Romosozomab and New Osteoanabolics

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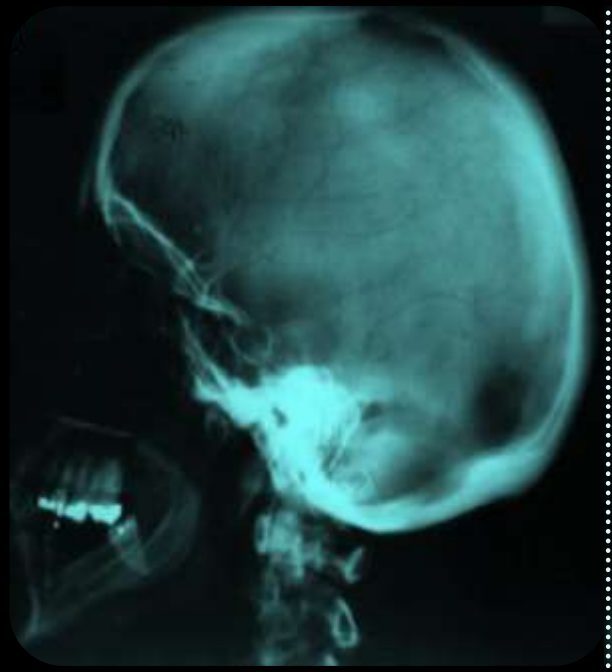
XXXII CONGRESO DE LA SOCIEDAD CHILENA DE OSTEOLOGÍA Y METABOLISMO MINERAL - SCHOMM

Sclerosteosis Highlighted Potential Role for Sclerostin Inhibition in Treatment of Osteoporosis[1]

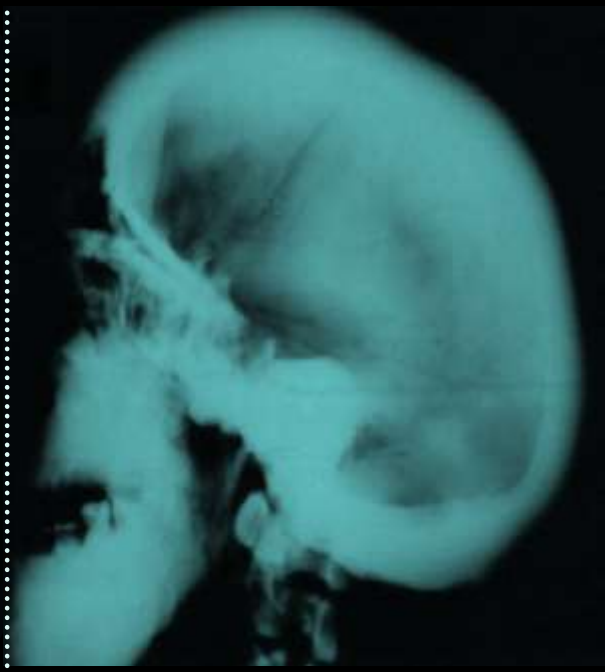
Sclerostin is an osteocyte-derived inhibitor of bone formation[2]

Sclerosteosis is a rare genetic disorder resulting in a sclerostin deficiency and increased modeling-based bone formation[3]

Sclerosteosis patients are typically fracture resistant[3]



HETEROZYGOUS CARRIER[4]

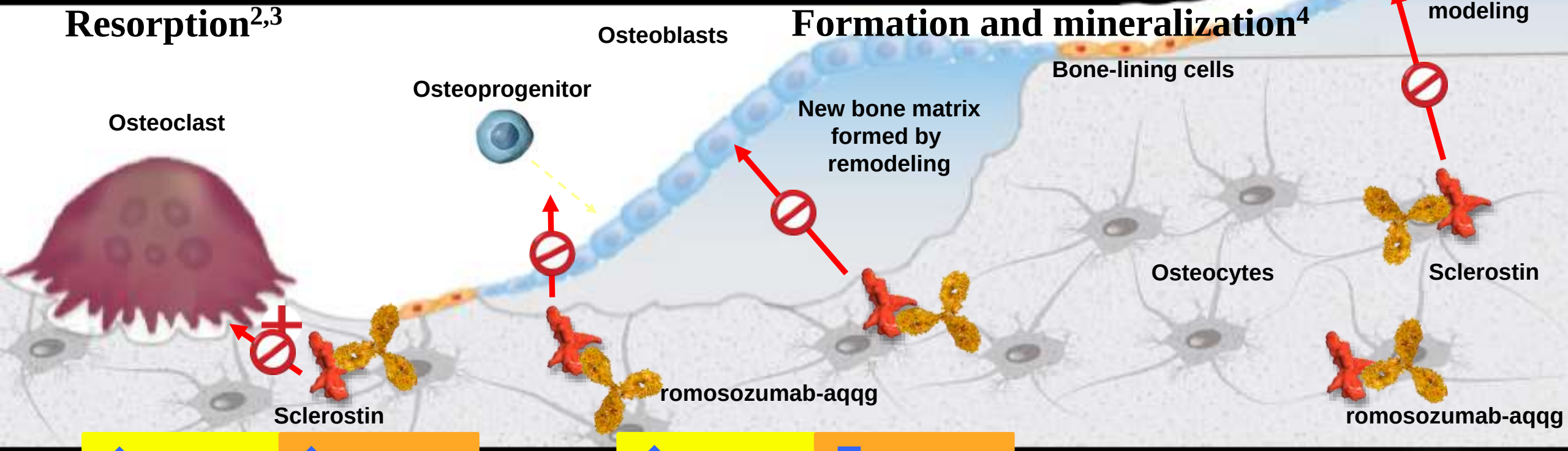


SCLEROSTEOSIS[4]

1. Brunkow ME *Am J Hum Genet*. 2001;68:577
2. Robling AG *J Musculoskelet Neuronal Interact*. 2006;6:354
3. Hamersma H *Clin Genet*. 2003;63:192
4. Gardner JC *J Clin Endocrinol Metab*. 2005;90:6392.

Sclerostin Dual Effects through Multiple Molecular Processes

Romosozumab increases bone formation and, to lesser extent, decreases bone resorption



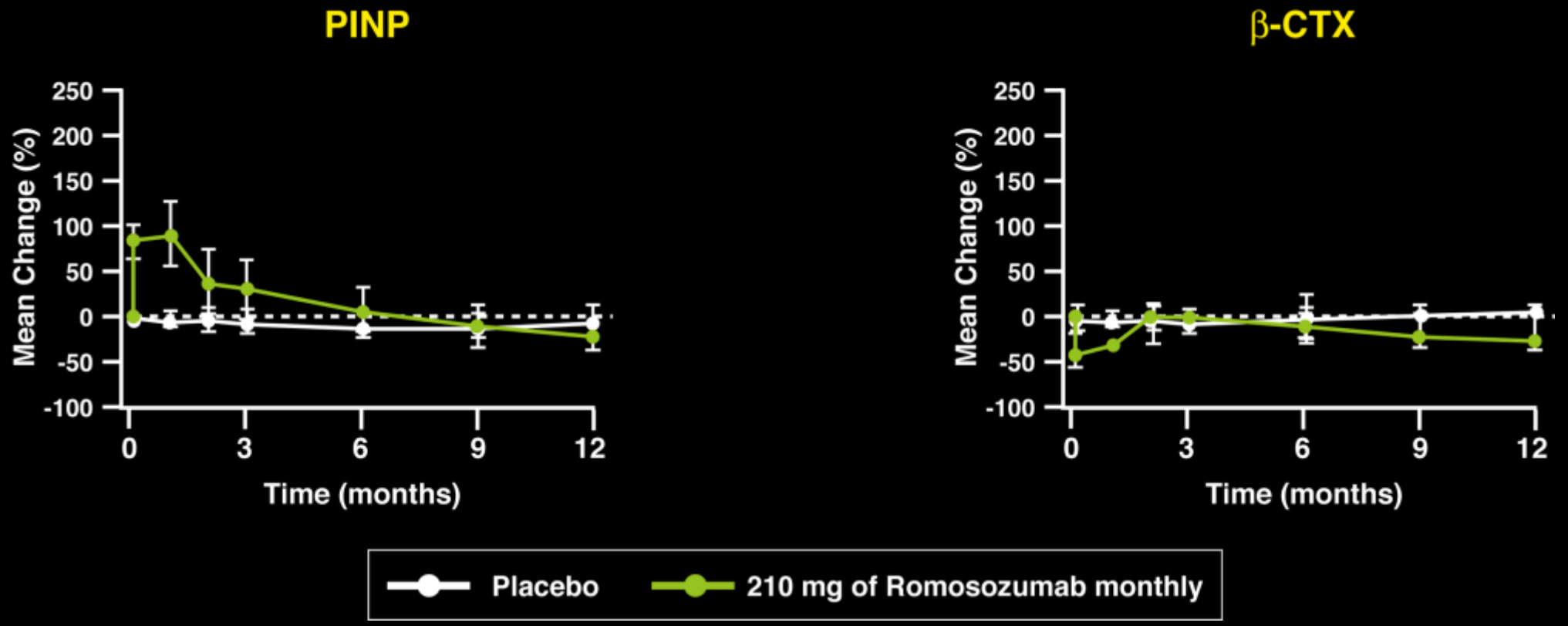
Sclerostin ↑ → Resorption ↑ …through changes in cytokines[5]

Sclerostin ↑ → Formation ↓ …through effects on osteoblast differentiation and activity[1,6]

Ominsky M. *Bone*. 2017;96:63
Crockett JC. *J Cell Sci*. 2011;124:991
Winkler DG. *EMBO J*. 2003;22:6267

Anti-Sclerostin Antibody

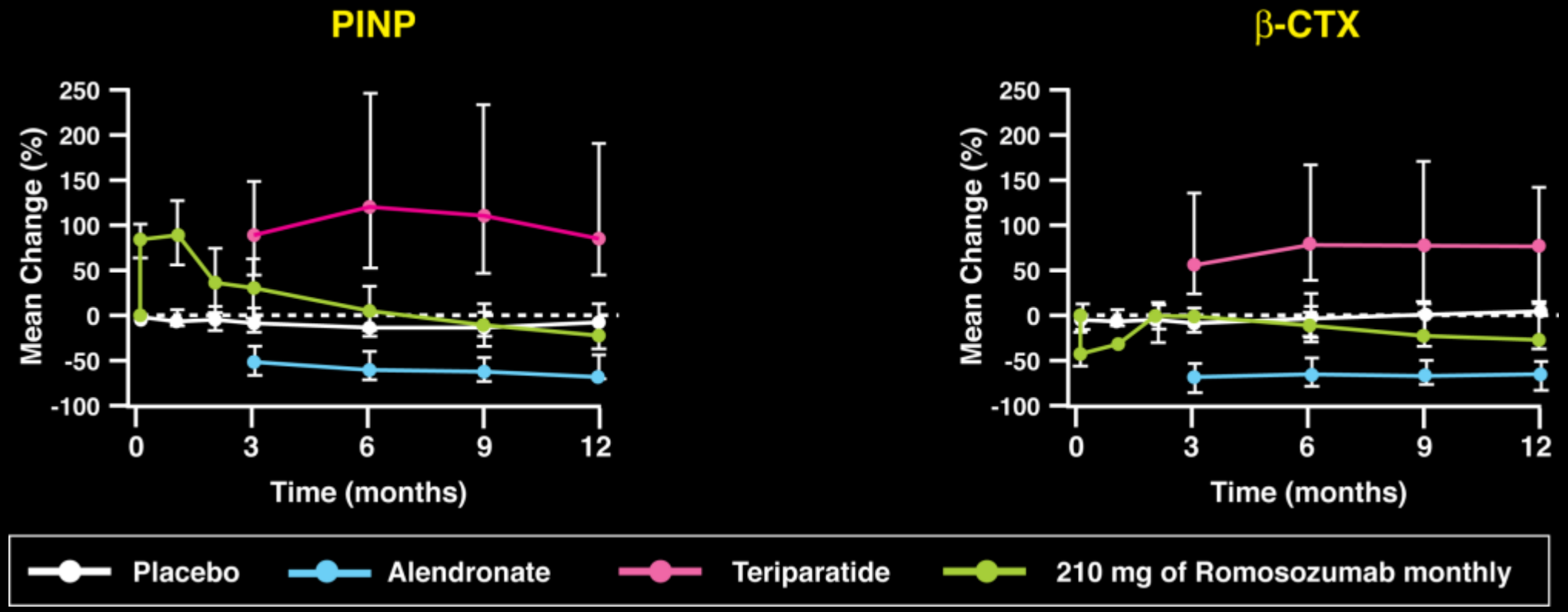
Romosozumab Phase 2, Bone Turnover Markers



McClung M. *N Engl J Med* 2014;370:412

Anti-Sclerostin Antibody

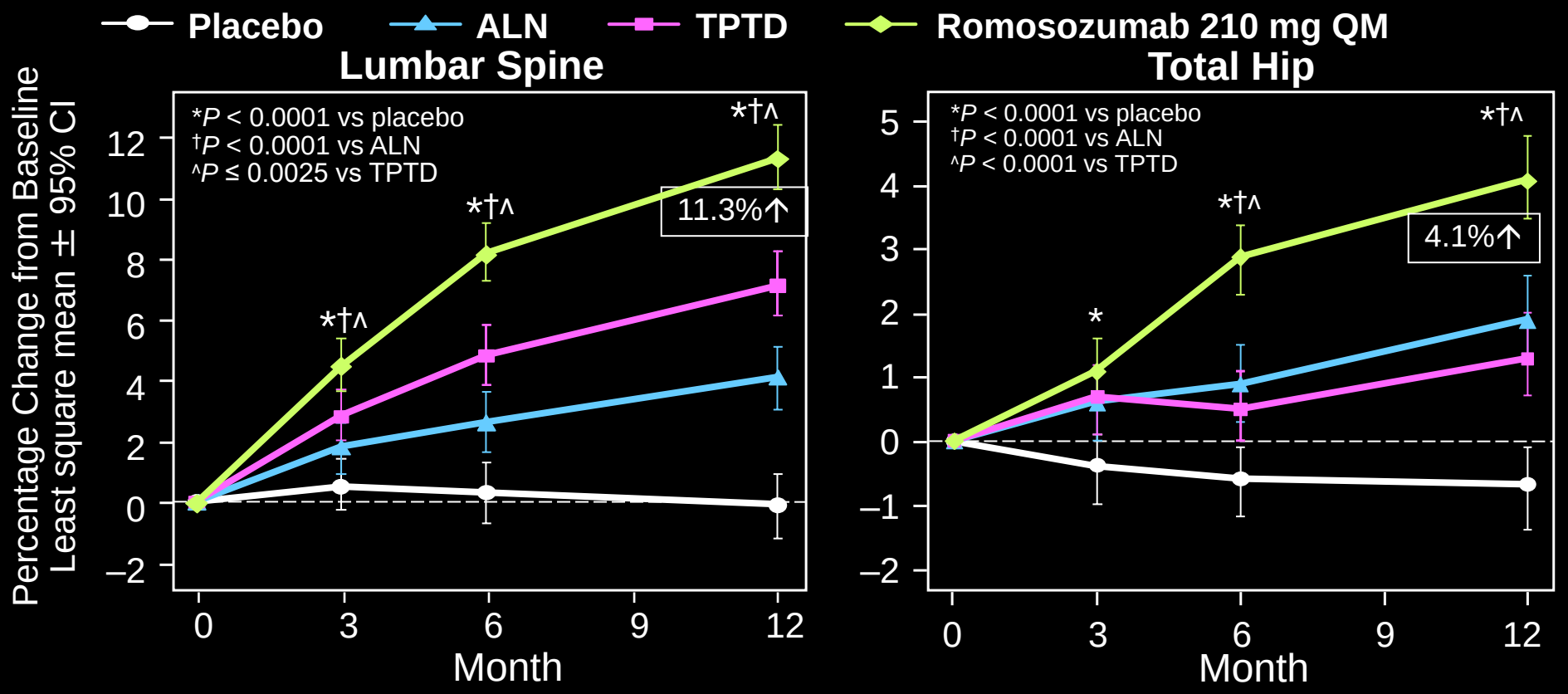
Romosozumab Phase 2, Bone Turnover Markers



