Myeloma Bone Disease & Proteasome Inhibition Therapies

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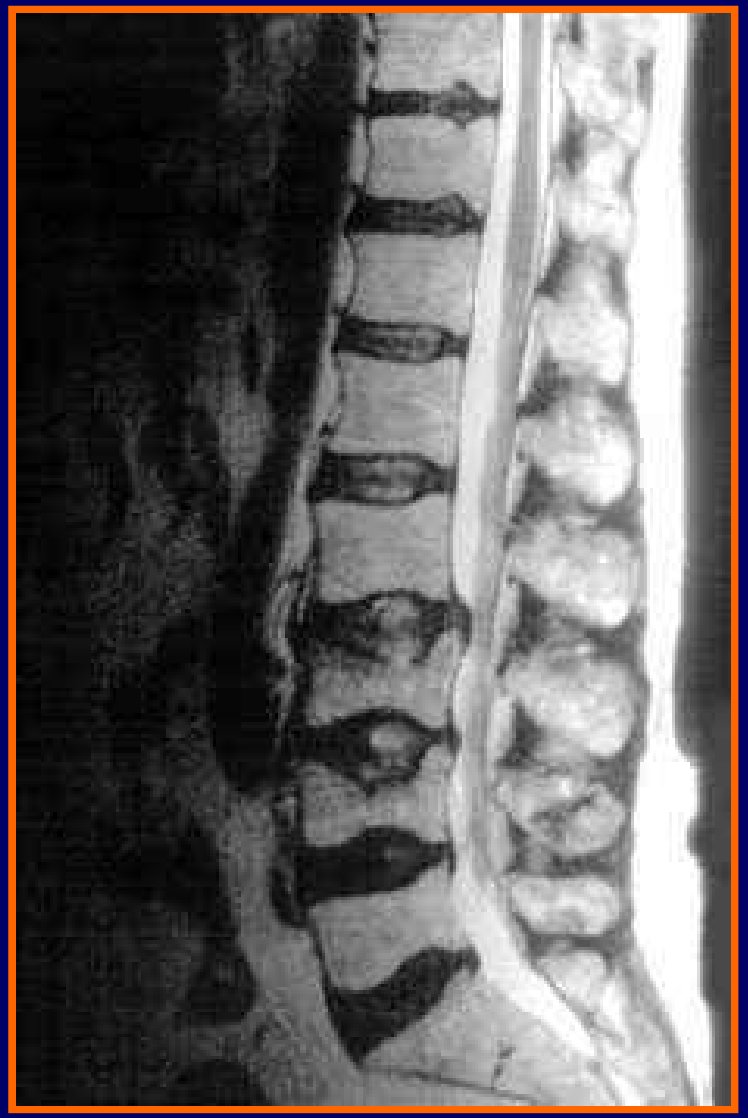
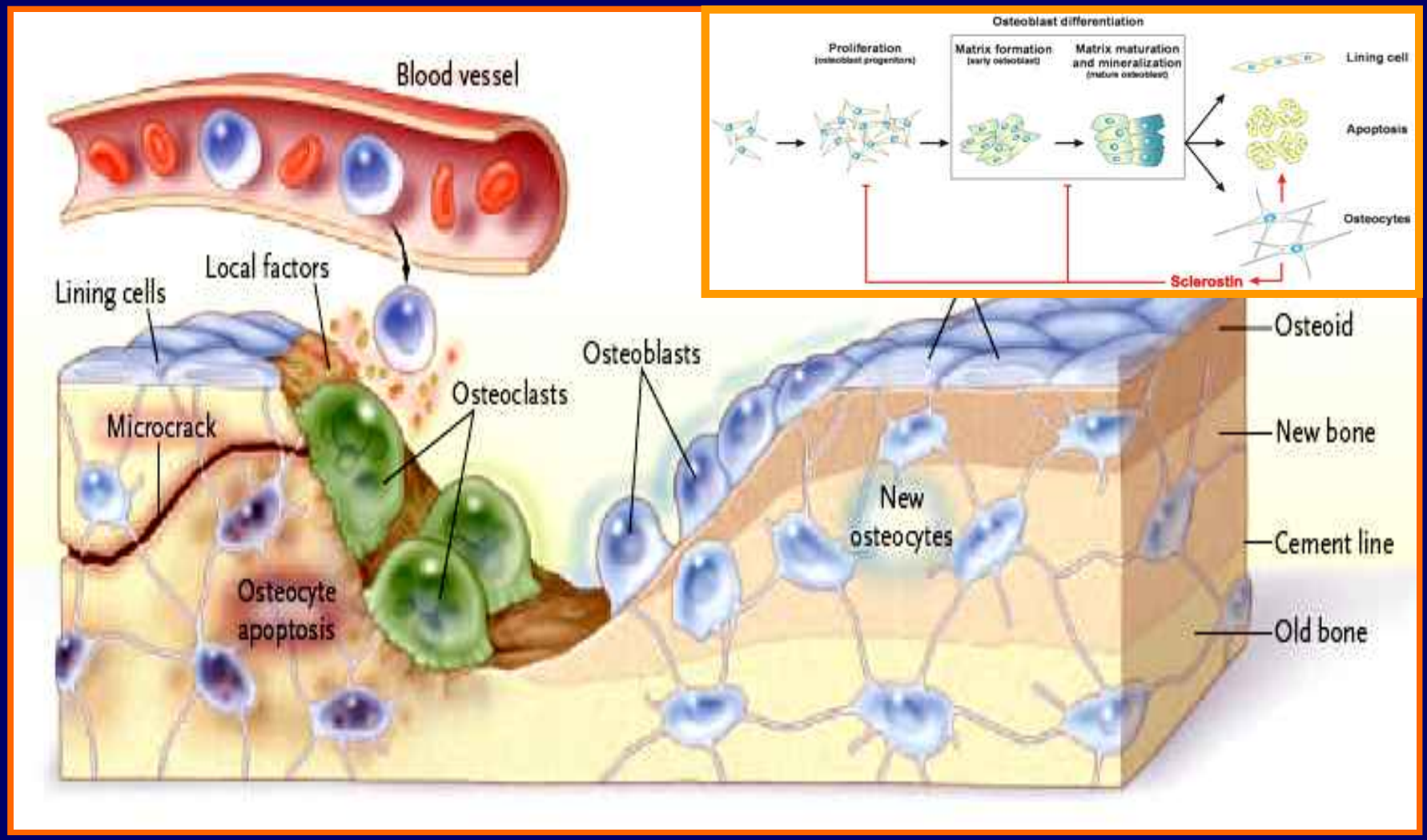
Bone Disease in Multiple Myeloma

- 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



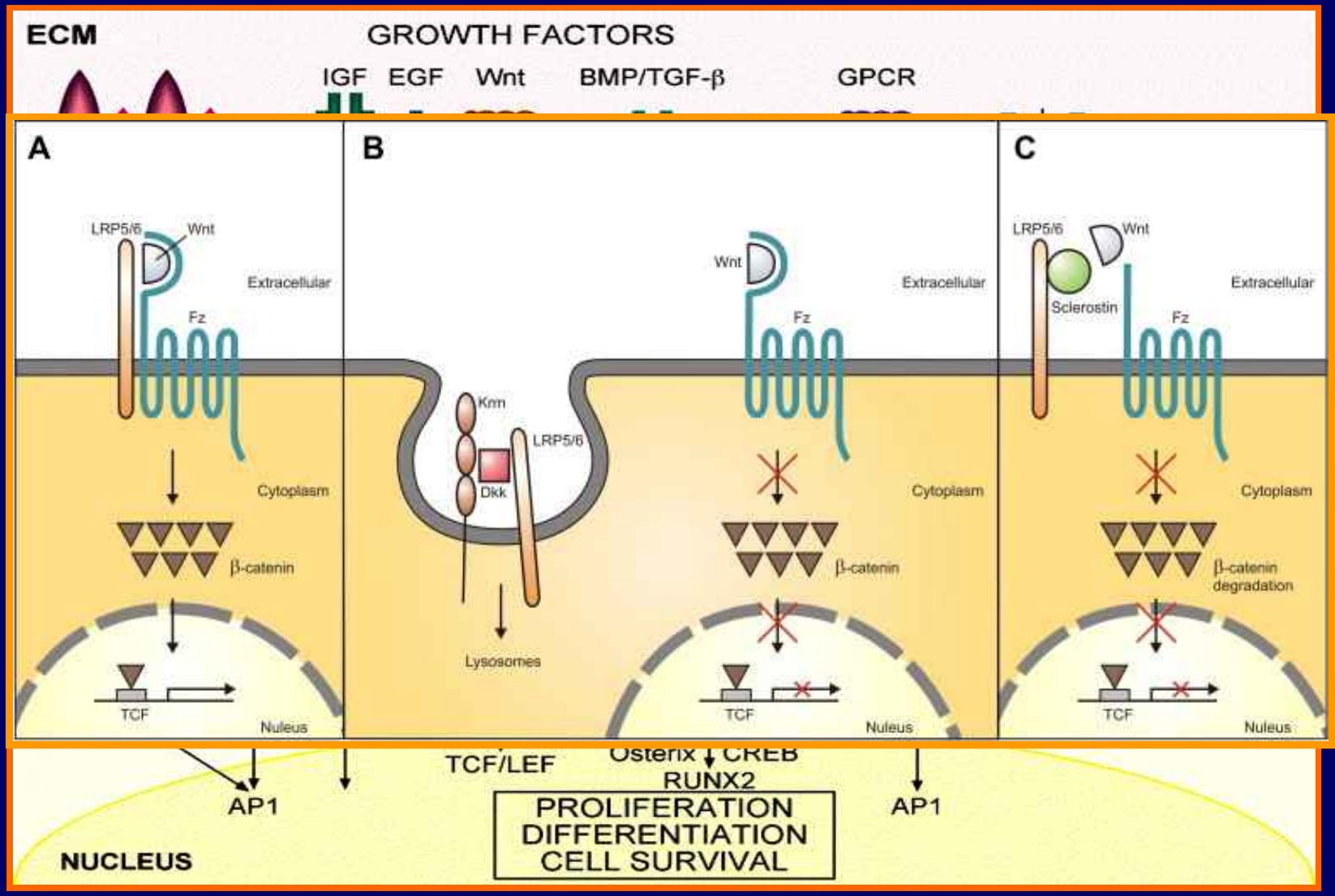
Kyle. Mayo Clin Proc 1975;50:29-40

Bone Metabolism: A Balance Between Osteoblasts and Osteoclasts



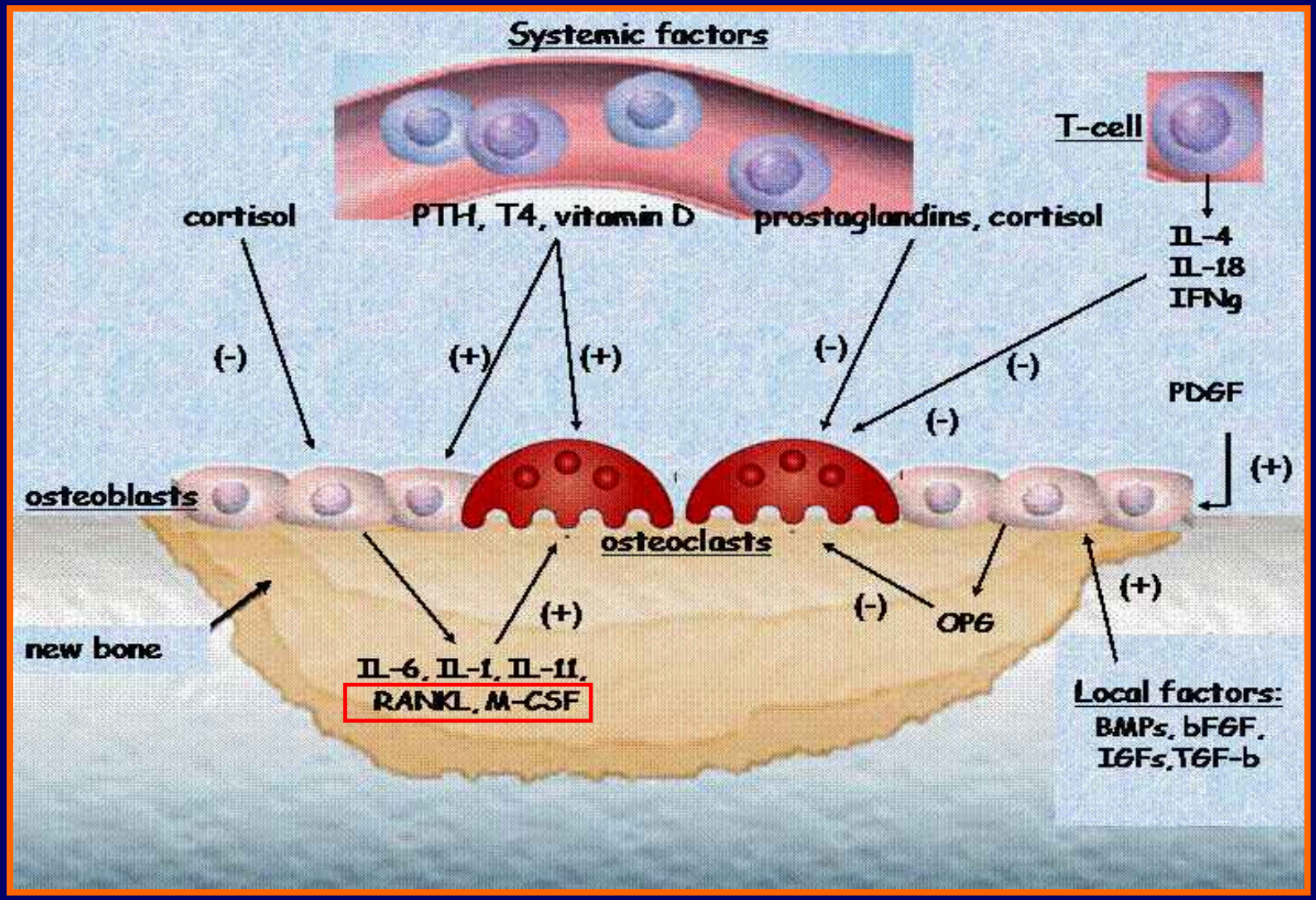
Seeman & Delmas. N Engl J Med 2006;354:2250-61

Regulation of Osteoblast Function



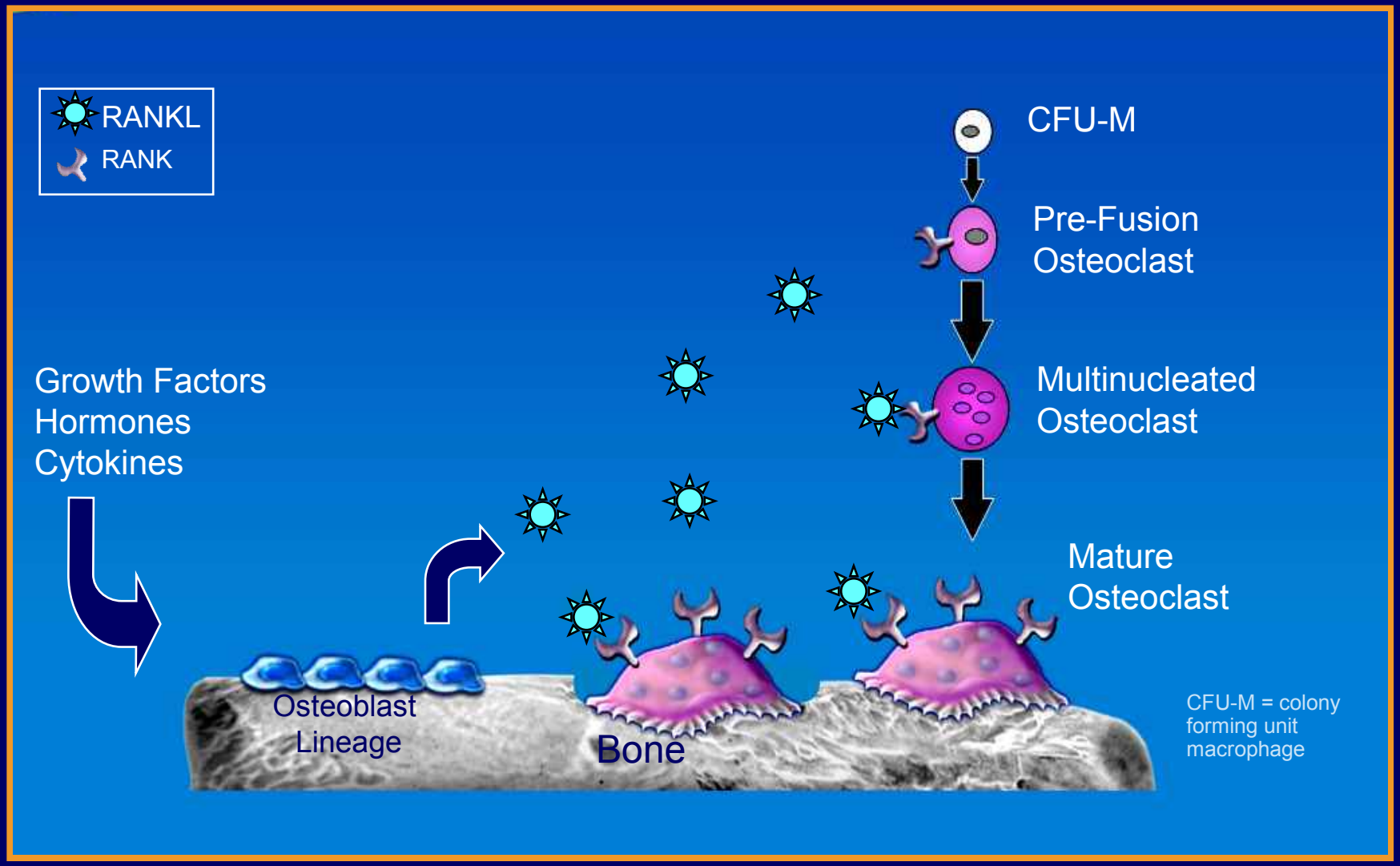
Peterson LJ. Arch Biochem Biophys 2008;473(2):198-105.

