NCCN 10th Annual Congress:
Hematologic Malignancies™

Bone Health in Patients with Multiple Myeloma

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Bone Health

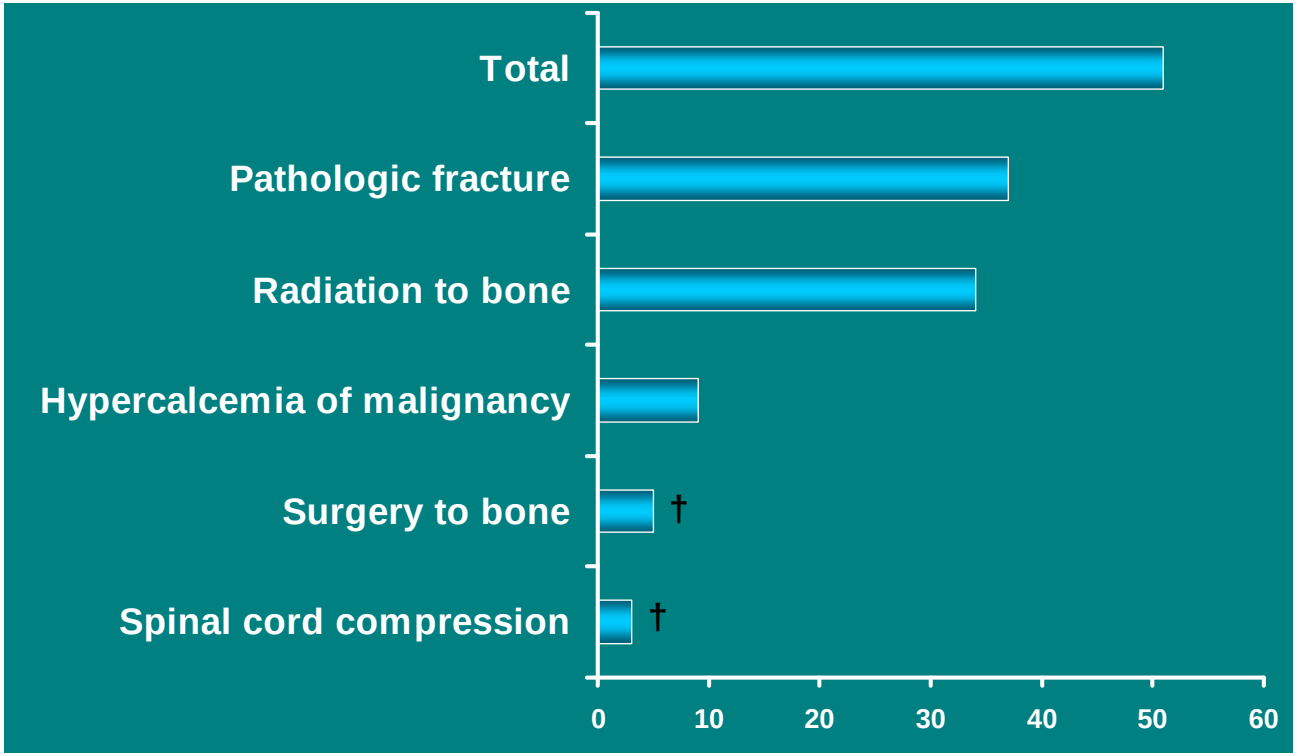
Bisphosphonates in Space

Bone Involvement in Different Tumor Types

	Disease Prevalence (US) (in Thousands)	Incidence of Bone Metastases in Patients With Advanced Disease, %	Median Survival of Patients With Bone Metastases, Mos
Myeloma	49.6[1]	84[2]	37-58[4]
Lung	327[1]	30-40[3]	8-10[5]
Breast	2051[1]	65-75[3]	19-25[6]
Prostate	1477[1]	65-75[3]	30-35[7]

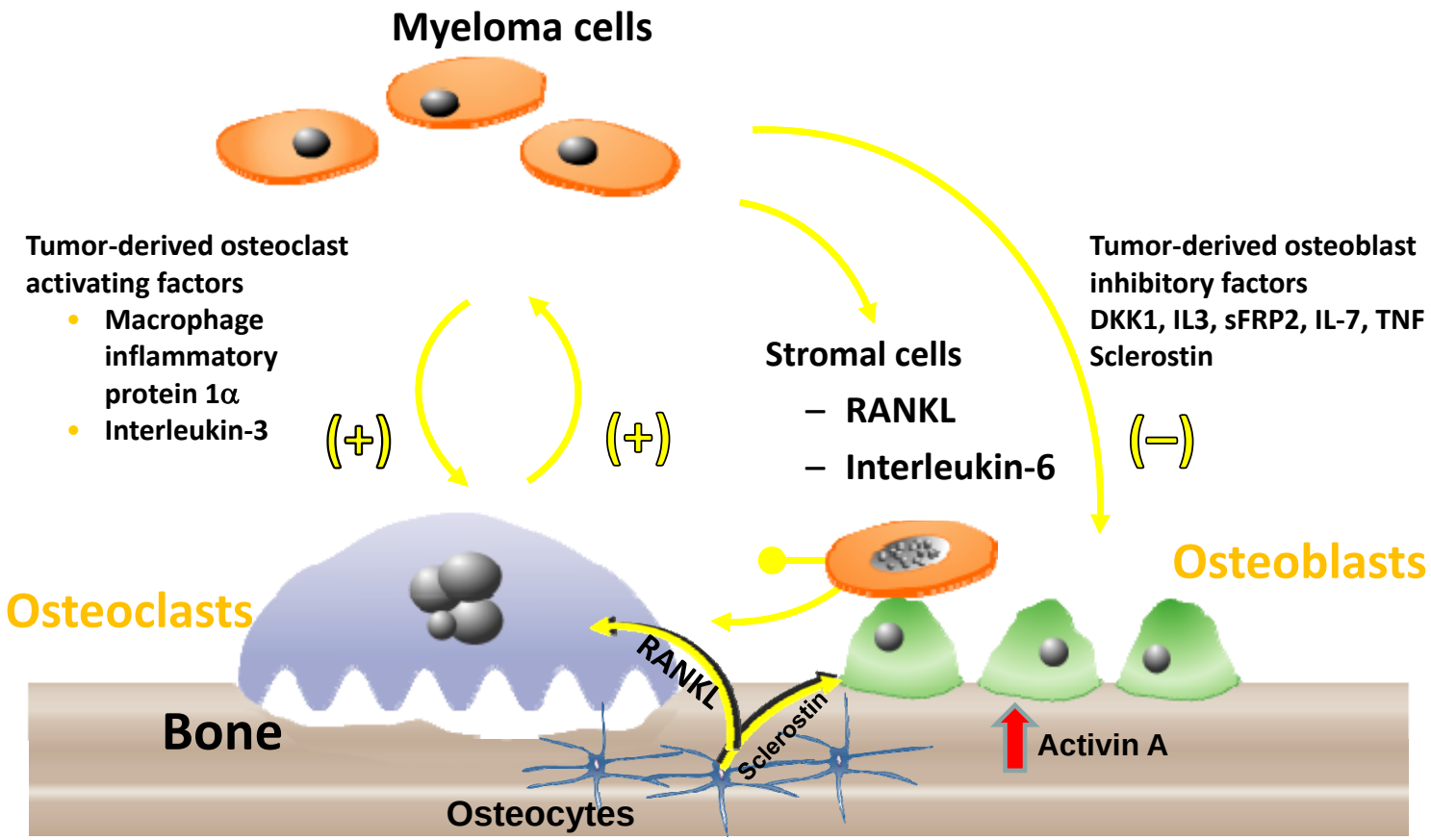
1. *National Cancer Institute. Available at: http://seer.cancer.gov/csr/1973-1999/prevalence.pdf.*
2. *Kyle RA, et al. Mayo Clin Proc. 2003;78:21-33.*
3. *Coleman RE. Oncologist. 2004;9(suppl 4):14-27.*
4. *Palumbo A, et al. Blood. 2004;104:3052-3057.*
5. *Smith W, et al. SeminOncol. 2004;31(suppl 4):11-15.*
6. *Lipton A. J Support Oncol. 2004;2:205-213.*
7. *Tu SM, et al. Cancer Treat Res. 2004;118:23-46.*

Prevalence of Skeletal Complications in Myeloma



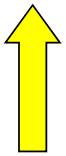
†9-month data.
‡Placebo arm of pamidronate randomized trial.
Berenson JR et al. *N Engl J Med*. 1996;334:488-493.
Berenson JR, et al. *J Clin Oncol*. 1998;16:593-602.

Myeloma Bone Disease

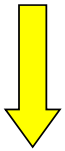


Adapted from Roodman GD. *N Engl J Med*. 2004;350(16):1655-1664.

