BONE HEALTH IN MULTIPLE MYELOMA

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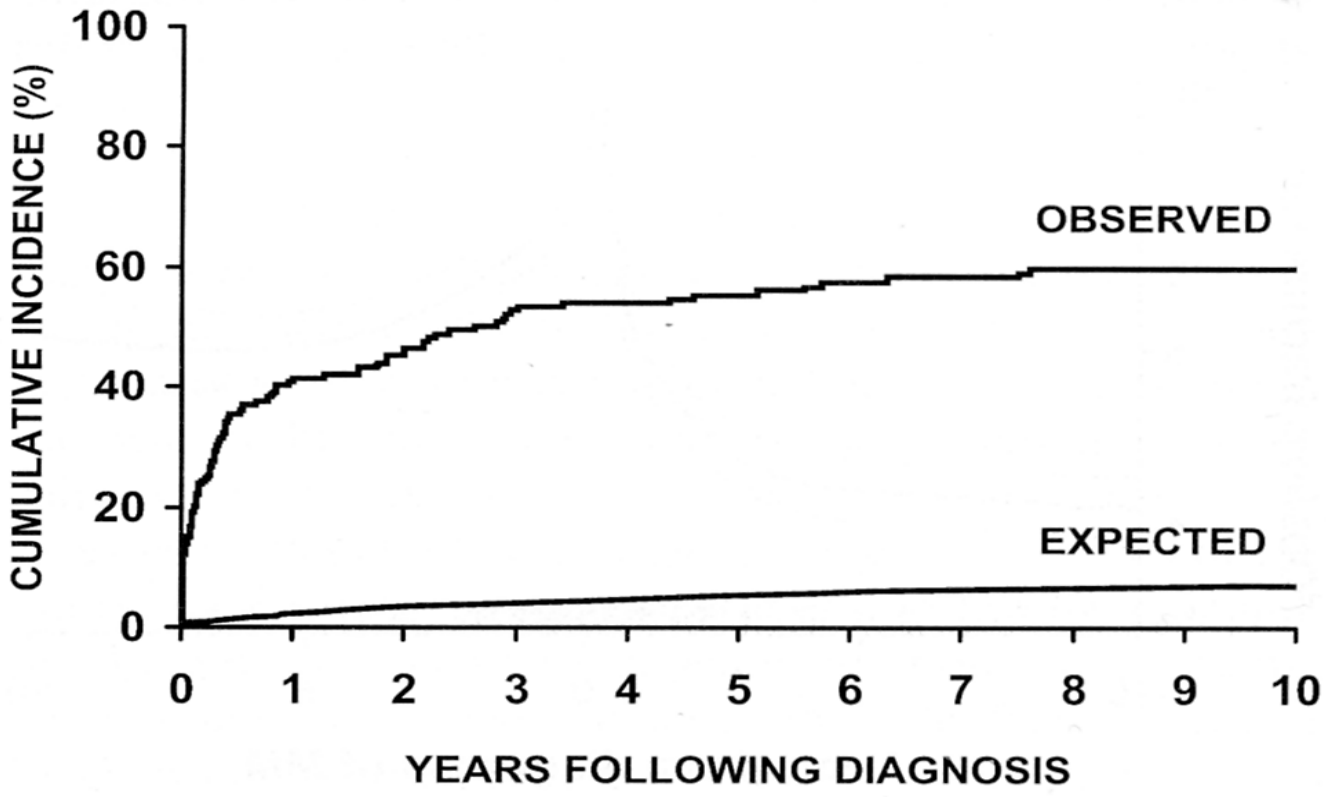
LEARNING OBJECTIVES

- Describe the physiologic/molecular bases for myeloma bone disease
- Define how treatment with a bisphosphonate differs from treatment with denosumab and the potential for subsequent fracture risk with therapy discontinuation
- Recognize the skeletal significance of MGUS

SKELETAL LESIONS IN MYELOMA

- 80-90% of patients with myeloma have bone involvement
  - Spine, ribs, pelvis, skull, femur, humerus
- Severe Features
  - Intractable pain
  - Increased fracture risk
  - Hypercalcemia (high blood calcium)
  - Risk for nerve compression
- Also generalized bone loss (osteoporosis)

FRACTURE INCIDENCE IN 168 PATIENTS WITH MULTIPLE MYELOMA



Melton et al. (2004) J Bone Mineral Res. 20:487

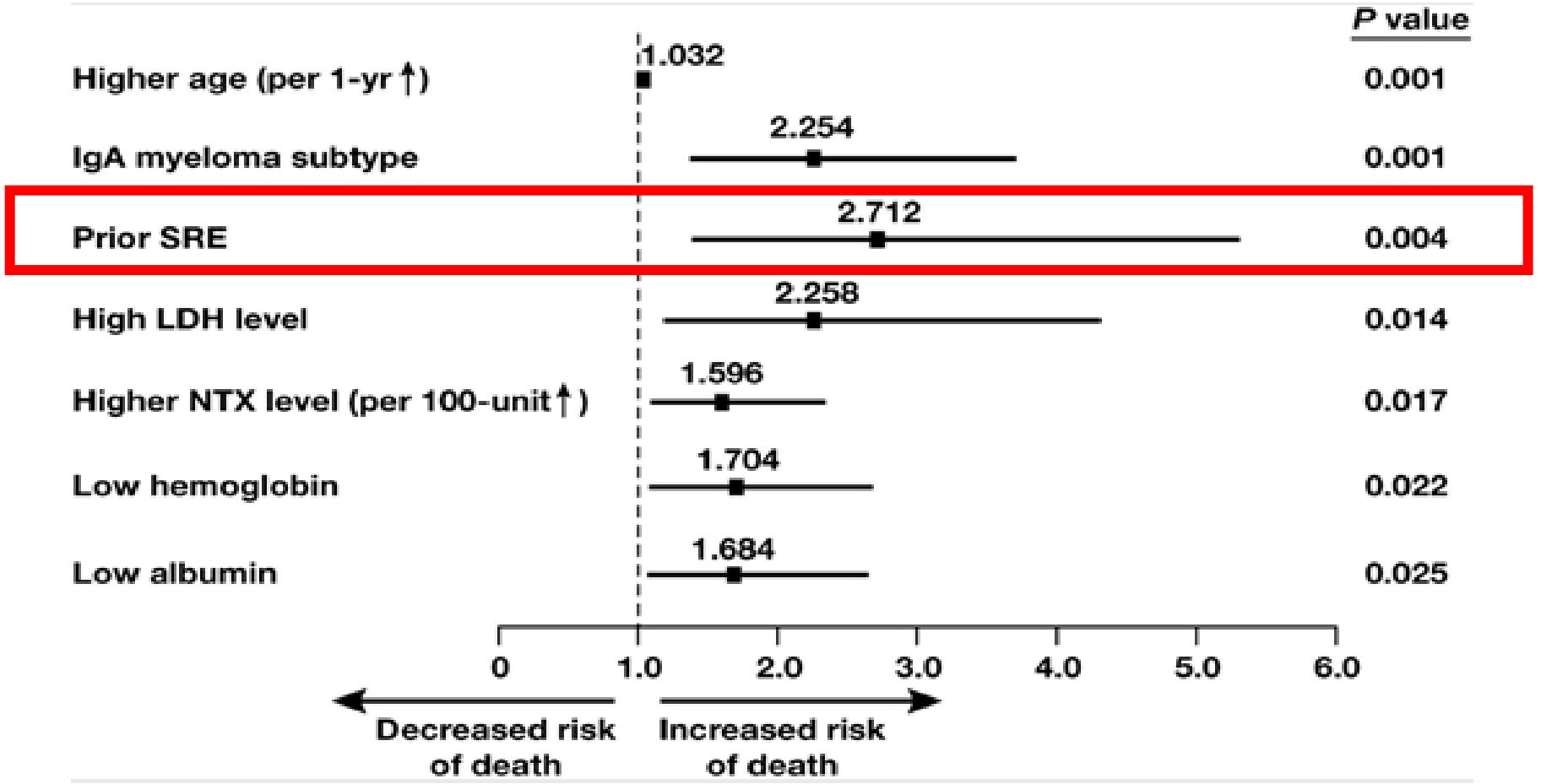
Melton et al J Bone Miner Res. 2005; 20:487-93.

