Optimizing Sequential Osteoporosis Therapy

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Antiresorptive and Anabolic Therapies

- Increase BMD
- Reduce vertebral fractures in high-risk populations
- Reduce non-vertebral fractures modestly
- Cannot restore skeletal integrity in most patients

Current Antiresorptive and Anabolic Therapies

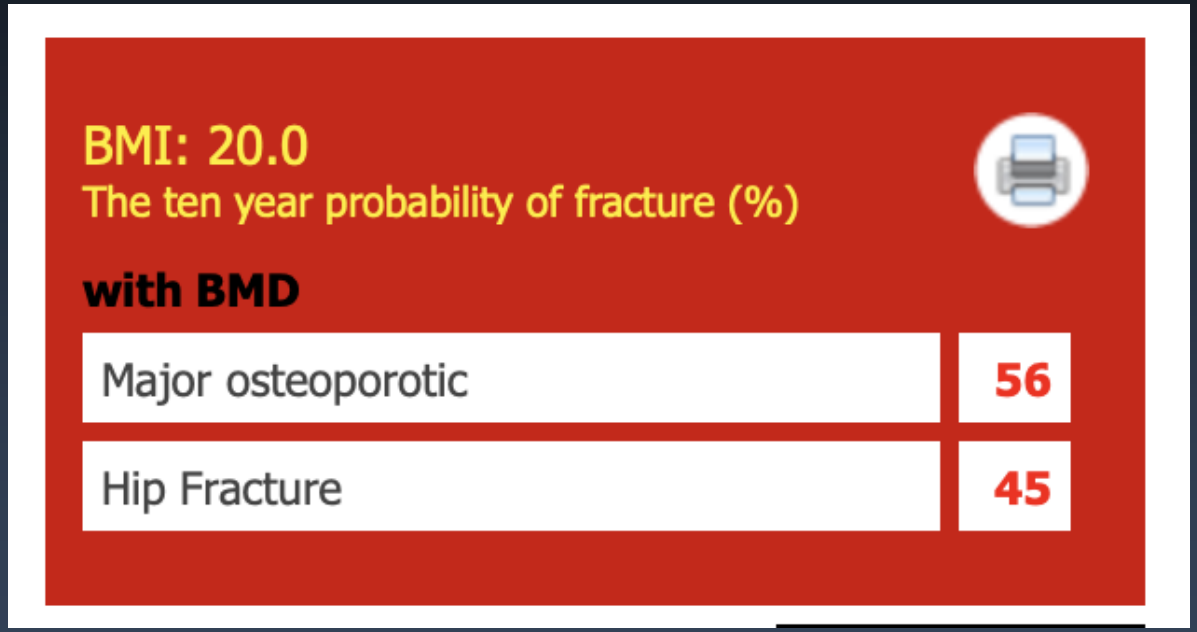
	mechanism of action	2-yr increase spine BMD	2-yr increase total hip BMD	RRR of spine fracture	RRR of non-spine fracture
Raloxifene	antiresorptive-SERM	2-3%	1%	50%	--
Oral BPs	antiresorptive-bisphosphonate	3-5%	2-3%	40-53%	0-20%
IV Zoledronic acid	antiresorptive-bisphosphonate	5-6%	3-4%	70%	25%
SC Denosumab	antiresorptive-RANKL-inhibitor	6-8%	3-4%	68%	20%
SC Teriparatide	anabolic-PTH analog	8-10%	1.5-2%	65-70%	35%
SC Abaloparatide	anabolic-PTH analog	10%	2-3%	70-80%	40%
Romosozumab	mixed anabolic/antiresorptive	11% (1 year)	4% (1 year)	48% vs. alendronate	20% vs. alendronate

Black et al. Lancet. 1996, Black et al. NEJM. 2007, Cummings et al. NEJM. 2009, Neer et al. NEJM. 2001, Miller et al JAMA 2017, Saag et al NEJM 2017

Patient Presentation

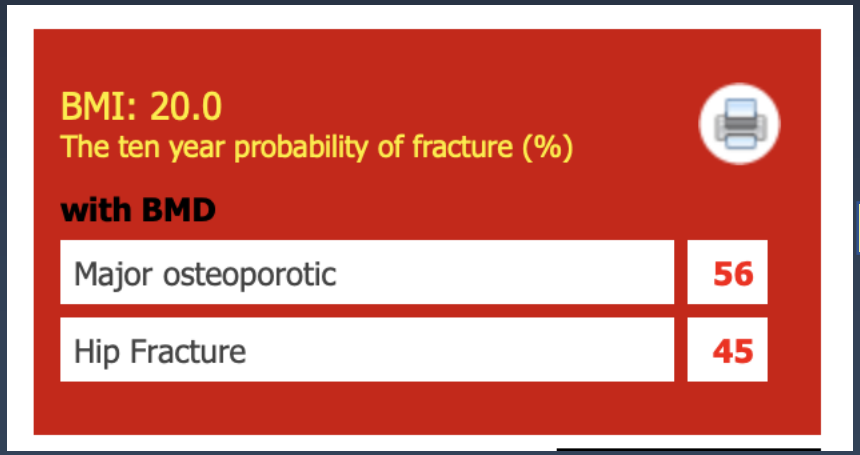
- 78-year-old female was referred for osteoporosis management.
- 4-inch height loss (now 63 inches, 115 pounds)
- Wrist fracture at age 57. +FH of hip fracture, non-smoker, no ETOH
- 2 vertebral compression fractures
- T10 kyphoplasty
- Bone density:
  - Femoral Neck BMD 0.47 g/cm^2 (score -3.2)

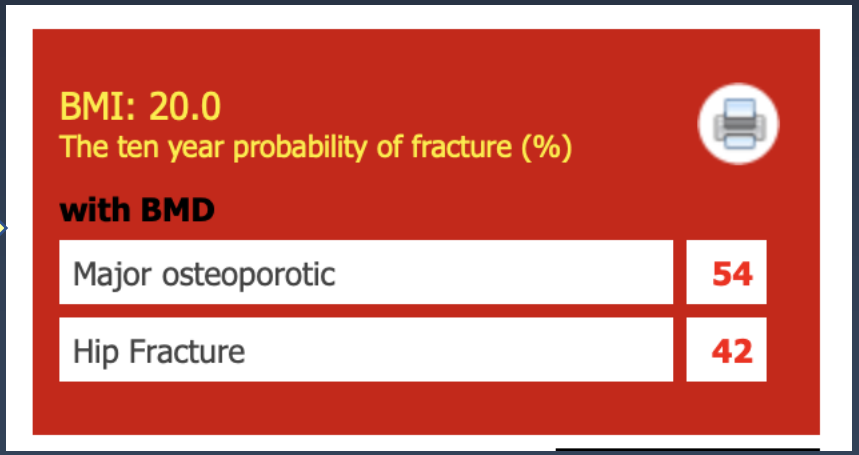
Patient Presentation: Current Risk



Patient Presentation: Risk after 3 years of zoledronic acid with average response

- 81-year-old female
- Femoral Neck BMD 0.486 g/cm^2



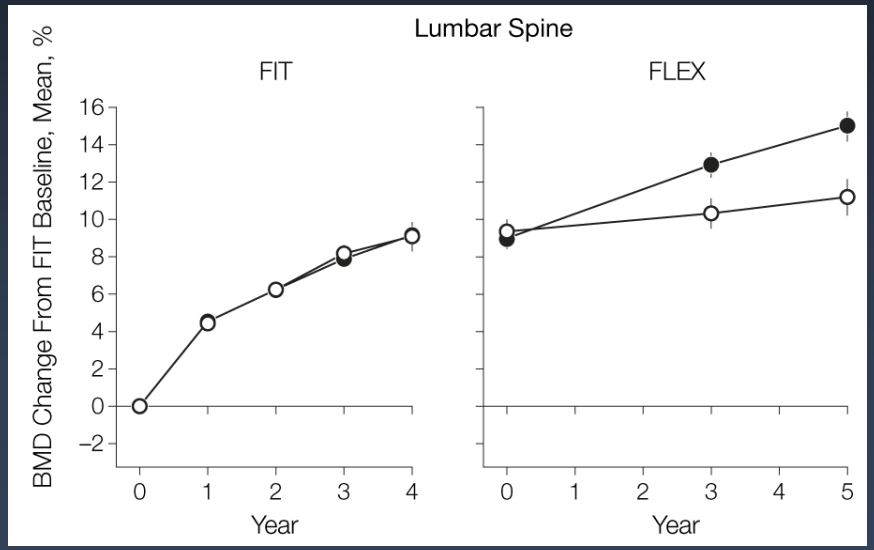


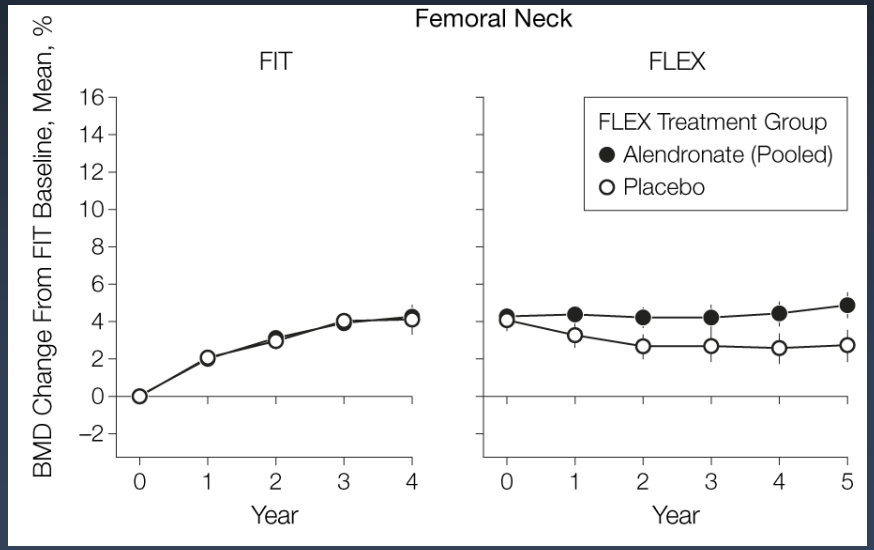
Sequential Therapy: Rationale

- Given the limitations of current therapies, the sequential use of individual agents has become common in patients with established disease.
- Limitations of individual drugs include:
  - Waning efficacy with prolonged use.
  - Greater risk of serious side effects with long term use.
- Designing the optimal drug sequence for individual patients requires understanding the long-term effects of each individual agent and the properties of specific drug transitions.