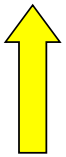
Factors Increasing OCL Activity in Myeloma



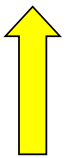
- **RANK Ligand**



- **OPG**

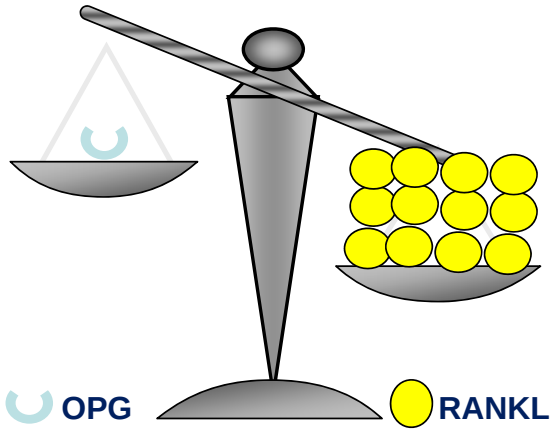


- **MIP-1 alpha**



- **IL-3**

The RANK/RANKL/OPG Pathway in Osteolytic Bone Disease

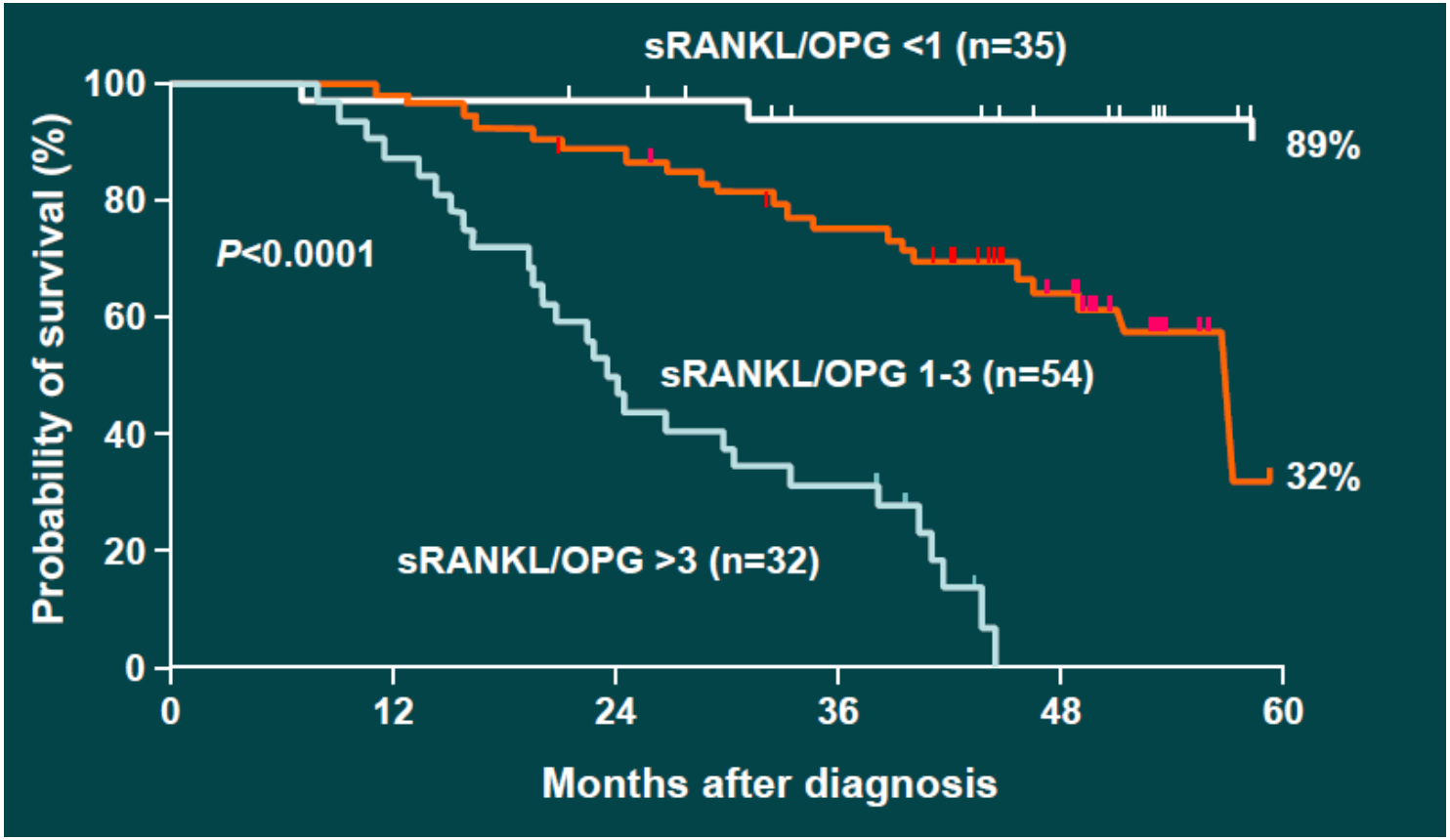


Increased Osteoclastic Activity and Decreased OPG

Lead to Increased Bone Destruction

Adapted from Roodman. *N Engl J Med*. 2004;350:1655.

Survival of Patients With Multiple Myeloma: Soluble RANKL/OPG



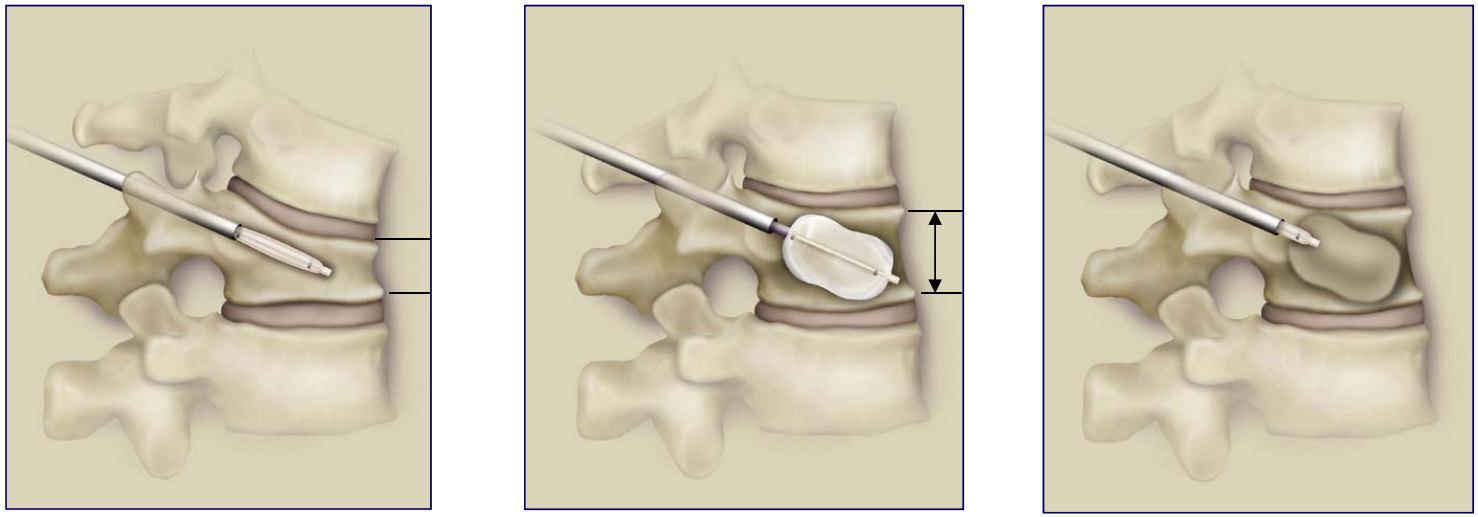
Terpos E., et al. *Blood*. 2003; 102 (3):1064-1069.

Current Management of Bone Disease

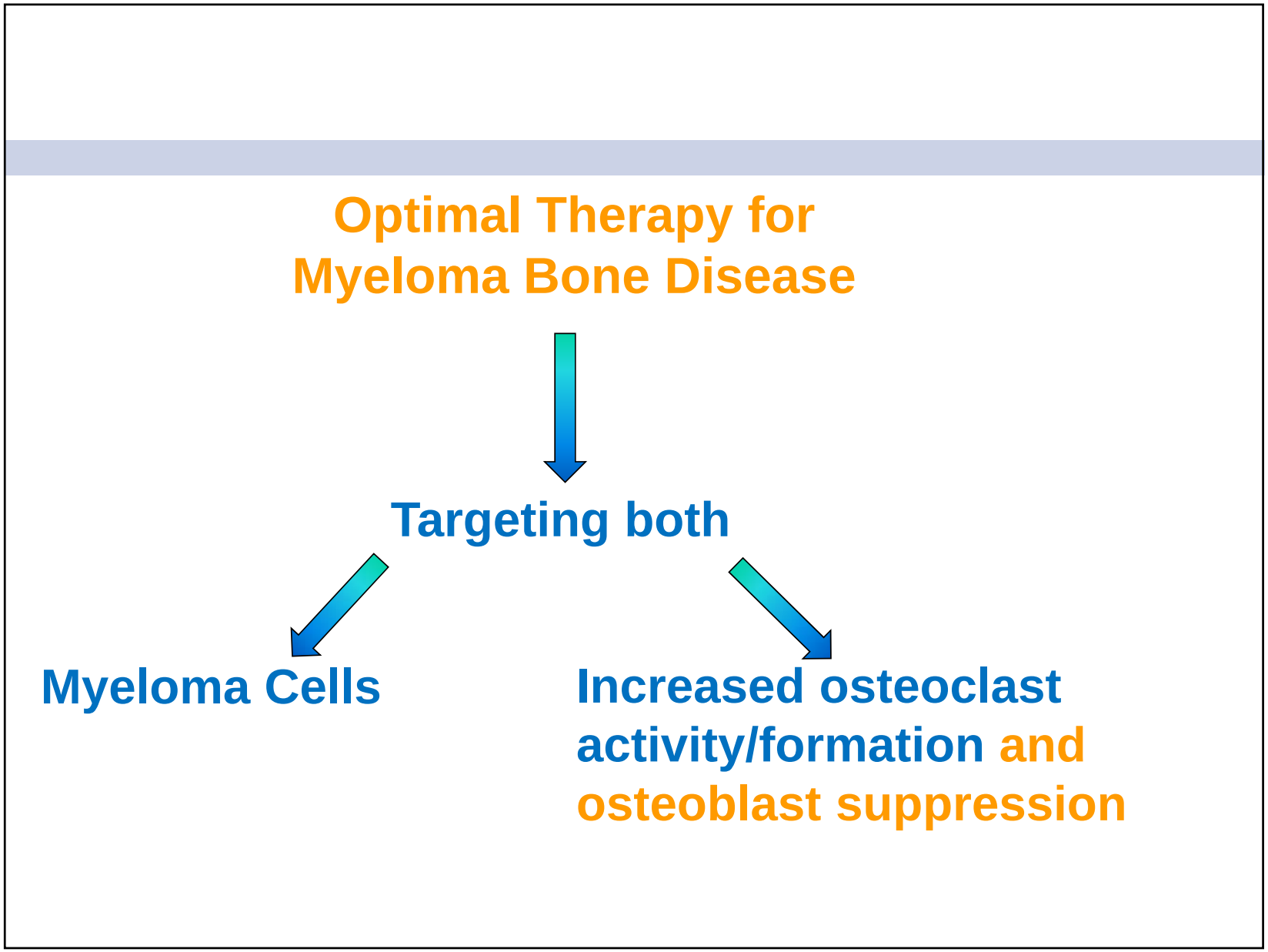
- **Treat the myeloma**
- **Novel therapies have benefits**
  - Direct effect on inflammatory cytokines
  - Inhibition of bone resorption
  - Osteoclast stimulation
- **Bisphosphonates**
  - Pamidronate
  - Zoledronic acid
- **Radiotherapy (low dose)**
  - Impending fracture
  - Cord compression
  - Plasmacytomas
- **Orthopedic consultation**
  - Impending or actual long-bone fractures
  - Bony compression of spinal cord
  - Vertebral column instability
- **Supplement with calcium and vitamin D3 to maintain calcium homeostasis**