Bone Metabolism Unit



Voskaridou & Terpos. Br J Hematol 2004;127:127-39

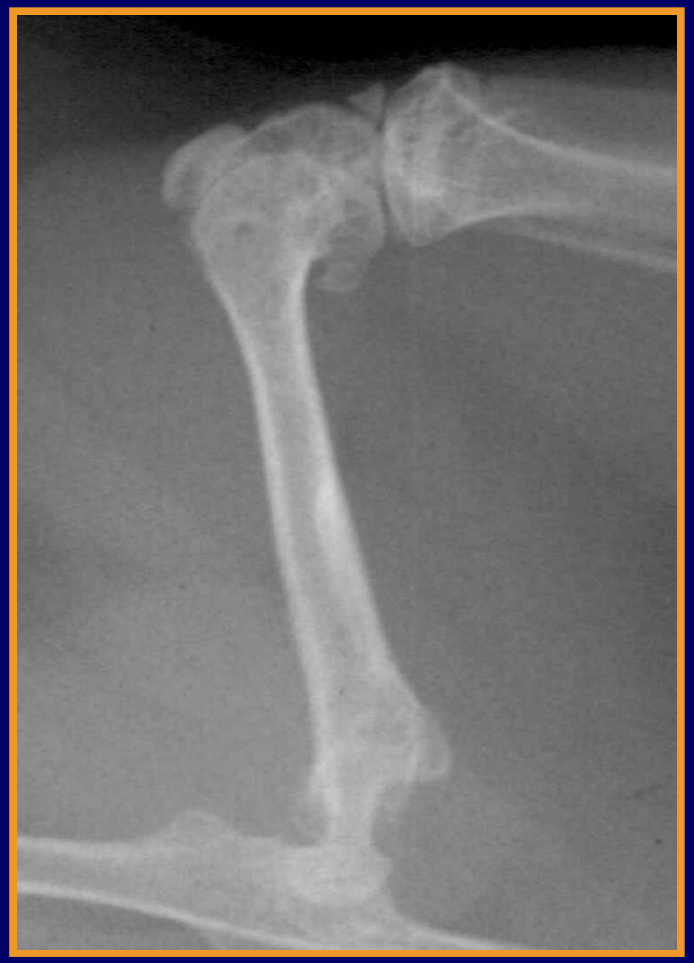
RANK Ligand: An Essential Mediator of Osteoclasts



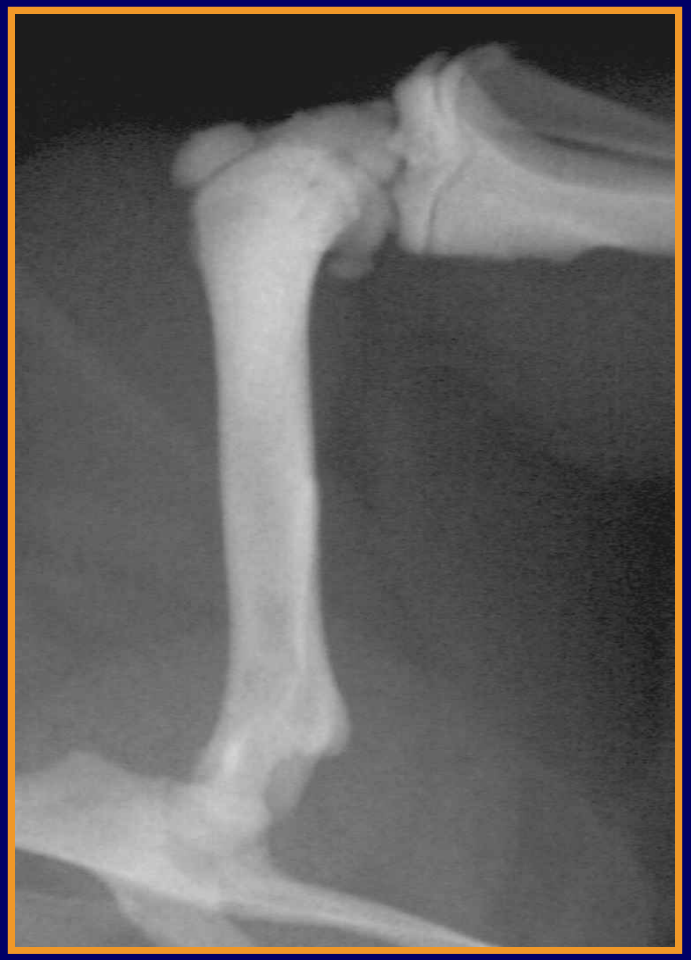
Boyle et al. Nature 2003;423:337-42

Increased Bone Density Associated With Absence of RANKL

Preclinical Experiments



Normal

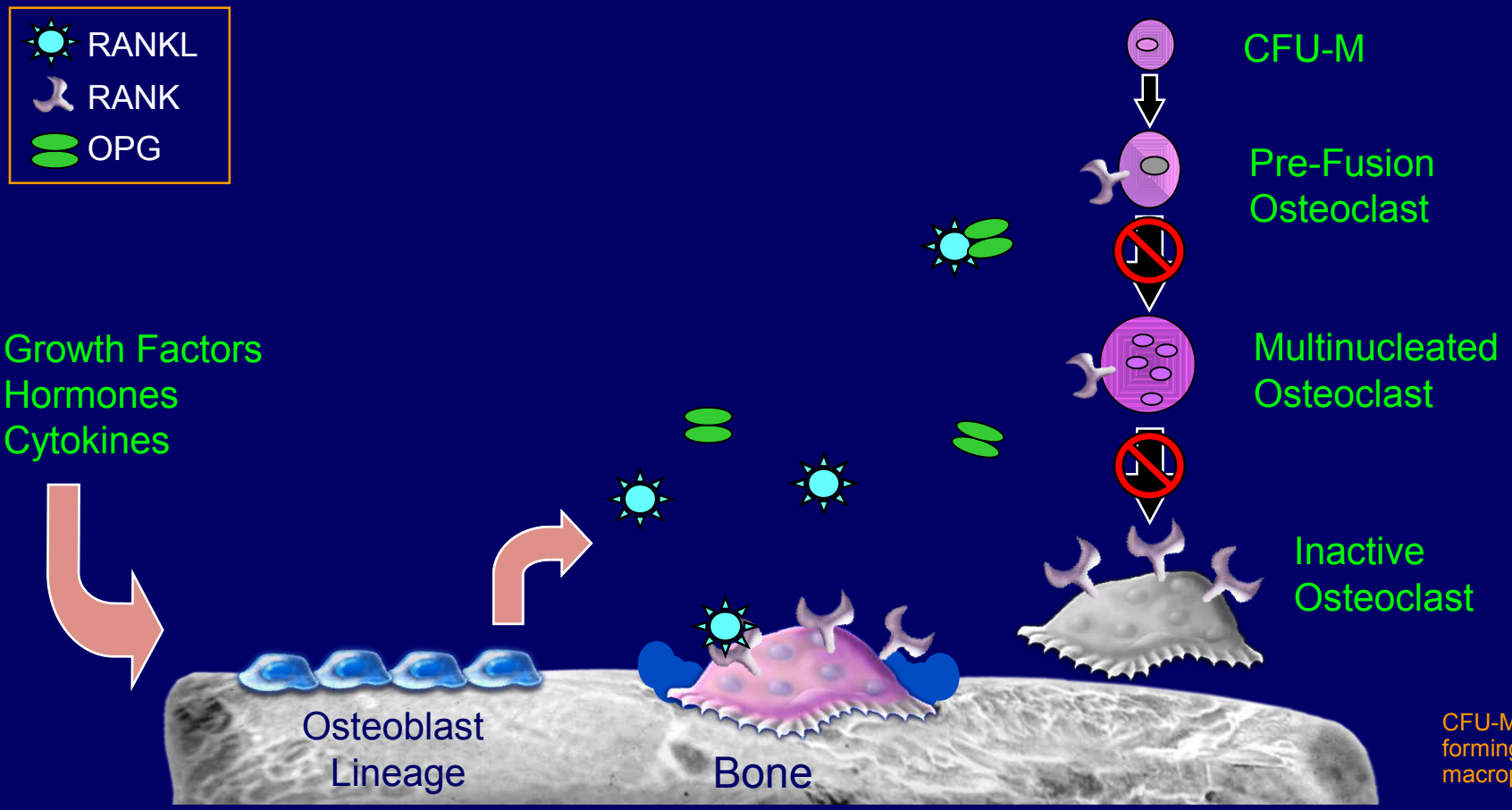


RANKL knockout

Li et al. PNAS 2000;97:1566-71

Osteoprotegerin (OPG): the Decoy Receptor of RANKL

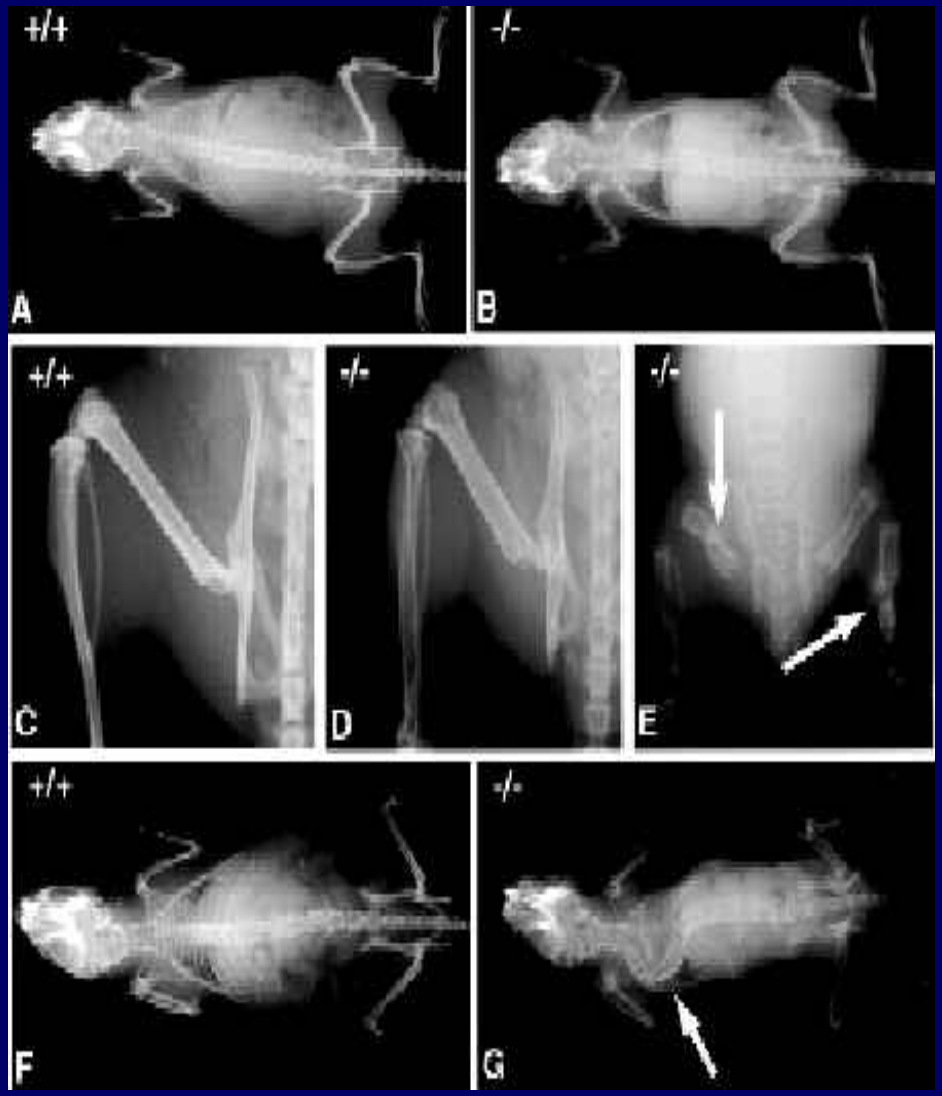
Osteoclast Formation, Function, and Survival Inhibited by OPG

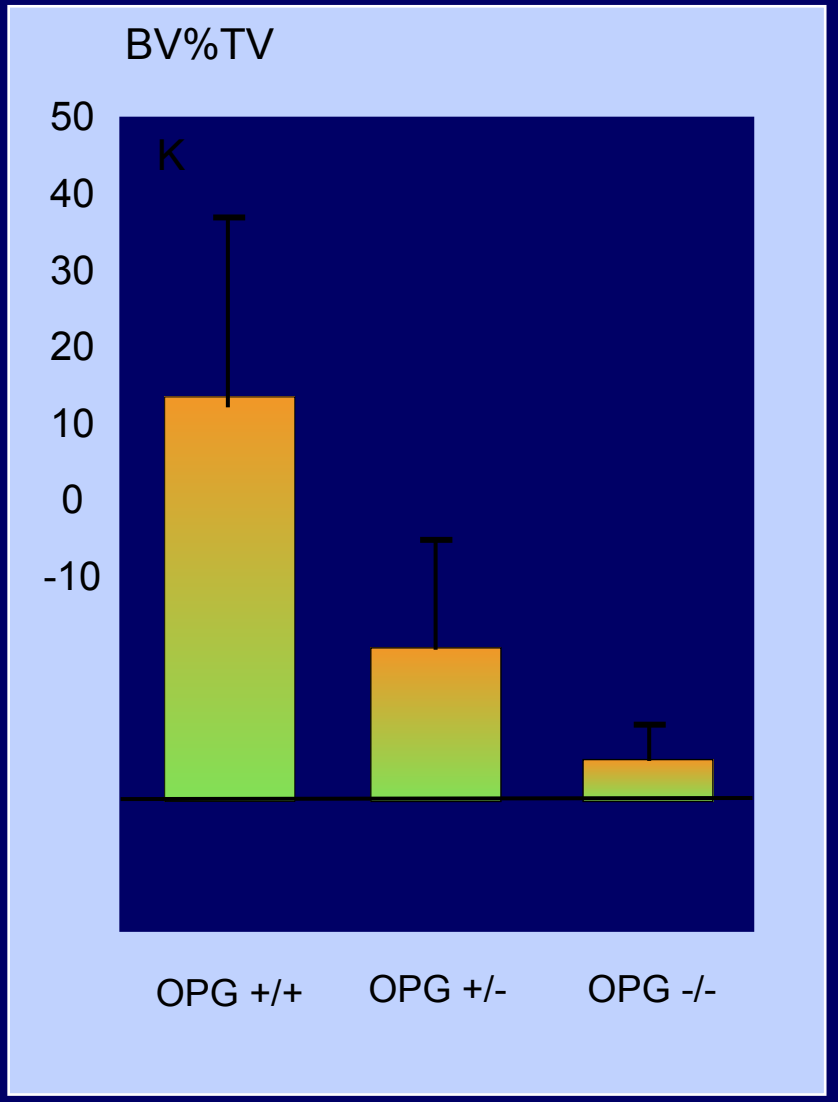


CFU-M = colony forming unit macrophage

Boyle et al. Nature 2003;423:337-42

Reduced Bone Density Associated With Absence of OPG

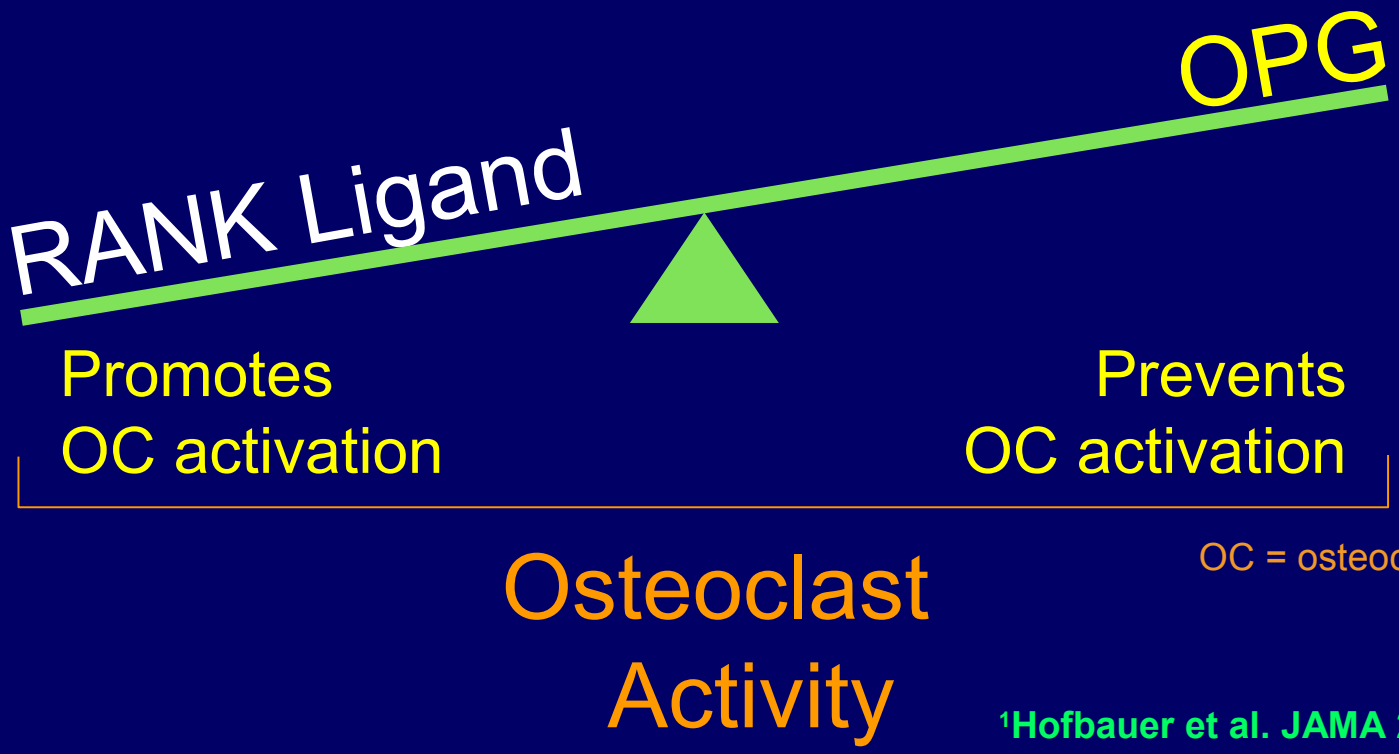




Bucay et al. Genes Dev 1998;12:1260-8

RANKL/OPG Balance Drives Osteoclast Activity

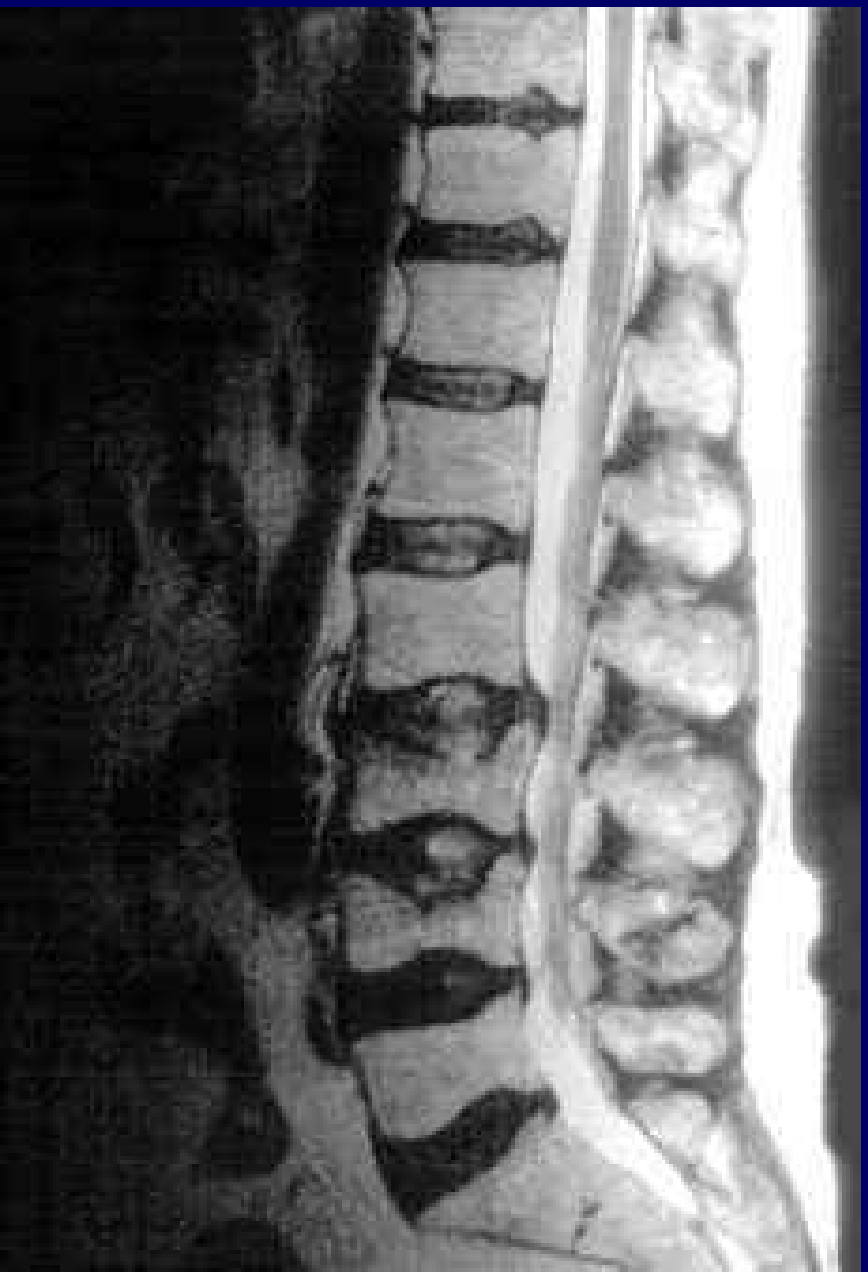
Alterations of the RANK Ligand / OPG ratio are critical in the pathogenesis of bone diseases that result from increased bone resorption[1-3]



