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Role of RANK Ligand in myeloma bone disease

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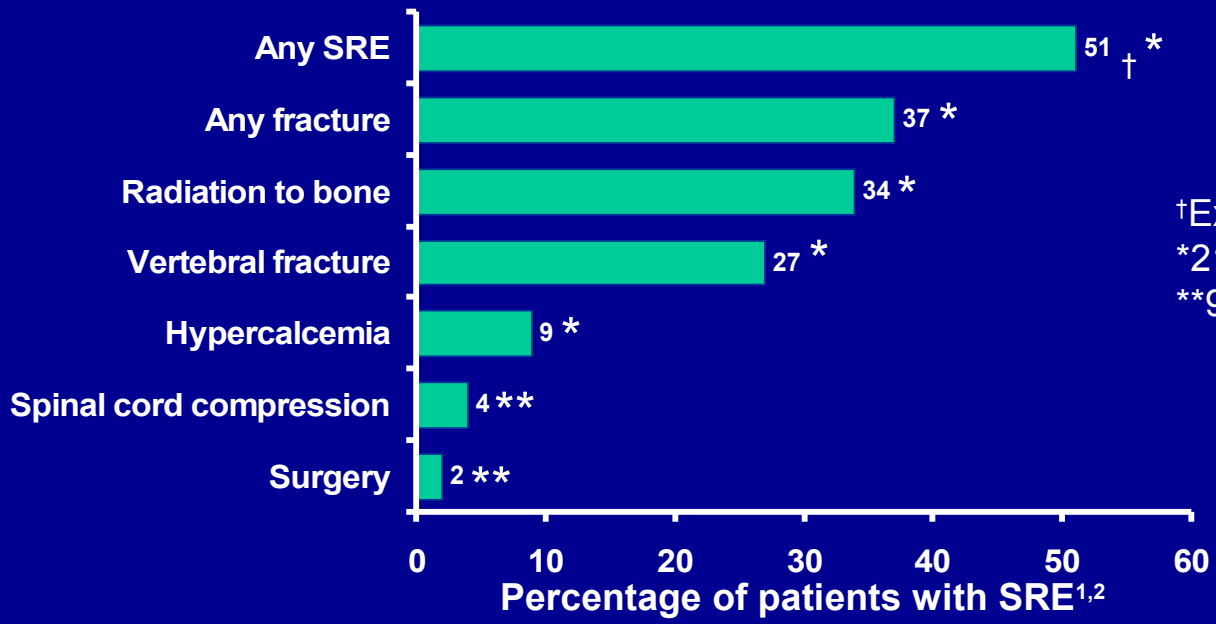
Myeloma bone disease

S. N., 1842, London

Bone metastasis is a catastrophic complication for most patients with cancer. It causes intractable pain and other clinical problems such as fracture after trivial injury, spinal cord compression, and hypercalcemia

Skeletal-related events (SRE) in MM



†Excl. hypercalcaemia
*21-month data
**9-month data

1. Berenson R et al. J Clin Onc 1998;16:593–602; 2. Berenson R et al. N Engl J Med 1996;488–493
Illustrations from http://www.kyphon.com/us/Physician.aspx?contentid=60&siteid=1 (accessed 28 May 2009)

Myeloma bone disease is an important feature of MM concerning the quality of life

In collaboration with the QLG of EORTC we developed a validated disease-specific questionnaire module (the QLQ-MY20) assessing the quality of life of patients with multiple myeloma.

This questionnaire module can be used together with the ‘core questionnaire’ QLQ-C30 to evaluate the quality of life of myeloma patients in clinical trials and is change-sensitive

Cocks K et al. Eur J Cancer 2007;43:1670–1678
Chow E et al. Eur J Cancer 2009;45:1146–1152

Increased bone resorption is an independent prognostic factor for survival in MM

ICTP: carboxy-terminal telopeptide of type-1 collagen

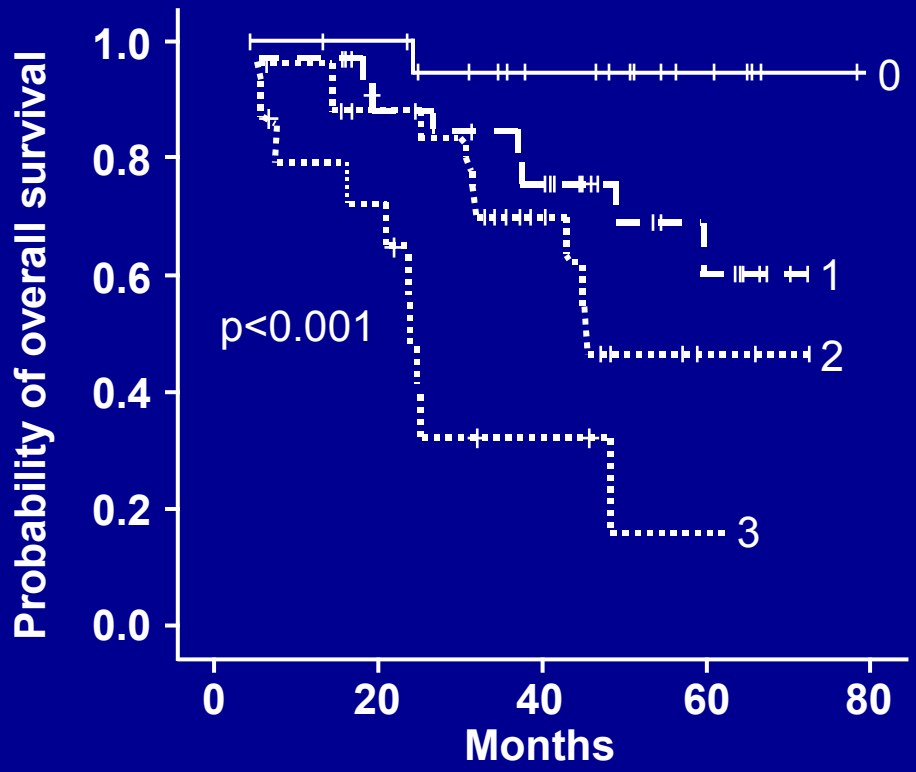
Parameter	Univariate analysis (log-rank)			Multivariate analysis (Cox regression)		
	P-value	Hazard ratio	(95% CI)	P-value	Hazard ratio	(95% CI)
ICTP>reference limit	<0.001	11.75	(2.78–49.50)	<0.001	9.17	(2.14–39.34)
ß2M ≥3.5 mg/L	0.005	3.06	(1.35–8.95)	0.012	2.80	(1.22–6.24)
del(13q14) FISH positive	0.043	2.12	(1.00–4.46)	0.015	2.49	(1.07–5.77)
High-dose chemotherapy	<0.001	0.22[a]	(0.09–0.52)	<0.001	0.18[a]	(0.07–0.44)
Albumin <3.5 g per 100 mL	0.015	2.50	(1.16–5.40)	NS	–	
BMPC ≥33%	NS	–				

MM, multiple myeloma; ß2M, ß2-microglobulin; FISH, fluorescence *in situ* hybridisation; BMPC, bone marrow plasma cells; CI, confidence interval

Jakob C et al. Leukemia 2008;22:1767–1772

Increased bone resorption is an independent prognostic factor for survival in MM

Combined ISS-ICTP score				ISS			
Risk factors (risk group)	Patients (%)	5-year OS	Hazard ratio (95% CI)	Stage	Patients (%)	5-year OS	Hazard ratio (95% CI)
0 (very low)	21	95	1.00 (reference)				
1 (low)	38	64	5.78 (0.72–46.27)	I	38	72	1.00 (reference)
2 (intermediate)	26	46	11.03 (1.40–86.72)	II	35	62	1.56 (0.58–4.21)
3 (high)	15	22	29.02 (4.19–265.43)	III	27	35	3.20 (1.27–8.00)



