the CrCl was ≤50 or >50ml/min.

	All Patients	<30	30-50	≤50	51-80	>80	>50
ORR (CR+PR)	38%	47%	37%	40%	40%	36%	38%
CR	6%	0	9%	7%	8%	4%	6%
PR	32%	47%	28%	33%	32%	31%	32%
TTR (Months)	1.4	1.6	0.7	1.4	1.2	1.4	1.4
TTP (Months)	6.2	4.2	5.6	4.9	6.2	6.3	6.2
OS (Months)	29.8	22	22.8	22.8	30.0	NE	30.0

San Miguel et al, Leukemia 2008;22:842-9

APEX: Renal Impairment/TTP

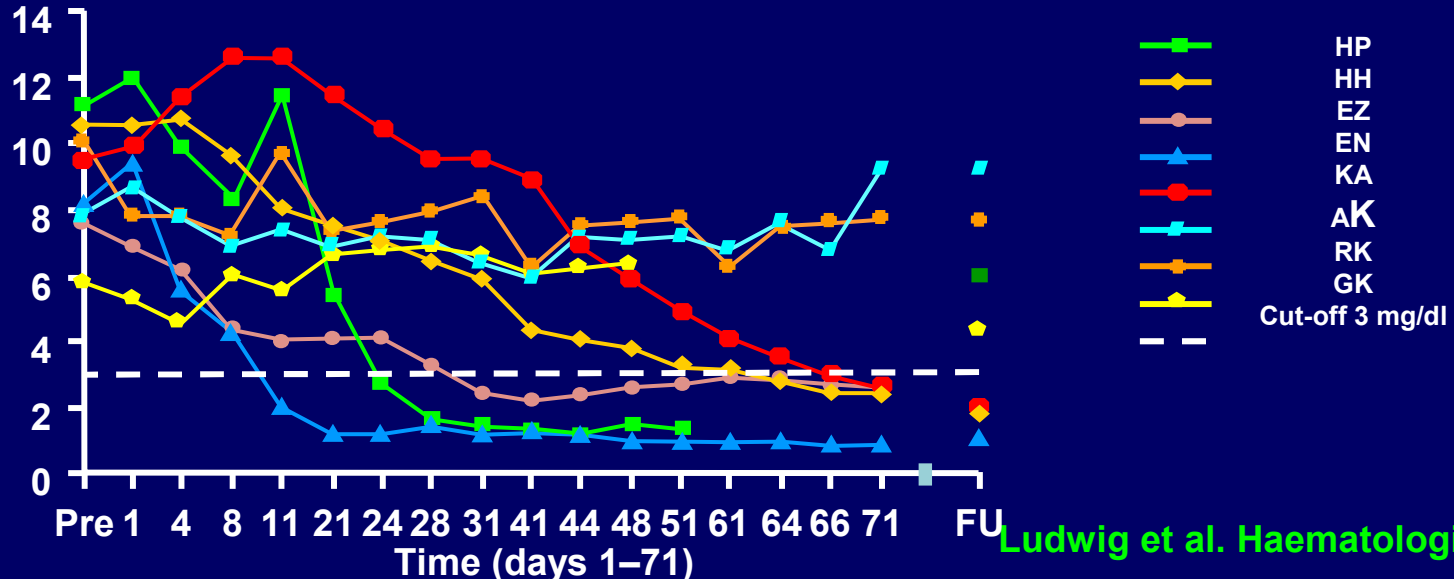


San Miguel et al, Leukemia 2008;22:842-9