Niesvizky R, et al. J Natl Compr Canc Netw. 2010;8(suppl 1):S13-S20. Christoulas D, et al. Expert Rev Hematol. 2009;2:385-398. Drake MT. Oncology (Williston Park). 2009;23(14 suppl 5):28-32. Terpos E, et al. J Clin Oncol. 2013;31:2347-2357. Webb SL, et al. British J Pharmacol. 2014;[Epub ahead of print].

Kyphoplasty: A Minimally Invasive Fracture Reduction Procedure



An inflated balloon

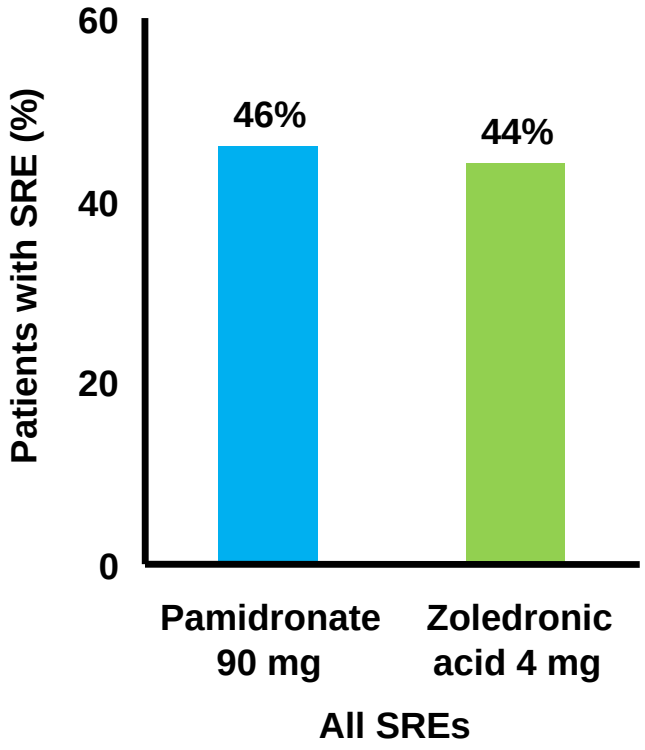


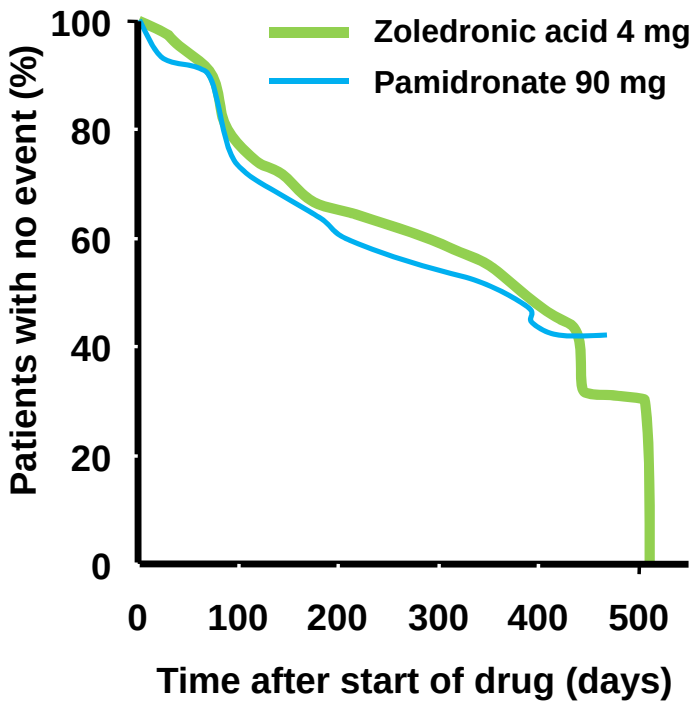
Bisphosphonate Therapy in Myeloma

- **Bisphosphonates (pamidronate and zoledronic acid) decrease pain and minimize bone-related complications**
  - Use in all patients with symptomatic myeloma, regardless of documented bone disease[1]
  - Zoledronic acid has been reported to increase OS in the Myeloma IX trial[2]
  - Monitor for renal dysfunction
  - Monitor for osteonecrosis of the jaw
  - Monitor vitamin D levels; consider vitamin D and calcium supplements

1. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. v.2.2016.
2. Morgan G, et al. Lancet Oncol. 2011;12:743-752.

Zoledronic Acid and Pamidronate in Multiple Myeloma





SREs=skeletal-related events

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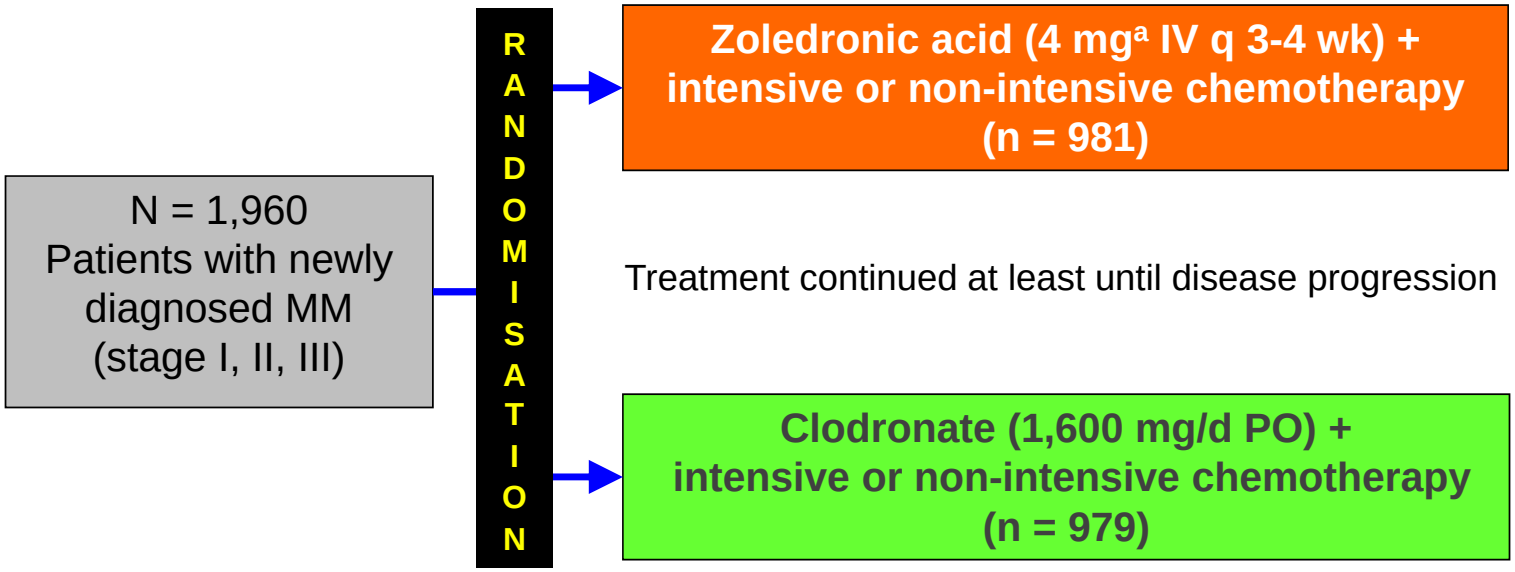
Rosen LS et al. Cancer J. 2001;7(5):377-387.