Carboxy-terminal telopeptide of type-1 collagen (ICTP) in previously untreated patients with ‘symptomatic’ MM

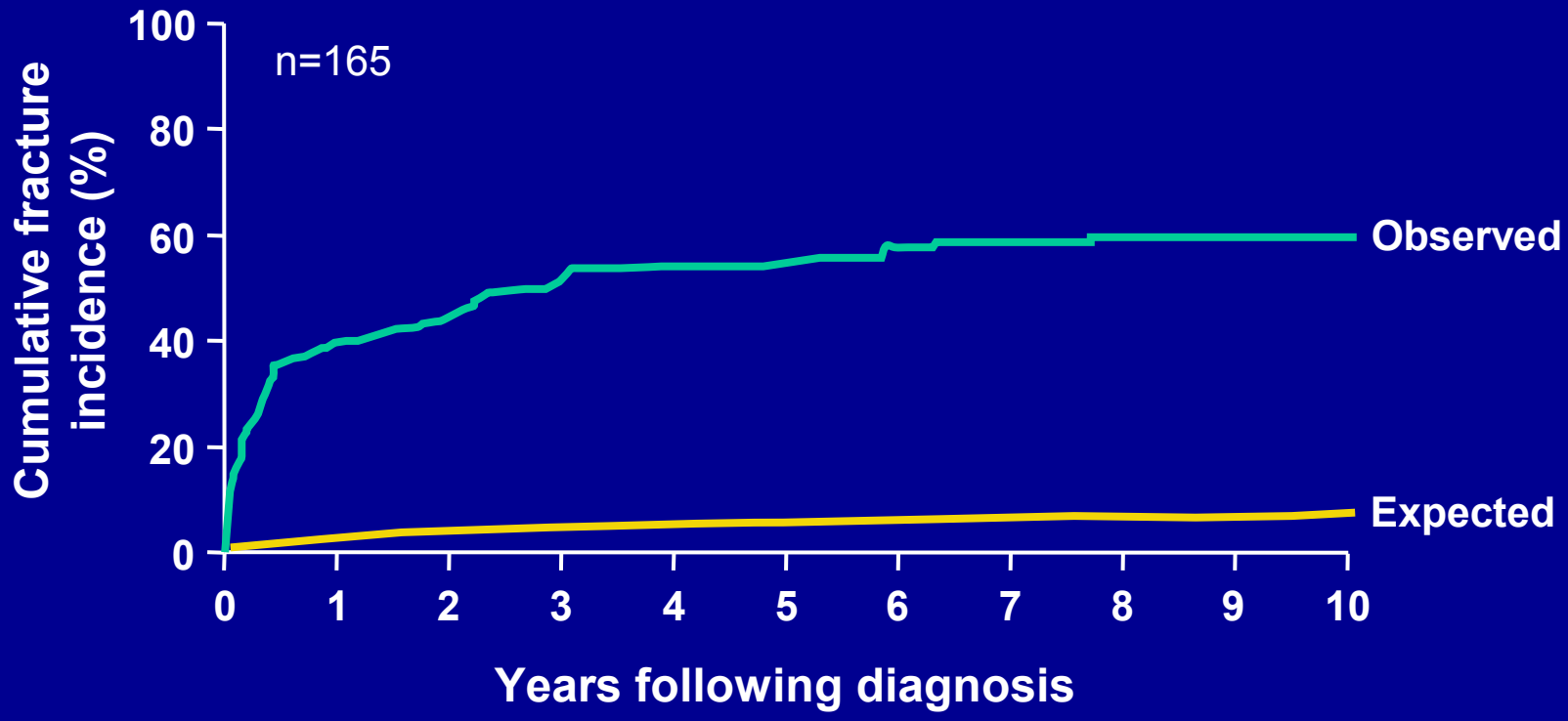
Jakob C et al. Leukemia 2008;22:1767–1772

Myeloma bone disease

- The overall prevalence of lytic bone lesions in MM is 85%
- At diagnosis, more than two thirds of patients with multiple myeloma present with bone pain
- Sudden pain may indicate the collapse of ≥1 vertebral body
- Sudden back pain in individuals ≥40 years of age should be investigated as a possible sign of multiple myeloma

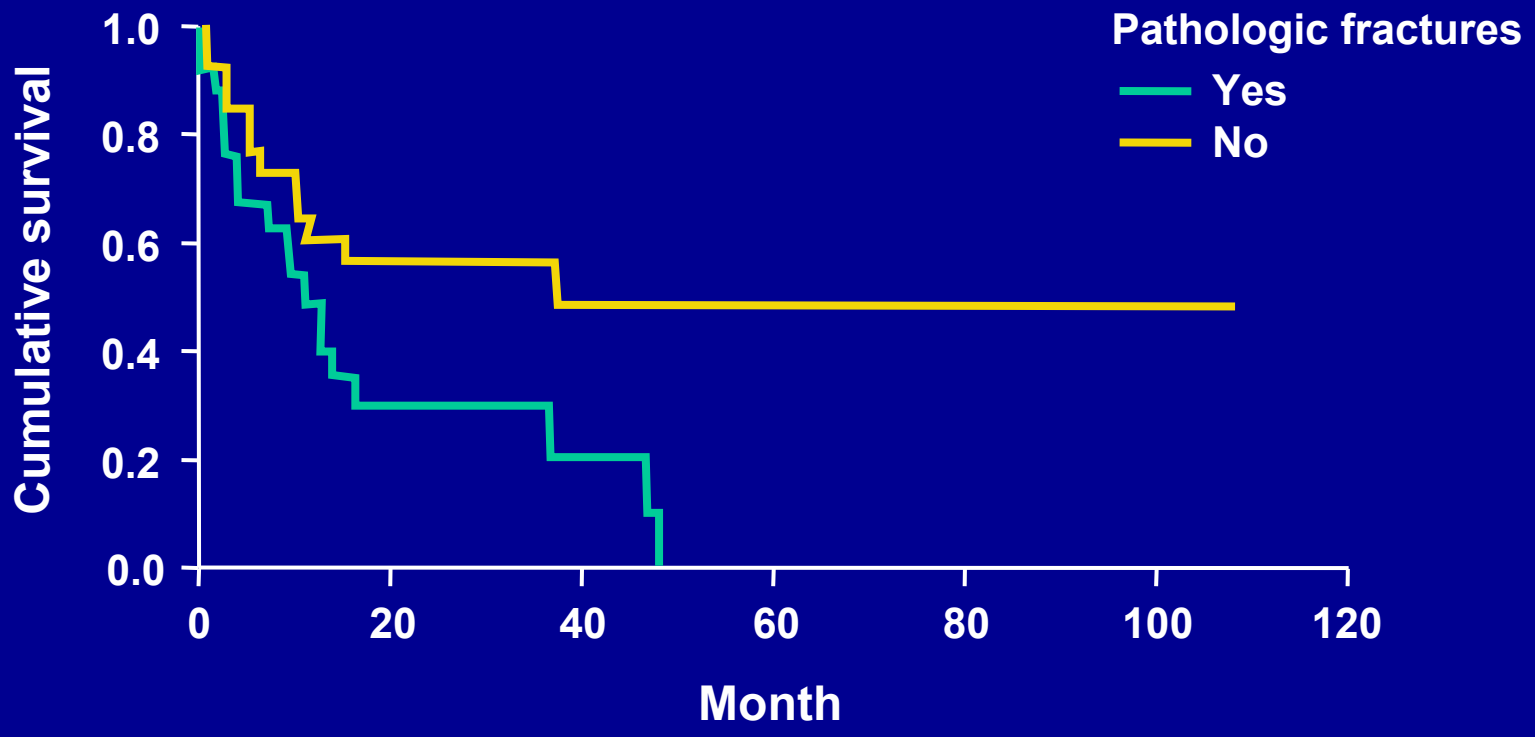
Sezer O. Oncologist 2009;14:276–283

Fracture incidence in MM



Melton LJ et al. J Bone Miner Res 2005;20:487–493

Pathologic fractures and survival in MM



In a recent study, OS was 17.6 months in patients with multiple myeloma and pathologic fractures and 57.3 months in those without pathologic fractures (p=0.03, n=49)