OC = osteoclast

[1]Hofbauer et al. JAMA 2004;292:490-5
[2]Lacey et al. Cell 1998;93:165-76
[3]Boyle et al. Nature 2003;423:337-42

MM Bone Disease: Pathogenesis

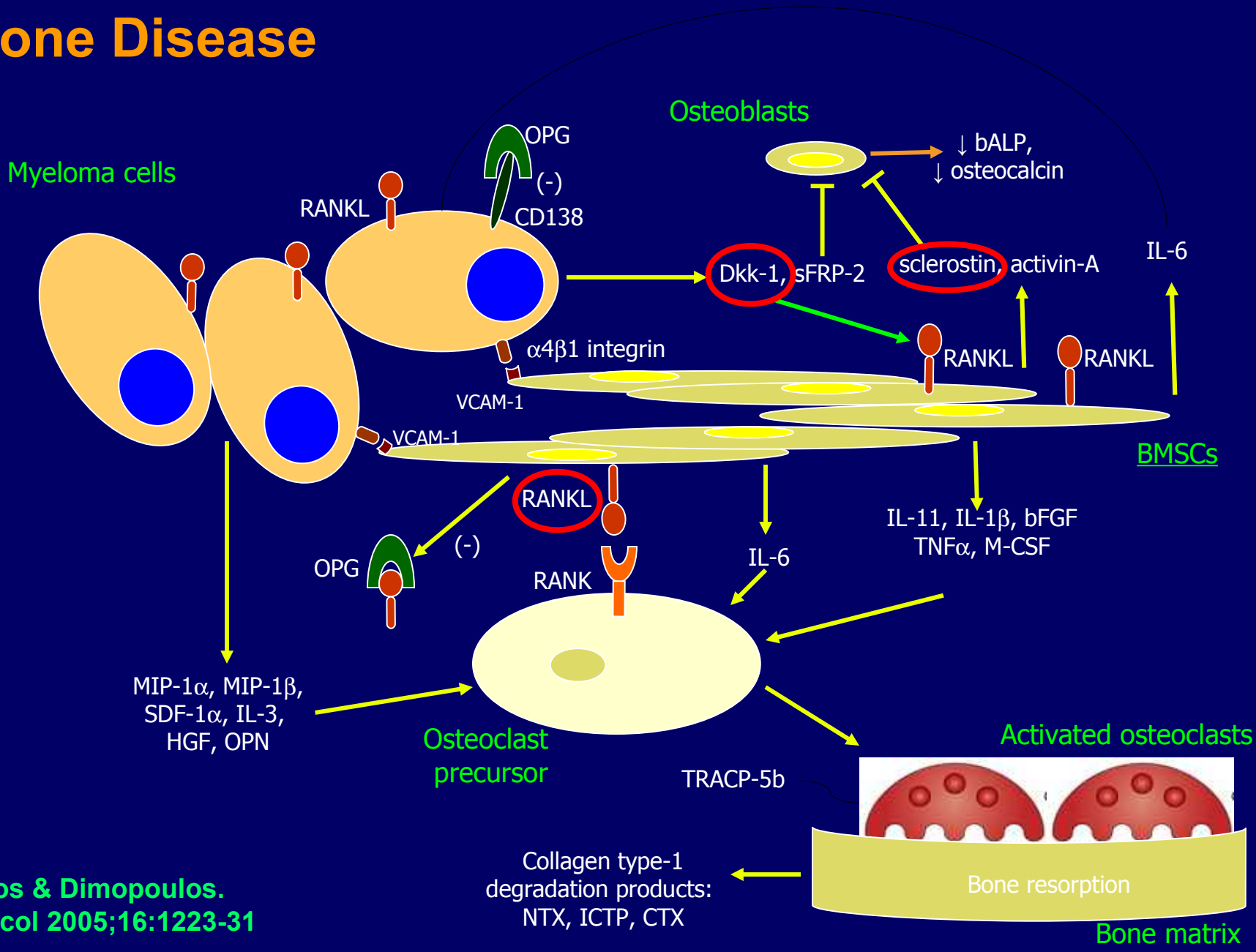


Skeletal destruction results from increased osteoclastic activity, which is not accompanied by a comparable increase in bone formation

↓

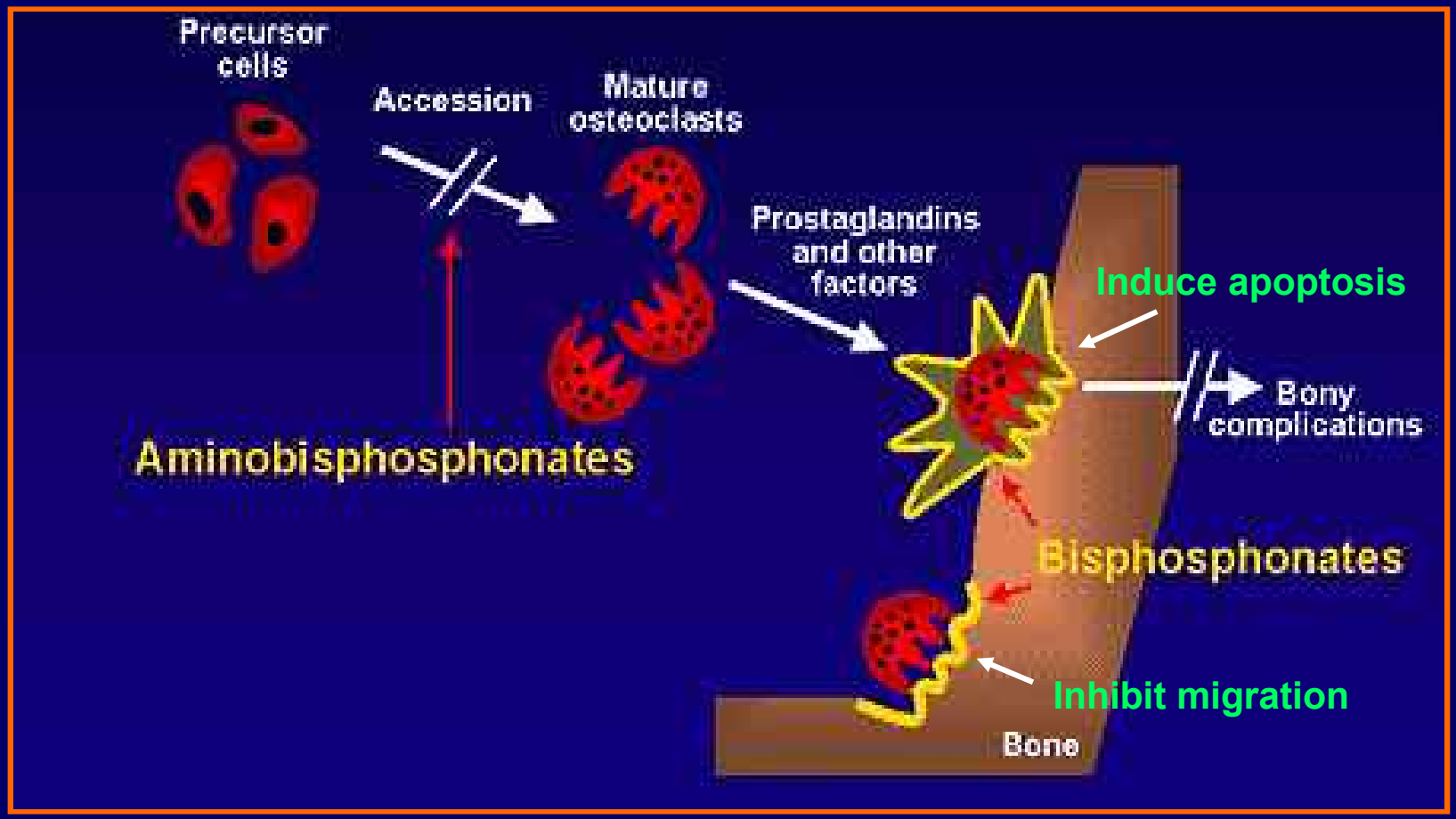
LYTIC LESIONS

Myeloma Microenvironment & Bone Disease



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

Bisphosphonates



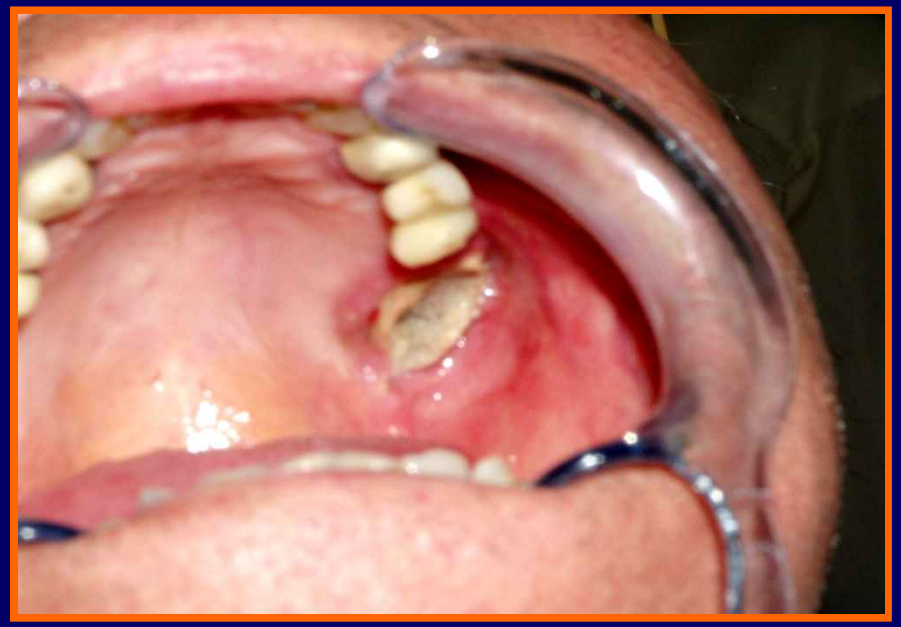
ONJ: characteristics

Symptoms

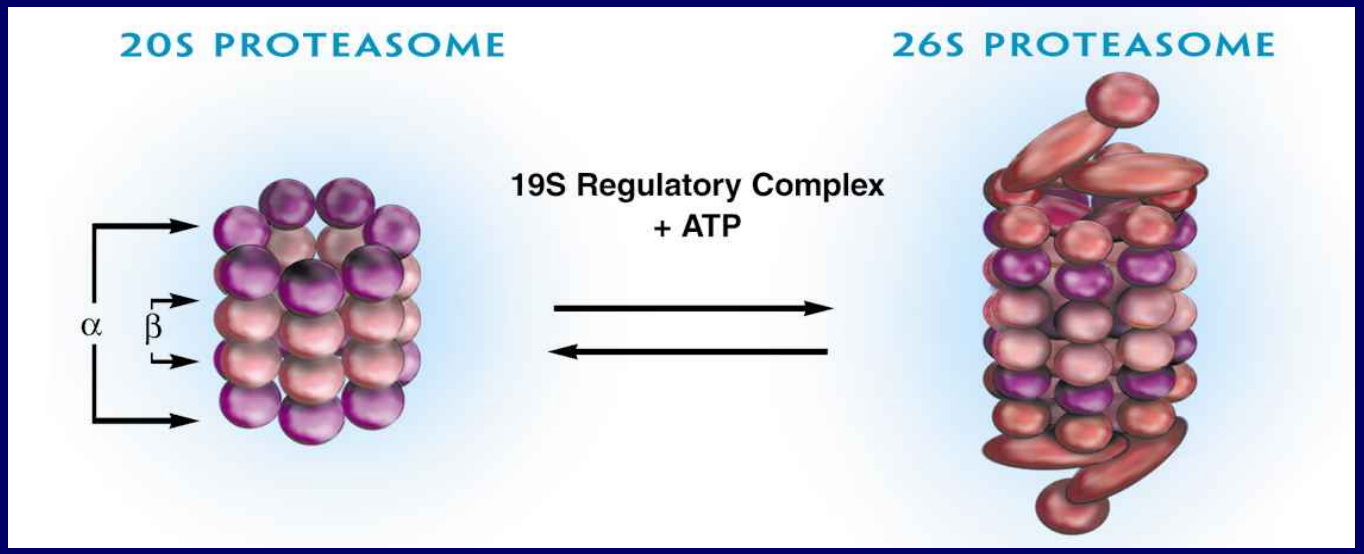
- “heavy jaw”, a dull aching sensation
- numbness/tingling of the jaw
- tooth pain
- undiagnosed oral pain