Bortezomib-treated patients with acute renal failure

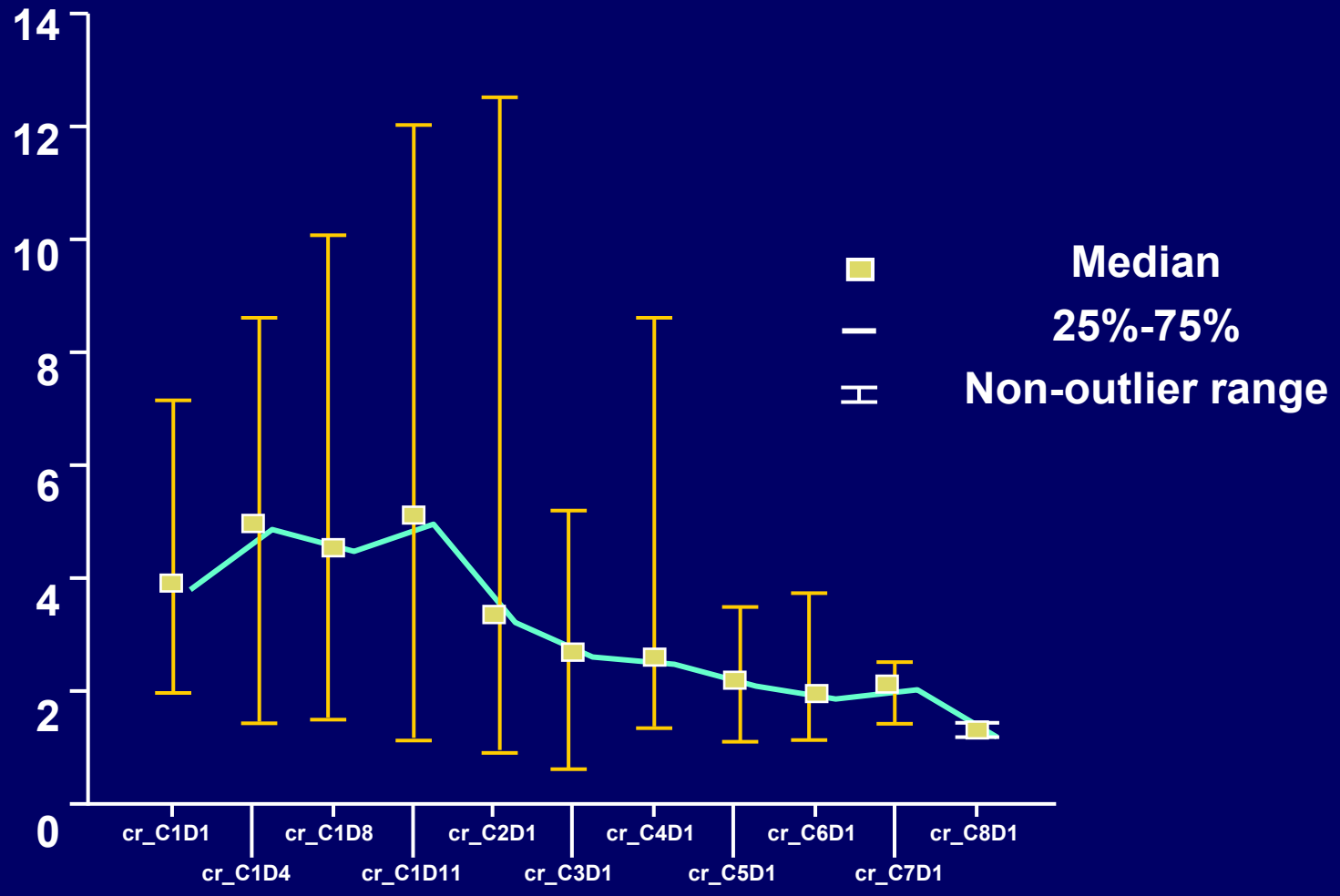
MM Patients with acute renal failure (ARF)

- Newly diagnosed (n=7), previously treated (n=1)
- **Treatment**
  - Bortezomib 1.0 or 1.3 mg/m^2, days 1,4,8,11 of 21-day cycle
  - Dexamethasone 20 mg added for 3 patients, doxorubicin 9 mg/m2 added for 3 patients
- **Results**
  - Reversal of renal failure in 5 out of 8 patients