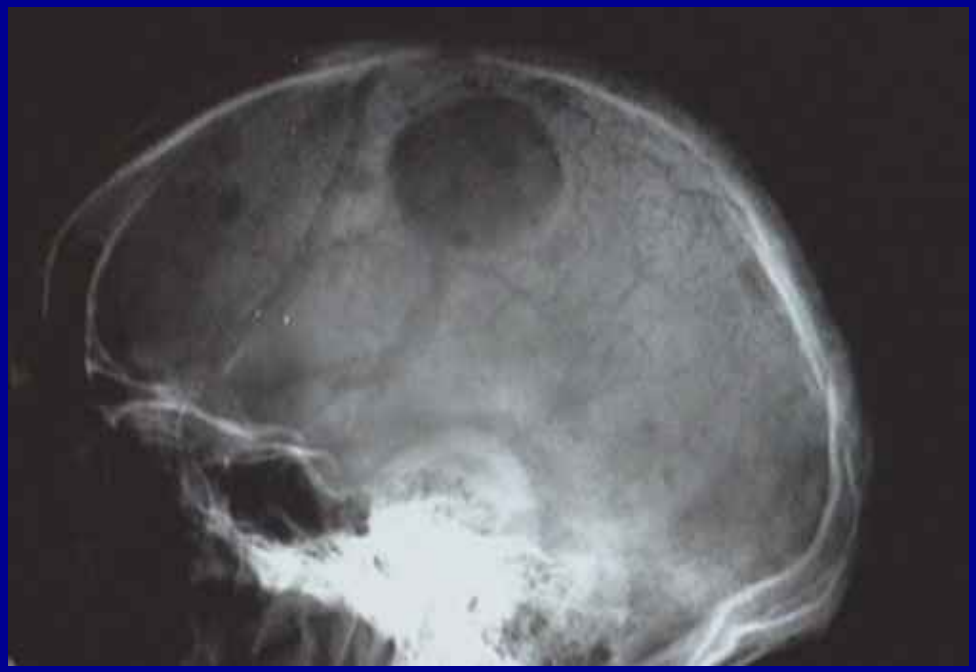
Sönmez M et al. J Exp Clin Cancer Res 2008;27:11

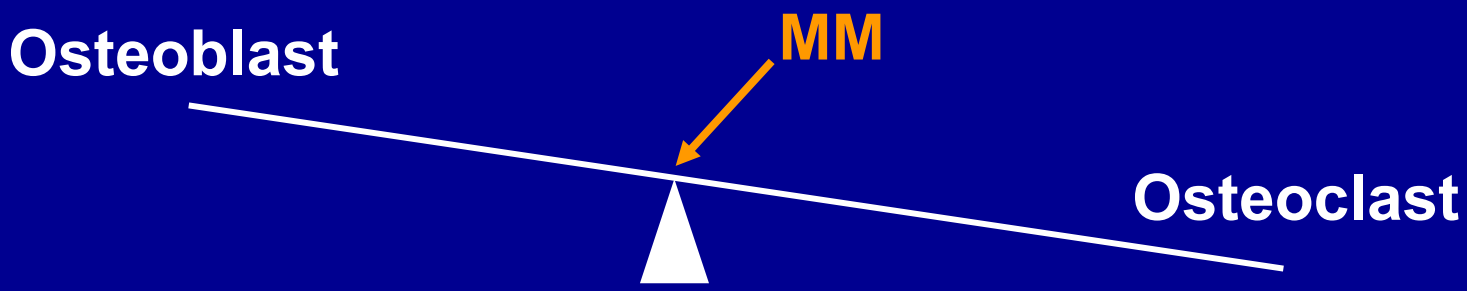
Economic consequences of SREs

- EU: medical costs directly attributed to SRE: €6,973 (range: €1,187 to €40,948)[1]
- US: medical costs directly attributed to SRE: US$9,783 per patient[2]
- SREs occur frequently and can potentially increase average healthcare costs by ~$52,000 per patient per year[3]

1. Groot MT et al. Proc Am Soc Clin Oncol 2002;21:201b
2. Mckiernan JM et al. Proc Am Soc Clin Oncol 2004;23:531
3. Delea T et al. Bone 2004;34:S86

