Associazione Medici Endocrinologi

17° Congresso Nazionale AME
Joint Meeting with AACE Italian Chapter
Update in Endocrinologia Clinica
ROMA 8 - 11 novembre 2018

ITALIAN CHAPTER

AULA ORANGE 2

SESSION 2
Osteoporosis

Chairs: F. Bandeira, L. Gianotti, F. Vescini

1. Double X-ray Absorptiometry (DXA): clinical usefulness and pitfalls
   S. Bonadonna
2. Bone turnover markers in clinical practice
   E. McCloskey
3. Therapy: anti-resorptive drugs
   F. Bandeira
4. Therapy: anabolic agents
   I. Chiodini
5. Conclusions
   F. Vescini

I. Chiodini
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Dichiarazione di trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessa commerciali relativi agli ultimi due anni

Il sottoscritto Iacopo Chiodini in qualità di moderatore/relatore/discussant
Al 27° Corso Nazionale Teorico – Pratico sulle Malattie Metaboliche dell'Osso
Torino, 15 – 16 giugno 2017
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009, per conto dell'Università degli Studi di Torino

Dichiara

Che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con i soggetti portatori di interessi commerciali in campo sanitario:

- ITALFARMACO
- KYOWA –KIRIN
- ELI-LILLY
- AMGEN
- SANDOZ

Iacopo Chiodini

ANABOLIC AGENTS: FIVE FREQUENTLY ASKED QUESTIONS

- **Teriparatide**
  - **Efficacy after antiresorptive therapy**
  - **Efficacy combined with antiresorptive therapy**
  - **What to do after anabolic therapy**
  - **Efficacy in men and GIOP**
  - **Safety**

- **New Agents (Abaloparatide, Romosozumab)**

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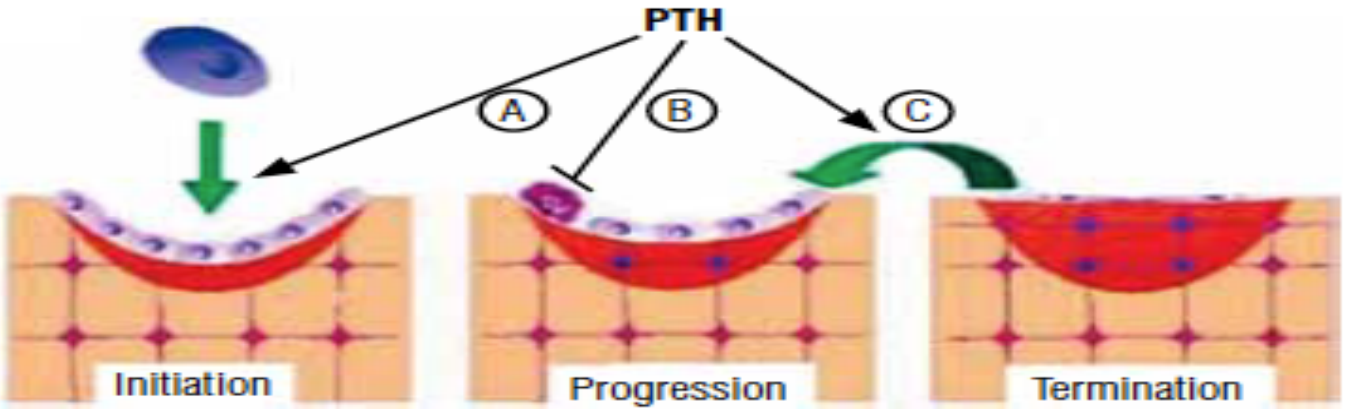
TERIPARATIDE: MAJOR CLINICAL TRIALS



- **Reduction in vertebral (65%) and non-vertebral (53%) fractures** (Neer et al. 2001)
- **As effective in women with mild or severe or multiple previous fragility fractures** (Gallagher et al. 2004)
- **Reduced back pain** (McClung et al. 2005; Miller et al. 2006)
- **In PM women with severe osteoporosis, the risk of new vertebral and clinical fractures is lower with TPT than with RIS** (Kendler DR et al, Lancet 2017)

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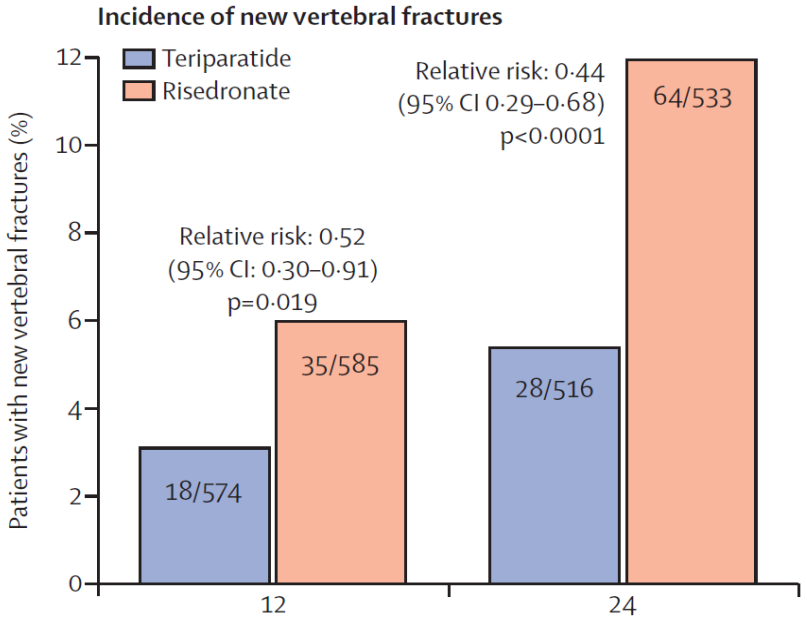
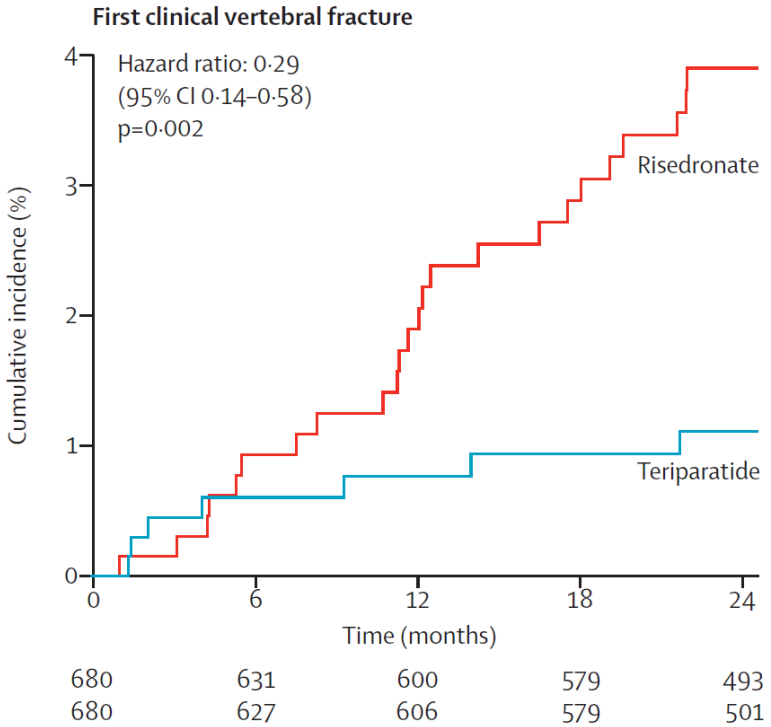
THE RISK OF NEW VERTEBRAL AND CLINICAL FRACTURES IS LOWER IN PATIENTS RECEIVING TERIPARATIDE THAN IN THOSE RECEIVING RISEDRONATE

1360 PM women with ≥2 moderate or 1 severe vtb fx and a T score ≤ -1.5, randomly assigned to 20 µg of teriparatide/d or 35 mg of oral risedronate





Non-vertebral fx: 4.0% in TPT group and 6.1% in RIS group, p=0·10

Kendler DR et al, Lancet 2017

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SEQUENTIAL THERAPY
BISPHOSPHONATES → TERIPARATIDE

- **The more potent the bisphosphonate to reduce bone turnover the greater the delay in subsequent PTH response. However, the delay if present, it does not seem to be related to reduced bone turnover**
- **The delay in response to PTH is not always seen and most patients respond eventually to PTH, irrespective of the prior use of BP**
- **The delay is independent of which BP is used and whether there is a few month wash-out from BP before starting PTH**

Ettinger, 2004; Miller, 2008

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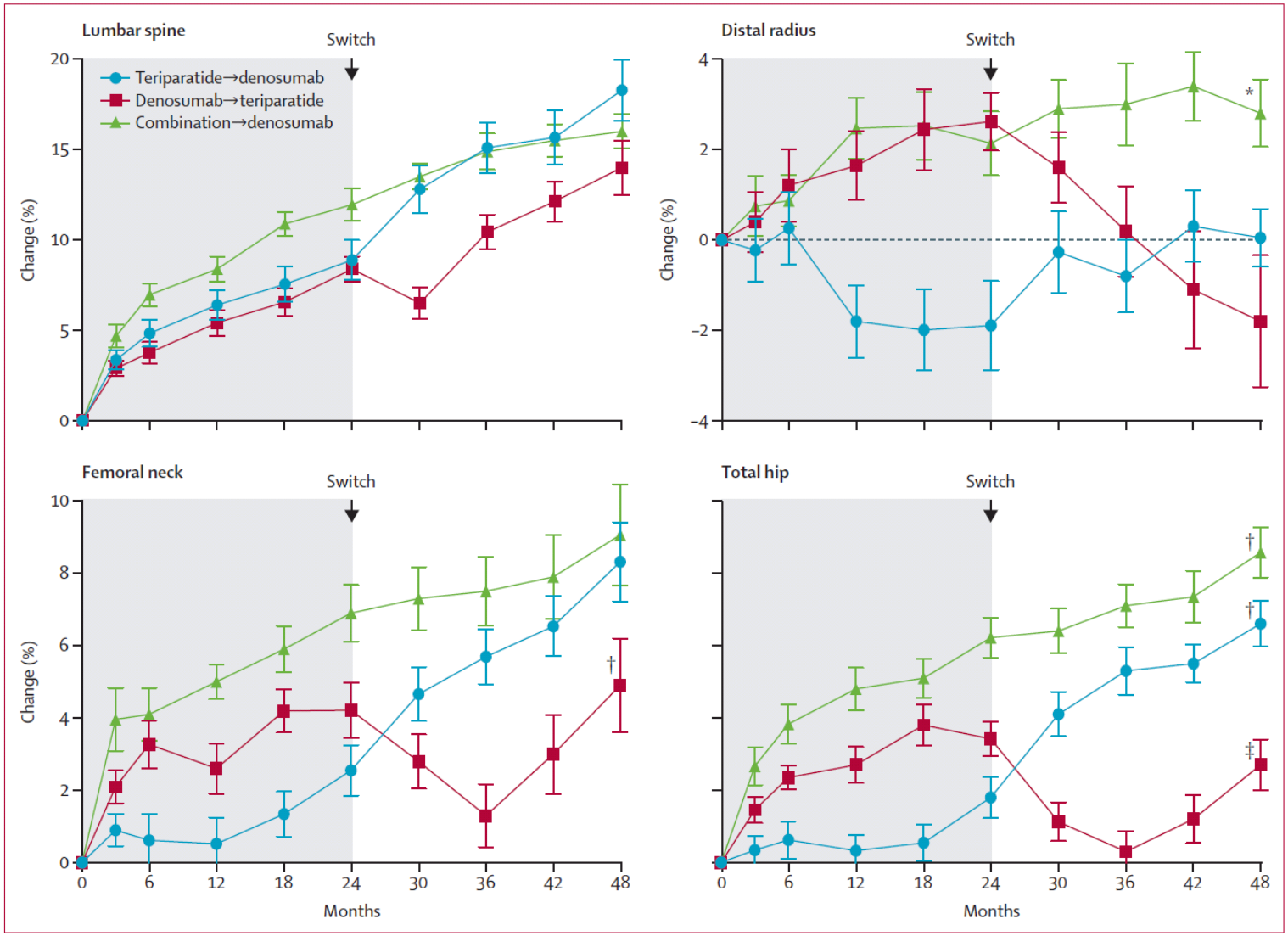
SEQUENTIAL THERAPY: DENOSUMAB→TERIPARATIDE