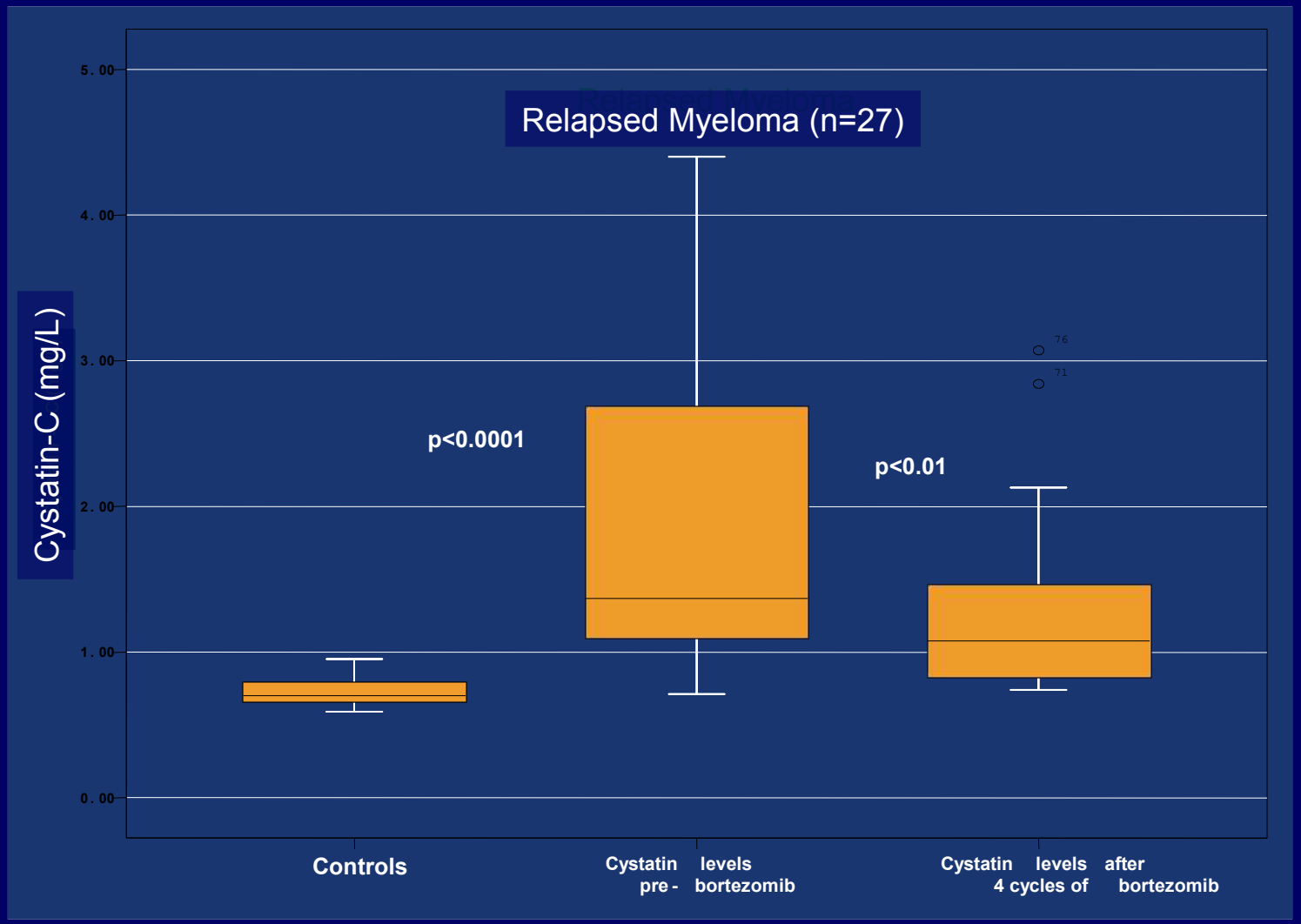
Ludwig et al. Haematologica 2007;92:1411-14

Median serum creatinine by cycles after treatment with bortezomib-based regimens



Roussou et al. Leuk Lymphoma 2008;49:890-5

Reduction of Cystatin-C after treatment with bortezomib ± dexa in relapsed myeloma



Terpos et al. Haematologica 2009;94:372-9

Bortezomib: Dialysis Patients

- Retrospective case analysis from 5 US cancer centers
- 24 patients with MM and advanced renal failure receiving or scheduled for dialysis
- Bortezomib 1.3 mg/m² 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

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

Bortezomib: Dialysis Patients

- Response
  - 1 patient responded rapidly (spared dialysis)
  - 3 patients became dialysis-independent

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

Bortezomib is effective in patients with renal impairment and leads to high ORR in patients requiring dialysis