SITE-SPECIFIC FRACTURE RISK IN MYELOMA

Site	Relative Risk
Thoracic/lumbar vertebrae	33
Ribs	15
Clavicle/scapula/sternum	13
Cervical vertebrae	7.4
Arm (other than humerus)	6.9
Pelvis	6.1
Humerus	1.8

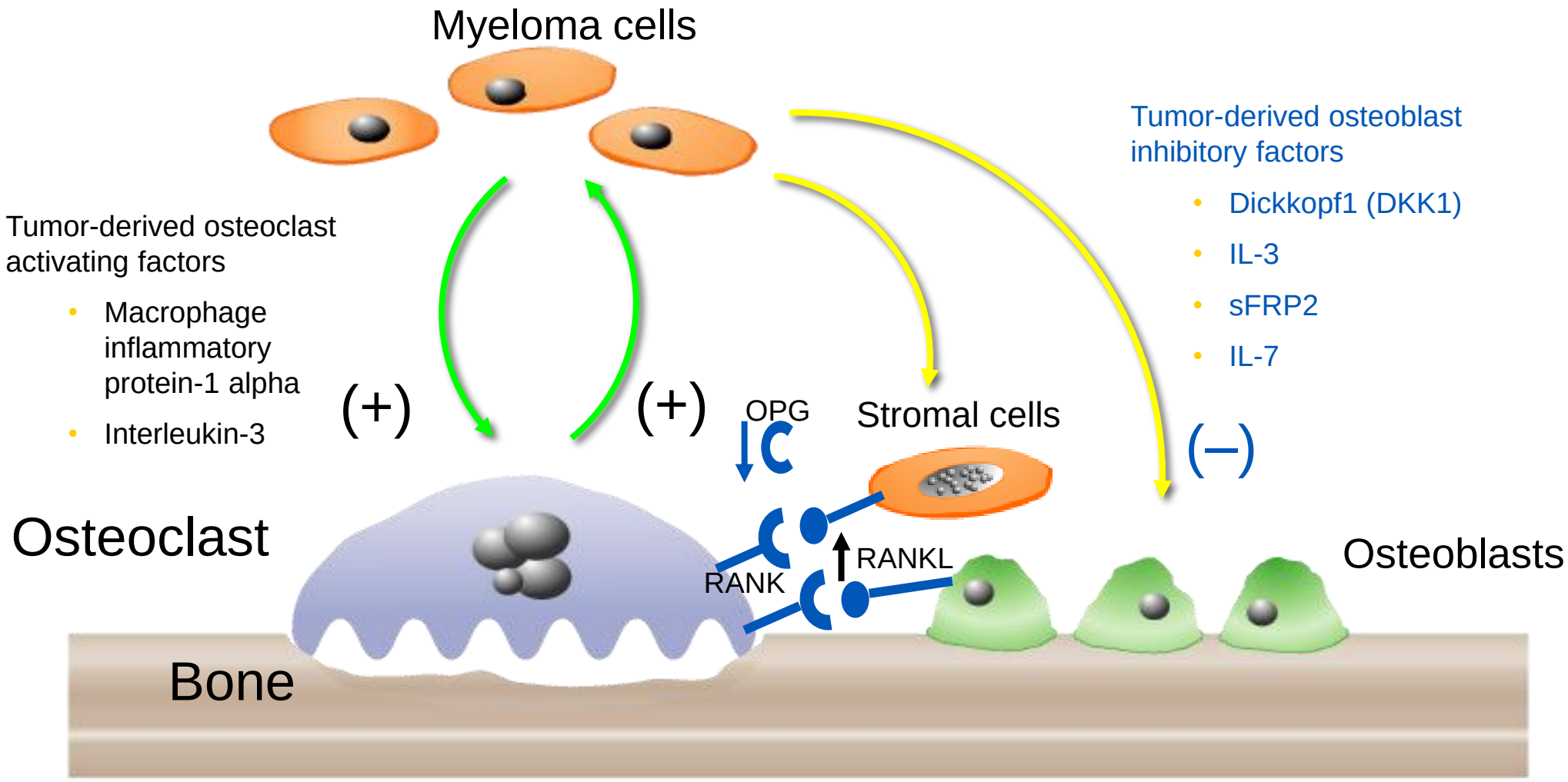
Melton et al. (2004) J Bone Mineral Res. 20:487