McClung M. *N Engl J Med* 2014;370:412

Anti-Sclerostin Antibody

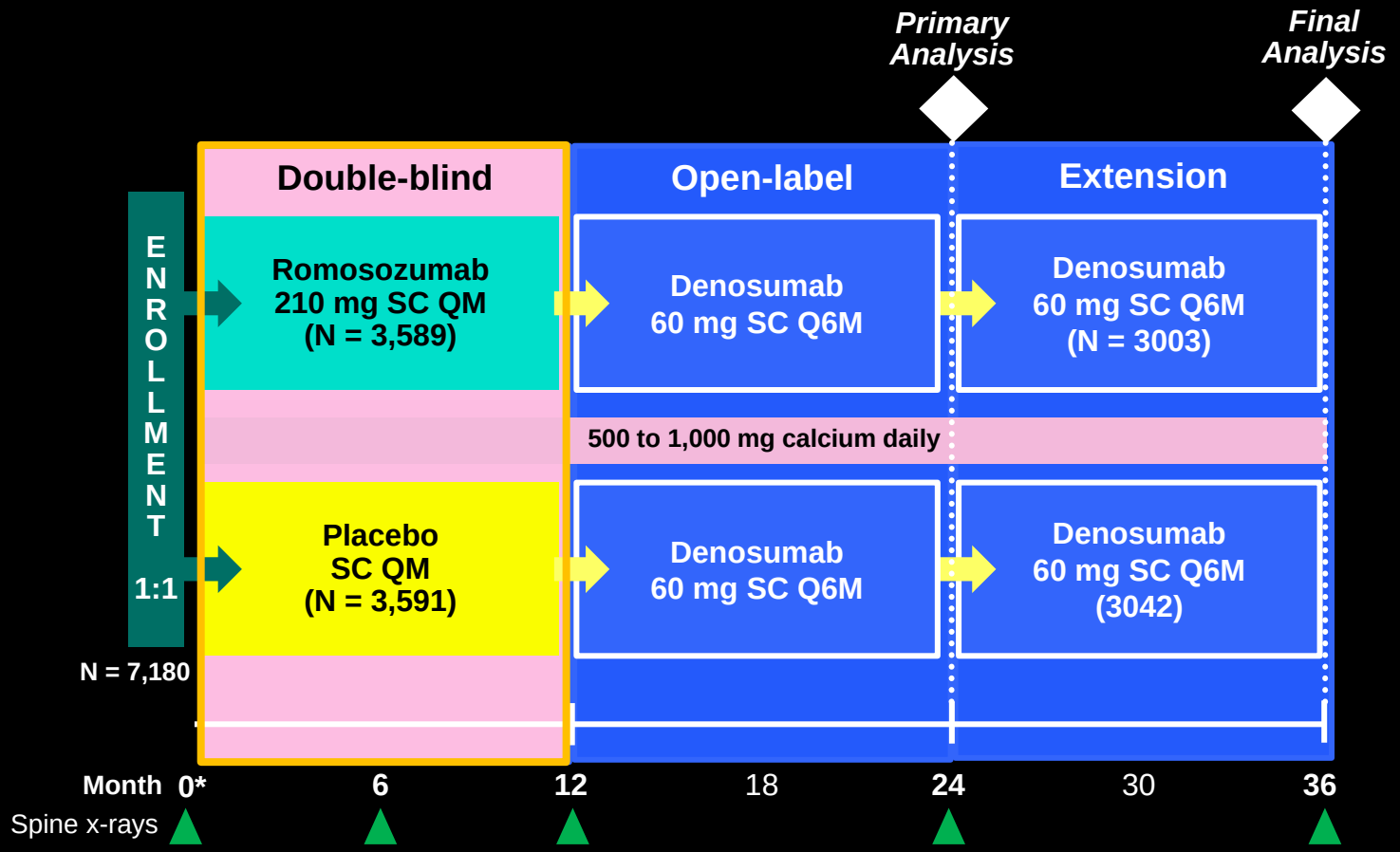
Romosuzumab Phase 2, BMD



McClung M. *N Engl J Med* 2014;370:412

Romosozumab In a Moderate Risk Population – FRAME Efficacy and Safety

FRAME Study Design



Inclusion:

- Postmenopausal women age 55 to 90 years
- BMD T-score ≤ -2.5 at the total hip or femoral neck

Exclusion:

- BMD T-score ≤ -3.5 at the total hip or femoral neck
- History of hip fracture, or any severe or more than 2 moderate vertebral fractures
- Recent osteoporosis therapy

Co-Primary Endpoints:

- Subject incidence of new vertebral fracture through 12 and 24 months

Secondary Fracture Endpoints:

- Clinical, nonvertebral, and other fracture categories through 12 and 24 months

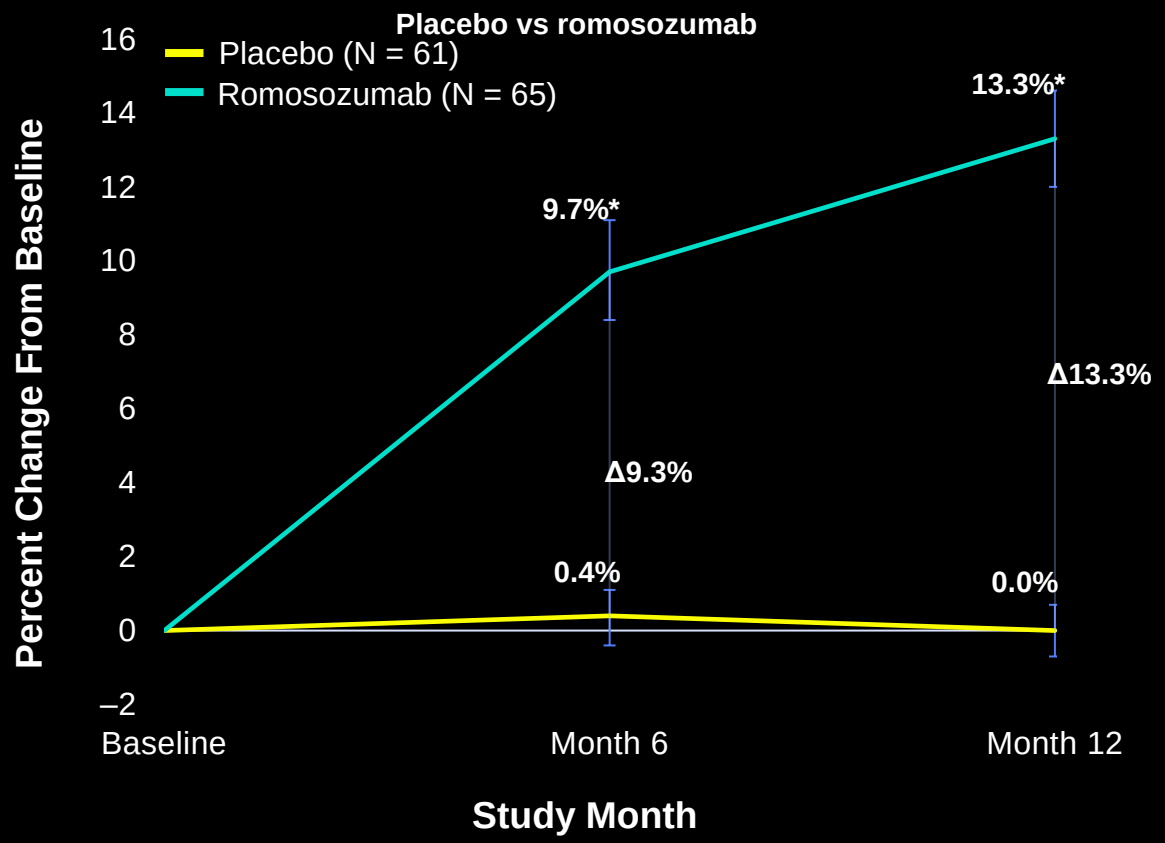
Extension Exploratory Endpoints:

- Clinical, nonvertebral, and other fracture categories through M36

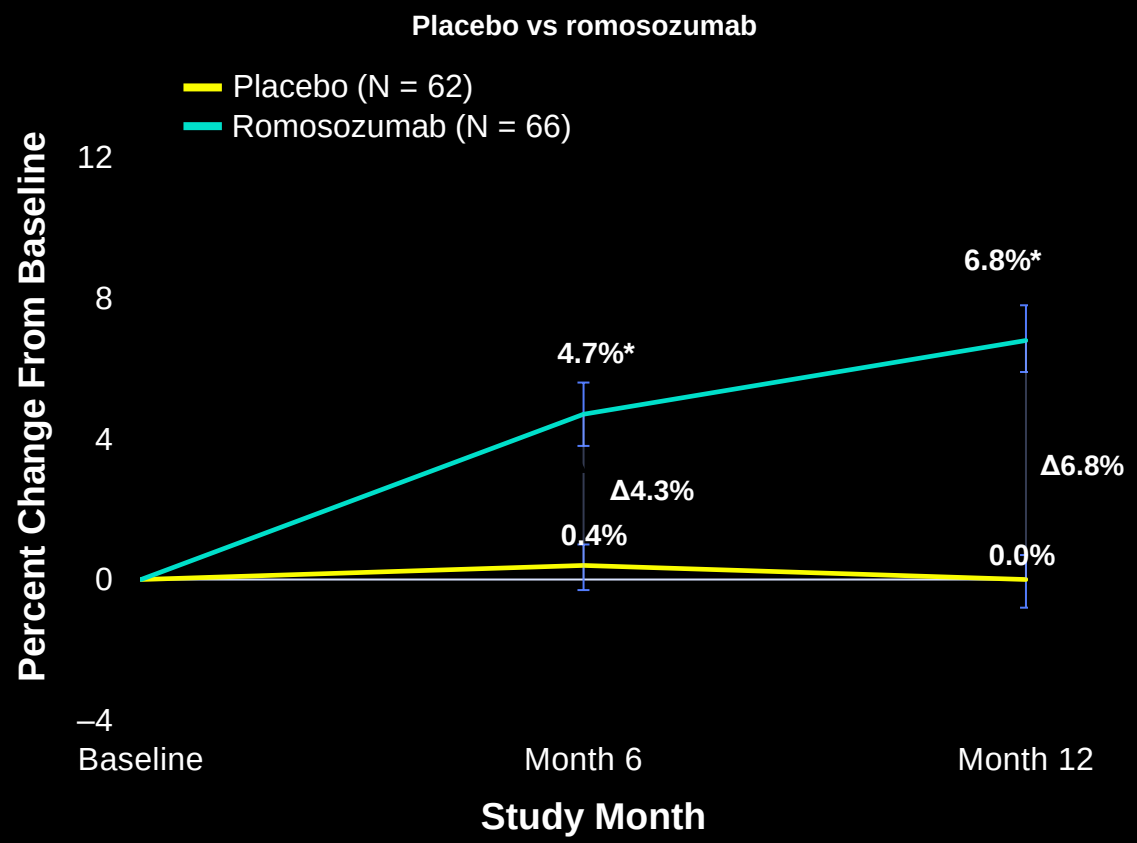
Cosman F. *N Engl J Med*. 2016;375:1532.

FRAME: Romosozumab vs Placebo: Lumbar Spine and Total Hip BMD Through Month 12

Lumbar Spine



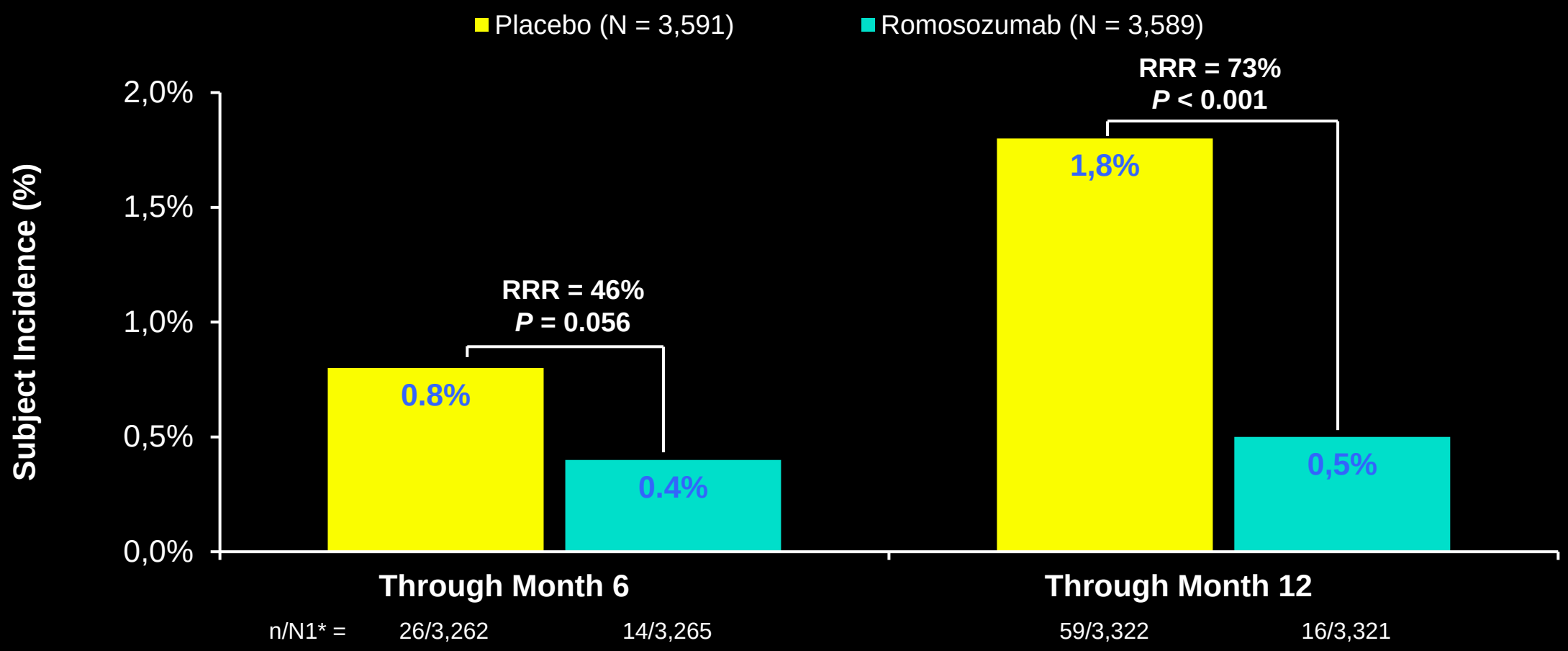
Total Hip



*P < 0.001 compared with placebo. Data are least square means (95% CI) adjusted for relevant baseline covariates.
BMD=bone mineral density; CI=confidence interval; Δ=difference

