Romosozumab
-
Sclerostin-Inhibition in der Osteoporosetherapie

Lothar Seefried

Der Inhalt des folgenden Vortrages wurde erstellt im Bemühen um größtmögliche Objektivität und Unabhängigkeit. Als Referent weise ich darauf hin, dass es persönliche Verbindungen zu Unternehmen gibt, deren Produkte im Kontext des folgenden Vortrages von Interesse sein könnten. Dabei handelt es sich um die folgenden Unternehmen und Verbindungen

Disclosures:

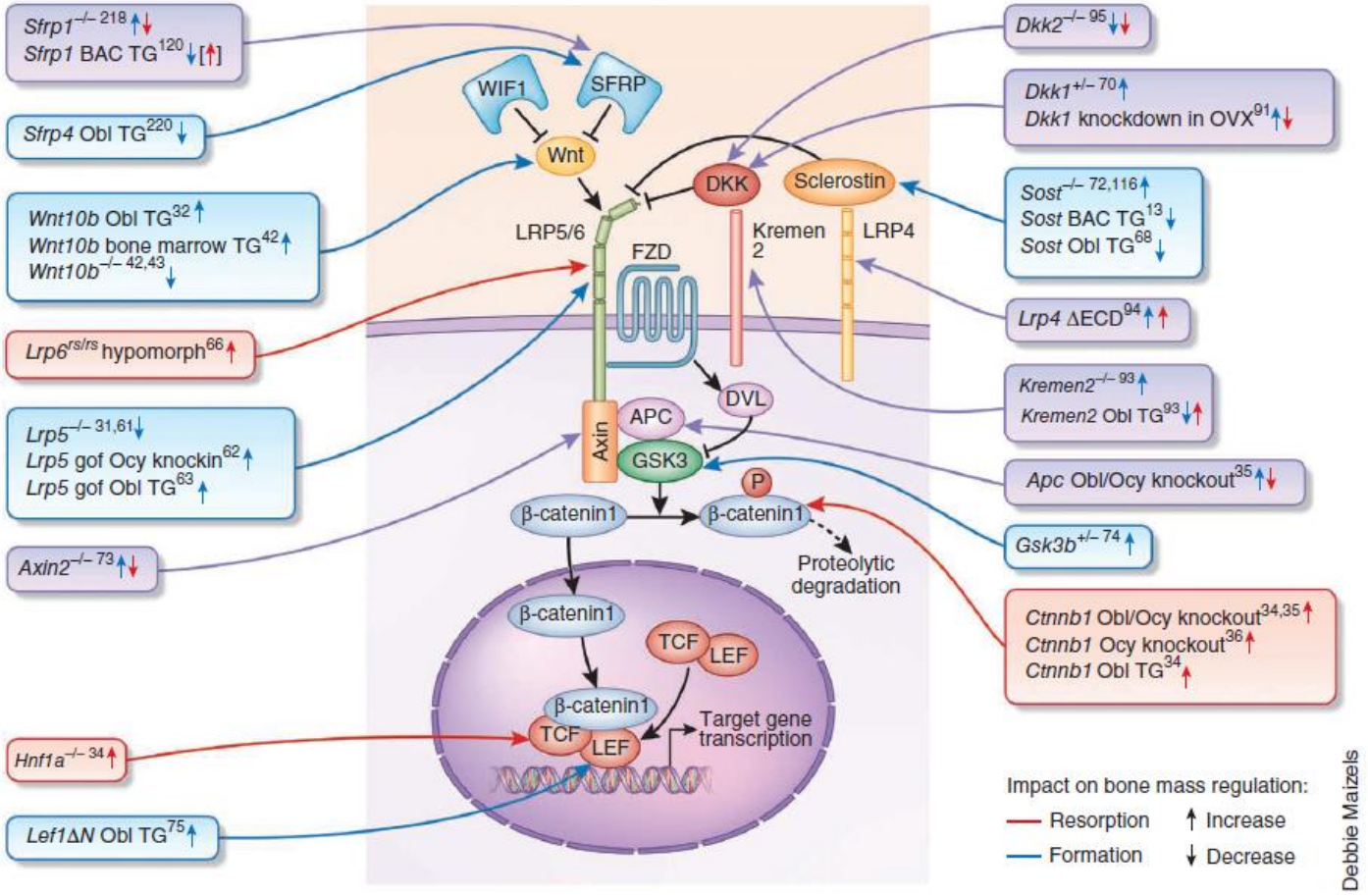
Honoraria for lectures and advice: Abbvie, AgNovos, Alexion, Amgen, Janssen, KyowaKirin, Lilly, medi, MSD, Novartis, Servier, UCB and Versameb.

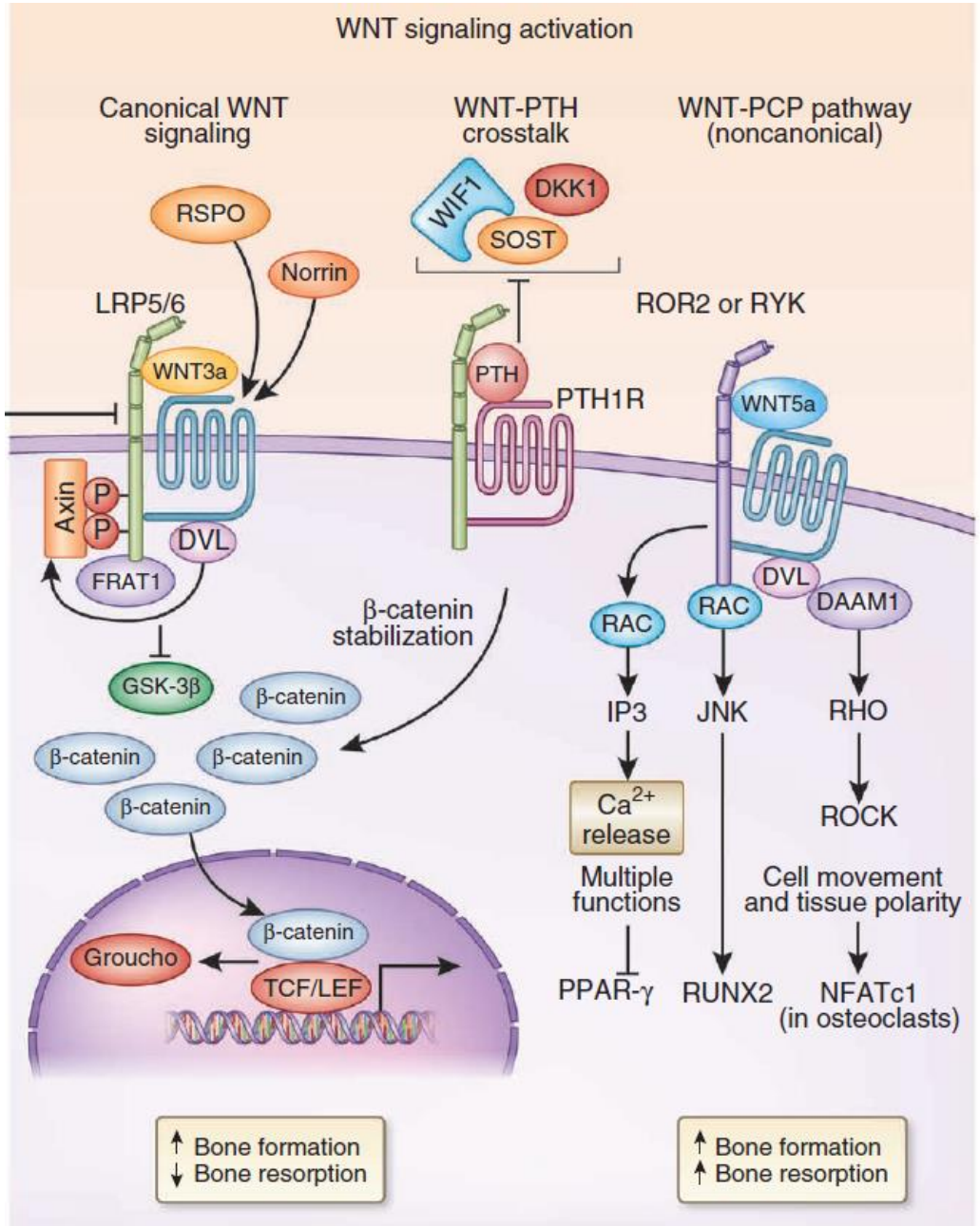
Support for scientific projects: Alexion, KyowaKirin and Novartis.

Conduct of clinical trials for: Alexion, Amgen, Bone Therapeutics, GlaxoSmithKline, Lilly, Novartis, SanofiPasteur and Servier.

Wnt-Signalling, Sclerostin and Bone

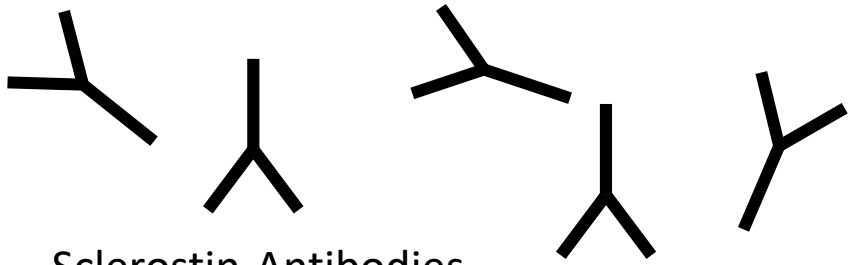
Across all studies, increases in bone mass were observed as a result of pathway activation, and decreases in bone mass were observed as a result of pathway inhibition.



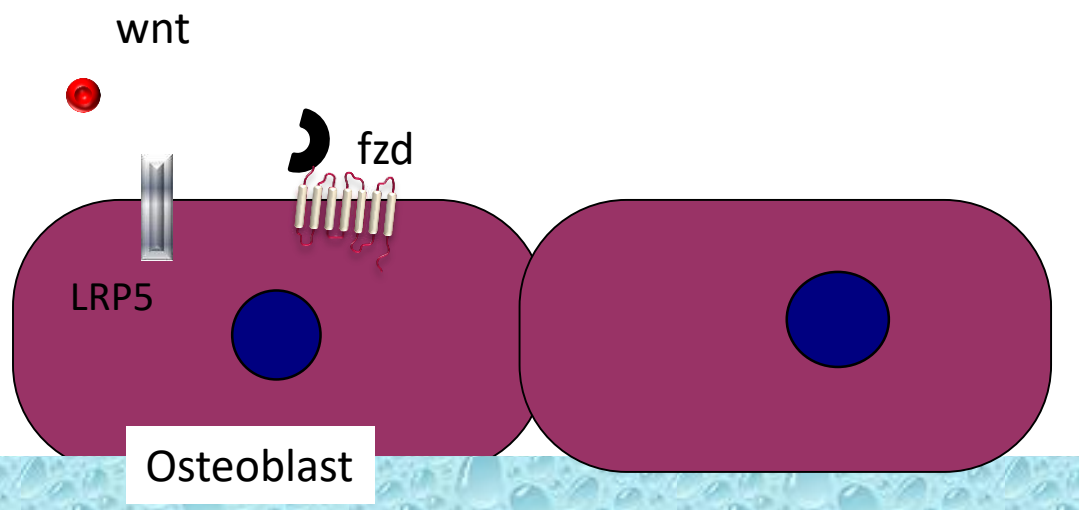


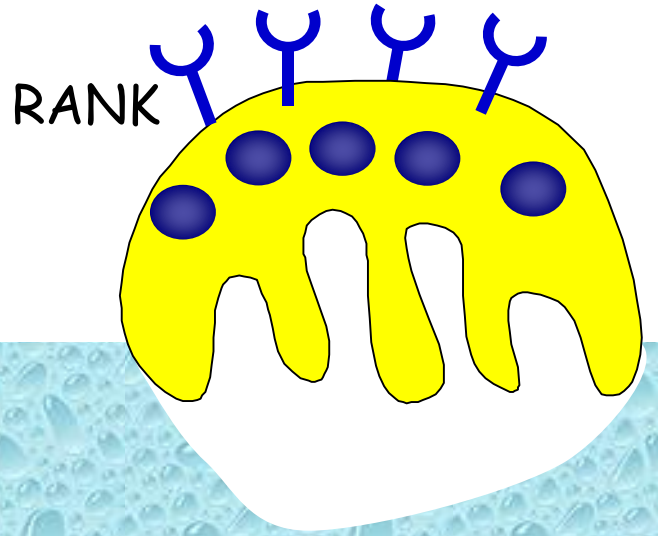
Baron & Kneissel, Nat Medicine 2013

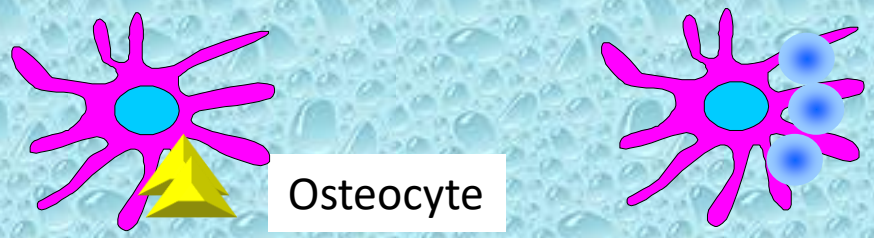
Sclerostin – Inhibition and Bone Turnover