Leder BZ et al, Lancet 2015

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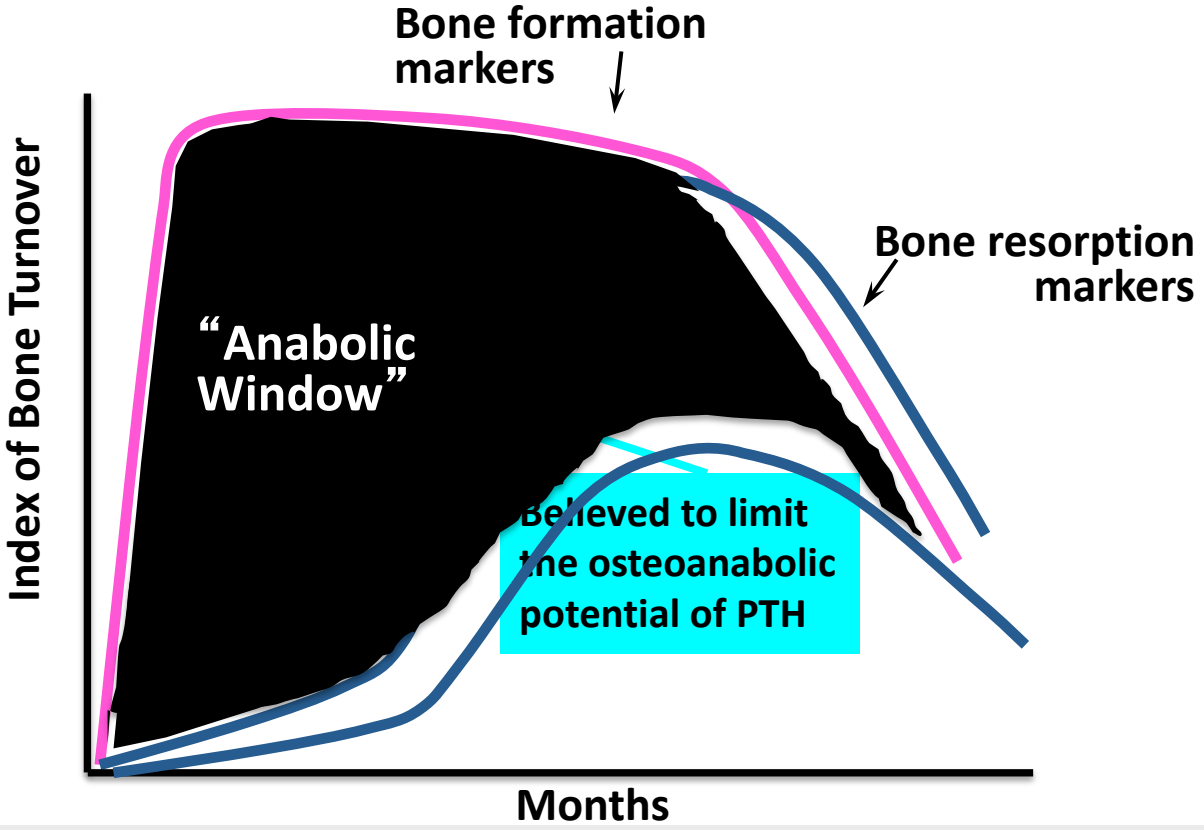
COMBINED THERAPY
BISPHOSPHONATES + TERIPARATIDE

Rationale: Two different mechanisms of action

- **It would prevent the increase in PTH-associated bone resorption that may limit the actions of PTH**
- **It would prevent the excessive reduction of bone apposition potentially associated with the antiresorptive therapy**



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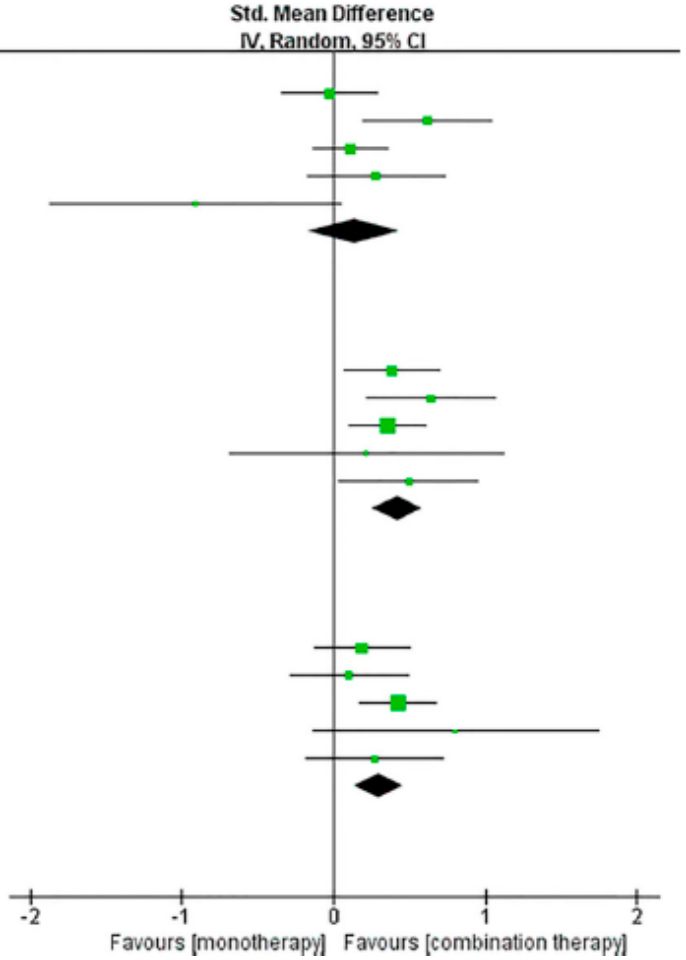
COMBINATION THERAPY OF ANABOLIC AGENTS AND BISPHOSPHONATES ON BONE MINERAL DENSITY IN OSTEOPOROSIS: A META-ANALYSIS OF RCTS

Study or Subgroup	combination therapy Mean	SD	Total	monotherapy Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
1.1.1 Lumbar spine									
Black 2003	6.1	4.43	59	6.3	7.12	119	25.0%	-0.03 [-0.34, 0.28]	2003
Cosman 2009	4.5	4	45	2	4	45	20.4%	0.62 [0.20, 1.04]	2009
Cosman 2011	7.5	4.4	122	7	4.6	131	27.8%	0.11 [-0.14, 0.36]	2011
Muschitz 2013	5	6.3	39	2.8	9.3	37	19.3%	0.28 [-0.18, 0.73]	2013
Walker 2013	2.82	4.7	10	7.21	4.5	9	7.6%	-0.91 [-1.87, 0.05]	2013
Subtotal (95% CI)			**275**			**341**	**100.0%**	**0.13 [-0.17, 0.43]**	
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 11.11$, df = 4 (P = 0.03); $I^2 = 64\%$									
Test for overall effect: Z = 0.87 (P = 0.39)									
1.1.2 Total hip									
Black 2003	1.9	3.3	59	0.3	4.5	119	26.7%	0.38 [0.07, 0.70]	2003
Cosman 2009	1.4	3.4	45	-0.8	3.4	45	14.7%	0.64 [0.22, 1.07]	2009
Cosman 2011	2.3	3.3	123	1.1	3.4	129	42.7%	0.36 [0.11, 0.61]	2011
Walker 2013	2.19	3.1	10	1.5	3	9	3.2%	0.22 [-0.69, 1.12]	2013
Muschitz 2013	4	5.3	39	1.4	5.1	37	12.7%	0.49 [0.04, 0.95]	2013
Subtotal (95% CI)			**276**			**339**	**100.0%**	**0.42 [0.26, 0.58]**	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.64$, df = 4 (P = 0.80); $I^2 = 0\%$									
Test for overall effect: Z = 5.05 (P < 0.00001)									
1.1.3 Femoral neck									
Black 2003	1.7	3.8	59	0.8	5.3	119	26.3%	0.18 [-0.13, 0.50]	2003
Cosman 2009	0.7	6	52	0.1	6	50	17.0%	0.10 [-0.29, 0.49]	2009
Cosman 2011	2.2	5	123	0.1	4.9	129	41.2%	0.42 [0.17, 0.67]	2011
Walker 2013	8.45	5.7	10	3.89	5.1	9	2.9%	0.80 [-0.14, 1.75]	2013
Muschitz 2013	4.6	9	39	2.4	6.9	37	12.6%	0.27 [-0.18, 0.72]	2013
Subtotal (95% CI)			**283**			**344**	**100.0%**	**0.30 [0.14, 0.46]**	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.58$, df = 4 (P = 0.47); $I^2 = 0\%$									
Test for overall effect: Z = 3.63 (P = 0.0003)									



BMD variation of the 6 to 12 months duration

Compared with anabolic monotherapy, the concomitant combination therapy of anabolic agents and bisphosphonates significantly improved the BMD at the total hip and femoral neck with a shorter term (6 to 12 months)

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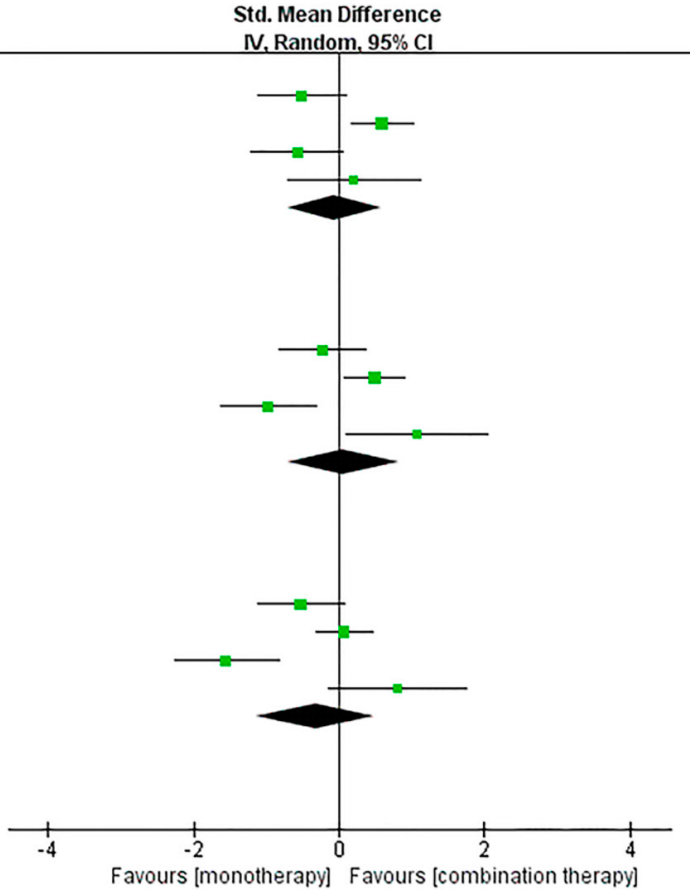
	combination therapy			monotherapy				Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
2.1.1 Lumbar spine									
Finkelstein 2003	14.8	6	25	18.1	6.8	20	25.8%	-0.51 [-1.11, 0.09]	2003
Cosman 2009	8.4	6	45	4.8	6	45	28.9%	0.59 [0.17, 1.02]	2009
Finkelstein 2010	11.9	9.2	20	17.8	10.9	20	25.1%	-0.57 [-1.21, 0.06]	2010
Walker 2013	6.95	6	10	5.68	5.7	9	20.2%	0.21 [-0.70, 1.11]	2013
Subtotal (95% CI)			**100**			**94**	**100.0%**	**-0.06 [-0.71, 0.59]**	
Heterogeneity: Tau² = 0.33; Chi² = 13.57, df = 3 (P = 0.004); I² = 78%									
Test for overall effect: Z = 0.19 (P = 0.85)									
2.1.2 Total hip									
Finkelstein 2003	5.3	3.6	25	6.4	5.9	20	26.1%	-0.23 [-0.82, 0.36]	2003
Cosman 2009	3.2	4.7	45	0.9	4.7	45	28.2%	0.49 [0.07, 0.90]	2009
Finkelstein 2010	2.9	4.8	20	8.1	5.7	20	25.1%	-0.97 [-1.63, -0.31]	2010
Walker 2013	3.86	3.48	10	0.29	2.85	9	20.6%	1.07 [0.09, 2.04]	2013
Subtotal (95% CI)			**100**			**94**	**100.0%**	**0.05 [-0.71, 0.82]**	
Heterogeneity: Tau² = 0.50; Chi² = 18.24, df = 3 (P = 0.0004); I² = 84%									
Test for overall effect: Z = 0.14 (P = 0.89)									
2.1.3 Femoral neck									
Finkelstein 2003	6.2	5.3	25	9.7	7.8	20	25.9%	-0.53 [-1.13, 0.07]	2003
Cosman 2009	2.7	6	52	2.3	6	50	28.1%	0.07 [-0.32, 0.45]	2009
Finkelstein 2010	3.1	4.5	20	10.8	5.2	20	24.5%	-1.55 [-2.27, -0.84]	2010
Walker 2013	8.45	5.69	10	3.89	5.1	9	21.5%	0.80 [-0.14, 1.75]	2013
Subtotal (95% CI)			**107**			**99**	**100.0%**	**-0.32 [-1.15, 0.50]**	
Heterogeneity: Tau² = 0.59; Chi² = 20.85, df = 3 (P = 0.0001); I² = 86%									
Test for overall effect: Z = 0.77 (P = 0.44)									