Cosman F. *N Engl J Med*. 2016;375:1532

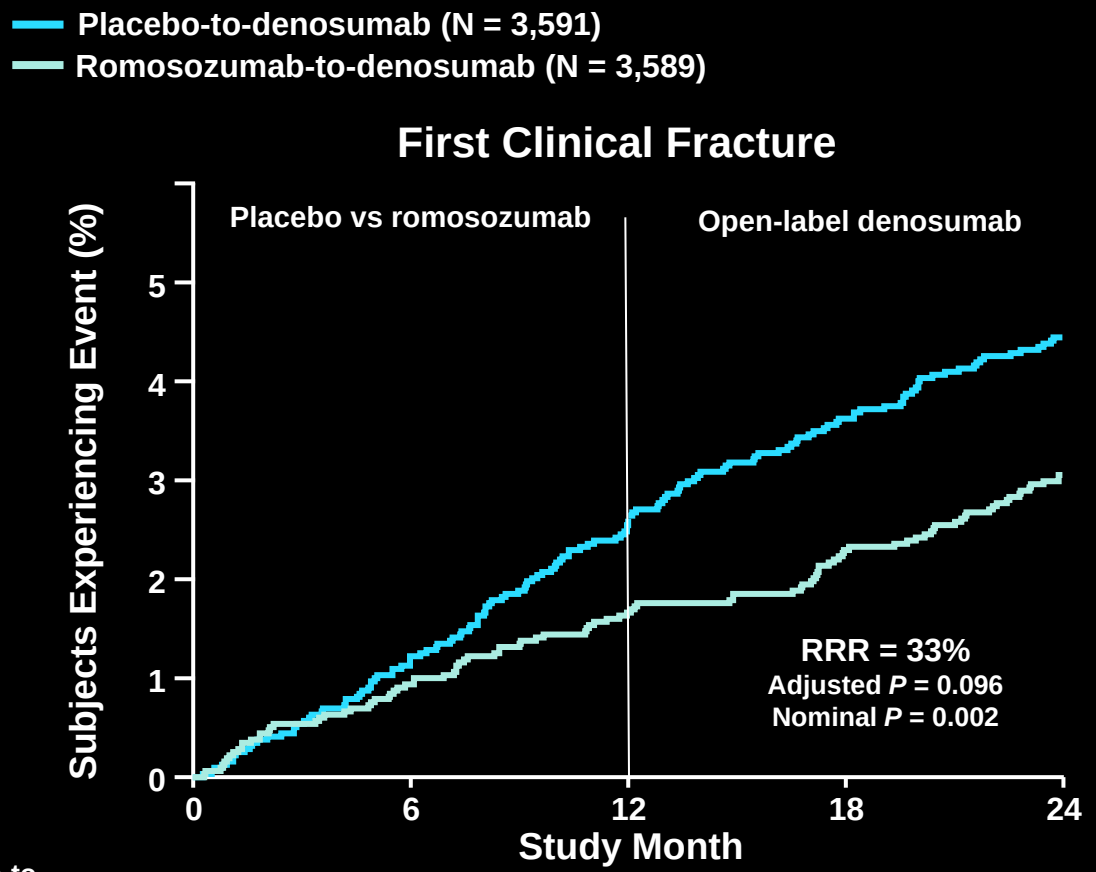
FRAME: Romosozumab vs Placebo: New Vertebral Fracture Through Month 12

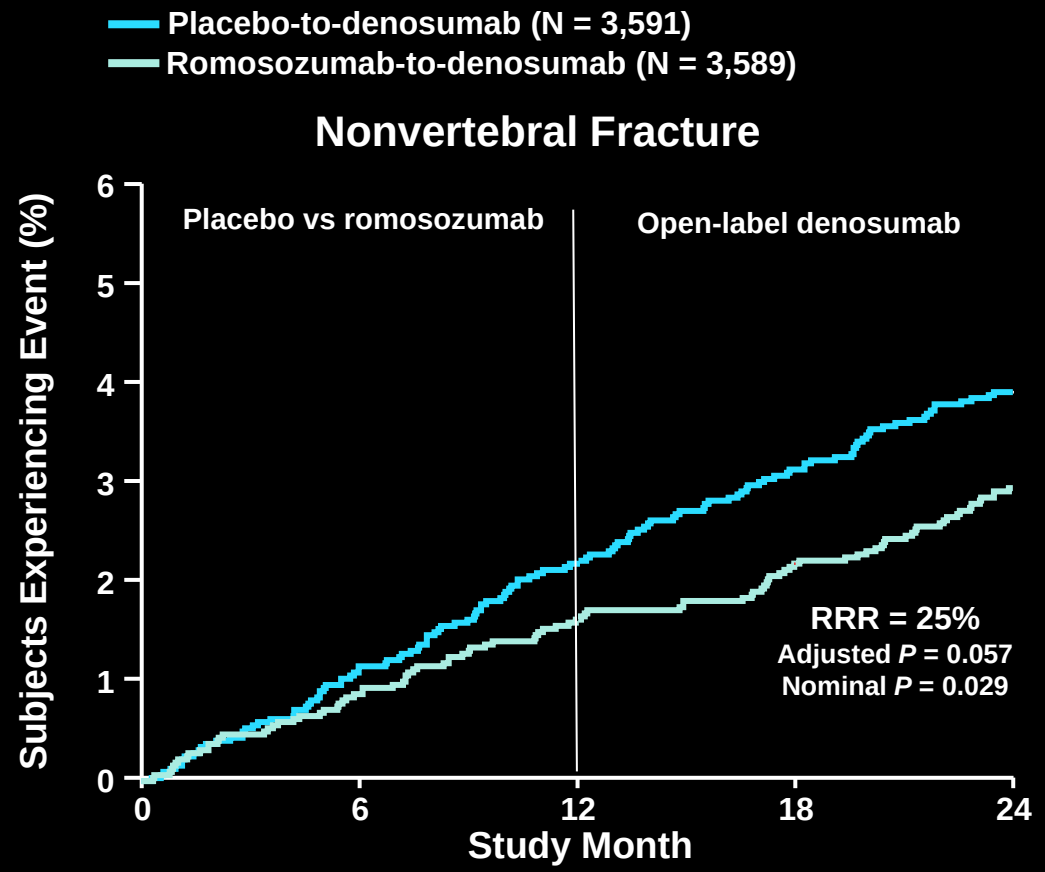


n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures; *P*-value based on logistic regression model adjusted for age (< 75, ≥ 75) and prevalent vertebral fracture. RRR=relative risk reduction

Cosman F. *N Engl J Med*. 2016;375:1532

FRAME: Time to First Clinical Fracture and Nonvertebral Fracture Through Month 24





Placebo-to-denosumab n =	3,591	3,316	3,134	3,037	2,955
Romosozumab-to-denosumab n =	3,589	3,317	3,148	3,050	2,968

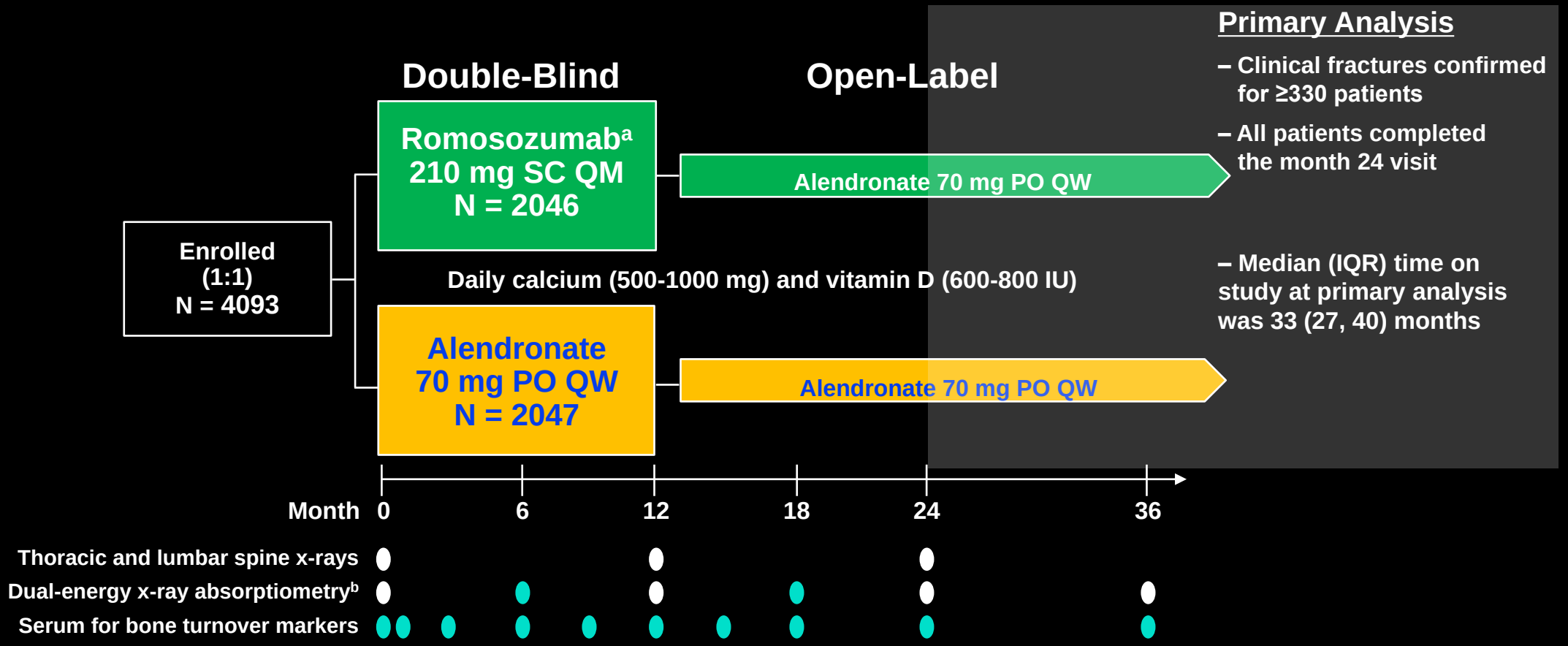
Placebo-to-denosumab n =	3,591	3,318	3,145	3,052	2,967
Romosozumab-to-denosumab n =	3,589	3,318	3,149	3,051	2,970

Clinical fractures included all nonvertebral and symptomatic vertebral fractures. Non-vertebral fractures comprised the majority (more than 85%) of clinical fractures and excluded fractures of the skull, facial bones, metacarpals, fingers, and toes, pathologic fractures and fractures associated with high trauma. n = number of subjects at risk for event at time point of interest. *P*-value based on RRR. RRR=relative risk reduction

Cosman F. *N Engl J Med*. 2016;375:1532

Romosozumab First Before Antiresorptive Therapy In High-Risk, Post-Fracture Patients – ARCH Efficacy and Safety

ARCH Study Design

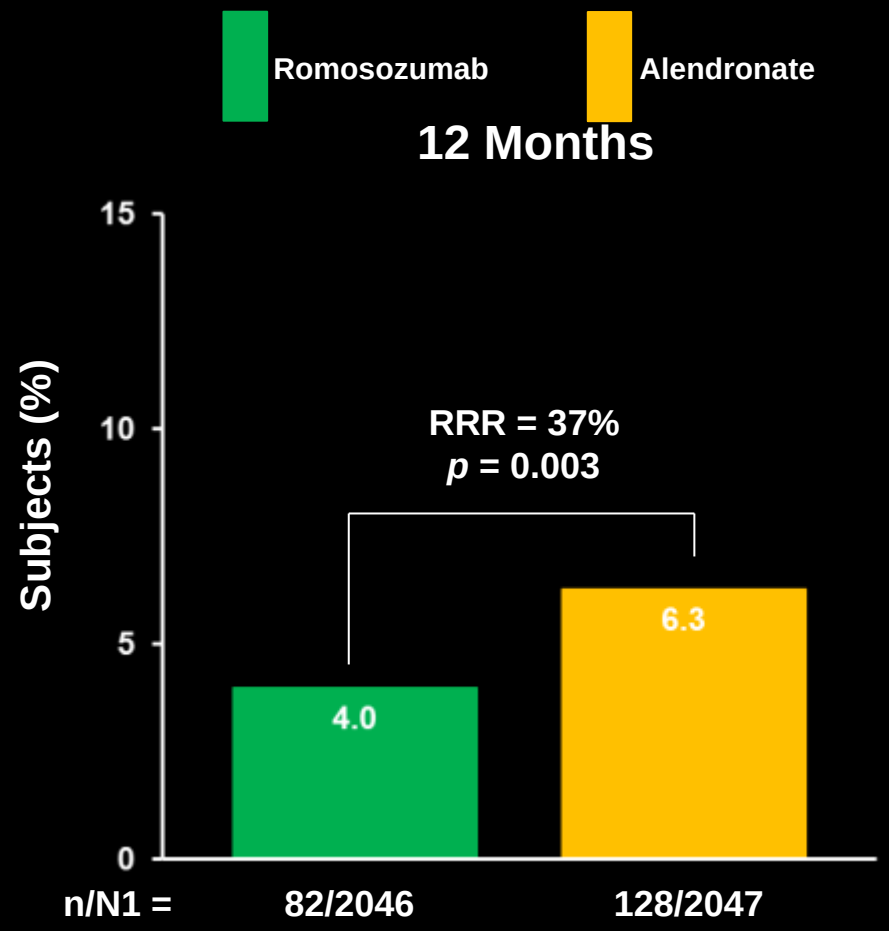


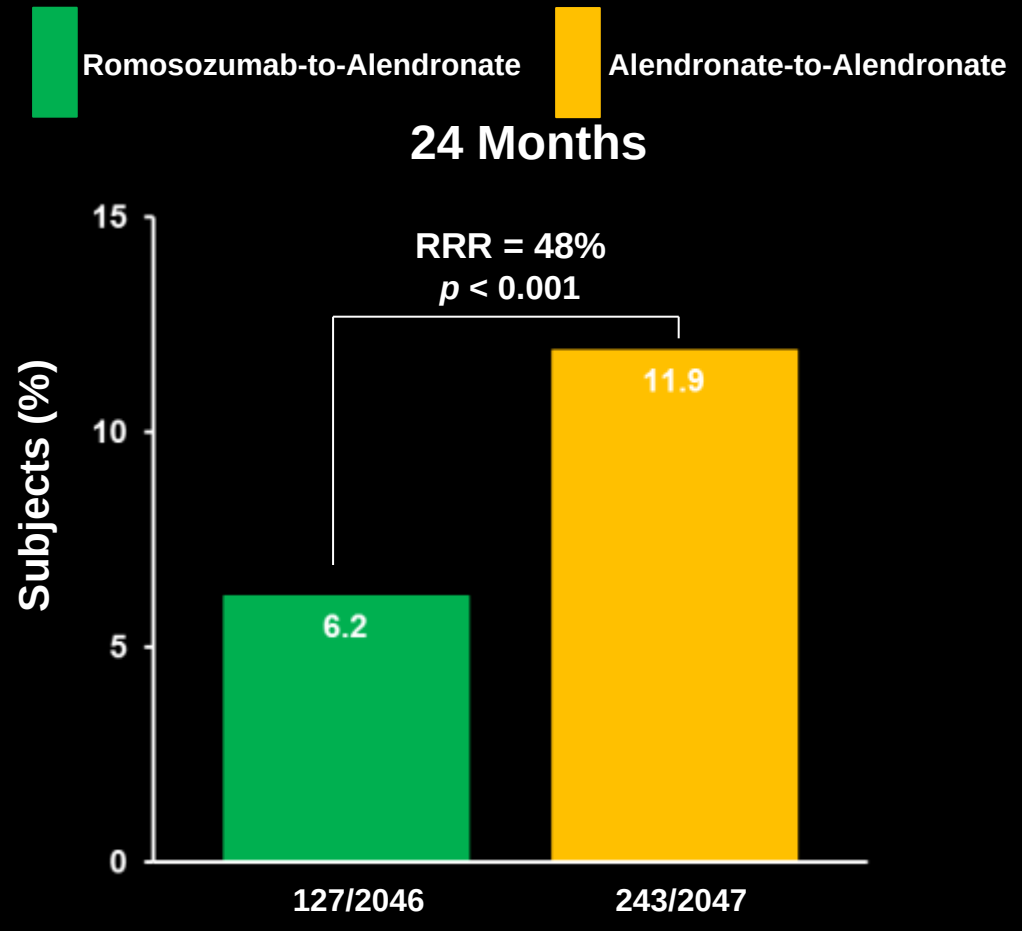
[a]Loading dose of 50,000–60,000 IU vitamin D ; [b]BMD assessed at months 6 and 18 in a subset of patients in substudy; n=167. Yellow ovals indicate timepoints for substudy.