Long Term Efficacy and Consequences of Bisphosphonate Discontinuation: FLEX

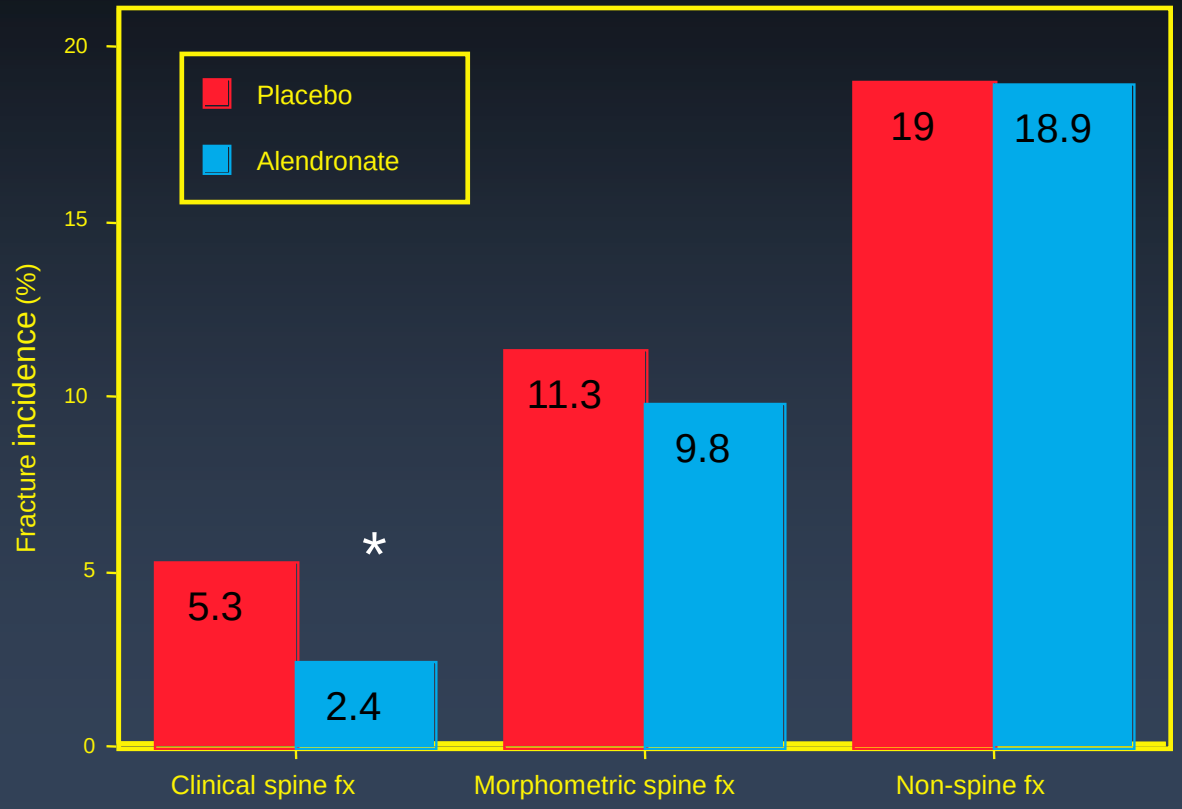
1099 osteoporotic women assigned to alendronate group in FIT (4 years)
Re-randomized to alendronate or placebo for an additional 5 years





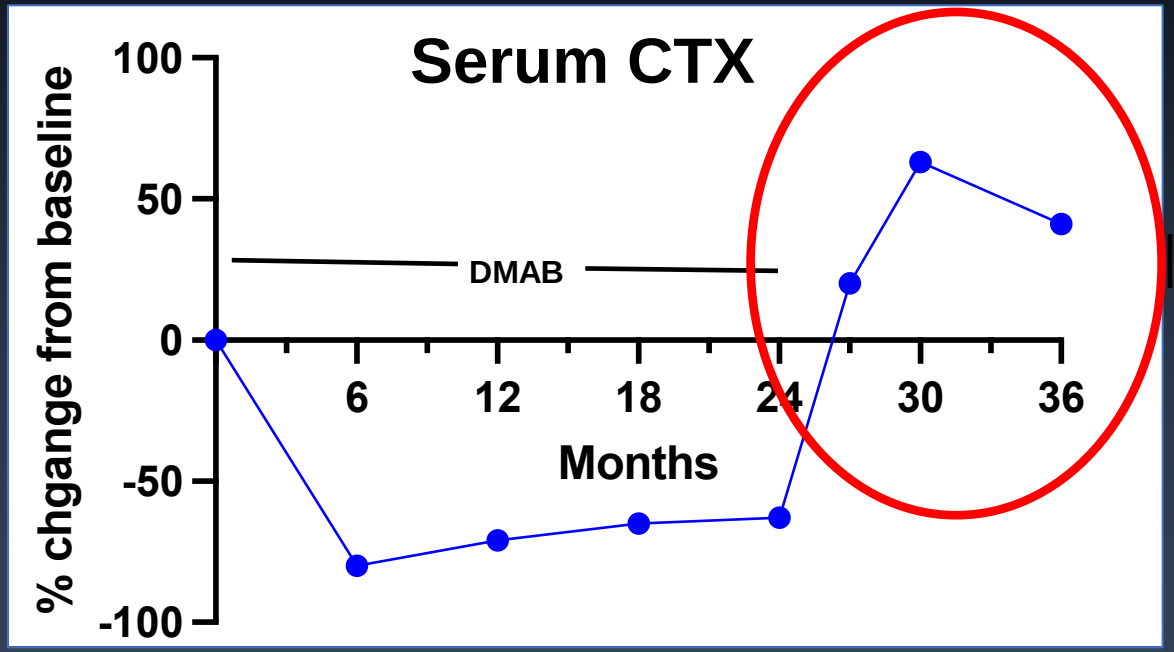
Black et al., JAMA 2006

Long Term Efficacy and Consequences of Bisphosphonate Discontinuation: FLEX



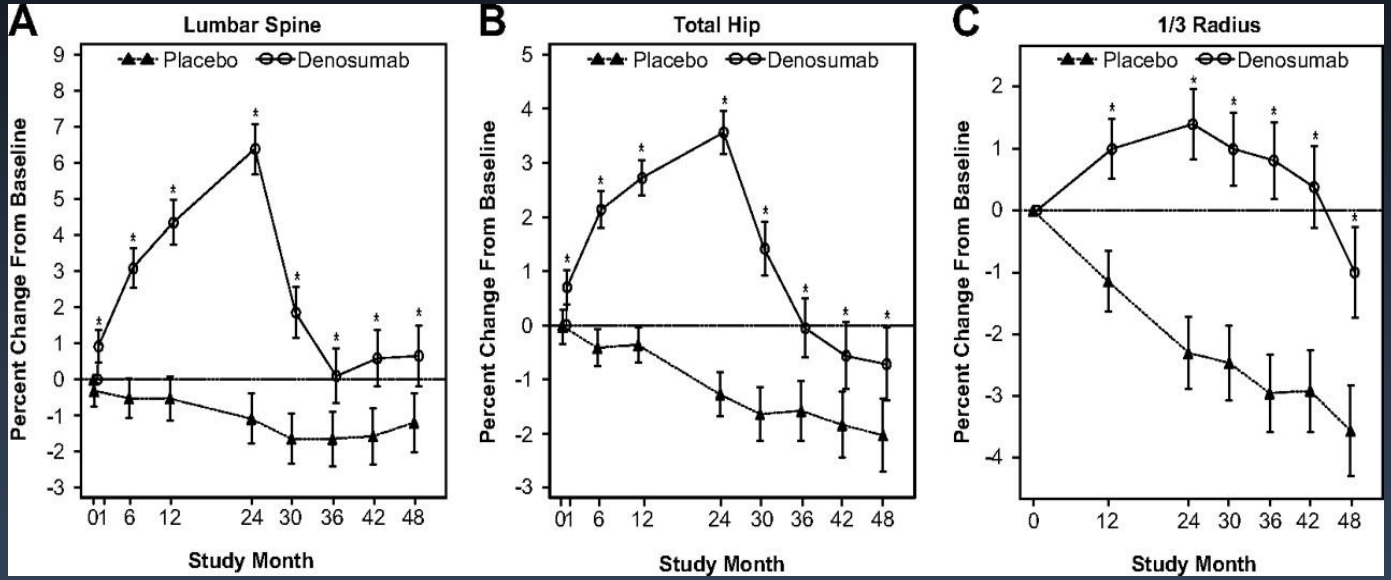
Schwartz et al., JBMR 2010

Long Term Efficacy and Consequences of Denosumab Discontinuation



Bone et al., JCEM 2011

Long Term Efficacy and Consequences of Denosumab Discontinuation



Bone et al., JCEM 2011

Long Term Efficacy and Consequences of Denosumab Discontinuation

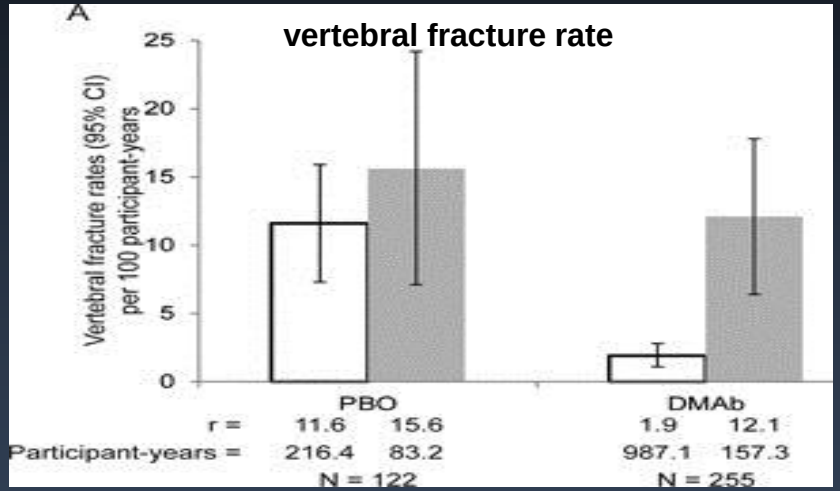
ORIGINAL ARTICLE

JBMR®

Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension

Steven R Cummings,[1] Serge Ferrari,[2] Richard Eastell,[3] Nigel Gilchrist,[4] Jens-Erik Beck Jensen,[5] Michael McClung,[6] Christian Roux,[7] Ove Törring,[8] Ivo Valter,[9] Andrea T Wang,[10] and Jacques P Brown[11]

- Analysis of the risk of new or worsening vertebral fractures in participants who discontinued denosumab during the FREEDOM study.
- Patients received ≥2 doses of denosumab or placebo Q6M, discontinued treatment, and stayed in the study ≥7 months after the last dose.