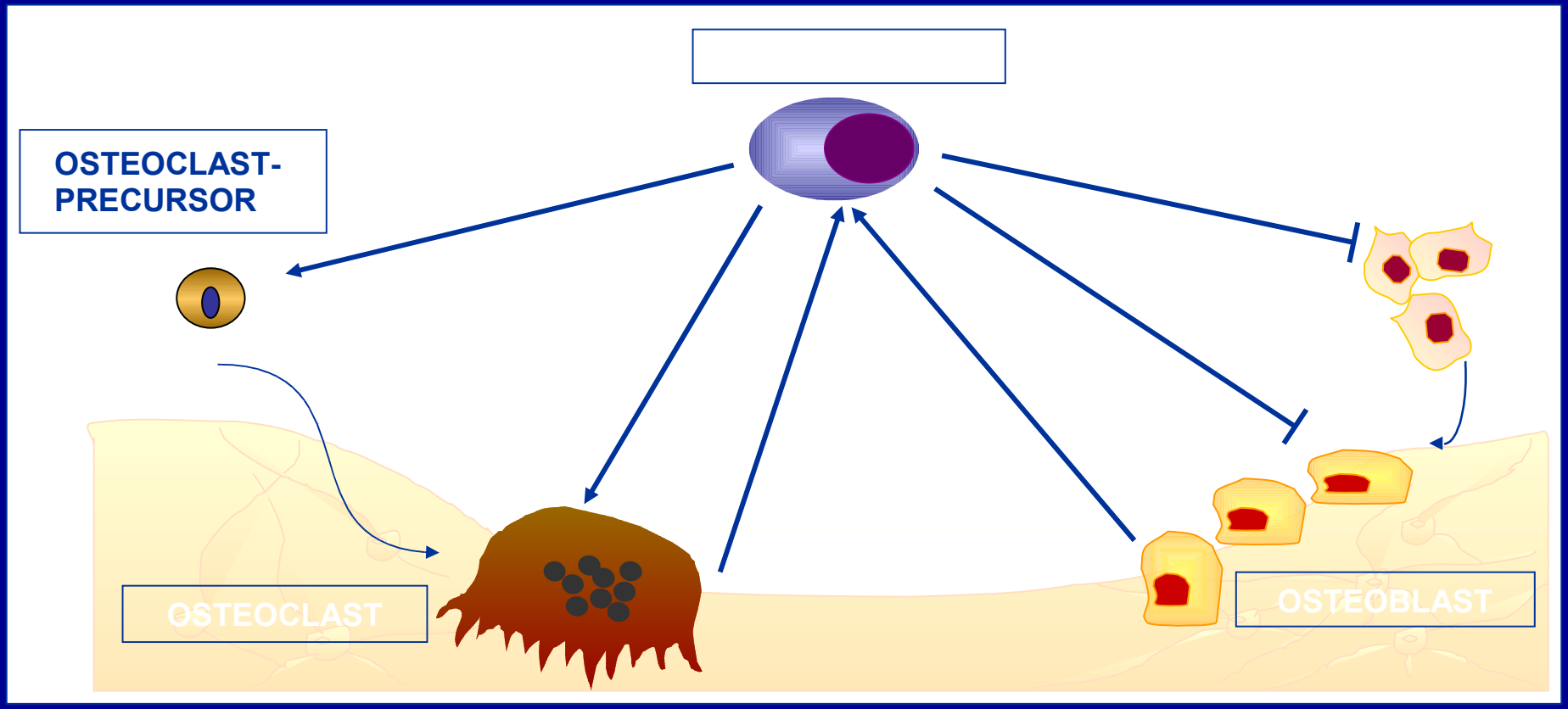
Biology of myeloma bone disease





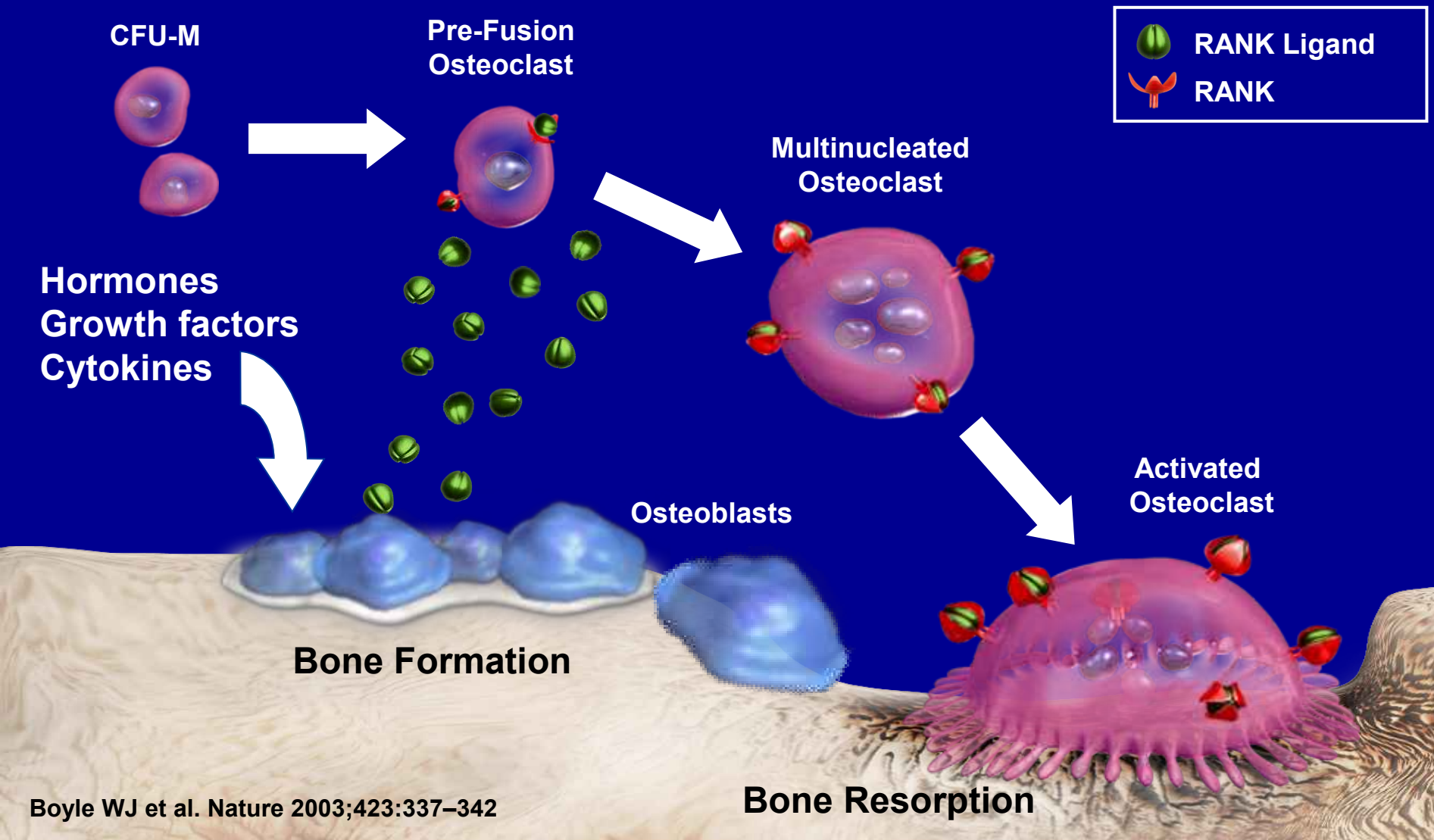
Heider U et al. Biochem Biophys Res Commun 2005;338:687–693
Heider U et al. Eur J Cancer 2006;42:1544–1553

Osteoclast activation and osteoblast inhibition in MM: a vicious cycle



Sezer O. Oncologist 2009;14:276–283
Roodman GD. N Engl J Med 2004;350:1655–1664

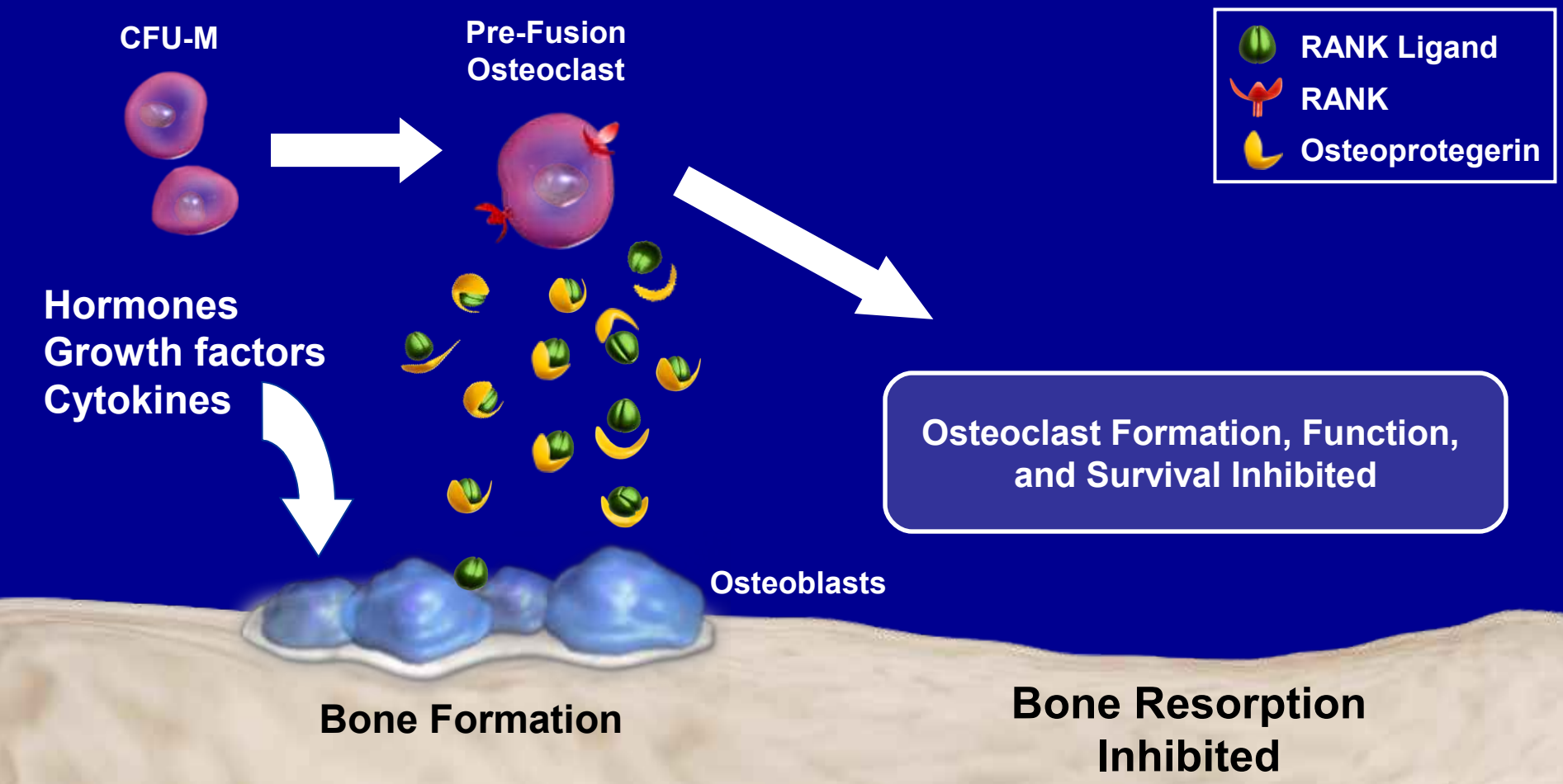
RANK Ligand is an essential mediator of osteoclast formation, function and survival