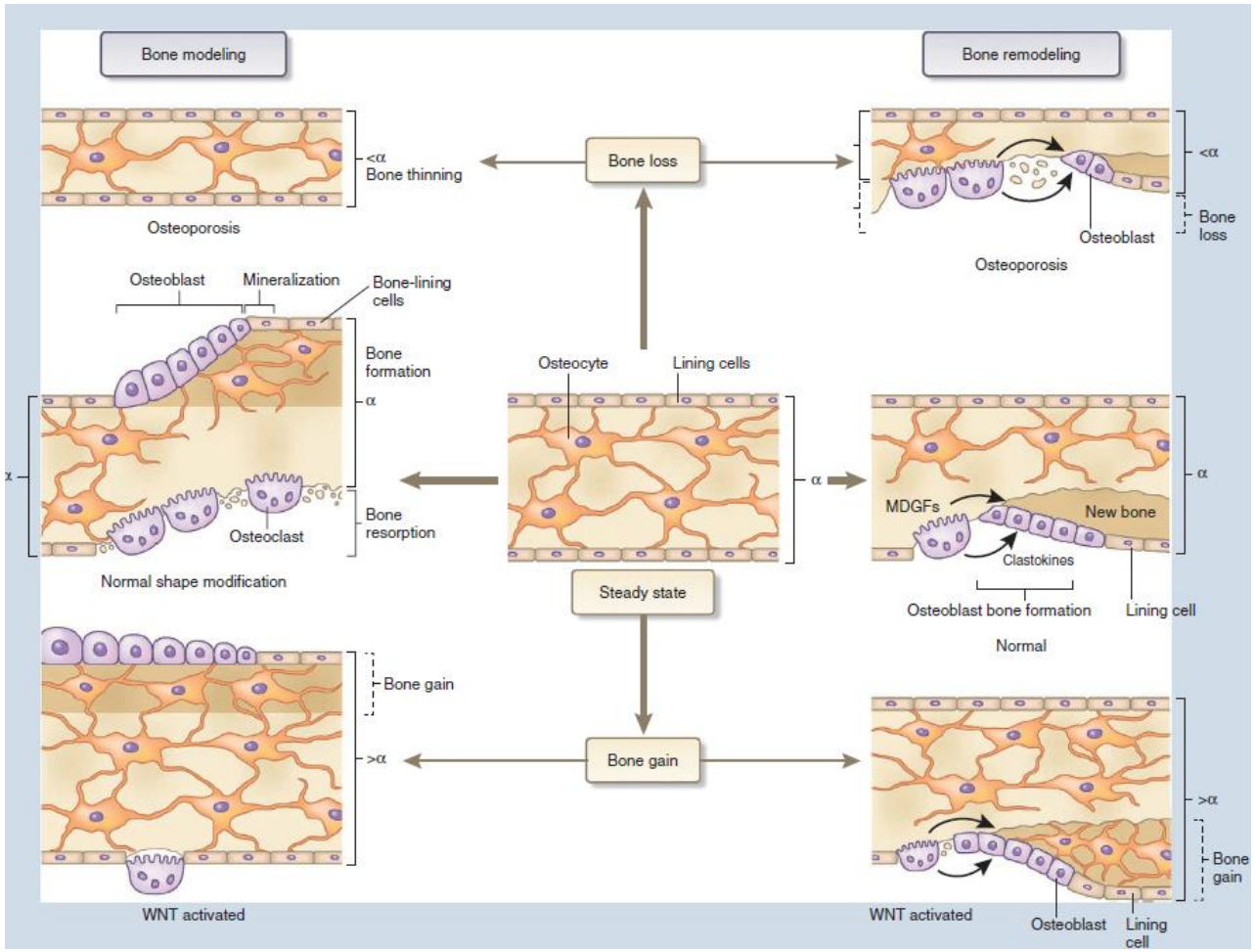
Sclerostin-Antibodies

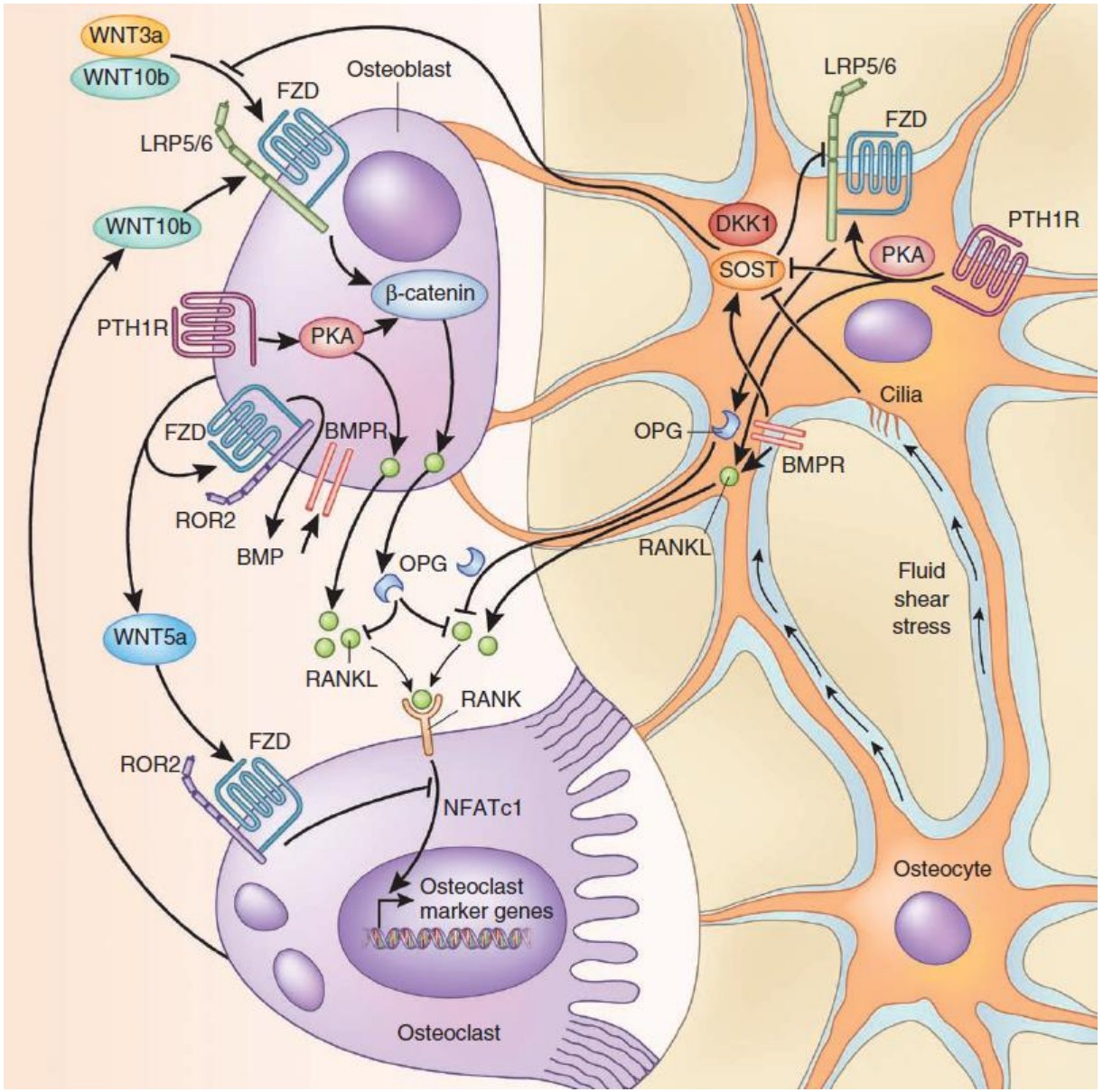






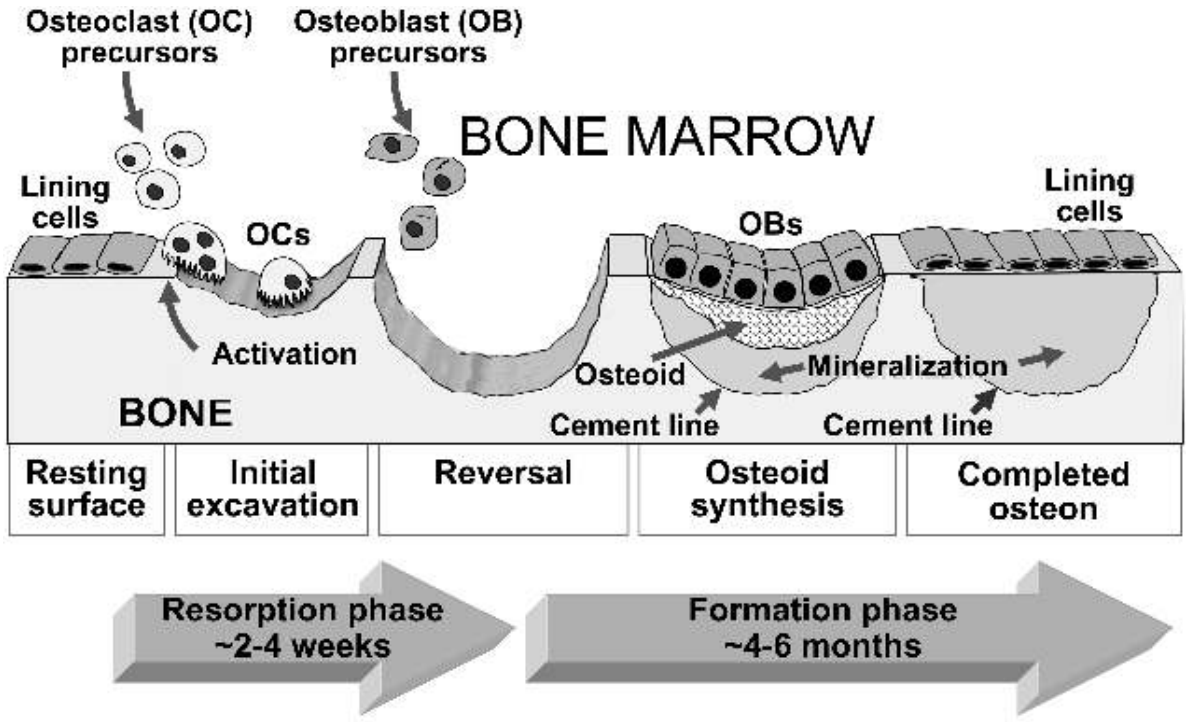
Wnt-Signalling, Sclerostin and Bone

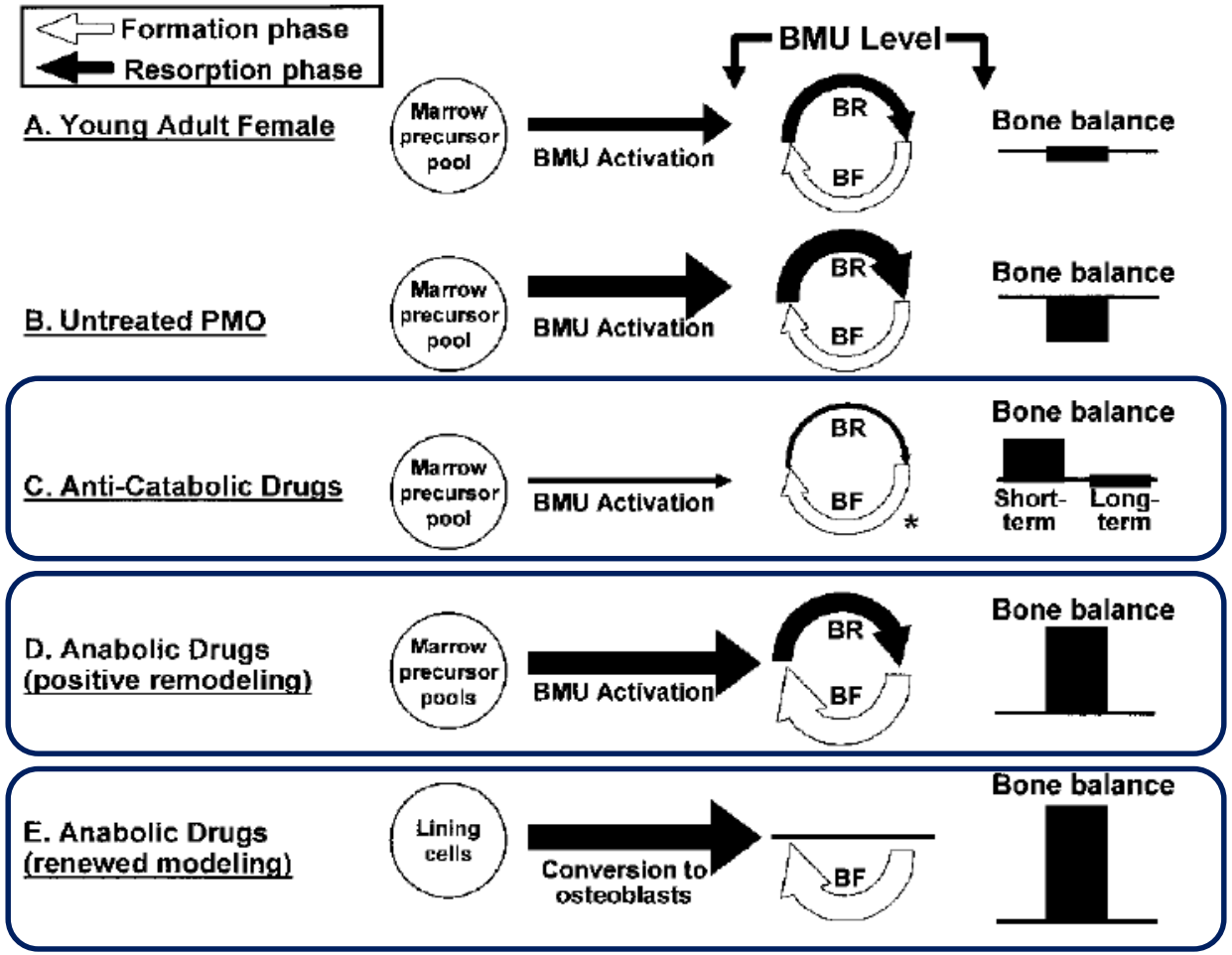




Baron & Kneissel, Nat Medicine 2013

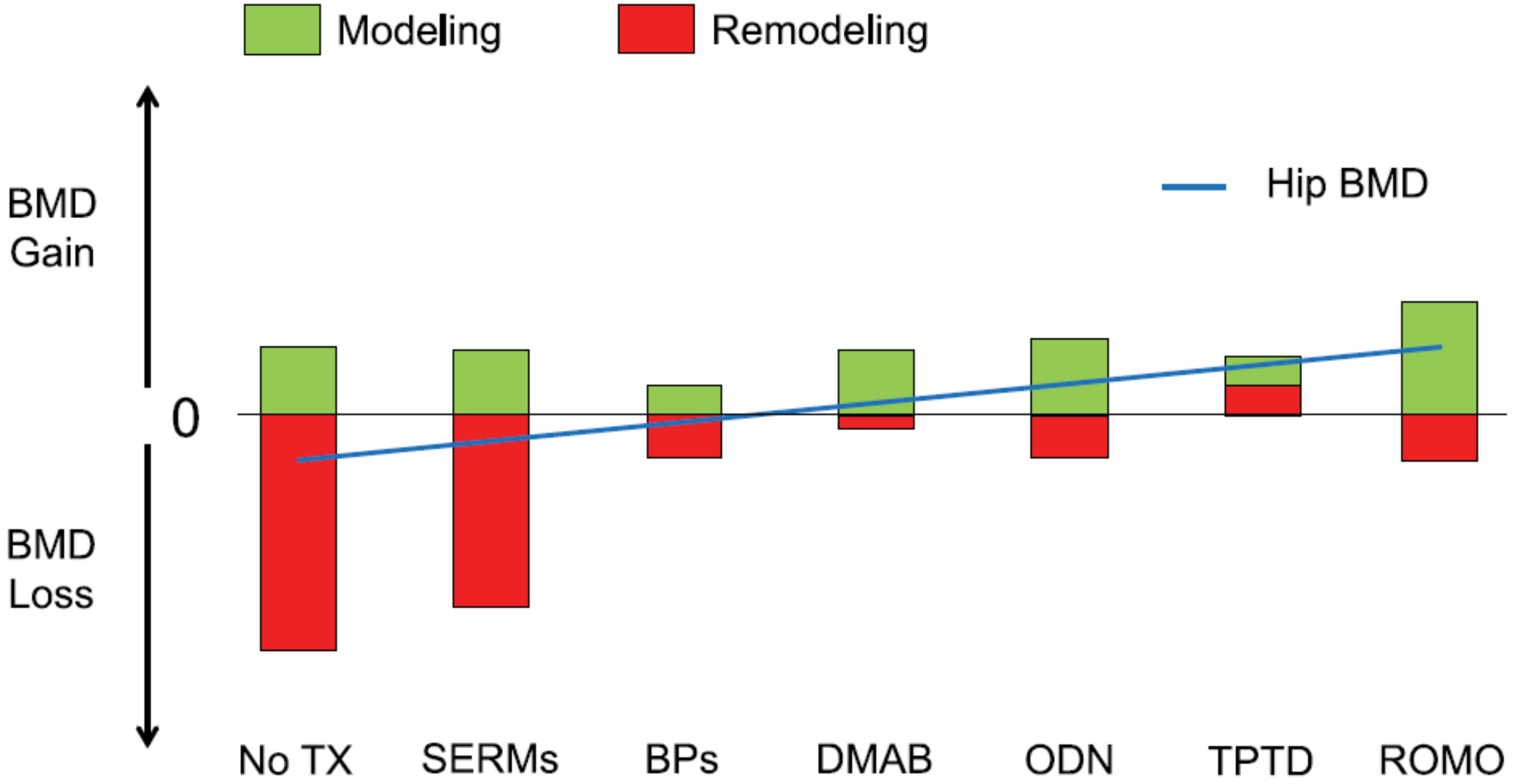
Bone Remodelling





Riggs et al., JBMR 2005, Drugs Used to Treat Osteoporosis - The Critical Need for a Uniform Nomenclature Based on Their Action on Bone Remodeling