MRC Myeloma IX—
Analysis Schematic for ZOL vs. CLO

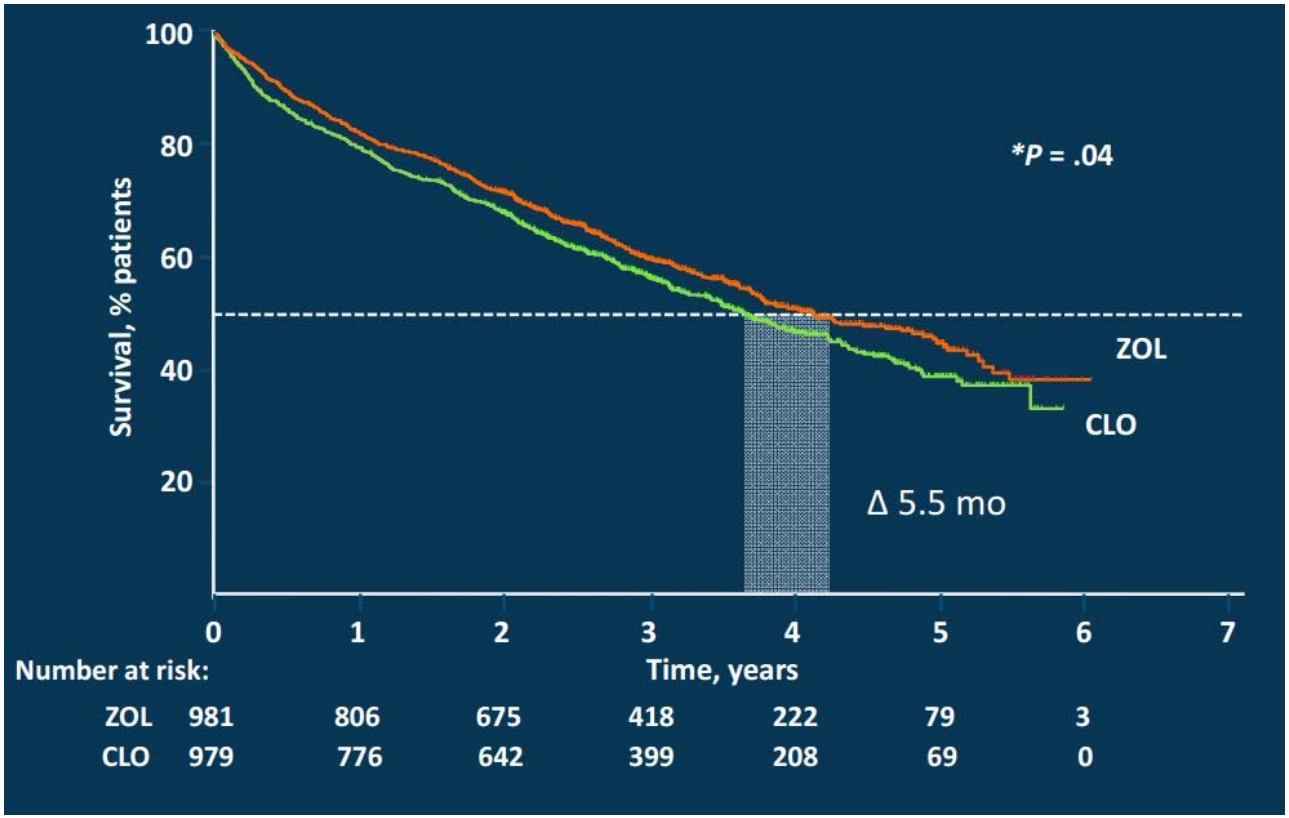


Endpoints (ZOL vs CLO)
Primary: PFS, OS, and ORR
Secondary: Time to first SRE, SRE incidence, and Safety

Abbreviations: CLO, clodronate; IV, intravenous; MM, multiple myeloma; ORR, overall response rate; OS, overall survival, PFS, progression-free survival; PO, oral; SRE, skeletal-related event; ZOL, zoledronic acid.
[a] Dose-adjusted for patients with impaired renal function, per the prescribing information.

Morgan G et al. Blood ;119;2012

MRC Myeloma IX—
ZOL Significantly Improved OS vs CLO[a]



Abbreviations: CLO, clodronate; OS, overall survival; ZOL, zoledronic acid.

*Log-rank, stratified by treatment pathway.

[a] Kaplan-Meier analysis adjusted for treatment pathway (intensive vs not).

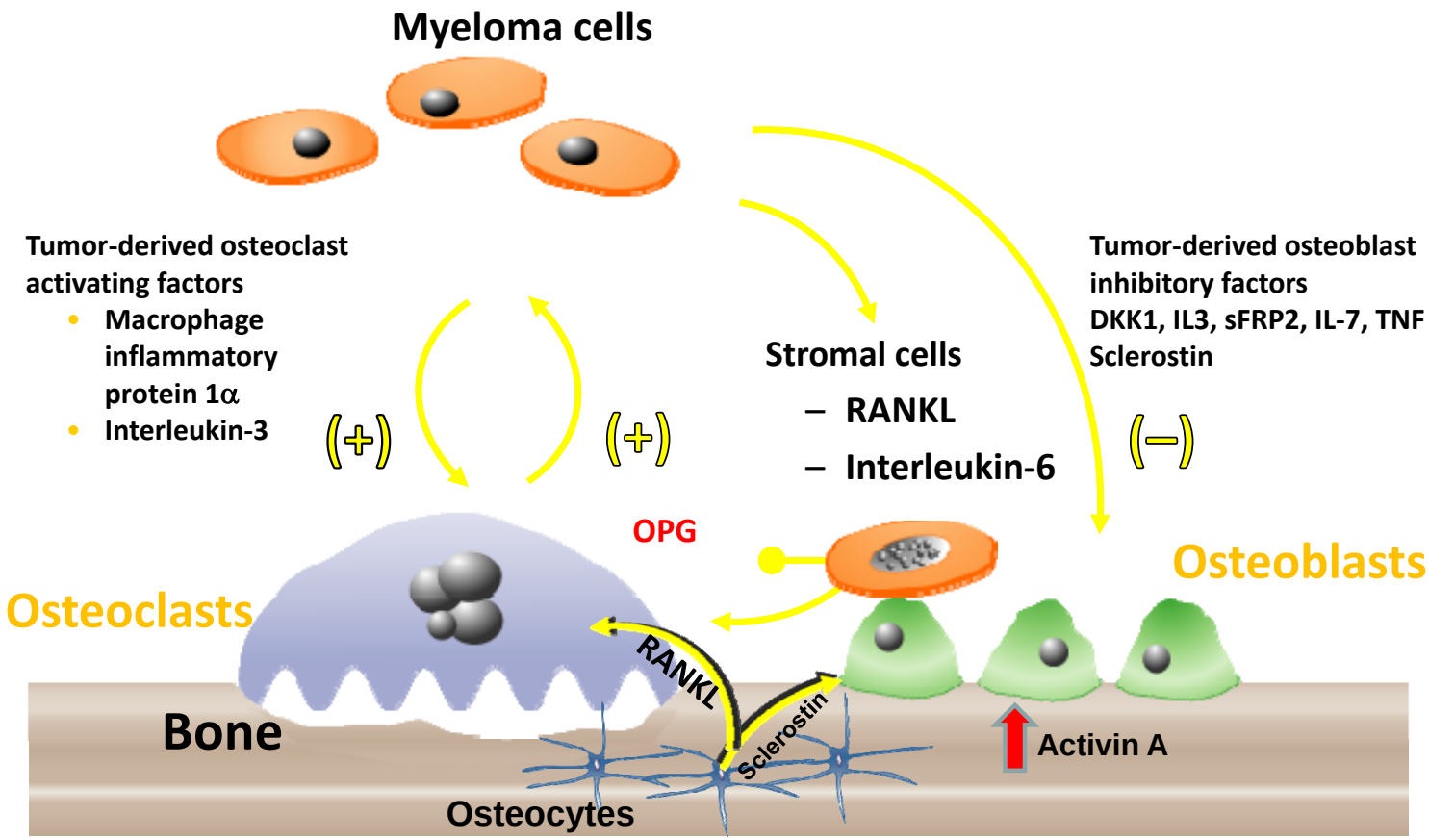
Morgan G, et al. Lancet. 2010;376(9757):1989-1999.