Boyle WJ et al. Nature 2003;423:337–342

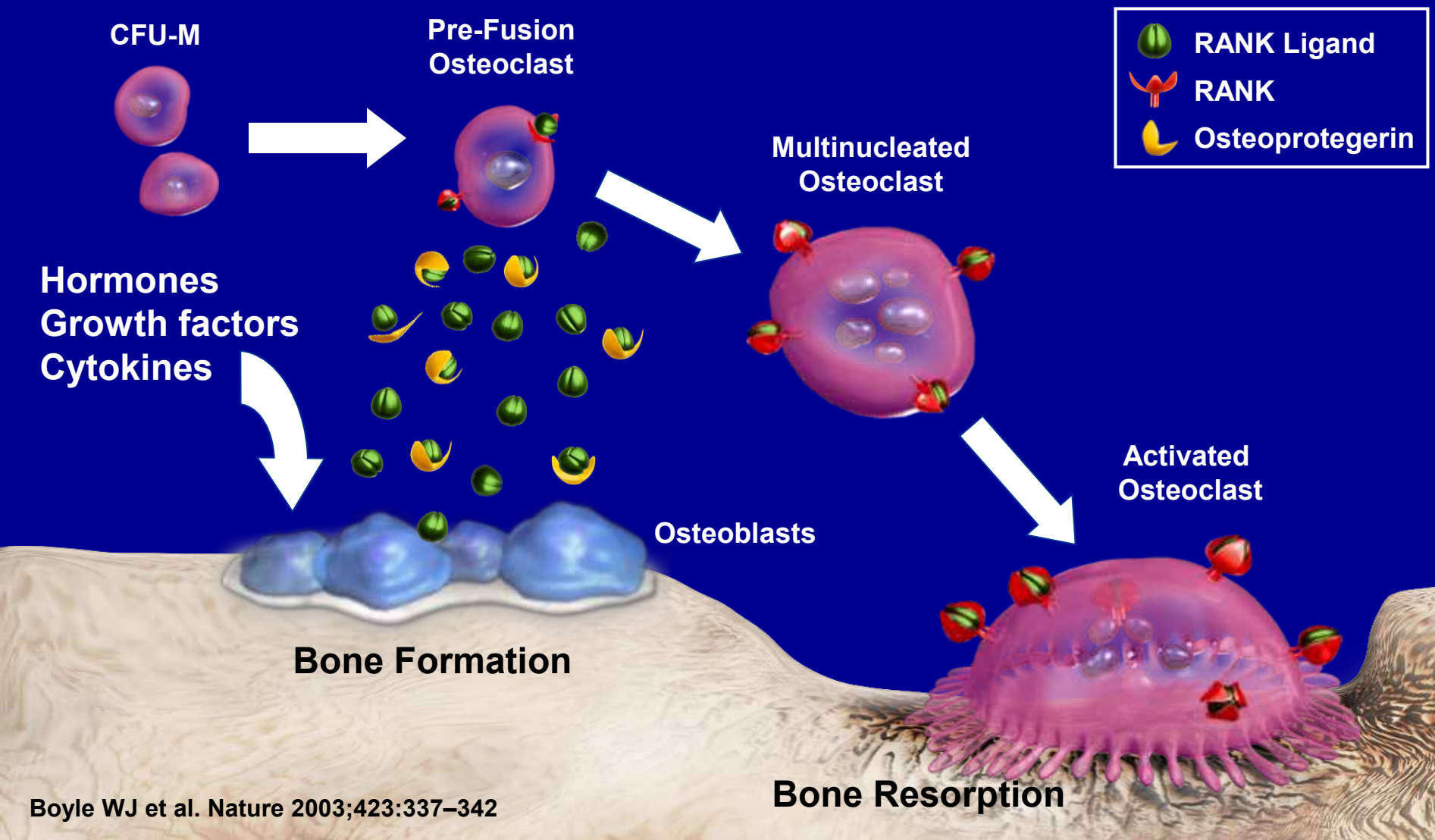
OPG inhibits RANK Ligand binding to RANK

