MALATTIE MUSCOLO-SCHELETRICHE

TERAPIA INTEGRATA, PERSONALIZZATA E QUALITÀ DI VITA

ROMA 6 - 7 ottobre 2023

Presidente del GISMO
Ranuccio Nuti

Presidenti del Congresso
Silvia Migliaccio | Giovanni Minisola

GISMO
Gruppo Italiano Studio
Malattie Metabolismo Osseo
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- Osteoporosi
- Malattie Muscolo-Scheletriche
- Malattie Metaboliche
- Dolore
- Nutrizione

Sistema Socio Sanitario
Ospedale Niguarda | Regione Lombardia

SABATO 7 OTTOBRE

08.00 *Registrazione ECM*

SESSIONE III
08.30 COMUNICAZIONI ORALI
Moderatori: Vincenzo Ortore - Alessandra Pompa

09.00 LETTURA
Moderatore: ***Bruno Frediani***
Hot topics reumatologici nella pratica clinica quotidiana
Giovanni Minisola

SESSIONE IV
UP TO DATE NELLA TERAPIA DELL'OSTEOPOROSI
Moderatori: Stefano Gonnelli - Sergio Salomone

09.30 La terapia sequenziale o combinata criteri di scelta
Iacopo Chiodini

09.50 La gestione della non responsività terapeutica nell'osteoporosi
Bruno Frediani

10.10 Terapia ormonale sostitutiva e SERMs
Stefano Lello - Anna Capozzi

10.30 Il corretto utilizzo dei farmaci anabolici
Daniela Merlotti

10.50 Abaloparatide, dalla ricerca alla pratica clinica
Fabio Vescini

I. Chiodini
Dpt of Medical Biotechnology and Translational Medicine, University of Milan. Unit for Endocrinology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

UNIVERSITÀ DEGLI STUDI DI MILANO

DICHIARAZIONE DI TRASPARENZA

Il sottoscritto **Iacopo Chiodini**
Dichiara

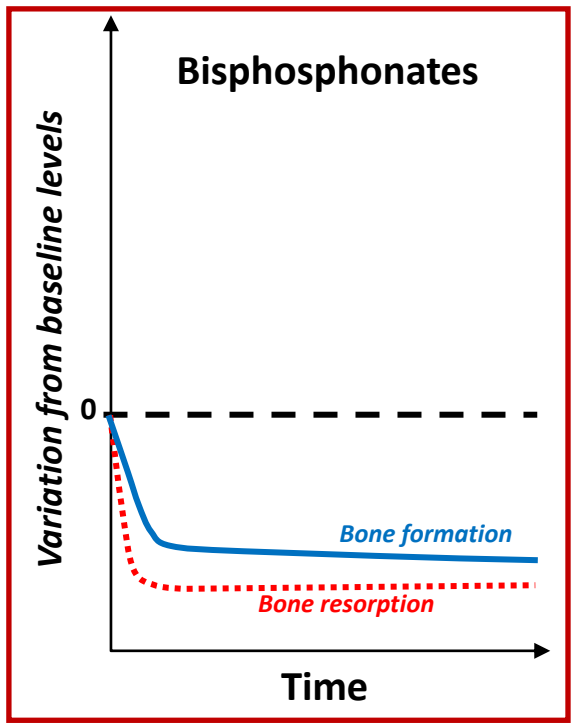
Che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con i soggetti portatori di interessi commerciali in campo sanitario:

- HRA Pharma
- Corcept Therapeutics
- UCB
- Amgen
- Sandoz

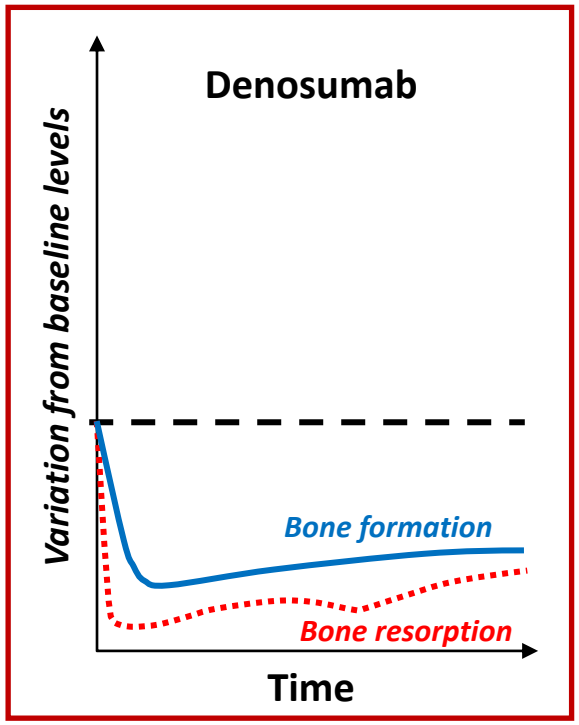
AGENDA

- Premesse
- Paziente naïve ad alto rischio di frattura o di rifrattura
- Paziente in terapia con bisfosfonati
- Terapia combinata
- Conclusioni

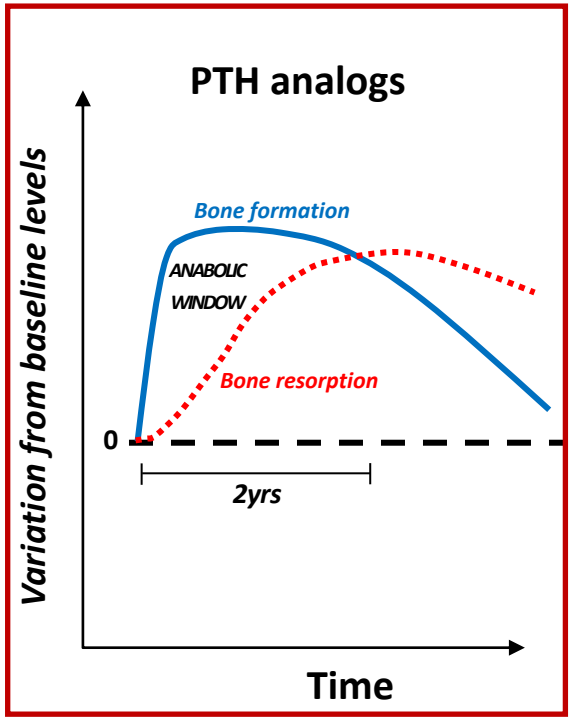
BONE TURNOVER CHANGES WITH THE AVAILABLE DRUGS FOR THE TREATMENT OF OSTEOPOROSIS



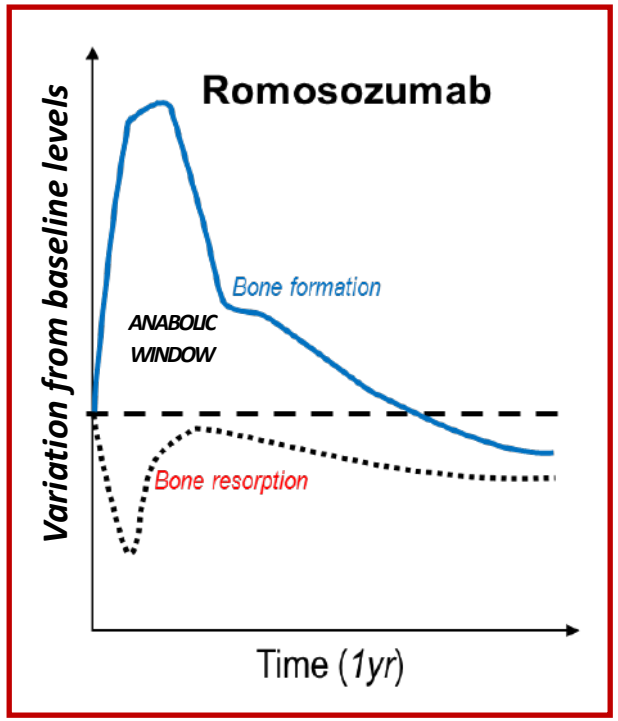
Long-standing effect



ON-OFF effect and rebound



Short-term effect



Short-term effect

AGENDA

- Premesse e definizioni
- Paziente naïve ad alto rischio di frattura o di rifrattura
- Paziente in terapia antiriassorbitiva
- Terapia combinata
- Conclusioni

QUESITO 4

Quale strategia terapeutica, sia a breve che a lungo termine, risulta più efficace nel trattamento del paziente con frattura da fragilità?

A causa dell'alta eterogeneità riscontrata in letteratura rispetto alle diverse strategie farmacologiche, si riportano di seguito le sequanzialità analizzate, e le relative pubblicazioni identificate:

ANABOLICO – ANTI-RIASSORBITIVO

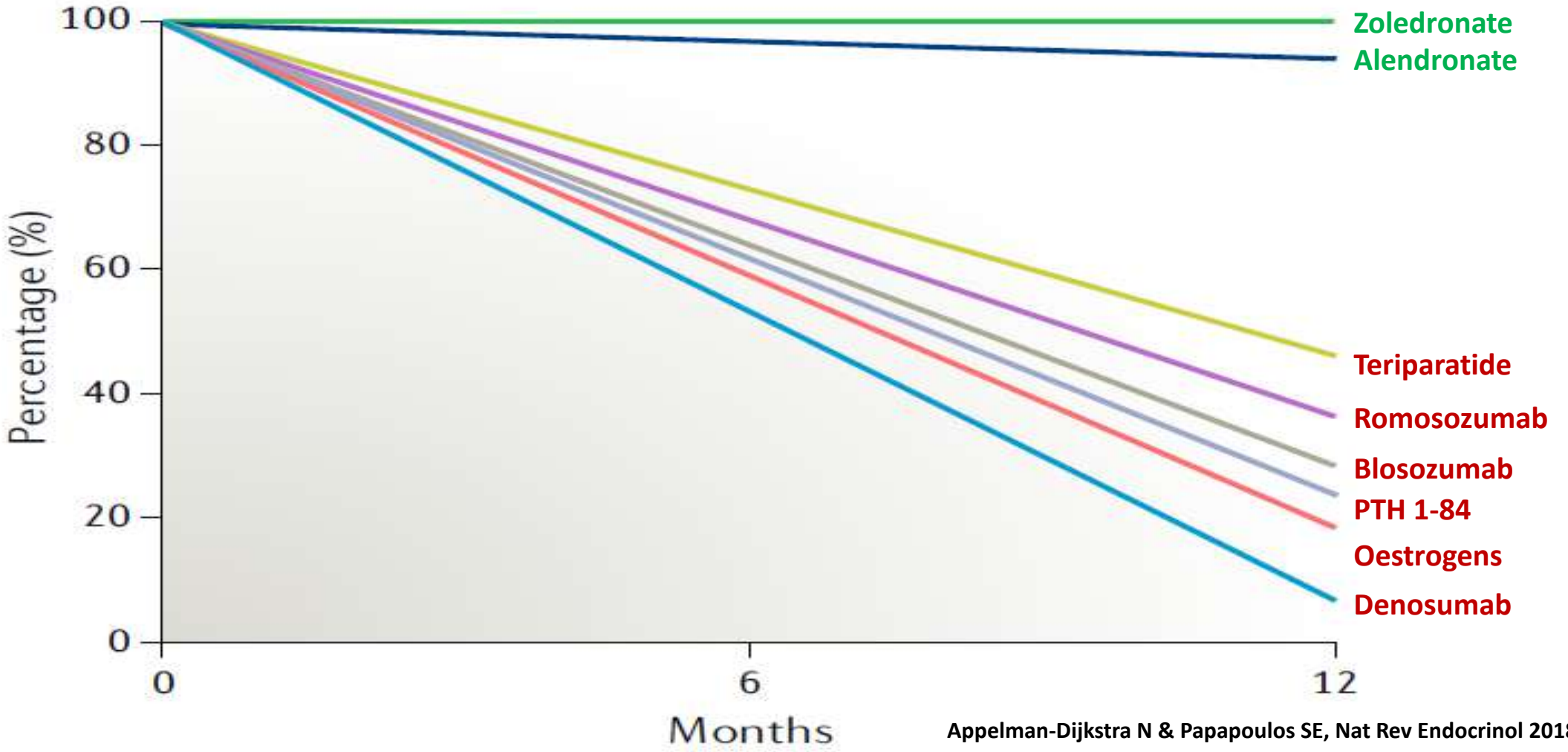
1. Romosozumab - Denosumab vs Placebo - Denosumab (Cosman 2016, Lewiecki 2019, Miyauchi 2019, Prince 2005)
2. Teriparatide - Denosumab vs Teriparatide – Alendronato o Minodronato (Niimi 2018)
3. Romosozumab - Alendronato vs Solo alendronato (Cosman 2020, Saag 2017)
4. Anabolico - Anti-riassorbitivo vs Anabolico-placebo (Black 2005, Kendler 2019)