Osteonecrosis

- **related to duration of therapy**
- **MRC IX study[1]**
  - 4% with zoledronic acid
  - < 1% with clodronate

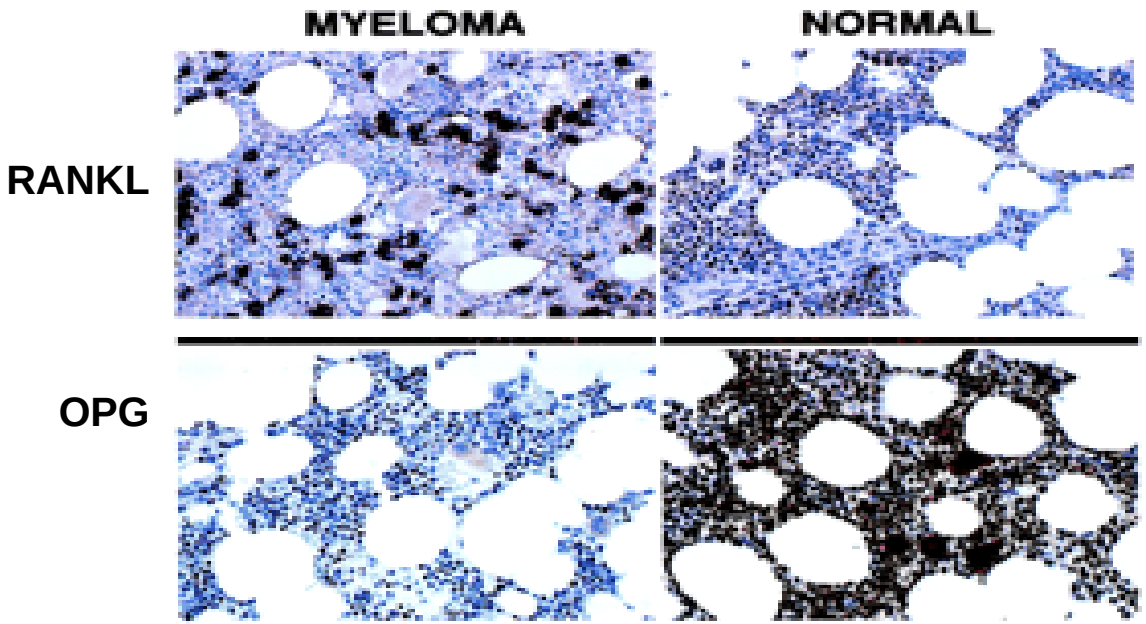
1. Morgan GJ, et al. Lancet. 2010;376:1989-1999.

RANK LIGAND OSTEOPROTOGERIN(OPG)



Adapted from Roodman GD. *N Engl J Med*. 2004;350(16):1655-1664.

RANK Ligand Is Increased and OPG Is Decreased in Myeloma



Pearse RN, et al. Proc Natl Acad Sci U S A. 2001;98:11581-11586. Copyright 2001. National Academy of Sciences, U.S.A.

Denosumab

- Human monoclonal antibody that binds RANKL
- High affinity and specificity for human RANKL
- Inhibits formation and activation of osteoclasts

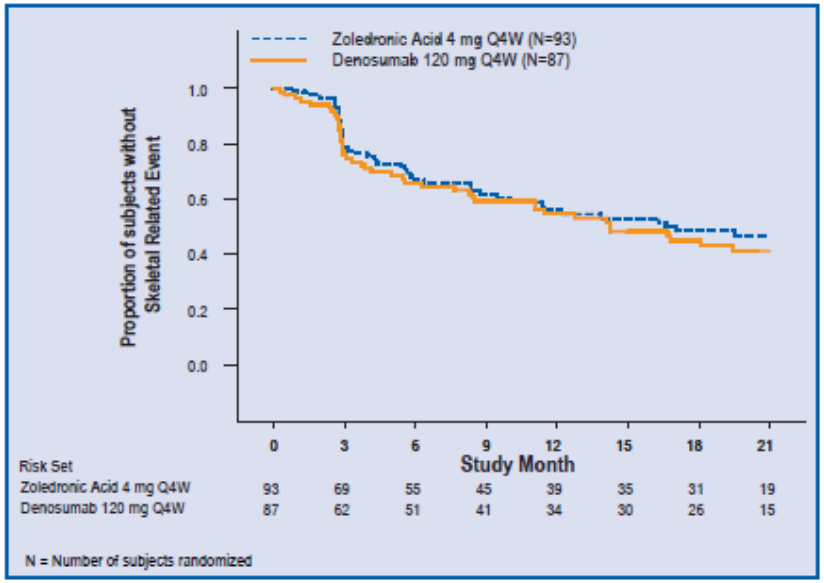
Randomized double-blind study of Denosumab versus Zoledronic Acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma

- Denosumab was non-inferior to Zoledronic Acid in delaying time to first SRE on study
- Overall survival for all patients similar, but inferior for MM subgroup
- ONJ rates similar
- Hypocalcemia more frequent with Denosumab

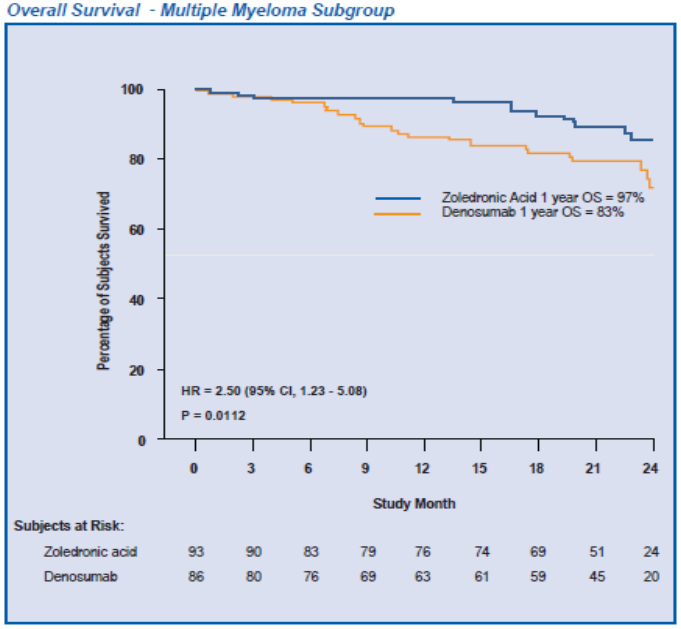
Henry, DH et al, JCO 29:1125, 2011

Denosumab vs. Zoledronate: MM Sub Study

Time to First SRE - Multiple Myeloma Subset



Overall Survival - Multiple Myeloma Subgroup



Zoledronic Acid Arm

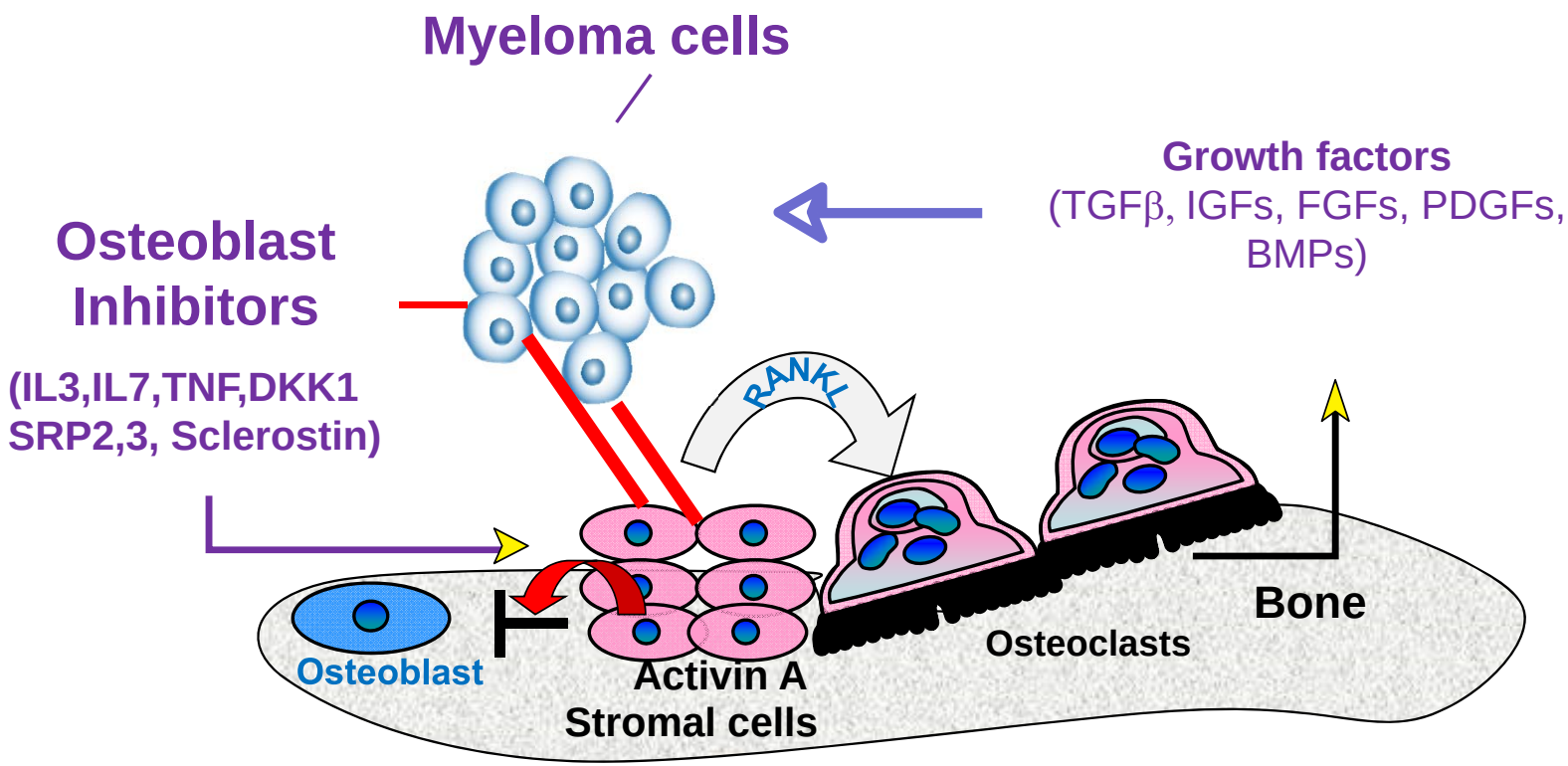
- More ECOG 0 patients
- More stage 1 tumors
- More stem cell transplants
- More study discontinuations due to withdrawal of consent or lost to follow up and discontinuations occurred earlier