BMD variation of the 18 to 24 months duration

The combination therapy does not have a greater advantage than anabolic monotherapy for full-length treatment (18 to 24 months)

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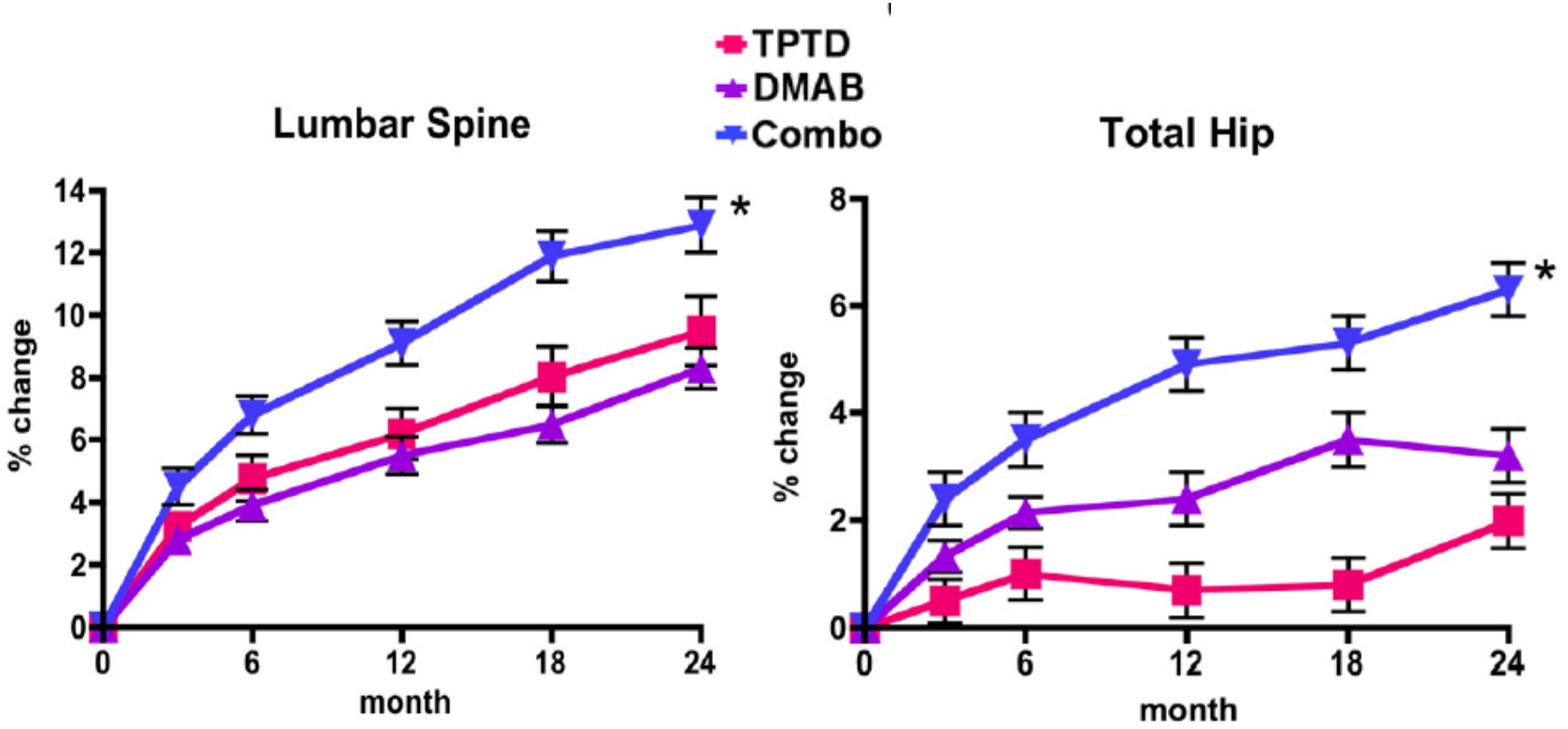
COMBINED THERAPY: TERIPARATIDE + DENOSUMAB

94 PM women received teriparatide (20 μg daily), denosumab (60 mg every 6 months), or both medications for 24 months



Two years of concomitant teriparatide and denosumab therapy increases BMD more than therapy with either medication alone and more than has been reported with any current therapy

Leder BZ et al, J Clin Endocrinol Metab 2014

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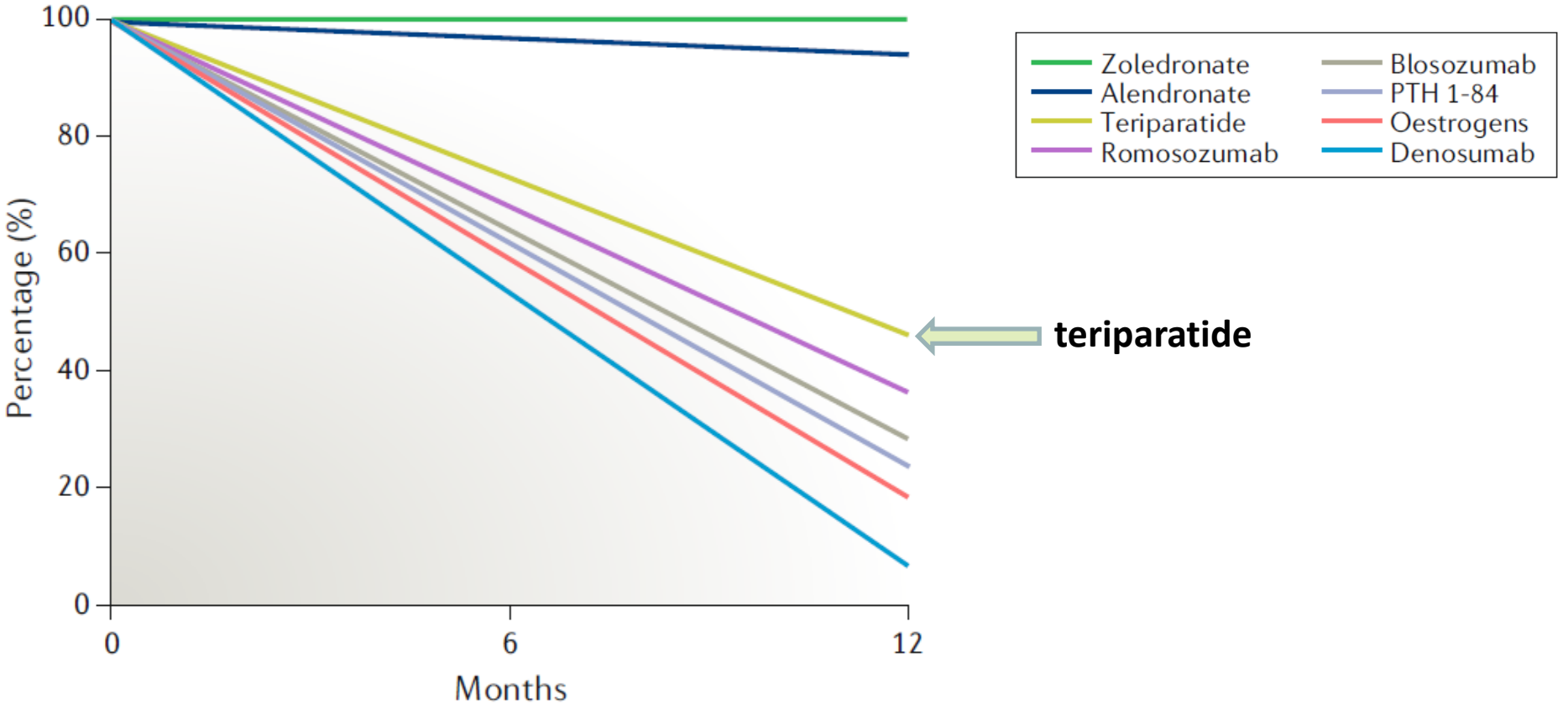
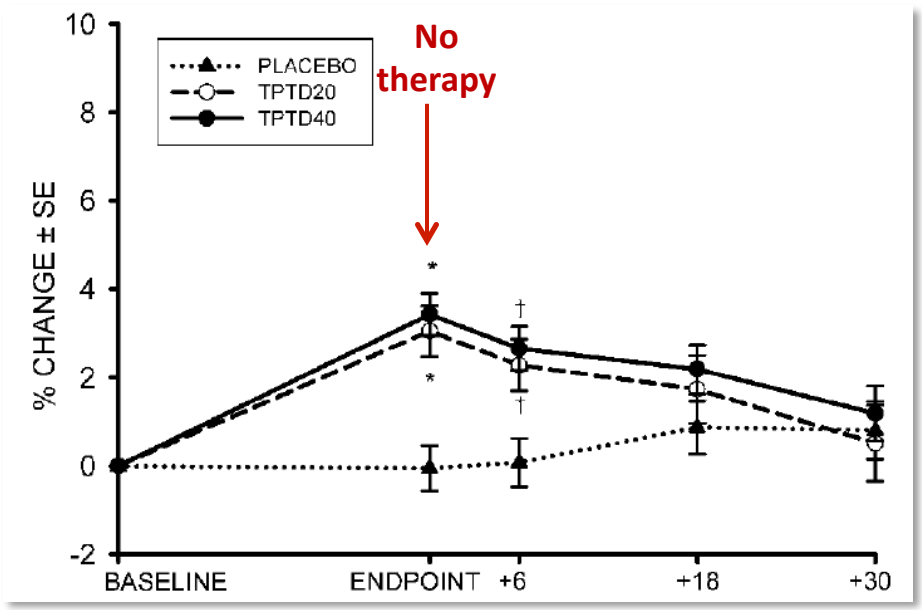
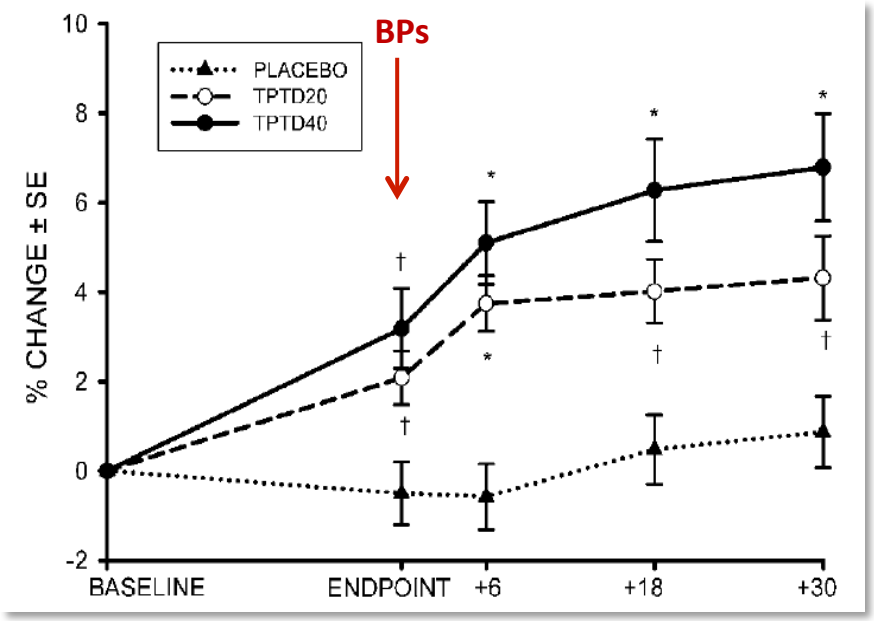
LUMBAR SPINE BMD 1 YEAR AFTER CESSATION OF TREATMENTS FOR OSTEOPOROSIS