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

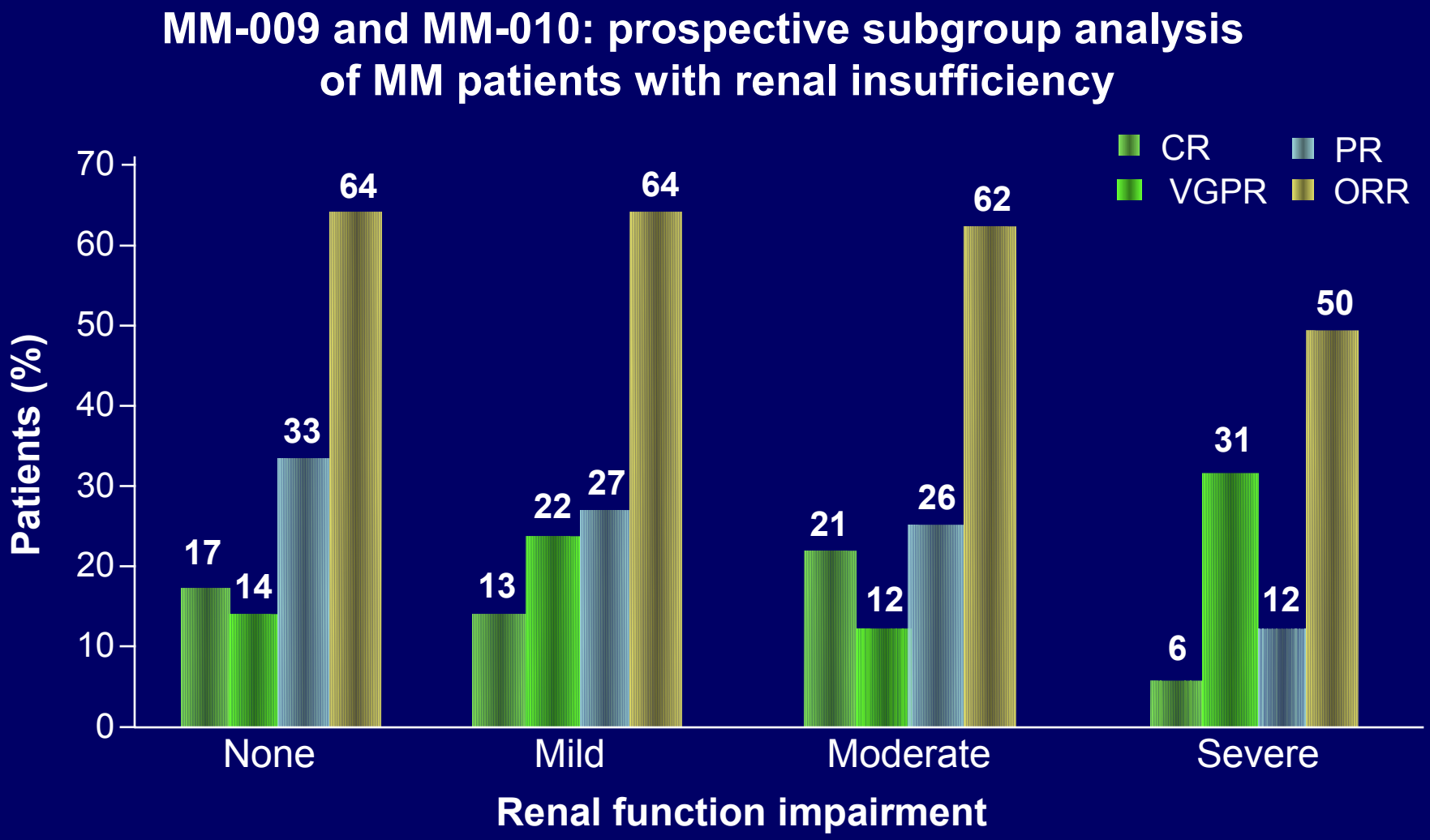
Lenalidomide: dosing recommendations for patients with renal insufficiency

Renal function impairment	Lenalidomide dosage
Mild ($Cl_{Cr} \geq 50$ ml/min)	25 mg/day (full dose)
Moderate ($30 \leq Cl_{Cr} < 50$ ml/min)	10 mg/day*
Severe ($Cl_{Cr} < 30$ ml/min, dialysis *not* required)	15 mg every 48 hours
End-stage renal disease ($Cl_{Cr} < 30$ ml/min, dialysis required)	5 mg/day; on dialysis days the dose should be administered after the dialysis

*Dose may be increased to 15 mg/day after 2 cycles if patient has no response to treatment.