OPG: Osteoprotegerin, decoy receptor for RANK Ligand



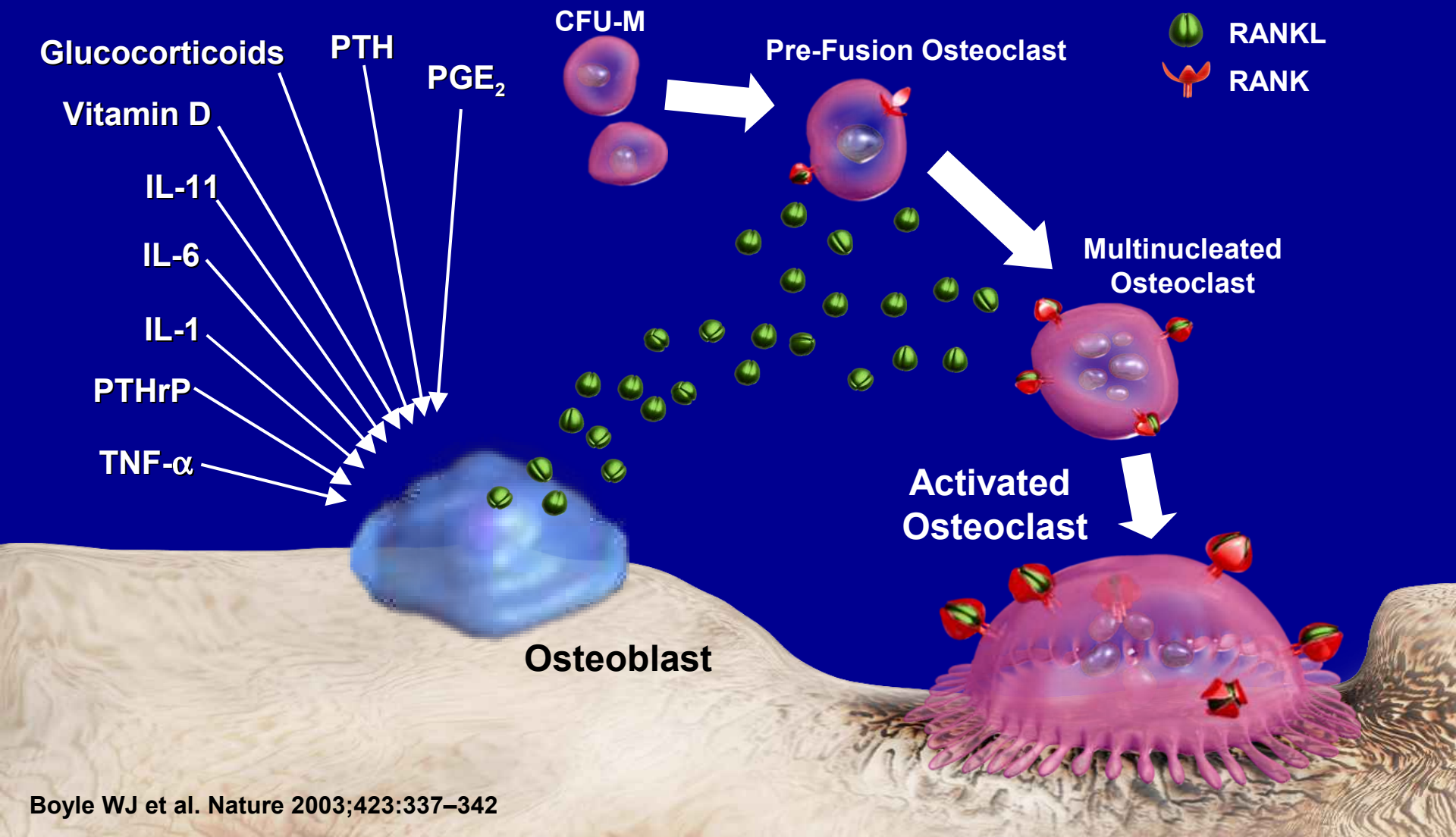
Boyle WJ et al. Nature 2003;423:337–342

When RANK Ligand overwhelms OPG, bone resorption becomes excessive



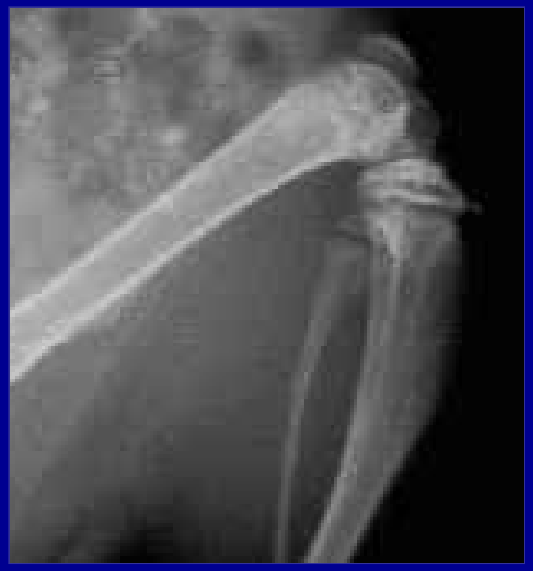
Boyle WJ et al. Nature 2003;423:337–342

Many factors stimulate expression of RANK Ligand

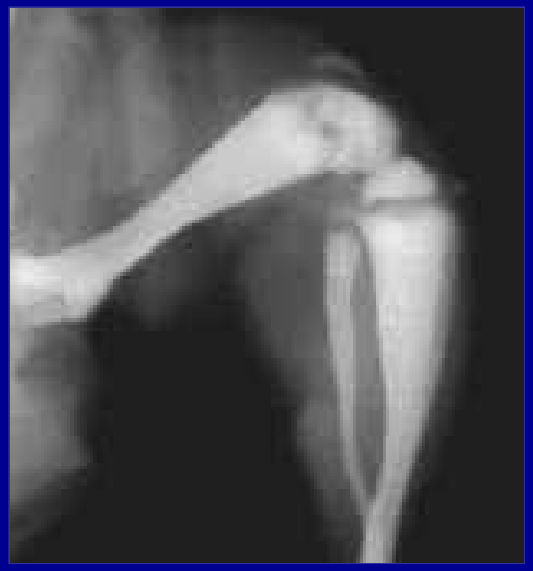


Boyle WJ et al. Nature 2003;423:337–342

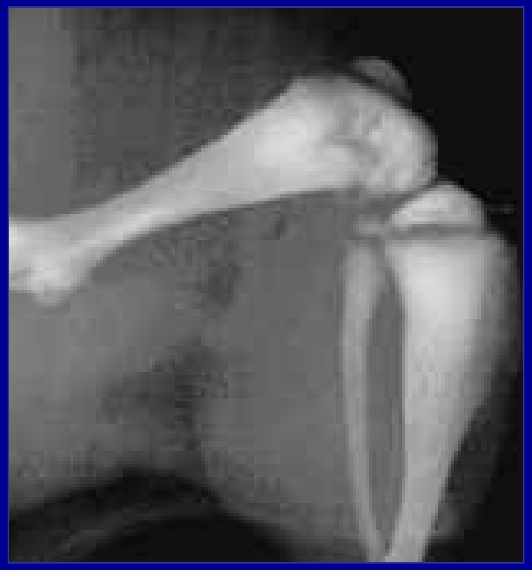
Role of RANK and RANK Ligand in the regulation of bone mineral density



Normal



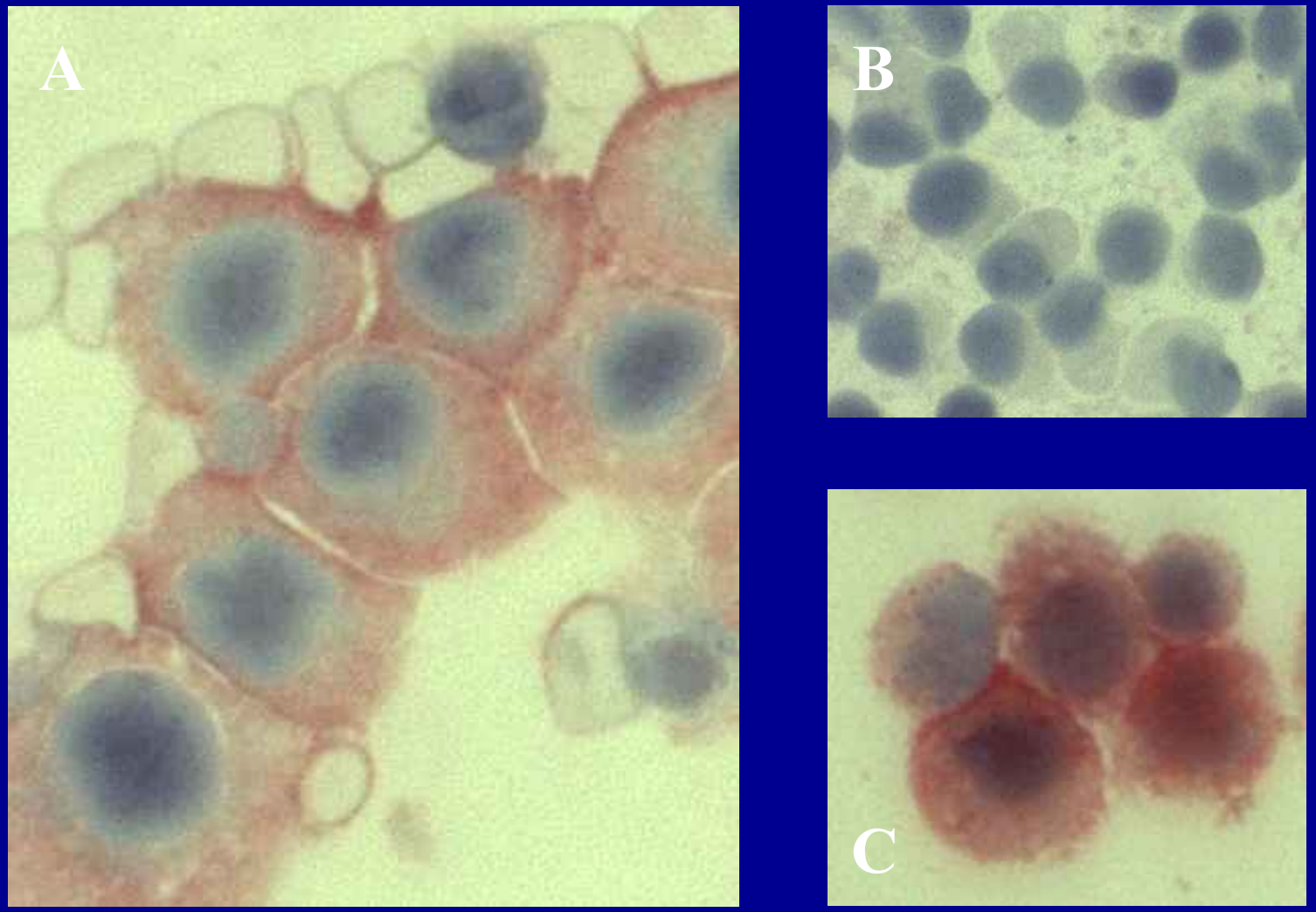
Absence of RANK Ligand[1]