Appelman-Dijkstra N & Papapoulos SE, Nat Rev Endocrinol 2018

THERAPY OF OSTEOPOROSIS AFTER TERIPARATIDE





Prince R et al, J Bone Miner Res 2005

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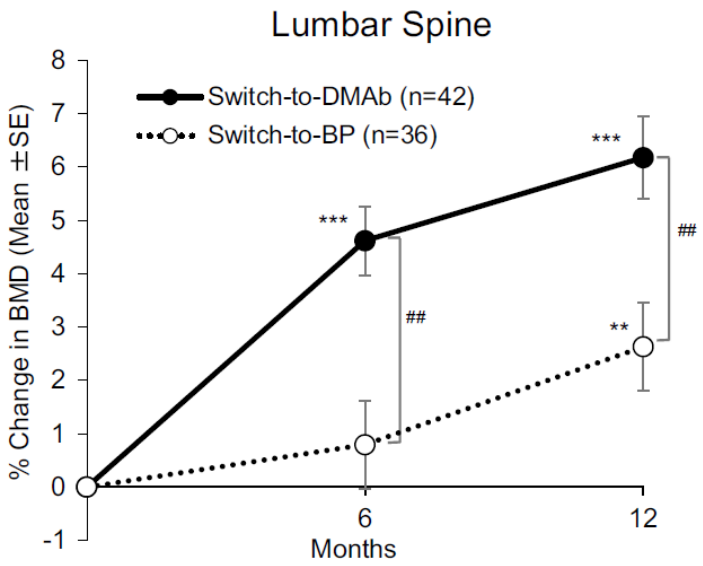
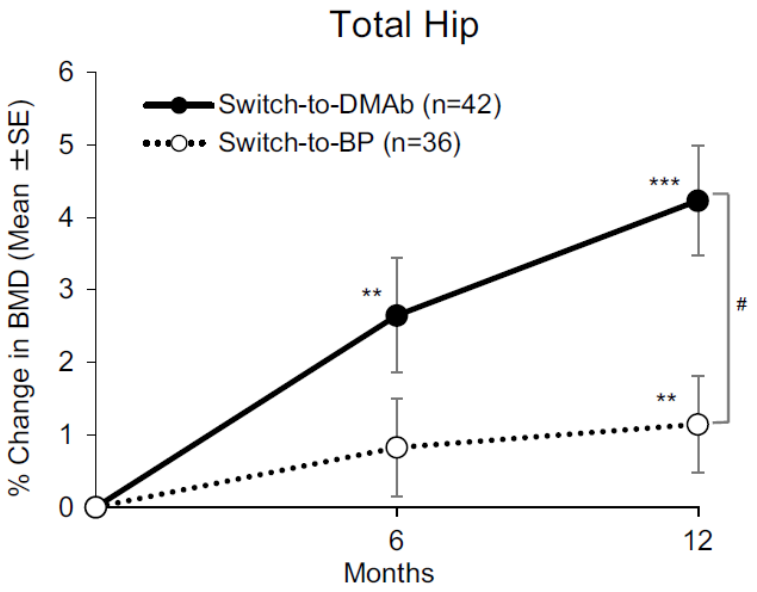
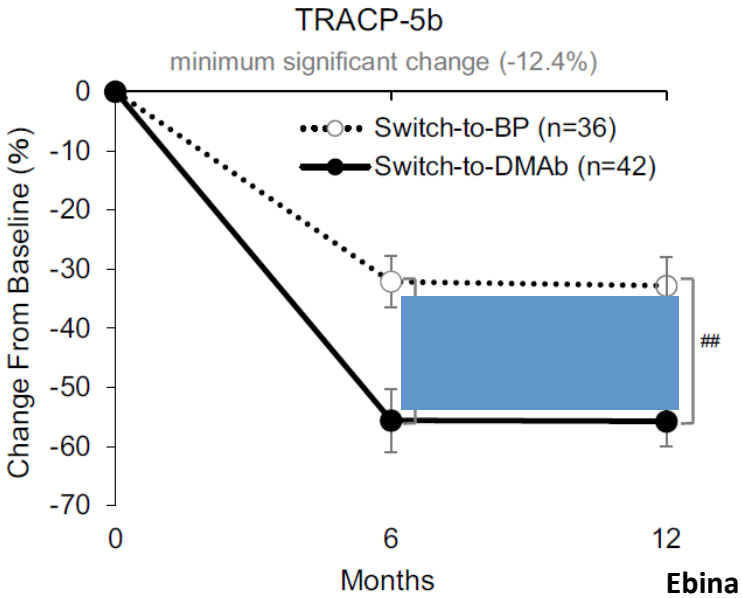
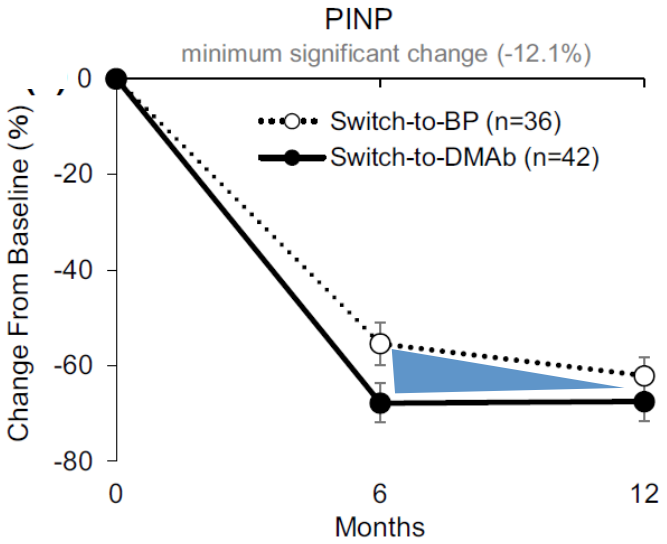
SWITCHING DAILY TPTD TO DMAB SIGNIFICANTLY INCREASED BMD AND DECREASED BONE RESORPTION COMPARED TO SWITCHING TO ORAL BP









Ebina K et al, J Bone Miner Metab, 2017

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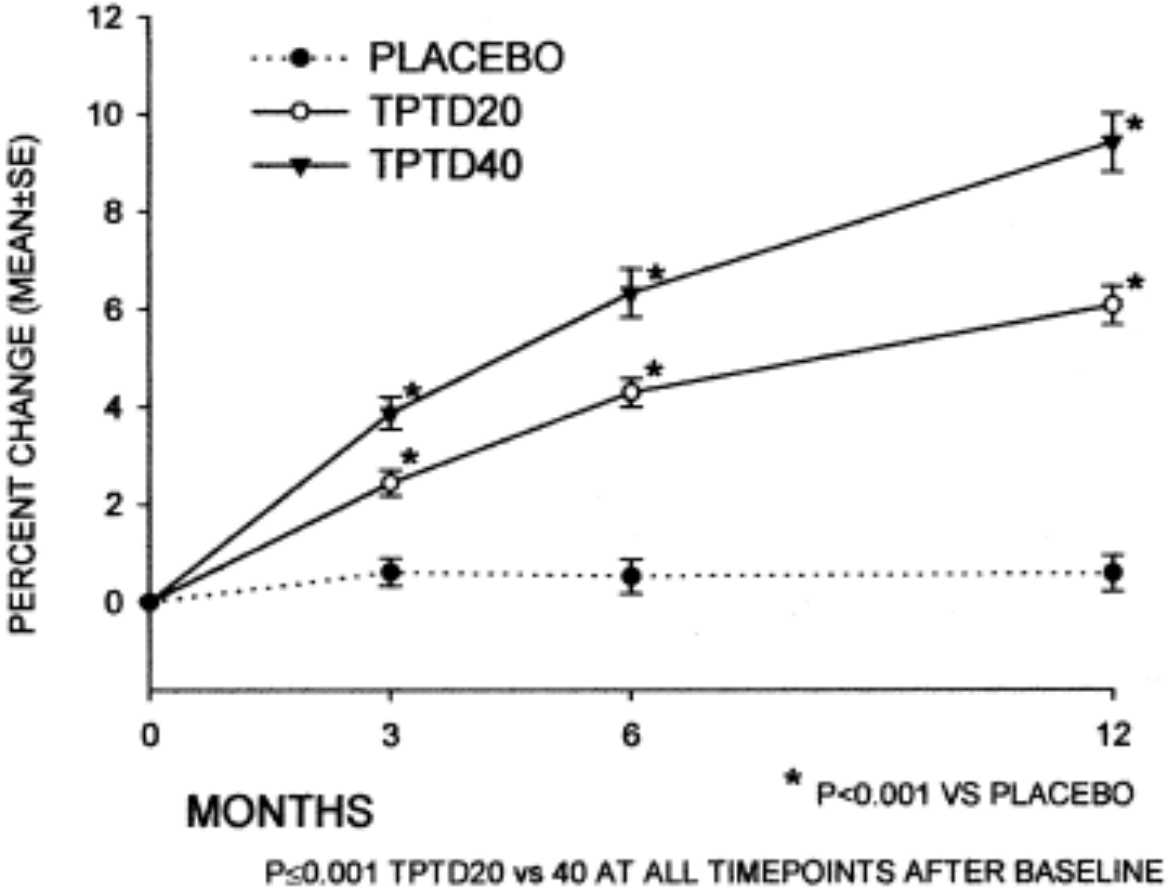
Orwoll ES et al, JBMR 2003

TERIPARATIDE IN MEN

437 men with BMD < -2.0 randomized to placebo, teriparatide 20 µ g, or 40 µg (12 months).

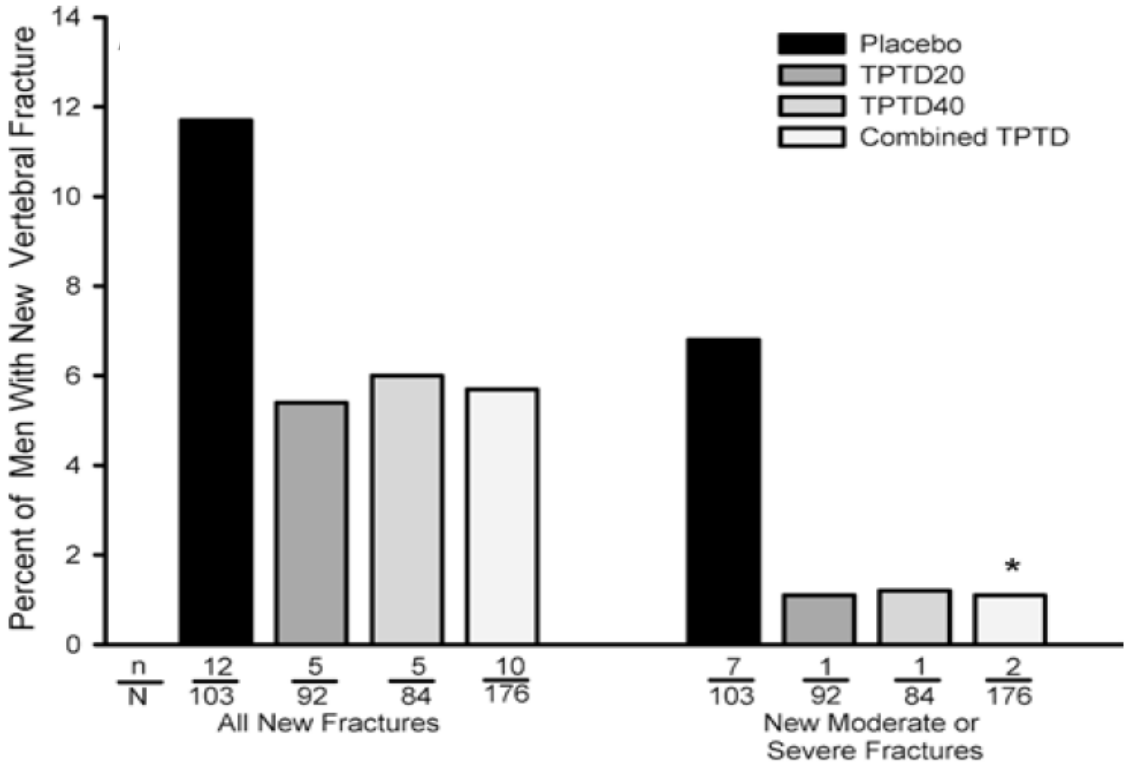


Teriparatide treatment results in an increase in BMD in men with low BMD

Orwoll ES et al, JBMR 2003

TERIPARATIDE IN MEN

355 men with BMD < -2.0 randomized to placebo, teriparatide 20 µg, or 40 µg (30 months)