ANTI-RIASSORBITIVO – ANABOLICO

1. Anti-riassorbitivo - Teriparatide vs Placebo - Teriparatide (Obermayer-Pietsch 2008, Middleton 2007, Fahrleitner-Pammer 2016)
2. Anti-riassorbitivo – Teriparatide vs solo Anti-riassorbitivo (Gonnelli 2016)
3. Anti-riassorbitivo – Anabolico (Romosozumab o Teriparatide) (Langdhal 2017)
4. Anti-riassorbitivo (Risedronato vs Alendronato) - Teriparatide (Miller 2008)
5. Anti-riassorbitivo (Risedronato, Alendronato, Etidronato, Non bisfosfonato) - Teriparatide (Boonen 2008)

CONFRONTO DIRETTO (Leder 2015)

LUMBAR SPINE BMD 1 YEAR AFTER CESSATION OF TREATMENTS FOR OSTEOPOROSIS

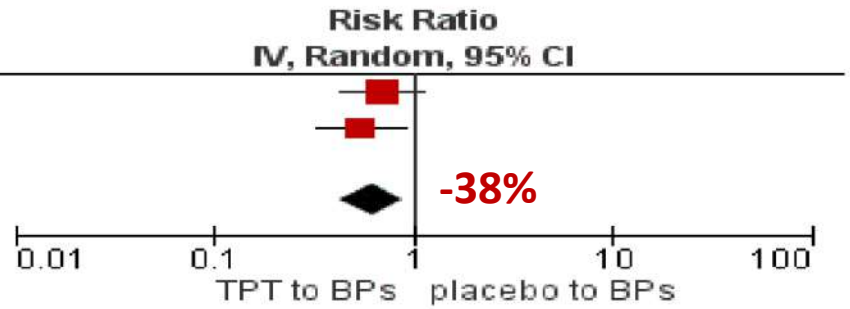


Appelman-Dijkstra N & Papapoulos SE, Nat Rev Endocrinol 2018

Riduzione del rischio di frattura NON VERTEBRALE a 30 mesi dallo switch da Teriparatide (o placebo) a bisfosfonati

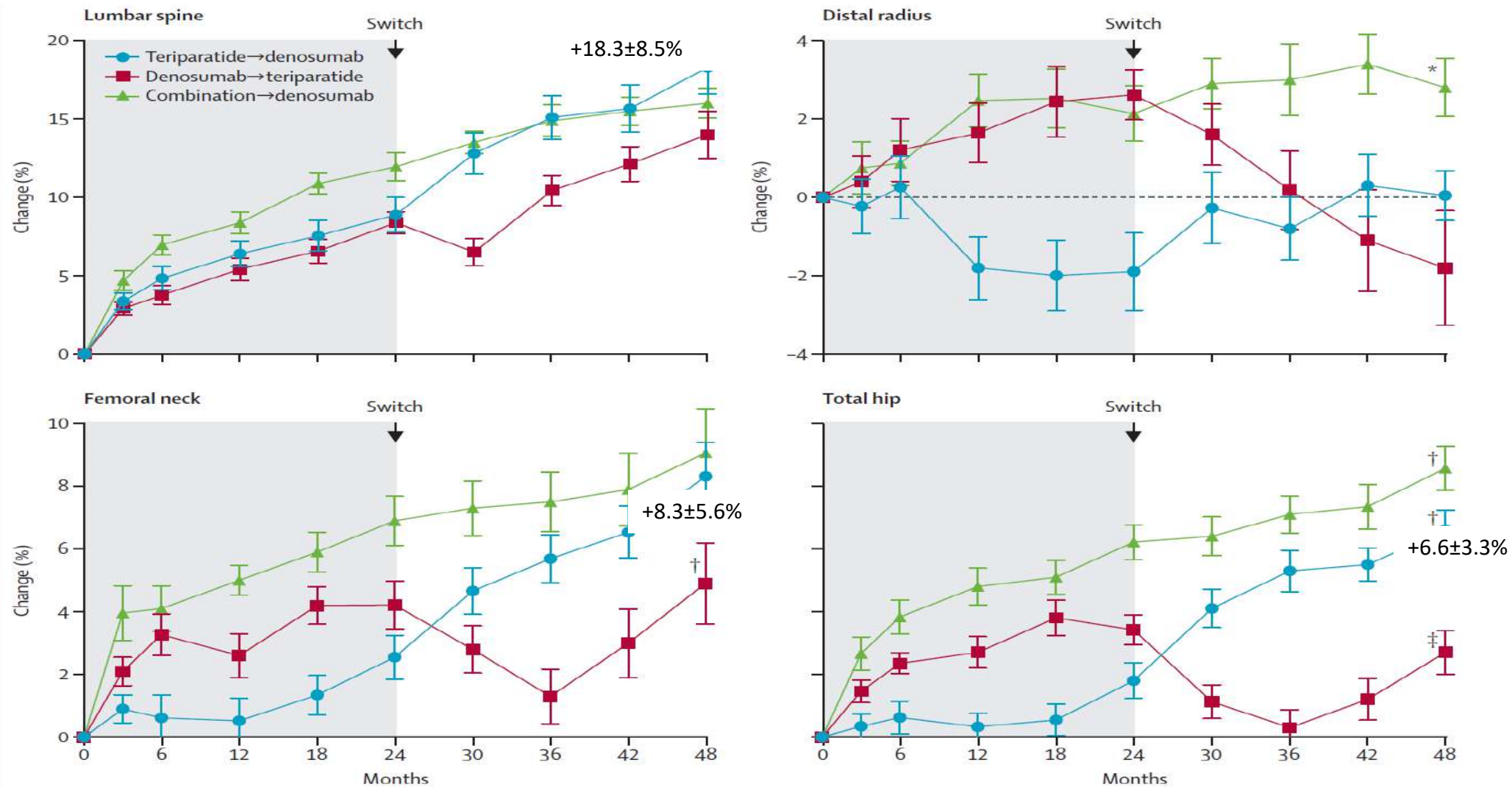
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Prince 2005_TPT 20 µg to BPs	-0.3567	0.2486	53.6%	0.70 [0.43, 1.14]
Prince 2005_TPT 40 µg to BPs	-0.6162	0.267	46.4%	0.54 [0.32, 0.91]
Total (95% CI)			**100.0%**	**0.62 [0.43, 0.89]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.51$, $df = 1$ ($P = 0.48$); $I^2 = 0\%$
Test for overall effect: $Z = 2.62$ ($P = 0.009$)



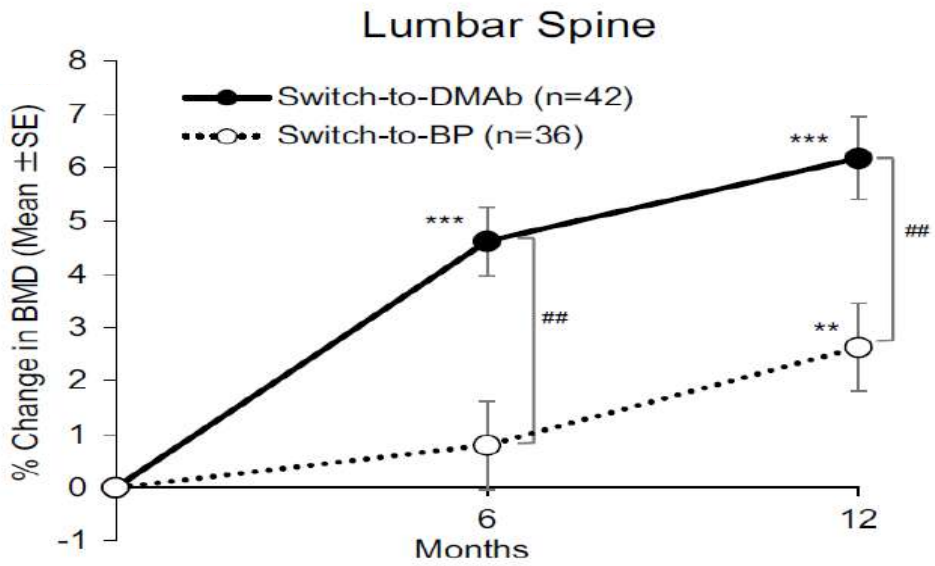
SEQUENTIAL THERAPY: TERIPARATIDE→DENOSUMAB