Saag K. *NEJM* 2017; 377:1417

Romosozumab ARCH Study

Vert Fractures Reduced More with Romosozumab than Alendronate



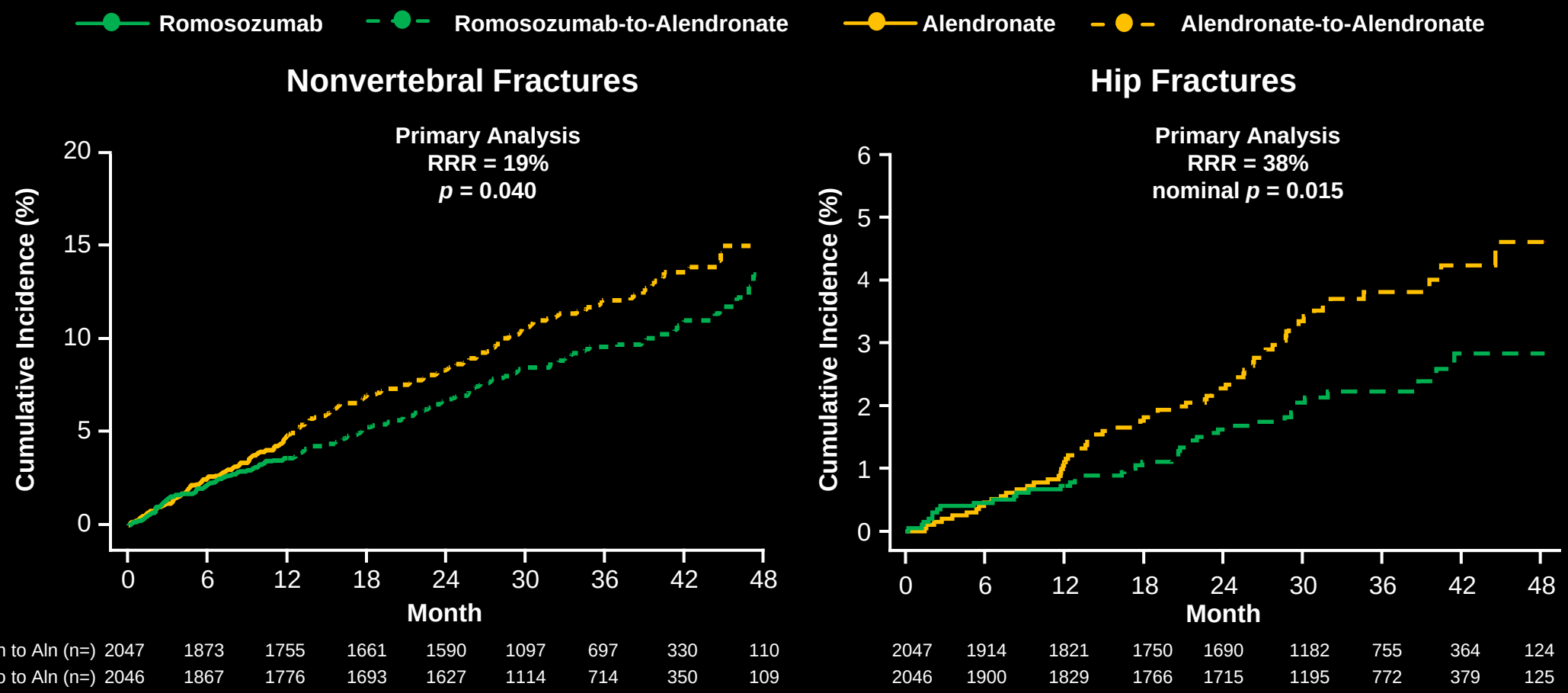


n/N1 = Number of subjects with fractures/Number of subjects in the primary analysis set for vertebral fractures. Missing fracture status was imputed by multiple imputation for patients without observed fracture at an earlier timepoint. n and % are based on the average across 5 imputed datasets. RRR = relative risk reduction.

Saag K. *NEJM* 2017; 377:1417

Romosozumab ARCH Study

Nonvertebral Fracture and Hip Fracture Trend Towards Greater Benefit with Romosozumab



n = number of subjects at risk for event at time point of interest. Aln = alendronate; Romo = romosozumab.

Saag K. *NEJM* 2017; 377:1417

Serious Adverse Events in ARCH

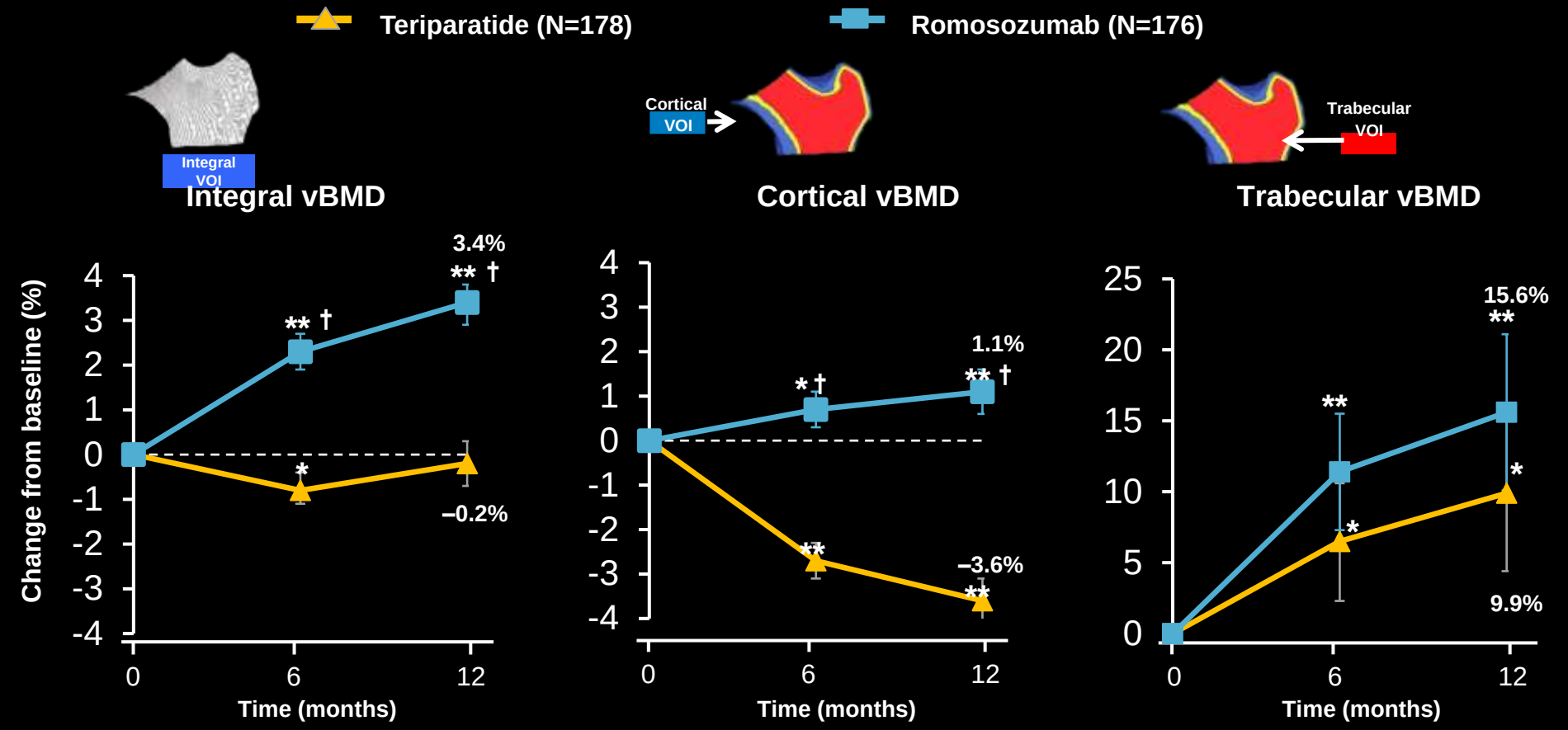
	Month 12 Double-Blind Period	
	Romosozumab N = 2040	Alendronate N = 2014
All adverse events	1544 (75.7)	1584 (78.6)
Serious adverse events	262 (12.8)	278 (13.8)
Adjudicated serious cardiovascular event[a]	50 (2.5)	38 (1.9)
Cardiac ischemic event	16 (0.8)	6 (0.3)
Cerebrovascular event	16 (0.8)	7 (0.3)
Heart failure	4 (0.2)	8 (0.4)
Cardiovascular death	17 (0.8)	12 (0.6)
Non-coronary revascularization	3 (0.1)	5 (0.2)
Peripheral vascular ischemic event not requiring revascularization	0 (0.0)	2 (< 0.1)
Death	30 (1.5)	21 (1.0)

Data are n (%). N = number of subjects who received ≥ 1 dose of investigational product. [a]Adverse events adjudicated positive by an independent adjudication committee. Cardiovascular deaths includes fatal events adjudicated as cardiovascular-related or undetermined (presumed cardiac-related). [b]Incidence rates through primary analysis were cumulative and included all events in the double-blind and open-label period in subjects who received ≥ 1 dose of investigational product.

Saag K. *NEJM* 2017; 377:1417

Romosozumab vs Teriparatide In Patients Transitioning From Oral Bisphosphonates – STRUCTURE Efficacy and Safety

STRUCTURE: Integral, Cortical and Trabecular vBMD at the Hip by QCT



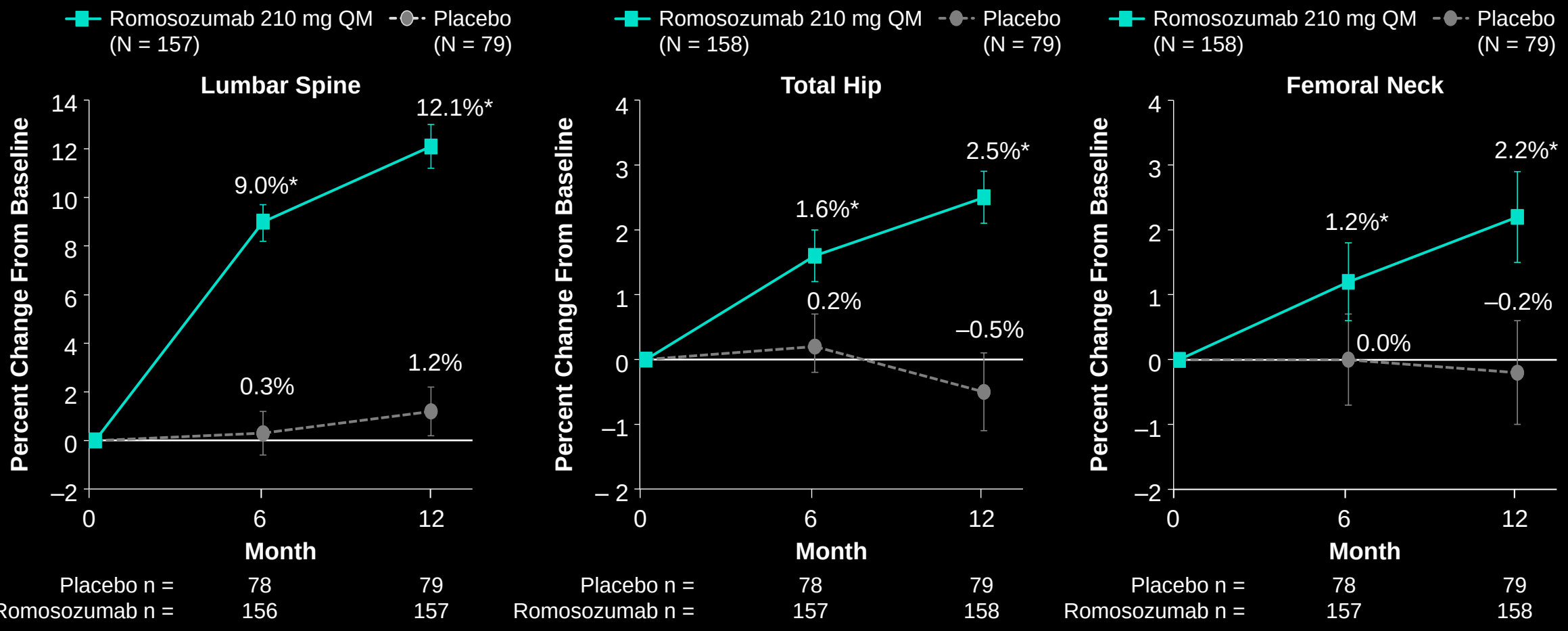
Langdahl BL. *Lancet*. 2017;390:1585

N = number of subjects in the primary efficacy analysis set for QCT and FEA endpoints
Data are shown as least squares means and 95% CIs
*p<0.05 compared with baseline; **p<0.0001 compared with baseline; †p<0.0001 compared with teriparatide
CI, confidence interval; vBMD, volumetric bone mineral density; VOI, volume of interest; QCT, quantitative computed tomography

Romosozumab vs Placebo In Men BRIDGE Efficacy and Safety

BRIDGE Study in Men

Percent Change From Baseline in BMD by Visit



N = all randomized subjects with a baseline and ≥ 1 postbaseline measurement. n = number of subjects with values at baseline and at or prior to the timepoint of interest. Data are least squares means estimates with 95% confidence intervals. BMD = bone mineral density; QM = once monthly.
*p < 0.01 vs placebo.