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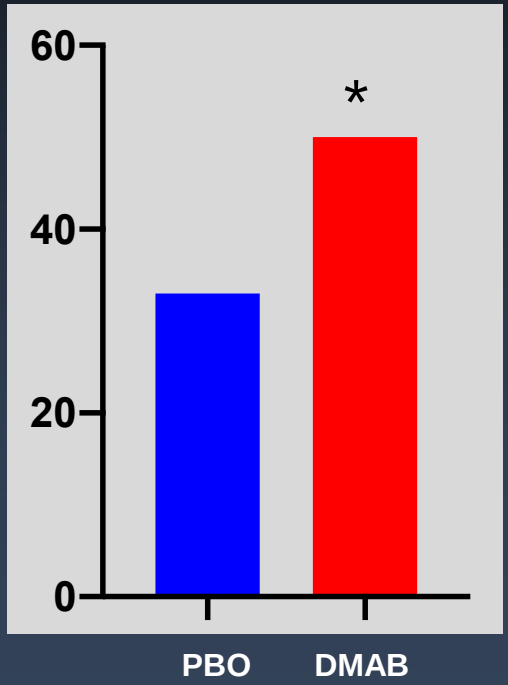
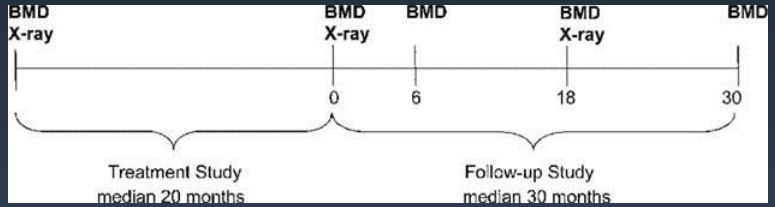
Among those who fractured, percent with multiple vertebral fractures

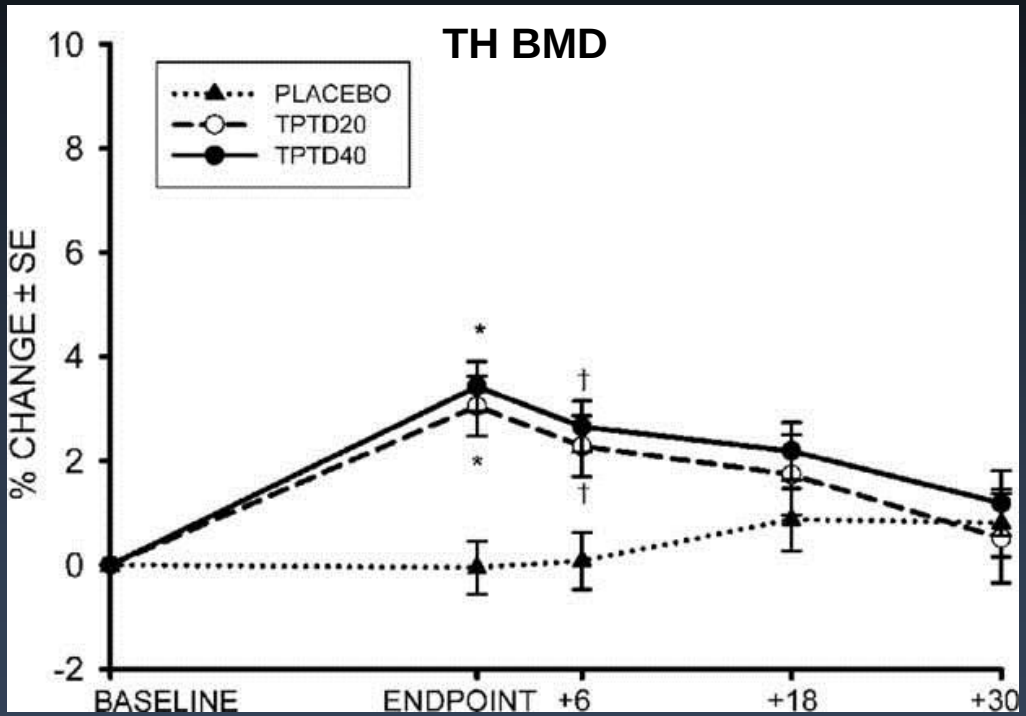


PTH/PTHrP Analog Discontinuation

Follow-up in 1262 women after the discontinuation of teriparatide in Phase 3 registration trial.



Prince et al. JBMR 2009



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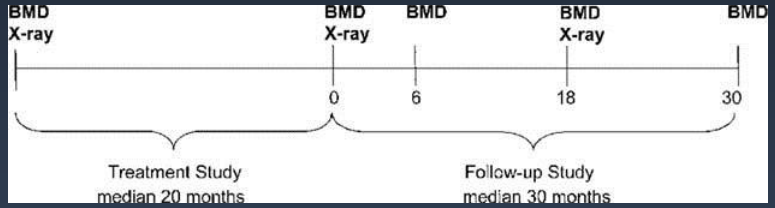
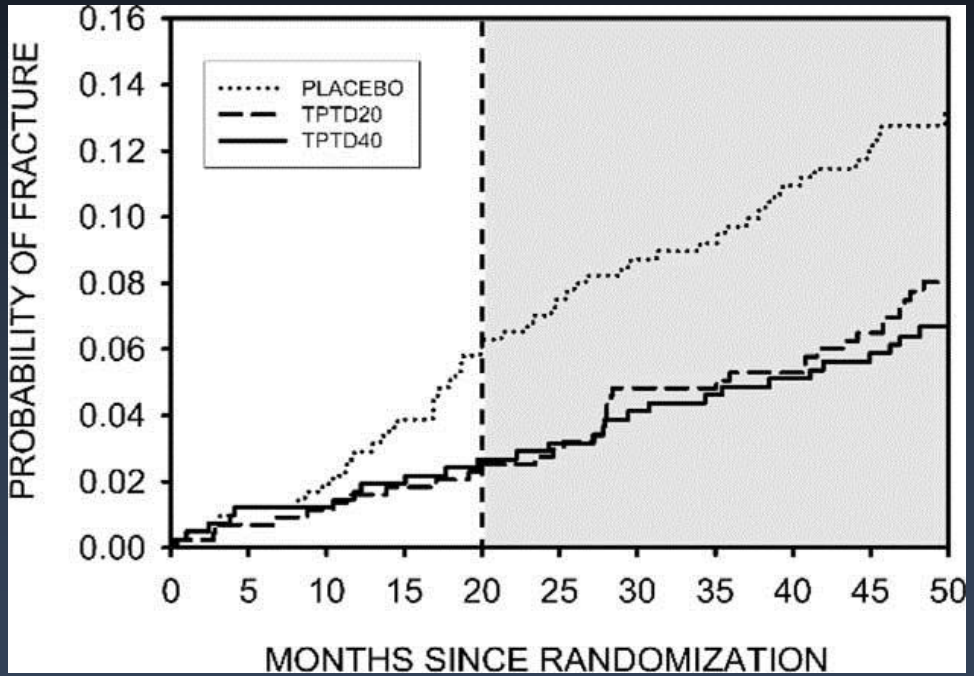
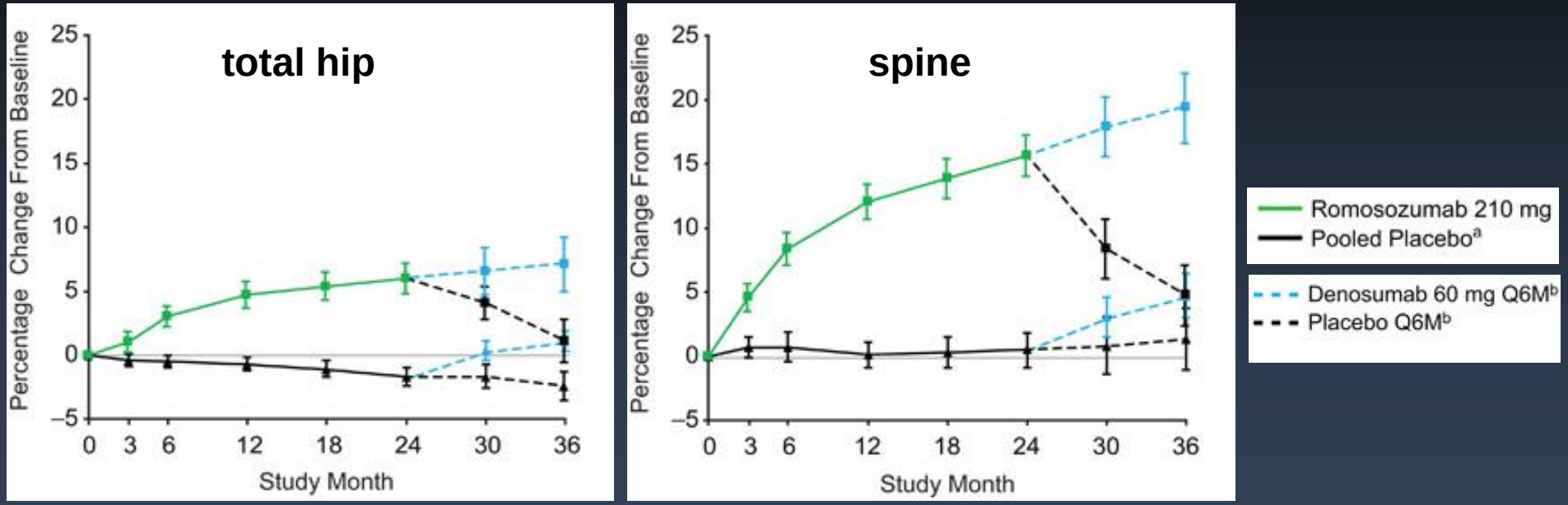


Prince et al. JBMR 2009

Probability of non-vertebral fracture



Romosozumab Discontinuation

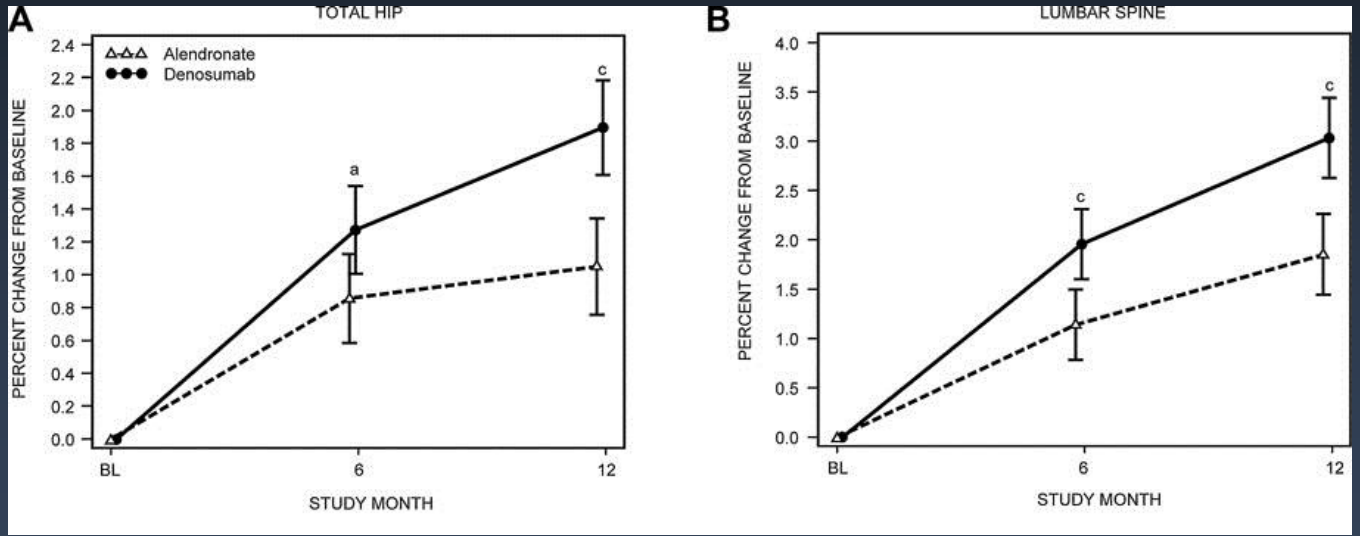


McClung et al. JBMR 2018

Sequential Osteoporosis Therapies

antiresorptive-to-antiresorptive: BP-to-denosumab

504 postmenopausal women who had been receiving alendronate for at least 6 months (mean 3 years).