Teriparatide decreases the risk of vertebral fractures in men with low BMD

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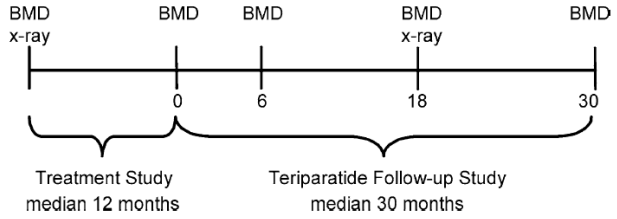
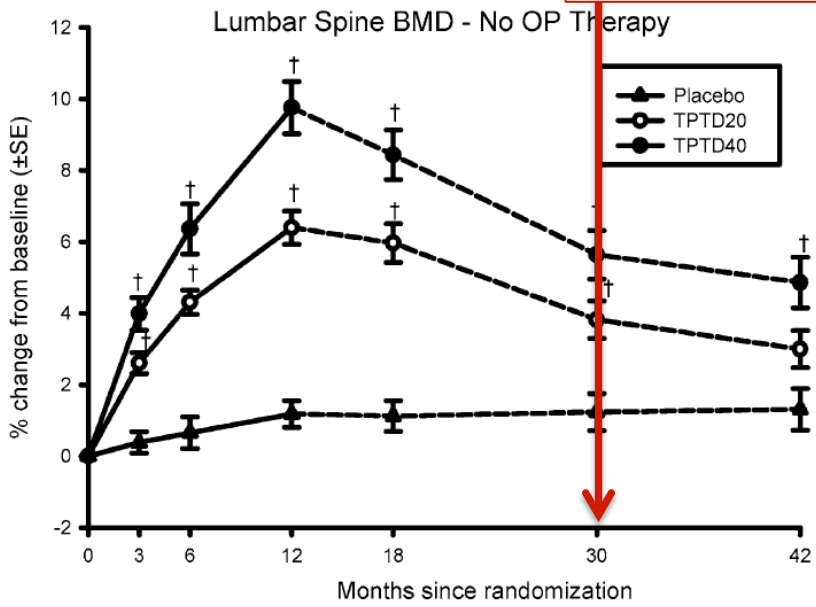
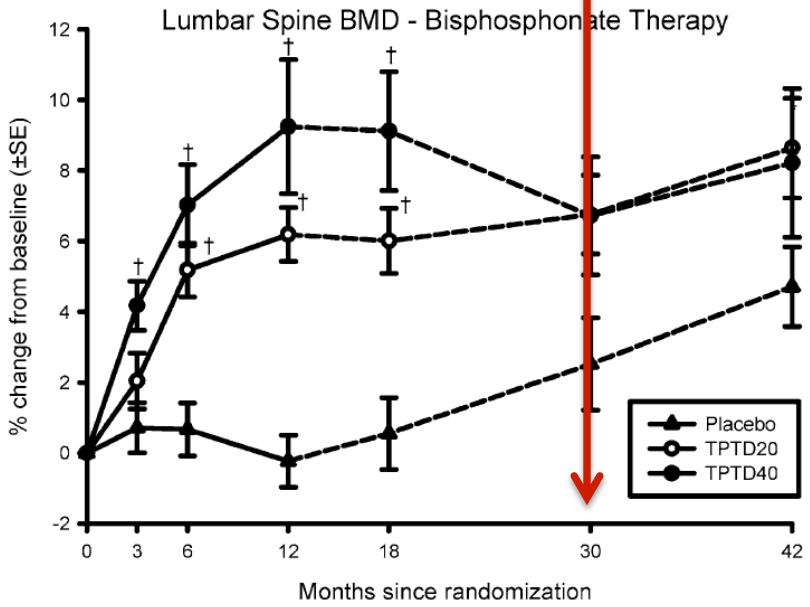


DISCONTINUATION





Antiresorptive treatment prevented the decline and tended to further increase BMD in male patients after discontinuation of TPT

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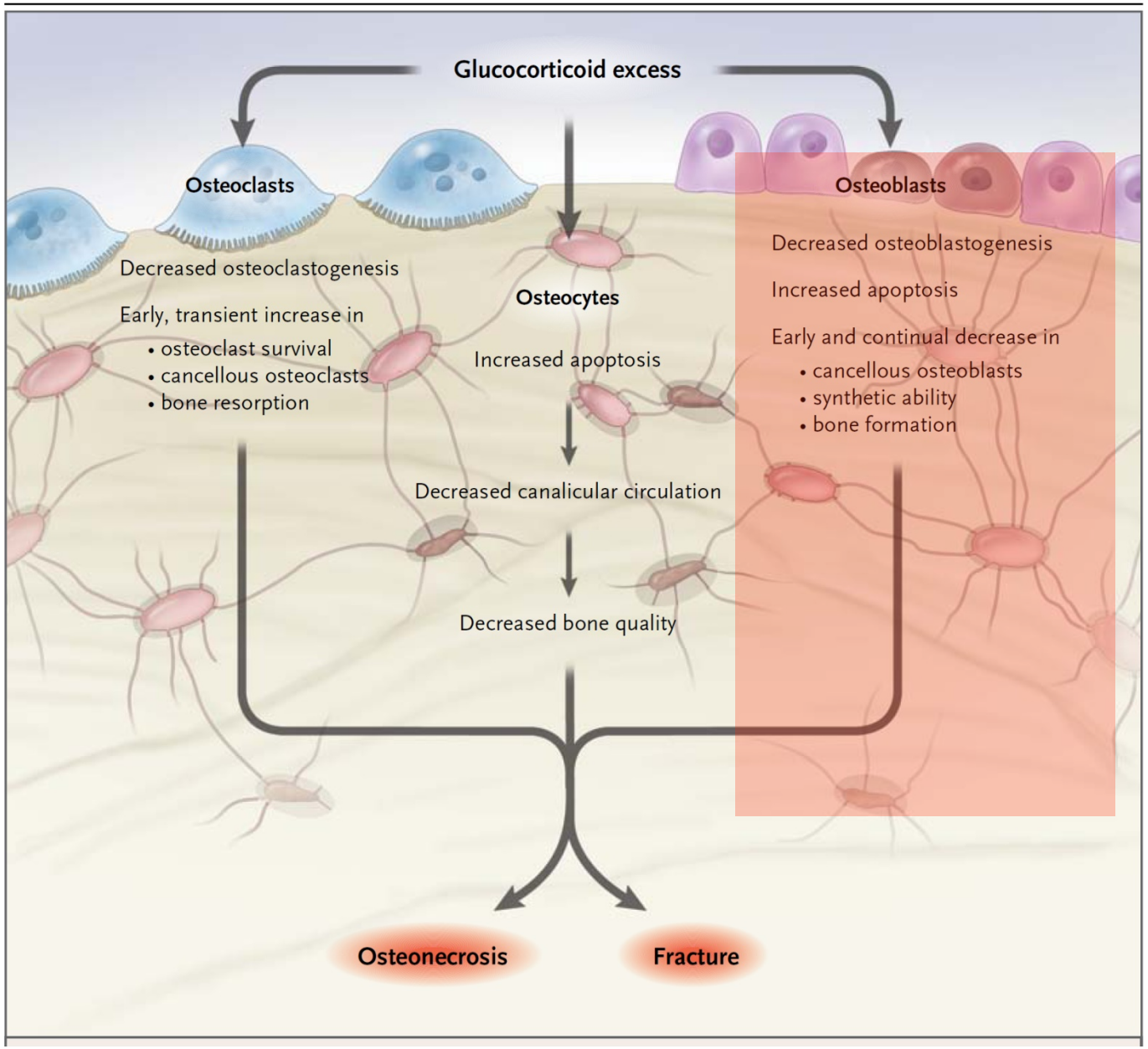

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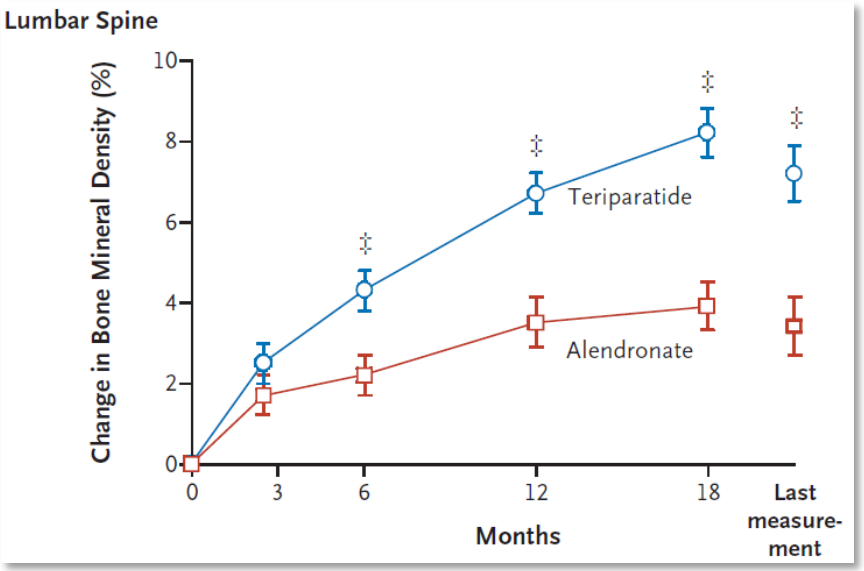
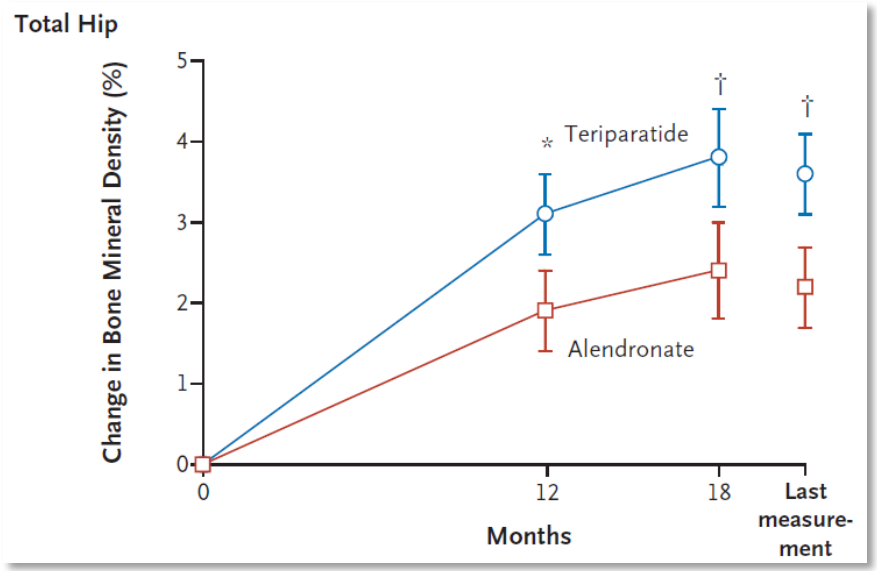
TERIPARATIDE IN GIOP

428 patients (women and men) who had received glucocorticoids for ≥3 months (prednisone equivalent, 5 mg daily or more) randomized to ALE or TPT (18 months)





Variable	Alendronate (N = 214)	Teriparatide (N = 214)	P Value
Fractures			
Vertebral — no./total no. (%)*			
Radiographic evidence	10/165 (6.1)	1/171 (0.6)	0.004
Clinical evidence†	3/165 (1.8)	0	0.07

- **In patients with GIOP, BMD increased more with TPT than with ALE**
- **Fewer new vertebral fractures occurred with TPT (0.6%) than with ALE (6.1%)**

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ANABOLIC AGENTS: FIVE FREQUENTLY ASKED QUESTIONS

- **Teriparatide**
  - Efficacy after antiresorptive therapy
  - Efficacy combined with antiresorptive therapy
  - What to do after anabolic therapy
  - Efficacy in men and GIOP
  - Safety

- New Agents (Abaloparatide, Romosozumab)

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TERIPARATIDE: SIDE EFFECTS

- Side effects were more frequent with TPT: headache (RR 1.4), nausea (RR 2.34), cramps (RR 3.22) and hypercalcemia (RR 9.73)
- Fracture Prevention Trial: hypercalcemia in 11% of the patients soon after administration (4-6 hours) and consecutive hypercalcemia was observed in 3% and was not sustained. The FDA (Food and Drug Administration): 1) observe the calcium and vitamin D intake including total dietary and supplemental 2) Check serum calcium at least once in the first month after starting the therapy.
- Hypercalciuria has a small risk of occurrence. Patients with renal stones or hypercalciuria before treatment should be investigated from a metabolic standpoint, define the cause and correct it as a first step.
- Monitoring calcium excretion is not recommended in patients with no renal stones or normal basal urinary calcium.