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

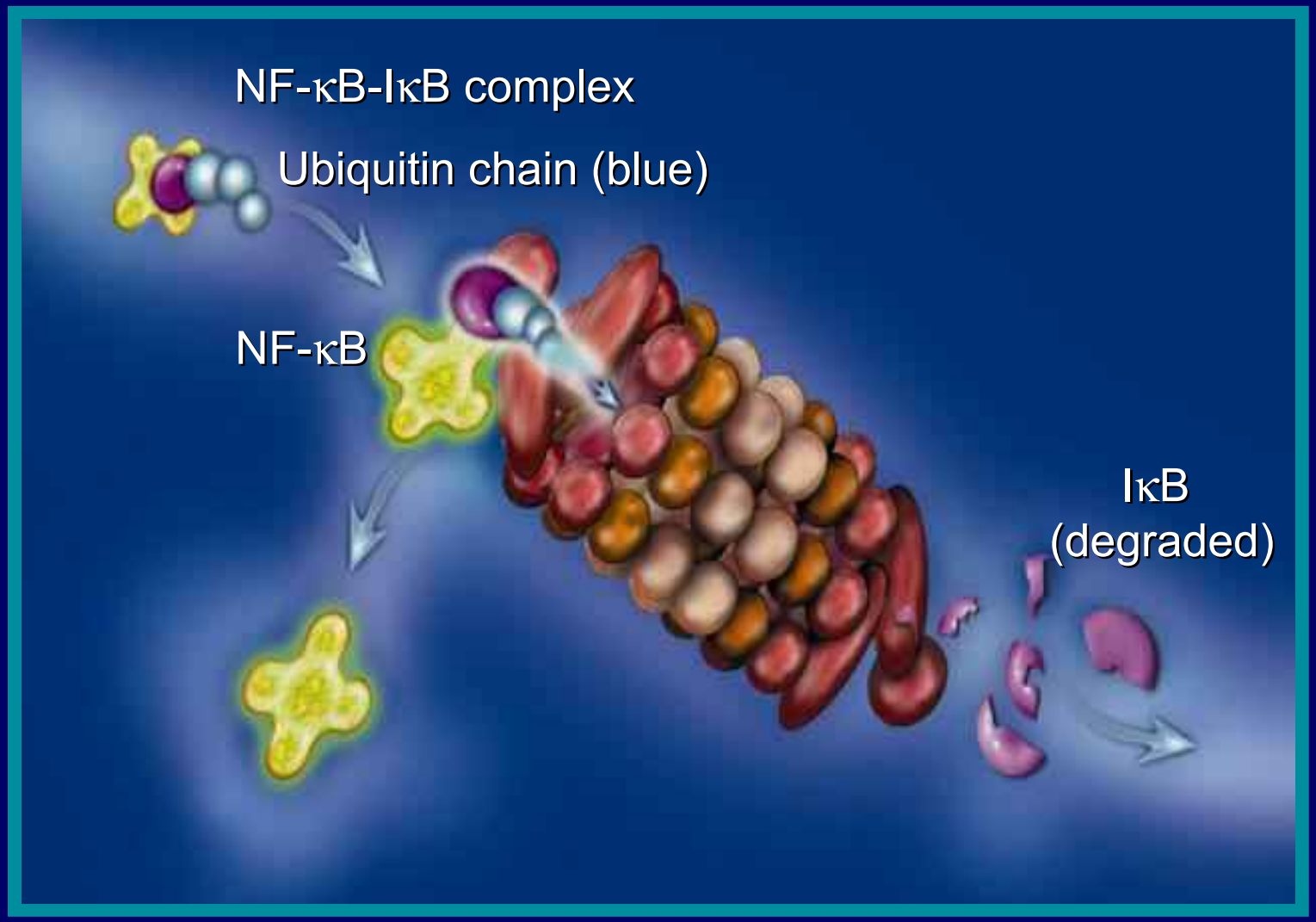


The Proteasome: Enzyme With Important Impact on Multiple Regulatory Pathways

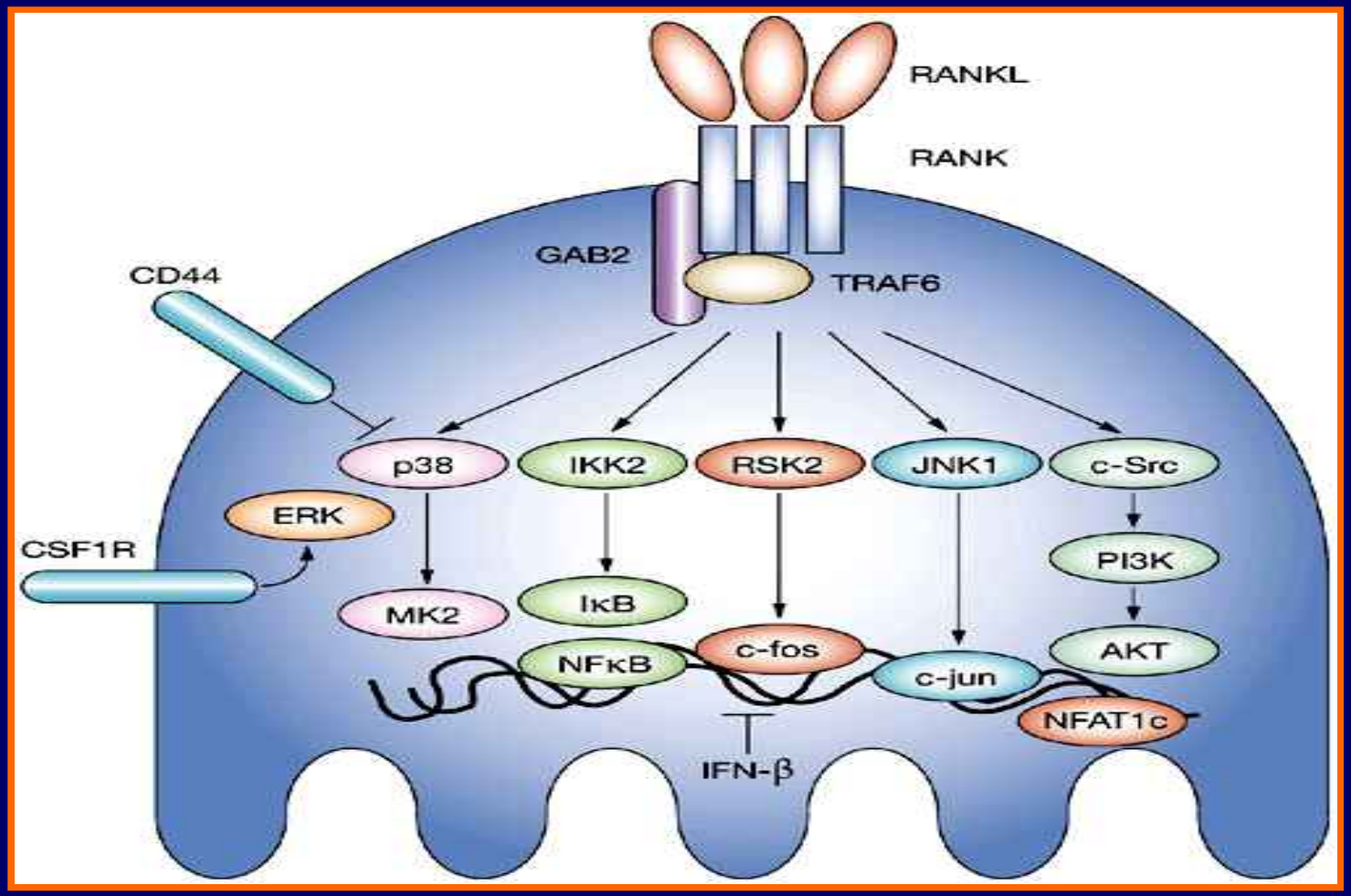


- Is found in all eukaryotic cells, from yeast to man
- Is present in the cytoplasm and nucleus
- Degrades proteins
- Represents approximately 1% of all cellular protein

NF-κB Activation After IκB Degradation by the Proteasome

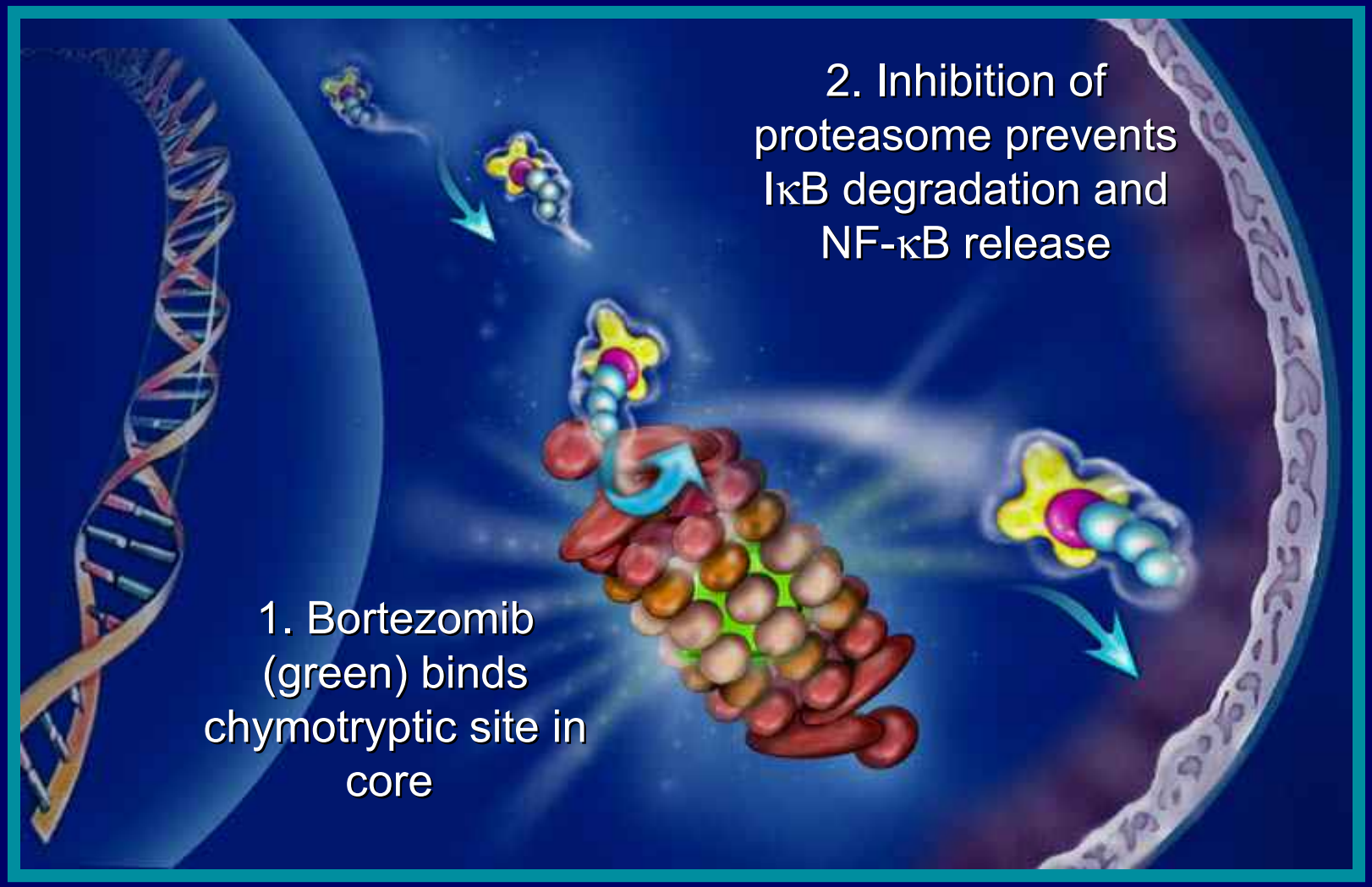


RANKL: Action Mainly Through NFkB & c-fos in Osteoclasts



Schett et al. Nat Clin Pract Rheumatol 2005;1:47-54

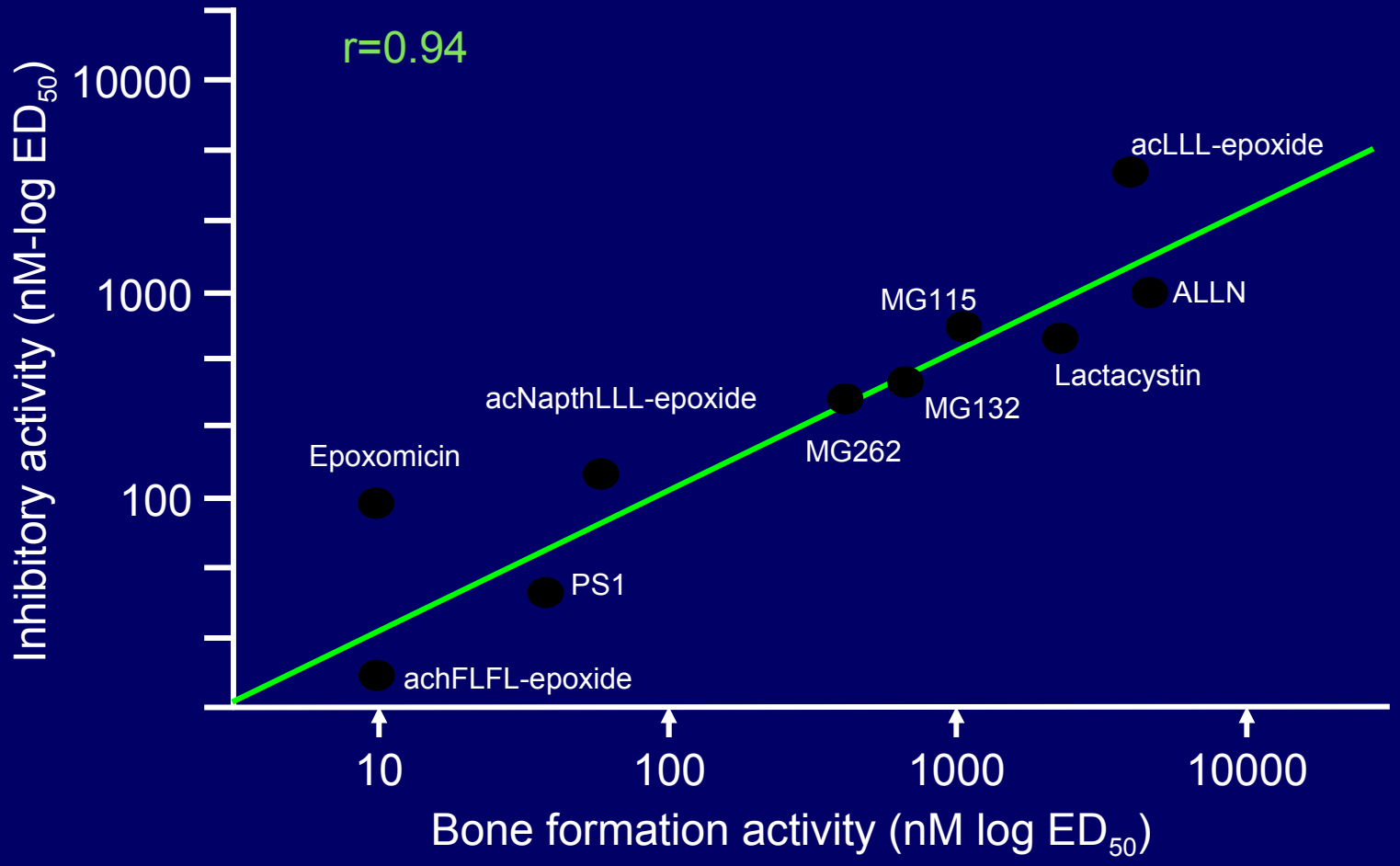
Effect of Proteasome Inhibition



Bortezomib Effect on Bone Metabolism: Preclinical Studies

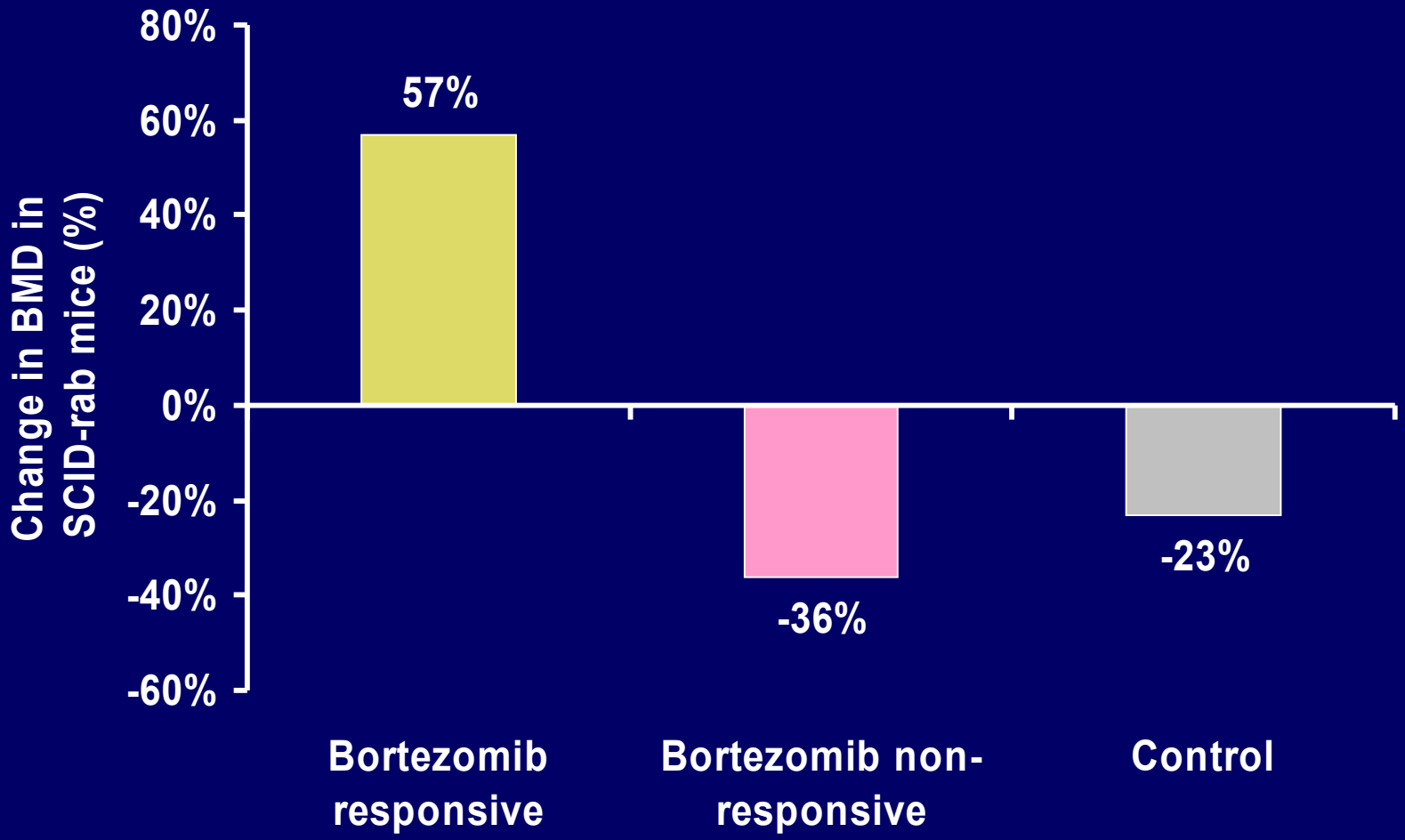
Reference	Results
von Metzler et al. Leukemia 2007;21:2025-2034	Bortezomib inhibited osteoclastogenesis
Boissy et al. Leuk Res 2008;32:1661-8	Bortezomib transiently inhibited osteoclast activity
Breitkreuz et al. Blood 2008;22:1925-32	Bortezomib inhibited osteoclast differentiation
Feng et al. BJH 2007;139:385-97	Synergistic inhibition of osteoclastogenesis by bortezomib and PXD101
Pennisi et al. Am J Hematol 2009;84:6-14	Bortezomib suppresses osteoclastogenesis through downregulation of NFκB activity in osteoclast precursors Bortezomib increased BMD in responding mice
Oyajobi et al. Br J Haematol 2007;139:434-438	Bortezomib promoted bone formation
Giuliani et al. Blood 2007;110:334-338	Bortezomib increased osteoblast differentiation Bortezomib induced bone nodule formation Bortezomib did not affect mature osteoblasts

Proteasome Inhibition and Bone Formation



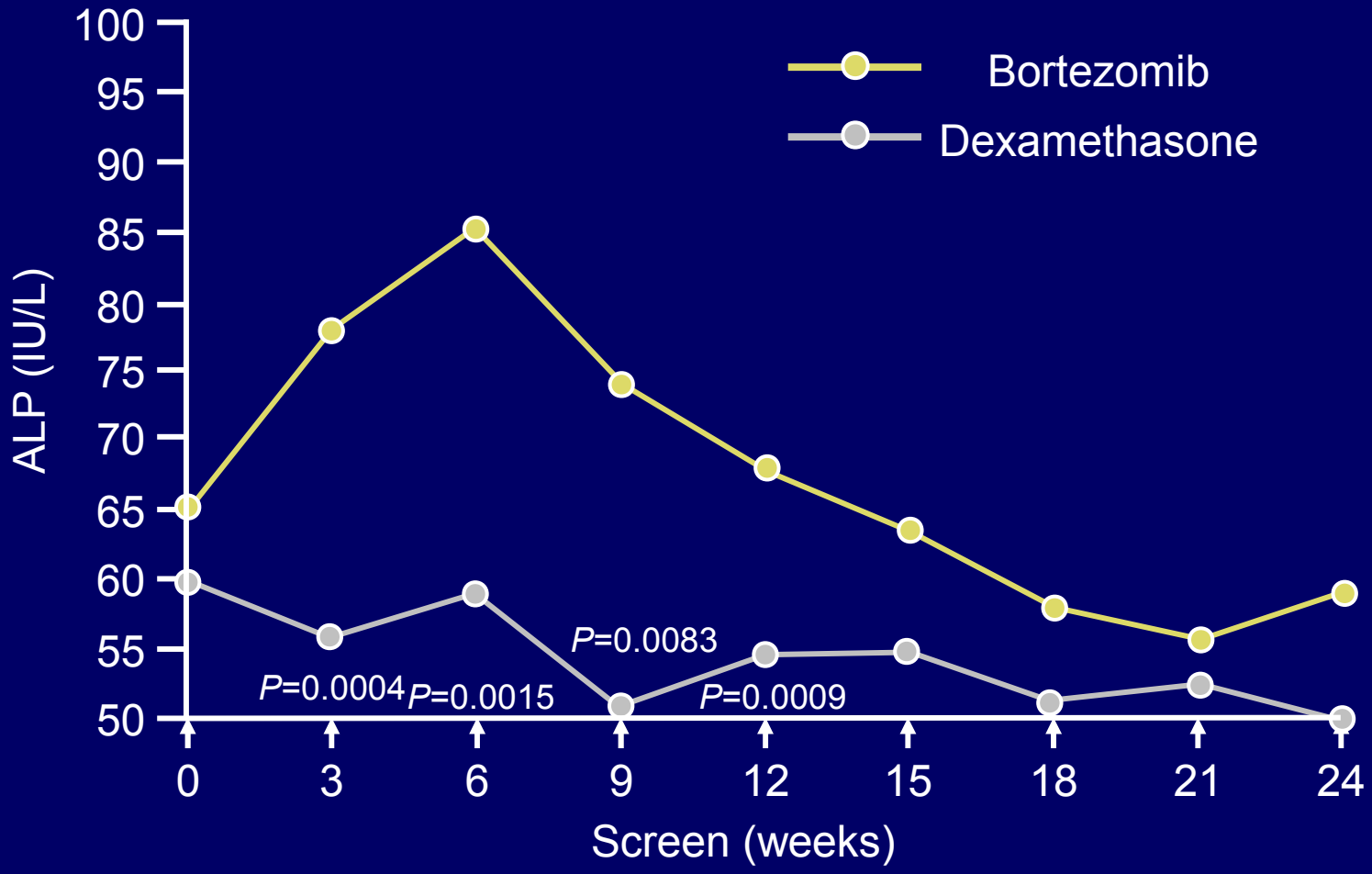
Garrett et al. J Clin Invest 2003;111:1771-8