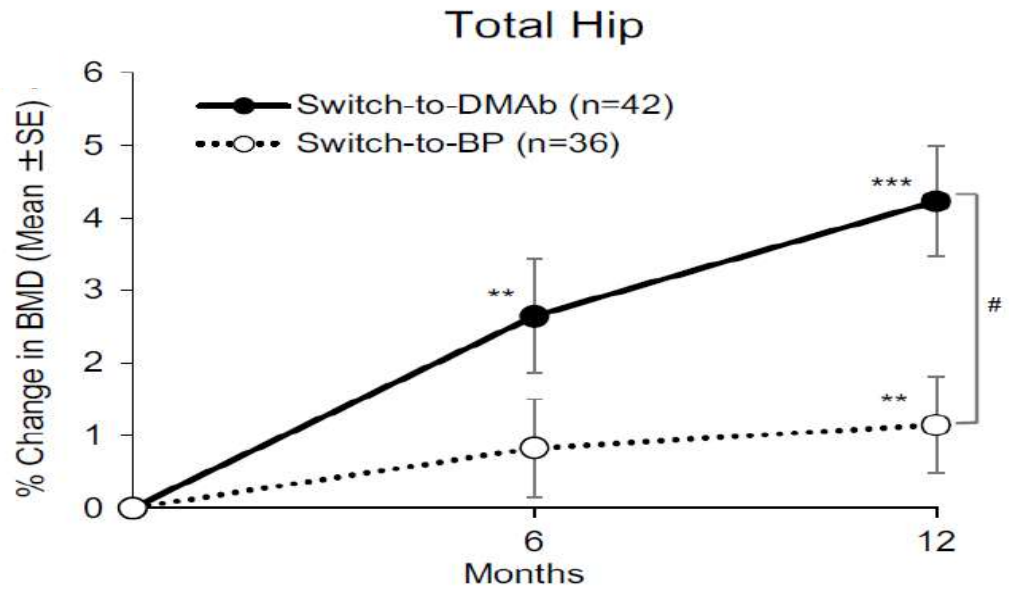
DATA SWITCH STUDY

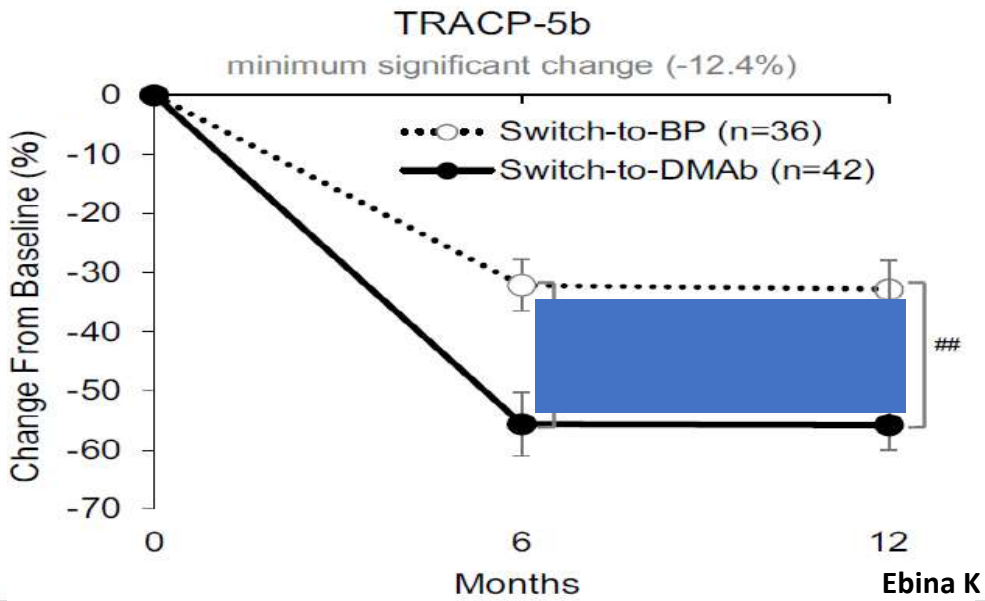


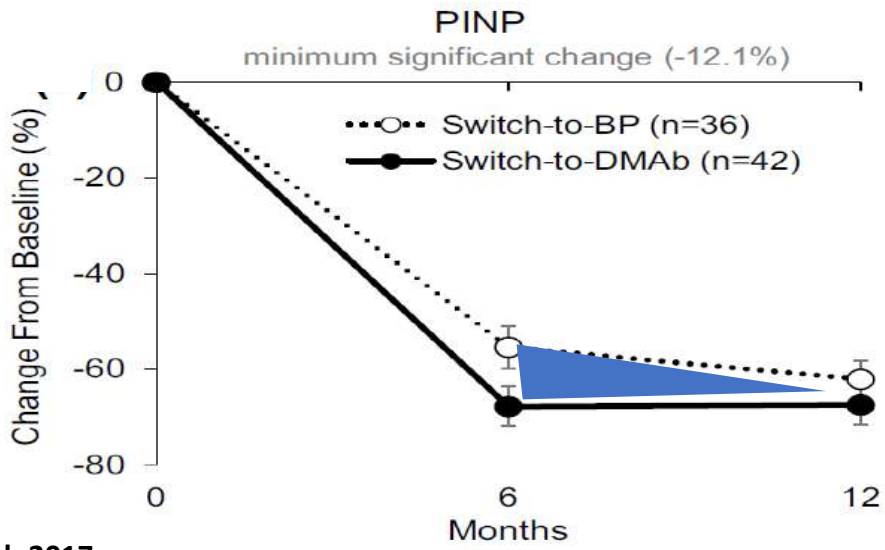
Leder BZ et al, Lancet 2015

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



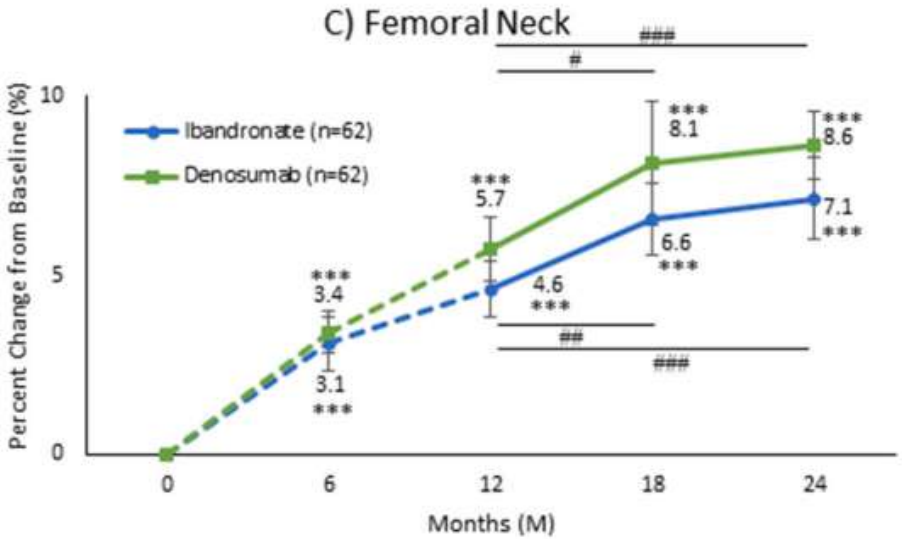


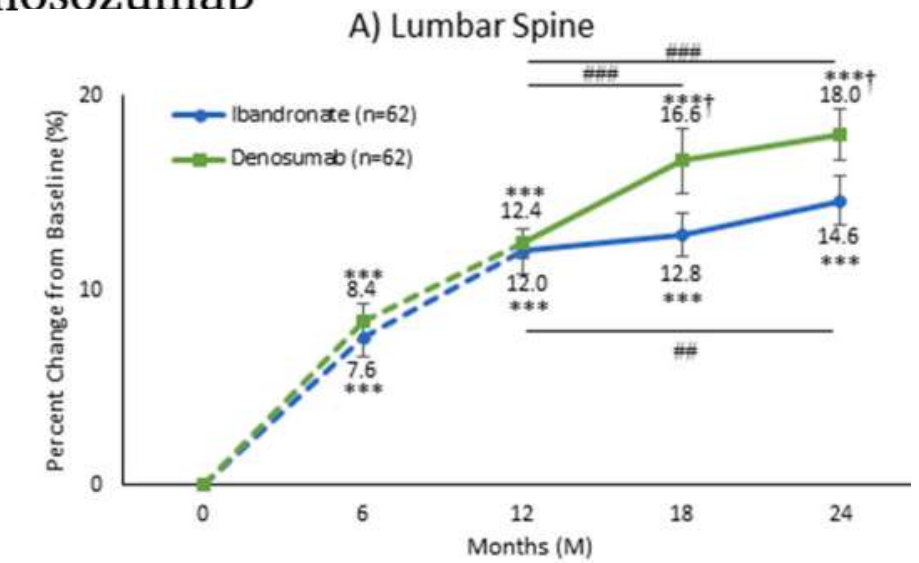


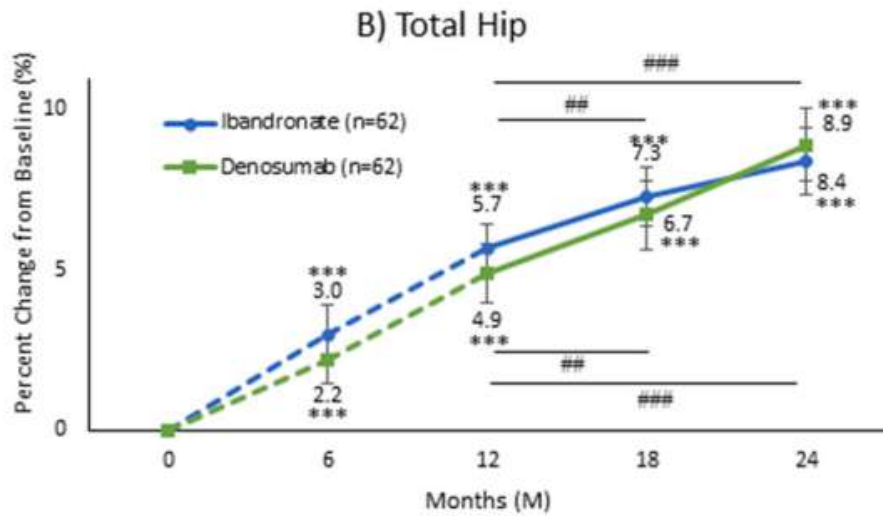


Ebina K et al, J Bone Miner Metab 2017

Verification of efficacy and safety of ibandronate or denosumab for postmenopausal osteoporosis after 12-month treatment with romosozumab as sequential therapy: The prospective VICTOR study