Kendler et al JBMR 2010

Sequential Osteoporosis Therapies

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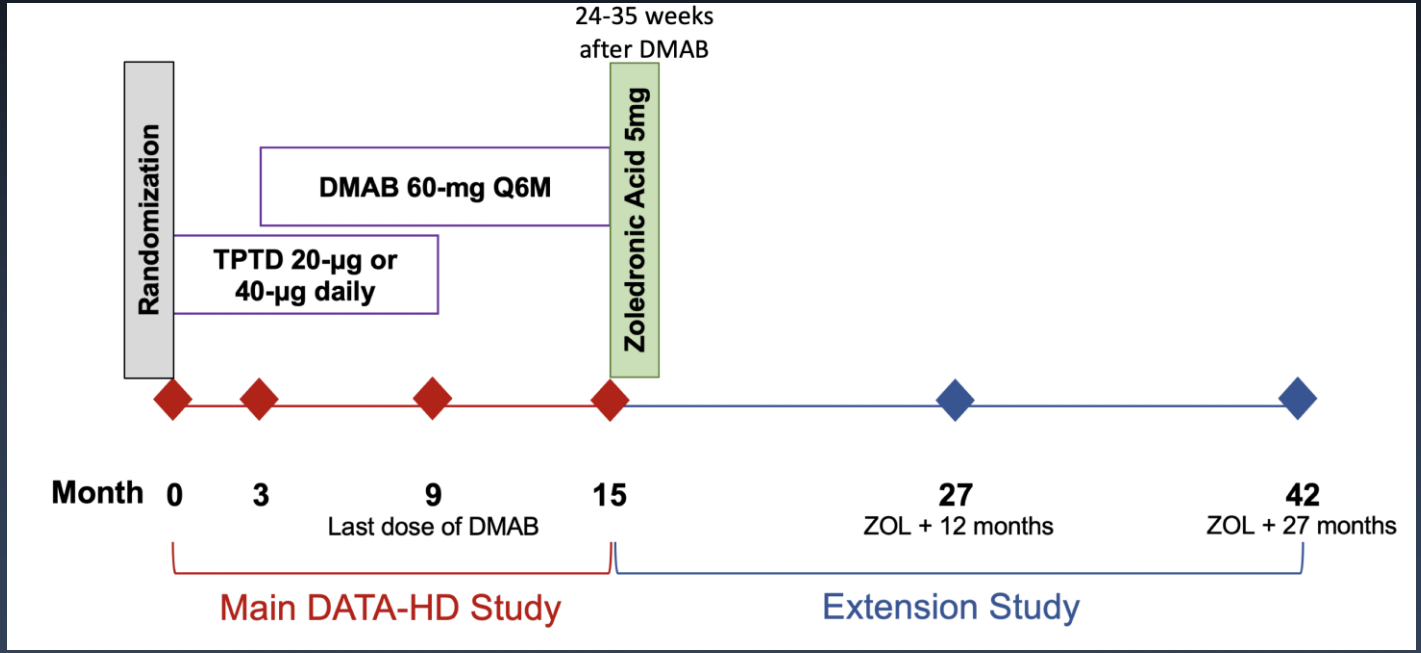
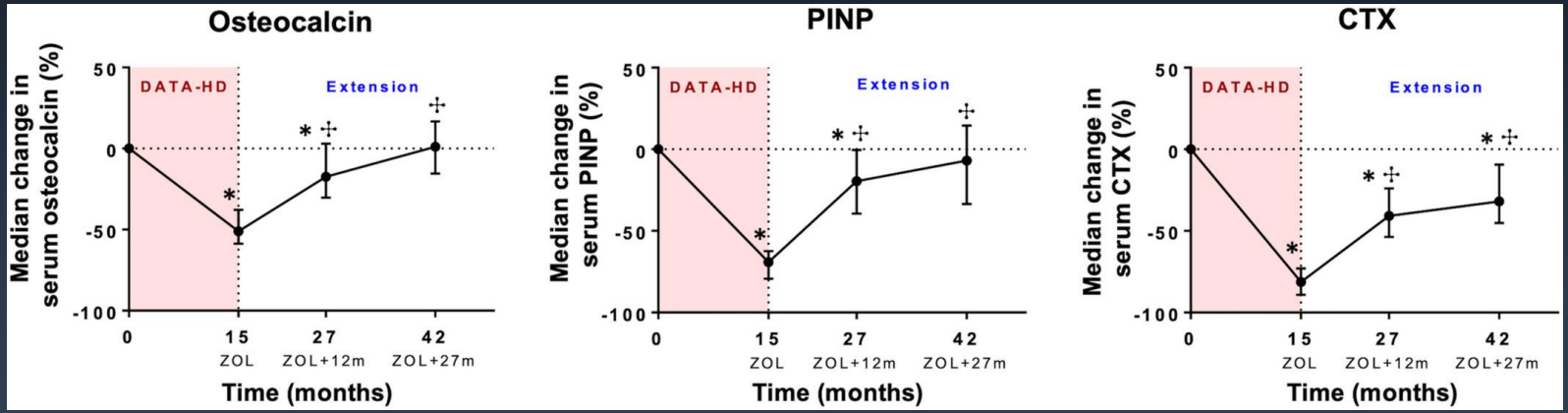


Ramchand et al. JBMR 2021

Sequential Osteoporosis Therapies

antiresorptive-to-antiresorptive: denosumab-to-BP

Bone Turnover

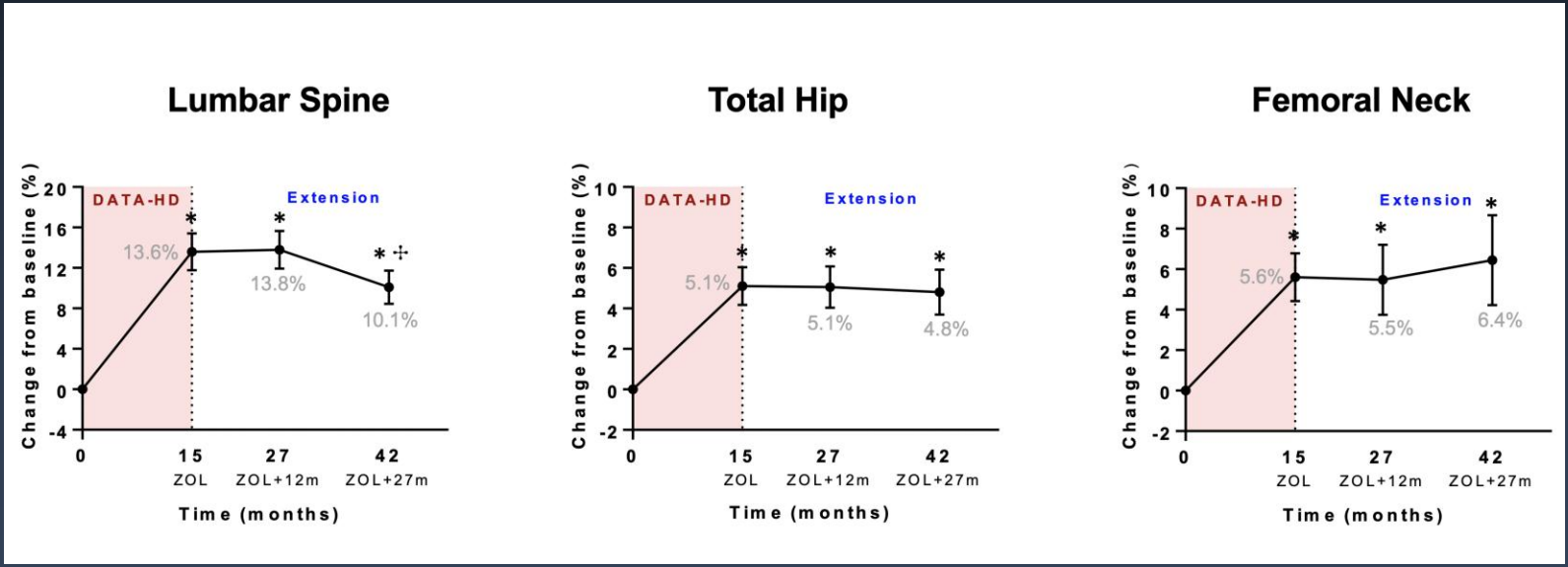


Ramchand et al. JBMR 2021

Sequential Osteoporosis Therapies

antiresorptive-to-antiresorptive: denosumab-to-BP

Areal BMD



Ramchand et al. JBMR 2021

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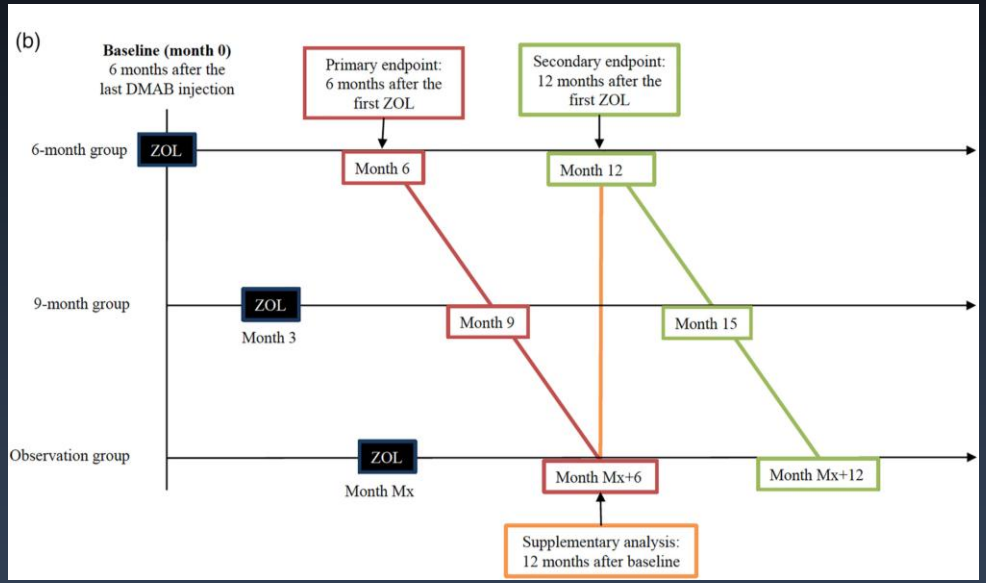
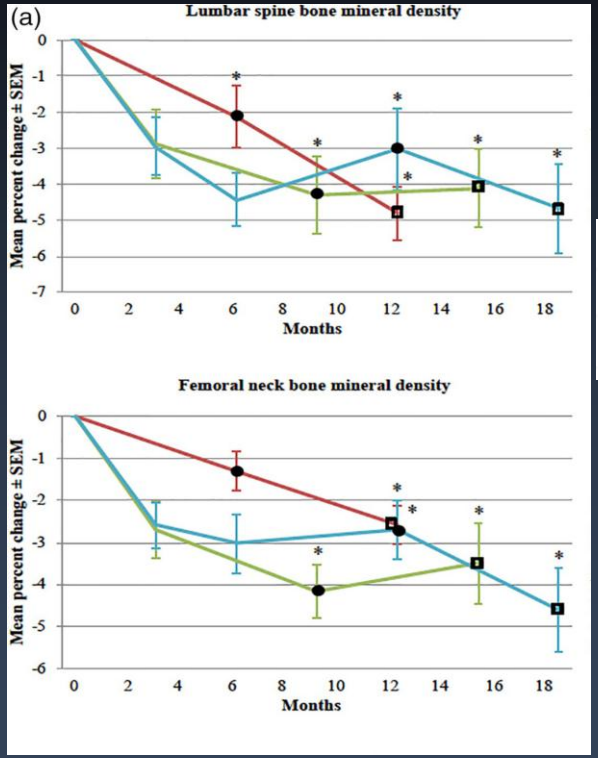
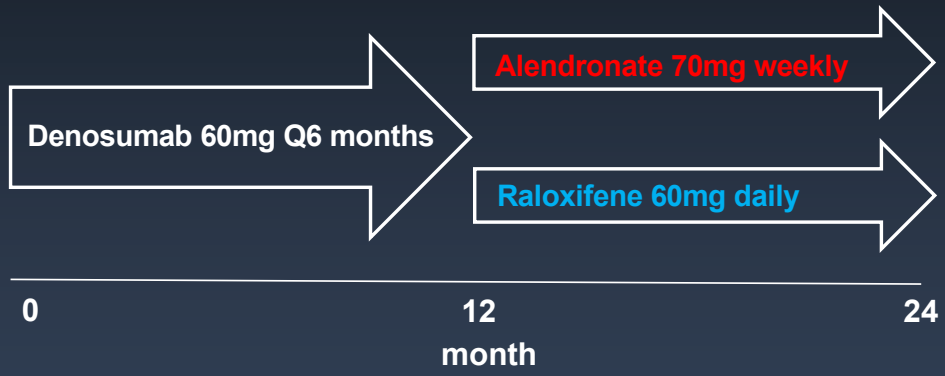