Absence of RANK[2]

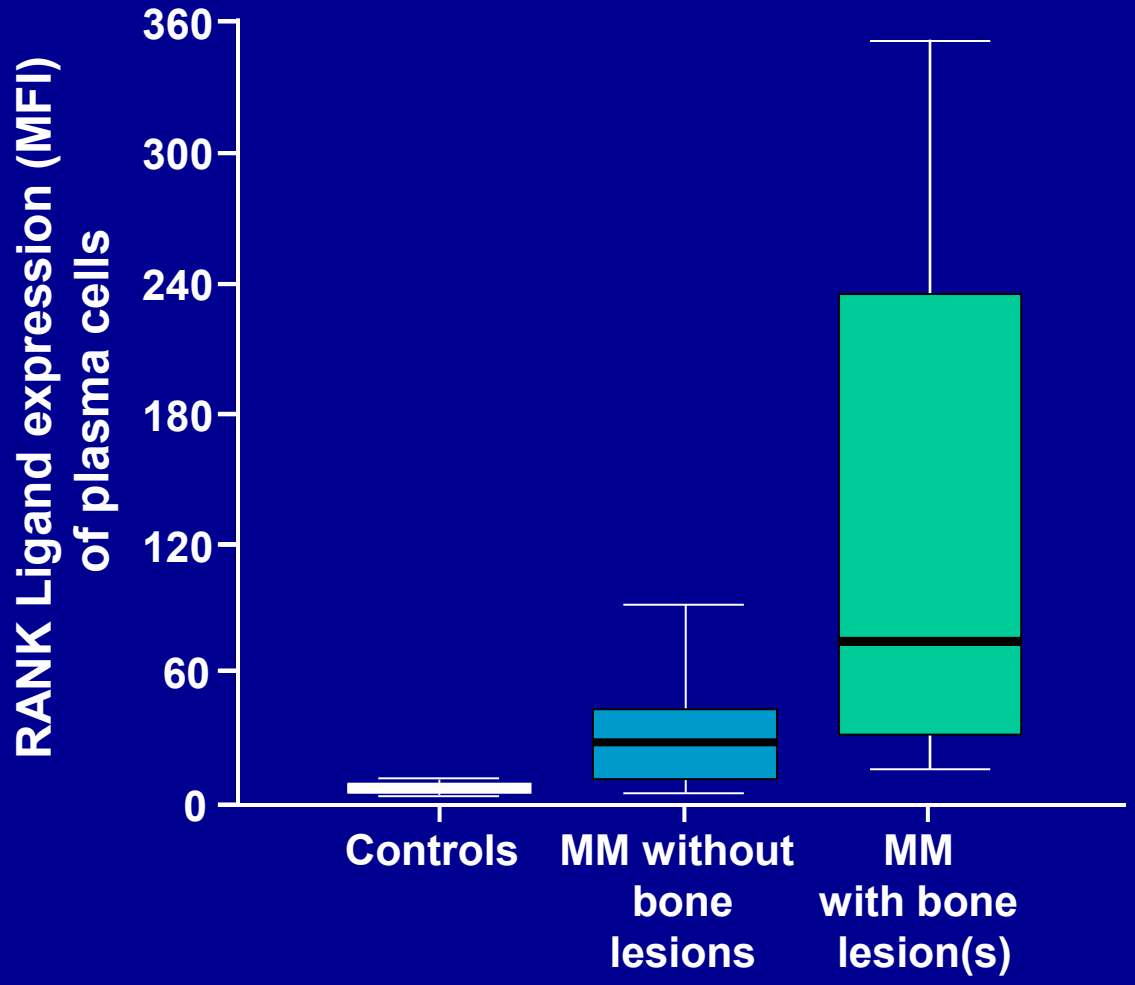
1. Kong YY et al. Nature 1999;402:304–309
2. Li J et al. Proc Natl Acad Sci USA 2000;97:1566–1571

RANK Ligand expression in myeloma cells



Sezer O et al. Blood 2002;99:4646–4647

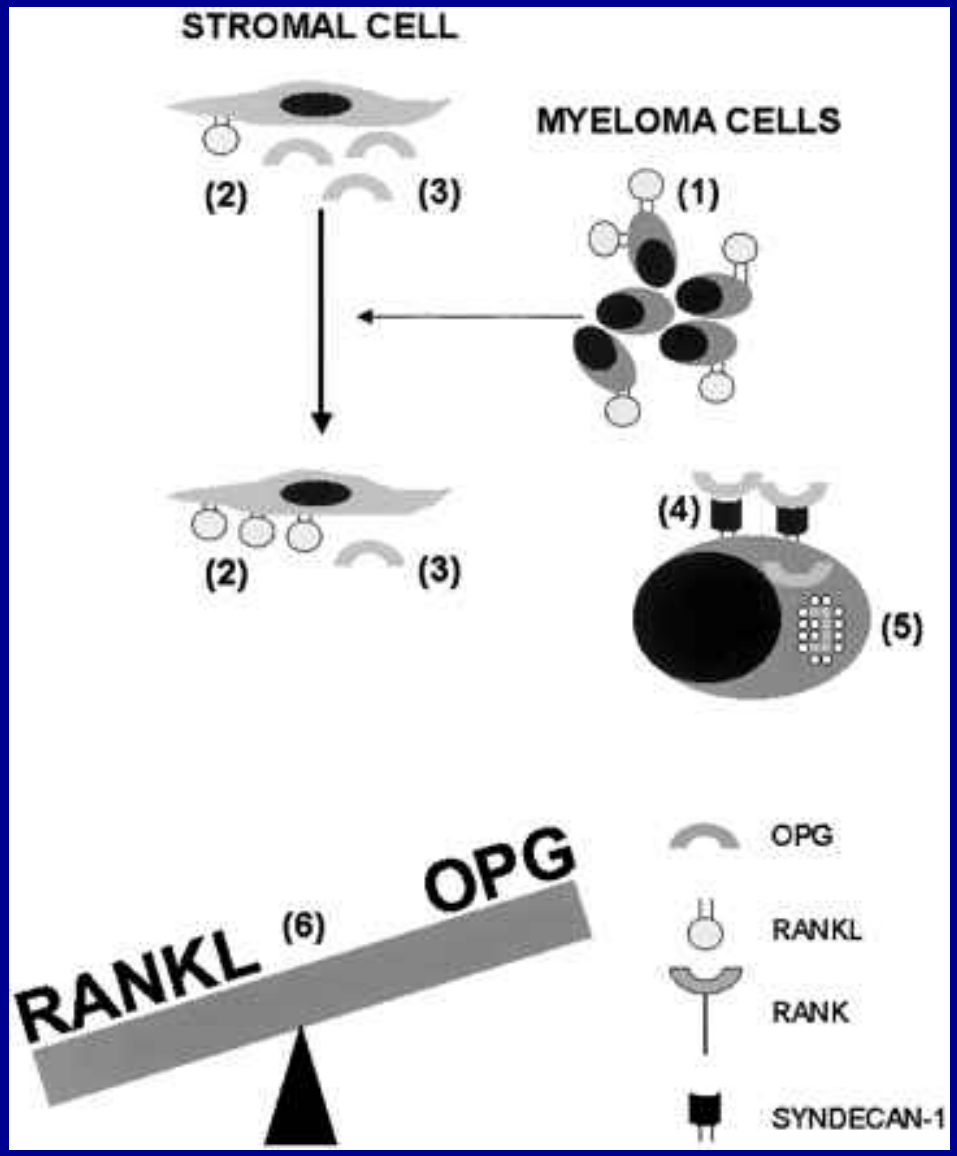
RANK Ligand expression correlates with presence of lytic lesions in MM



p<0.0005

Heider U et al. Clin Cancer Res 2003;9:1436–1440

RANK Ligand/OPG in multiple myeloma



Myeloma cells express RANK Ligand (1) and cause bone marrow-residing stromal cells to overexpress RANK Ligand (2). In addition, myeloma cells inhibit OPG production by stromal cells (3). Syndecan (CD138) is expressed on the surface of myeloma cells and binds the heparin-binding domain of OPG (4), thus facilitating internalisation and lysosomal degradation of OPG (5). The physiologic balance between RANK Ligand and OPG is tilted by these combined effects (6), and the ensuing enhanced RANK Ligand-to-OPG ratio promotes osteoclast formation and activation, which is responsible for osteolysis, hypercalcemia, fractures, and pain