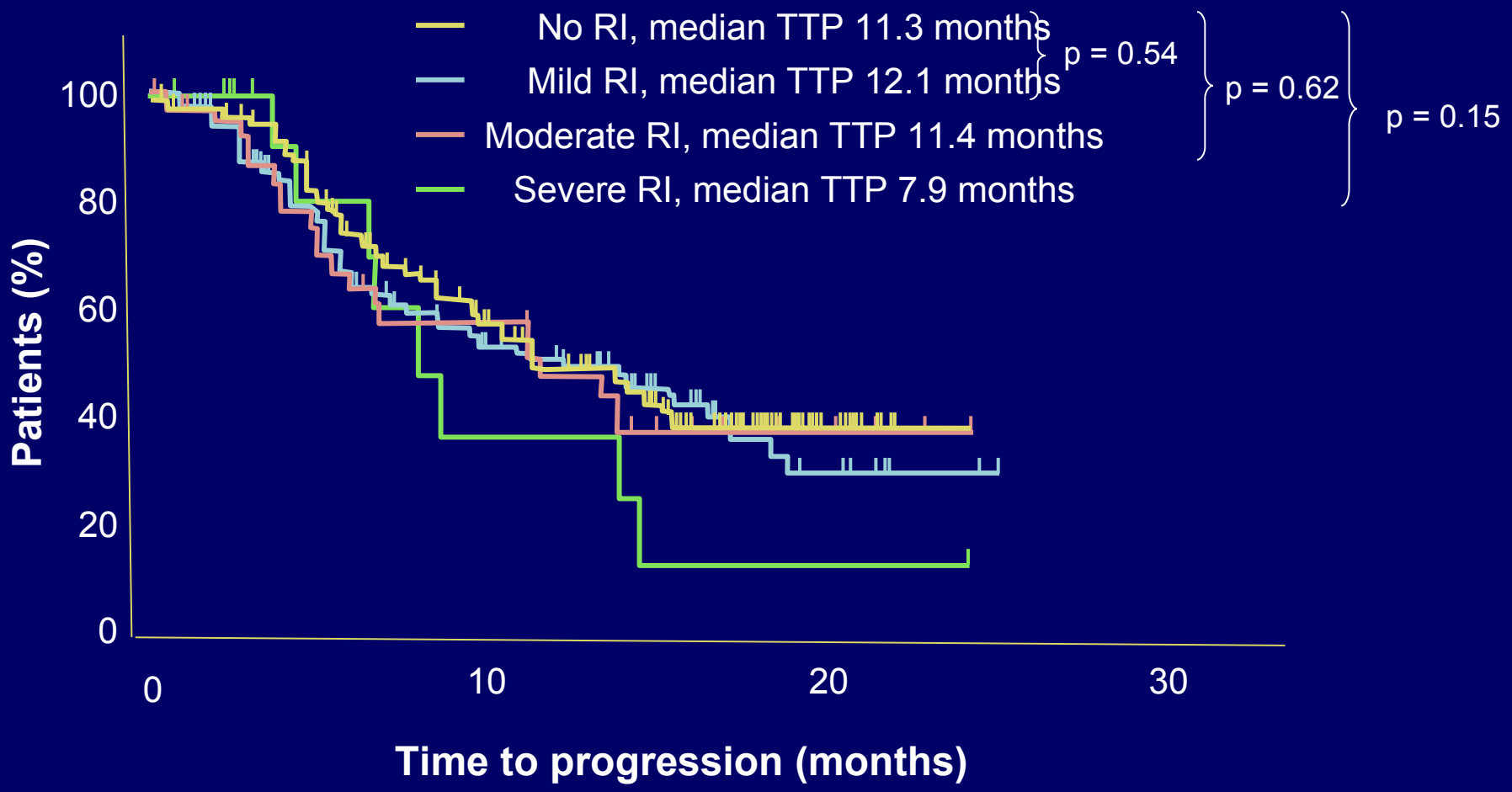
Revlimid® SmPC

Len + Dex is effective regardless of renal insufficiency



Weber D, et al. J Clin Oncol. 2008;26:[abstract 8542]

TTP with Len + Dex is consistent regardless of the extent of renal impairment



Weber et al. J Clin Oncol 2008;26:[abstract 8542]

Reversibility of Renal Failure

Recovery of renal impairment by ASCT

- 46 patient with MM and renal failure, defined as serum creatinine >2 mg/dL sustained for >1 month before the start of preparative regimen received ASCT
- 10 patients (21%) were dialysis-dependent
- Post-ASCT: CR 9pts (22%) and PR 22pts (53%)
- TRM 2pts (4%)
- Significant improvement in renal function, defined as an increase in GFR by 25% above baseline, was seen in 15 patients (32%).
- 3-year PFS and OS were 36% and 64%, respectively

Parikh et al. Biol Blood Marrow Transplant 2009;15:812-6

Phase II: recovery of renal impairment by bortezomib-doxorubicin-dex (BDD)

Patients

N=40, median age, 64 (41–82) years;
60% newly diagnosed

Evaluable patients	N=32
CR/nCR, n (%)	9 (28)
VGPR, n (%)	9 (28)
PR, n (%)	4 (13)
ORR, n (%)	22 (69)

Baseline GFR, ml/min (range)	16.8 (4-48)
GFR after BDD, ml/min (range)	
All pts, n=32	54 (19–>180)
≥VGPR, n=18	59 (19 –>180)
PR, n=4	35 (20–>180)
Pts achieving ↓ GFR >50 ml/min, n (%)	14 (43)

Main grade 3/4 AE:

- **infections (16%),**
- **neutropenia (16%),**
- **cardiovascular (10%), weakness (10%)**

Ludwig et al. EHA 2008 (Abstract 439)

Recovery of renal impairment by bortezomib-based regimens: our experience

- 149 patients received bortezomib-based regimens over the last 5 years for the treatment of newly diagnosed or refractory/relapsed myeloma
- 46 had renal impairment, defined as a eGFR <50 ml/min

✓ 17 received bortezomib with dexamethasone (VD)

✓ 29 patients received VD-based regimens [VTD, PAD, VMTD, BRD]

Dimopoulos et al. Clin Lymphoma Myeloma 2009:9:302-6

Criteria for evaluation of renal response

- Renal complete response (CRrenal): improvement of baseline GFR from <50 ml/min to ≥60 ml/min (Stage ≥3 to 1/2 CKD)