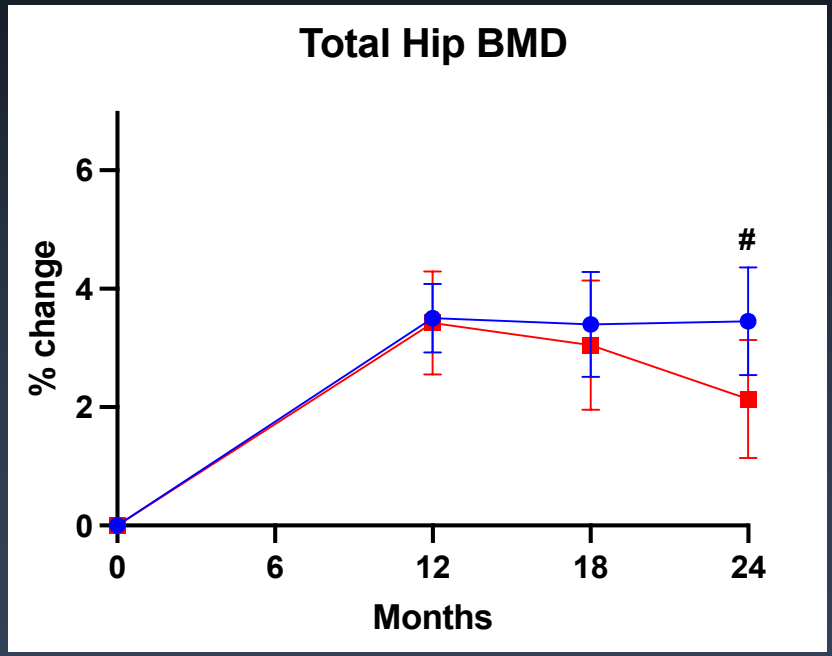
Solling et al. JBMR 2020



Sequential Osteoporosis Therapies

antiresorptive-to-antiresorptive: denosumab-to-SERM





Leder et al. ASBMR 20222

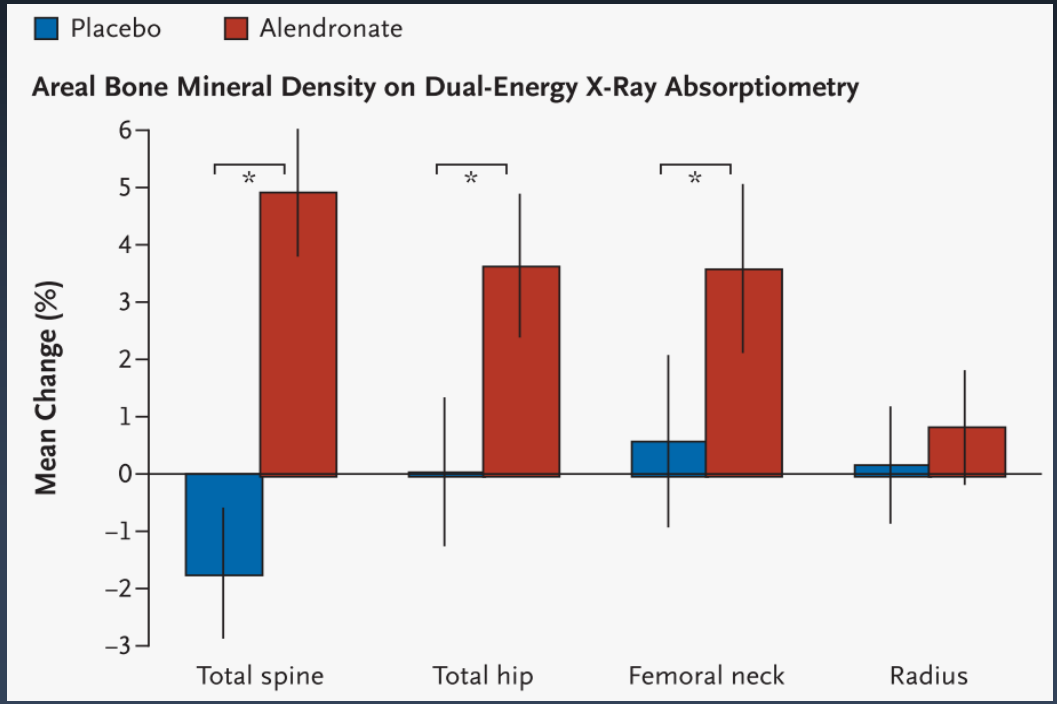
Sequential Osteoporosis Therapies

anabolic-to-antiresorptive: PTH analogs-to BP

- **When switching from PTH analogs to BPs, BMD increases as quickly or more quickly than *de novo* BP treatment.**

BMD in women previously treated with 1 year of PTH 1-84

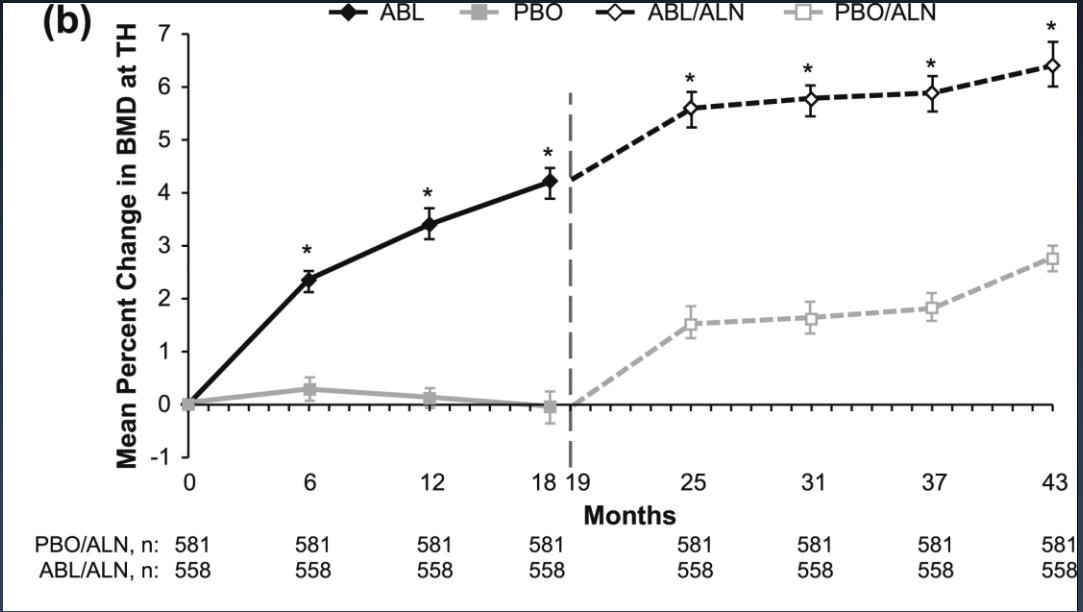
Black et al NEJM 2005



Sequential Osteoporosis Therapies

anabolic-to-antiresorptive: PTH analogs-to BP

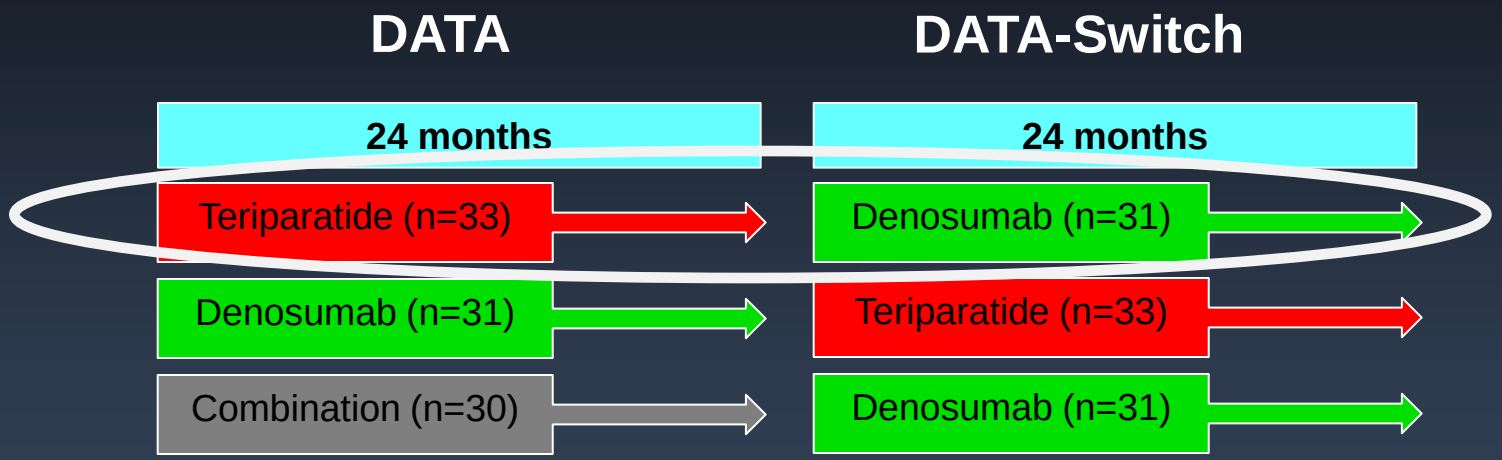
1169 postmenopausal women who completed abaloparatide or placebo transitioned to up to 24 months of alendronate