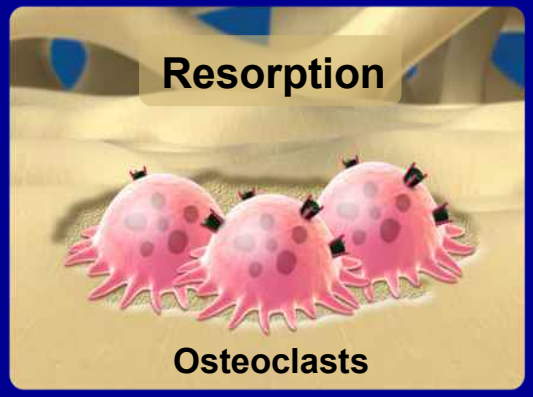
Sezer O et al. Blood 2003;101:2094–2098

Imaging in multiple myeloma

- Annual skeletal survey recommended to monitor for bony lesions
- Conventional radiography still remains the ‘gold standard’, but plain films are positive only if ca. 50% of trabecular bone is lost. CT without contrast is more sensitive
- Urgent MRI (or CT if MRI is not available) is the diagnostic procedure of choice to assess suspected cord compression
- Bone scans are not recommended in MM

Dimopoulos M et al. International Myeloma Working Group Imaging Guidelines Leukemia 2009;epub ahead of print

Bone markers in multiple myeloma

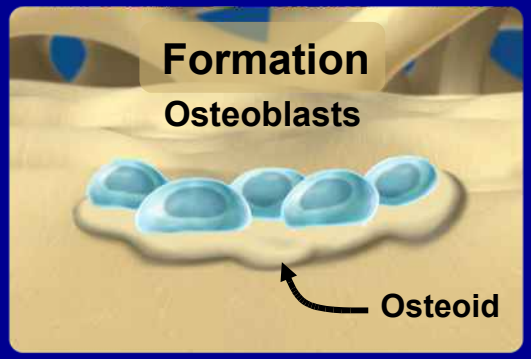


Collagen degradation

- Urinary N-telopeptide of type I collagen (uNTx)
- Serum Carboxy-terminal telopeptide of type I collagen (ICTP)
- Serum C-telopeptide of type I collagen (sCTx)

Osteoclasts

- Tartrate-resistant acid phosphatase (TRAP)



Osteoblasts

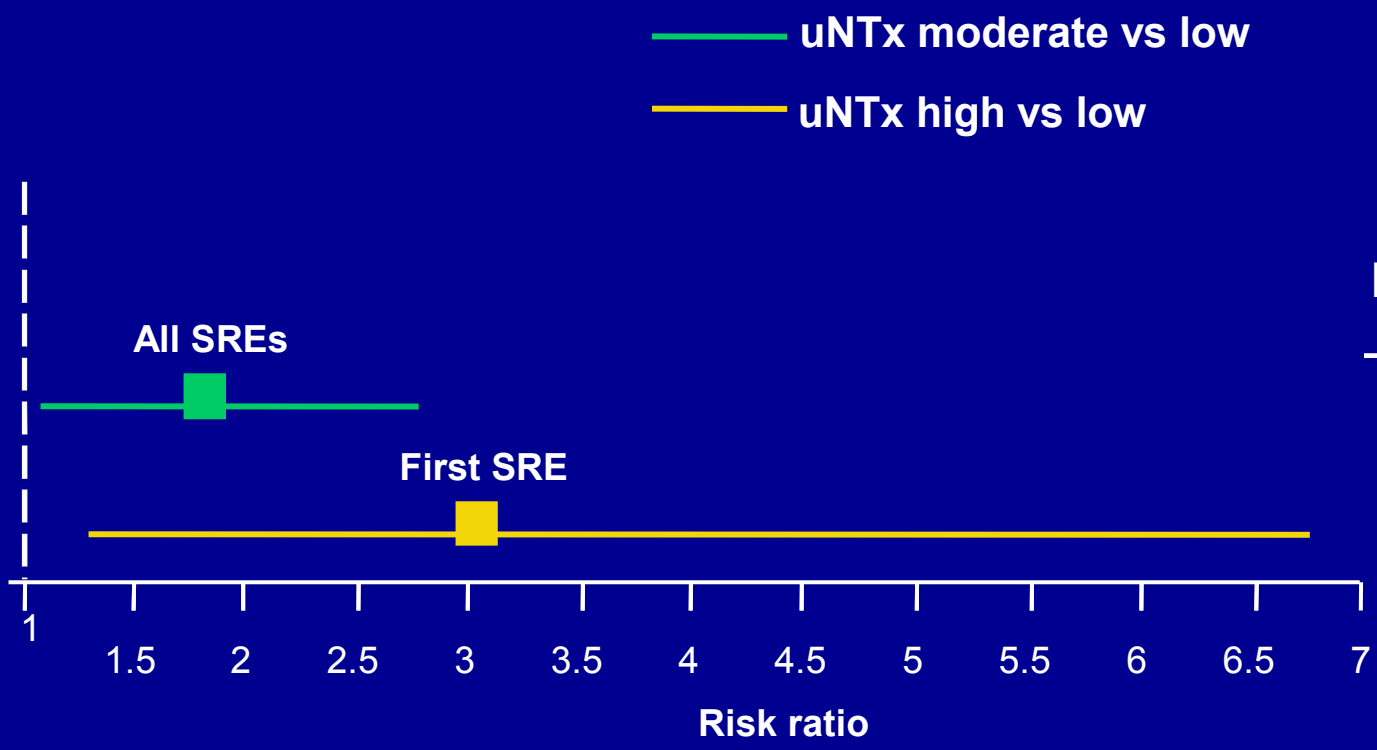
- Bone-specific alkaline phosphatase (BALP)
- Osteocalcin (OC)

Collagen production

- N-terminal propeptide of type I collagen (PINP)

Heider U et al. Eur J Cancer 2006;42:1544–1553

Relative risk of SREs depends on level of uNTx in MM



	Risk ratio	p value
All SREs	1.75	0.016
First SRE	3.01	0.008

Coleman RE et al. J Clin Oncol 2005;23:4925–4935

Current management of myeloma bone disease

- Bisphosphonates: Start when bone disease diagnosed. Consider stopping at 2 years if in plateau or remission
- Systemic therapy of MM (CRAB)
- Orthopedic interventions: surgery for fracture or impending fracture, kyphoplasty or vertebroplasty
- Radiotherapy
- Analgesics

European Myeloma Network Recommendations, Ann Oncol 2009; doi:10.1093/annonc/mdn796

Summary

- Myeloma is characterized by a unique form of bone disease with lytic bone destruction, which is not followed by reactive bone formation (uncoupling)
- Bone disease is found in more than two thirds of patients with multiple myeloma and is a major source of morbidity, mortality and cost
- Close monitoring and prompt treatment of bone disease are important in optimal management of patients with multiple myeloma
- RANK Ligand is a key molecule in osteoclast activation in myeloma and other diseases, thus results of studies with RANK Ligand antibody are eagerly awaited

Sezer O. Oncologist 2009;14:276–283

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