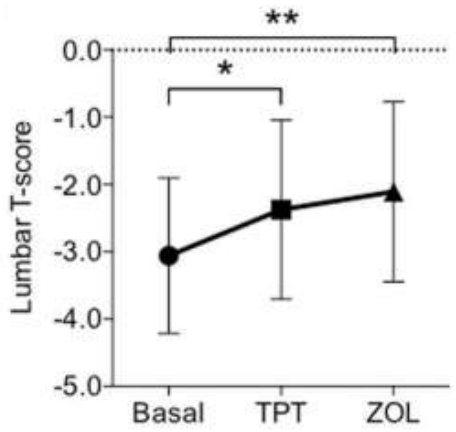
81 Ibandronato post Romosozumab

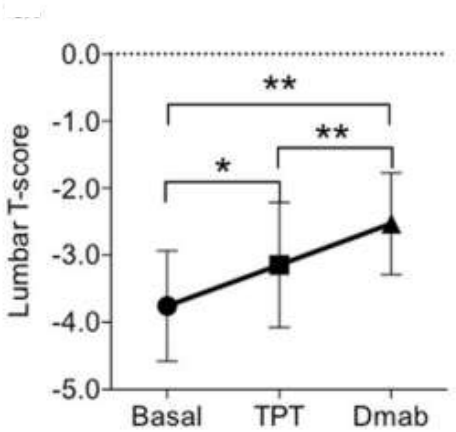
80 Denosumab post Romosozumab

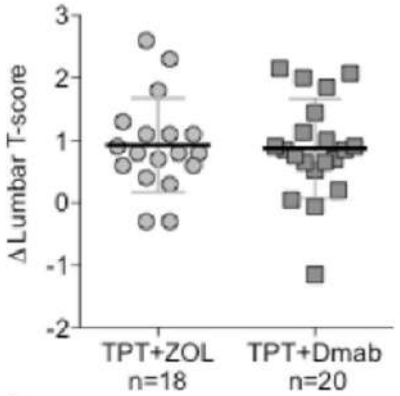
Tomonori Kobayakawa et al Bone 2022

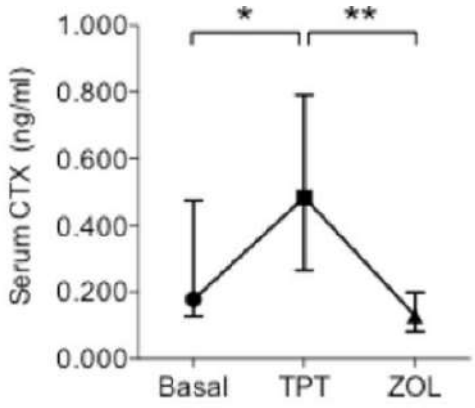
Efficacy of switching from teriparatide to zoledronic acid or denosumab on bone mineral density and biochemical markers of bone turnover in older patients with severe osteoporosis: a real-life study

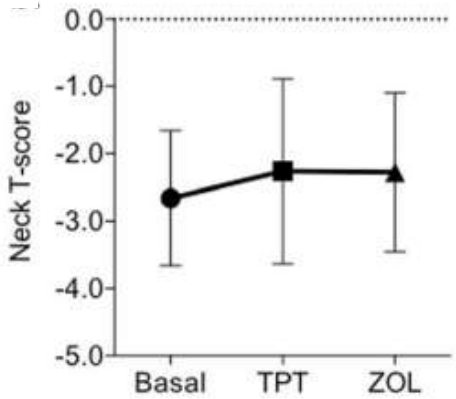
Retrospective study on 56 severe osteoporotic patients
TPT for 24 months followed by 24 months of zoledronic acid (ZOL) (TPT + ZOL) or Dmab (TPT+Dmab).

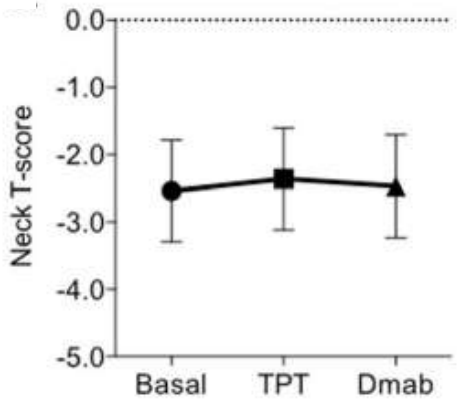


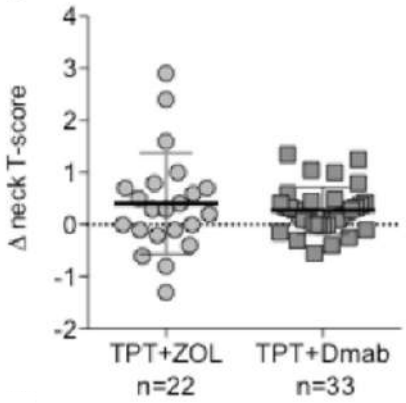


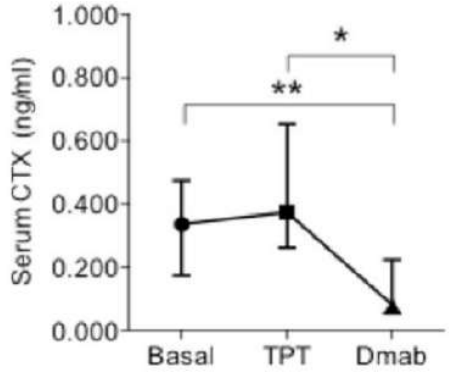










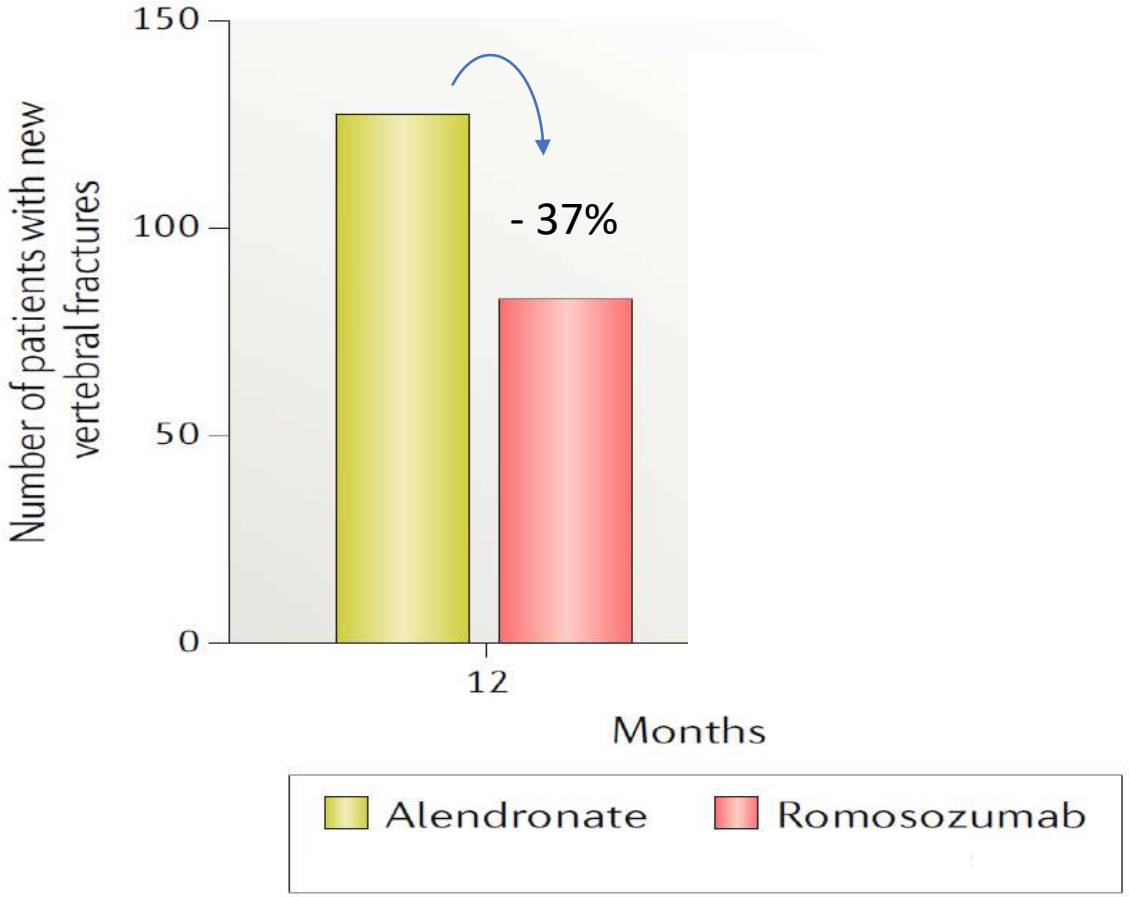


Sequential TPT + ZOL therapy is likely to increase bone mineralization at the lumbar level and to stabilize it at the femoral level, similarly to what obtained with the sequential TPT+Dmab

Dito G et al, Endocrine 2023, epub ahead of print

ROMOSOZUMAB → ALENDRONATE: 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

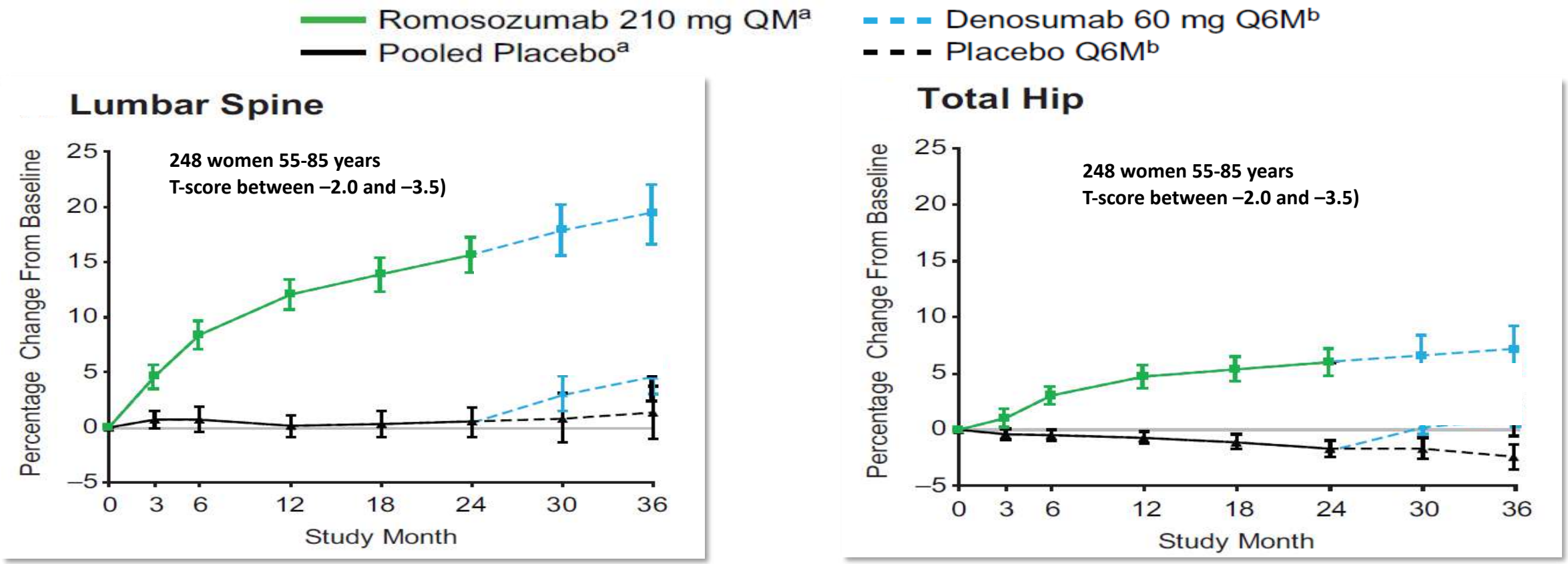
- clinical fx -27%
- non-vertebral fx -19%
- hip fx -38%