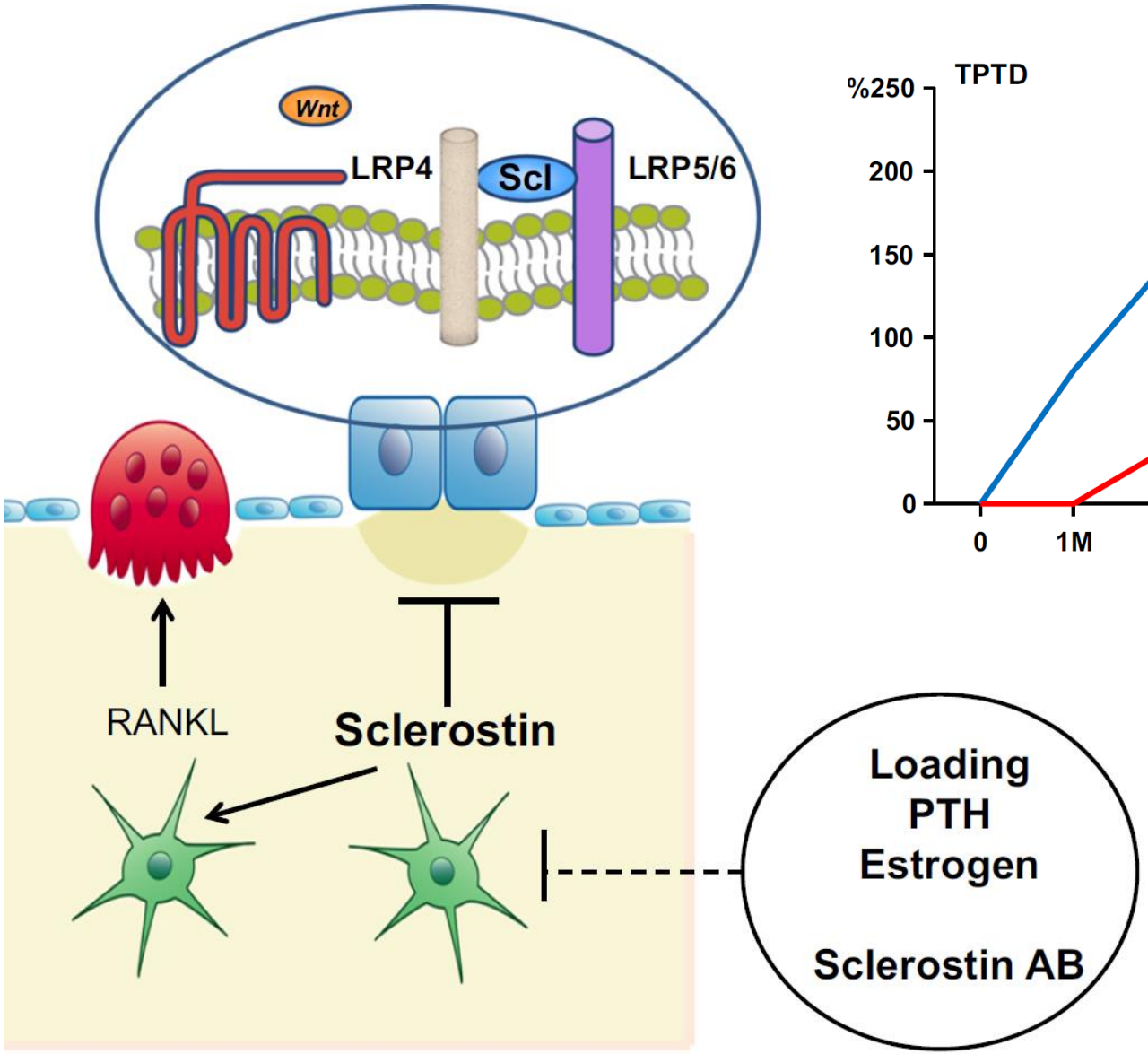
Therapeutic Interference with Bone Turnover

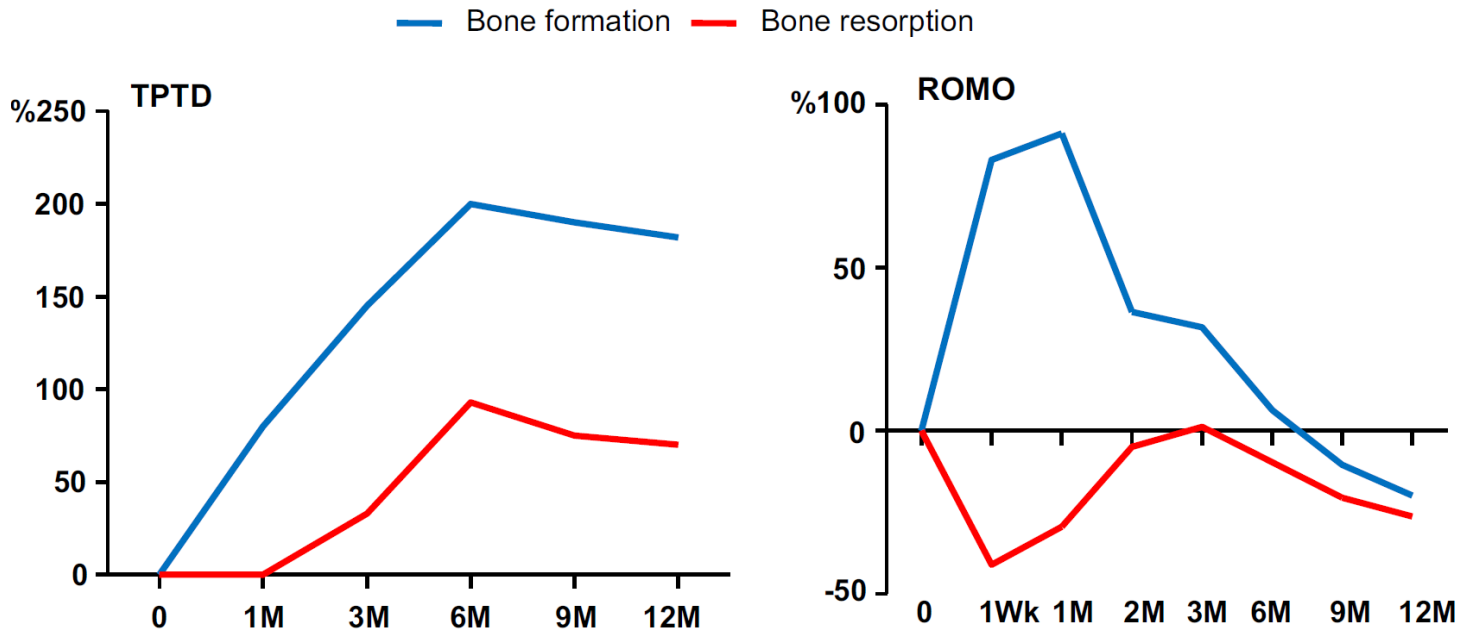


Baron & Kneissel, Nat Medicine 2013

Langdahl et al., Therapeutic Advances in Musculoskeletal Disease 2016, Bone modeling and remodeling - potential therapeutic targets

Formation vs Resorption

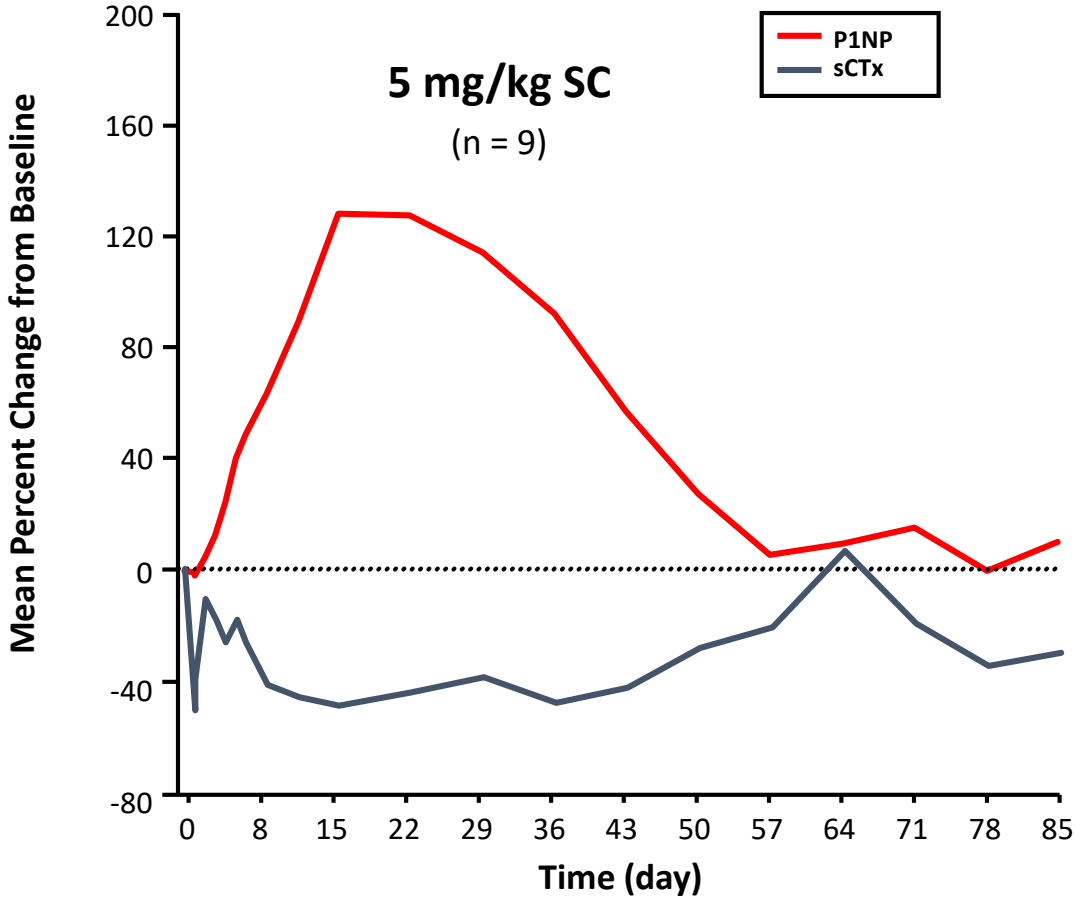




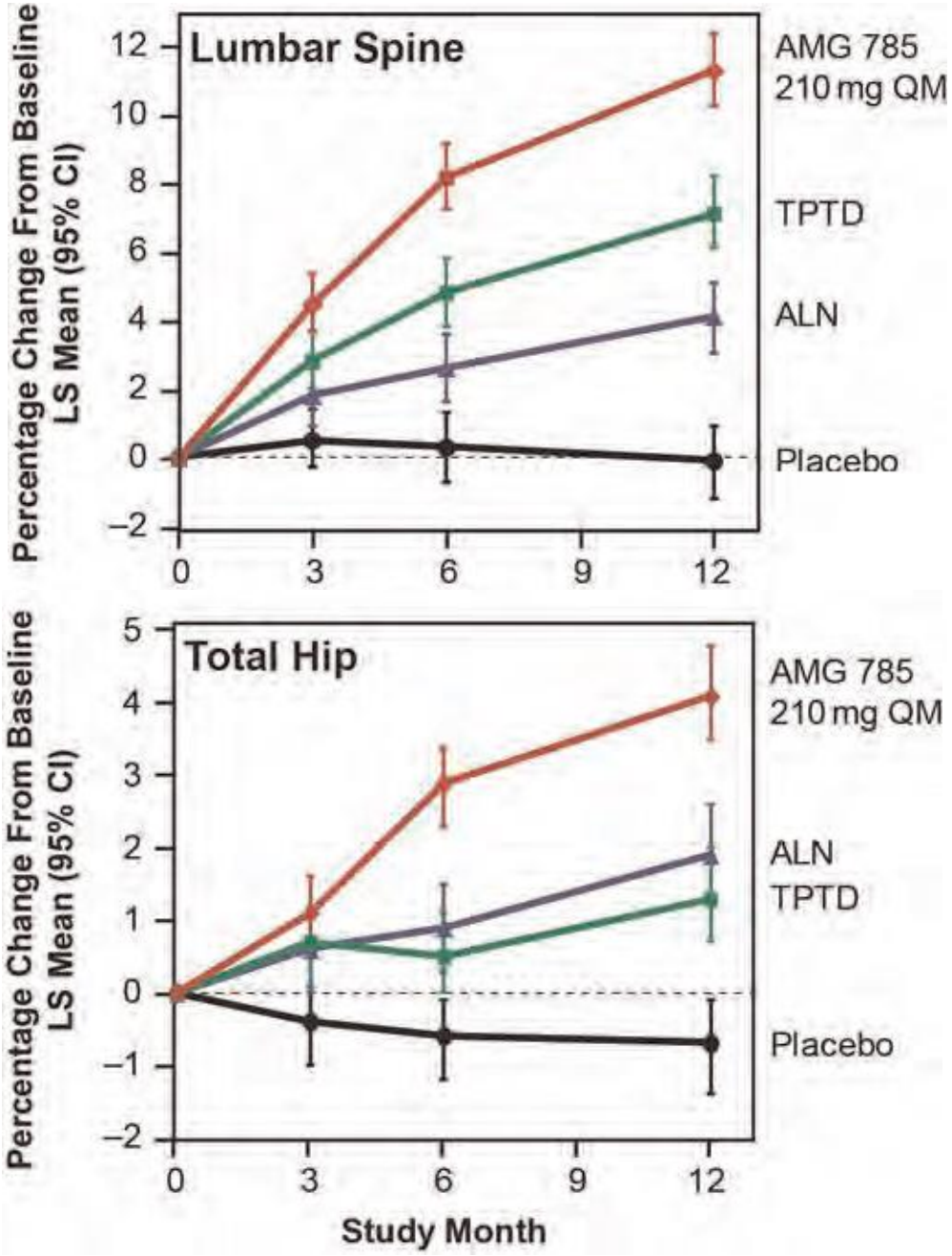
Sclerostin simulates production of RANKL by neighboring osteocytes

Appelman-Dijkstra, Papapoulos, Drugs 2015, Modulating Bone Resorption and Formation in Opposite Directions, Anti-Sclerostin, Osteoporosis