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TERIPARATIDE: OSTEOSARCOMA

Animal toxicity data (osteosarcoma) still a concern to some prescribers and patients

Cases of osteosarcoma

3-5 cases of osteosarcoma have been reported in patients who have received teriparatide since 2002 (Harper et al. JBMR, 2007)

Epidemiological considerations

- >2.0 million patients have been treated with **teriparatide** and PTH(1-84)
- The background incidence of osteosarcoma in adults: 1/250,000
- **The cases reported are fewer than what would be expected on coincidental, epidemiological grounds**
- 15-year FDA-mandated surveillance "Osteosarcoma Surveillance Study": 1448 cases of osteosarcoma identified: no history of teriparatide use in any patient

Conclusions

- The likelihood that osteosarcoma is a human toxicity when used in the way it is being used would appear to be remote
- Surveillance (and the black box) continues
- Avoid in patients with cancer history and Paget

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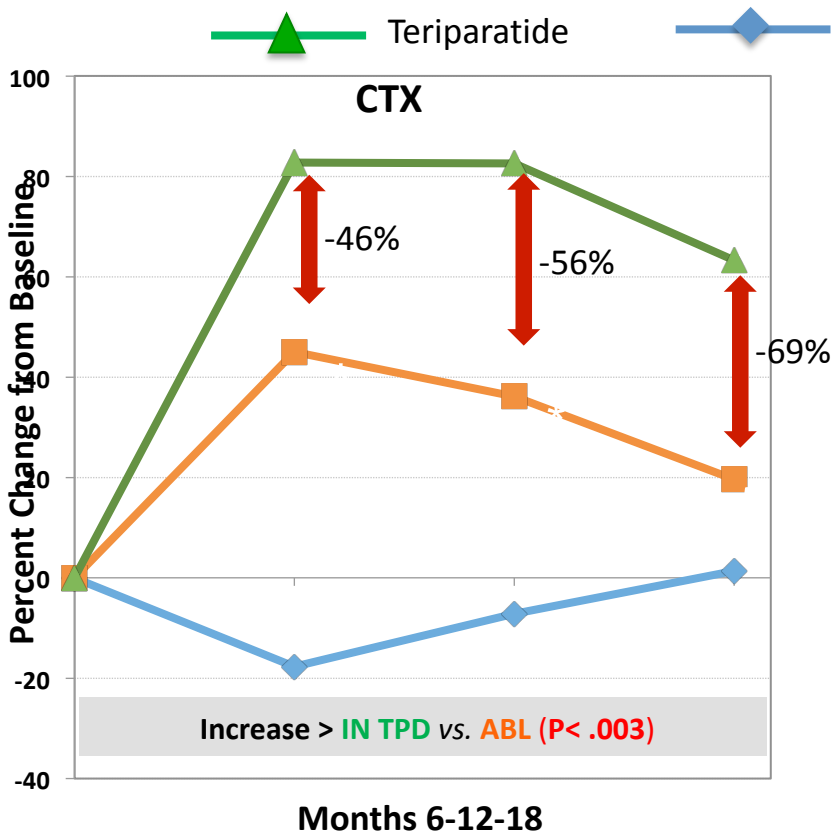
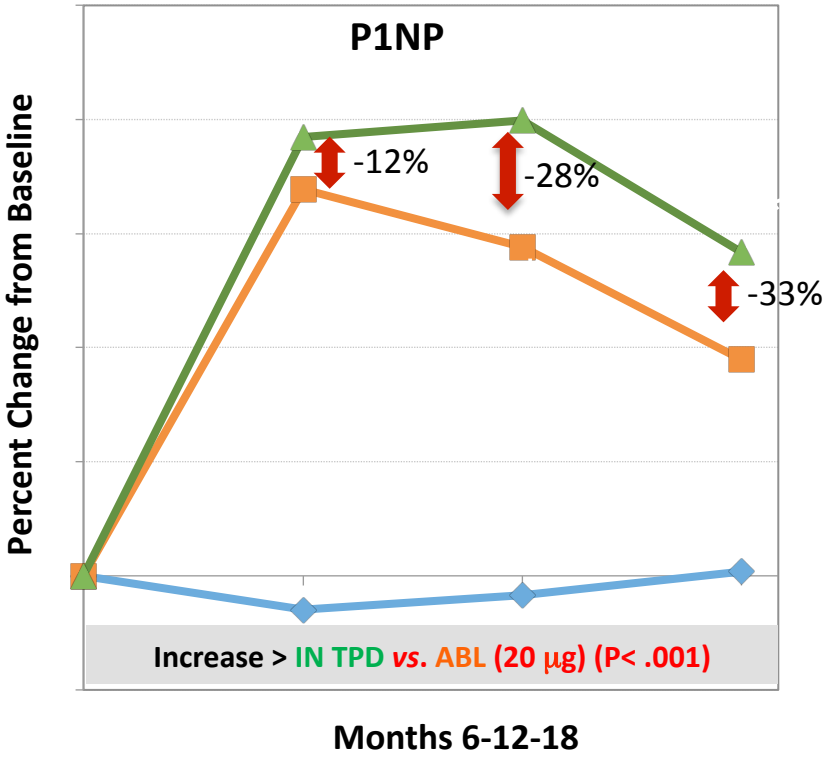
Leder BZ et al, JCEM 2015
Cosman F. Bonekey Rep. 2015

ABALOPARATIDE

Abaloparatide is a 1–34 PTHrP-like molecule in which several amino acids have been modified in order to improve its pharmacokinetics and pharmacodynamic profiles





Abaloparatide is a synthetic analog of PTHrP that retains anabolic activity with less bone resorption, compared with PTHrP

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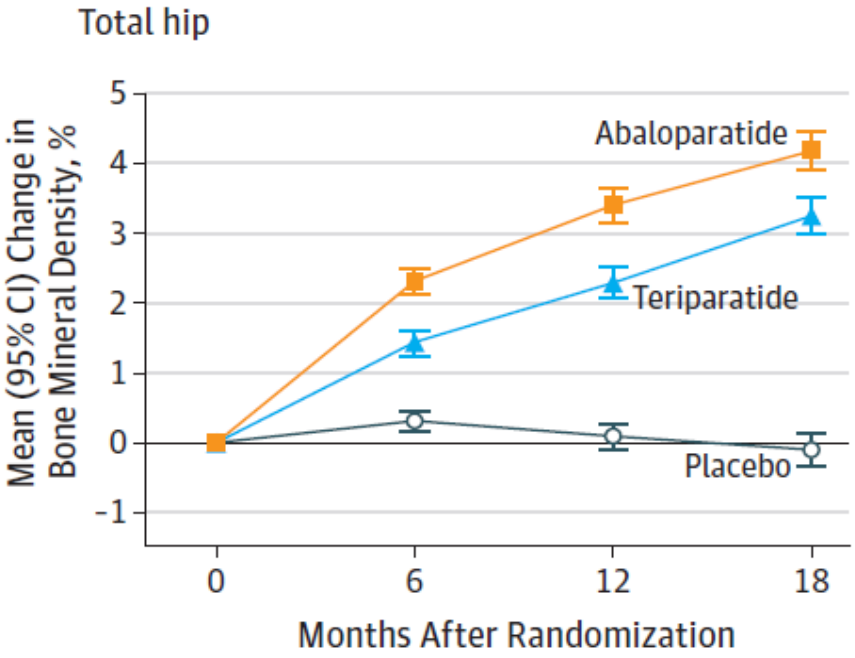
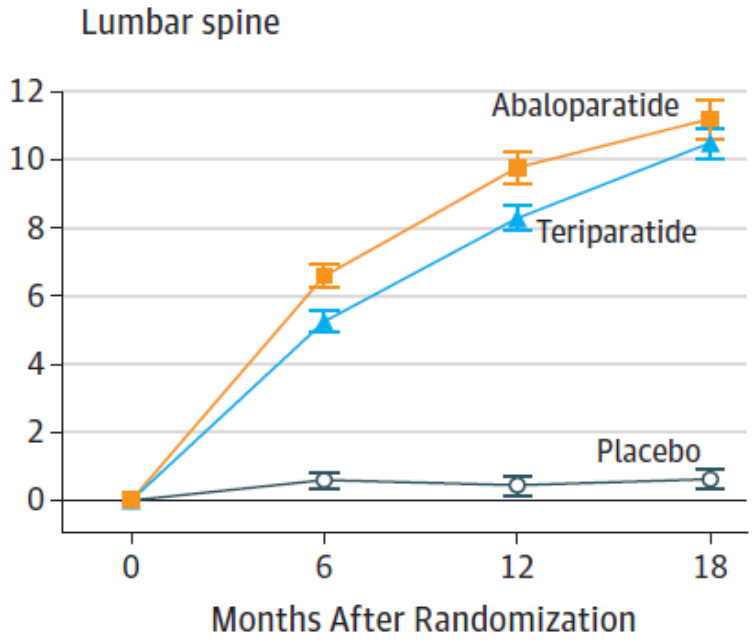
THE ABALOPARATIDE COMPARATOR TRIAL IN VERTEBRAL ENDPOINTS (ACTIVE)

Daily subcutaneous injections of placebo (n = 821), abaloparatide 80 µg (n = 824), or open-label teriparatide, 20 µg (n = 818) for 18 months





BMD improvements with abaloparatide were greater than those with teriparatide at the total hip at all time points and at lumbar spine at 6 and 12 months

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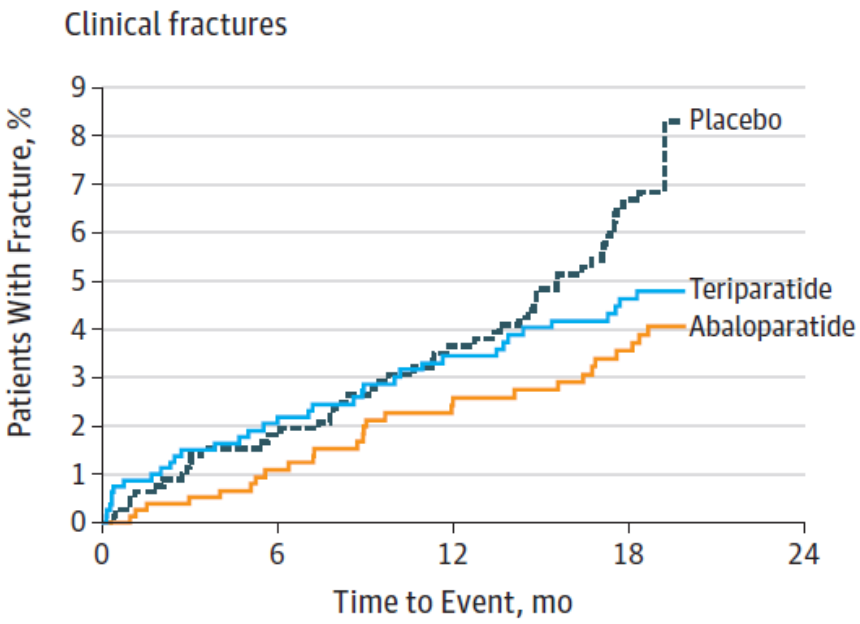