Saag KG et al, NEJM 2017

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

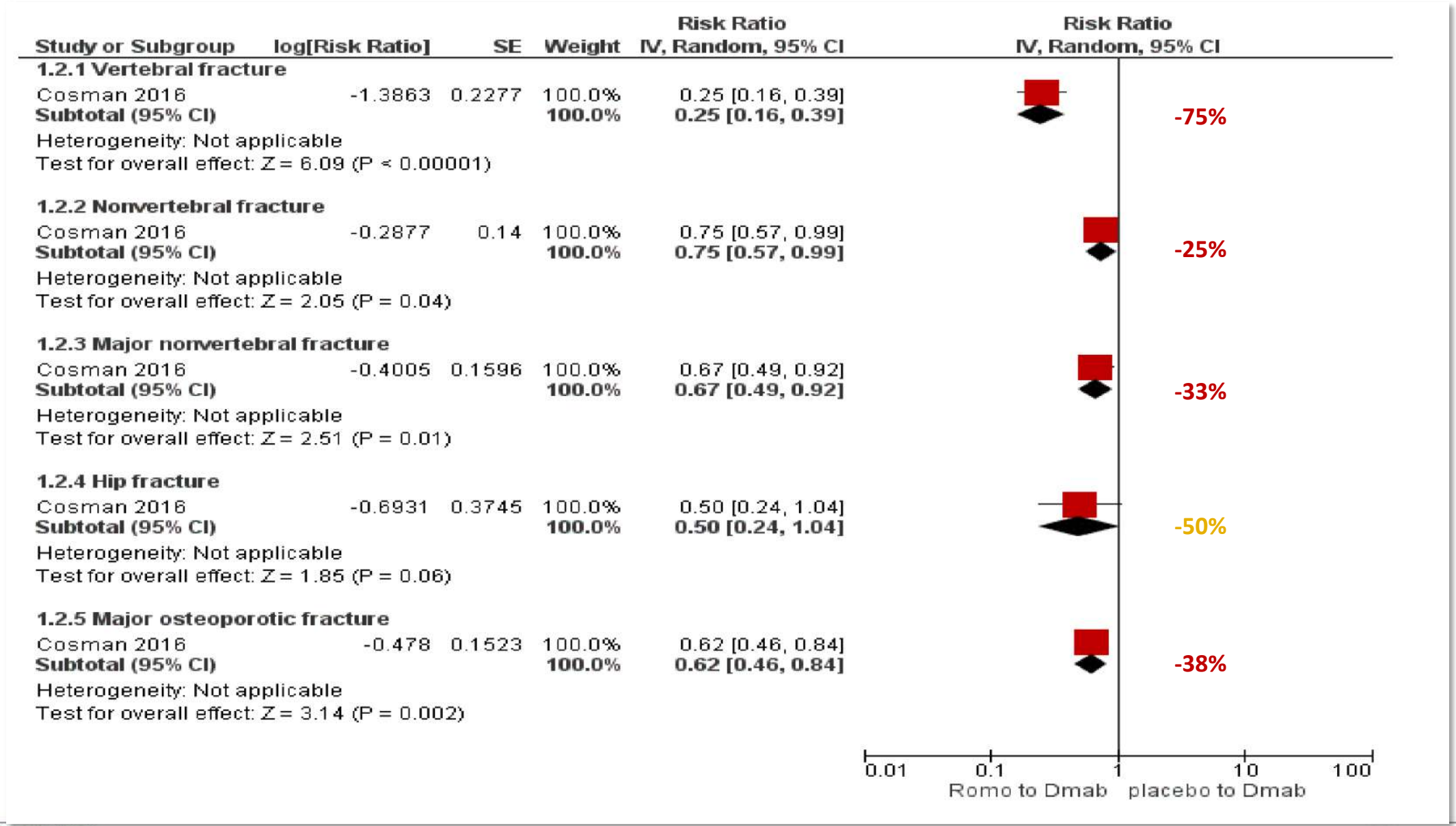
ROMOSOZUMAB → DENOSUMAB

419 PM women (age 55-85 years, T-score between -2.0 and -3.5) and not at high risk for fractures receiving ROMO (24 months) who transitioned to DMAB continued to accrue BMD, whereas BMD returned toward pretreatment levels with placebo

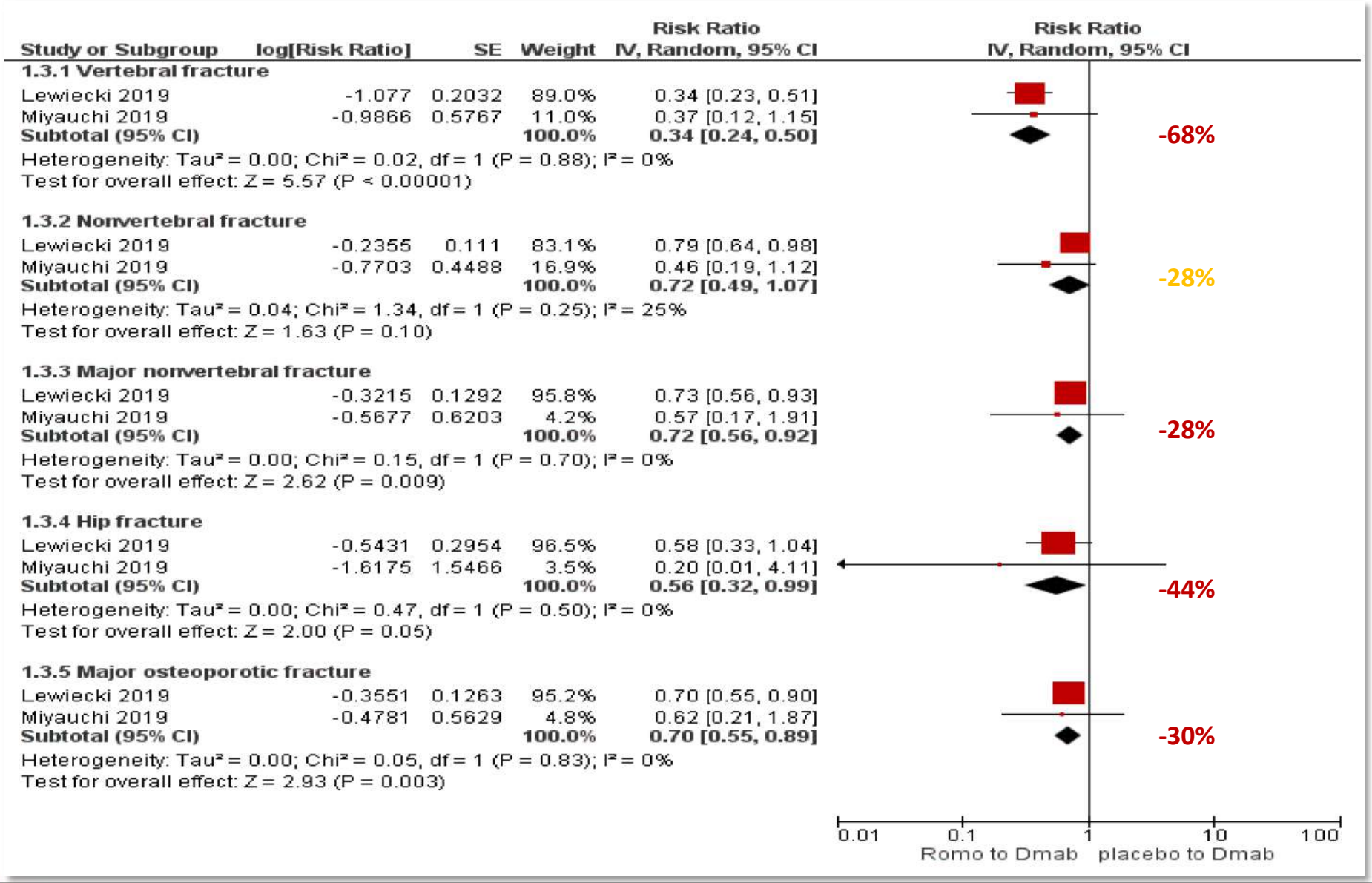


McClung ER et al, J Bone Mineral Res 2018

Riduzione del rischio di frattura in pazienti a 12 mesi da switch da Romosozumab (o placebo) a Denosumab