Romosozumab and Bone Turnover



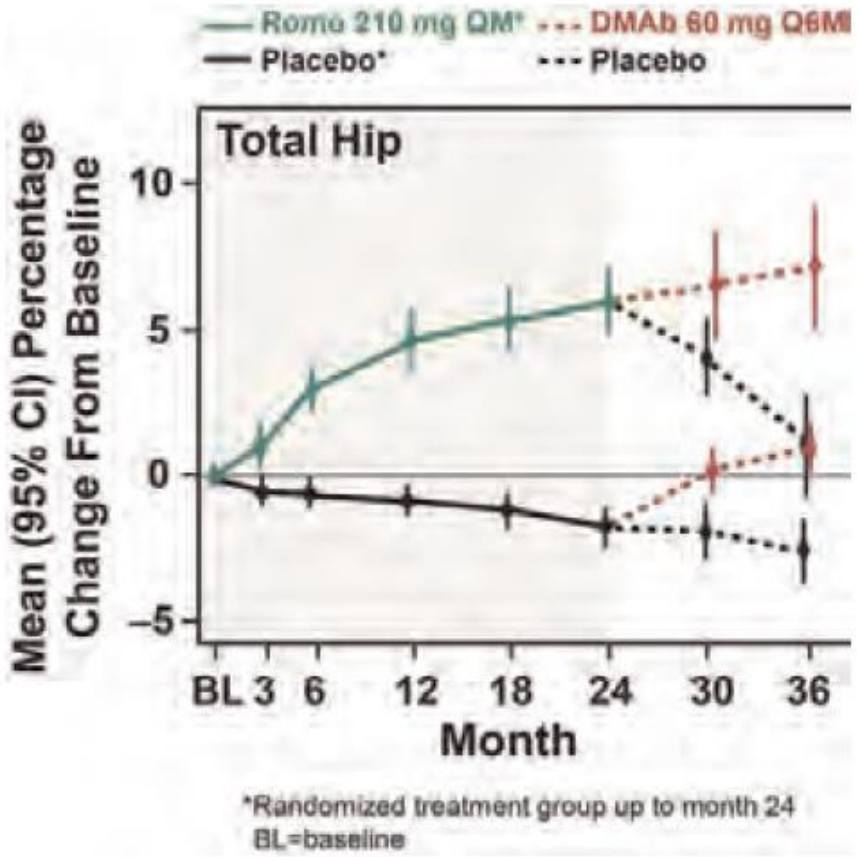
Adapted from: Padhi D, et al. *J Bone Miner Res.* 2011;26:19-26.

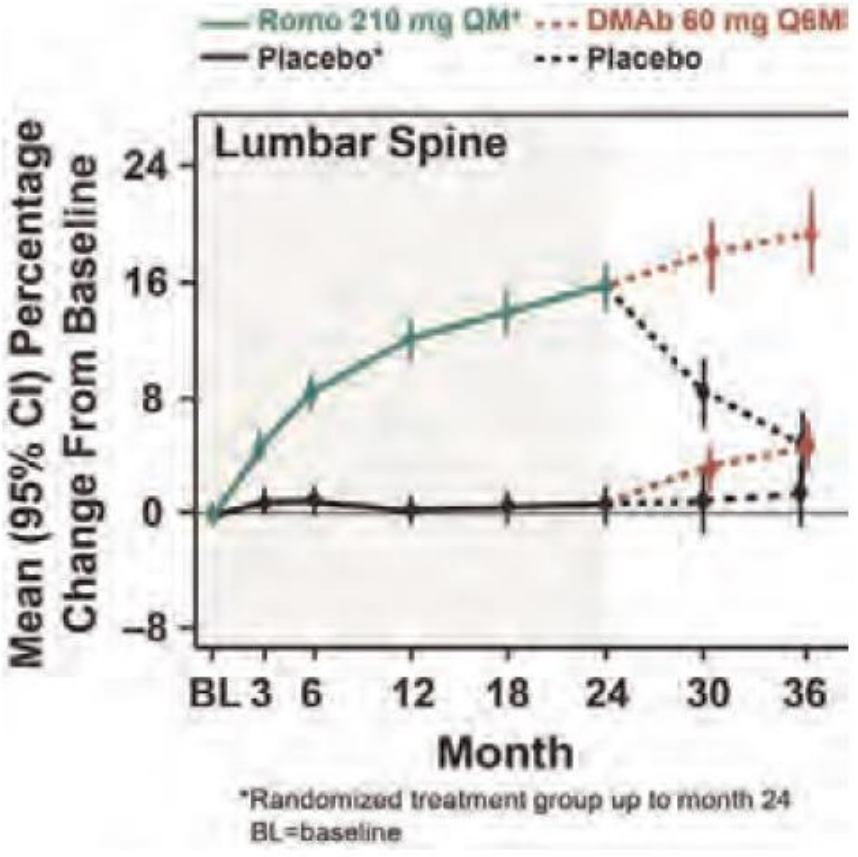


McClung, ASBMR, 2012

Romosozumab and Bone Turnover

Effects of 2 Years of Treatment With Romosozumab Followed by 1 Year of Denosumab or Placebo in Postmenopausal Women with Low Bone Mineral Density.

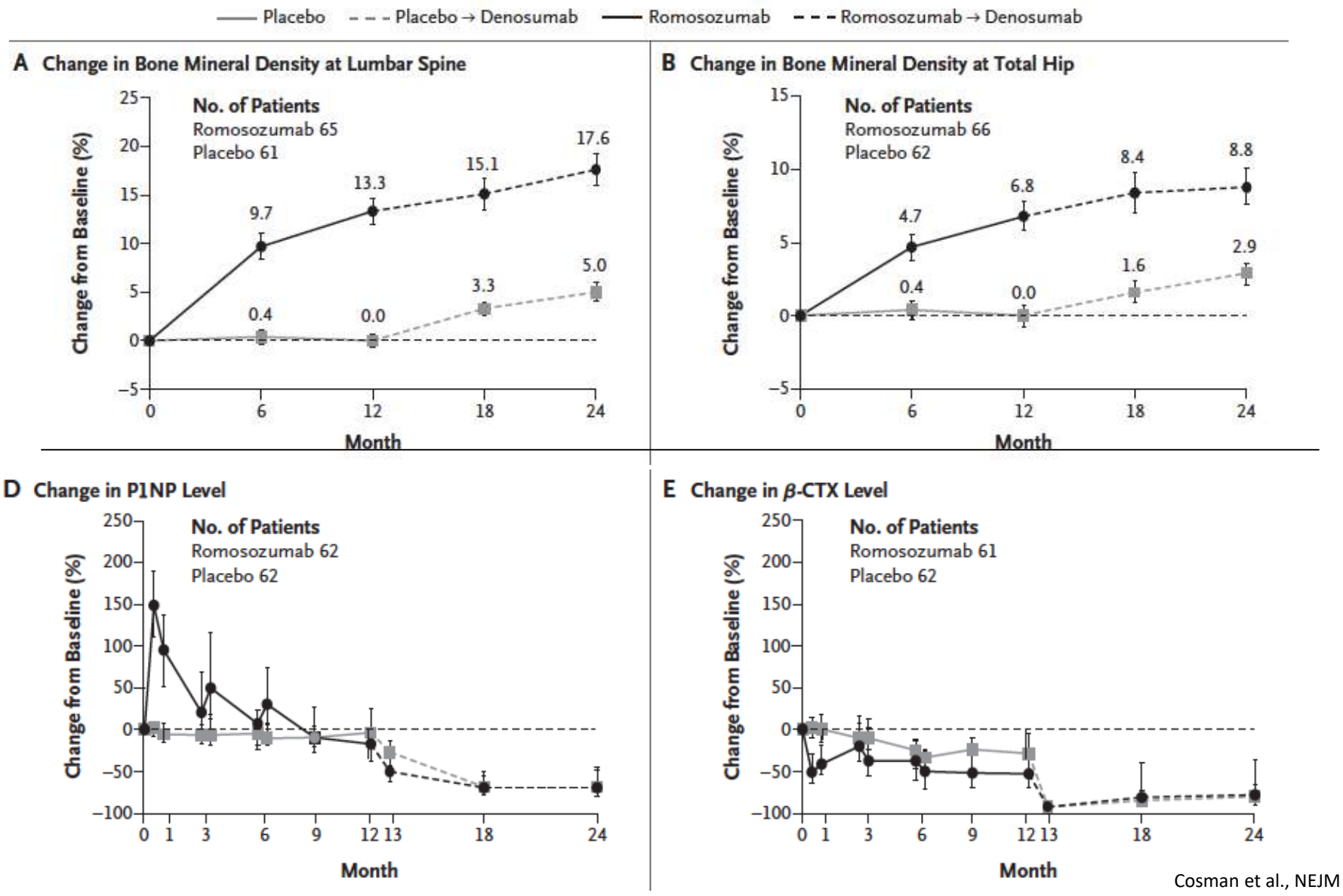




McClung et al. ASBMR 2014

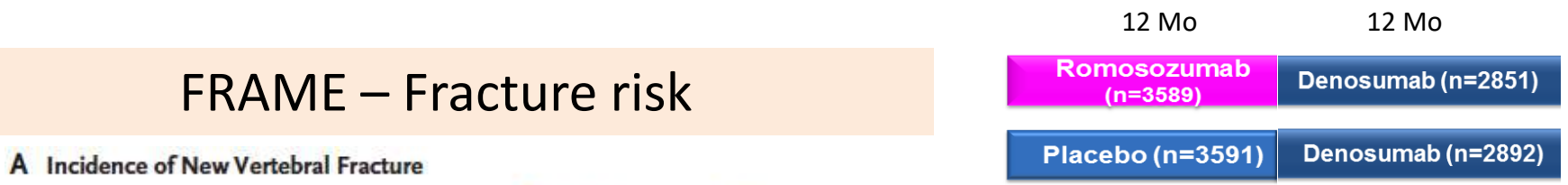
FRAME - Bone Turnover and BMD

12 Mo	12 Mo
Romosozumab (n=3589)	Denosumab (n=2851)
Placebo (n=3591)	Denosumab (n=2892)

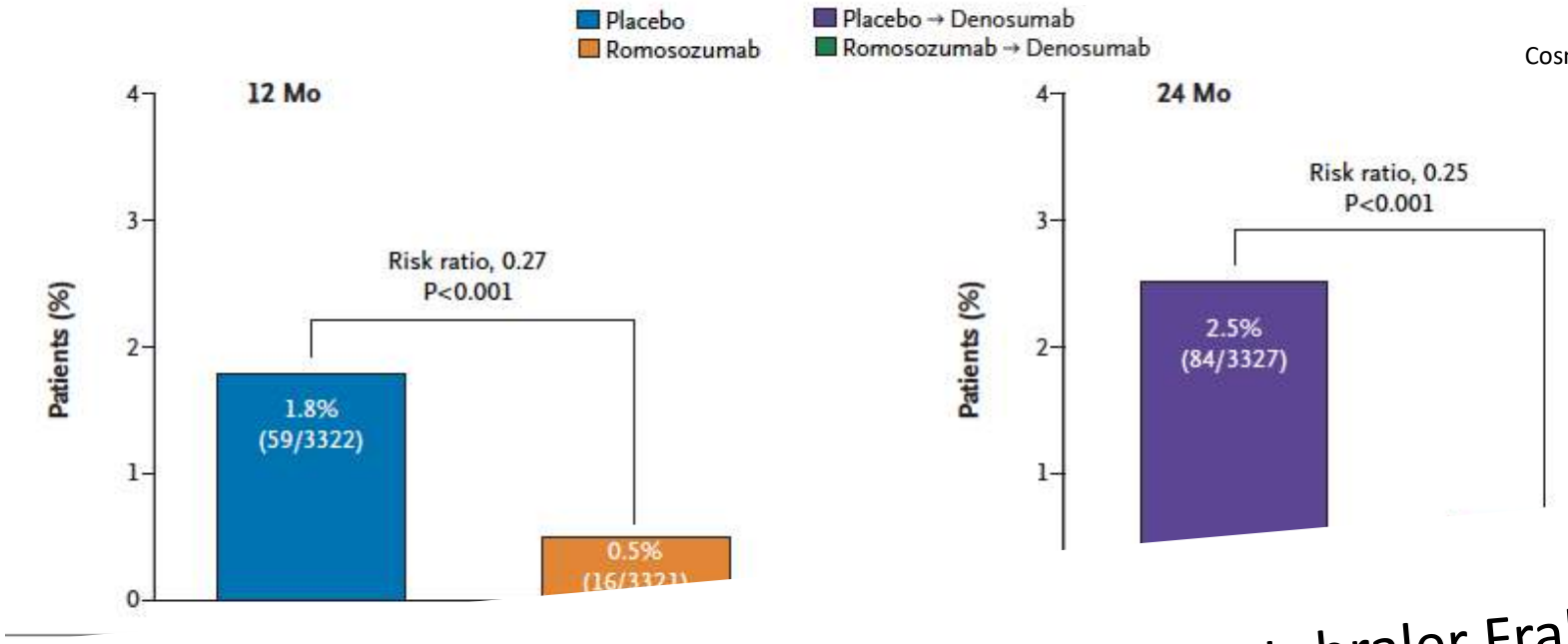


Cosman et al., NEJM 2016

FRAME – Fracture risk



Cosman et al., NEJM 2016



Regionale Unterschiede in der Inzidenz non-vertebraler Frakturen

- Lateinamerica: 1.5% (Romo) vs 1.2% (Placebo)
- Außerhalb Lateinamerica: 1.6% (Romo) vs 2.7% (Placebo)
- Hazard Ratio außerhalb Lateinamerika 0,58 (p = 0.04)

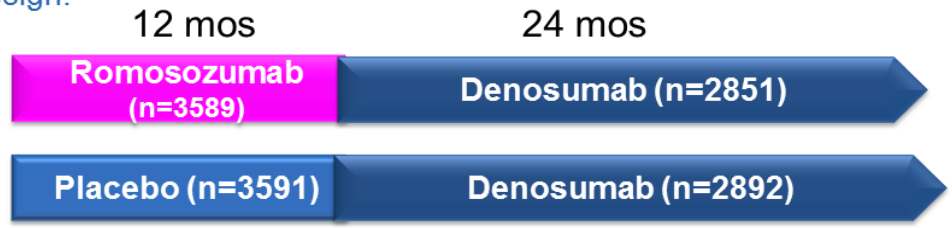
			0.75 (0.53–1.05)	0.096
		37/3589 (1.0)	0.67 (0.44–1.02)	0.060
[illegible] vertebral fracture[a]	59/3322 (1.8)	17/3321 (0.5)	0.29 (0.17–0.49)	<0.001
Hip fracture[c]	13/3591 (0.4)	7/3589 (0.2)	0.54 (0.22–1.35)	0.18
Major osteoporotic fracture[c,e]	63/3591 (1.8)	38/3589 (1.1)	0.60 (0.40–0.90)	0.012

Continued Fracture Risk Reduction After 12 Months of Romosozumab Followed by Denosumab Through 36 Months in the Phase 3 FRAME (FRActure study in postmenopausal woMen with ostEoporosis) Extension.