Lewiecki EM. *Clin Endocrinol Metab.* 2018;103:3183

BRIDGE Study
Summary of Treatment-Emergent Adverse Events

	Romosozumab 210 mg QM N = 163 n (%)	Placebo N = 81 n (%)
Any adverse event	123 (75.5)	65 (80.2)
Serious adverse event	21 (12.9)	10 (12.3)
Adjudicated cardiovascular event	8 (4.9)	2 (2.5)
Death	1 (0.6)	1 (1.2)
Adjudicated cardiovascular death	1 (0.6)	1 (1.2)
Leading to discontinuation of investigational product	5 (3.1)	1 (1.2)
Events of interest		
Hypocalcemia	0 (0.0)	0 (0.0)
Hypersensitivity	8 (4.9)	4 (4.9)
Injection site reactions	9 (5.5)	3 (3.7)
Malignancy	3 (1.8)	2 (2.5)
Hyperostosis	0 (0.0)	0 (0.0)
Osteoarthritis	8 (4.9)	4 (4.9)
Atypical femoral fracture	0 (0.0)	0 (0.0)
Osteonecrosis of the jaw	0 (0.0)	0 (0.0)
Subject incidence of anti-romosozumab antibody formation		
Binding antibodies	29 (18.0)	NA
Neutralizing antibodies	0 (0.0)	NA

Lewiecki EM. *Clin Endocrinol Metab.* 2018;103:3183

N = number of subjects who received ≥ 1 dose of drug; n = number of subjects with ≥ 1 event. NA = not applicable; QM = once monthly

Theories on Numerical Differences in Cardiovascular Adverse Events in Romozosumab ARCH and BRIDGE

Cons

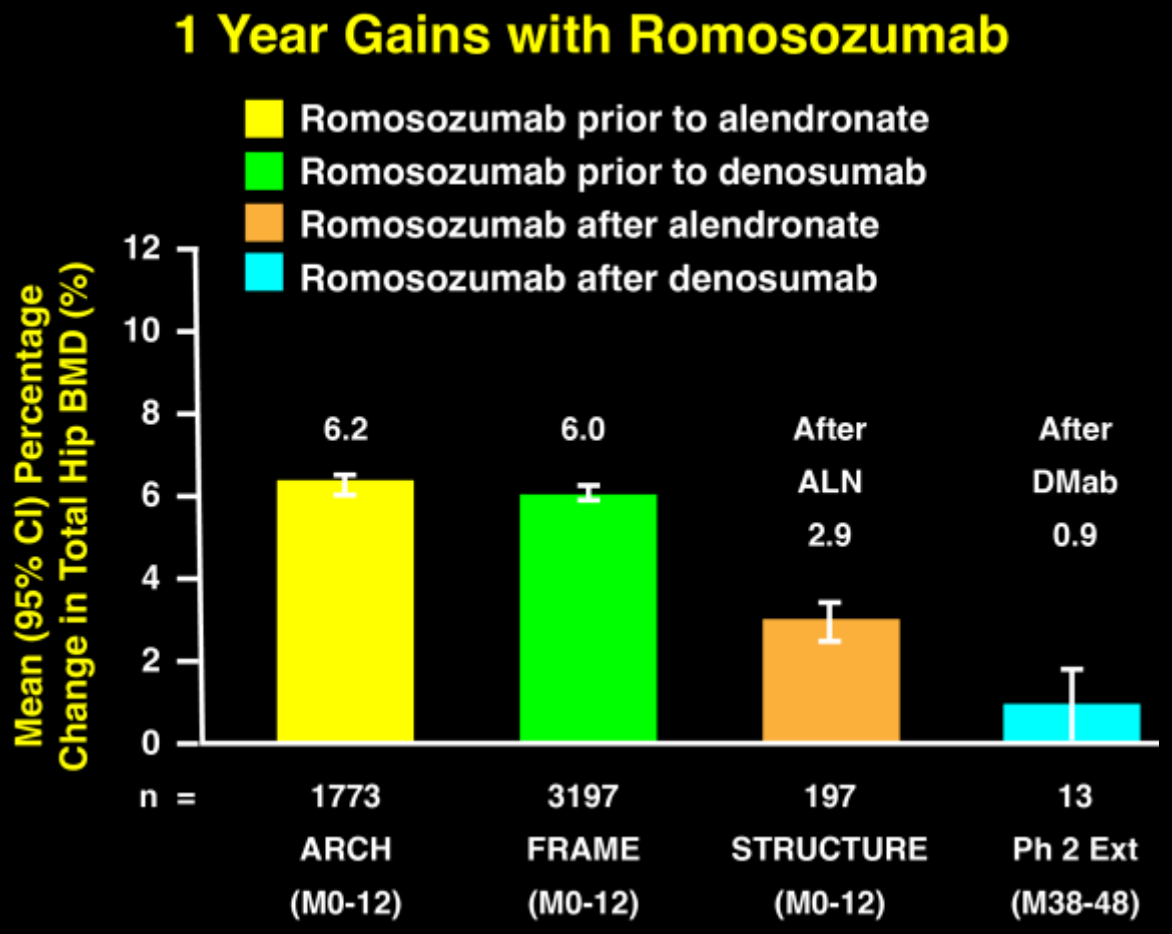
- Possibly due to alendronate being cardioprotective?
- Possibly due to chance since not seen in larger FRAME study?
- Problems with ARCH ALN data?

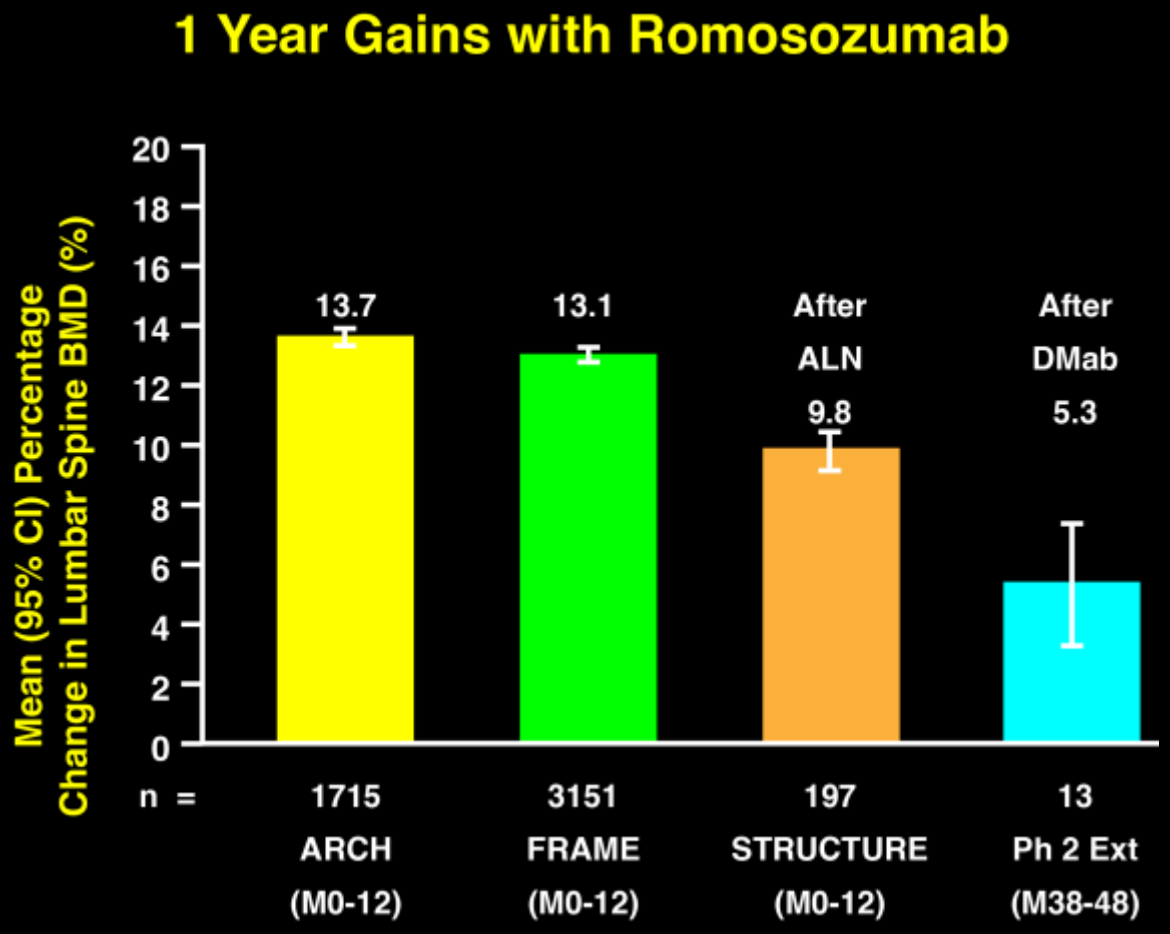
Pros

- Real concern based on Mendelian Randomization data?[1]
- Possibly real and just not seen in a lower risk population (FRAME)?

1. Zheng J. *Arth Rheum* 2023;75:1781

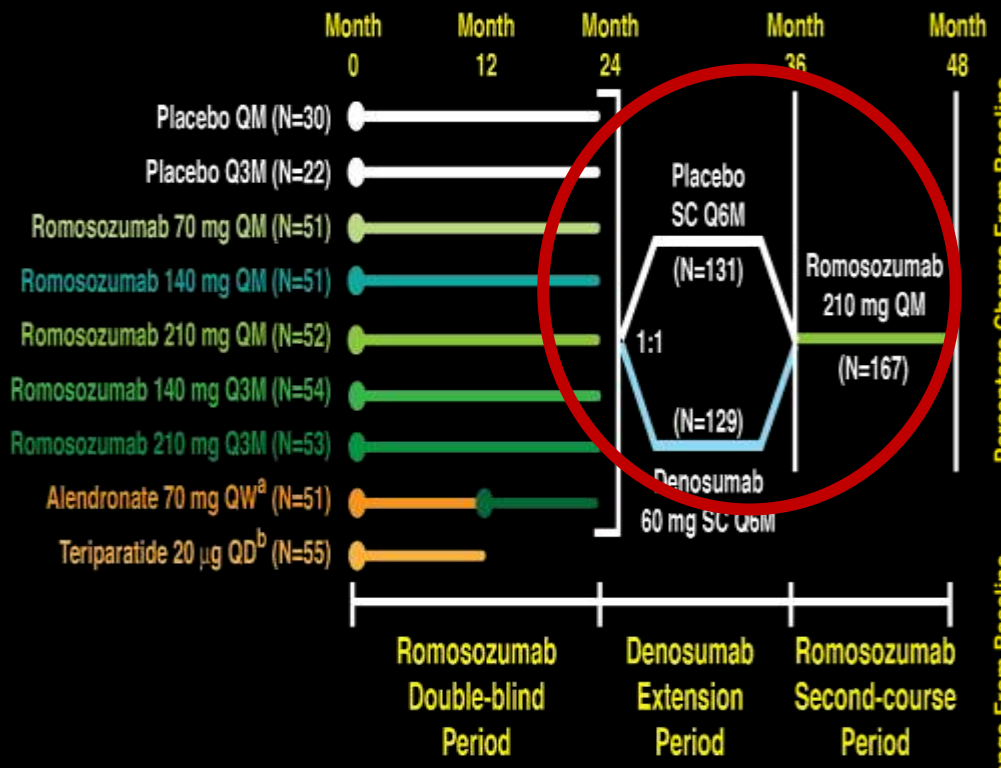
Treatment Sequence Strategies with Romosozumab