Denosumab Arm

- More patients with low renal function

Raje et al, ASCO 2013

Osteoblast Inhibitors in Myeloma



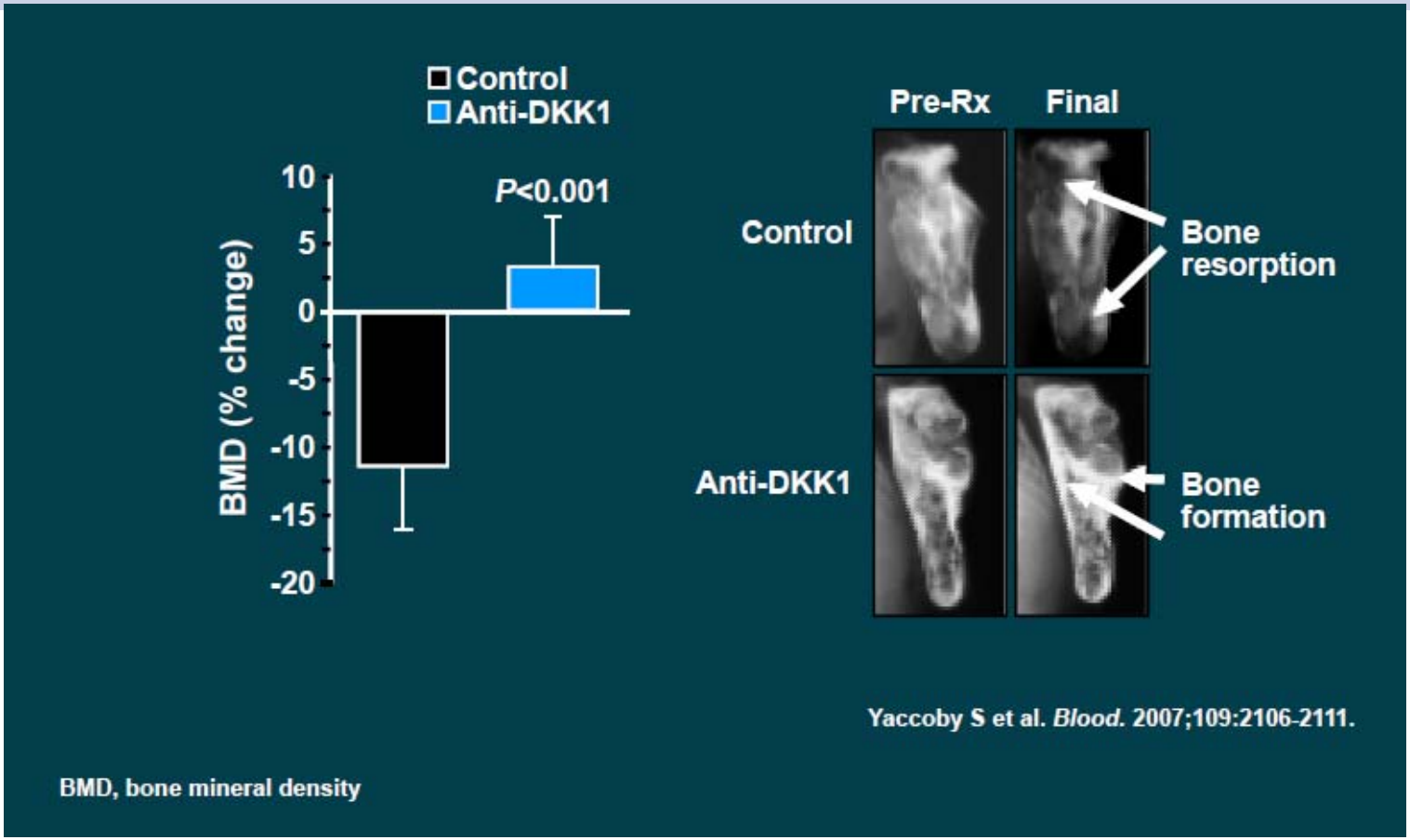
Adapted from Roodman. N Engl J Med. 2004;350:1655.

DKK1 and sFRP-2 in Myeloma Bone Disease

- Inhibitors of the WNT signaling pathway
- WNT signaling is a critical pathway for OBL differentiation
- Secreted by myeloma cells
- Marrow plasma from patients with high levels of DKK1 or sFRP-2 inhibit murine OBL differentiation
- DKK1 gene expression levels correlated with extent of bone disease in MM patients

Tian et al NEJM 349:2483,2003, Oshima T. et al.Blood.;106:3160, 2005

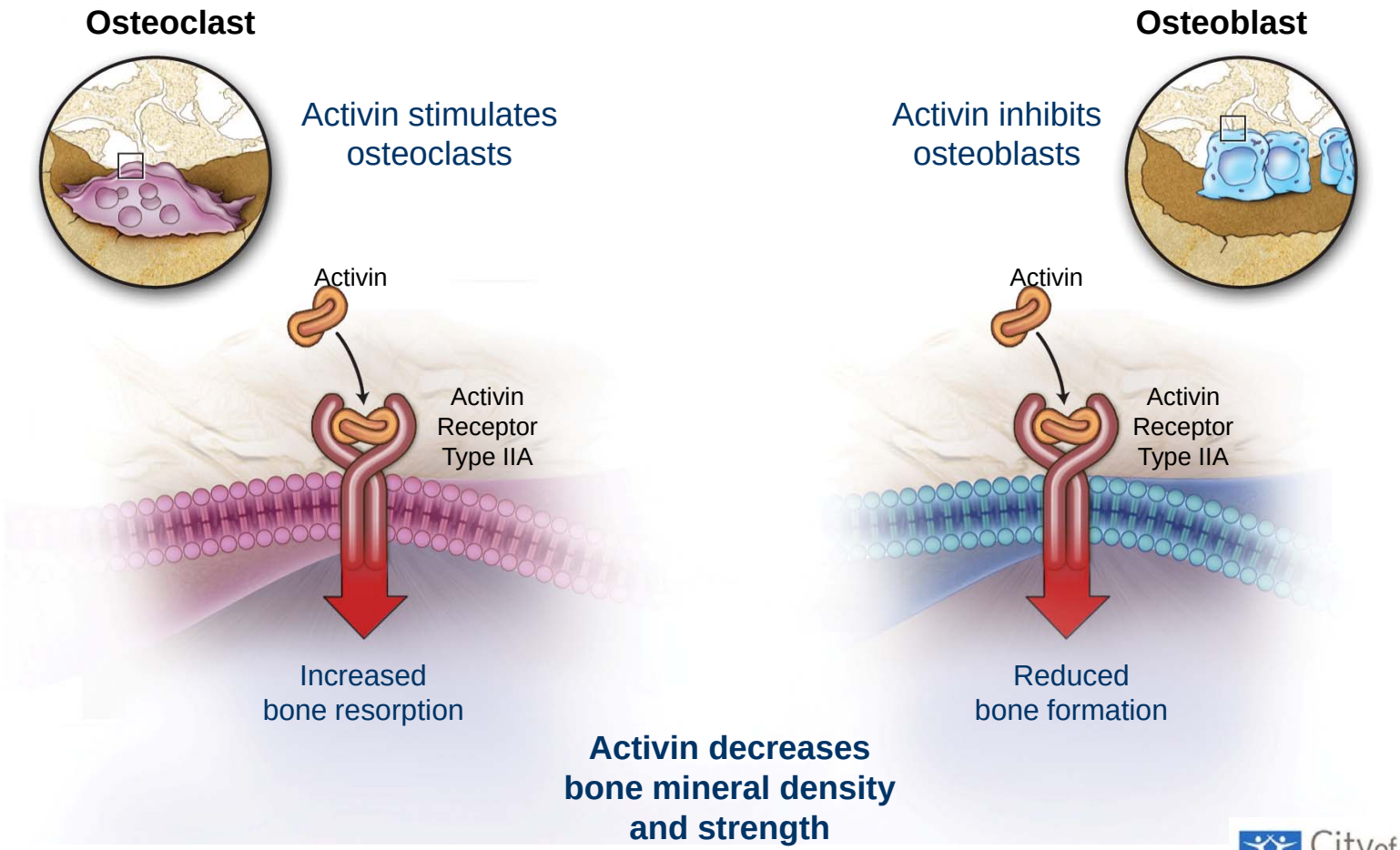
Anti-DKK1 Increases Bone Formation in the SCID-Rab Multiple Myeloma Model