Background: Romosuzumab for 12 mos followed by Denosumab for 12 mos results in BMD gains and reductions in vertebral and clinical fractures (Cosman et al, 2016)

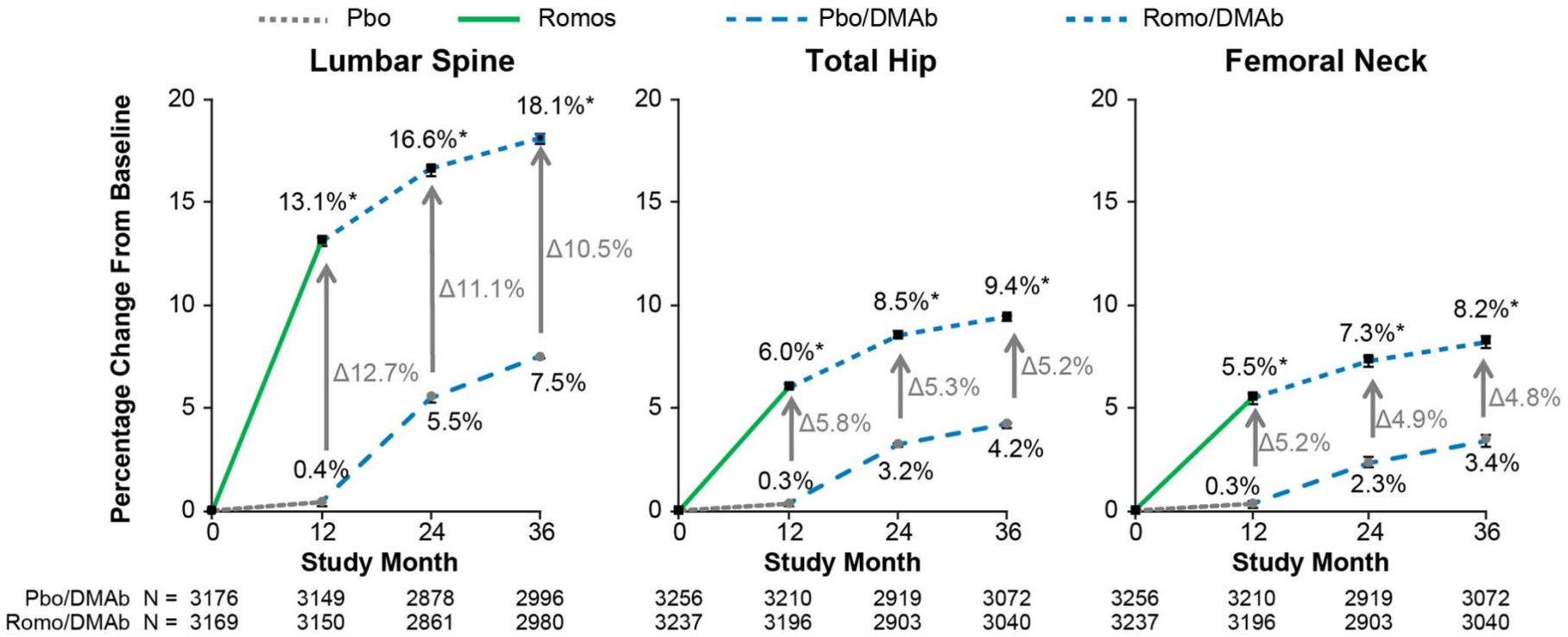
Question: Upon transition to denosumab for 2 years, does the earlier Romosozumab effect persist?

Design:



Lewiecki 2017, J Bone Miner Res 32 (Suppl 1) #1071

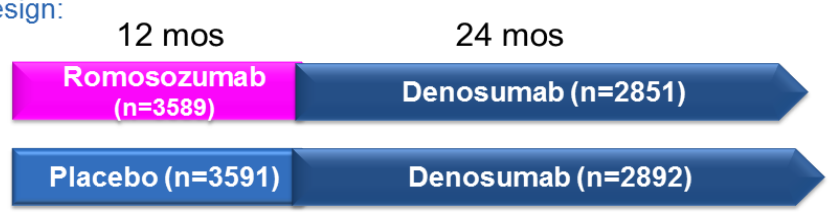
Figure. Percentage change from baseline in BMD



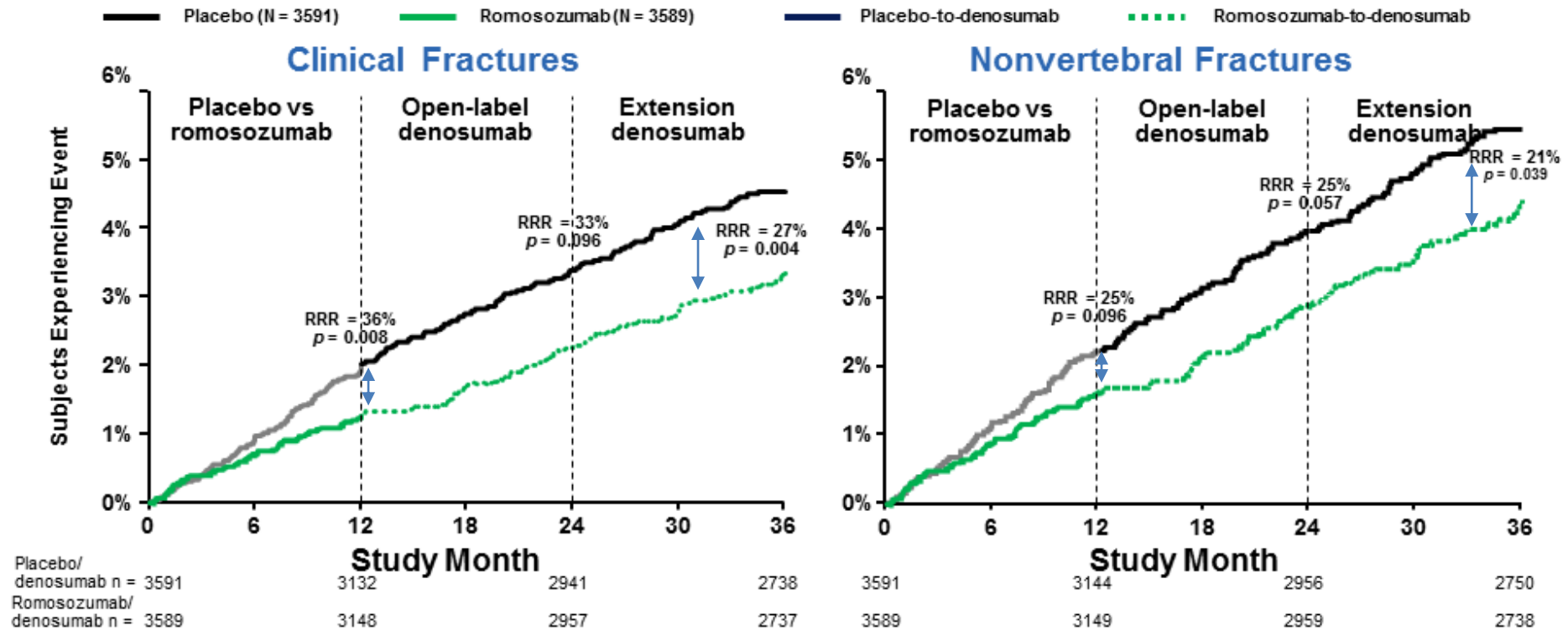
*P<0.001 for group comparisons. Data are least square mean (95% CI).

Fracture Risk Reduction After 12 Months of Romosozumab Followed by Denosumab Through 36 Months in the Phase 3 FRAME

Design:



Time to First Clinical and Nonvertebral Fracture Through Month 36

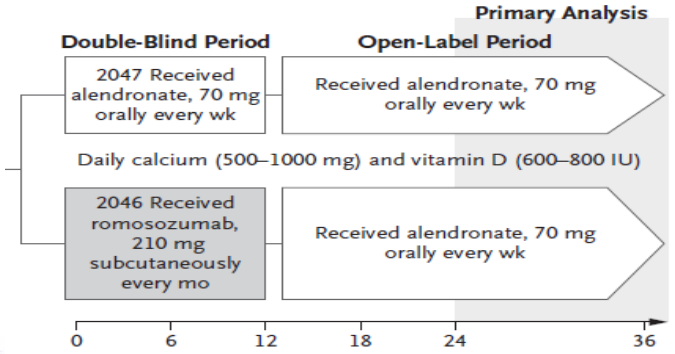


Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures. n = number of subjects at risk for event at time point of interest. Relative risk reduction and *P*-values for 12-month and 24-month periods are adjusted values based on a sequential testing procedure as reported for the primary analysis. *P*-values for month 36 are nominal.

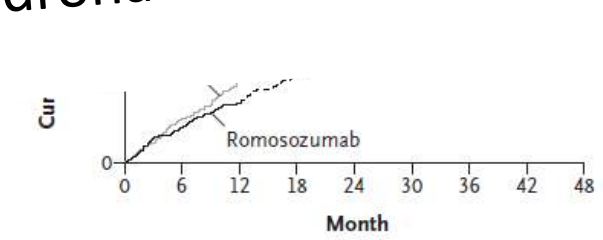
Romosozumab followed by DMAb ….reduced new vertebral, clinical, and non-vertebral fracture risk vs Pbo followed by DMAb for 24…..underscoring a potential foundational effect of Romo.

Lewiecki 2017, J Bone Miner Res 32 (Suppl 1) #1071

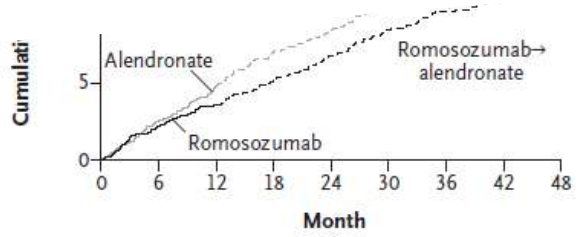
A Randomized Alendronate-Controlled Trial of Romosozumab: Results of the Phase 3 **ARCH Study** (Active-contRolled fraCture study in postmenopausal women with osteoporosis at High risk)



In postmenopausal women with osteoporosis at high risk for fracture, romosozumab treatment for 12 months followed by alendronate resulted in a significantly lower risk of fracture than alendronate alone.



No. at Risk									
Alendronate	2047	1868	1743						
Romosozumab	2046	1865	1770						
Alendronate→ alendronate				1645	1564	1066	680	325	108
Romosozumab→ alendronate				1683	1615	1103	705	347	109



No. at Risk									
Alendronate	2047	1873	1755						
Romosozumab	2046	1867	1776						
Alendronate→ alendronate				1661	1590	1097	697	330	110
Romosozumab→ alendronate				1693	1627	1114	714	350	109

Saag, NEJM 2017

A Randomized Alendronate-Controlled Trial of Romosozumab: Results of the Phase 3 **ARCH Study** (Active-contRolled fraCture study in postmenopausal women with osteoporosis at High risk)

Observed imbalance in CV SAEs compared with ALN not seen in the FRAME study

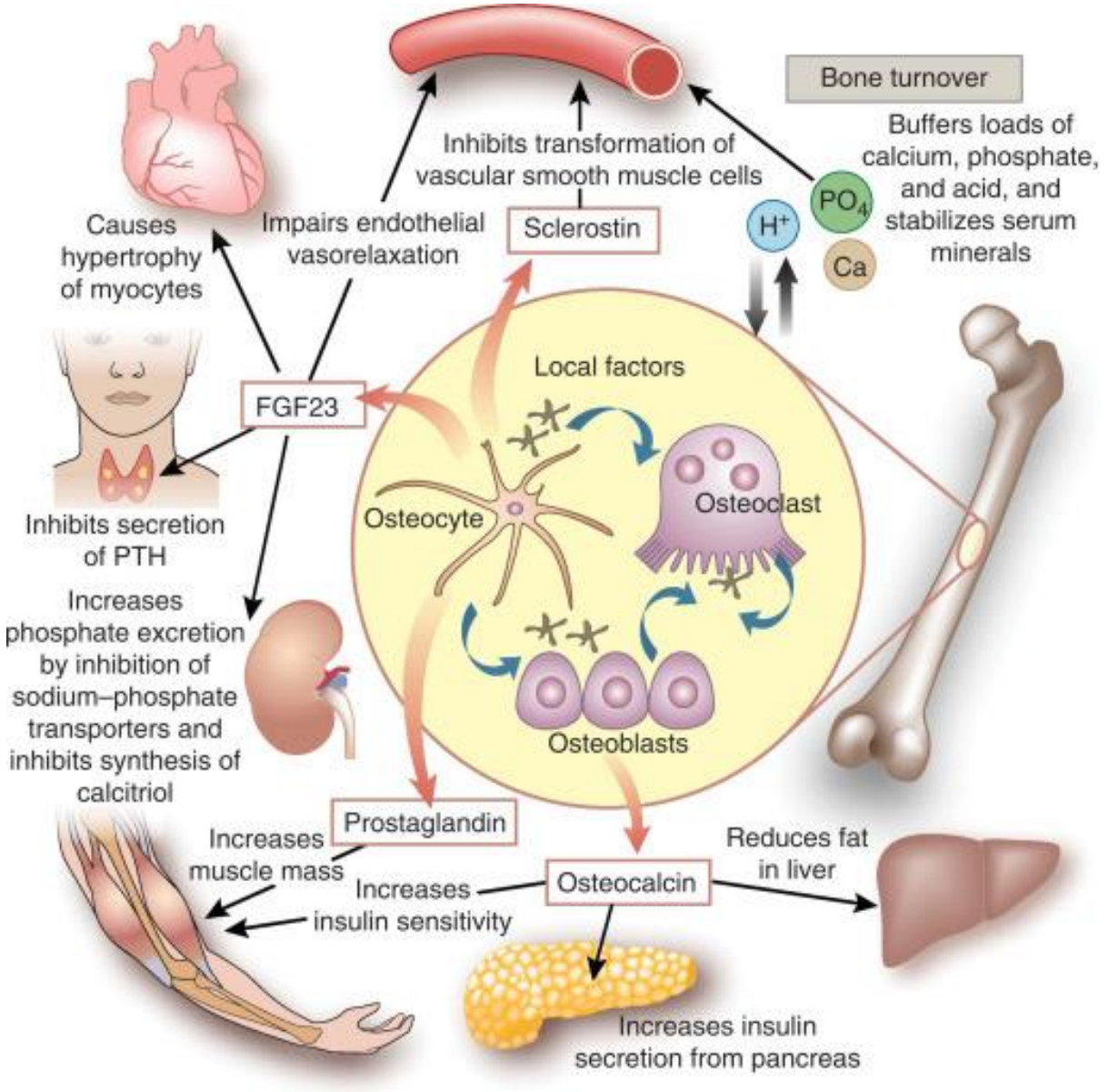
Event	Month 12: Double-Blind Period		Primary Analysis: Double-Blind and Open-Label Period*	
	Alendronate (N=2014)	Romosozumab (N=2040)	Alendronate to Alendronate (N=2014)	Romosozumab to Alendronate (N=2040)
	number of patients (percent)			
Adverse event during treatment	1584 (78.6)	1544 (75.7)	1784 (88.6)	1766 (86.6)
Back pain†	228 (11.3)	186 (9.1)	393 (19.5)	329 (16.1)
Nasopharyngitis†	218 (10.8)	213 (10.4)	373 (18.5)	363 (17.8)
Serious adverse event	278 (13.8)	262 (12.8)	605 (30.0)	586 (28.7)
Adjudicated serious cardiovascular event‡	38 (1.9)	50 (2.5)	122 (6.1)	133 (6.5)
Cardiac ischemic event	6 (0.3)	16 (0.8)	20 (1.0)	30 (1.5)
Cerebrovascular event	7 (0.3)	16 (0.8)	27 (1.3)	45 (2.2)
Heart failure	8 (0.4)	4 (0.2)	23 (1.1)	12 (0.6)
Death	12 (0.6)	17 (0.8)	55 (2.7)	58 (2.8)
Noncoronary revascularization	5 (0.2)	3 (0.1)	10 (0.5)	6 (0.3)
Peripheral vascular ischemic event not requiring revascularization	2 (<0.1)	0	5 (0.2)	2 (<0.1)
Death	21 (1.0)§	30 (1.5)	90 (4.5)§	90 (4.4)