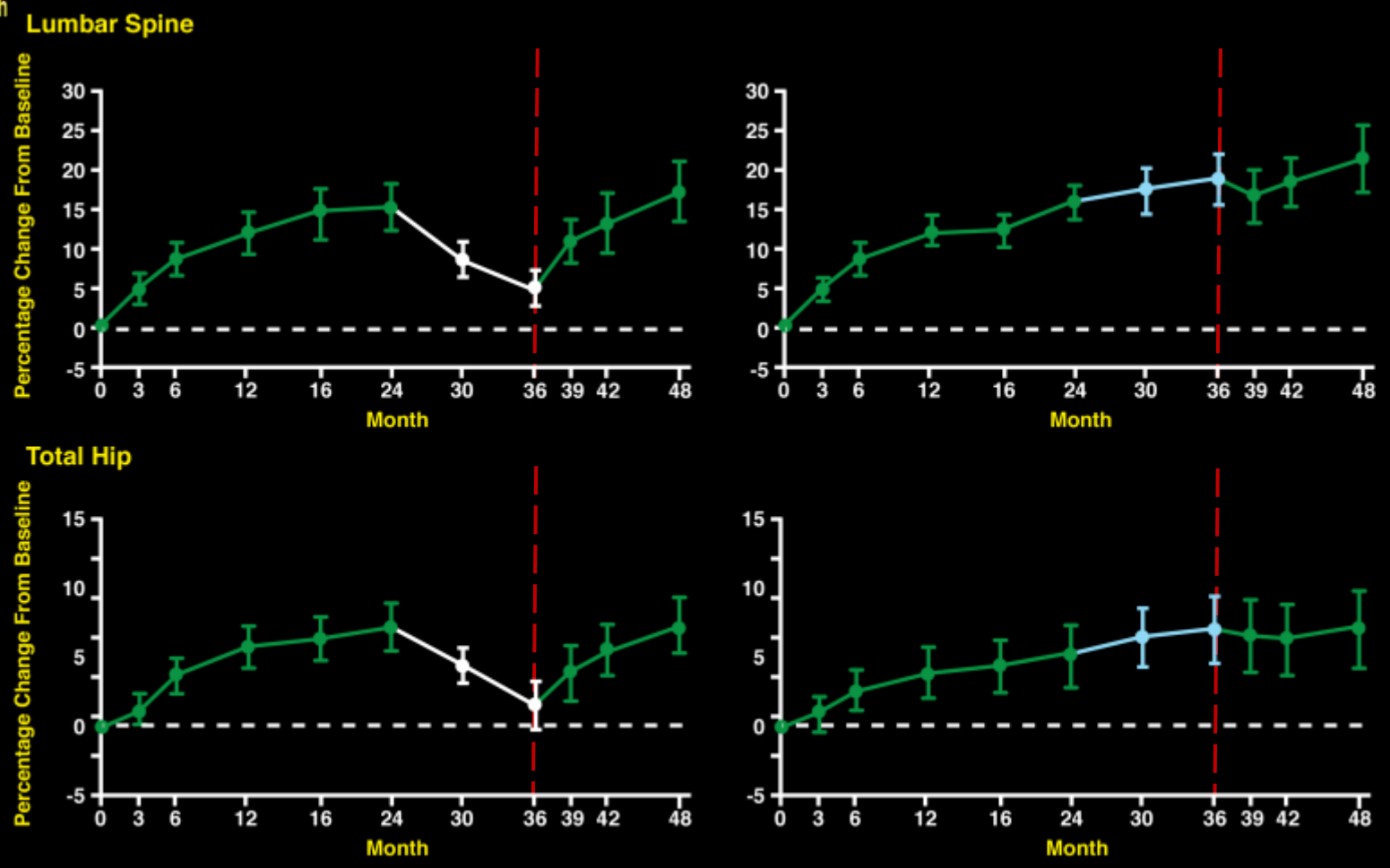




Cosman F. *Osteop Int* 2022;3:1243

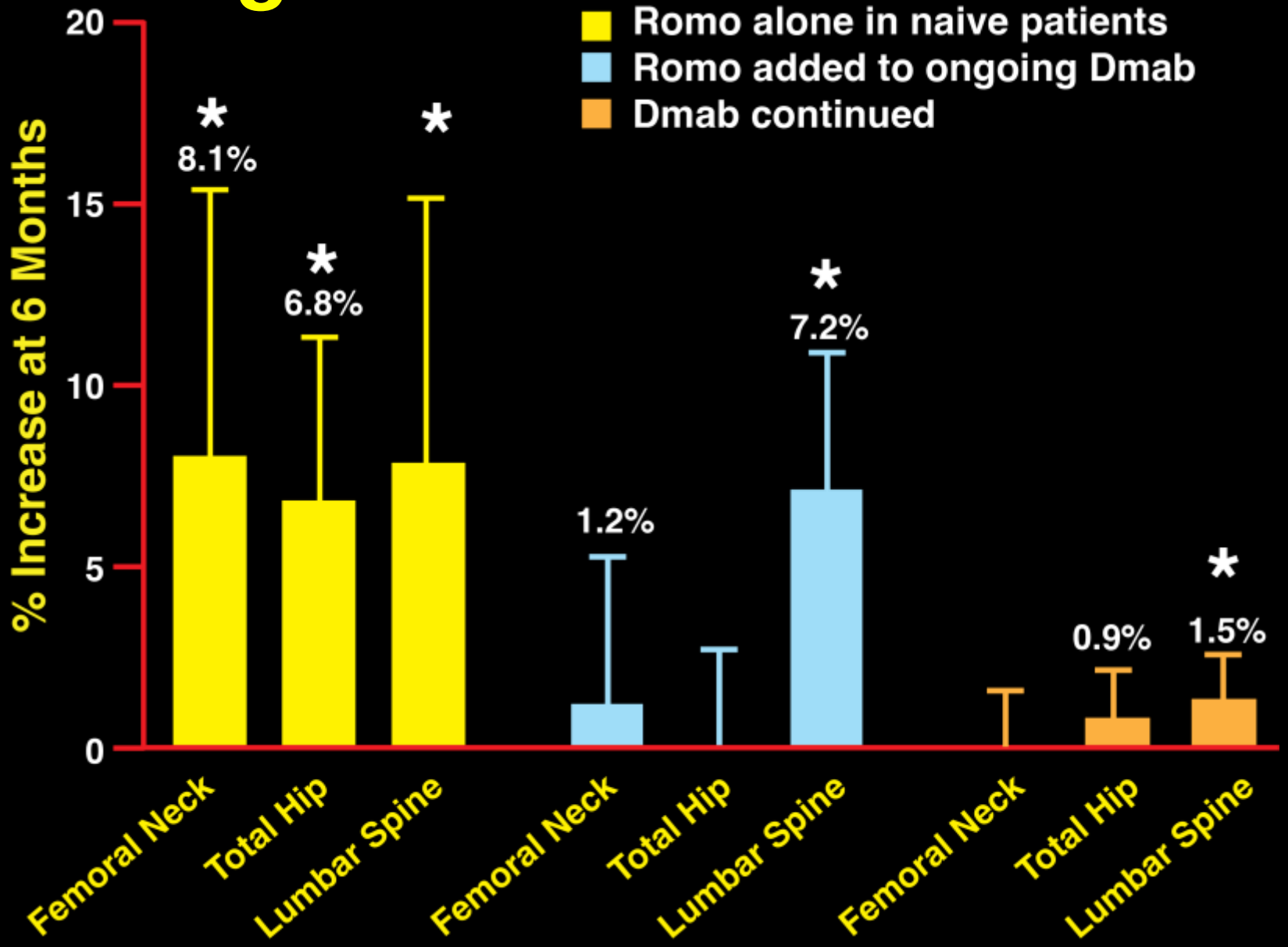
Switching to Romosozumab Following Placebo or Denosumab





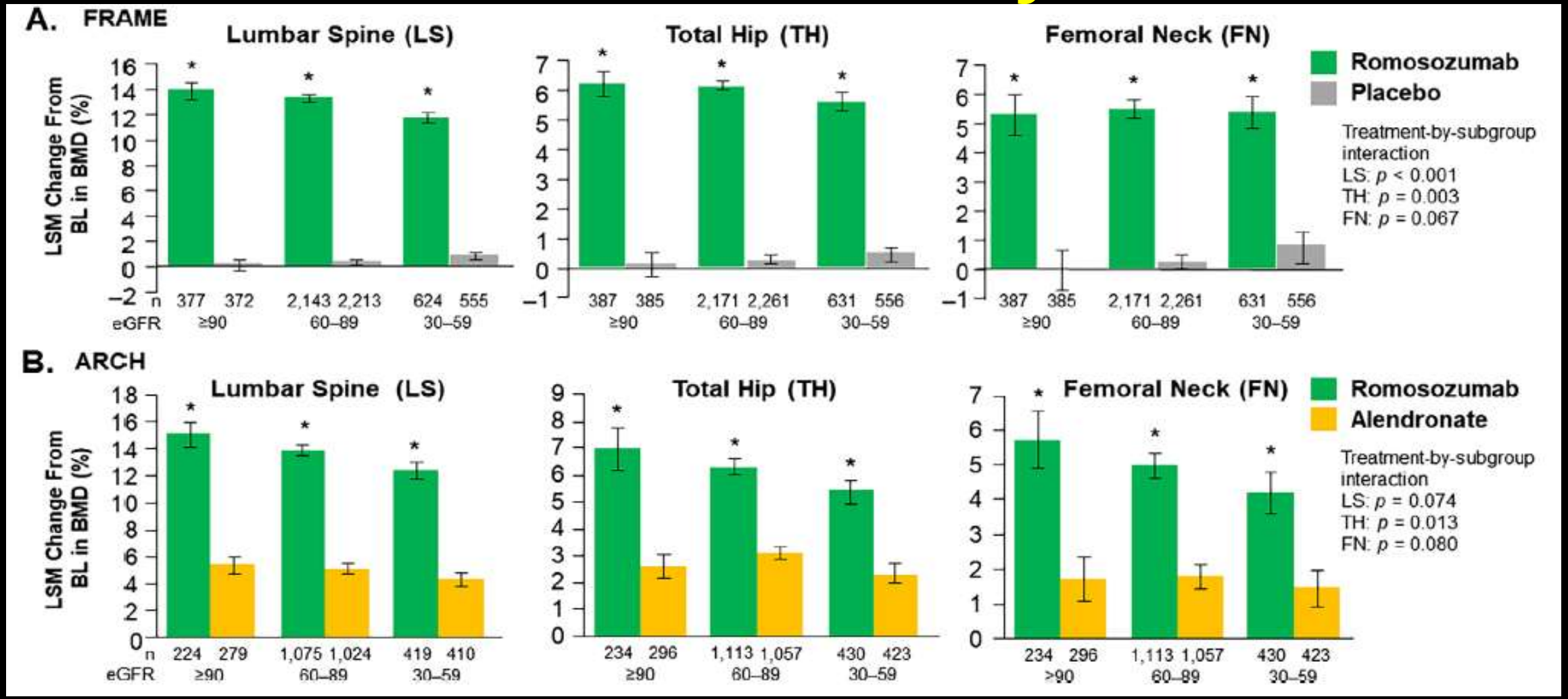
Kendler DL. *Osteoporosis Int* 2019; 30:37

Adding Romozosumab to DMAB



Adami G. *JBMR Open* 2024

Romosozumab with Mild to Moderate Chronic Kidney Disease



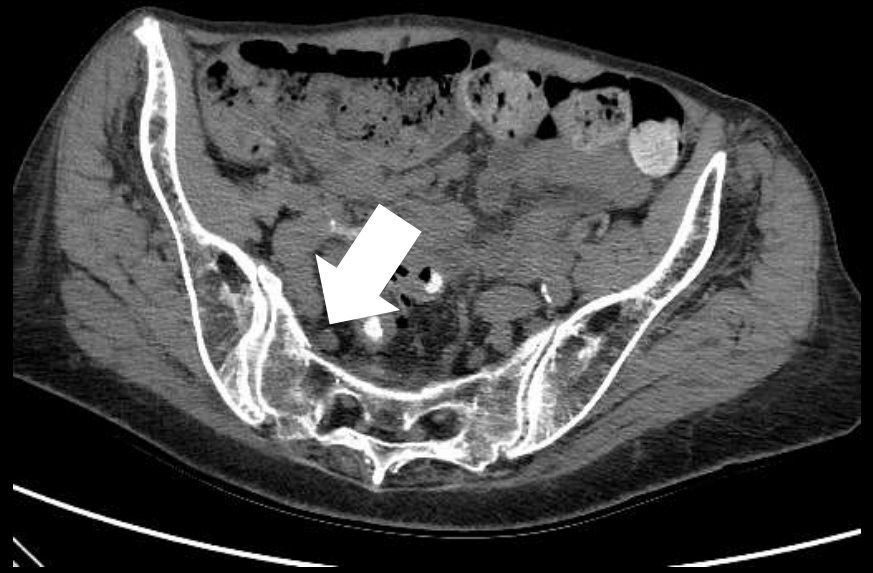
Miller PD. *JBMR* 2022;37:1437

When Do I Consider Use of Romosozumab?

- Very bad osteoporosis evidenced by very low bone mass or history of prior fractures, often multiple prior fractures
- Failure or contra-indications to other bone therapies
- No recent CV events (? None in past year)
- Patient fully understands potential benefits compared to potential risks

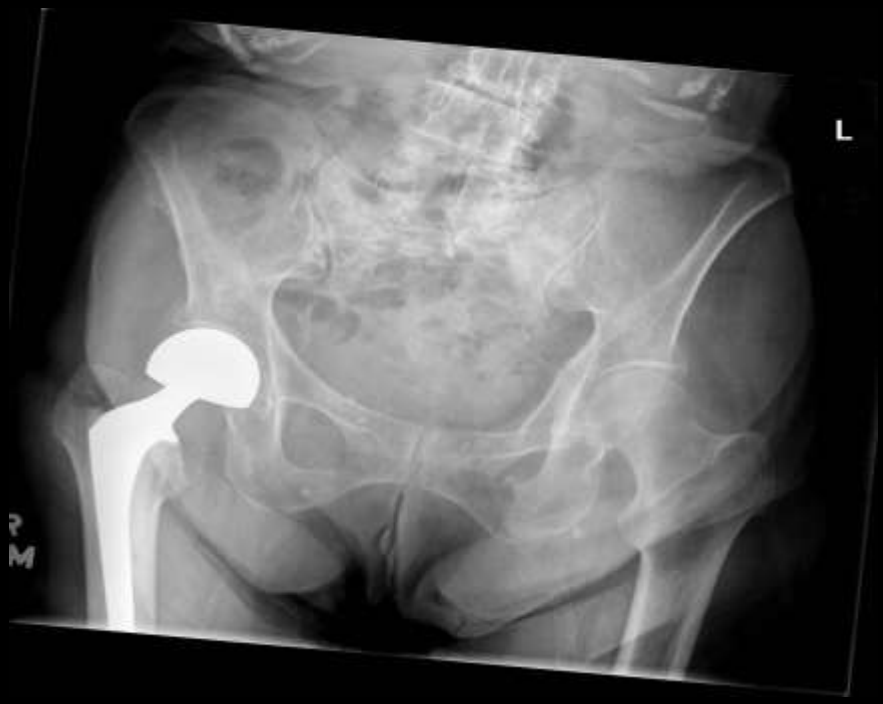
Patient H.L.

- 92 yo woman, history of diastolic dysfunction, CKD 4, asthma
- Bilateral sacral alar fractures early October, 2019
- Past use of alendronate for many years, then off for many years
- Doing home rehabilitation using rolling walker
- DXA -3.4 left femoral neck (spine with degenerative changes
- Metabolic bone evaluation
  - Normal calcium, phosphorous, 25-OH vitamin D
  - Estimated glomerular filtration rate 23
  - PTH 46.5 (sl low), and alkaline phosphatase 135 (sl high)
- Planned to begin teriparatide or abaloparatide (as insurance would allow)



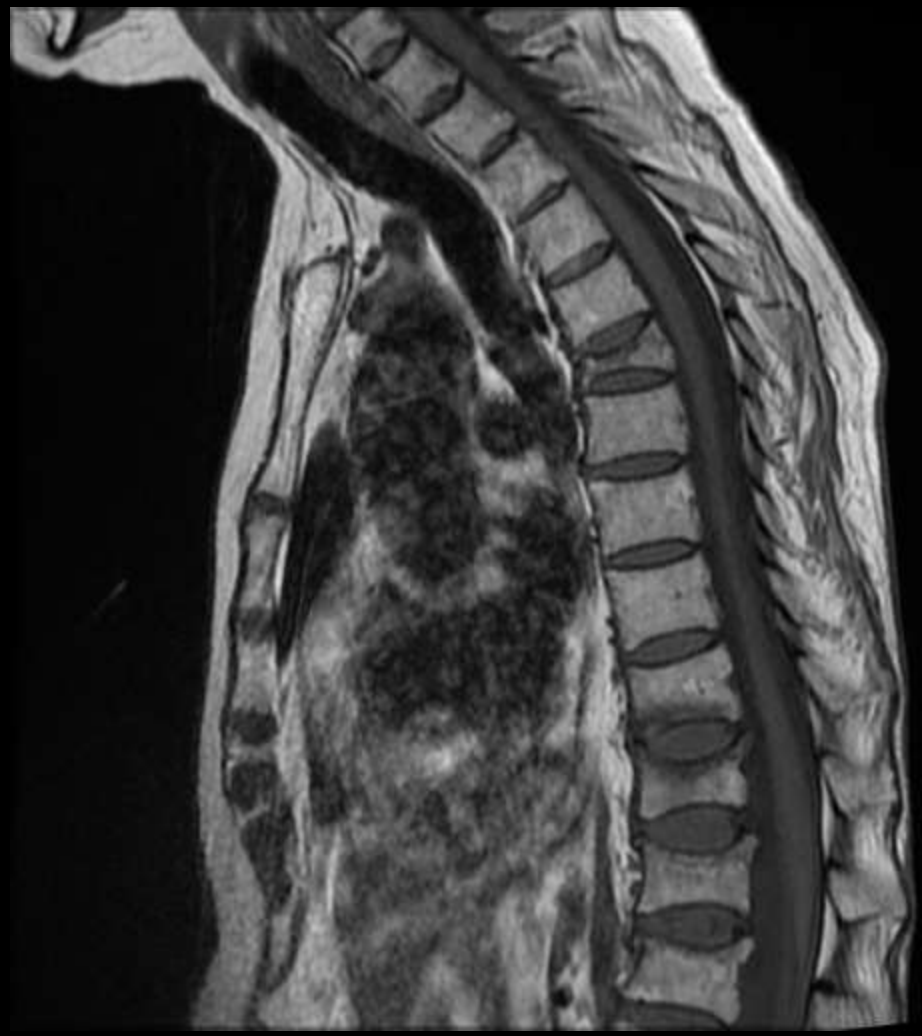
Patient H.L. - follow-up

- Unable to procure teriparatide or abaloparatide due to out of pocket cost
- January 14,th 2020 plan to start romosozumab
- January 20th, fall with hip fracture requiring total hip replacement
- After rehabilitation and start of covid, started romosozumab 3/20
- Ambulating without pain 7/20
- No further fractures 3/21, switched to denosumab



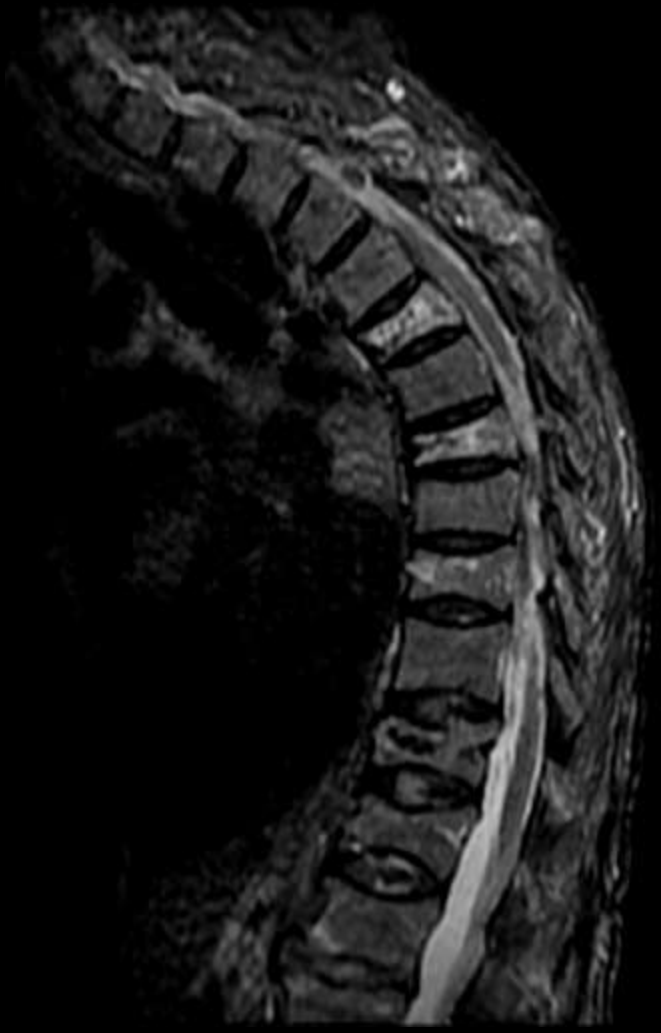
Patient S.F.