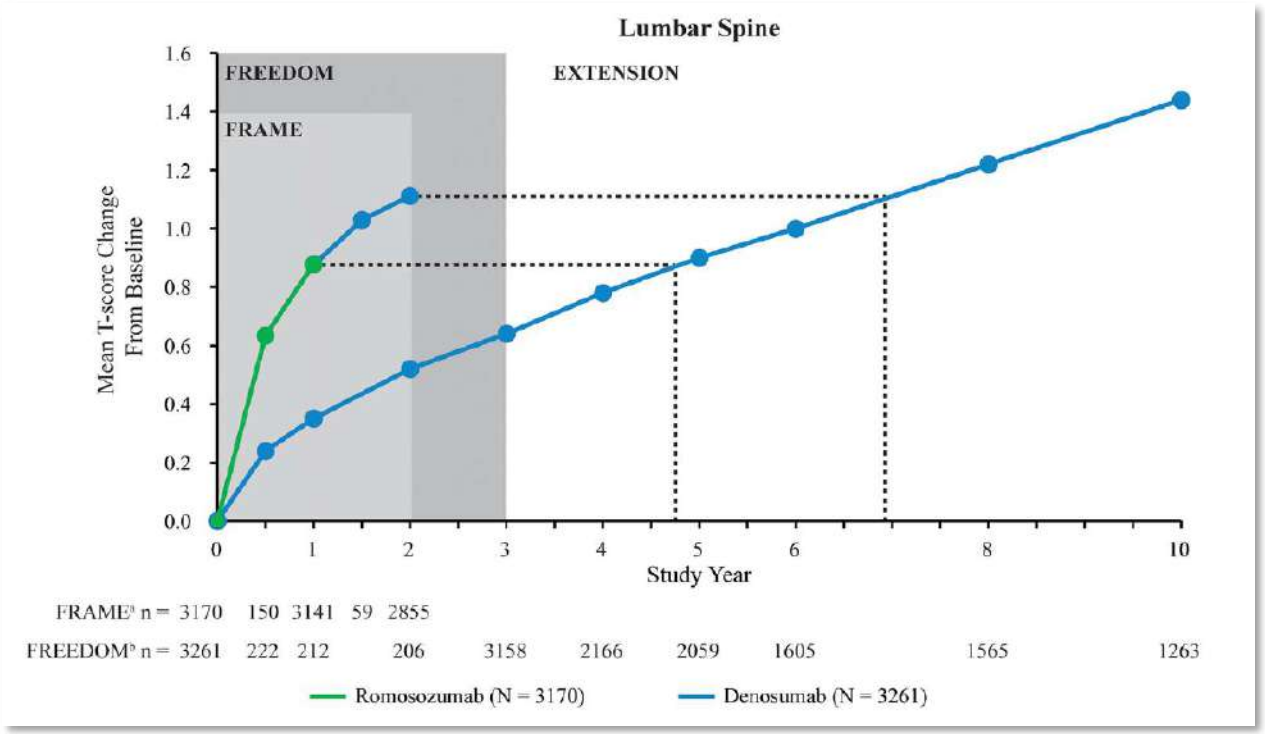


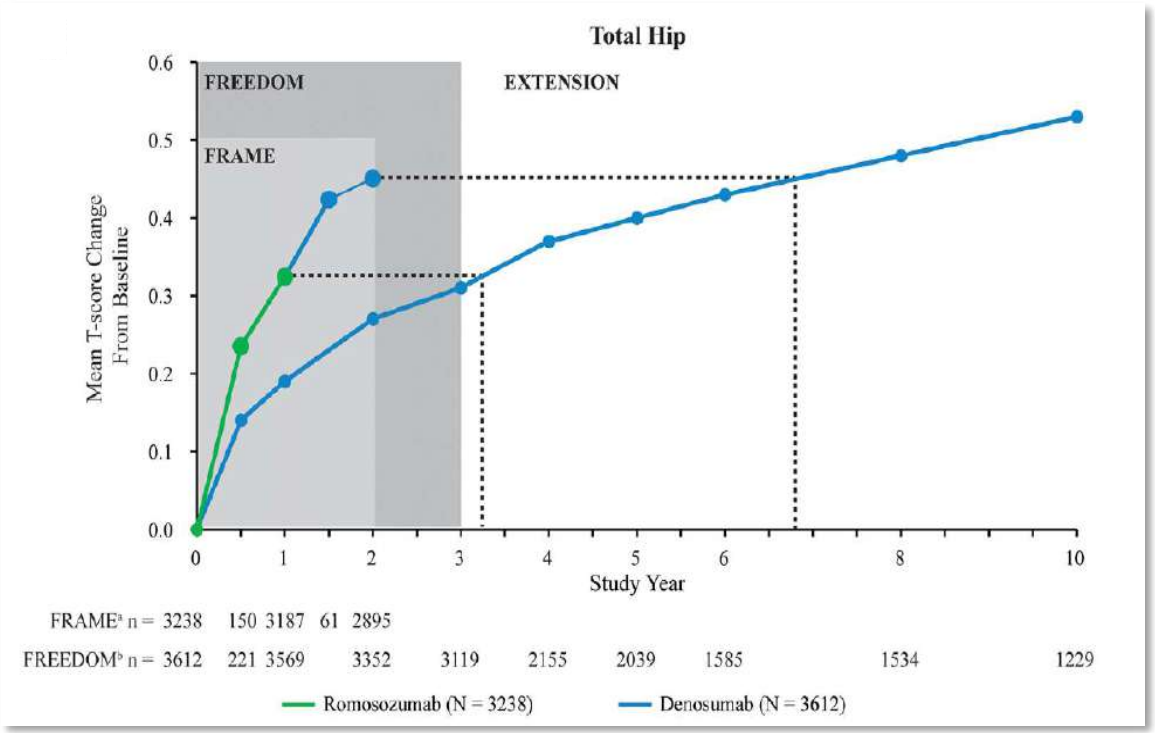
Riduzione del rischio di frattura in pazienti a 24 mesi da switch da Romosozumab (o placebo) a Denosumab



ROMOSOZUMAB → DENOSUMAB

One year Romosozumab followed by one year Denosumab gains approximating the effect of 7 years of continuous Denosumab administration





Cosman F et al, J Bone Mineral Res 2018

qualità delle prove moderata

QUESITO 4

Pag 810-909/1178

Metodologia PICO	
P	*patient* (paziente)
I	*intervention* (intervento)
C	*comparison* (controllo)
O	*outcomes* (risultati)
Quesito di ricerca	

Quale strategia terapeutica, sia a breve che a lungo termine, risulta più efficace nel trattamento del paziente con frattura da fragilità?

Nei pazienti a più elevato o imminente rischio di rifrattura si raccomanda di pianificare un trattamento sequenziale da anabolico ad antiriassorbitivo.

★ ★ ★ ★ ★ Raccomandazione forte a favore dell'intervento

Considerazioni pratiche

Al termine del trattamento anabolico è indispensabile avviare al più presto un trattamento antiriassorbitivo

AGENDA

- Premesse e definizioni
- Paziente naïve ad alto rischio di frattura o di rifrattura
- Paziente in terapia antiriassorbitiva
- Terapia combinata
- Conclusioni

Osteoporos Int (2012) 23:2769–2774
DOI 10.1007/s00198-012-2093-8

POSITION PAPER

Treatment failure in osteoporosis

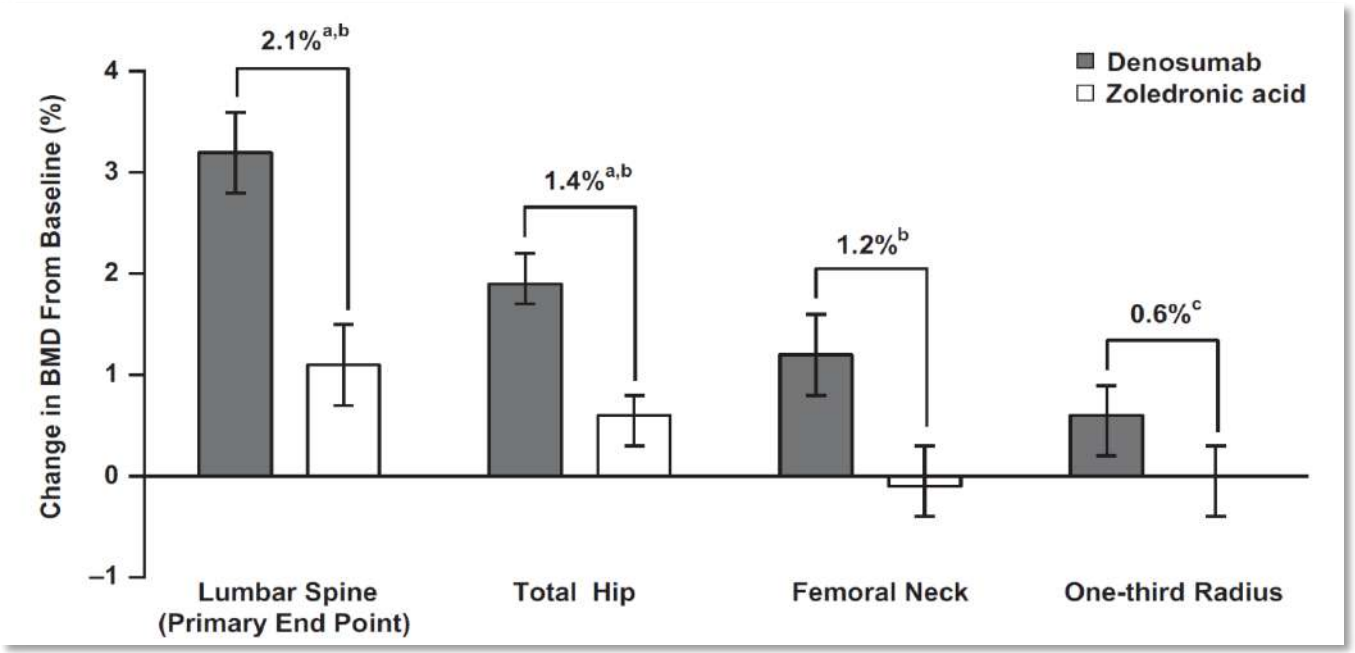
A. Diez-Perez · J. D. Adachi · D. Agnusdei · J. P. Bilezikian · J. E. Compston · S. R. Cummings · R. Eastell · E. F. Eriksen · J. Gonzalez-Macias · U. A. Liberman · D. A. Wahl · E. Seeman · J. A. Kanis · C. Cooper
for the IOF CSA Inadequate Responders Working Group

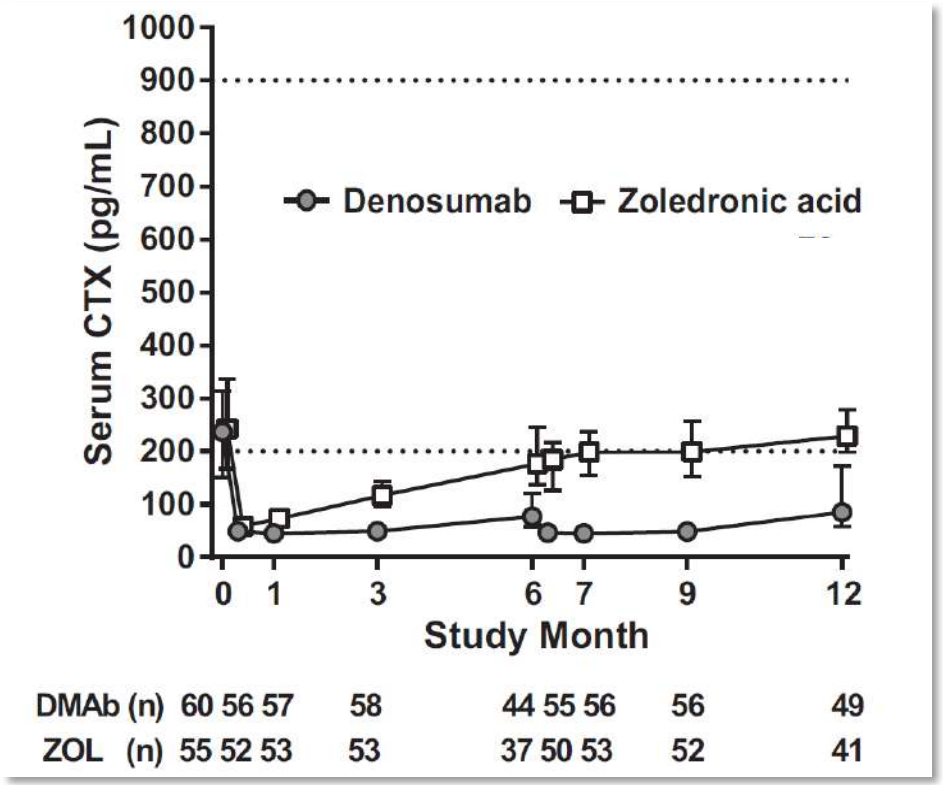
Three general rules, based on the opinion of the working group, are recommended:

(1) A weaker anti-resorptive is reasonably replaced by a more potent drug of the same class.
(2) An oral drug is reasonably replaceable by an injected drug.
(3) A strong anti-resorptive is reasonably replaceable by an anabolic agent.