Bone et al. JCEM 2018

Sequential Osteoporosis Therapies

anabolic-to-antiresorptive: PTH analogs-to-denosumab



Leder et al. Lancet, 2015

Sequential Osteoporosis Therapies

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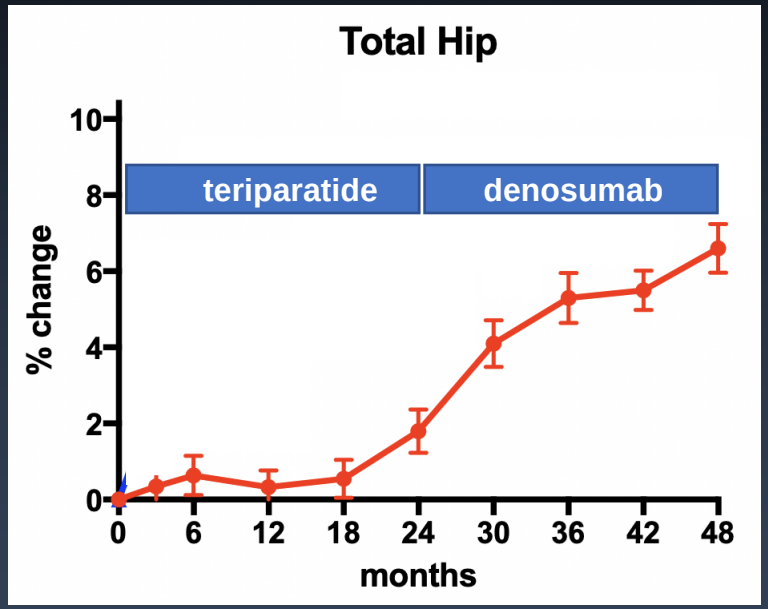
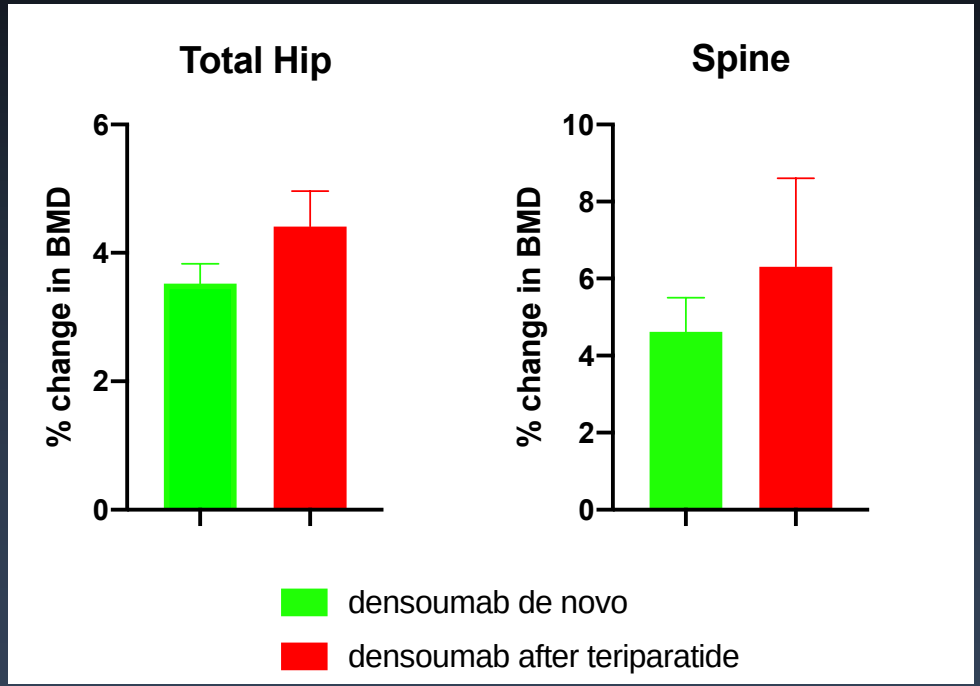




Leder et al. Lancet, 2015

Sequential Osteoporosis Therapies

antiresorptive-to-anabolic

- When switching from bisphosphonates to teriparatide, BMD increases are blunted compared to *de novo* teriparatide.

Treatment Sequence Matters: Anabolic and Antiresorptive Therapy for Osteoporosis

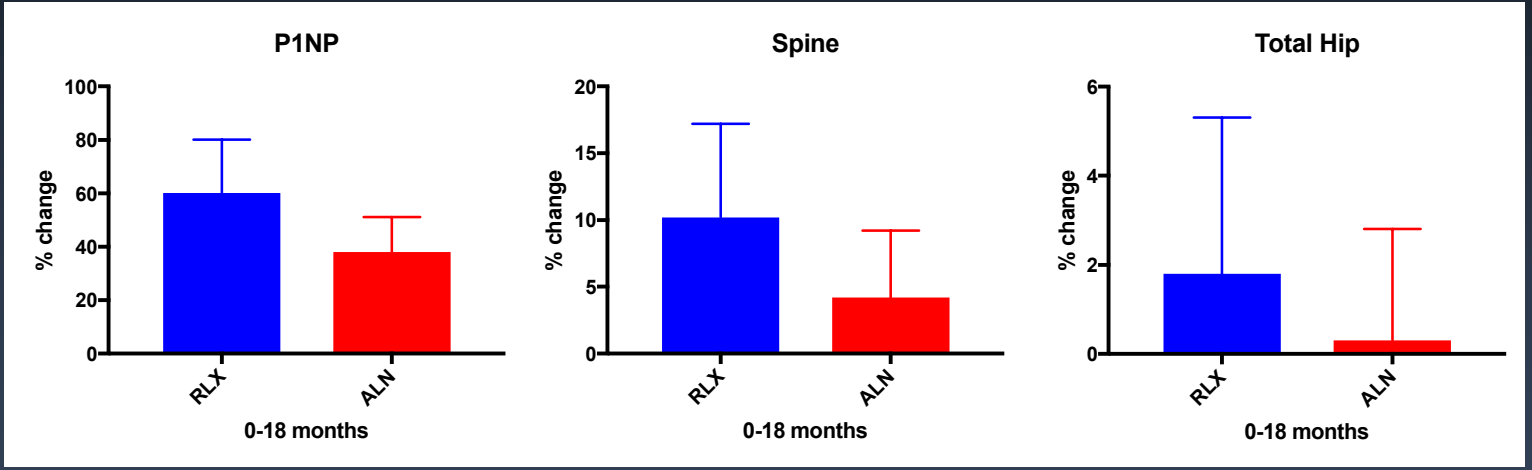
Felicia Cosman,[1,2] Jeri W Nieves,[1,3] and David W Dempster[1,4]

study	treatment	18 mo TH BMD
Ettinger et al.[27]	Alendronate (mean 29.3 mo) → TPTD (18 mo)	+0.3%
Boonen et al.[24]	Alendronate (median 29.2 mo) → TPTD (24 mo)	+0.6%
Boonen et al.[24]	Risedronate (median 23.4 mo) → TPTD (24 mo)	+0.9%
Miller et al.[30]	Risedronate (mean 37.2 mo) → TPTD (12 mo)	–
Miller et al.[30]	Alendronate (mean 38.0 mo) → TPTD (12 mo)	–
Cosman et al.[26]	Alendronate (mean 45.7 mo) → TPTD (18 mo)	+0.9%

Sequential Osteoporosis Therapies

antiresorptive-to-anabolic

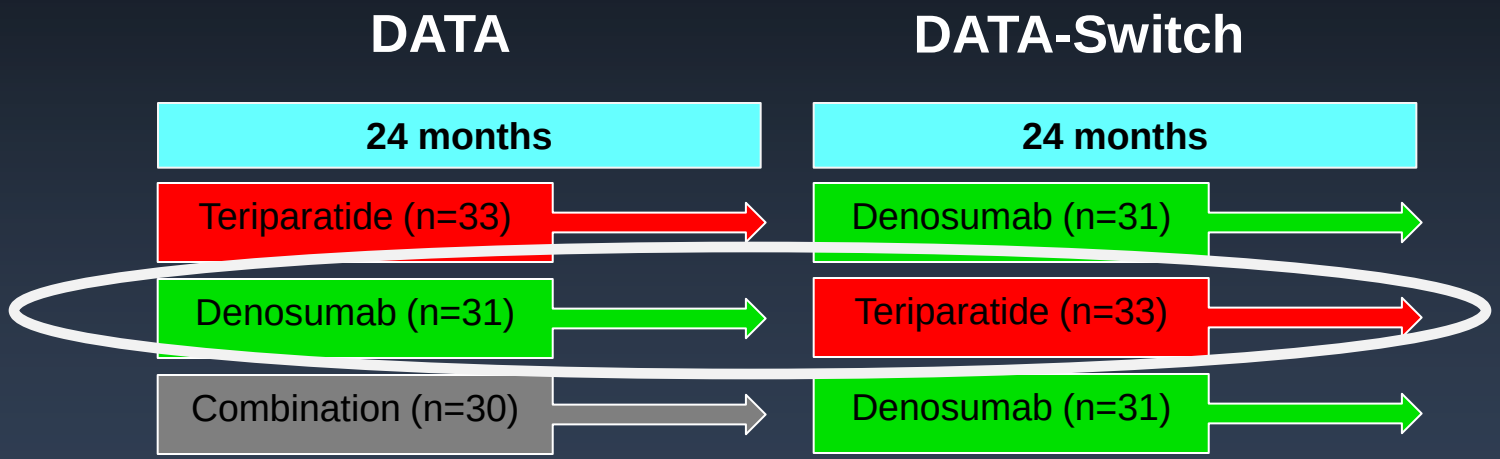
Teriparatide administered for 18 months to 59 postmenopausal women who had previously received either alendronate or raloxifene