- Renal partial response (PRrenal): improvement of baseline GFR from <15 to 30–59 ml/min

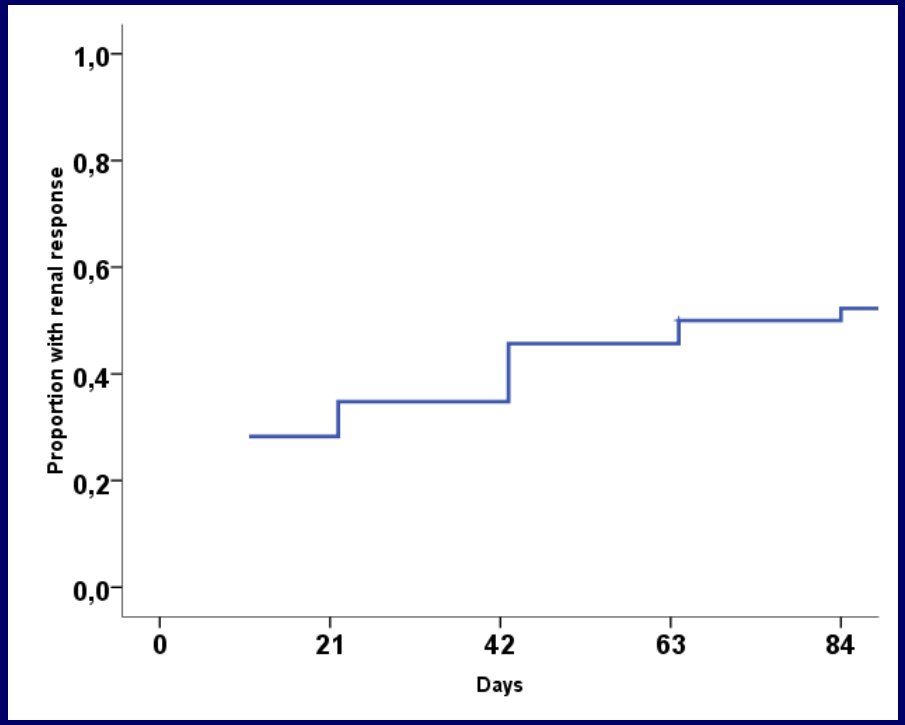
- Renal minor response (MRrenal) : improvement of baseline GFR of <15 ml/min to 15–29 ml/min or from 15–29 ml/min to 30–59 ml/min.

Ludwig H. Haematologica 2008: 93(s1):177 Abs.0439

Results

- Renal response, N=27 (59%),
  - CRrenal in 14 (30%) patients,
  - PRrenal in 5 (11%)
  - MRrenal in 8 (17%)