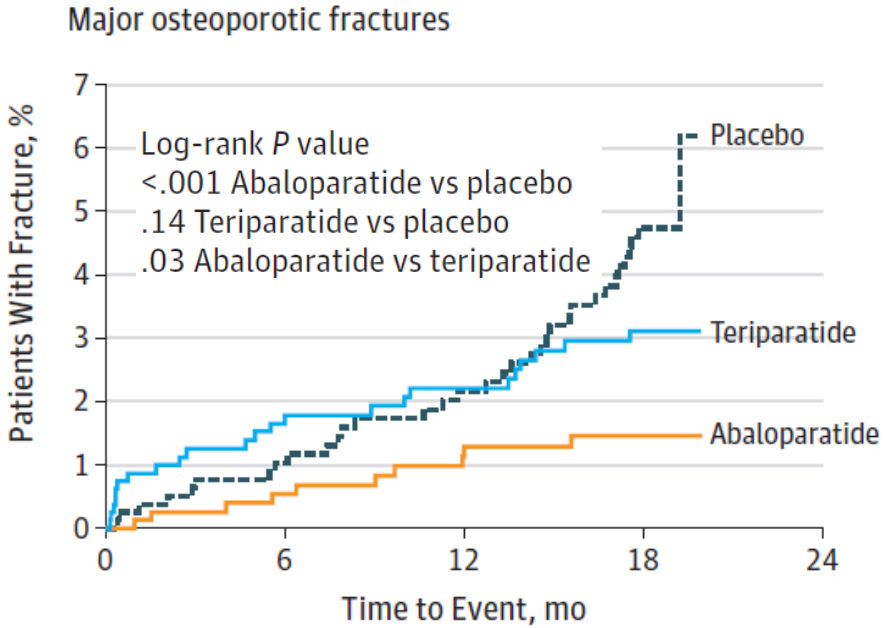

- **In PM osteoporotic women ABL, compared with placebo, reduced the risk of new vertebral (-86%) and nonvertebral (-43%) fractures over 18 months.**
- **ABL was superior to TPT in reducing the incidence of major osteoporotic fractures; no difference in non vertebral or clinical fractures between ABL and TPT (not endpoints of the study)**

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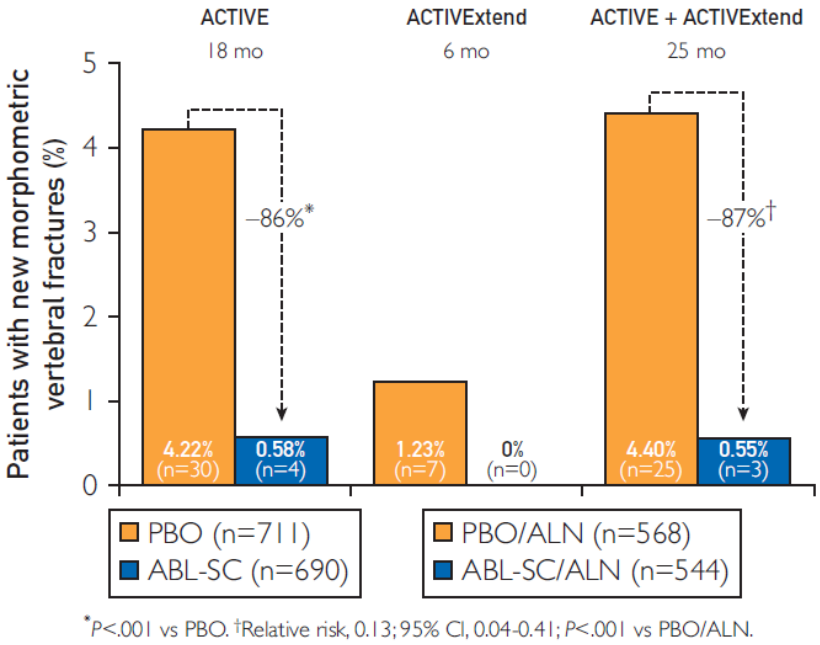
ABALOPARATIDE FOLLOWED BY 6 MONTHS ALENDRONATE (Pre-planned interim analysis)

ACTIV Extend, an extension of ACTIVE, enrolled patients who completed 18 months of ABL-SC or PBO in ACTIVE to receive up to 24 additional months of open-label ALN



*P<.001 vs PBO. †Relative risk, 0.13; 95% CI, 0.04-0.41; P<.001 vs PBO/ALN.

Sequential treatment with alendronate for 6 months further reduced the risk of new morphometric vertebral fractures and non-vertebral fractures in the group of patients treated with abaloparatide for 18 months compared with the sequential administration of the same alendronate dosage to the placebo group

ABALOPARATIDE: SAFETY

- Serious treatment-emergent adverse events appeared balanced between treatment groups: placebo, 90 (11.0%); abaloparatide, 80 (9.7%); and teriparatide, 82 (10.0%).
- Nausea (1.6%), dizziness (1.2%), headache (1.0%), and palpitations (0.9%), which were generally mild to moderate in severity.
- Hypercalcemia (albumin adj Calcium ≥10.7 mg/dL, ≥2.67 mmol/L) was less frequent in the abaloparatide group (3.4%) than the teriparatide group (6.4%)

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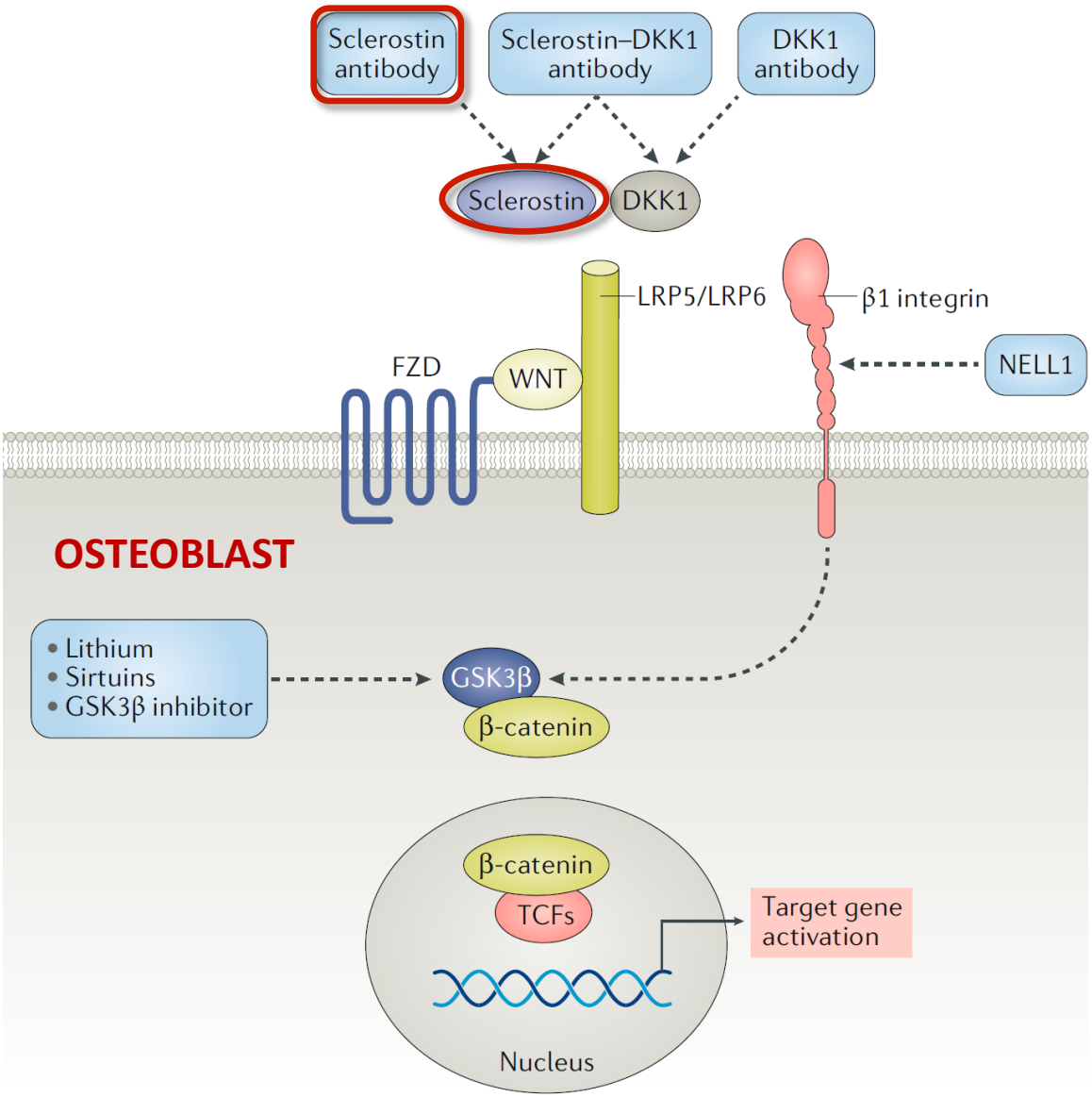
ROMOSOZUMAB: MECHANISM OF ACTION



Appelman-Dijkstra N & Papapoulos SE, Nat Rev Endocrinol 2018

- Sclerostin, a glycoprotein produced primarily by osteocytes, blocks the canonical Wnt signaling pathway.
- Romosozumab, a monoclonal antibody to sclerostin, permits the engagement of Wnt ligands with their co-receptors, resulting in an increase in bone formation
- Clinical studies with romosozumab have shown dramatic improvements in BMD at the spine and hip.
- Romosozumab is associated with improvement in bone strength through mechanisms that include increases in bone formation and, different from classical osteoanabolic agents, suppression of bone resorption.

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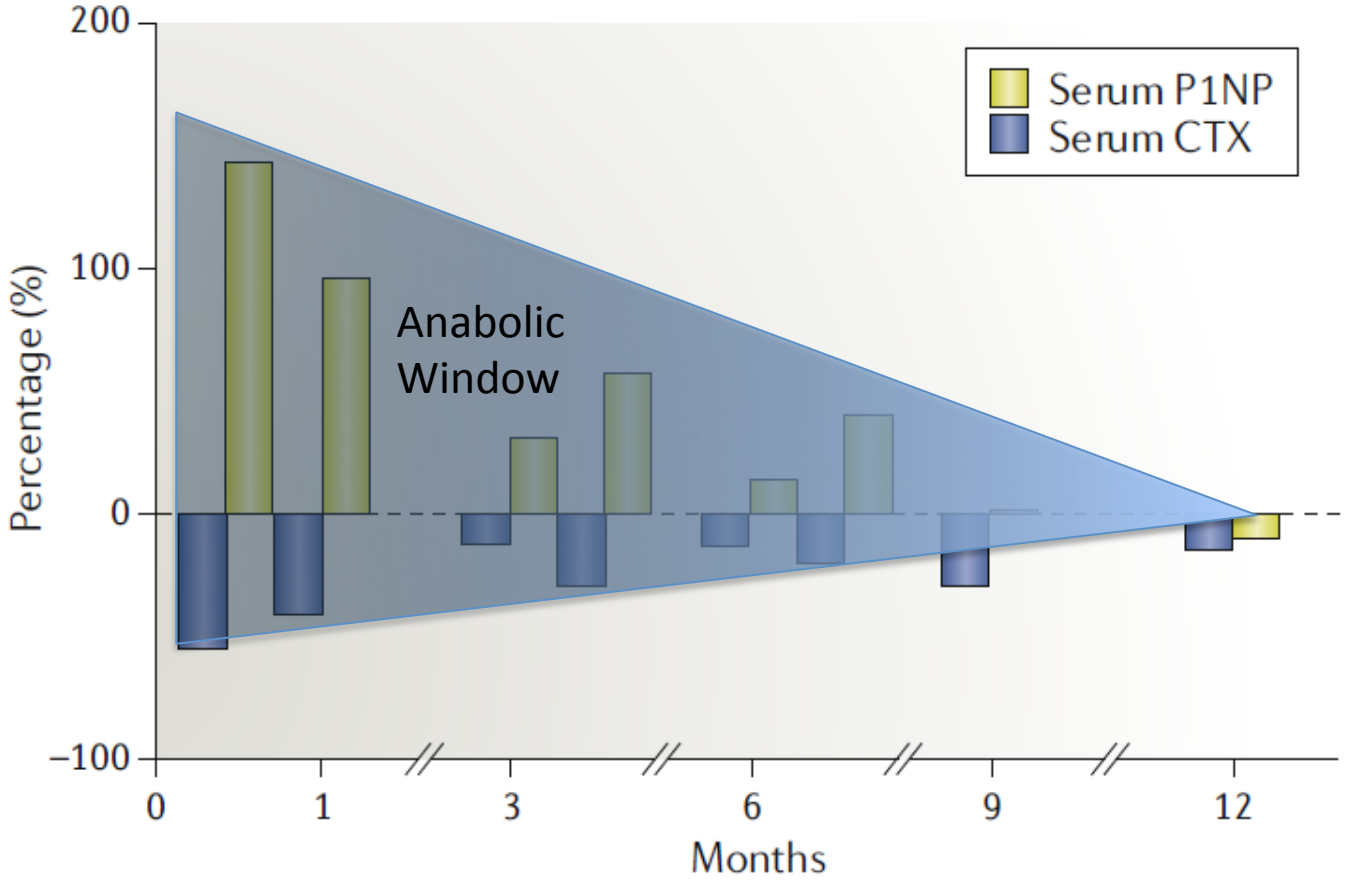
ROMOSOZUMAB: BONE TURNOVER