Saag, NEJM 2017

Possible underlying mechanisms:

- Role for sclerostin in vasc. regeneration: *SOST* is expressed in aortic vascular smooth muscle
- Alendronate / BP might be cardioprotective, and the rate of cardiovascular events in the romosozumab group appears relatively higher than expected
- The number of adverse events was small, leading to the possibility of a type I error

Wnt-Signalling, Sclerostin and the vasculature



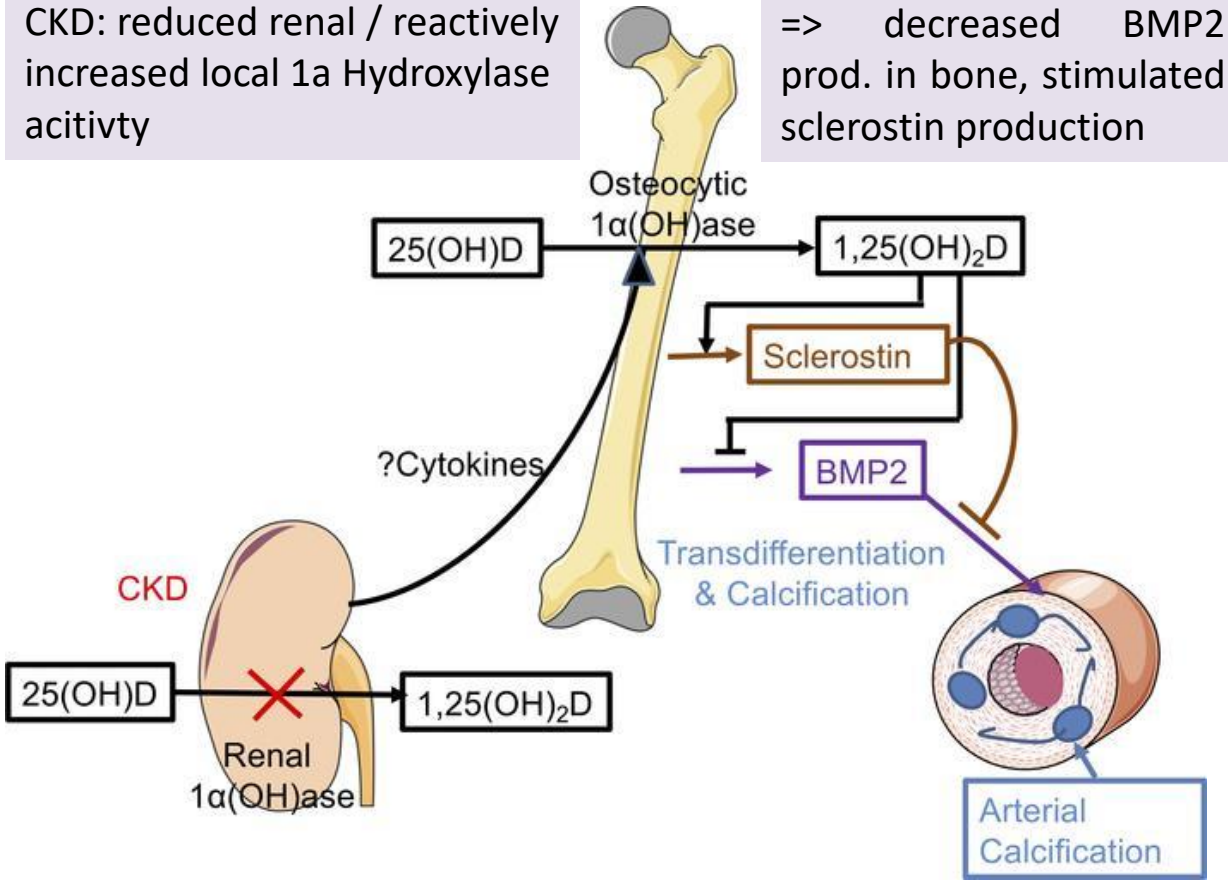
Ott, Kidney Int 2015, Bone cells, sclerostin, and FGF23 - what's bred in the bone will come out in the flesh

Wnt-Signalling, Sclerostin and the vasculature

Sclerostin can inhibit BMP2 - induced transdifferentiation of osseous cells in the arterial wall and reduce arterial calcification

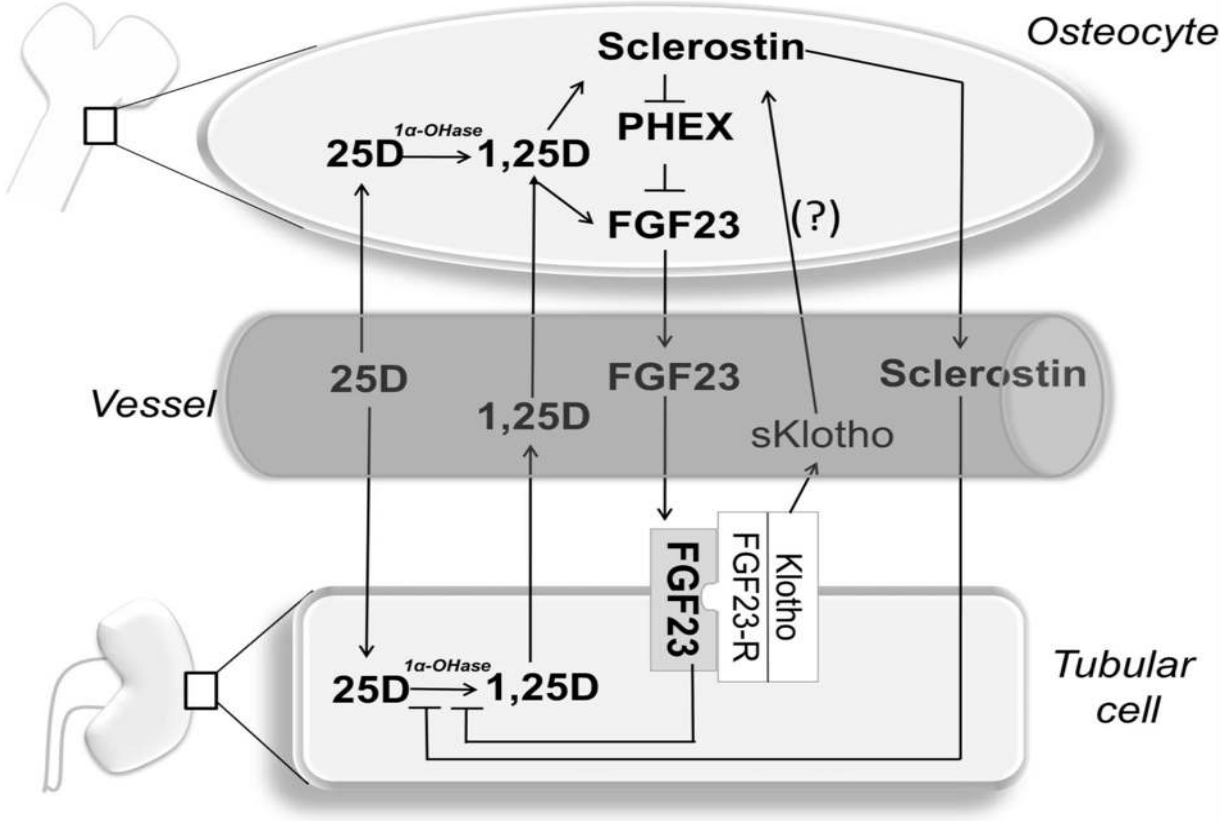
CKD: reduced renal / reactively increased local 1a Hydroxylase acitivty

=> decreased BMP2 prod. in bone, stimulated sclerostin production



Nguyen-Yamamoto et al., JCI Insight 2019: Sclerostin can inhibit BMP2-induced transdifferentiation of osseous cells in the arterial wall and reduce arterial calcification

Intracellular 1,25D stimulates Sclerostin synthesis. Sclerostin, through inhibition of PHEX (an FGF23 inhibitor), indirectly increases FGF23
production. Also, Sclerostin inhibits 1,25D synthesis through direct (inhibition of renal 1-αOH-ase) and indirect (stimulation of FGF23) effects.



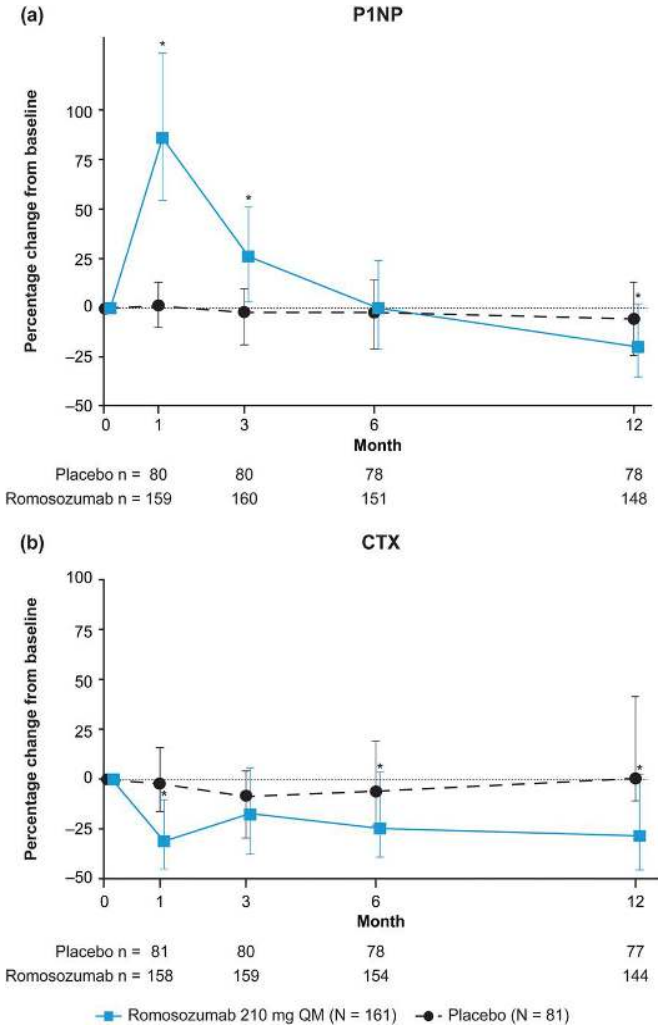
Tartaglione et al., PLoS one 2017: Sclerostin indirectly increses FGF-23 ans inhibits 1,25D synthesis

A Phase III Randomized Placebo-Controlled Trial to Evaluate Efficacy and Safety of Romosozumab in Men With Osteoporosis

BRIDGE Study, n=245 men, 55-90y

Ramdom. 2:1, Romo vs PBO

Primary efficacy endpoint was percentage change from baseline in LS BMD at month 12



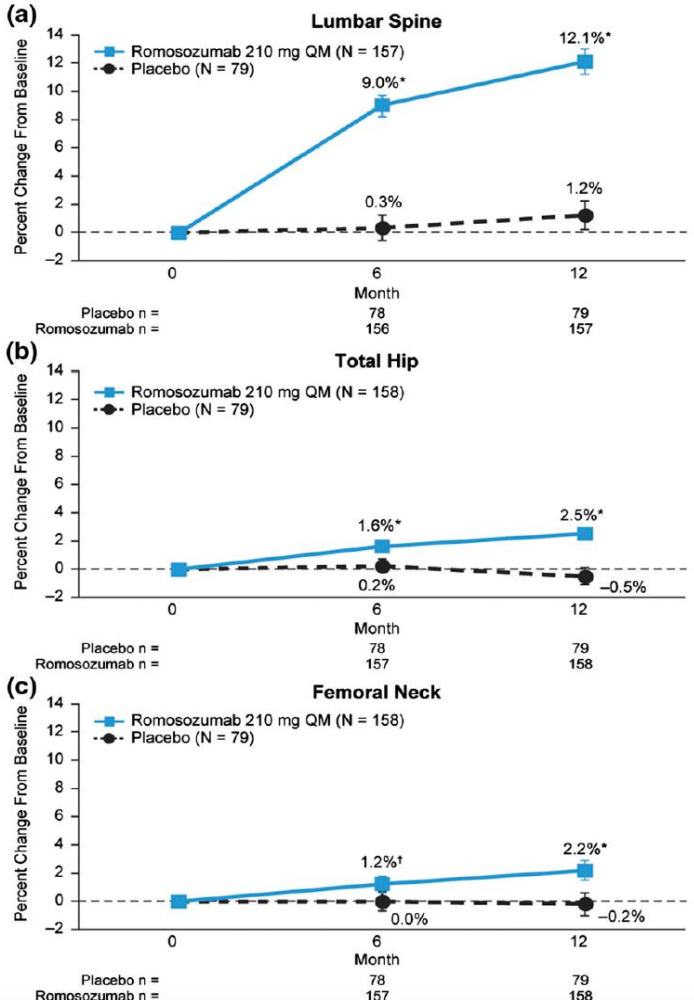


Table 2. Summary of Subject Incidence of Treatment-Emergent Adverse Events Through Month 12

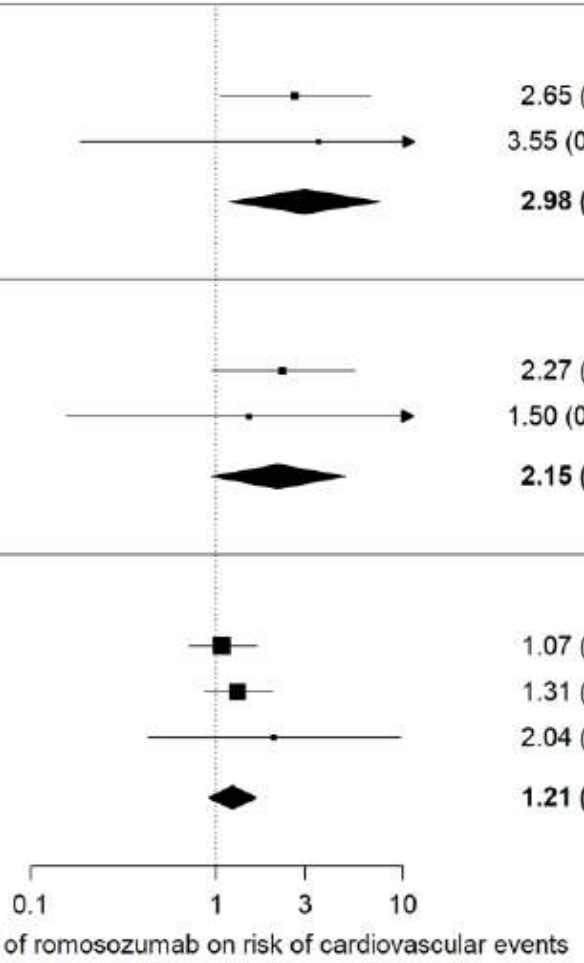
Adverse event, n (%)	Romosozumab 210 mg QM (N = 163)	Placebo (N = 81)
Any adverse event	123 (75.5)	65 (80.2)
Serious adverse event	21 (12.9)	10 (12.3)
Adjudicated cardiovascular serious adverse event[a]	8[b] (4.9)	2 (2.5)
Cardiac ischemic event	3 (1.8)	0 (0.0)
Cerebrovascular event	3 (1.8)	1 (1.2)
Death[c,d]	2[e] (1.2)	1 (1.2)
Heart failure	1 (0.6)	0 (0.0)
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 reaction[f]	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[a]	0 (0.0)	0 (0.0)
Osteonecrosis of the jaw[a]	0 (0.0)	0 (0.0)
Incident fracture[g]	3 (1.8)	2 (2.5)
Subject incidence of anti-romosozumab antibody formation		
Binding antibodies	28 (17.2)	NA
Neutralizing antibodies	1 (0.6)	NA

Conclusions: Treatment with romosozumab for 12 months increased the spine and hip BMD compared with placebo and was well tolerated in men with osteoporosis.