- 2 of 9 patients became dialysis independent



Median time to renal response: 11 days

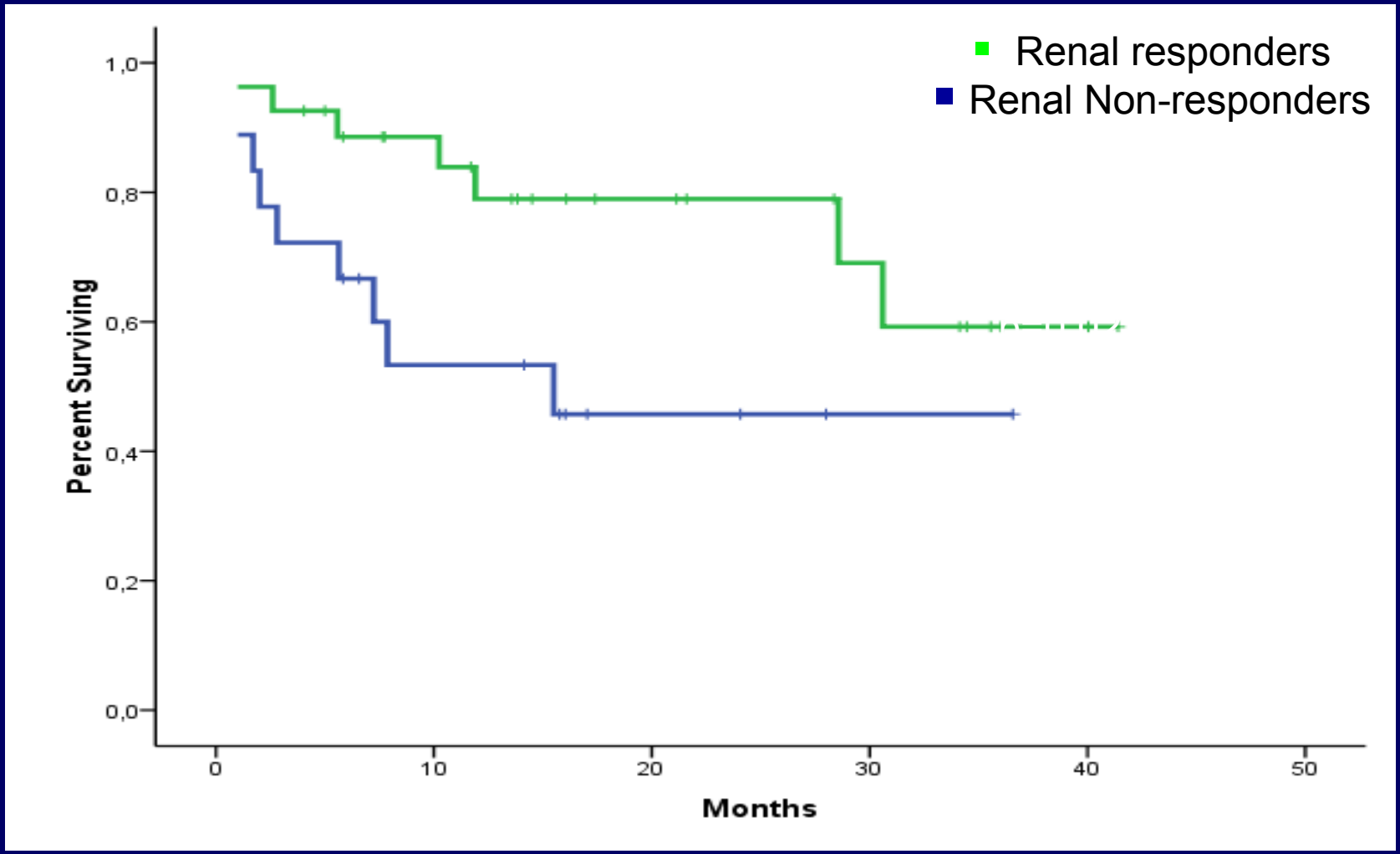
Factors associated with renal response

	Renal response	p-value
Age >=75	50%	0.371
Pretreated Untreated	53% 80%	0.160
Male Female	63% 56%	0.763
BJ <2 gr BJ≥2 gr	54% 65%	0.551
Ca ≥10.5 Ca<10.5	57% 59%	1.0
VD VD+ other agents	41% 69%	0.120
Light chain only Yes No	81% 47%	0.031
Myeloma Response ≥PR NR	76% 29%	0.004
Baseline eGFR <30 m/ min ≥30 ml/min	63% 46%	0.331

Factors associated with a complete renal response

N=46 patients	CRrenal (eGFR>60 ml/min)	p-value
Pretreated Untreated	22% 60%	0.047
Age≥75 Age<75	25% 35%	0.535
Male Female	32% 30%	1.0
Ca ≥10.5 Ca<10.5	25% 57%	0.176
BJ <2 gr BJ≥2 gr	23% 40%	0.333
VD VD+ other agents	24% 35%	0.520
Baseline eGFR <30 ml min ≥30	24% 46%	0.171
Light chain only Heavy Chain	38% 27%	0.512

Impact of renal response on survival (1-month landmark – only pretreated patients)



eGFR with cystatin-C can identify patients with low probability of renal recovery

	eGFR by cystatin-C only	eGFR by Cystatin-C, age , gender	eGFR by Cystatin-C, creatinine , age, gender	eGFR by MDRD (creatinine, age , gender)
Median (ml/min)	21	20	15	14
Stage IV-V Stage V	11/19 (58%) 4/19 (21%)	13/19 (68%) 5 / 19 (26%)	13/19 (68%) 9 / 19 (47%)	16/19 (84%) 11 / 19 (58%)
Stage IV-V CRrenal	1	2	2	5
Stage V Any renal Response	2	5	7	9
Stage V CRrenal	0	0	1	2
	P=0.041	P=0.046	P=0.046	P=1.0