SIGNIFICANT FACTORS FOR INCREASED RISK OF DEATH IN MULTIPLE MYELOMA



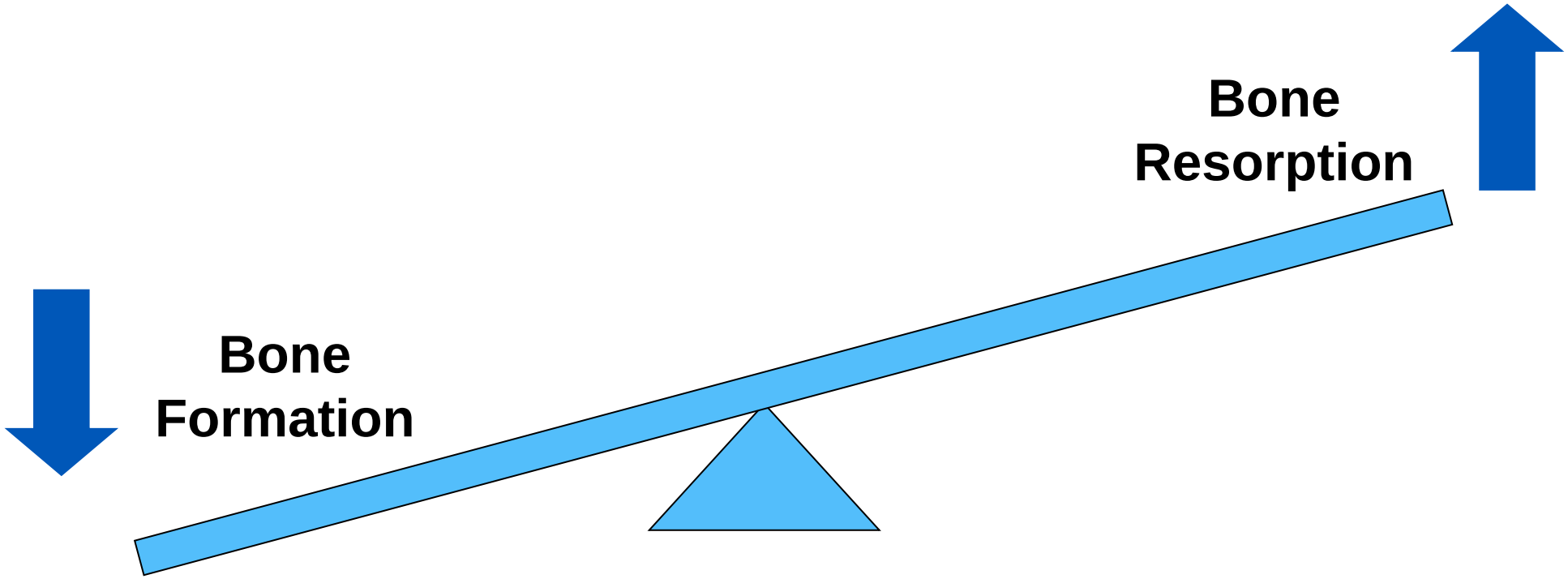
Terpos et al. Leukemia 2010; 24:1043

MYELOMA BONE DISEASE



Adapted from Roodman. N Engl J Med. 2004;32:290-292.

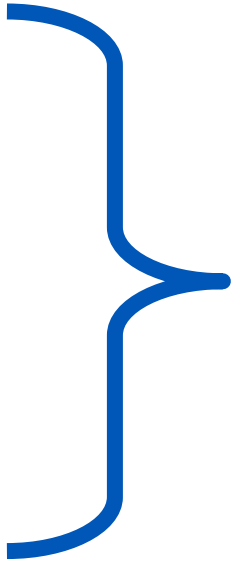
MYELOMA CELLS DISRUPT BONE REMODELING



Net Result = Bone Loss

CLINICAL CONSEQUENCES OF MYELOMA BONE DISEASE

- Pathological fractures
  - Non-vertebral
  - Vertebral compression
- Spinal cord compression/collapse
- Radiation therapy
- Surgery to bone
- Hypercalcemia
- Bone pain
- Use of analgesics
- Quality-of-life effects
- Survival