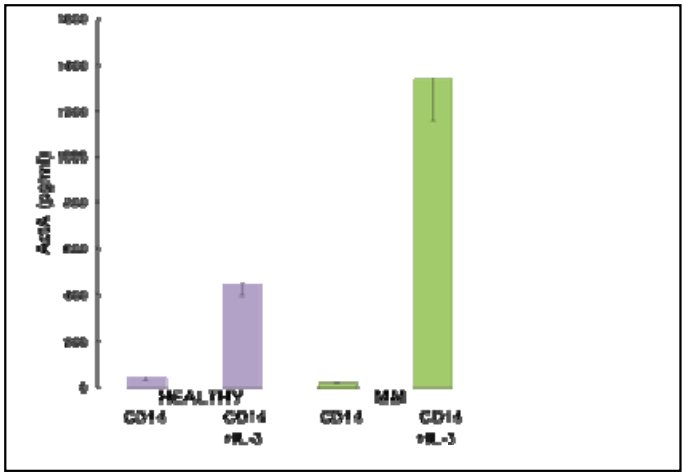
Ongoing Trials

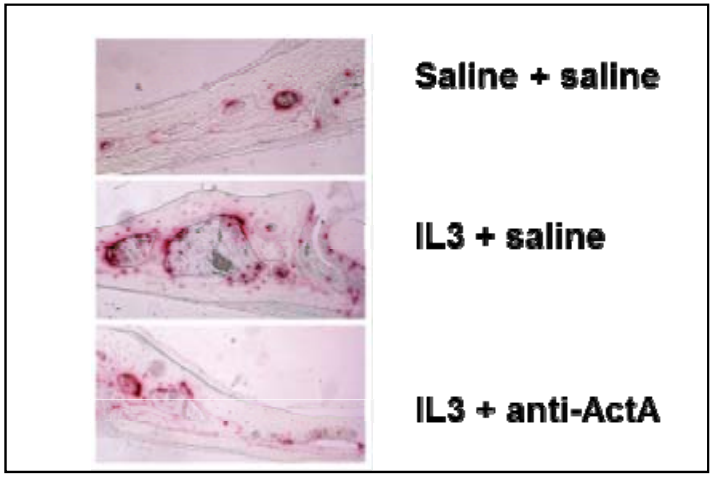
Phase I/II Study of BHQ880, an Anti-DKK1 Human Monoclonal Antibody, in Relapsed/Refractory MM Patients Treated with Zoledronic Acid and Anti-Myeloma Therapy and a Phase II Study in Smoldering Myeloma Have Been Completed.

Activin and Bone Growth



IL-3 induces Osteoclasts via Activin A



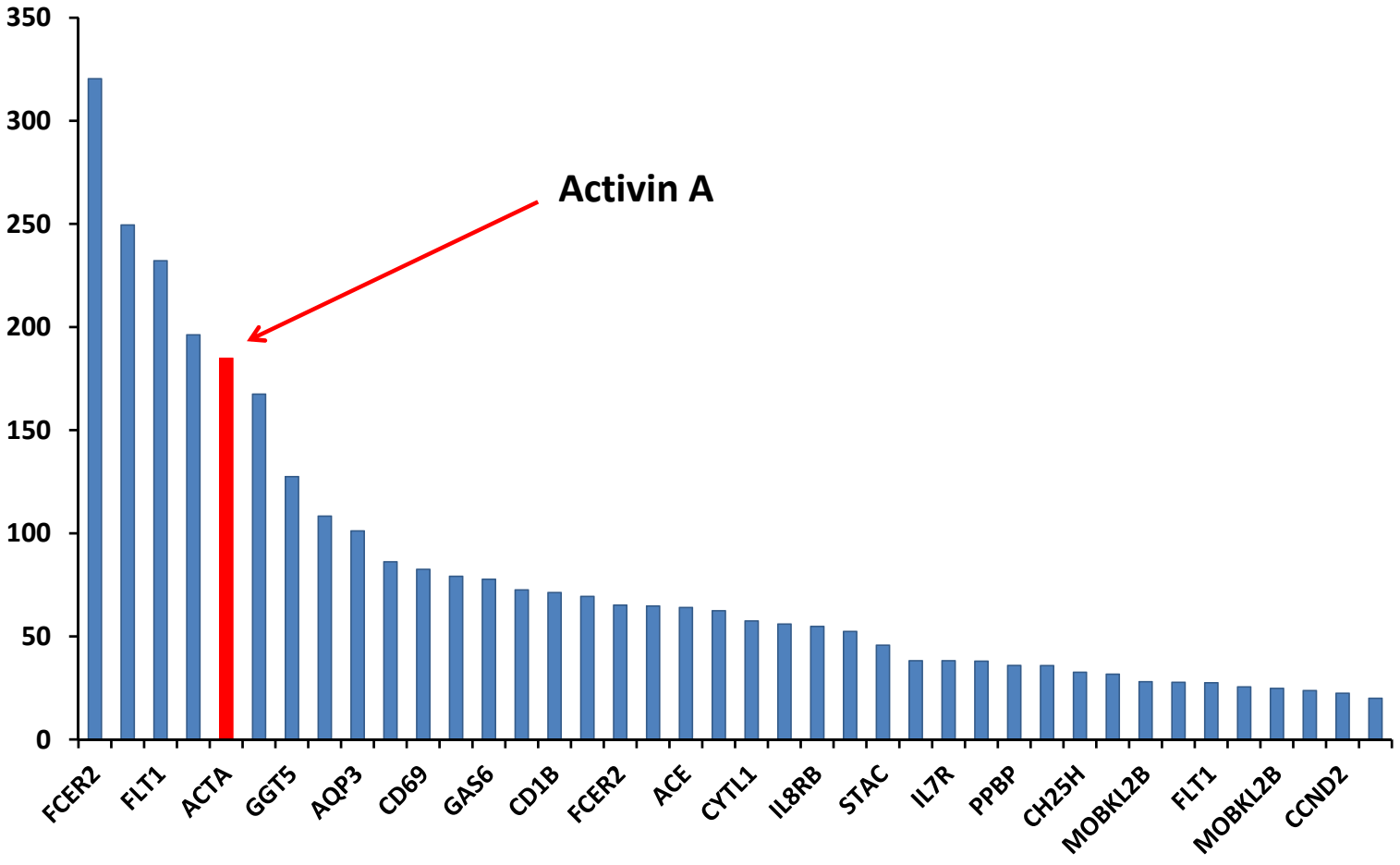


Silbermann R, et al: Leukemia, 2013

"Phase II Study of ACE -011 (Activin A Receptor Antagonist) on bone mass and turnover in patients with multiple myeloma"

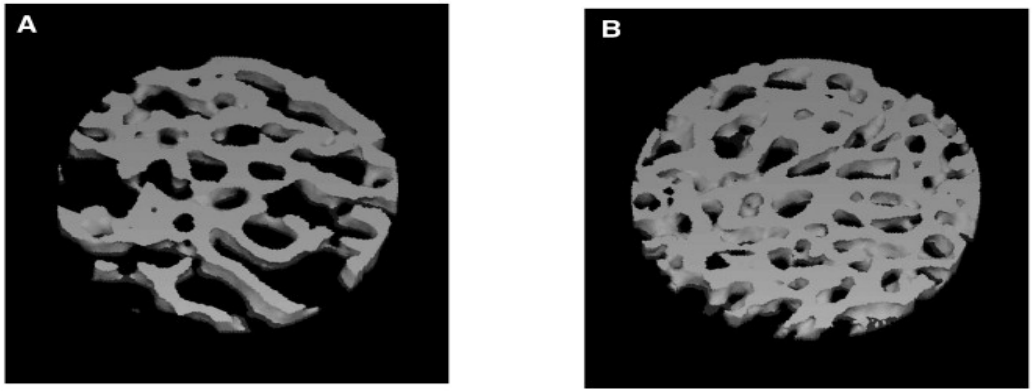
IL-3 Treatment of MM CD14+ Bone Marrow Cells Increases Activin A Expression 184-Fold