Bortezomib increased bone mineral density (BMD) in murine model of MM



Pennisi et al. Am J Hematol 2009;84:6-14

Clinical studies: Total ALP levels in bortezomib and dexamethasone responders in APEX



Zangari et al. Br J Haematol 2005;131:71–73
Zangari et al. Clin Lymphoma Myeloma 2006;7:109–114

Bortezomib Increases Osteoblast Activity in Myeloma Patients

- Treatment
  - Bortezomib ± dex
  - Control group: adriamycin + dex, melphalan + prednisone or thal-containing regimen

	Bortezomib (n=25)		Control group (n=58)	
	Mean	*P*	Mean	*P*
bALP				
Before treatment	19.7	<0.0005	24.8	NS
After treatment	30.2		23.3	
Osteocalcin				
Before treatment	6.3	0.024	6.97	NS
After treatment	10.8		6.6	

bALP = bone-specific alkaline phosphatase

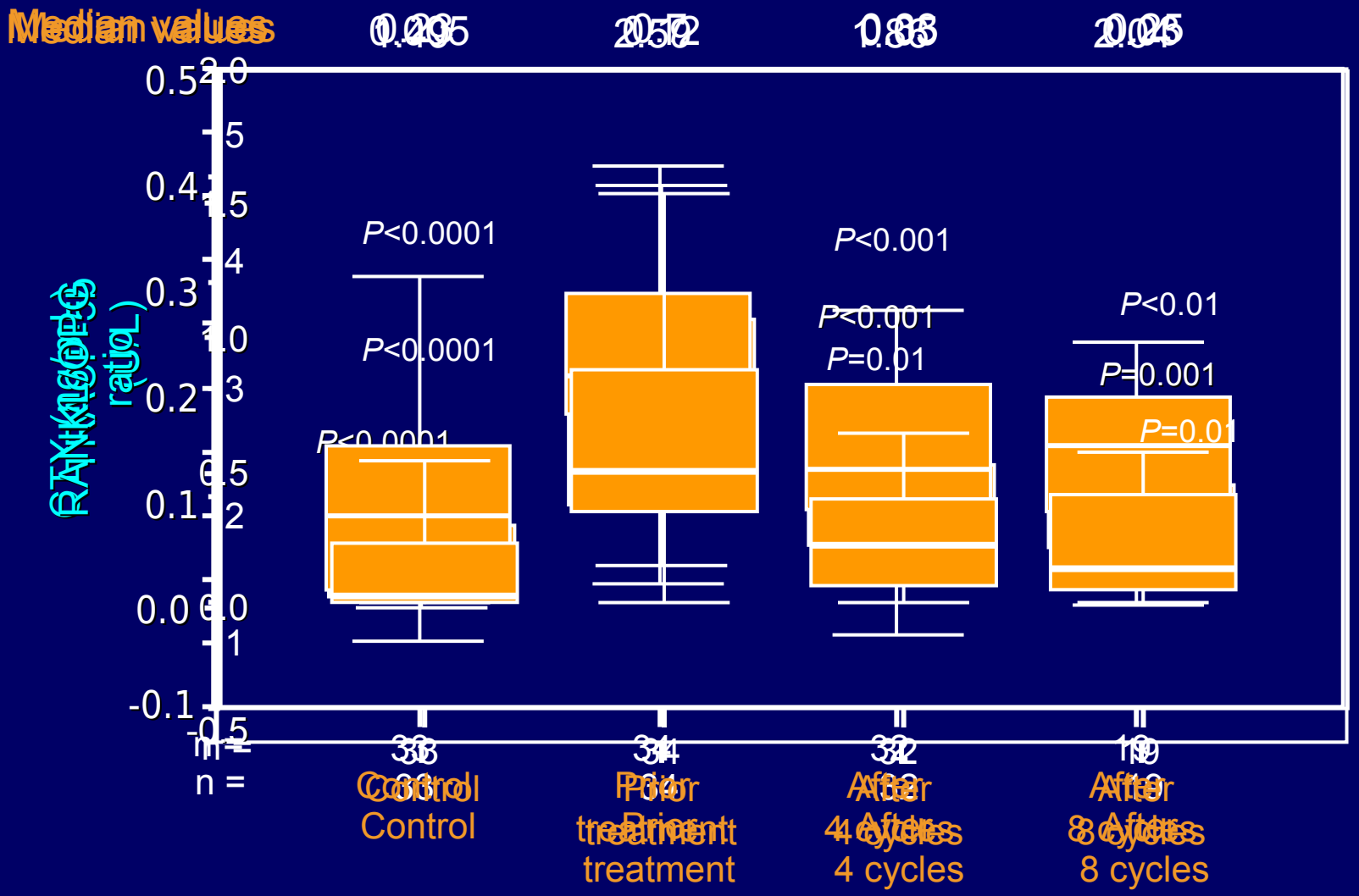
Heider et al. Eur J Haematol 2006;77:233–238

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

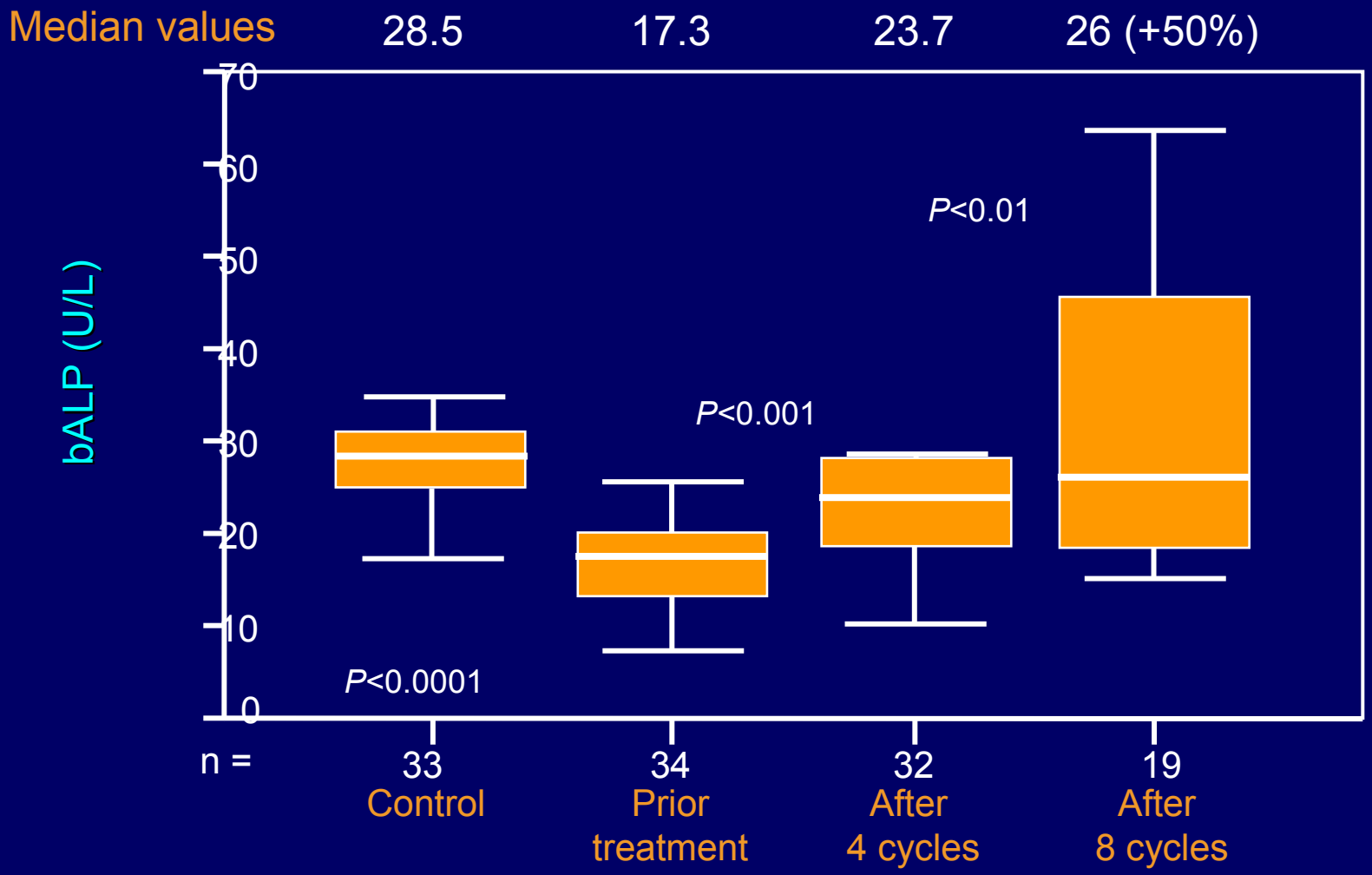
Terpos et al. Br J Haematol 2006;135:688–92

Bone Resorption: Pre- and Post-bortezomib



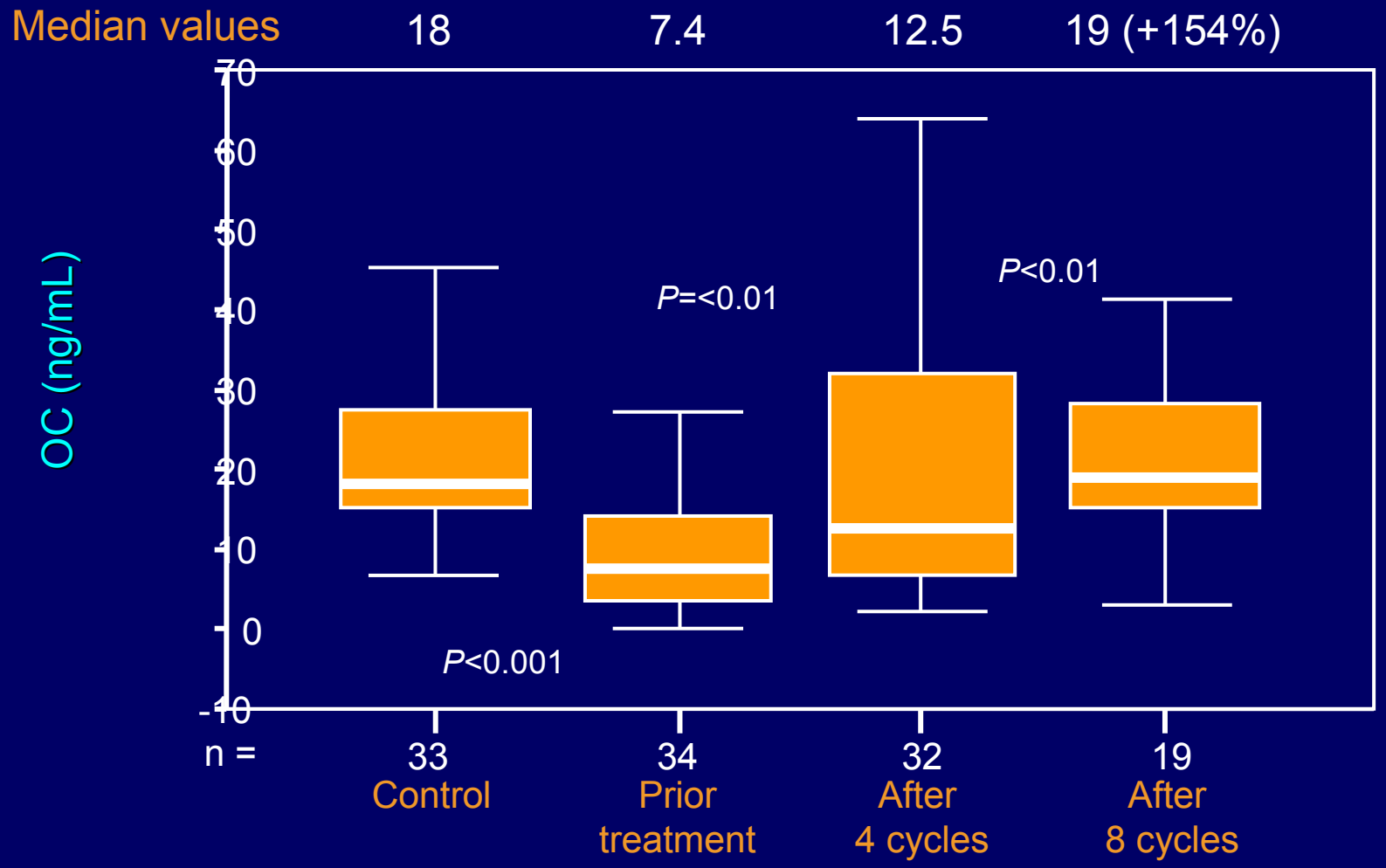
Terpos et al. Br J Haematol 2006;135:688–692

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



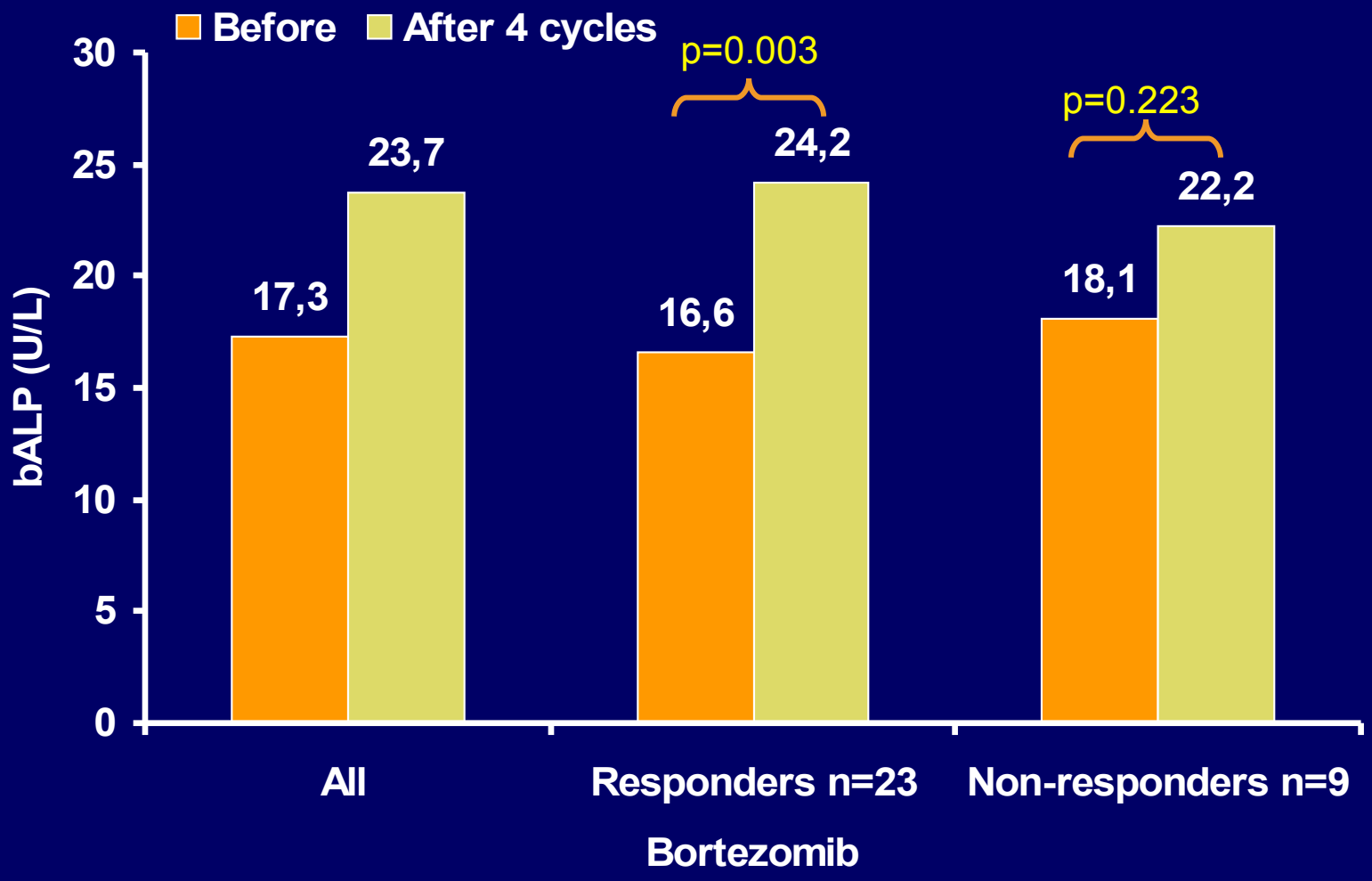
Terpos et al. Br J Haematol 2006;135:688–92