*SREs

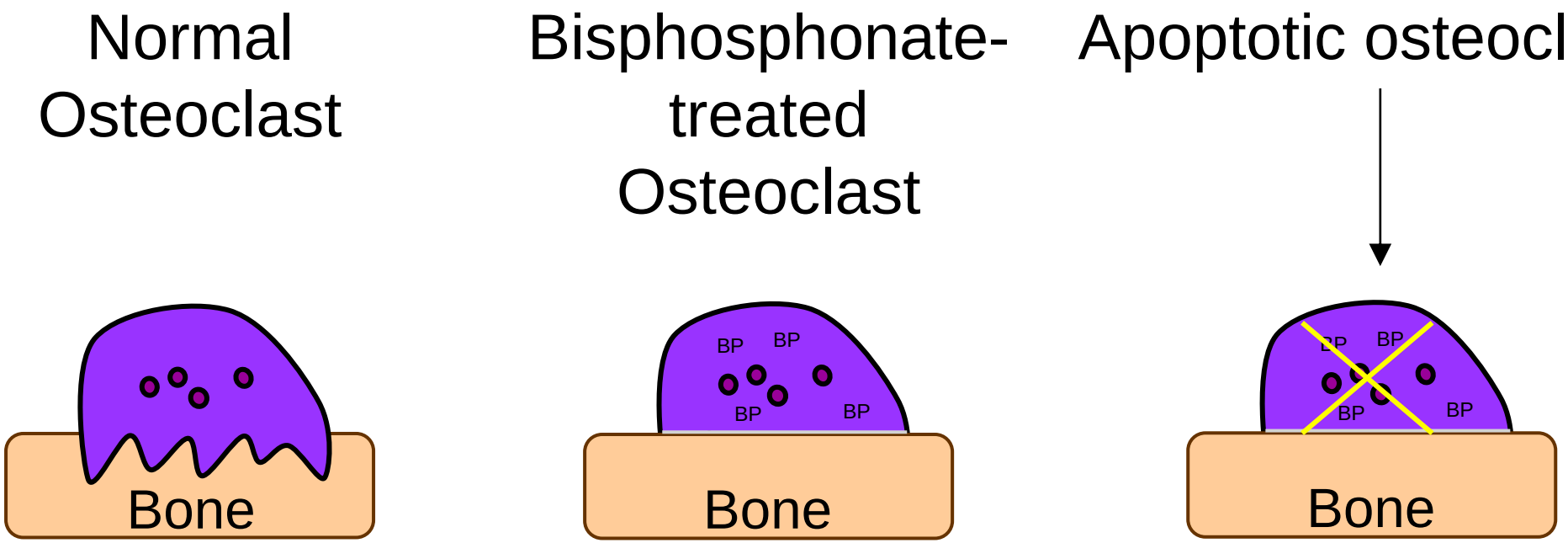
*SREs- skeletal-related events

PHARMACOLOGIC MANAGEMENT OF MYELOMA BONE DISEASE

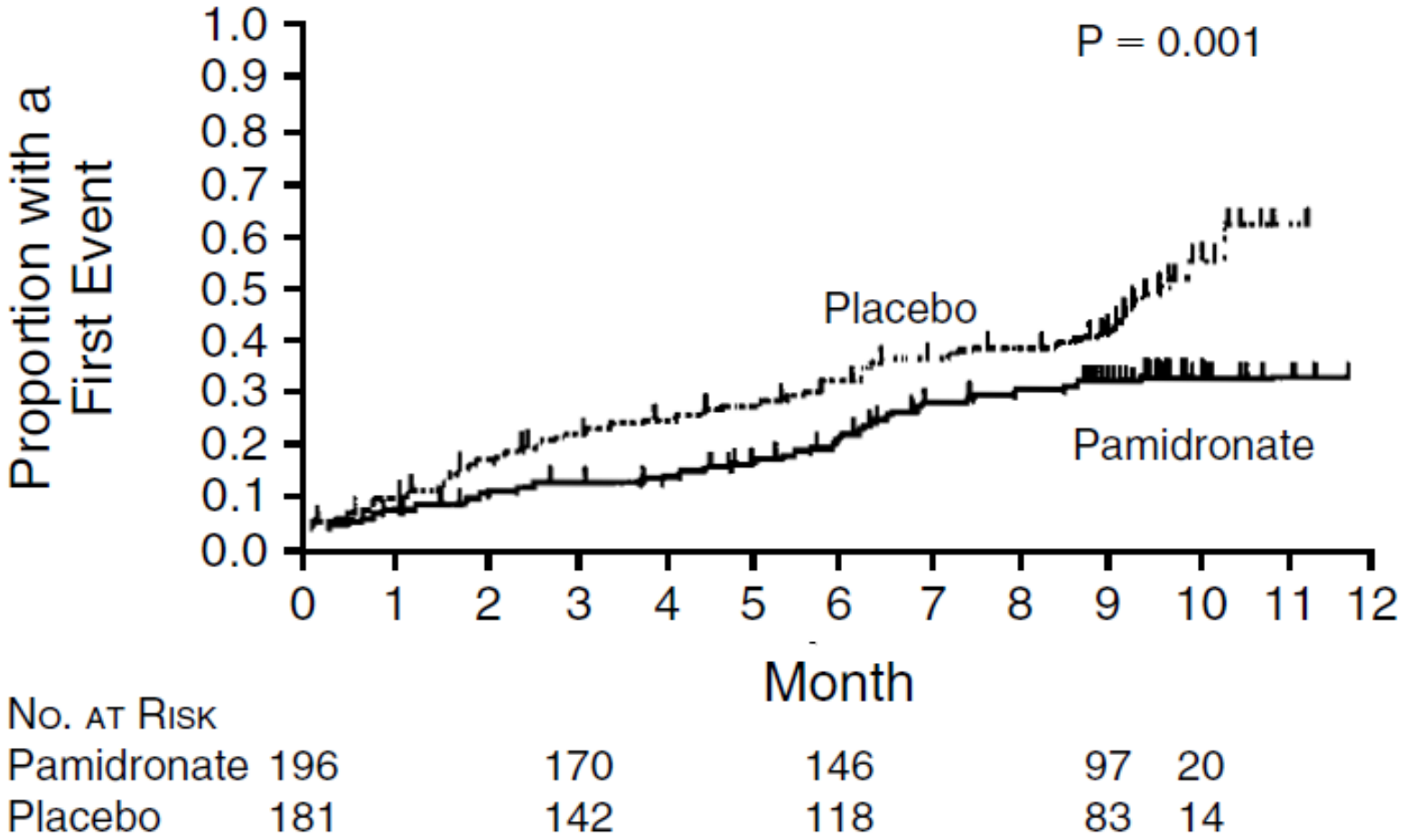
- Current recommendations
  - Pamidronate (Aredia) 90 mg/monthly (or less often)
  - Zoledronate (Zometa) 4 mg/monthly (or less often)
  - Denosumab (Xgeva) 120 mg/monthly

- Anti-resorptives improve skeletal outcomes
  - Bone pain
  - Hypercalcemia
  - Fractures