- 55 yo woman hx of anaplastic astrocytoma
  - Treatment with high dose dexamethasone
  - Radiation therapy
- Multiple thoracic compression fractures
  - Pain in upper back with severe spasms
  - Worsening for past 1 month
- DXA with T score L1-L4 -3.9, femoral neck -4.0
- Improved back pain 2 months later
- Romosozumab x 6 injections, then alendronate
- No fracture, hospice 2/21



Patient E.B.

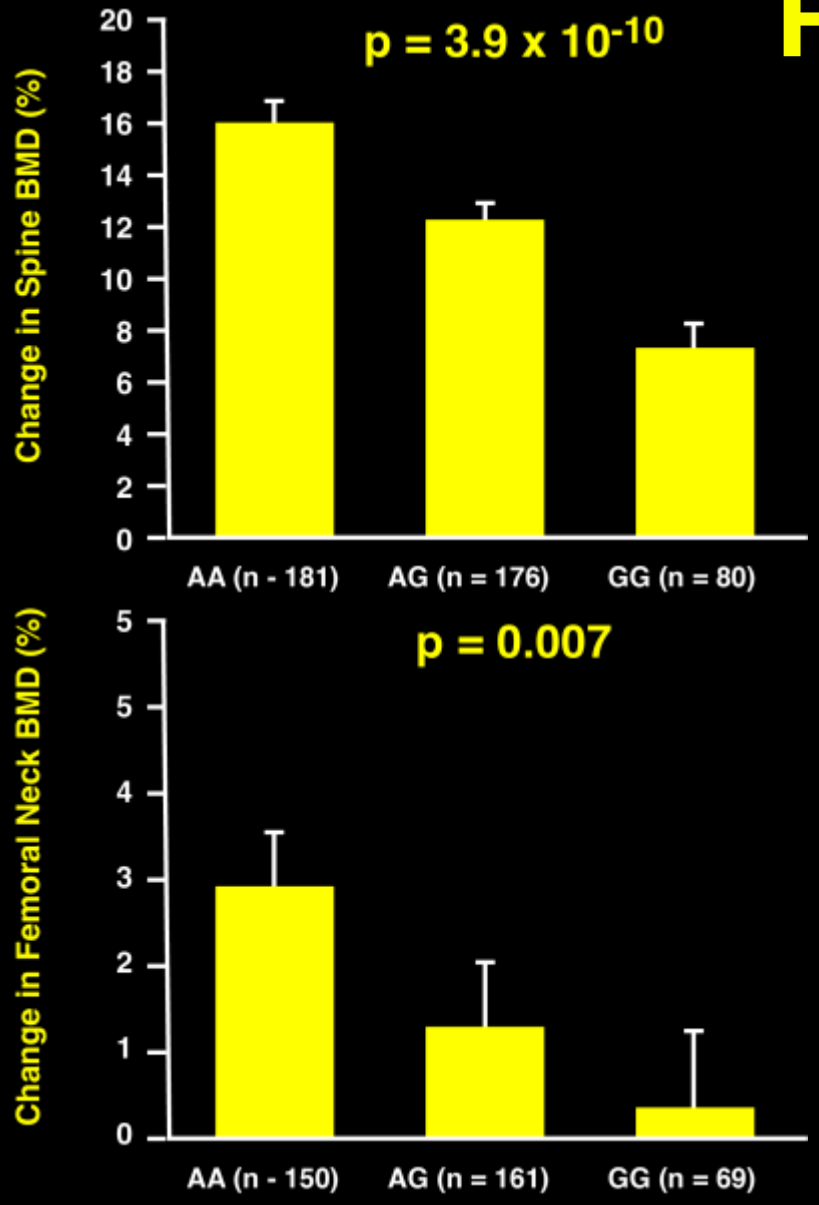
- 87 yo woman, hx breast CA, s/p lumpectomy and XRT on letrozole, Afib, NSTMI 7 months ago
- Remote risedronate (> 1 yr). Past nasal calcitonin
- Denosumab for past 5 yrs without difficulties
- DXA: T score L1-L4 -4.0 and femoral neck -3.4
- Initial Plan- continue denosumab
- 9 months later- new compression fractures of low back, L1, L2 compression fracture noted imaging done 5/20
  - Severe back pain
  - Missed denosumab by 2 months
  - Recommended romosozumab
- 2 months later- new compression fx after kyphoplasty
- 2 months later- still no romosozumab, concerns with “cost” Willing to take denosumab again
- 2 months later- still not back on denosoumab, requesting narcotic analgesics regularly



What's New(er) with Older Osteoanabolics?

What's Possibly on the Horizon?

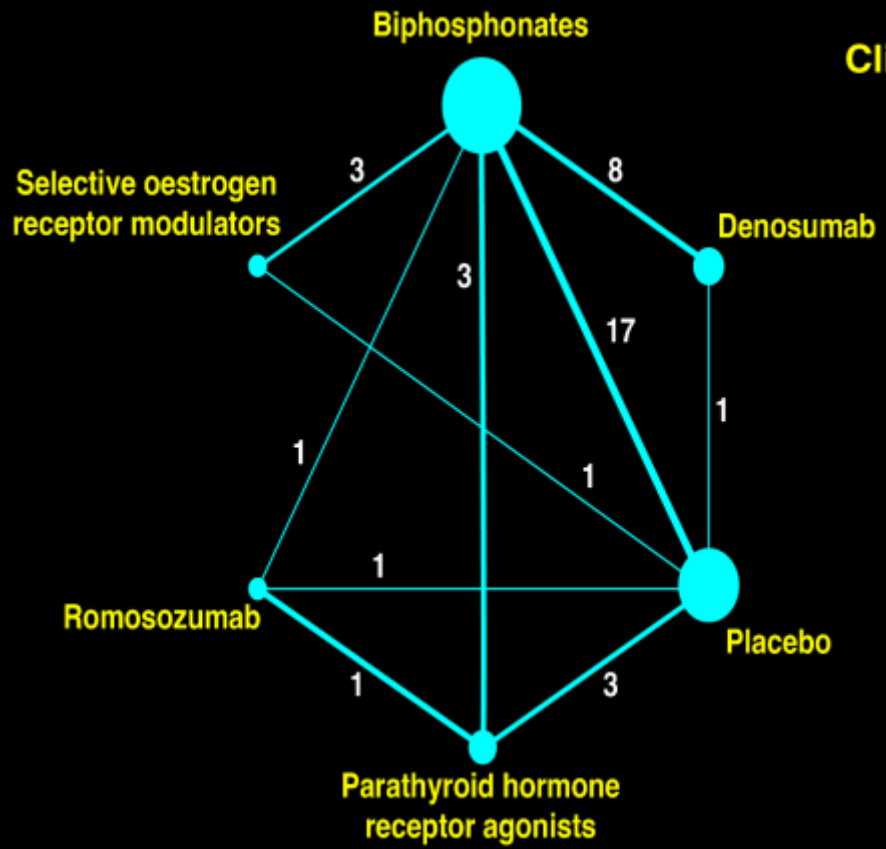
Genotyping for Prediciting Response to Teriparatide



- Teriparatide responses vary by patient for uncertain reasons
- Response at hip and spine vary by genetic factors
- Potential for future genotyping of teriparatide response – personalized medicine!

Alonso N. *Ann Rheum Dis* 2023;82:985

Network Meta-Analyses Support Superiority of Osteoanabolic Treatments



Clinical fractures	Odds ratio (95% CI)	Odds ratio (95% CI)
Bisphosphonates v denosumab		0.81 (0.57 to 1.15)
Bisphosphonates v placebo		0.79 (0.70 to 0.89)
Bisphosphonates v PTHR		1.49 (1.12 to 2.00)
Bisphosphonates v romosoozumab		1.26 (0.99 to 1.60)
Bisphosphonates v SERM		1.40 (0.72 to 2.71)
Denosumab c placebo		0.98 (0.68 to 1.41)
Denosumab c PTHR		1.85 (1.18 to 2.92)
Denosumab c romosoozumab		1.56 (1.02 to 2.39)
Denosumab c SERM		1.74 (0.82 to 3.66)
Placebo v PTHR		1.90 (1.41 to 2.55)
Placebo v romosoozumab		1.60 (1.24 to 2.05)
Placebo v SERM		1.78 (0.91 to 3.47)
PTHR v romosoozumab		0.84 (0.59 to 1.21)
PTHR v SERM		0.94 (0.46 to 1.93)
Romosoozumab v SERM		1.11 (0.55 to 2.25)

Handel MN *BMJ* 2023;381:e068033 | doi: 10.1136/bmj-2021-068033

Using Lowest T-score to Stratify Treatment Options

How to achieve T score > -2.5 in 3yrs in 50%

Treatment	Total Hip	Total Spine
Alendronate	-2.7	-3.0
Denosumab	-2.8	-3.1
Romosozumab/Alendronate	-2.9	-3.5
Abaloparatide/Alendronate	-2.9	-3.5
Romosozumab/Denosumab	-3.1	-3.7

Cosman F. *JBMR* 2024;39:1393

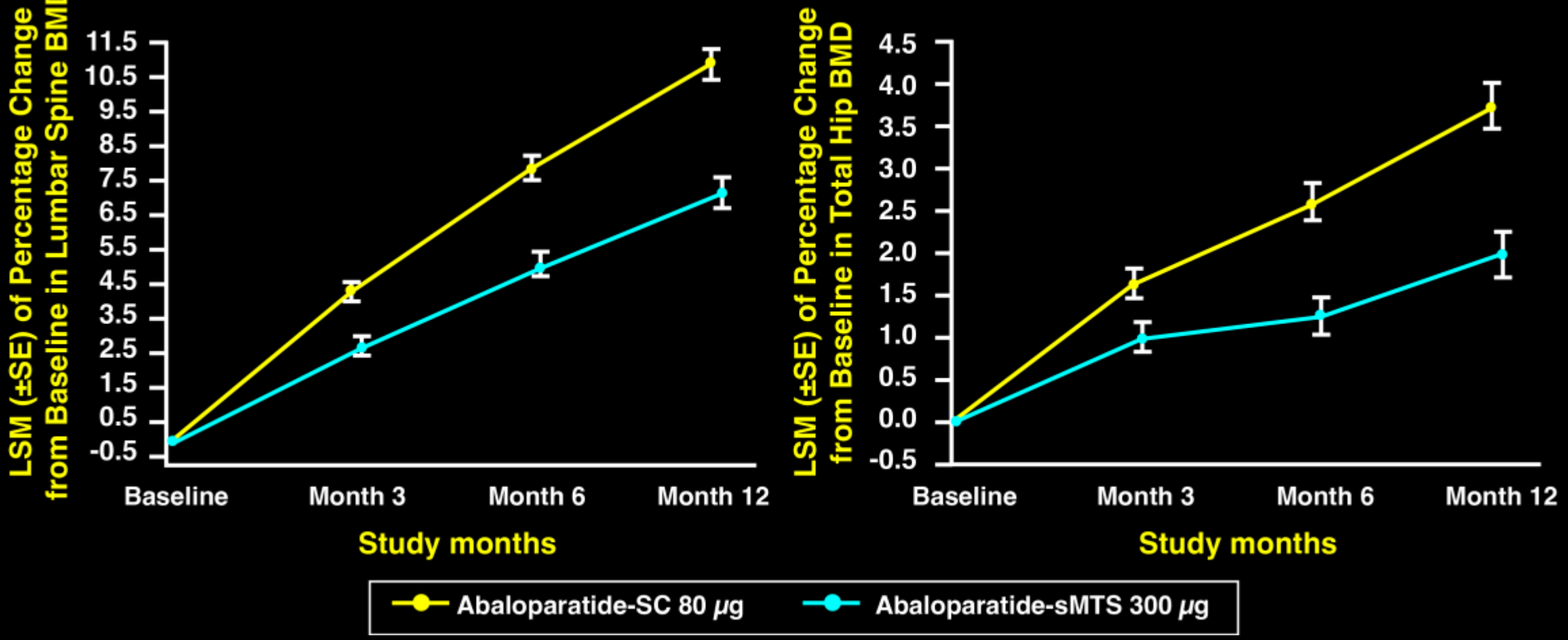
Testosterone Risks in Older Men

- No increased risk in cardiovascular events
- Slight increase in fractures over placebo
  - Fractures disproportionately of ankles and ribs (trauma)
  - No substantial between group differences in osteoporotic fractures
- Study limitations
  - Testosterone levels not low
  - No data on bone strength
  - Change in behaviors associated with fractures not measured
- Implications- Consider non-testosterone therapy if bone health is the only goal

Snyder P. *N Engl J Med* 2024;390:203
Grossman M. *N Engl J Med* 2024;390:267

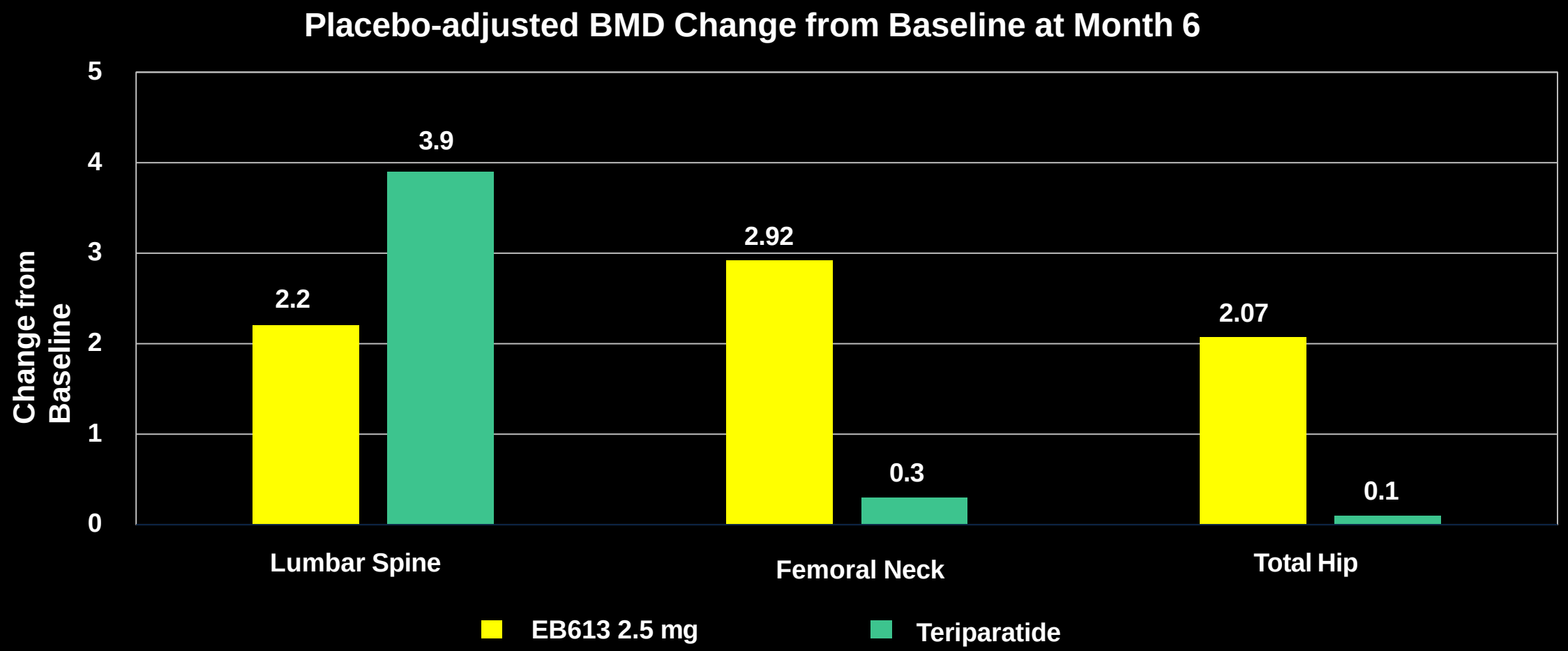
Are there New Ways to Give Osteoanabolics?