Lewiecki et al., J Clin Endocrinol Metab 103: 3183–3193, 2018

Meta-Analysis Romosozumab and Risk of Cardiovascular Events

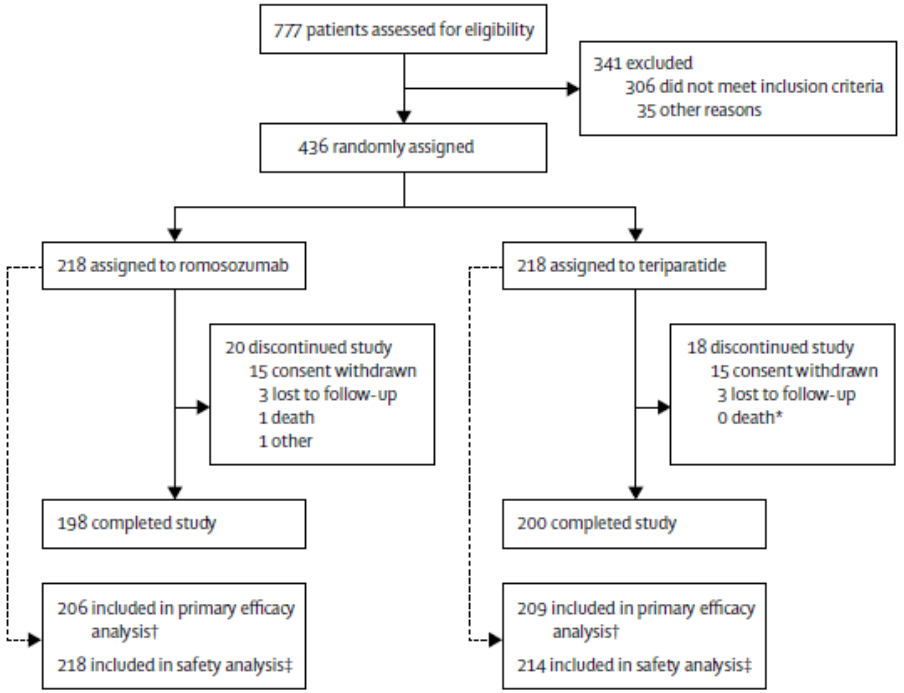
Endpoint & Trial	Romosozumab Events	Romosozumab Total	Comparator Events	Comparator Total	OR (95% CI)	P value
Cardiac ischemic events						
ARCH	16	2040	6	2014	2.65 (1.03-6.77)	
BRIDGE	3	163	0	81	3.55 (0.18-69.65)	
Overall	**19**	**2203**	**6**	**2095**	**2.98 (1.18-7.55)**	**0.02**
Cerebrovascular events						
ARCH	16	2040	7	2014	2.27 (0.93-5.52)	
BRIDGE	3	163	1	81	1.50 (0.15-14.65)	
Overall	**19**	**2203**	**8**	**2095**	**2.15 (0.94-4.92)**	**0.07**
Serious cardiovascular events						
FRAME	44	3581	41	3576	1.07 (0.70-1.65)	
ARCH	50	2040	38	2014	1.31 (0.85-2.00)	
BRIDGE	8	163	2	81	2.04 (0.42-9.83)	
Overall	**102**	**5784**	**81**	**5671**	**1.21 (0.90-1.63)**	**0.20**



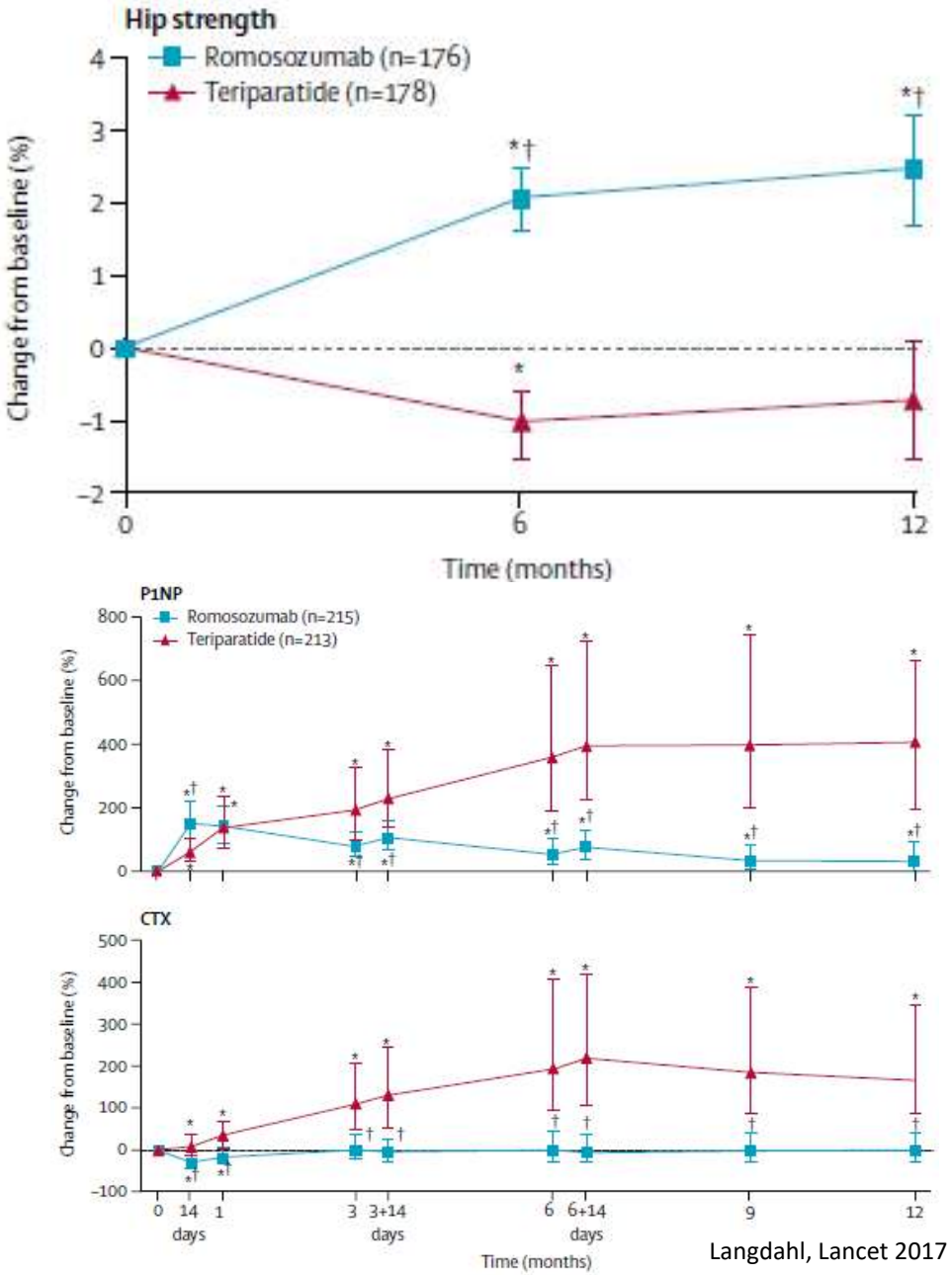
Genetically and therapeutically lowered sclerostin leads to higher risk of cardiovascular events. Rigorous evaluation of the cardiovascular safety of romosozumab and other sclerostin inhibitors is warranted.

Bovijn et al., BioRxiv 2019, Lifelong genetically lowered sclerostin and risk of cardiovascular disease

Romosozumab vs Teriparatid following oral Bisphosphonates



Transition to a bone-forming agent is common practice in patients treated with bisphosphonates, such as those who fracture while on therapy. In such patients, romosozumab led to gains in hip BMD that were not observed with teriparatide. These data could inform clinical decisions for patients at high risk of fracture

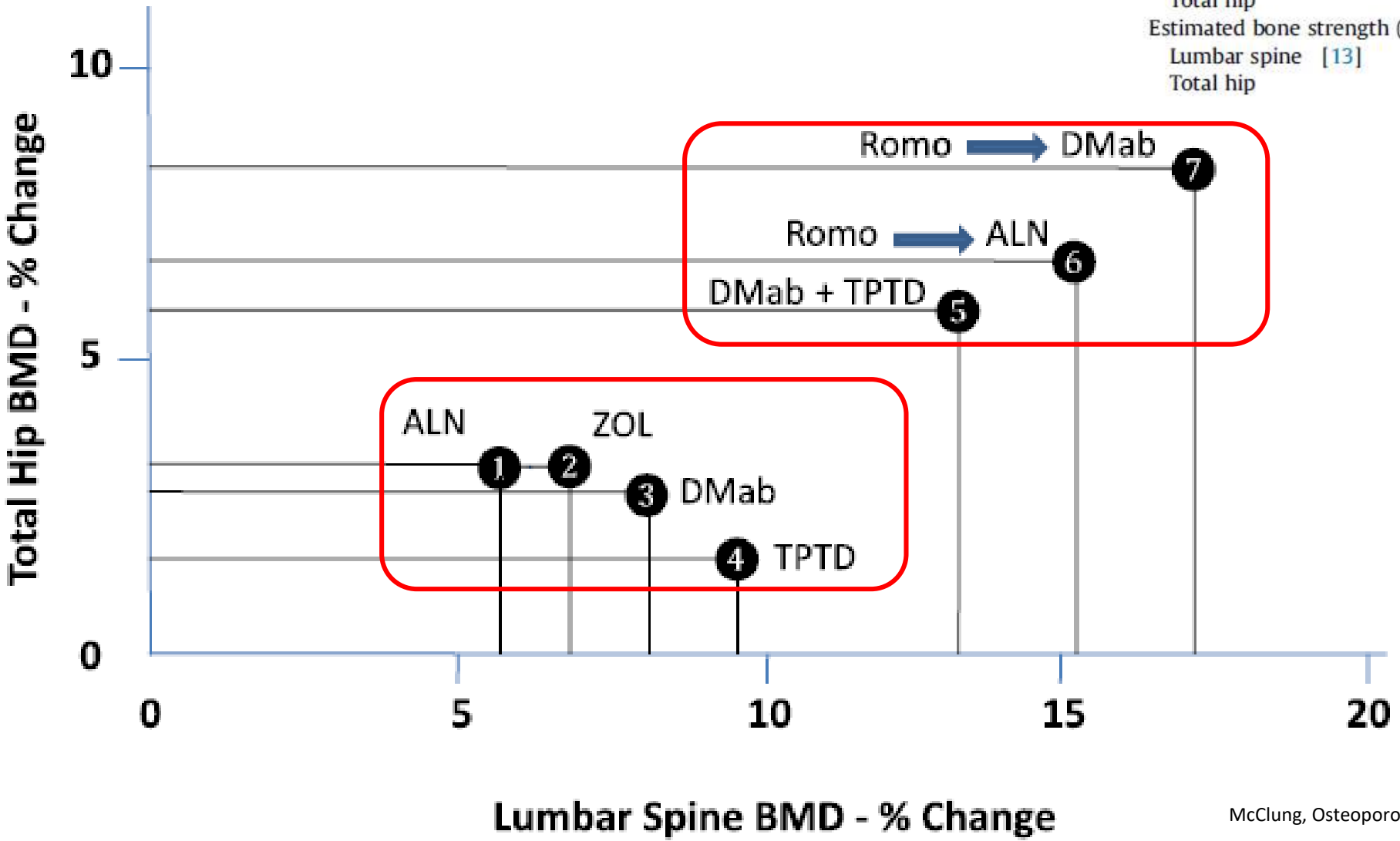


Langdahl, Lancet 2017

Bone Mineral Density Effects of various Combination Treatment Regimens

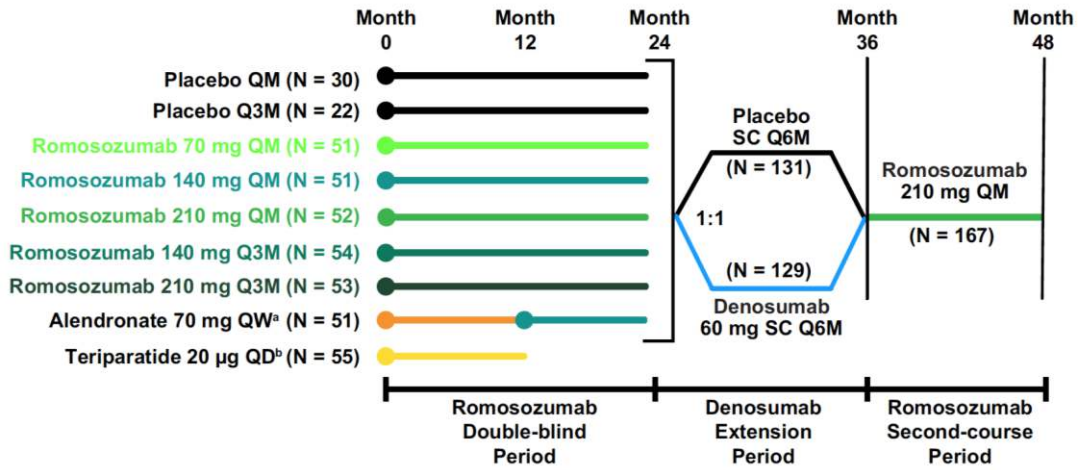
Comparison of changes in areal and volumetric BMD and in estimated bone strength over 12 months of therapy with romosozumab and teriparatide.