BISPHOSPHONATES TARGET MATURE OSTEOCLASTS

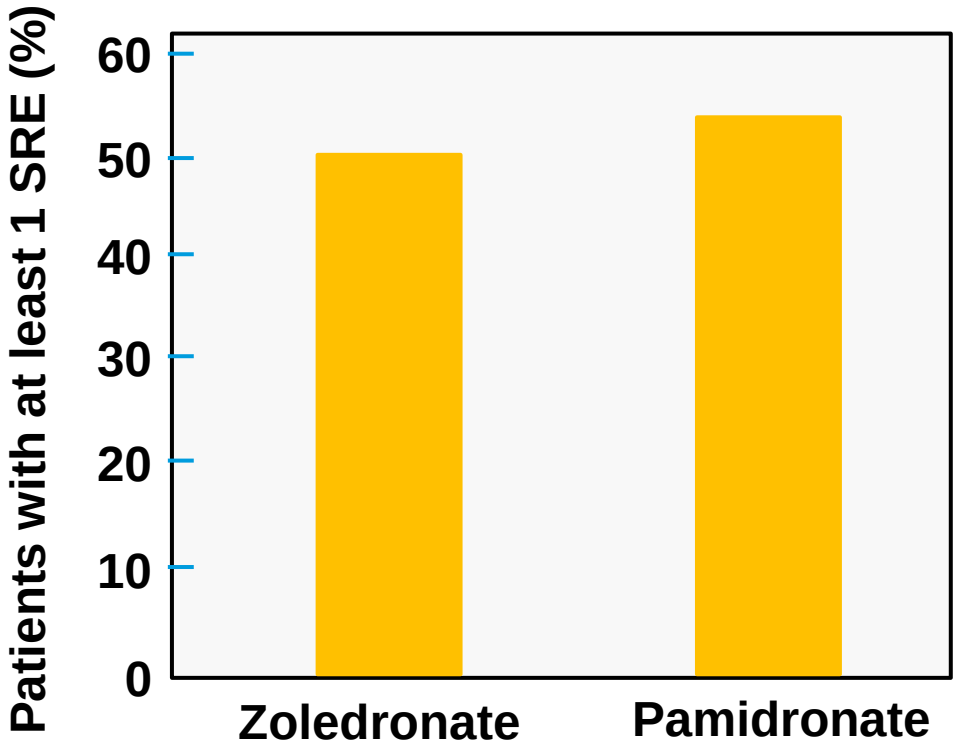


TIME TO FIRST SRE WITH PAMIDRONATE



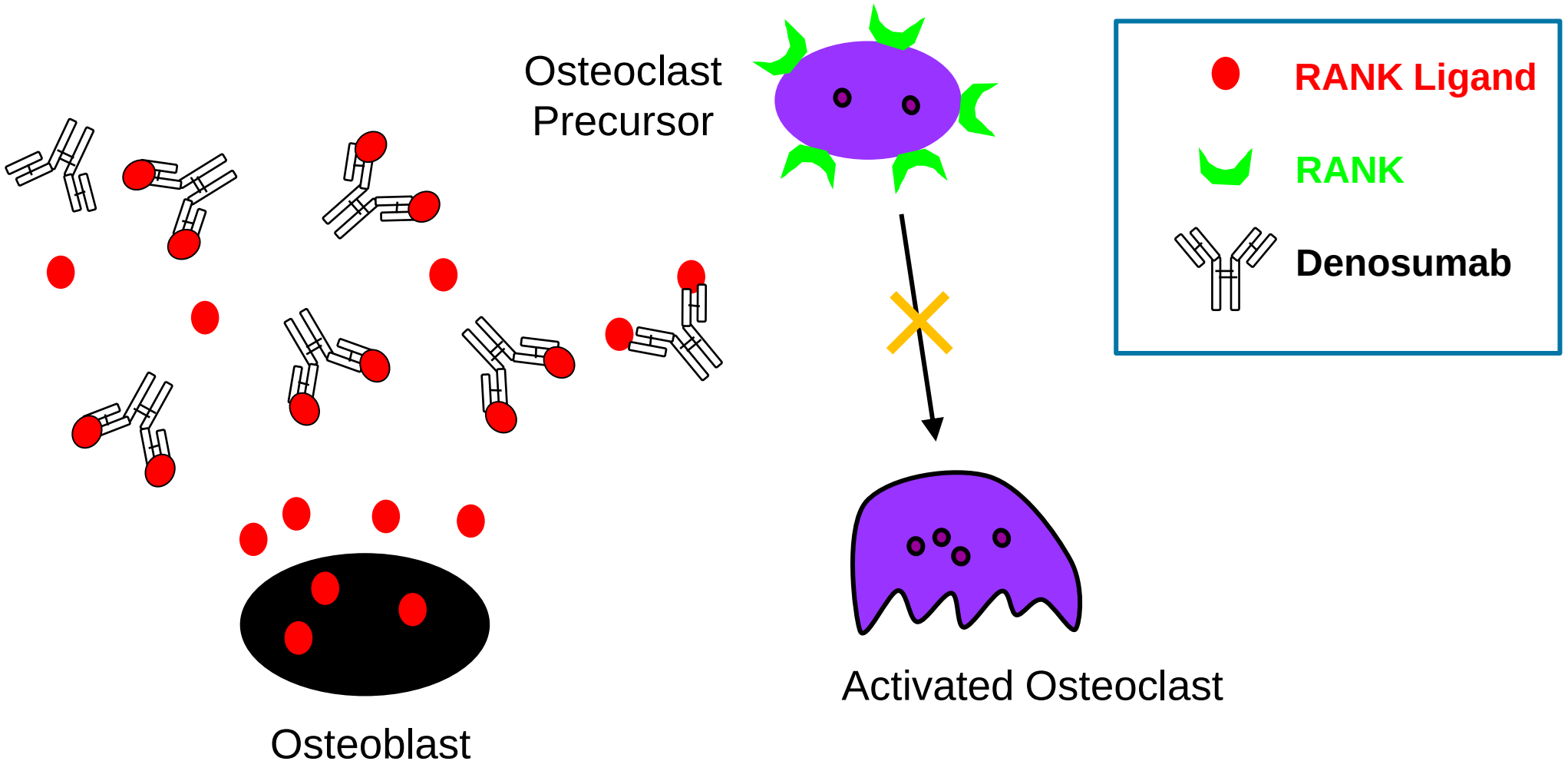
Berenson et al. (1996) NEJM 334:488.

SKELETAL RELATED EVENT RISK – ZOLEDRONATE VS PAMIDRONATE

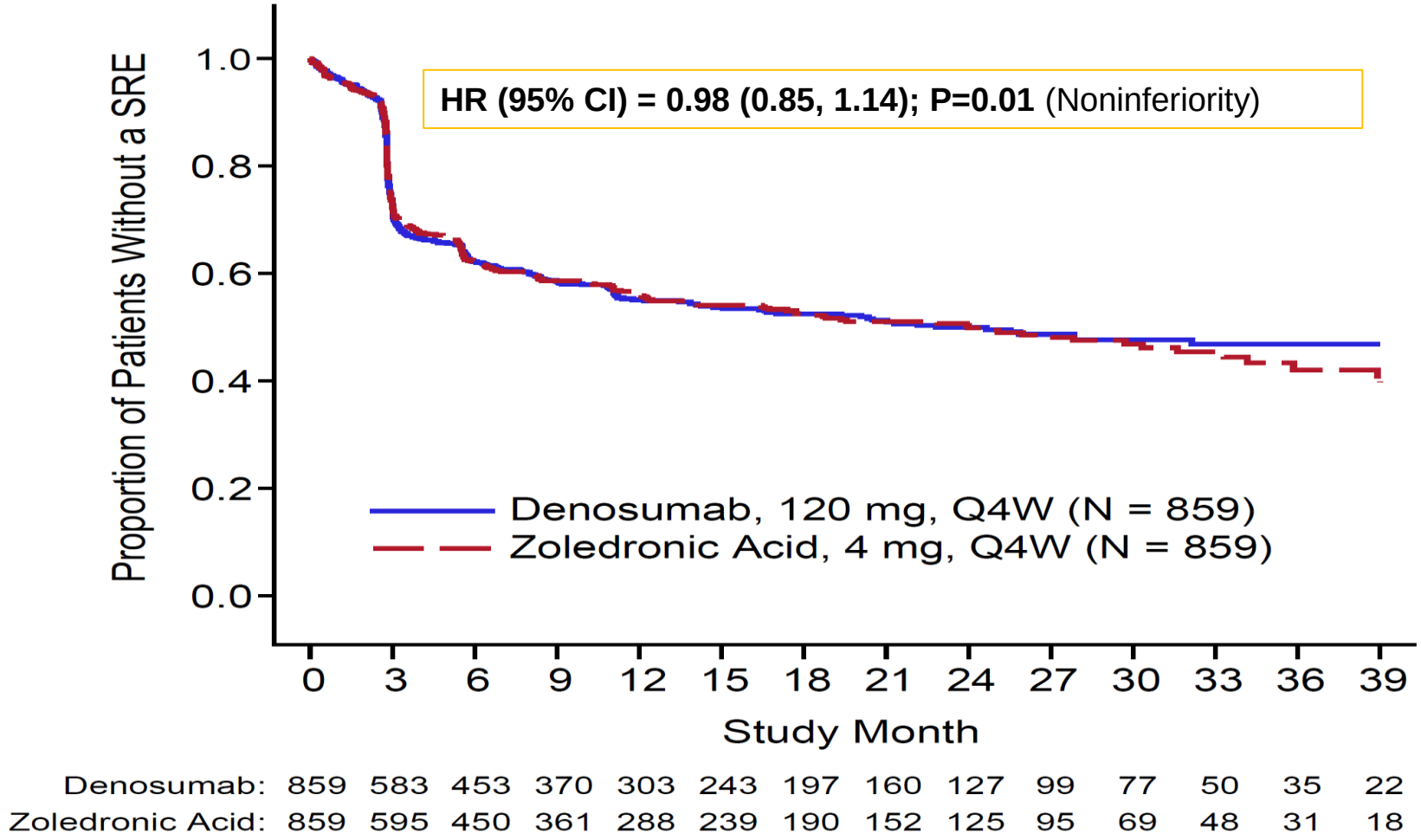


Lipton et al. (2003) Cancer J. 98:1735.