Transdermal Abaloparatide NOT Non-inferior to Subcutaneous Route



Lewiecki M. *JBMR* 2023;38: 1404

Non-head-to-head Comparison of Oral PTH (EB613) with Teriparatide (Historical Comparison Data)



* Teriparatide data based on Leder BZ et.al. JCEM (2015)

Tripto-Shkolnik L. *JBMR* 2024; 39:672

Oral PTH Adverse Effects

Most Common Treatment Emergent AE (≥5% of participants)	
	EB613 Treated (N=118) n (%)
Headache	21 (17.8)
Nausea	18 (15.3)
Diziness	13 (11.0)
Nasopharyngitis	7 (5.9)
Back pain	7 (5.9)
Palpitation	6 (5.1)
Dyspepsia	6 (5.1)
Presyncope	6 (5.1)

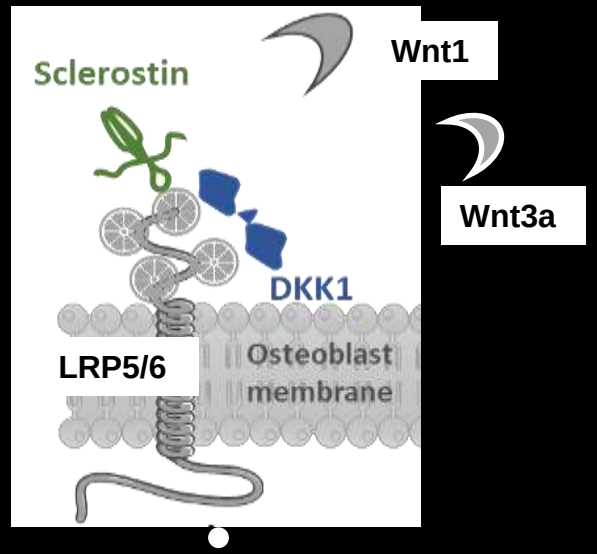
- AEs commonly attributed to vasodilatation (headache, nausea, presyncope and dizziness)
- Orthostatic hypotension
- Not associated with serum calcium increases or hypercalcemia adverse events
- No serious AEs

Tripto-Shkolnik L. *JBMR* 2024; 39:672

Tissue Specific WNT signaling Pathway in Osteoblasts

WNT1 & 3a inhibition

Tissue specific WNT signaling in osteoblasts controls bone formation and bone resorption



Sclerostin and DKK1 key negative regulators of bone formation via inhibition of WNT signaling

Florio M. *Nature Communications*. 2016;7:11505

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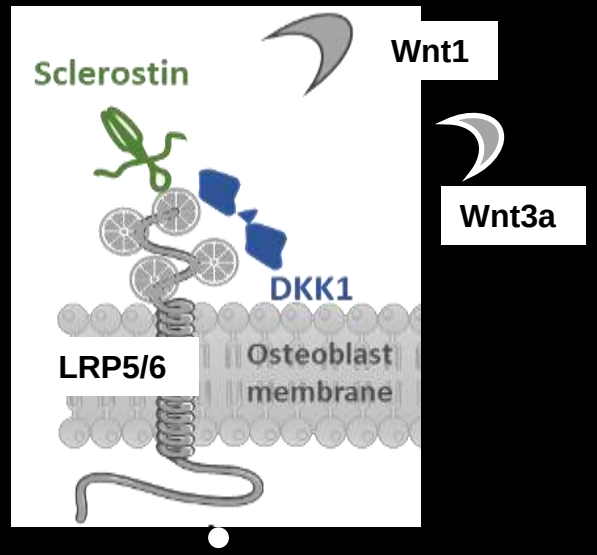
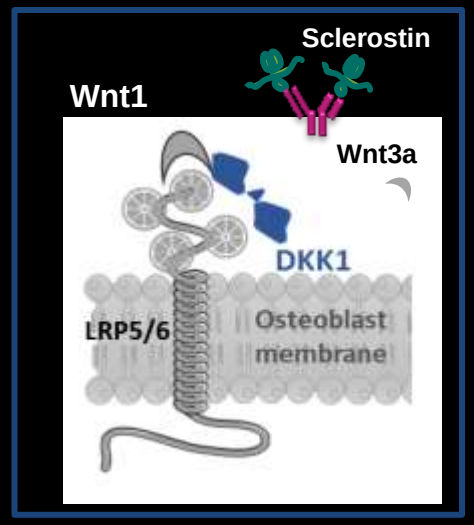
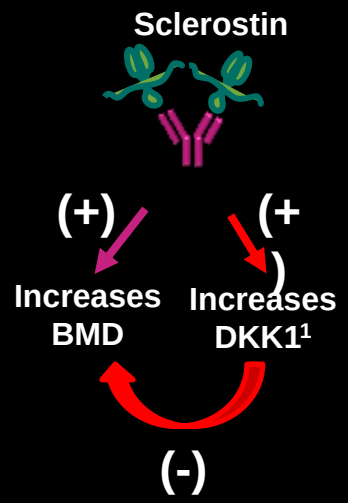


Sclerostin and DKK1 key negative regulators of bone formation via inhibition of WNT signaling

WNT1 activation

Monoclonal antibodies that neutralize sclerostin increase bone formation, decrease bone resorption, and increase BMD





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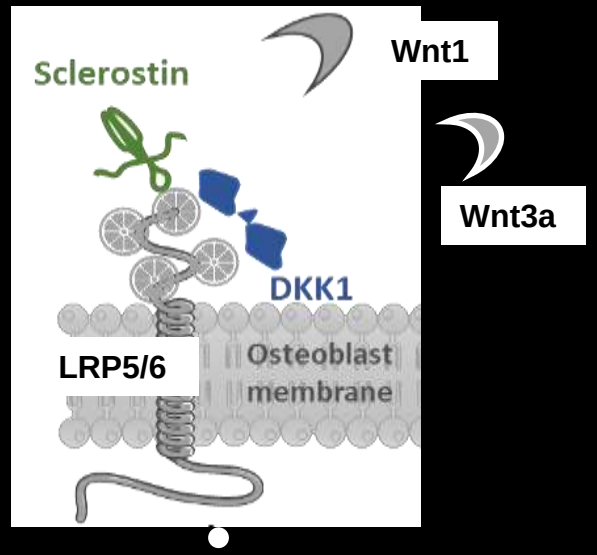

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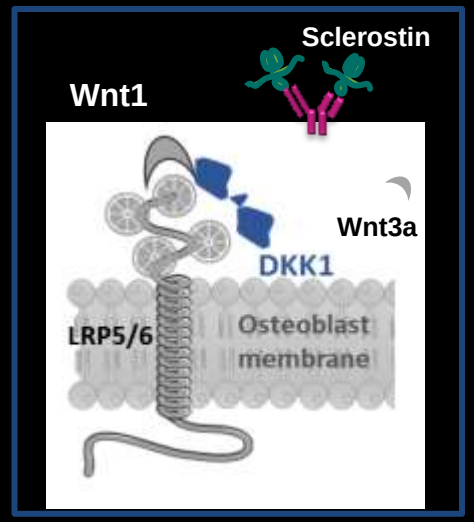

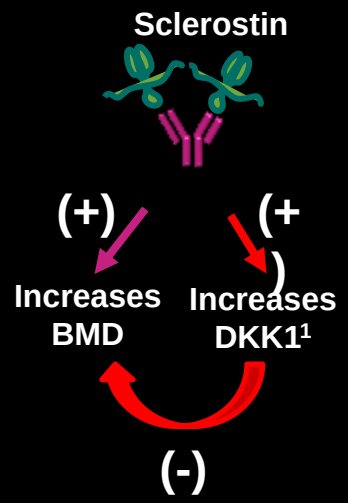

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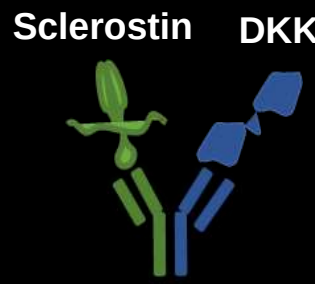
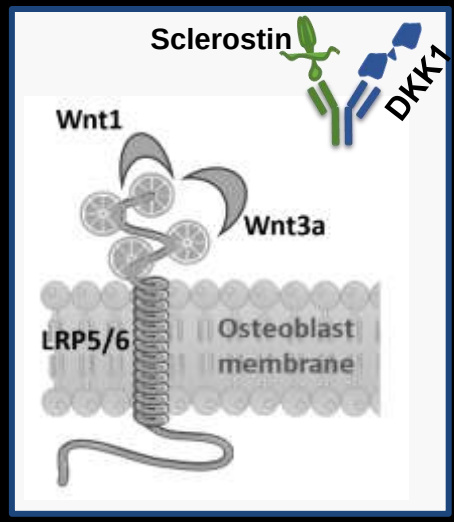
WNT1 & 3a activation

Neutralizing both sclerostin and DKK1 increases new bone formation more than blocking either target alone



AGA2118

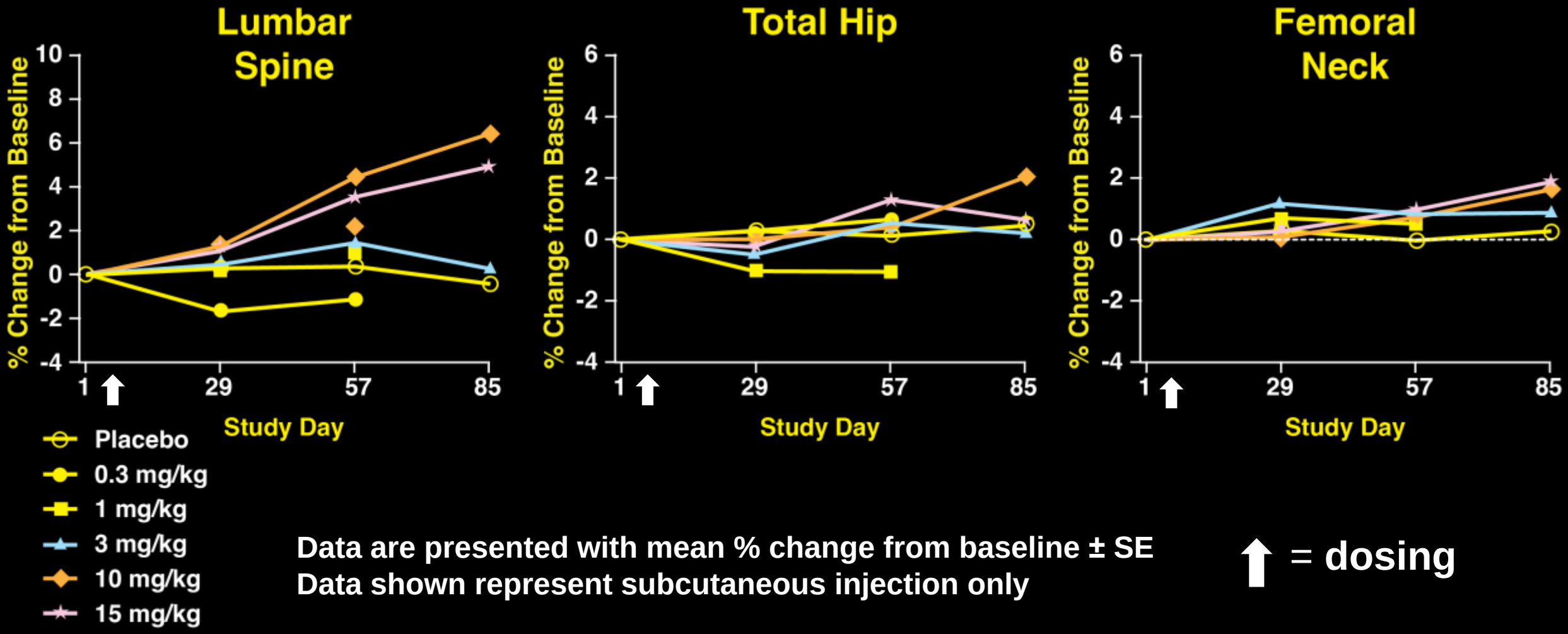


Associated with larger BMD gains and increased bone strength

Florio M. *Nature Communications*. 2016;7:11505

BMD Effects – AGA2118 Bispecific Antibody to Sclerostin and DKK1

Single Ascending Dose



Data are presented with mean % change from baseline ± SE
Data shown represent subcutaneous injection only

⬆ = dosing

Drake M. ASBMR, 2024

Why Don’t we Have New Drugs Approved in Osteoporosis Yet?

- Pharma has been hesitant to develop new ones
  - Misadventures with bisphosphonates, denosumab, and romosozumab
  - One billion dollars and over 20 years spent by Merck on odanacatib with CV safety signal cancelling entire program
- Conducting pivotal phase 3 studies of new drugs complex and very costly
  - Many study sites can not ethically do placebo-controlled fracture studies
  - Active comparator studies require thousands of participants
- Could use of surrogate biomarkers for regulatory approval favorably change new drug development?

ASBMR –Foundation of National Institutes of Health (FNIH) New Regulatory Endpoints

- FDA Biomarker Quantification Program accepted Strategy to Advance BMD as Regulatory Endpoint (SABRE)
- 50 randomized trials and individual data
- Meta-regression of 38 placebo-controlled trials of 19 therapeutic agents
- Total hip BMD best predictor of Fx– moving forward with FDA

ASBMR®
The American Society for Bone and Mineral Research

Romosozumab and New Osteoanabolics 2025

- Romosozumab has unique mechanism of action with dual anabolic and anti-resorptive properties
- Large effects on bone density and significant fracture risk reduction, even against potent comparators
- Cardiovascular safety questions for Romosozumab
- New approaches to other osteoanabolics of interest, but not proven
- New treatments would be aided by surrogate endpoints and new ways to detect osteoporosis at a system level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DRINK
WINE


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