VISTA: Reversal of Renal Impairment

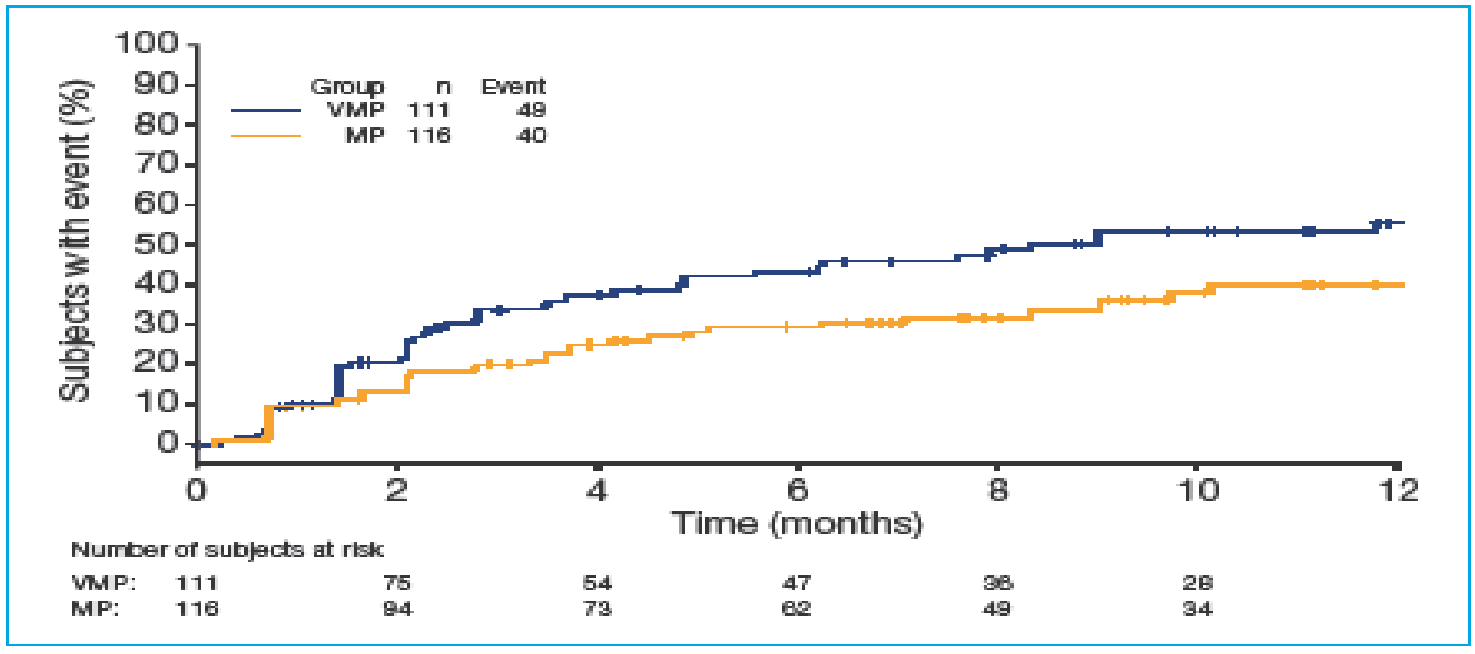
- The rate of renal impairment reversal was more pronounced with VMP
  - The rate of CR^{renal} was higher with VMP vs.MP

	VMP	MP
Rate of reversal of renal failure (Baseline CrCl <50 improving to ≥ 60mL/min on treatment)		
All Patients CrCl <50mL/min	44%	34%
CrCl 30 - <50mL/min	46%	39%
CrCL <30mL/min	37%	7%
CrCl increases ≥20mL/min	86%	63%
Renal Responses		
CR^{renal}	44%	34%
PR^{renal}	-	50%
MR^{renal}	42%	67%

Dimopoulos et al. Blood 2008; 112: Abstract 1727

VISTA: Time to Reversal of Renal Impairment

- Median time to renal impairment reversal in all patients with baseline CrCl <50 mL/min significantly shorter with VMP vs MP
  - 9.0 months (VMP) vs 13.6 months (MP) for all patients with baseline CrCl <50 mL/min



Dimopoulos et al. Blood 2008; 112: Abstract 1727

Lenalidomide can be safely used in patients with renal insufficiency

Adverse events, %	Degree of renal function impairment			
	None (n = 158)	Mild (n = 125)	Moderate (n = 42)	Severe (n = 16)
Neutropenia	31	39	43	38
Thrombocytopenia	7	16*	19*	38**
Thrombotic events	11	12	14	6

*p < 0.05 versus no renal impairment; **p < 0.001 versus no renal impairment.

Of 174 patients with renal insufficiency, 119 (68%) had improvement in their renal function by at least one level within 4 months, as assessed by peak creatinine clearance rate

Weber D, et al. J Clin Oncol. 2008;26:[abstract 8542]

Conclusions

- Myeloma cast nephropathy is the most common type of myeloma-related renal impairment
- Prevention is very important
- Bortezomib-based regimens may rapidly improve renal function even in pretreated myeloma patients and in patients requiring dialysis
- Lenalidomide is also safe to be given in myeloma patients with renal impairment and improve renal function in a substantial subset of patients
- Renal recovery is associated with improvement of survival
- Cystatin-C may identify patients at lower probability for renal recovery

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