Silberman et al Leukemia 2014



ACE-011(sotatercept) Increases Bone in Animal Models

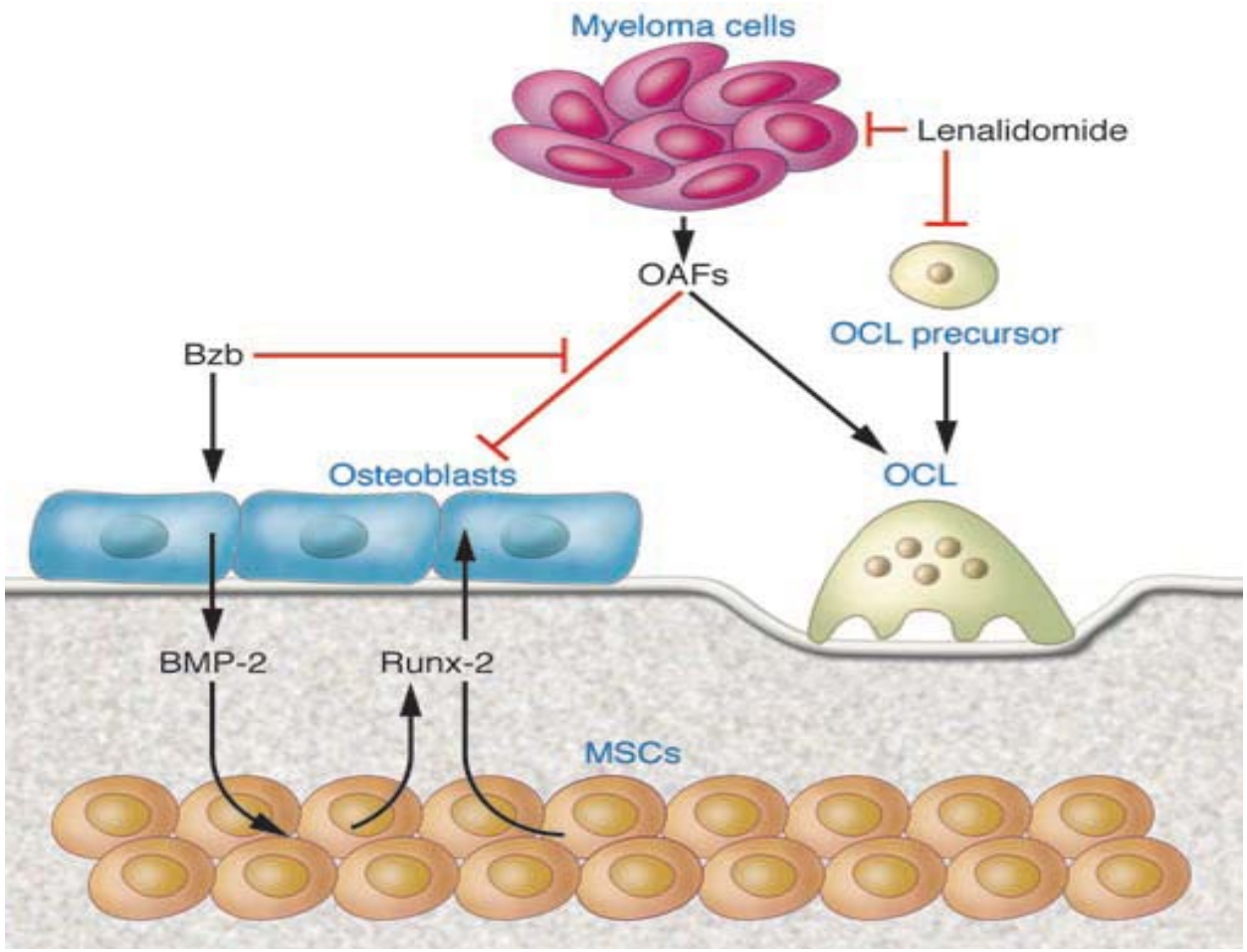
VEH **ACE-011**



Also increases Hemoglobin: phase 2 trial in MDS

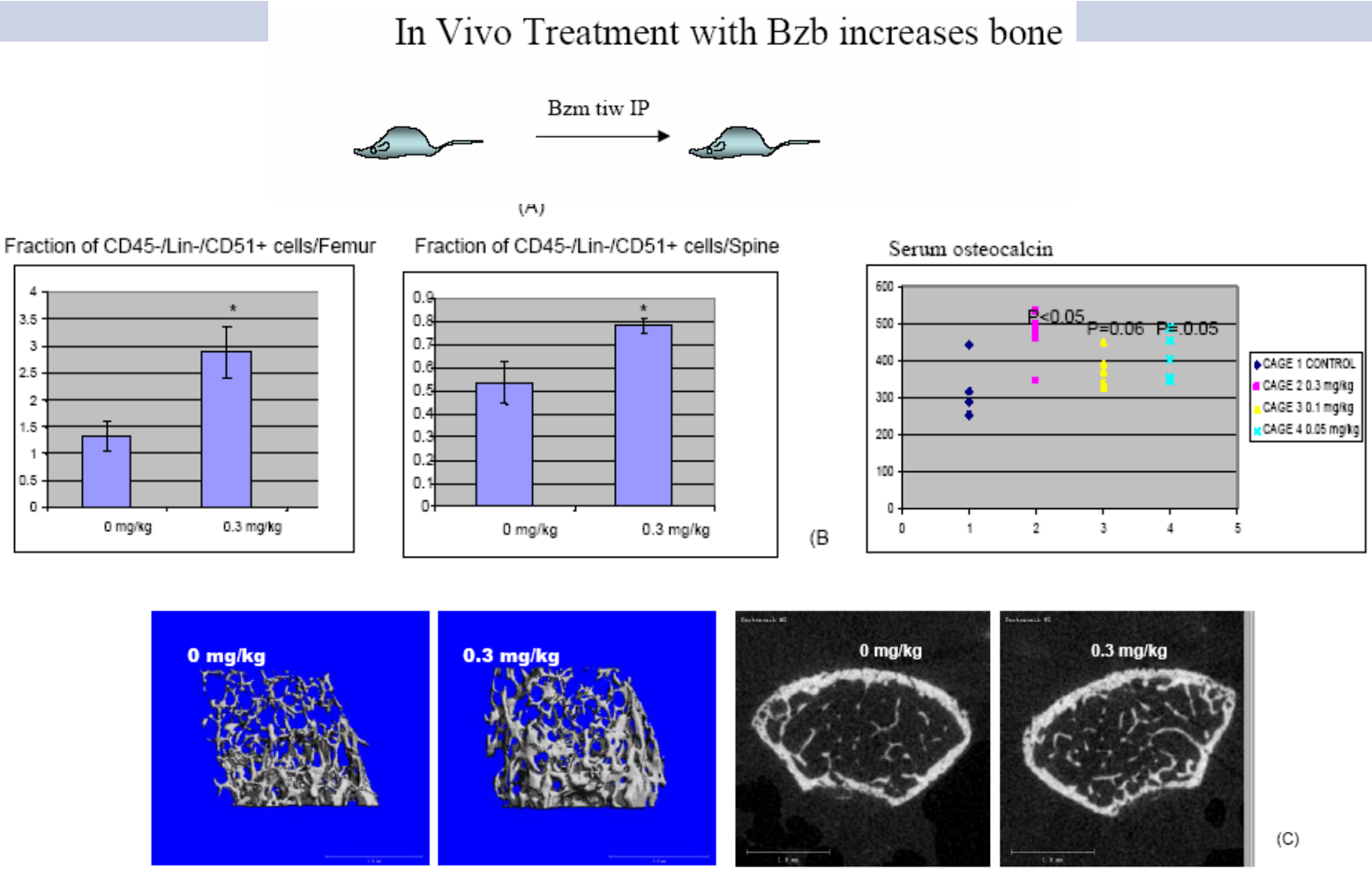
Lotinun S, et al Bone. 2010 Jan 18.

Bortezomib / Lenalidomide in Myeloma Bone Disease



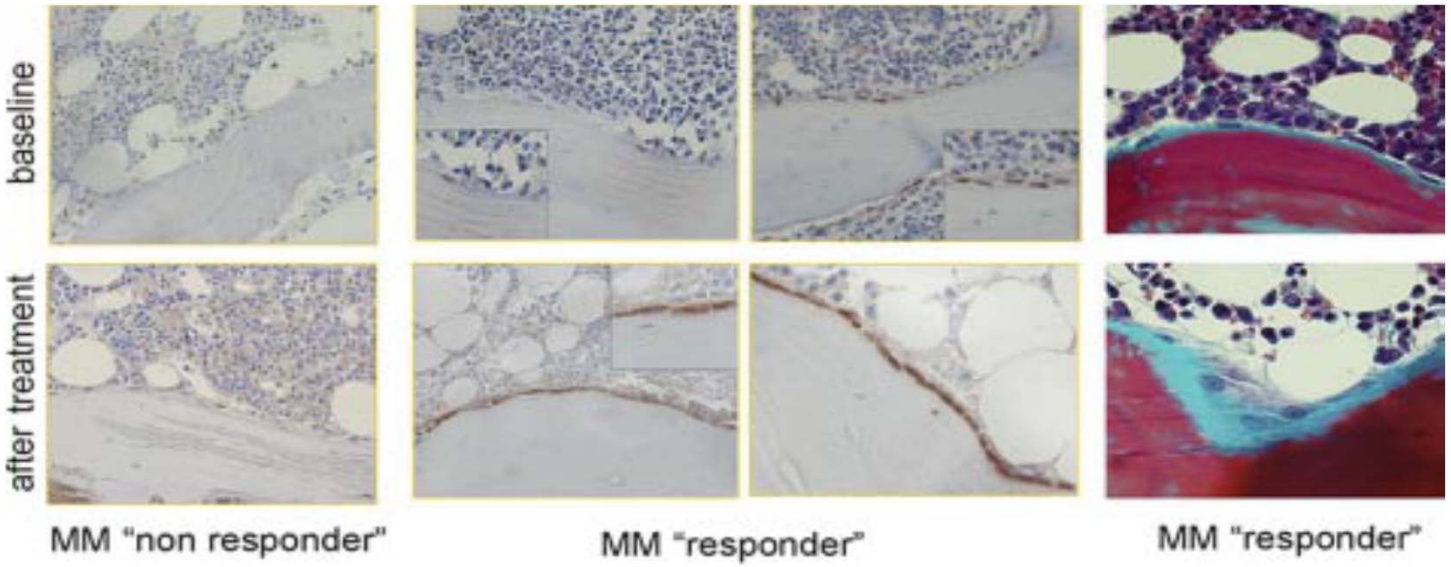
Roodman GD JCI 2008 118:462-4

Bortezomib induces OBL Differentiation



Mukherjee et al. J Clin Inv 2008

Bortezomib Increases Bone Formation in Responding MM Patients



Giuliani N et al BLOOD 2007 :110,334

Novel Approaches for MM Bone Disease

Target	Potential Therapy
RANKL	Denosumab
MIP-1 alpha	CCR1 Receptor antagonist
DKK1/sFRP-2	Anti-DKK1, Bortezomib
Activin A	ACE-011
Sclerostin	Anti-Sclerostin
GFI-1	HDAC1 inhibitors

Summary

- Bone disease continues to be a major cause of severe morbidity and increased mortality in myeloma patients.
- Studies delineating the pathophysiology of myeloma bone disease have provided multiple potential therapeutic targets for treating patients.
- Current strategies;bisphosphonates, Vitamin D, weight bearing exercise
- Novel agents that target Myeloma can also target bone cells.

Acknowledgements

David Roodman; Noopur Raje

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