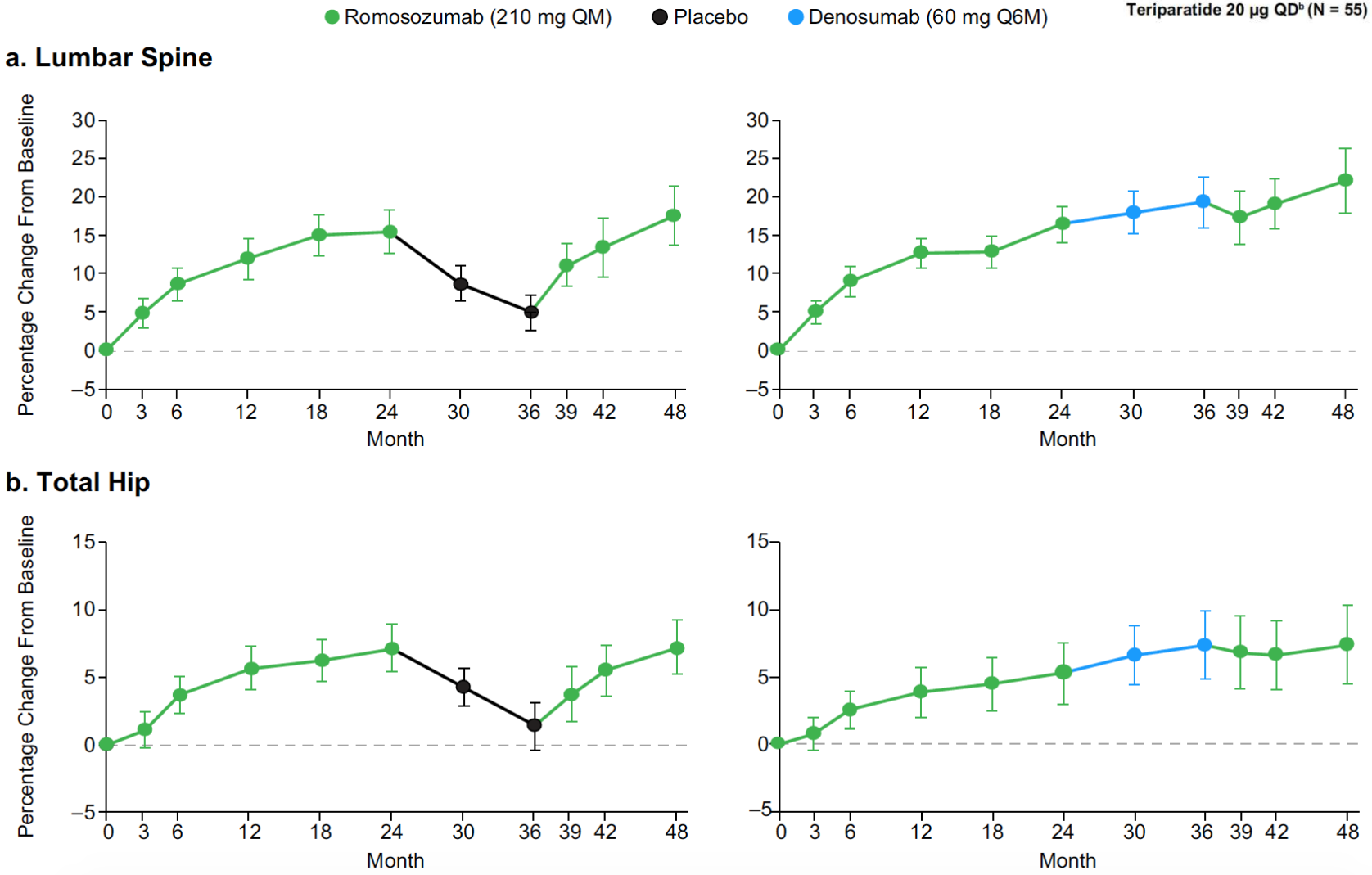
	Reference	Romosozumab 210 mg QM	Teriparatide 20 µg/d
Areal BMD (DXA)			
Lumbar spine	[12]	12.3%[a]	6.9%
Total hip		3.9%[a]	0.8%
Integral volumetric BMD (QCT)			
Lumbar spine	[12]	17.7%[a]	12.9%
Total hip		4.1%[a]	1.2%
Estimated bone strength (FEA by QCT)			
Lumbar spine	[13]	27.3%[a]	18.5%
Total hip		3.6%[a]	−0.7%



McClung, Osteoporosis and Sarcopenia 2018

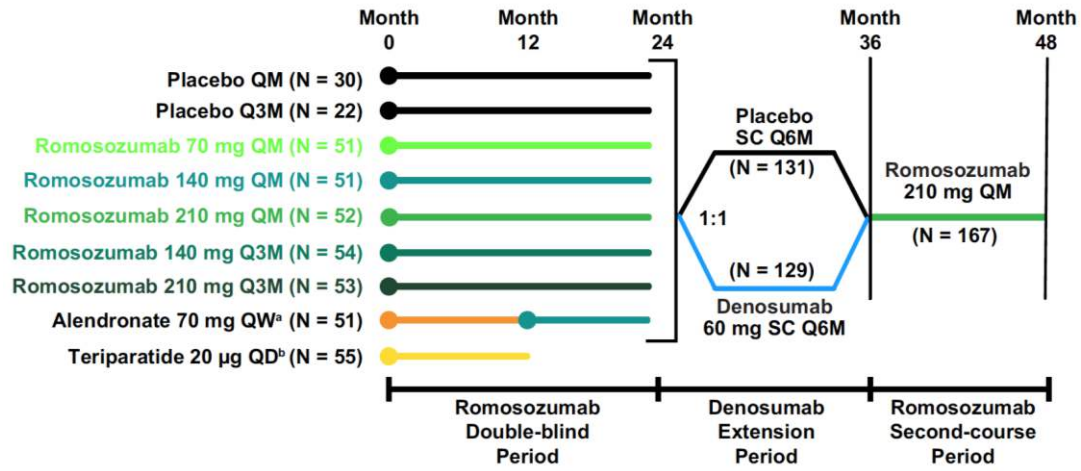
Bone mineral density gains with a second 12-month course of romosozumab therapy following placebo or denosumab



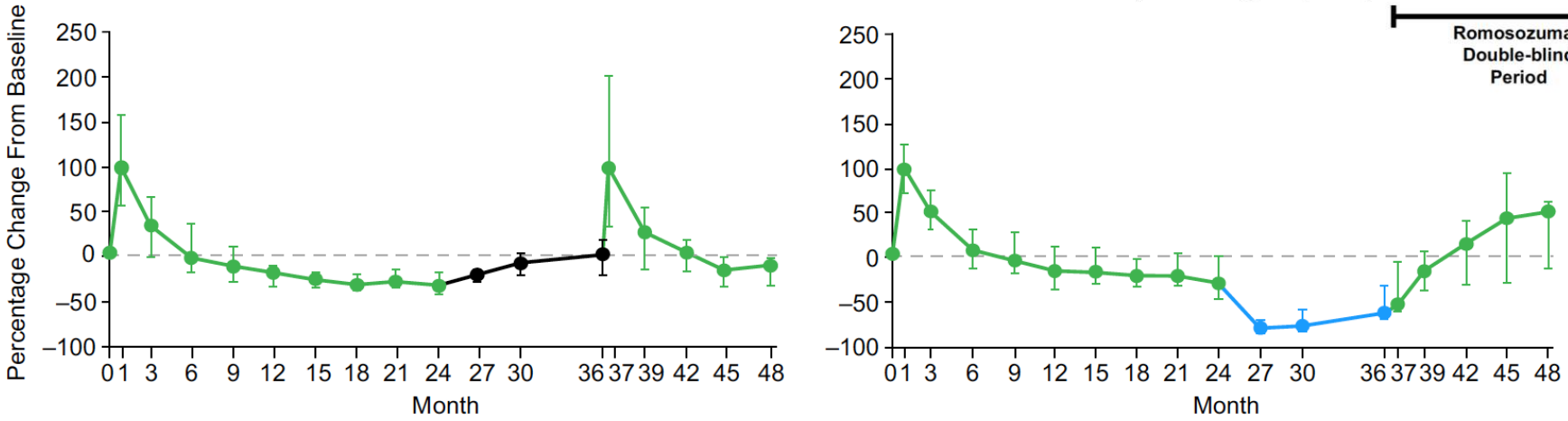


Kendler et al., Osteoporos Int 2019, Bone mineral density gains with a second 12-month course of romosozumab therapy following placebo or denosumab

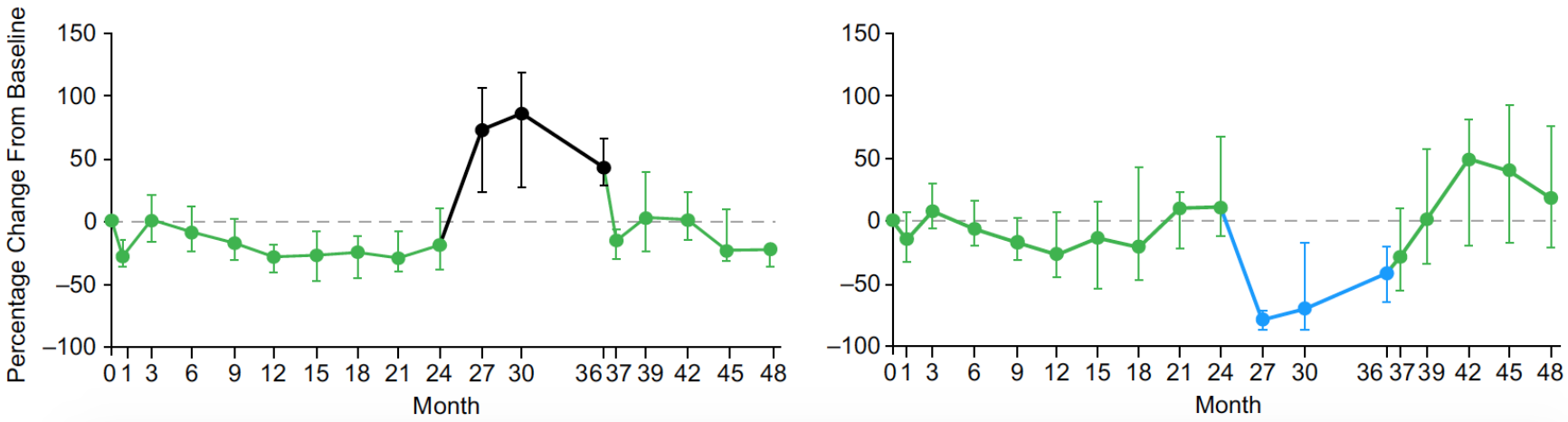
Bone mineral density gains with a second 12-month course of romosozumab therapy following placebo or denosumab



c. P1NP



d. β-CTX

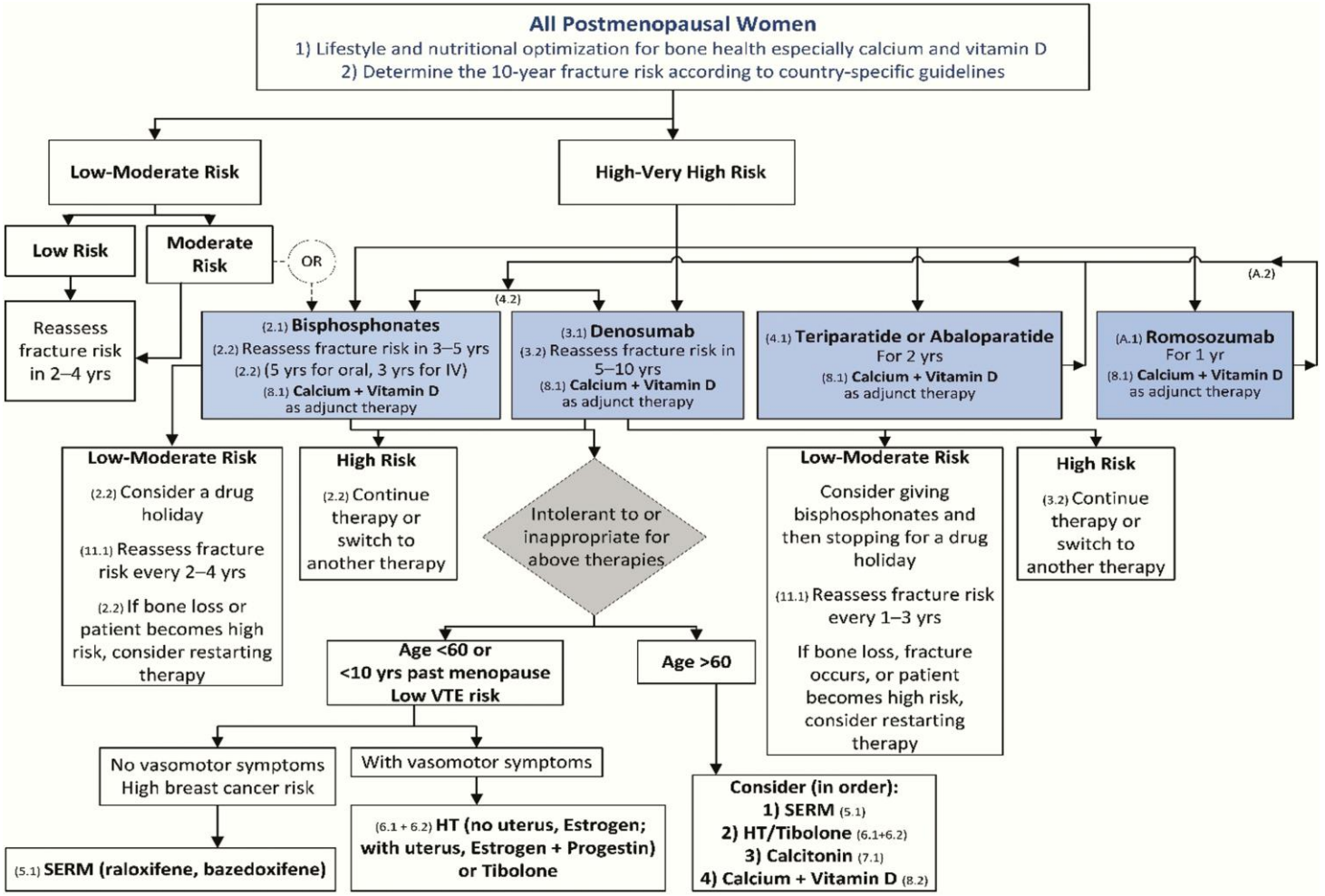


Kendler et al., Osteoporos Int 2019, Bone mineral density gains with a second 12-month course of romosozumab therapy following placebo or denosumab

Endocrine Society Guideline Update 2020

"…**romosozumab**, a monoclonal antibody targeting sclerostin, for the prevention of fractures and concluded that this agent can be **considered a treatment option for postmenopausal women at very high risk for osteoporotic fracture**"

Shoeback et al., JCEM 2020, Pharmacological Management of Osteoporosis in Postmenopausal Women - An Endocrine Society Guideline Update



Fracture Risk	BMD, Hip or Spine, T-Score	Fx History (Hip + Spine)	FRAX 10y Fracture risk, Hip	FRAX 10y Fracture risk, Major osteop. Fracture
Low	> -1.0	none	< 3%	< 20%
Moderate	> -2.5	none	< 3%	< 20%
High	≤ -2.5	one	≥ 3%	≥ 20%
Very high	≤ -2.5	multiple	n.a.	n.a.

Alle großen Leute waren einmal Kinder,
aber nur wenige erinnern sich daran.

Antoine de Saint-Exupéry