DENOSUMAB INHIBITS OSTEOCLAST FORMATION

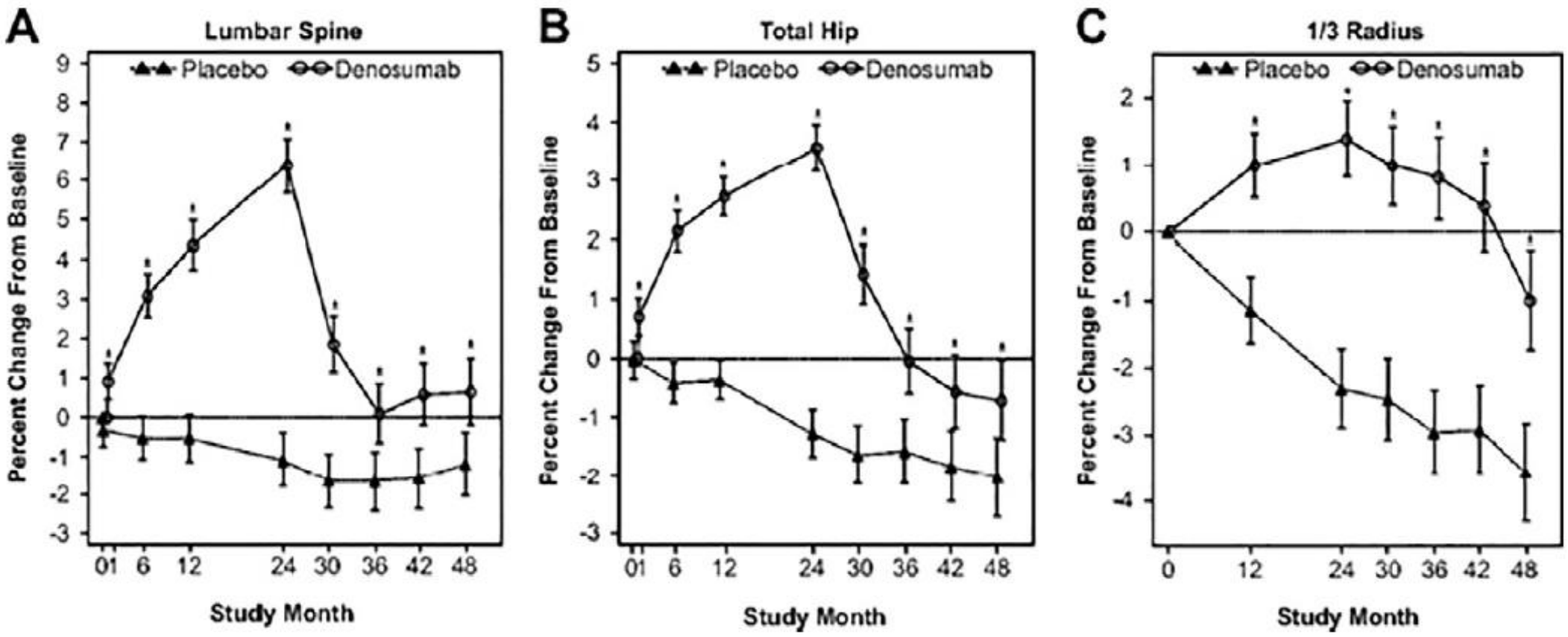


PRIMARY ENDPOINT: NON-INFERIORITY FOR TIME TO FIRST ON-STUDY SKELETAL RELATED EVENT



Raje et al Lancet Oncol. 2018; 19:370

BONE LOSS WITH DENOSUMAB DISCONTINUATION



Tsourdi et al. Bone (2017) 105:11

J Clin Endocrinol Metab. 2017 Feb 1;102(2):354-358. doi: 10.1210/jc.2016-3170.

Severe Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: 9 Clinical Cases Report.

Lamy O[1], Gonzalez-Rodriguez E[1], Stoll D[1], Hans D[1], Aubry-Rozier B[1].

Author information

Abstract

CONTEXT: Denosumab inhibits bone resorption, increases bone mineral density, and reduces fracture risk. Denosumab was approved for the treatment of osteoporosis and the prevention of bone loss in some oncological situations. Denosumab discontinuation is associated with a severe bone turnover rebound (BTR) and a rapid loss of bone mineral density. The clinical consequences of the BTR observed after denosumab discontinuation are not known.

CASES DESCRIPTION: We report 9 women who presented 50 rebound-associated vertebral fractures (RAVFs) after denosumab discontinuation. A broad biological and radiological assessment excluded other causes than osteoporosis. These 9 cases are unusual and disturbing for several reasons. First, all vertebral fractures (VFs) were spontaneous, and most patients had a high number of VFs (mean = 5.5) in a short period of time. Second, the fracture risk was low for most of these women. Third, their VFs occurred rapidly after last denosumab injection (9-16 months). Fourth, vertebroplasty was associated with a high number of new VFs. All the observed VFs seem to be related to denosumab discontinuation and unlikely to the underlying osteoporosis or osteopenia. We hypothesize that the severe BTR is involved in microdamage accumulation in trabecular bone and thus promotes VFs.

CONCLUSION: Studies are urgently needed to determine 1) the pathophysiological processes involved, 2) the clinical profile of patients at risk for RAVFs, and 3) the management and/or treatment regimens after denosumab discontinuation. Health authorities, physicians, and patients must be aware of this RAVF risk. Denosumab injections must be scrupulously done every 6 months but not indefinitely.

PMID: 27732330 DOI: 10.1210/jc.2016-3170

Lamy et al. (2017) JCEM. 102:354-358

Bone. 2017 Dec;105:11-17. doi: 10.1016/j.bone.2017.08.003. Epub 2017 Aug 5.

Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS.

Tsourdi E[1], Langdahl B[2], Cohen-Solal M[3], Aubry-Rozier B[4], Eriksen EF[5], Guañabens N[6], Obermayer-Pietsch B[7], Ralston SH[8], Eastell R[9], Zillikens MC[10].

Author information

Abstract

INTRODUCTION: The optimal duration of osteoporosis treatment is controversial. As opposed to bisphosphonates, denosumab does not incorporate into bone matrix and bone turnover is not suppressed after its cessation. Recent reports imply that denosumab discontinuation may lead to an increased risk of multiple vertebral fractures.

METHODS: The European Calcified Tissue Society (ECTS) formed a working group to perform a systematic review of existing literature on the effects of stopping denosumab and provide advice on management.

RESULTS: Data from phase 2 and 3 clinical trials underscore a rapid decrease of bone mineral density (BMD) and a steep increase in bone turnover markers (BTMs) after discontinuation of denosumab. Clinical case series report multiple vertebral fractures after discontinuation of denosumab and a renewed analysis of FREEDOM and FREEDOM Extension Trial suggests, albeit does not prove, that the risk of multiple vertebral fractures may be increased when denosumab is stopped due to a rebound increase in bone resorption.