Ettinger et al. JBMR 2004

Sequential Osteoporosis Therapies

antiresorptive-to-anabolic: denosumab



Leder et al. Lancet, 2015

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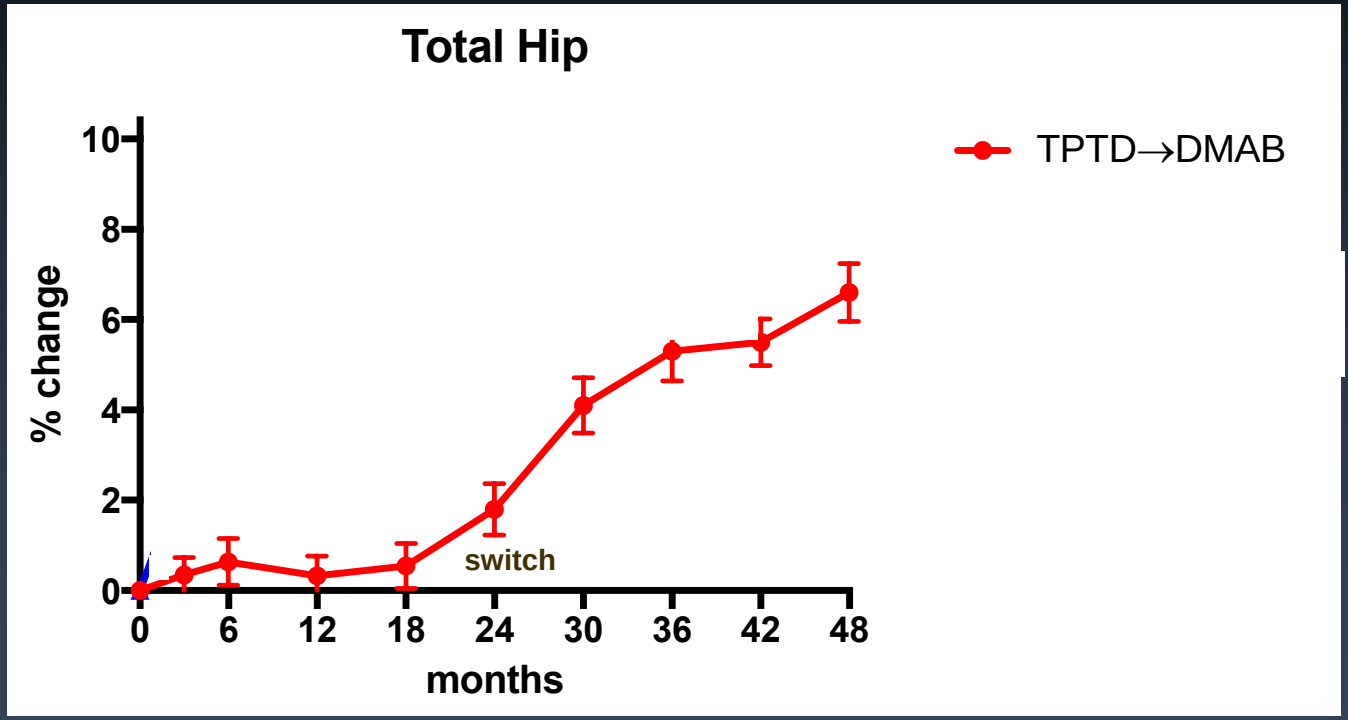

Sequential Osteoporosis Therapies

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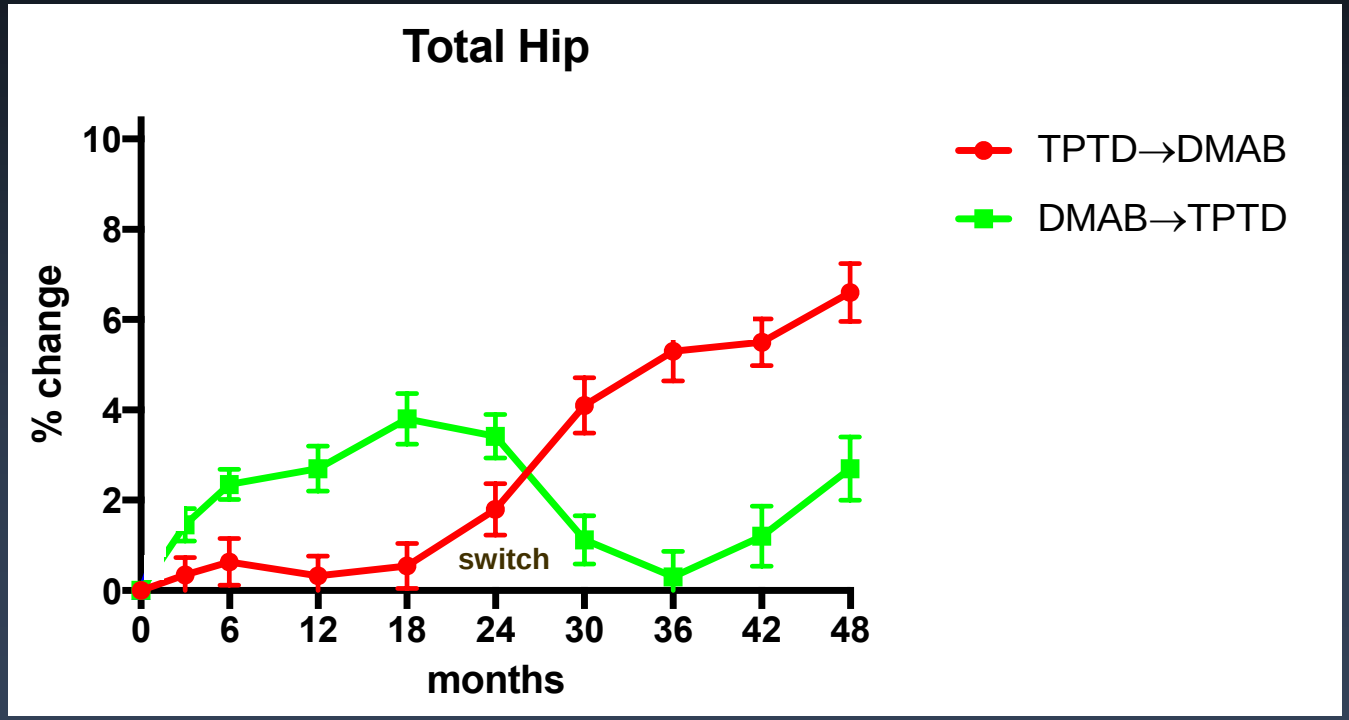
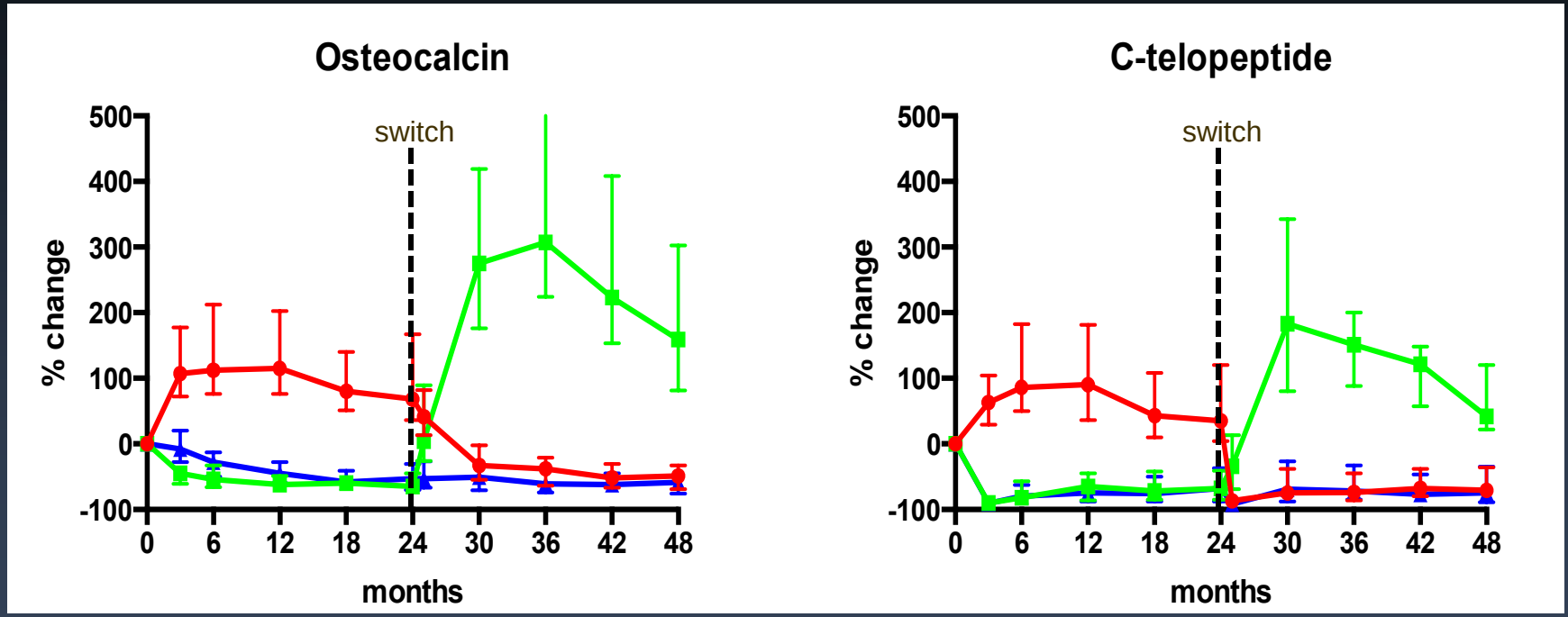


Sequential Osteoporosis Therapies

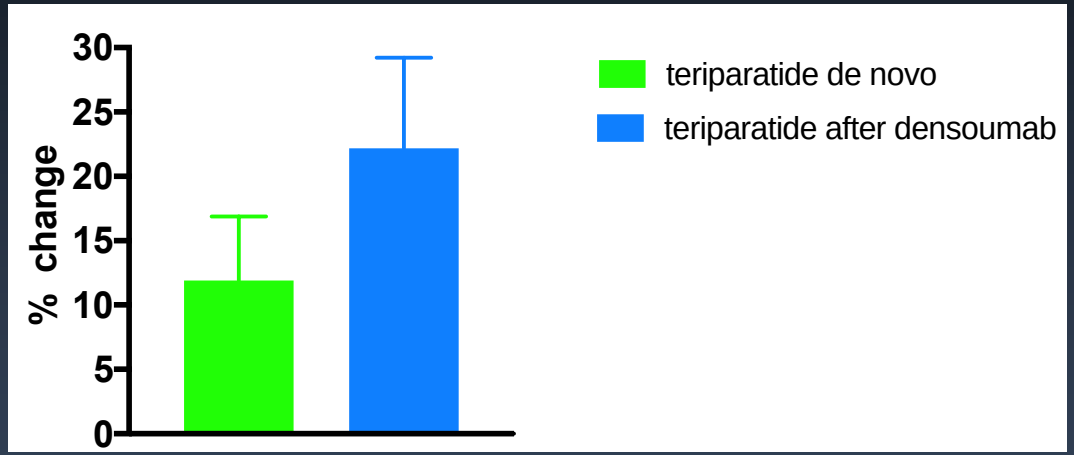
antiresorptive-to-anabolic: denosumab



Sequential Osteoporosis Therapies

antiresorptive-to-anabolic: denosumab

Cortical porosity by HR-pQCT- tibia

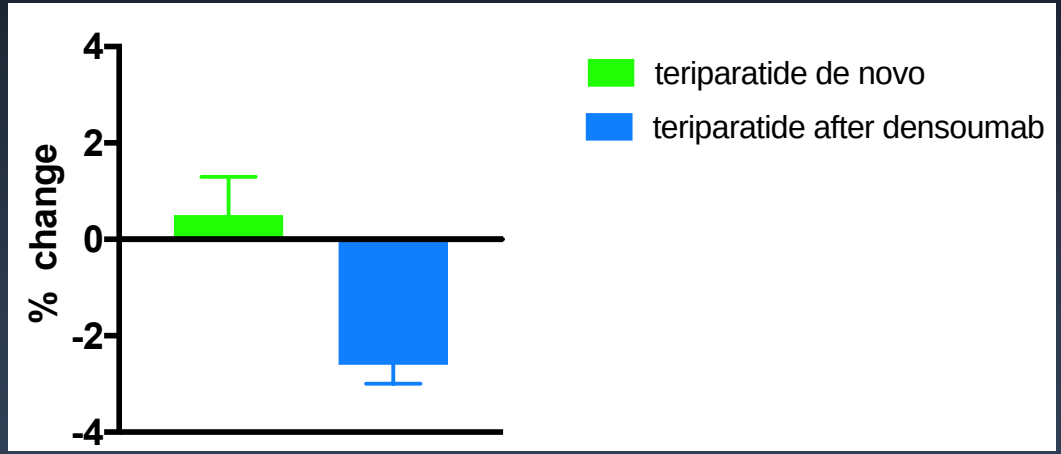


Tsai et al JBMR 2017

Sequential Osteoporosis Therapies

antiresorptive-to-anabolic: denosumab

Estimated strength by finite element analysis (FEA) - tibia



Tsai et al JBMR 2017

Romosozumab Transitions

romosozumab-to-antiresorptives

7180 women randomly assigned to receive subcutaneous romosozumab or placebo monthly for 12 months followed by 12 months of denosumab.