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



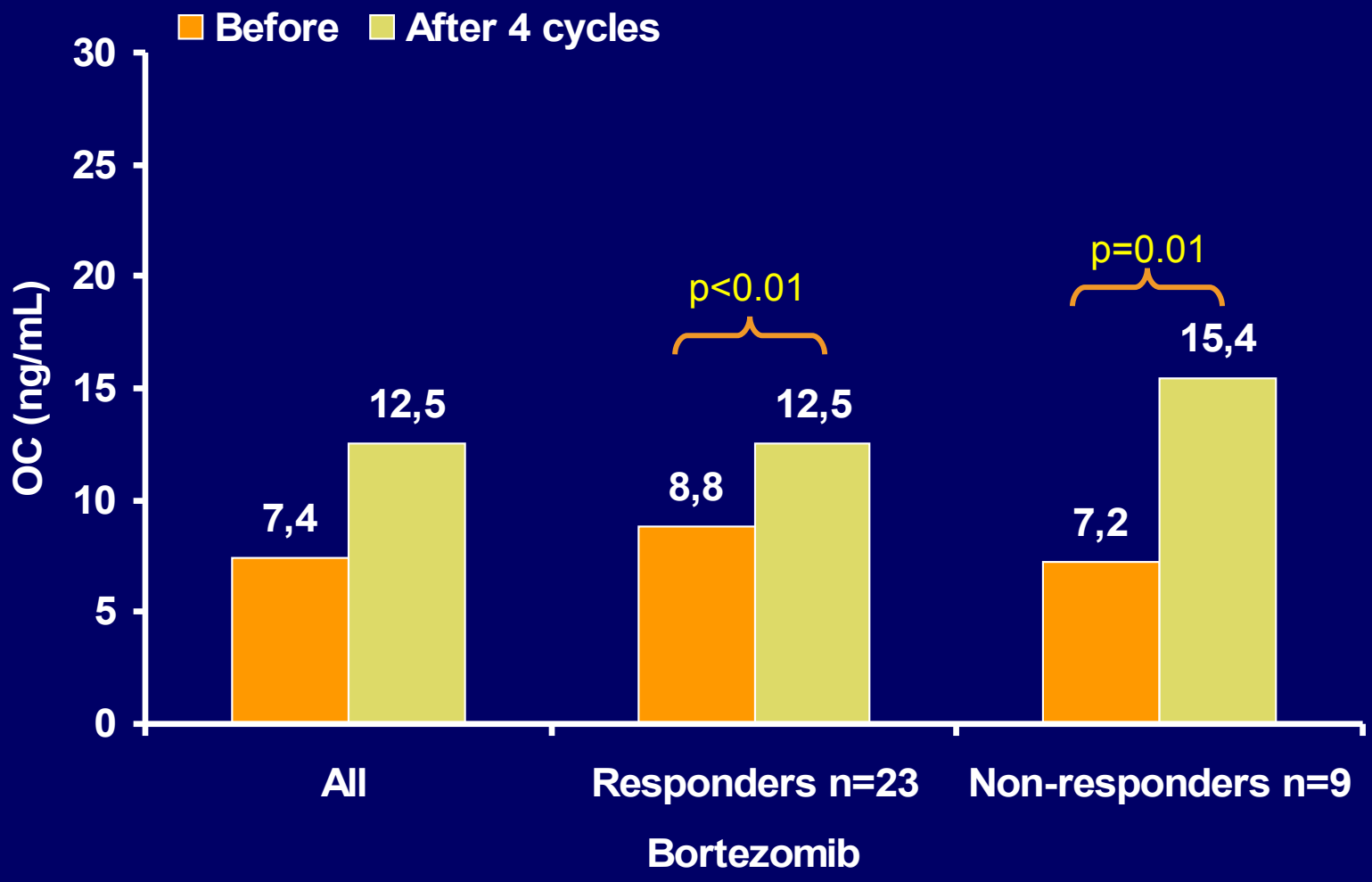
Terpos et al. Br J Haematol 2006;135:688–92

Changes in bALP Levels



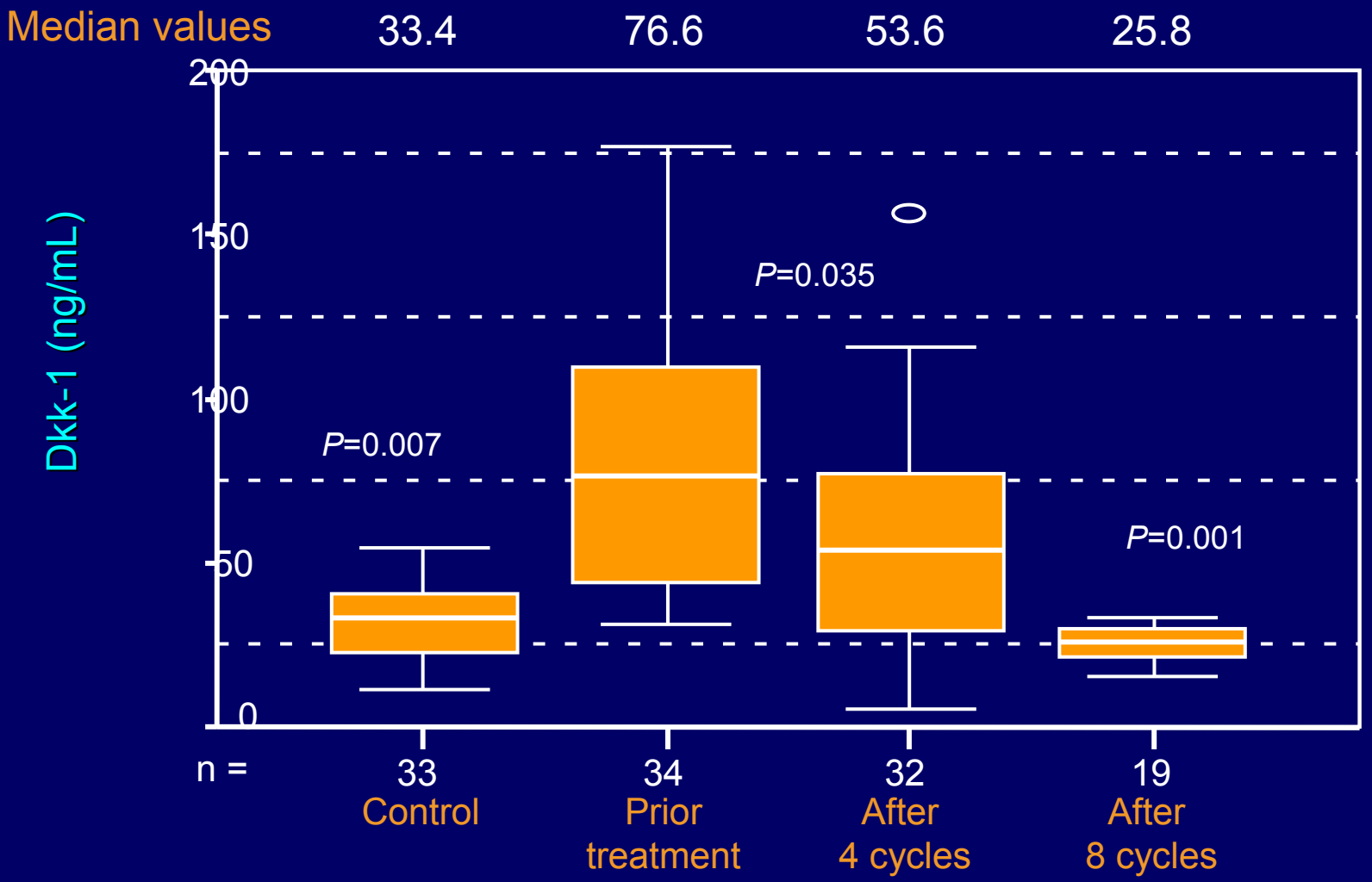
Terpos et al. Br J Haematol 2006;135:688–92

Changes in Osteocalcin Levels



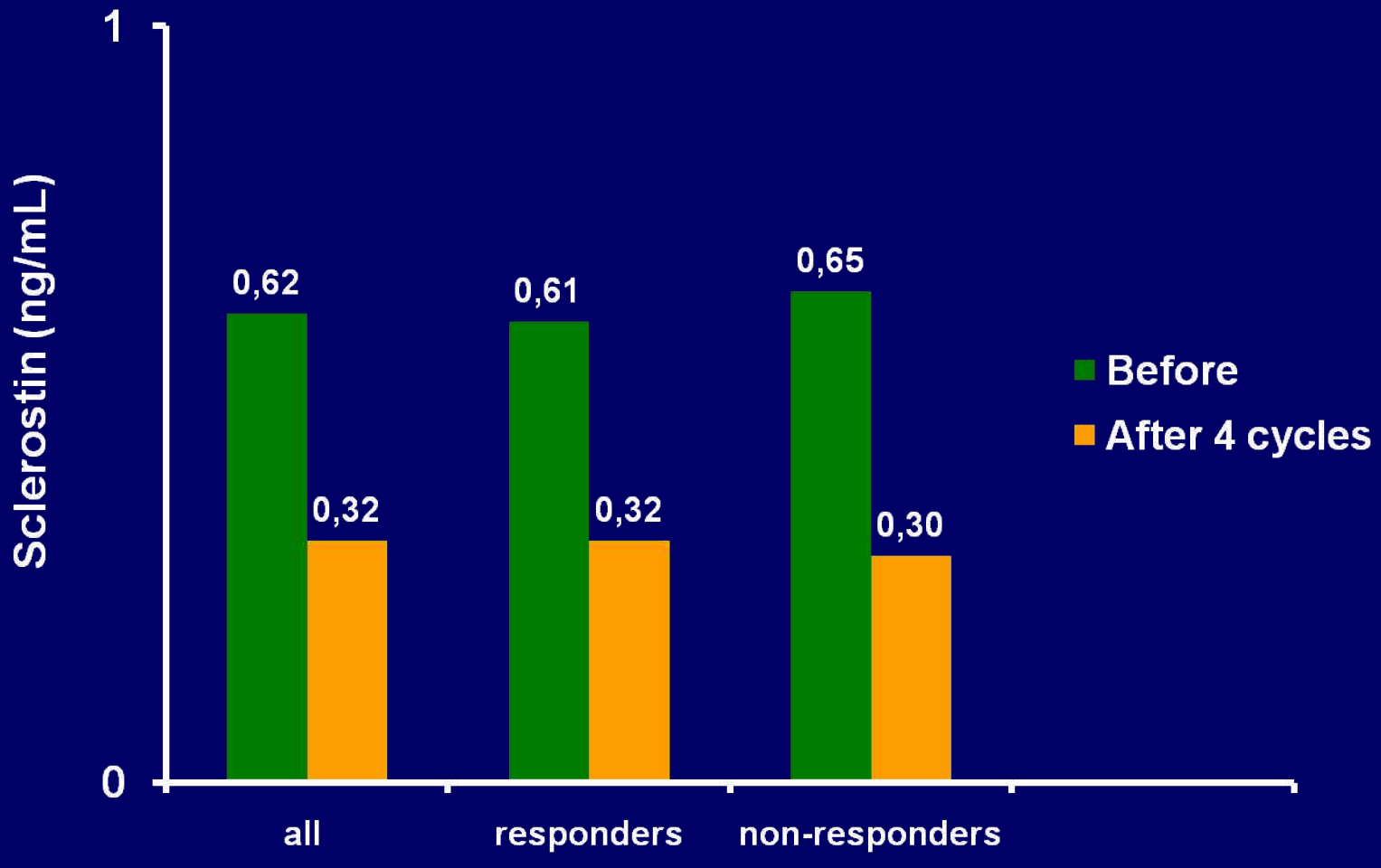
Terpos et al. Br J Haematol 2006;135:688–92

Dkk-1: Pre- and Post-bortezomib



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

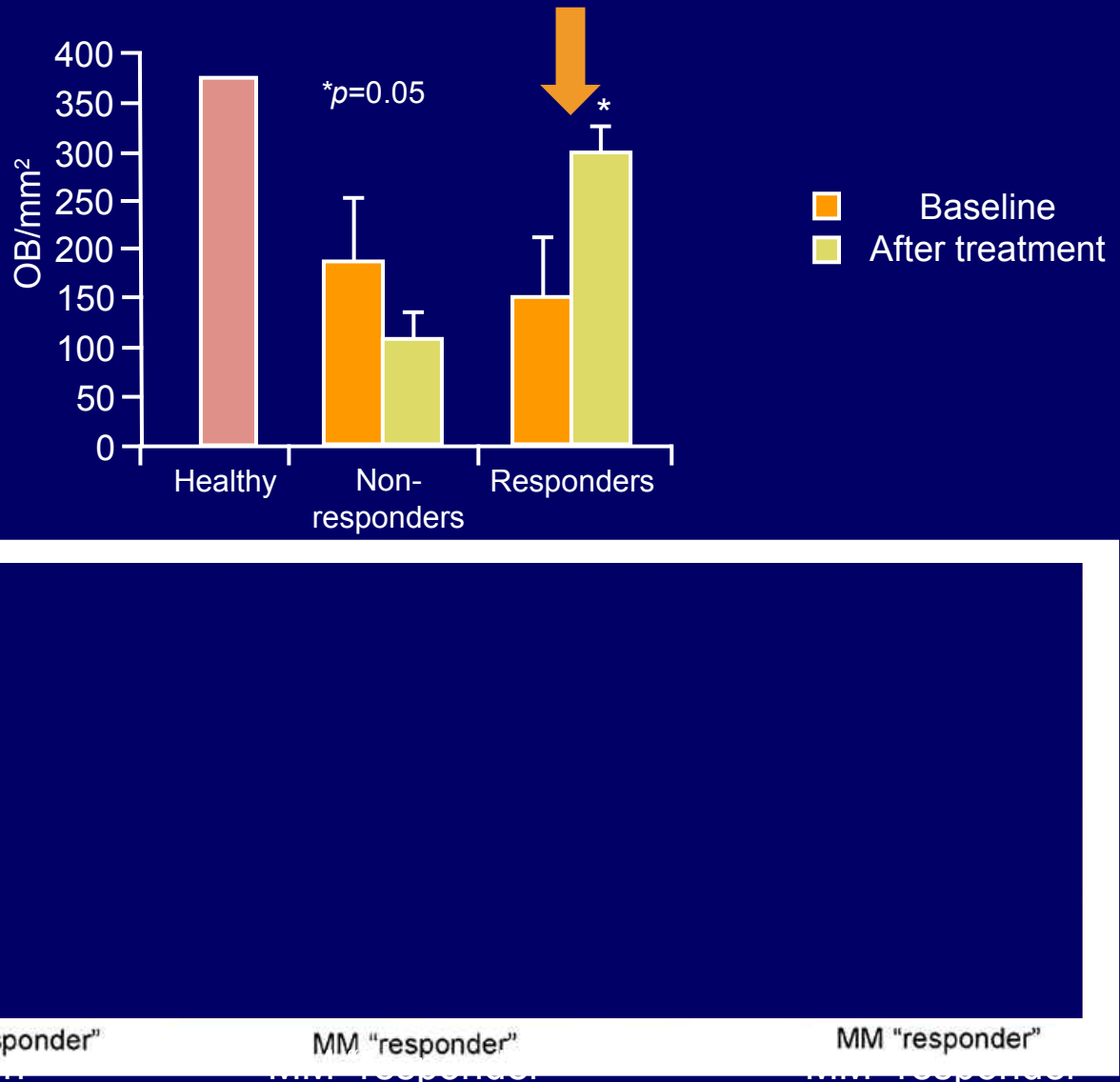
Changes of sclerostin post-bortezomib in relapsed MM



Post-VD

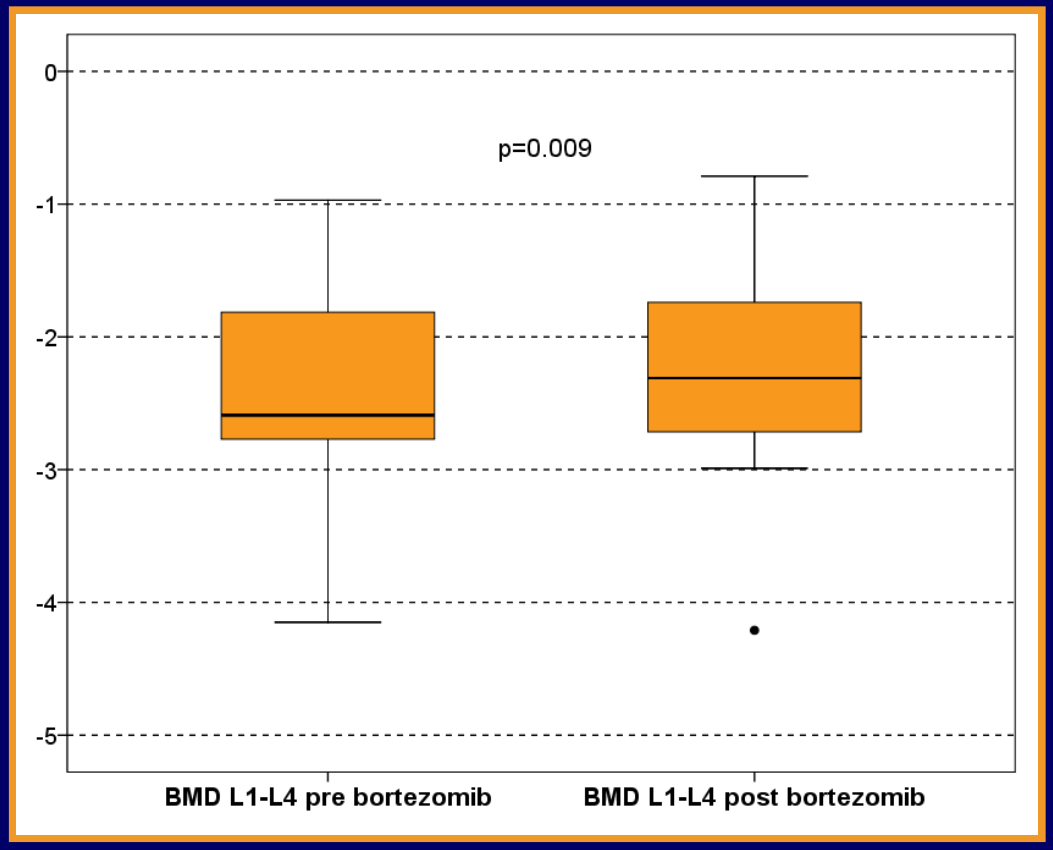
Terpos et al, EHA 2010

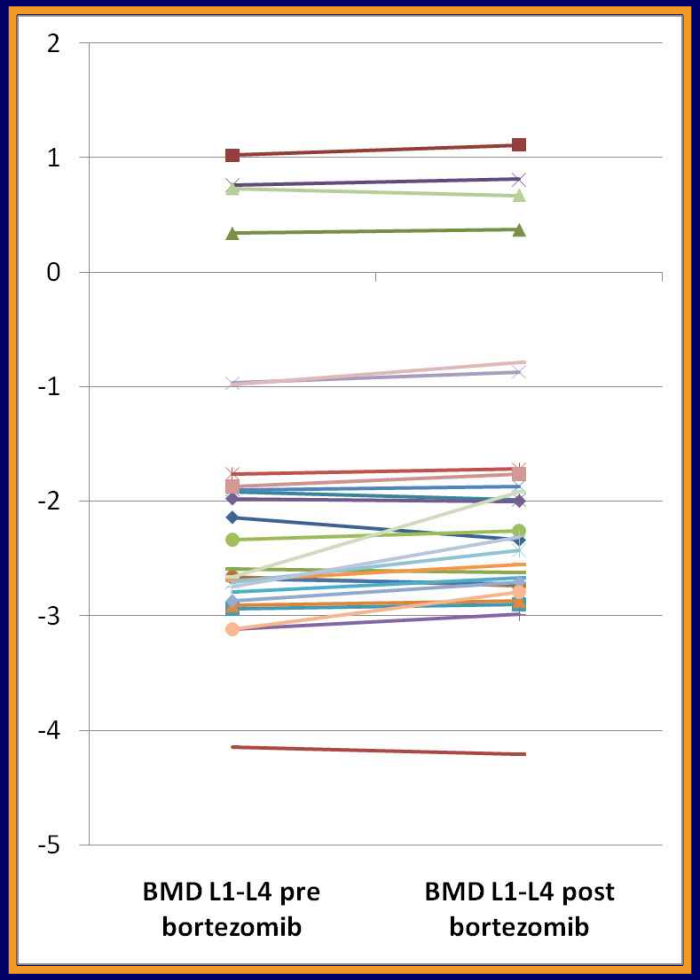
Bortezomib increases osteoblast counts in responding patients