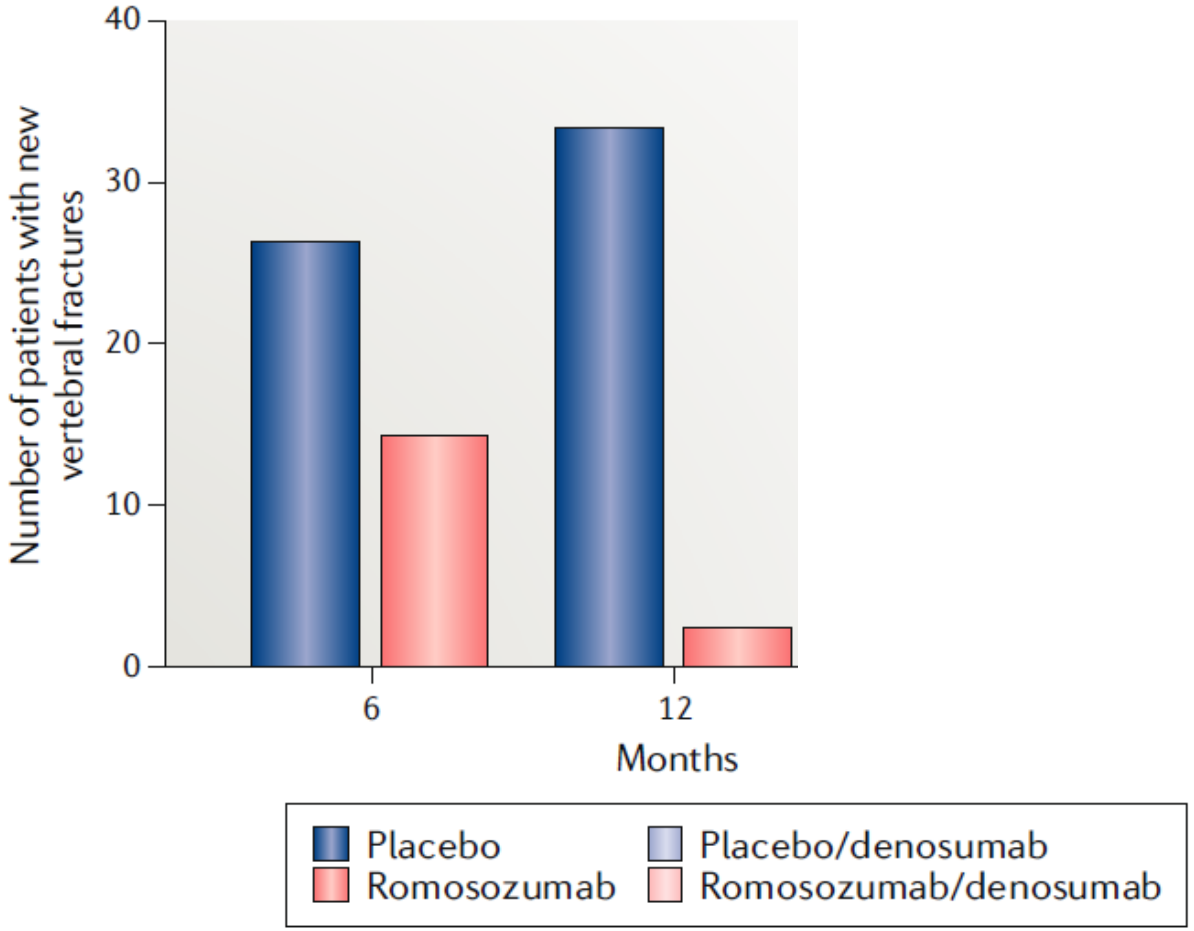
Percentage change in serum procollagen type 1 amino-terminal (P1NP) and carboxy-terminal telopeptide (CTX) during 1-year treatment of postmenopausal women with osteoporosis with subcutaneous romosozumab (210 mg once a month) in the FRAME study



Appelman-Dijkstra N & Papapoulos SE, Nat Rev Endocrinol 2018; Cosman F et al, NEJM 2016

ROMOSOZUMAB: FRAME STUDY

7,180 PM women aged 55-90 years with BMD T-scores TH or FN between −2.5 and −3.5, Romu 210 mg/month vs placebo for 1 year; than open-label Dmab (60 mg sc/6 months) for a further 12 months



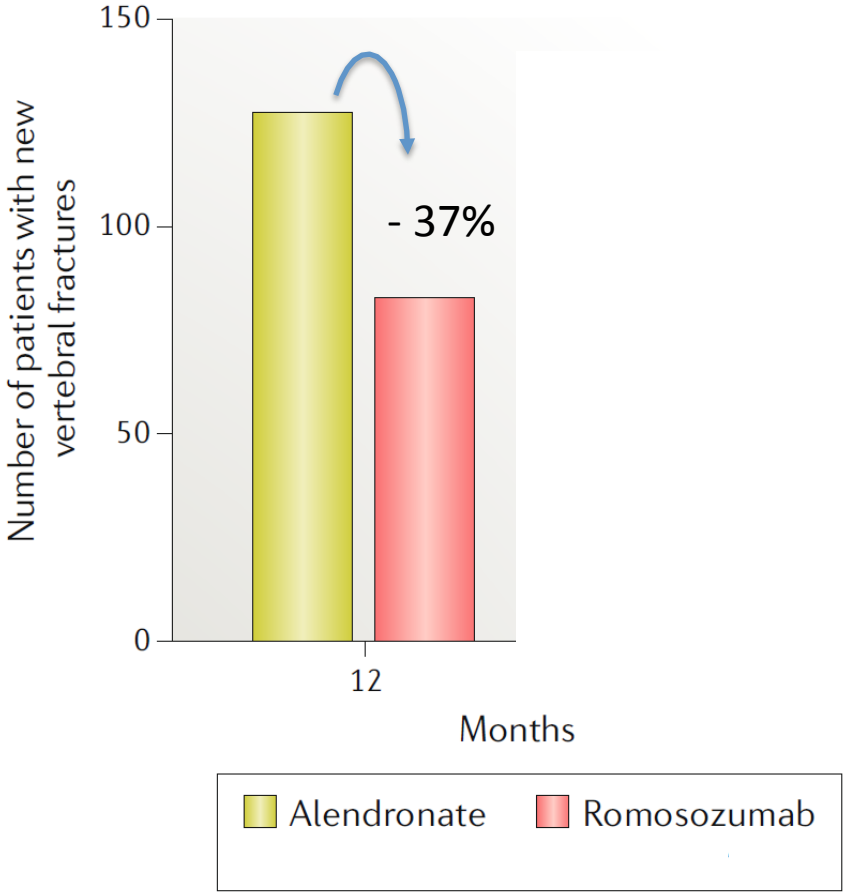
These results indicate not only an early reduction in the risk of vertebral fractures with treatment with romosozumab but also a sustained protective effect during follow-up treatment with a very potent agent with established antifracture efficacy.

Non-vertebral fractures decreased by 25%, (n.s.)

Appelman-Dijkstra N & Papapoulos SE, Nat Rev Endocrinol 2018; Cosman F et al, NEJM 2016

ROMOSOZUMAB: ARCH STUDY

4,039 women, mean age of 74.3 years, with severe PM osteoporosis (Romo 210 mg/month vs Ale 70 mg/week for 12 months, than Ale in all)



I year

- Clinical fx -28%
- Non-vertebral fx -26%

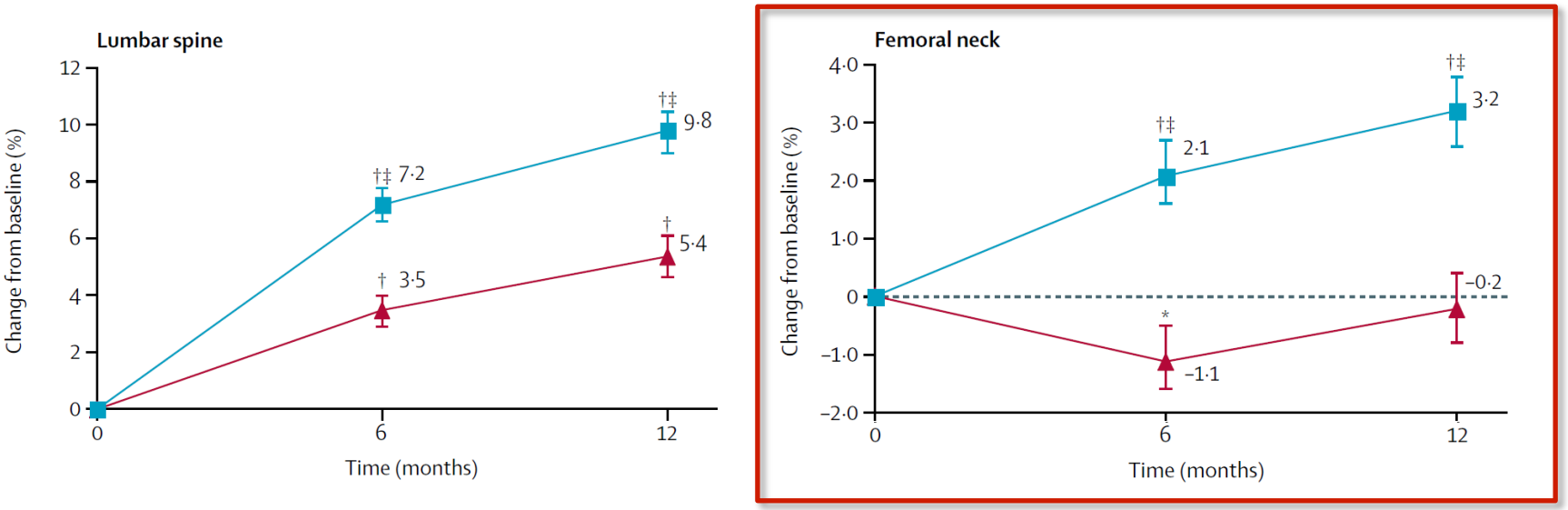
II year

- clinical fx -27%
- non-vertebral fx -19%
- hip fx -38%

Appelman-Dijkstra N & Papapoulos SE, Nat Rev Endocrinol 2018; Saag KG et al, NEJM 2017

ROMOSOZUMAB: STRUCTURE STUDY

436 women with a mean age of 71.5 years who had received bisphosphonate treatment for ≥ 3 years and Ale in the year prior to screening randomized to Romu (210 mg monthly) or TPT (20 µg daily)



Increases in BMD with romosozumab treatment were significantly greater than with teriparatide at all measured skeletal sites (P<0.0001).

Langdahl, B. L. et al., Lancet 2017

ROMOSOZUMAB: SAFETY

- More local reactions at the injection site
- Serious cardiovascular adverse events more often with Romo than with ale in the ARCH study: 50 patients (2.5%) in the Romo group, 38 patients (1.9%) in the Ale group.
- Given concerns for increased cardiovascular events, Romo's approval remains pending.

ANABOLIC AGENTS: TAKE HOME MESSAGES

Teriparatide: Efficacy after antiresorptive therapy?

- The more potent the BP the greater the delay in BMD response, but most patients respond eventually to PTH
- Do not give DMAB after TPT (ideally TPT should be given as first drug)

Teriparatide: Efficacy combined with antiresorptive therapy?

- Improved femoral BMD at 6-12 months vs TPT monotherapy
- No advantage than TPT monotherapy for full-length treatment (18-24 months)

Teriparatide: what to do after?

- Give antiresorptives

Teriparatide: men and GIOP?

- Decreases vertebral fractures risk in men with low BMD
- Decreases vertebral fx risk as compared to alendronate in patients taking GC

Abaloparatide

- Reduced the risk of new vertebral (-86%) and nonvertebral (-43%) fractures at 18 months; ABL seems superior to TPT in reducing major osteoporotic fractures

Romosozumab

- -75% vertebral fx risk vs placebo; -48% vertebral fx -38% risk of hip fx at 24 months vs alendronate; greater increase in BMD than with TPT at all sites
- Increased risk of serious cardiovascular events

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THANK YOU FOR THE ATTENTION

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