DENOSUMAB OR ZOLEDRONATE AFTER BISPHOSPHONATES

Design and Setting: multicenter, randomized, double-blind trial.
Participants: A total of 643 postmenopausal women with osteoporosis previously treated with oral bisphosphonates





Miller PD et al, JCEM 2020

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POSITION PAPER

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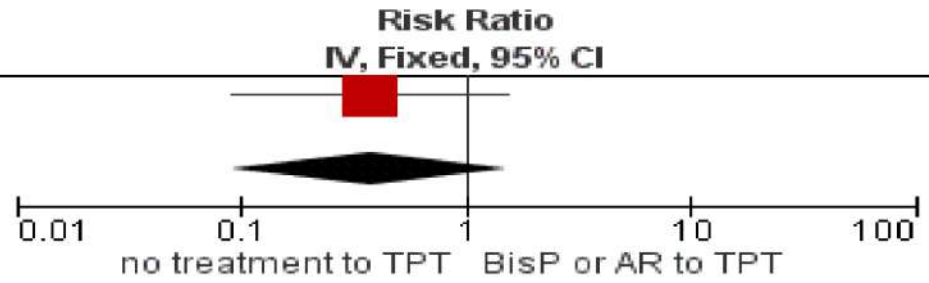
(3) A strong anti-resorptive is reasonably replaceable by an anabolic agent.

Riduzione del Rischio di QUALSIASI frattura a 12 mesi

dallo switch da Anti-riassorbitivo (o placebo) a Teriparatide

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Obermayer-Pietsch 2008	-0.9778	0.7169	100.0%	0.38 [0.09, 1.53]
Total (95% CI)			**100.0%**	**0.38 [0.09, 1.53]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)



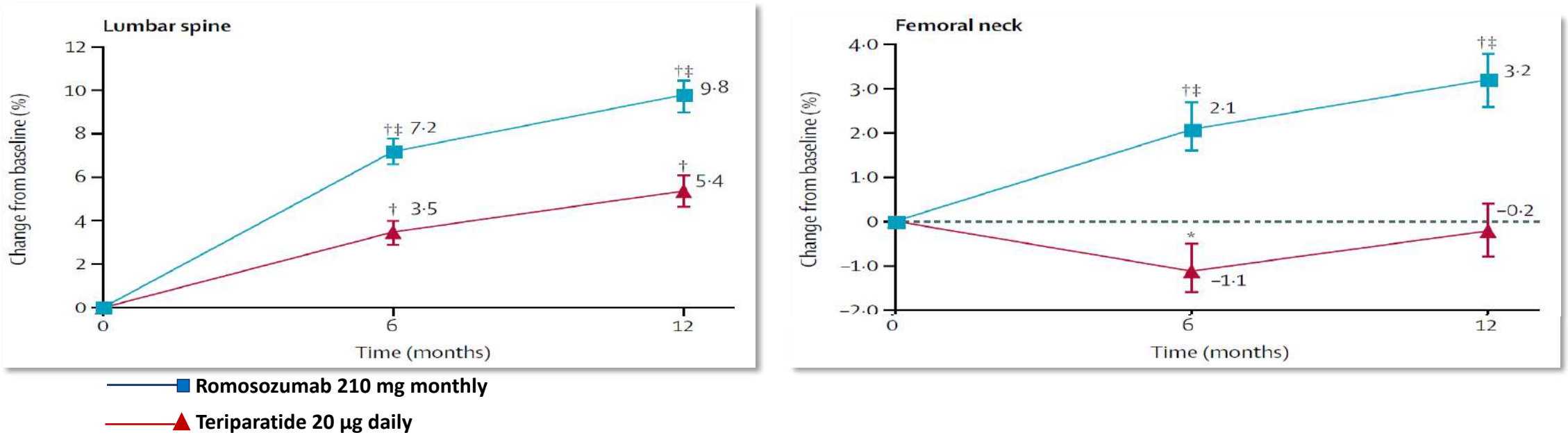
SEQUENTIAL THERAPY AFTER ANTIRESORPTIVES
BISPHOSPHONATES → TERIPARATIDE

- The more potent the bisphosphonate the greater the delay in TPT response.
- The delay in response to PTH is not always seen
- The delay is independent of which BP is used and of BP wash-out
- BMD increases are lower than those achieved when TPT is administered in naïve patients

Ettinger, 2004; Miller, 2008; Obermayer-Pietssch 2008, Lewiecki 2020

SEQUENTIAL THERAPY AFTER ANTIRESORPTIVES
BISPHOSPHONATES → ROMOSOZUMAB OR TERIPARATIDE?

436 women (mean age 71.5 years) who had received bisphosphonate treatment for ≥3 years and Ale in the year prior to screening randomized to Romosozumab or Teriparatide

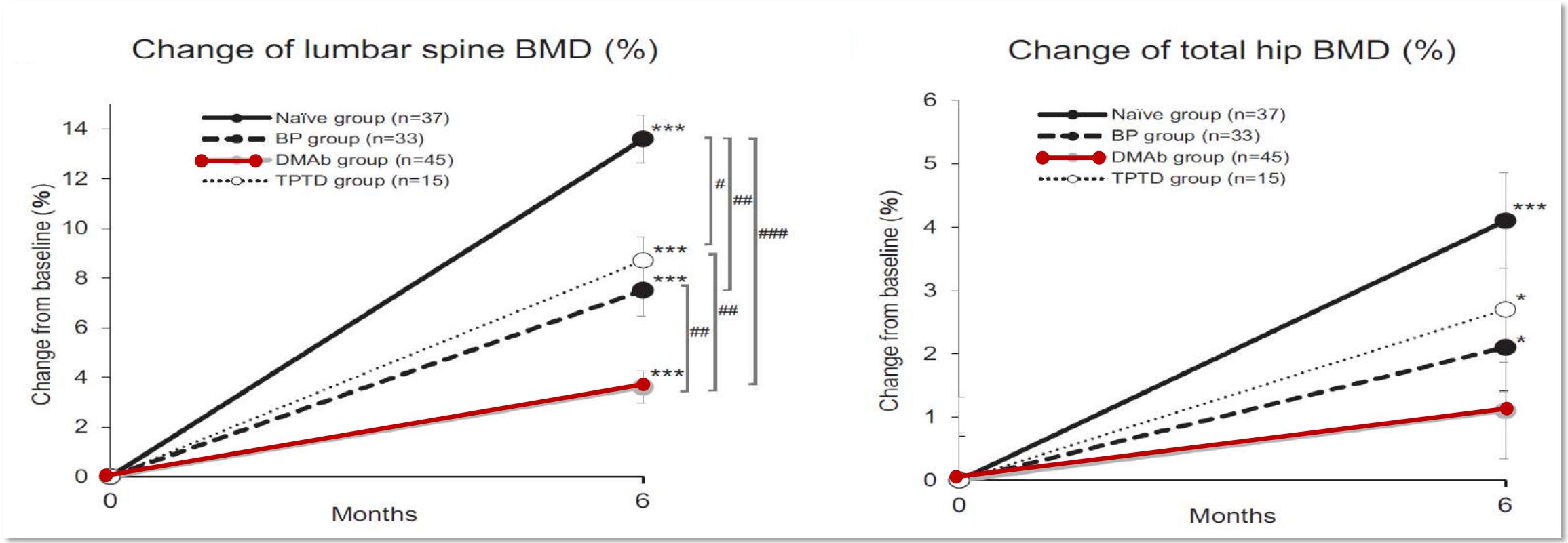


Increases in BMD with romosozumab treatment were significantly greater than with teriparatide at all measured skeletal sites (P<0.0001).

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

PREVIOUS TREATMENTS→ROMOSOZUMAB

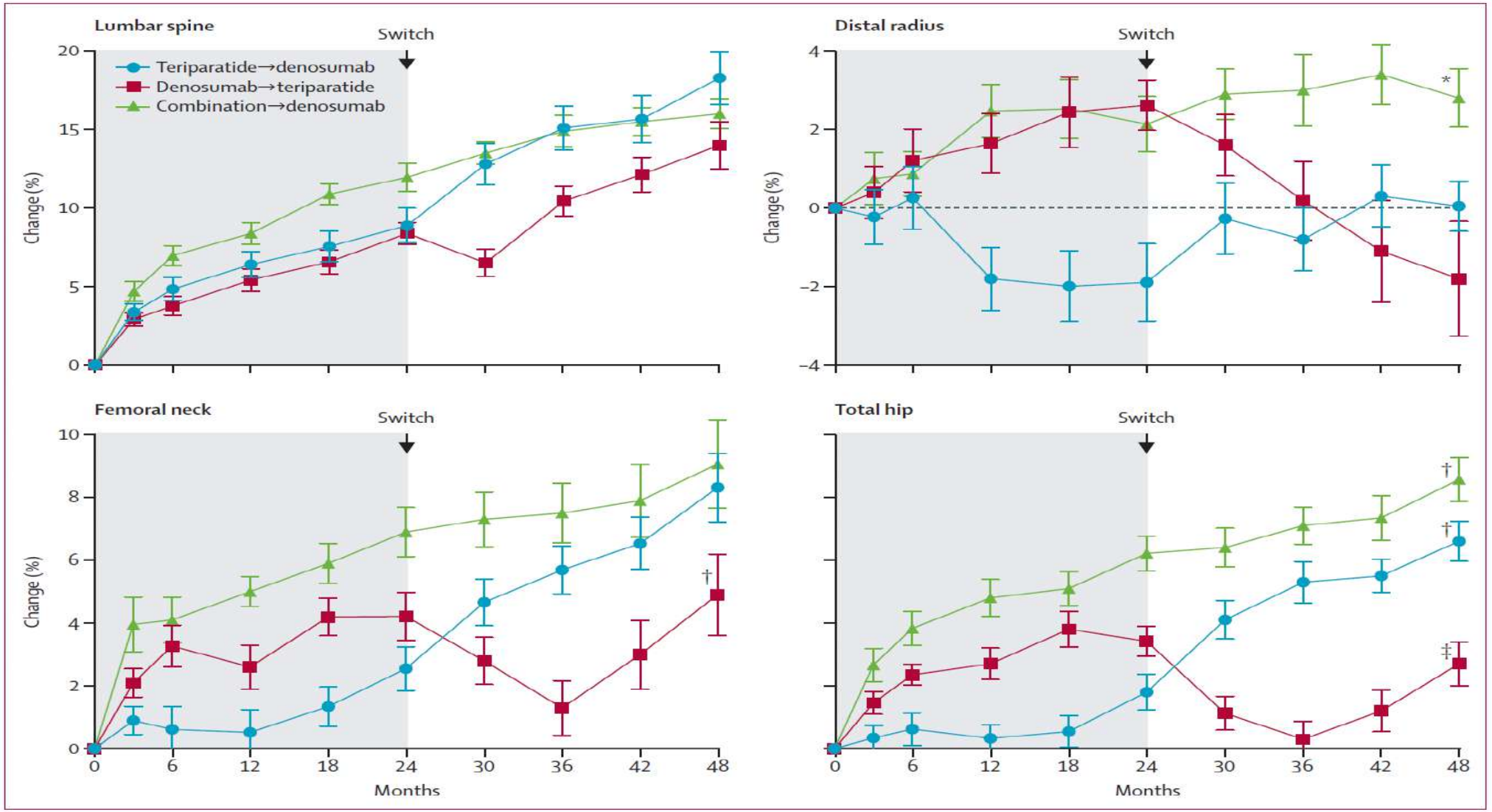
130 treatment-naïve patients (Naïve; n = 37) or patients previously treated with bisphosphonates (BP; n = 33), denosumab (DMAb; n = 45), or teriparatide (TPTD; n = 15) (age, 75.0 years; LS T-scores −3.2 and FN T-scores −2.9) were switched to ROMO based on their physician's decision