Giuliani et al. Blood 2007;110:334-338

BMD: Pre- and Post-bortezomib

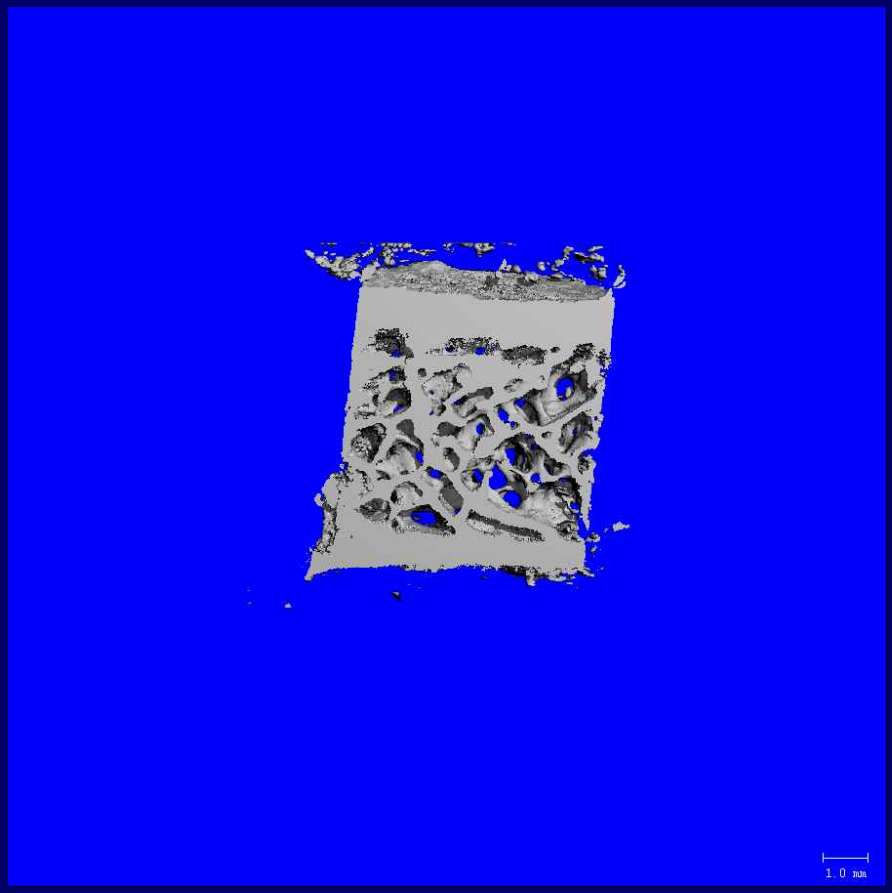




4/27 patients (14%) showed at least 10% of increase in L1-L4 BMD; all these patients had osteoporosis according to DXA, had responded to VD therapy (3 PR and one CR), and had received VD as second line treatment

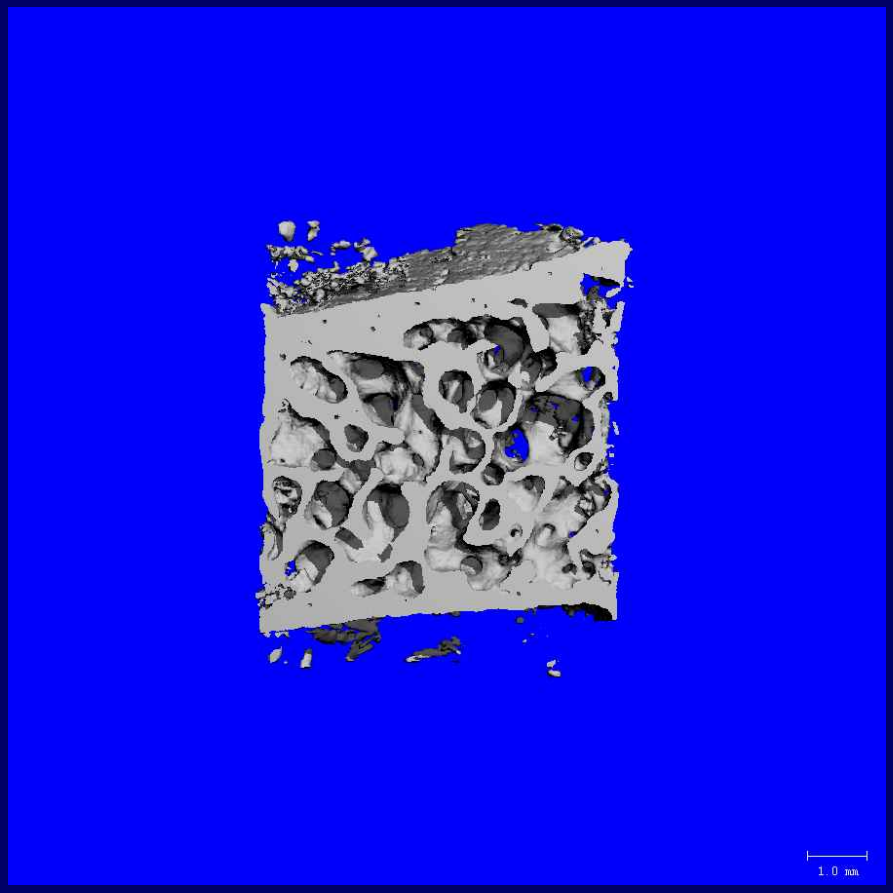
Terpos et al. Ann Oncol 2010;27:1561-2

Pre-Bor



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

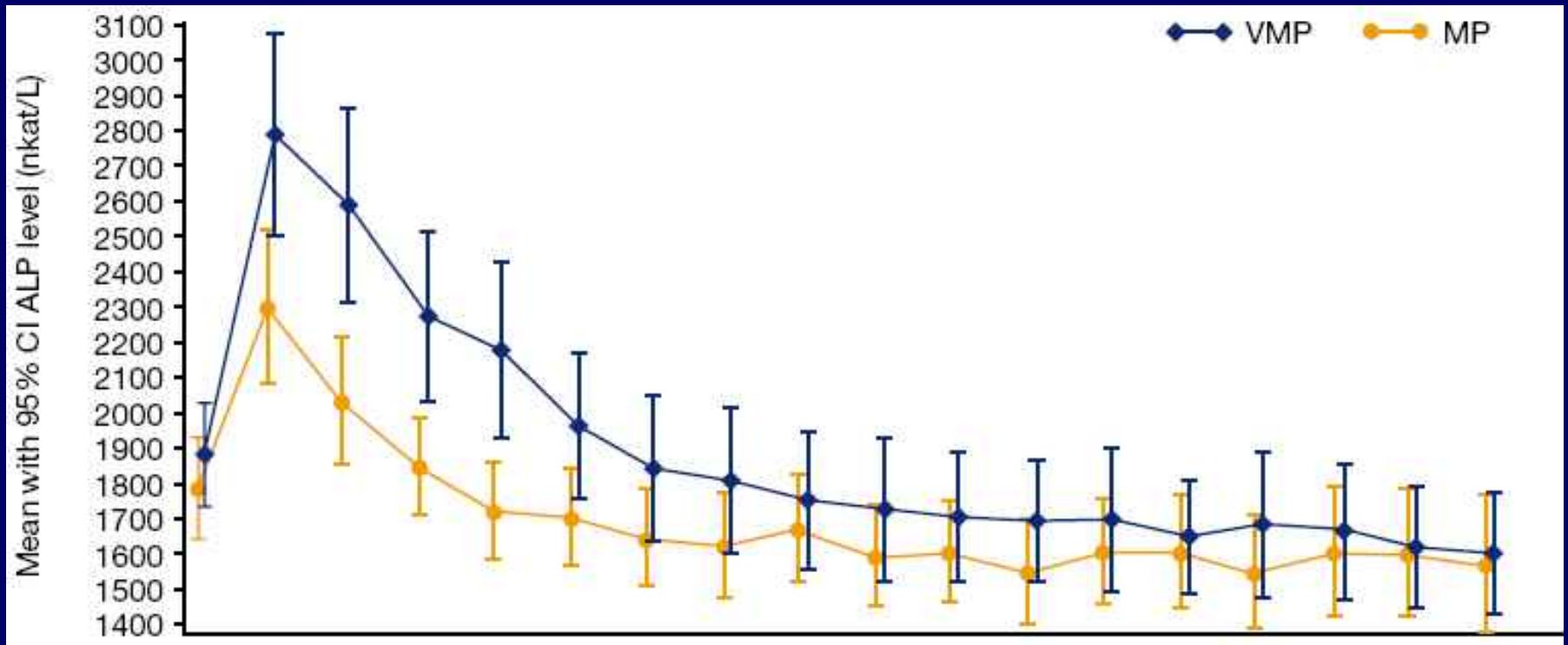
Post-Bor



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

Zangari et al.
Haematologica submitted

VISTA: ALP Analysis



	Baseline	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	C9 D1
MP	220	298	280	264	225	206	185	166	125
VMP	228	290	269	263	242	220	201	172	154

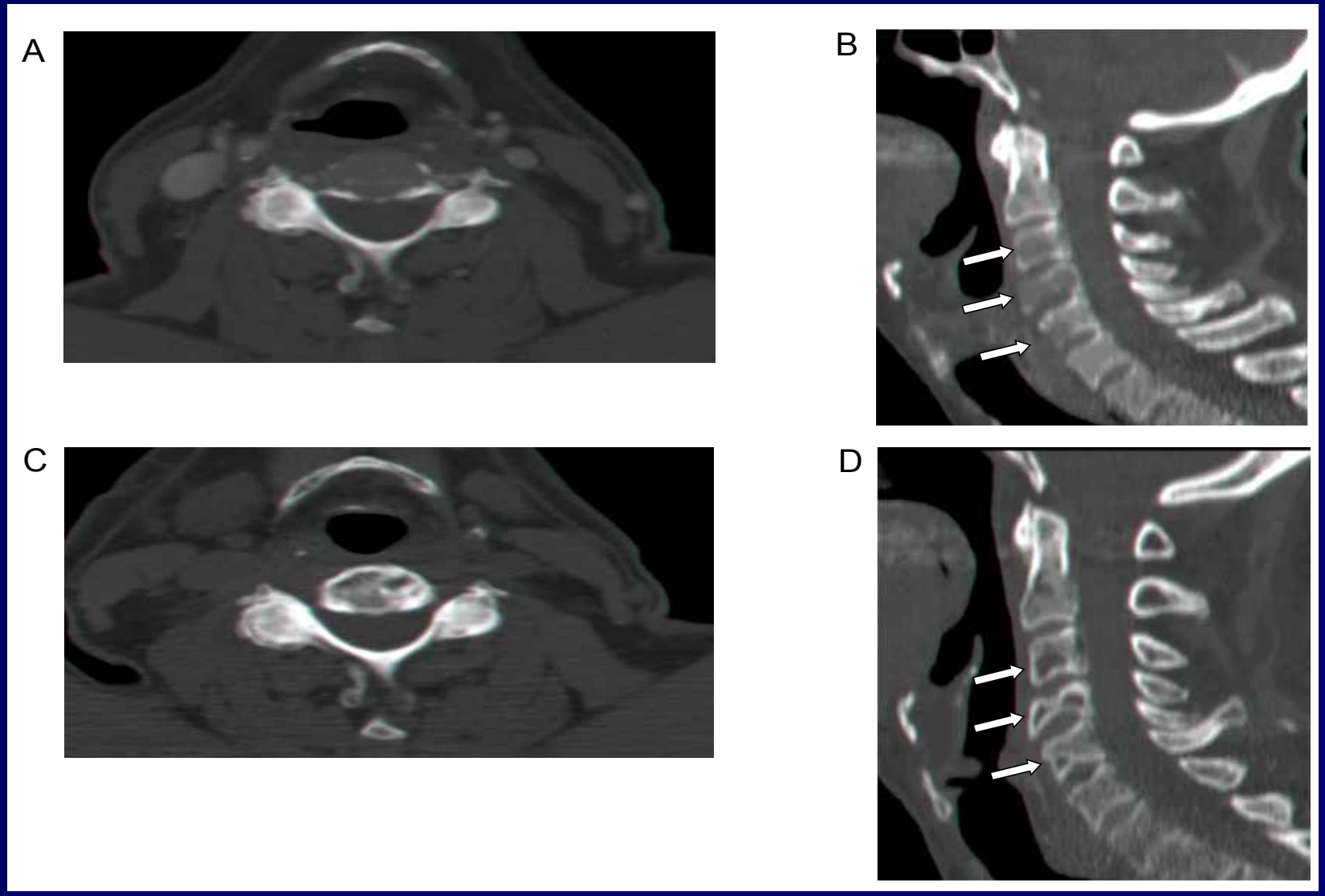
Note: days (D) 1 and 22 of each cycle (C) are displayed; CI, confidence interval.

Delforge et al. Submit

VISTA: Dkk-1 analysis

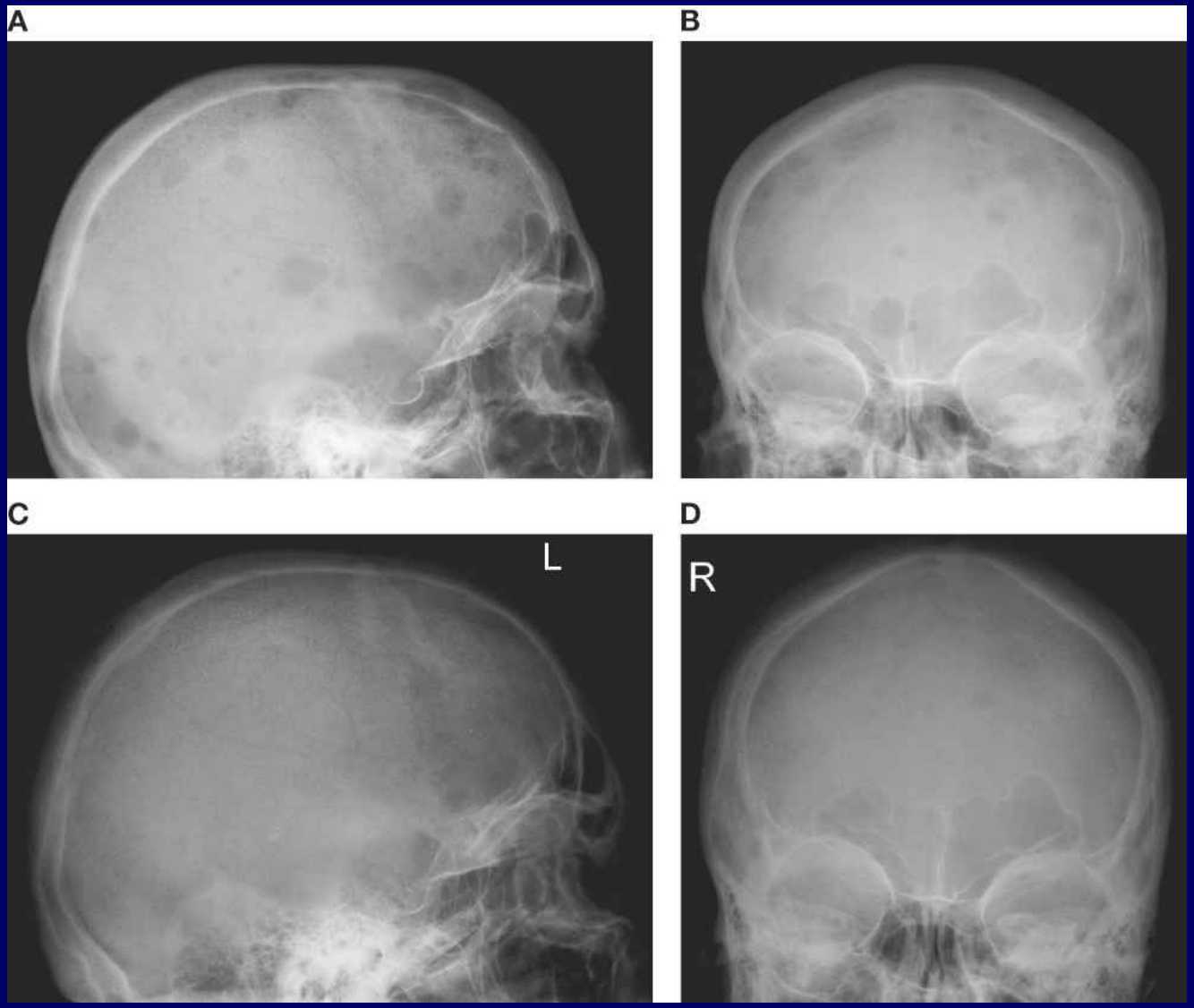
	VMP			MP		
DKK-1 (pg/mL), median (range)	**All n = 78**	**Responders n = 60**	**Non-responders n = 18**	**All n = 76***	**Responders n = 23**	**Non-responders n = 50**
Baseline	10587.9 (2532.6–64000.0)	10630.2 (2532.6–64000.0)	10579.3 (3846.8–45460.5)	9240.7 (2436.2–64000.0)	13852.9 (3941.6–64000.0)	8256.2 (2436.2–64000.0)
Cycle 1, Day 4	9911.7 (2217.6–64000.0)	9388.3 (2217.6–64000.0)	10858.9 (4027.9–64000.0)	10565.8 (2511.8–64000.0)	16135.0 (5237.0–64000.0)	9399.1 (2511.8–64000.0)
Change from baseline	**-694.4†** **(-59059.9–35501.6)**	**-1110.9 (-59059.9–35501.6))**	**259.5 (-11931.6–18539.5)**	**1273.3 (-38233.9–24681.3)**	**2089.6 (-38233.9–24681.3)**	**1208.2 (-28078.3–24063.0)**

VMP: results in a patient after 9 cycles of therapy (1)