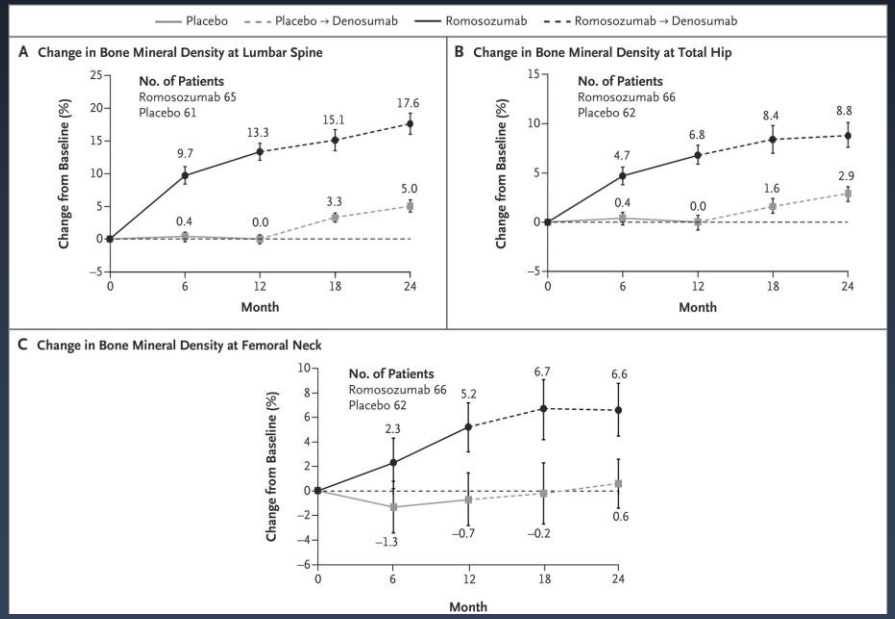


Table 2. Adverse Events.

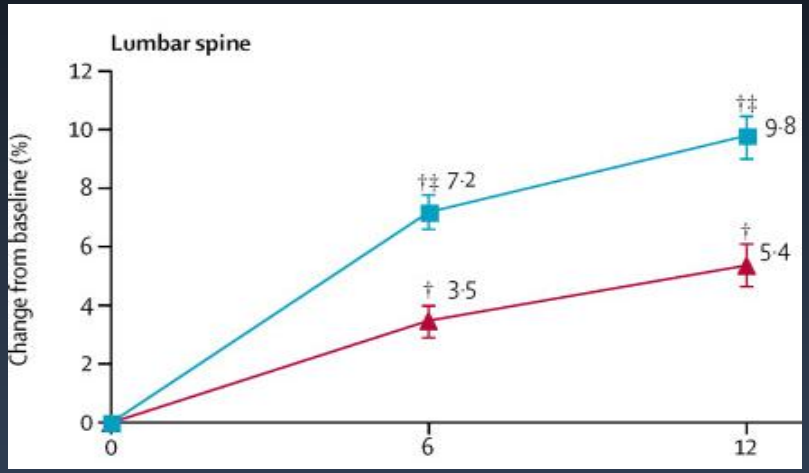
Event	Month 12: Double-Blind Period		Primary Analysis: Double-Blind and Open-Label Period*	
	Alendronate (N=2014)	Romosozumab (N=2040)	Alendronate to Alendronate (N=2014)	Romosozumab to Alendronate (N=2040)
	number of patients (percent)			
Adverse event during treatment	1584 (78.6)	1544 (75.7)	1784 (88.6)	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)
Event leading to discontinuation of trial regimen	64 (3.2)	70 (3.4)	146 (7.2)	133 (6.5)
Event leading to discontinuation of trial participation	27 (1.3)	30 (1.5)	43 (2.1)	47 (2.3)

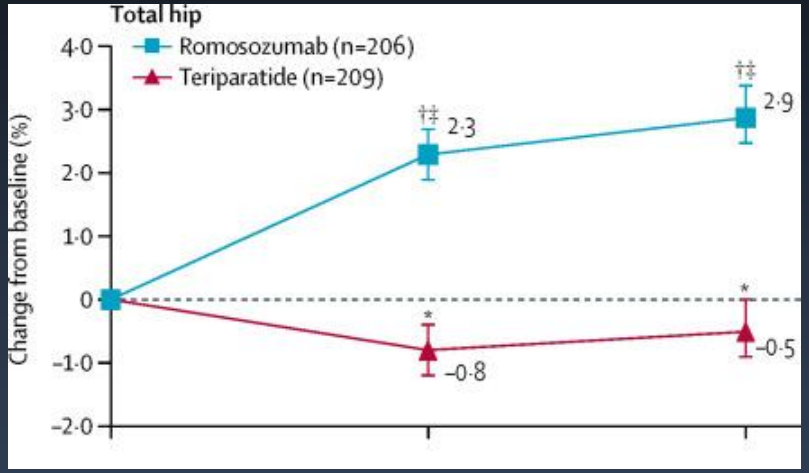
Cosman et al. NEJM 2016

Romosozumab Transitions

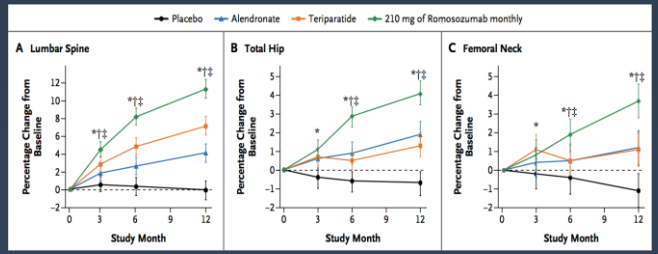
bisphosphonate-to-romosozumab

436 postmenopausal women with osteoporosis who had taken an oral bisphosphonate for at least 3 years (last year alendronate)





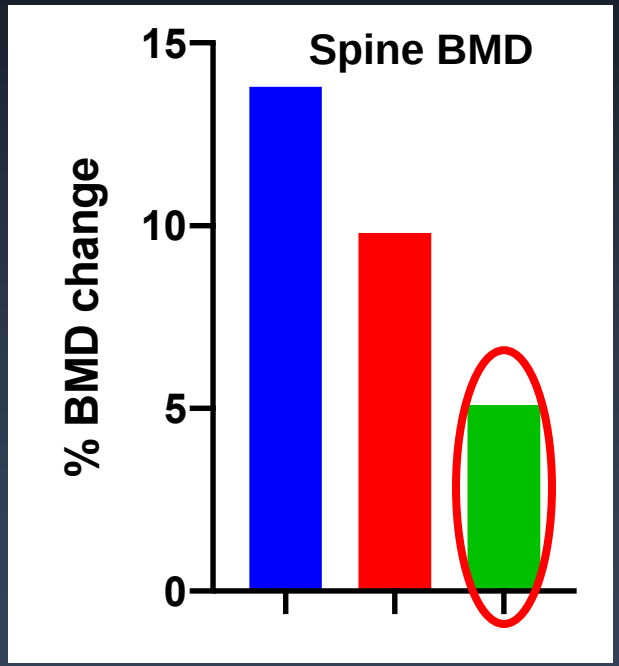
Langdahl et al. Lancet 2017

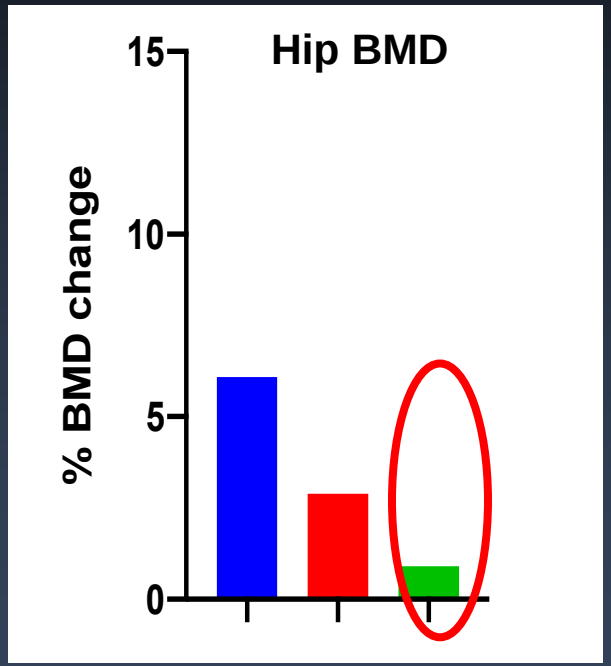


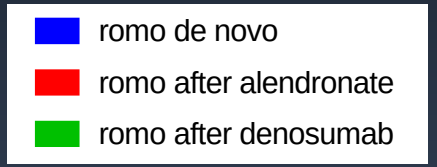
Romosozumab Transitions

denosumab-to-romosozumab

Small study of patients receiving denosumab followed by 12 months of romosozumab shows blunting







McClung et al. ASBMR 2020

Summary

Given the limitations of current therapies, long term therapy is indicated for most patients with significant disease.

Long term treatment with a single agent has numerous limitations, including waning efficacy and increase risk of serious adverse events.

As switching medications becomes the norm, an in-depth understanding of the effects of specific medication transitions is crucial necessary to provide optimal care.

The transition from anabolic agents to antiresorptive therapy consistently results in either maintenance of BMD gains or further increases BMD with sustained fracture reduction.

Summary 2

Switching from a bisphosphonates to PTH-analog anabolic therapy also results in further BMD gains but the increases are blunted when comparted to *de novo* anabolic therapy.

BMD gains after the transition from bisphosphonates to romosozumab therapy are also modestly blunted.

The direct transition from denosumab to PTH analogs results in accelerated bone remodeling and rapid bone loss.

The transition from denosumab to bisphosphonates mitigates the expected post-denosumab high-turnover bone loss but the optimal agent, dose and frequency are not defined.

Conclusions

In patients with severe or established osteoporosis, who have not received prior therapy and in whom therapy with multiple agents is likely necessary, the initial use of an anabolic should increasingly be considered as standard-of-care.

Thank you