CONCLUSION: There appears to be an increased risk of multiple vertebral fractures after discontinuation of denosumab although strong evidence for such an effect and for measures to prevent the occurring bone loss is lacking. Clinicians and patients should be aware of this potential risk. Based on available data, a re-evaluation should be performed after 5years of denosumab treatment. Patients considered at high fracture risk should either continue denosumab therapy for up to 10years or be switched to an alternative treatment. For patients at low risk, a decision to discontinue denosumab could be made after 5years, but bisphosphonate therapy should be considered to reduce or prevent the rebound increase in bone turnover. However, since the optimal bisphosphonate regimen post-denosumab is currently unknown continuation of denosumab can also be considered until results from ongoing trials become available. Based on current data, denosumab should not be stopped without considering alternative treatment in order to prevent rapid BMD loss and a potential rebound in vertebral fracture risk.

KEYWORDS: Denosumab; Discontinuation; Fractures; Osteoporosis treatment; Position paper

PMID: 28789921 DOI: 10.1016/j.bone.2017.08.003

DENOSUMAB THERAPY CONSIDERATIONS

- Denosumab does not cause osteoclast apoptosis like bisphosphonates; rather it prevents pre-osteoclasts from becoming active osteoclasts.
- Therefore, any treatment with denosumab must be followed by a bisphosphonate (such as zoledronate) to limit rebound bone resorption.
- The timing of bisphosphonate treatment relative to the last dose of denosumab is not clear.
- RANKL is not specific to osteoclasts but has a role in the regulation of other immune cells. This may explain the slightly increased rates of infection in denosumab-treated patients.
- Denosumab may be a good option in patients with kidney dysfunction

MULTIPLE MYELOMA WITHOUT BONE LESIONS

- Limited data exists on the routine use of bisphosphonates in myeloma patients without osteolytic disease

- Data from the MRC IX Trial showed that myeloma patients without bone lesions at baseline who received zoledronate had fewer skeletal related events compared to patients treated with clodronate

- Guidelines from the European Myeloma Network suggest that patients with symptomatic patients but without lytic lesions can be treated with zoledronate based on this data

Morgan et al (2011) Lancet Oncology 12:743; Terpos (2015) Haematologica 100:1254.

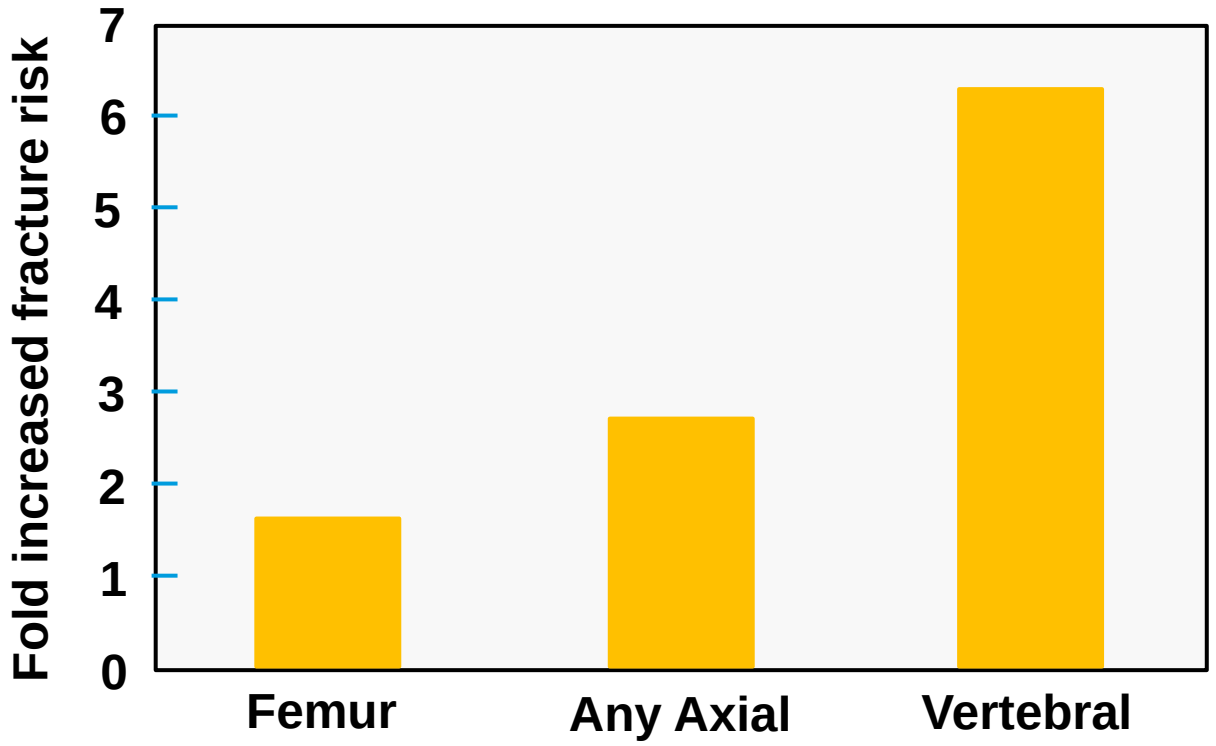
BONE LOSS ALSO OCCURS IN MGUS

- MGUS is a common pre-malignant condition with an ~ 1% annual risk of progression to MM

- MGUS prevalence increases with age and affects ~ 3.4 million Americans
  - 3.2% adults aged ≥ 50 years
  - 7.5% adults aged ≥ 85 years

Kyle et al. (2006) *NEJM* 354:1363; Melton et al. (2004) *J Bone Miner Res*. 19:25.