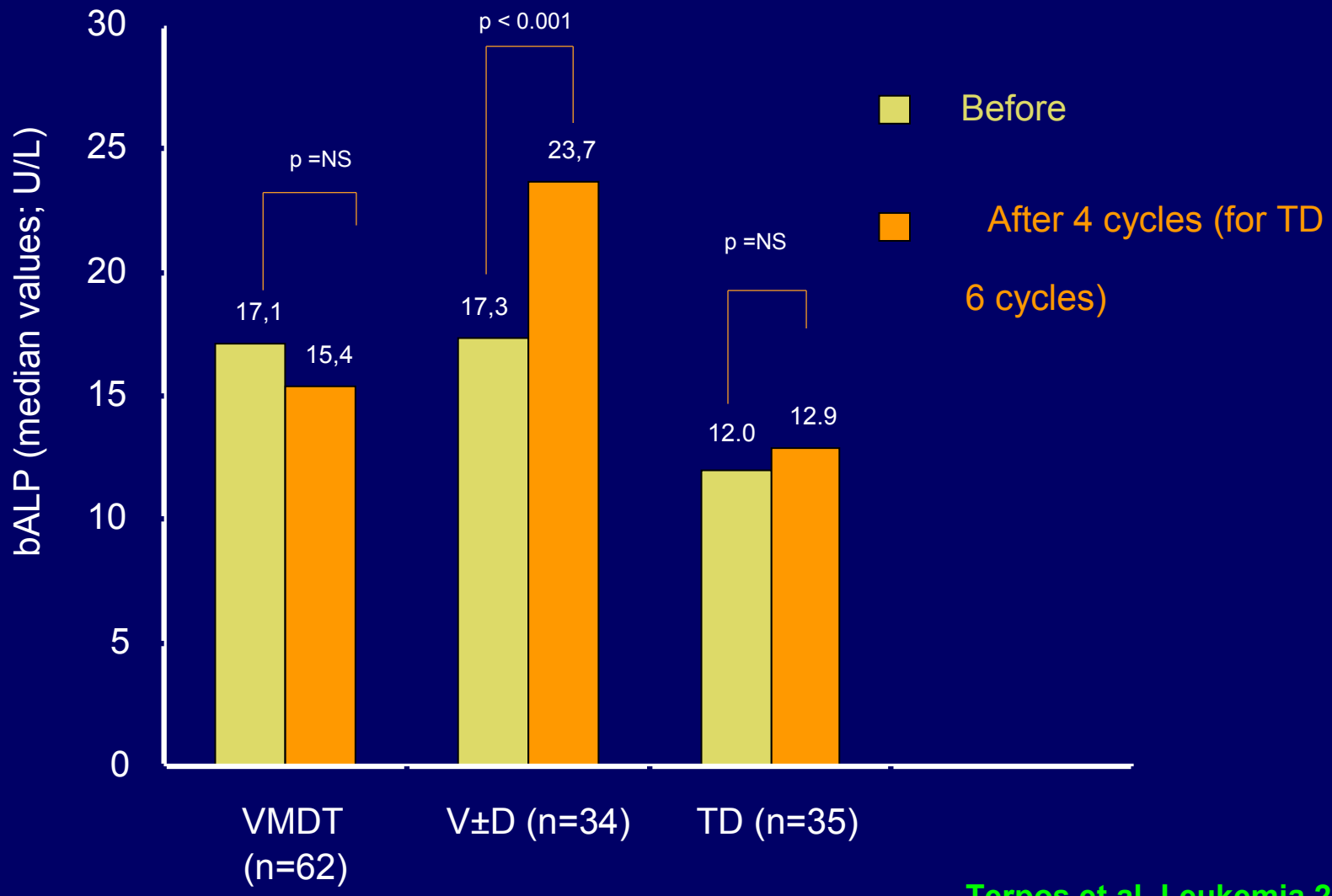
Delforge et al. Submitt

VMP: results in a patient after 9 cycles of therapy (2)



Delforge et al. Submitt

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=49

≥ grade 2

R on days 1 to 21 according to CrCl

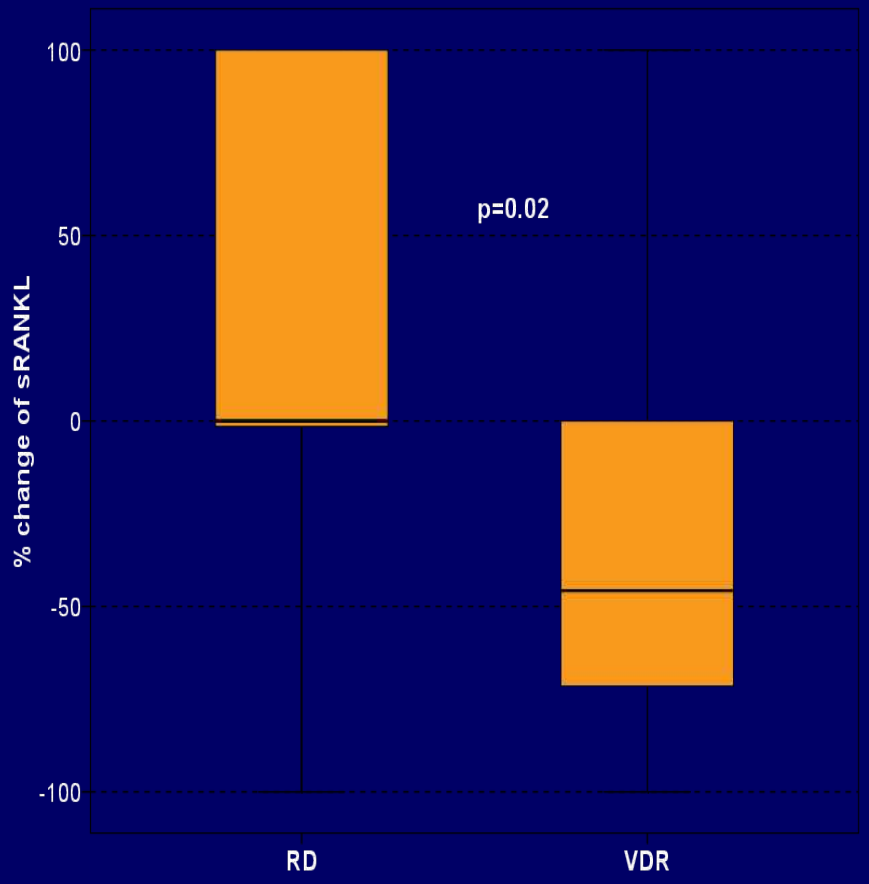
D 40 mg PO on days 1-4 and 15-28 for the first 4 cycles and only days 1-4 thereafter

Courses are repeated every 28d

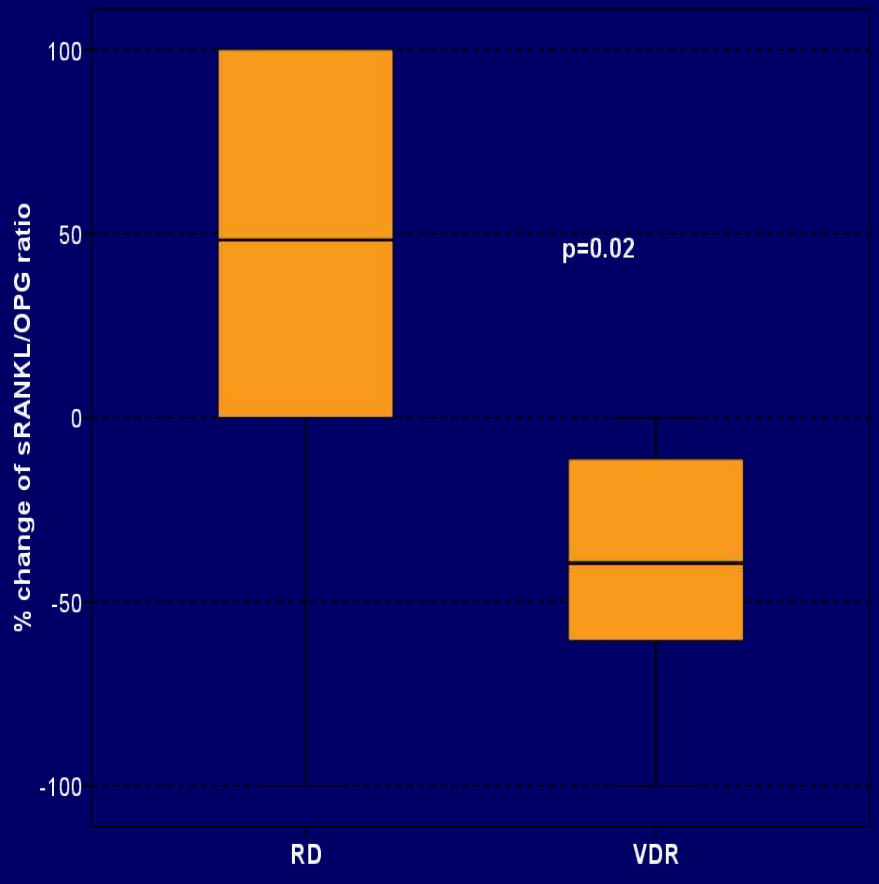
N=50

Dimopoulos et al. Leukemia 2010; in press

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



after 6 cycles of therapy



after 6 cycles of therapy

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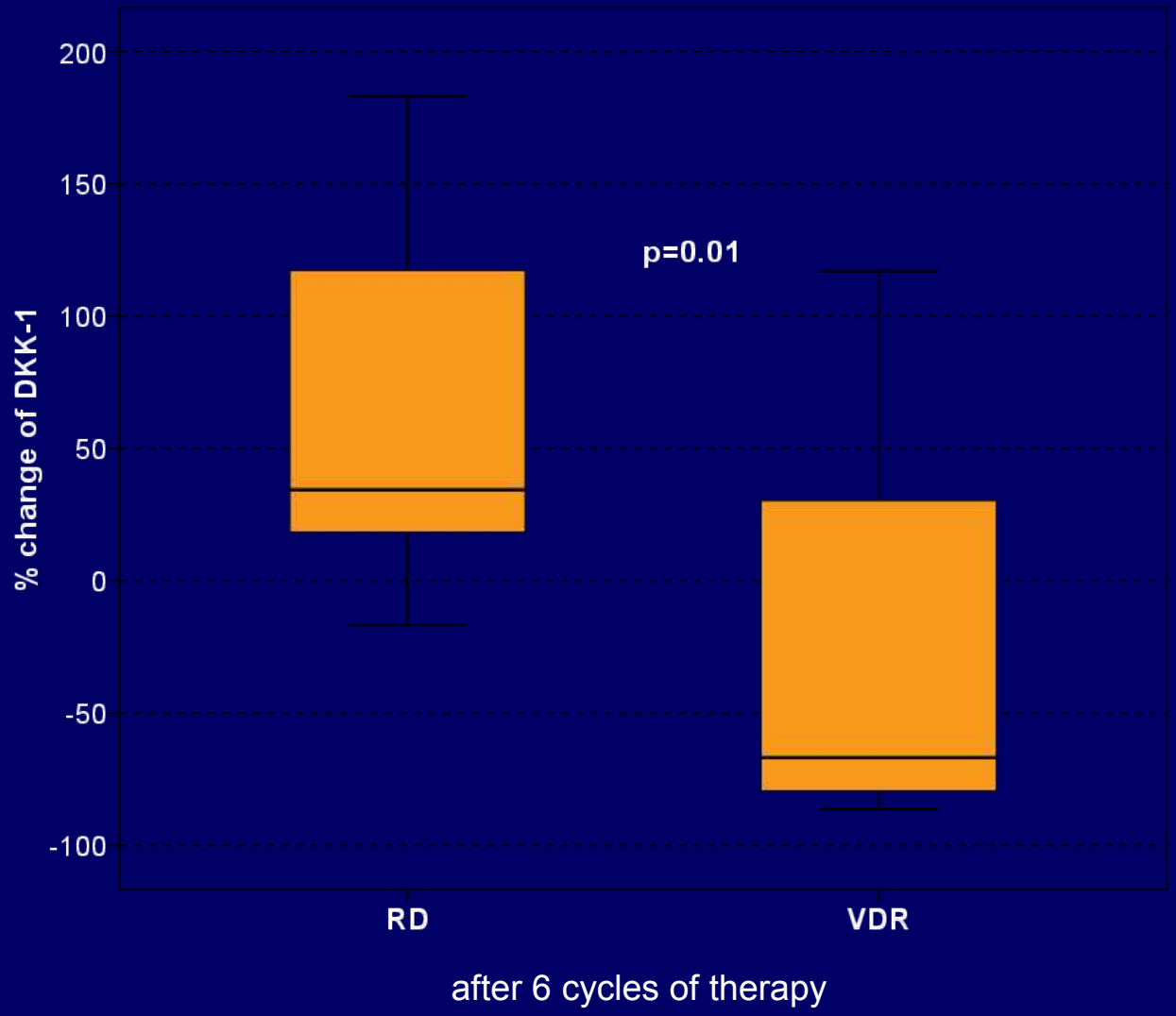
Effect of RD and VRD on Dickkopf-1



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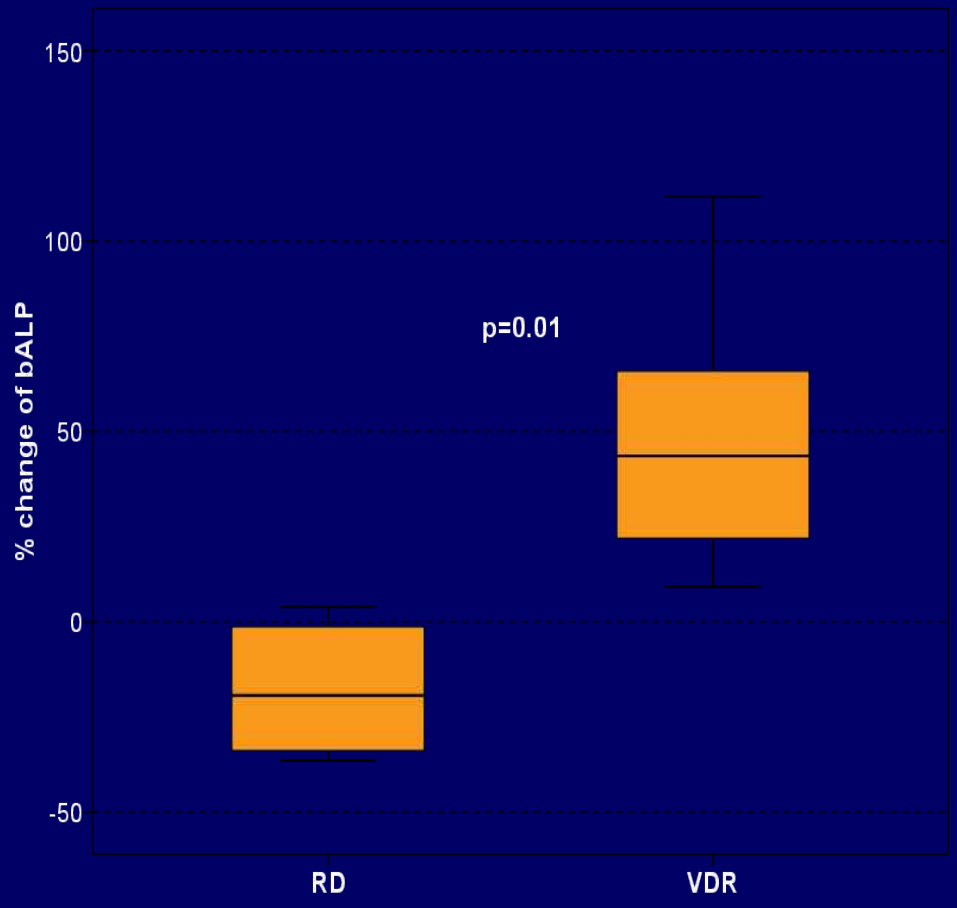
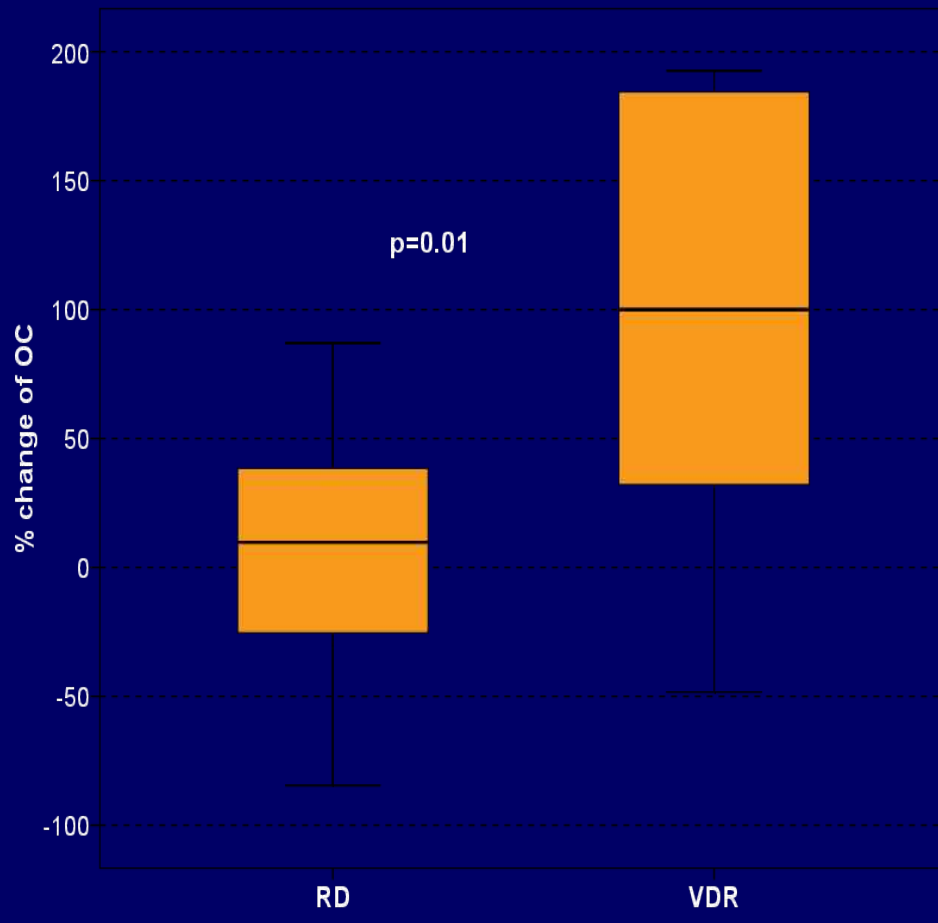
Effect of RD and VRD on Bone Formation



after 6 cycles of therapy



after 6 cycles of therapy

Terpos et al. ASH 2009

Conclusions

- Bone disease is a frequent and debilitating complication of myeloma
- Preclinical and clinical data indicate that bortezomib reduces bone resorption
- Bortezomib increases also bone formation due to reduction of Dkk-1, sclerostin and possible other osteoblast inhibitors
- Increases on BMD and healing of the lytic lesions in subsets of myeloma patients. Long-term bortezomib studies with clinical endpoints (SRE and BMD) are needed.

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