FRACTURE RISK IS INCREASED IN MGUS



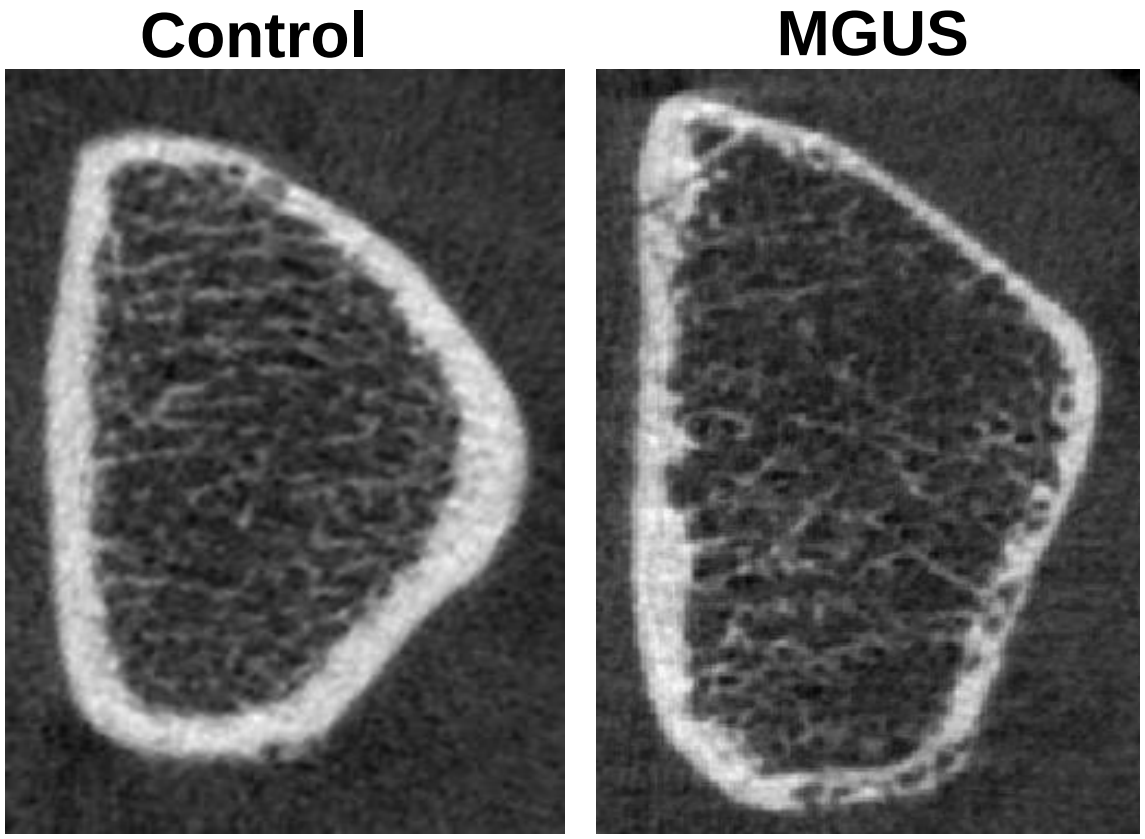
Melton et al. (2004) JBMR 19:25; Kristinsson et al. (2010) Blood 116:2651

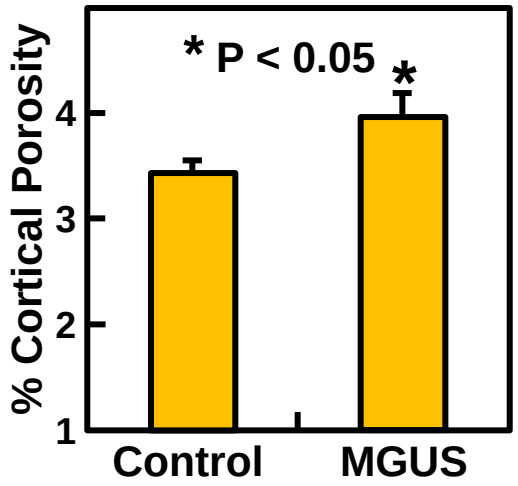
MGUS Patients have Decreased Volumetric Bone Mineral Density and Microstructure

	Controls (Mean±SEM)	MGUS (Mean±SEM)	Difference (%)	P-value
Trabecular vBMD (mg/cm^3)	335±7	300±10	-10.4%	0.005
Trabecular BMD (mg/cm^3)	161±4	150±6	-6.8%	0.080
Cortical vBMD (mg/cm^3)	862±7	822±12	-4.7%	0.001
Cortical Thickness (mm)	0.88±0.03	0.80±0.03	-9.5%	0.029
Trabecular Thickness (mm)	0.074±0.001	0.068±0.001	-8.1%	0.004

Ng et al. (2011) Blood 118:6529

MGUS is Associated with Increased Cortical Porosity





Farr et al. (2014) Blood 123:647.

PERSPECTIVE

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Unveiling Skeletal Fragility in Patients Diagnosed With MGUS: No Longer a Condition of Undetermined Significance?

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ABSTRACT

Monoclonal gammopathy of undetermined significance (MGUS) is a common finding in clinical practice, affecting greater than 3% of adults aged 50 years and older. As originally described, the term MGUS reflected the inherent clinical uncertainty of distinguishing patients with a benign stable monoclonal plasma cell disorder from subjects destined to progress to malignancy. There is now clear epidemiologic evidence, however, that patients with MGUS suffer from a significantly increased fracture risk and that the prevalence of MGUS is increased in patients with osteoporosis. Despite this relationship, no clinical care guidelines exist for the routine evaluation or treatment of the skeletal health of patients with MGUS. Recent work has demonstrated that circulating levels of at least two cytokines (CCL3/MIP-1α and DKK1) with well-recognized roles in bone disease in the related monoclonal gammopathy multiple myeloma are also increased in patients with MGUS. Further, recent imaging studies using high-resolution peripheral quantitative CT have documented that patients with MGUS have substantial skeletal microarchitectural deterioration and deficits in biomechanical bone strength that likely underlie the increased skeletal fragility in these patients. Accordingly, this Perspective provides evidence that the "undetermined significance" portion of the MGUS acronym may be best replaced in favor of the term "monoclonal gammopathy of skeletal significance" (MGSS) in order to more accurately reflect the enhanced skeletal risks inherent in this condition.

KEY WORDS: MGUS; OSTEOPOROSIS; FRACTURE; DXA; HRPQCT

Drake (2014) J Bone Min Res. 29:2529

BISPHOSPHONATE USE IN MGUS

- Alendronate (70 mg/weekly) ↑ bone density at the spine and hip in osteoporotic MGUS patients
- Zoledronic acid (4 mg/every 6 months) ↑ bone density at the spine and hip in MGUS patients with osteopenia/osteoporosis
- Neither study was large enough to evaluate fracture as an endpoint

Pepe et al. (2008) Calcif. Tissue Int. 82:418; Berenson et al. (2008) Clin. Cancer Res. 14:6289.

TREATMENT OF THE MGUS PATIENT

- Patients with MGUS are at increased fracture risk
- A pro-active approach is warranted
  - May include DXA, counseling on fall risks, lifting recommendations, ensuring adequate calcium and vitamin D intake
- In patients with documented osteoporosis (by DXA, history of a fragility fracture, height loss, or kyphosis), medical intervention with anti-resorptive therapy (such as a bisphosphonate) is warranted
- In patients with osteopenia, medical therapy to limit bone loss and fracture risk may be appropriate and must be considered carefully

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Treatment of multiple myeloma-related bone disease: recommendations from the Bone Working Group of the International Myeloma Working Group

Prof Evangelos Terpos, MD [a] · Elena Zamagni, MD [b] · Prof Suzanne Lentzsch, MD [c] · Matthew T Drake, MD [d] · Ramón García-Sanz, MD [e] · Prof Niels Abildgaard, MD [f] · et al. Show more

IMAGING GUIDELINES IN MONOCLONAL PLASMA CELL DISORDERS

- Optimal imaging supports clinical care decisions
- Bone disease supports the immediate start of systemic therapy
- Imaging can identify painful bone lesions or skeletal sites at increased risk for pathologic fractures or neurologic complications (spinal cord compression)

Hillengass et al./IMWG (2019) Lancet Oncol e302.

QUESTIONS & DISCUSSION