Early effects of ROMO on the increase in LS BMD are significantly affected by the difference of prior treatment

Ebina K et al, Bone 2020

SEQUENTIAL THERAPY AFTER ANTIRESORPTIVES
DENOSUMAB → TERIPARATIDE



Leder BZ et al, Lancet 2015

DISCONTINUATION OF DENOSUMAB THERAPY FOR OSTEOPOROSIS: A SYSTEMATIC REVIEW AND POSITION STATEMENT BY ECTS

- **There appears to be an increased risk of multiple vertebral fractures after discontinuation of denosumab.**
- **A re-evaluation should be performed after 5 years of DMAb treatment:**
  - **Patients at high fracture risk should either continue DMab therapy for up to 10 years or be switched to an alternative treatment.**
  - **For patients at low risk, if DMAb is discontinued a bisphosphonate therapy should be considered to reduce or prevent the rebound increase in bone turnover.**
- **However, since the optimal bisphosphonate regimen post-denosumab is currently unknown continuation of denosumab can also be considered until results from ongoing trials become available.**

Tsourdi E et al, Bone 2017

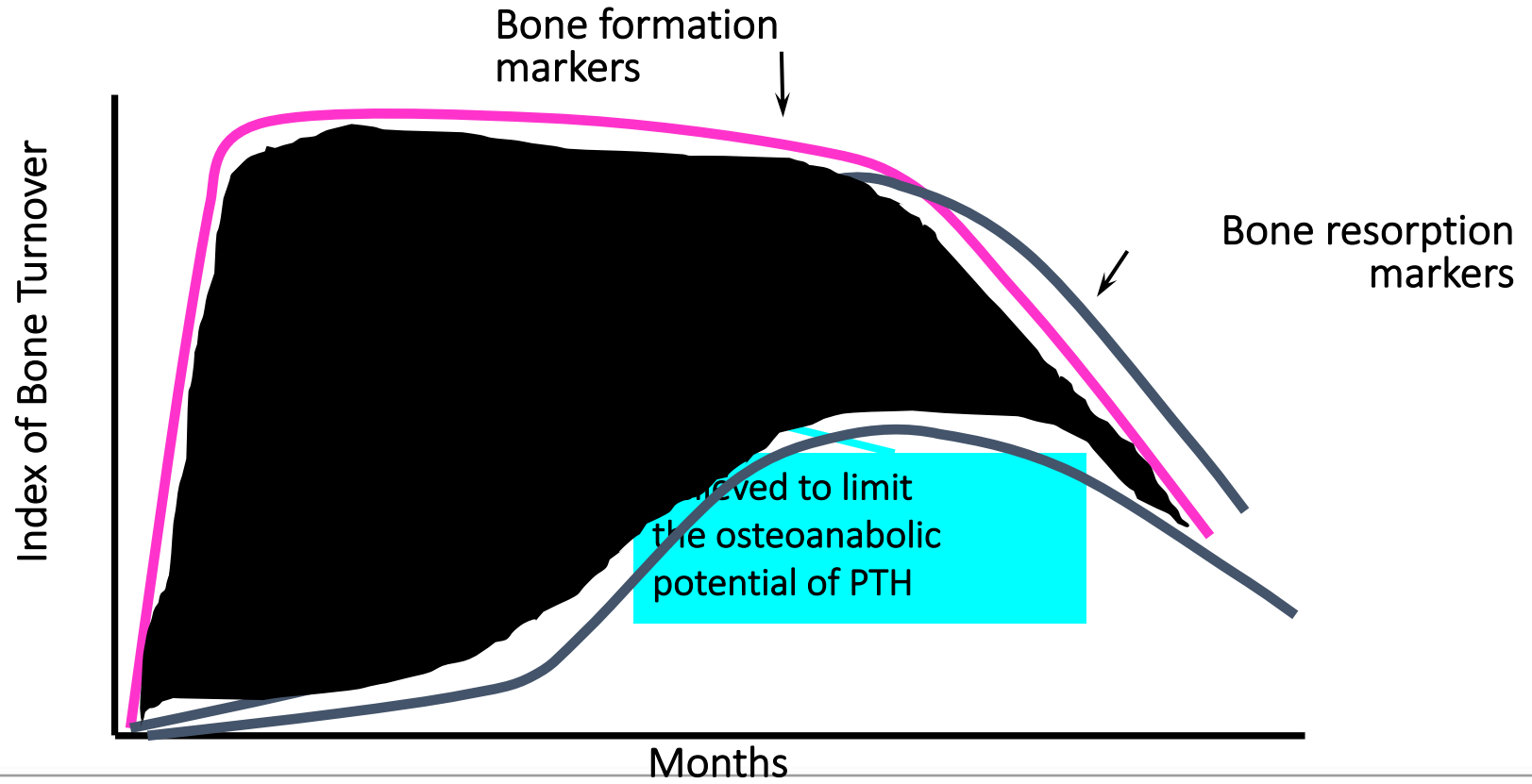
AGENDA

- Premesse e definizioni
- Paziente naïve ad alto rischio di frattura o di rifrattura
- Paziente in terapia antiriassorbitiva
- Terapia combinata
- Conclusioni

COMBINED THERAPY
BISPHOSPHONATES+TERIPARATIDE

Rationale: Two different mechanisms of action

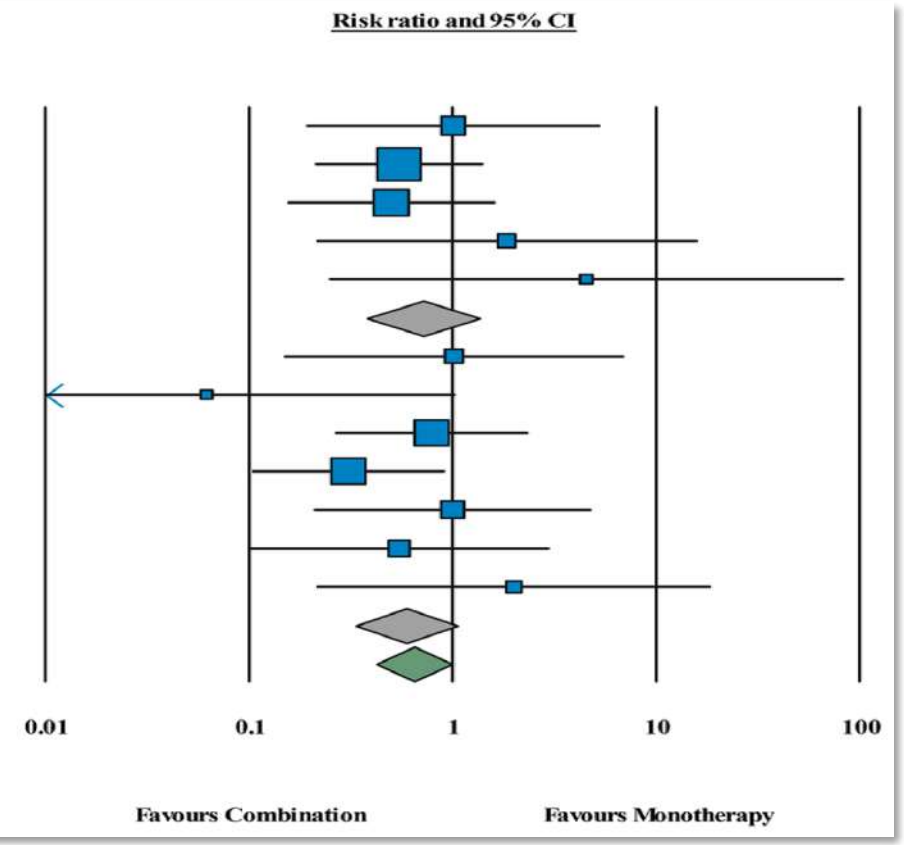
- **It would prevent the increase in the PTH-associated bone resorption that may limit the actions of PTH**
- **It would prevent the excessive reduction of bone apposition potentially associated with the antiresorptive therapy**



COMBINATION THERAPY WITH PARATHYROID HORMONE ANALOGS AND ANTIRESORPTIVE AGENTS FOR OSTEOPOROSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Forest plot fracture events

Group by Comparator	Study name	Events / Total		Statistics for each study			
		Combination	Monotherapy	Risk ratio	Lower limit	Upper limit	p-Value
VS ANA	Black 2003(1)	2 / 59	4 / 119	1.01	0.19	5.35	0.99
VS ANA	Cosman 2009	6 / 99	11 / 99	0.55	0.21	1.42	0.21
VS ANA	Cosman 2011(1)	4 / 137	8 / 137	0.50	0.15	1.62	0.25
VS ANA	Muschitz 2013	4 / 80	1 / 37	1.85	0.21	15.98	0.58
VS ANA	Walker 2013(1)	2 / 10	0 / 9	4.55	0.25	83.70	0.31
VS ANA		18 / 385	24 / 401	0.71	0.38	1.34	0.29
VS ANTI	Black 2003(2)	2 / 59	2 / 60	1.02	0.15	6.98	0.99
VS ANTI	Cosman 2001	0 / 27	7 / 25	0.06	0.00	1.03	0.05
VS ANTI	Cosman 2005	5 / 38	6 / 36	0.79	0.26	2.36	0.67
VS ANTI	Cosman 2011(2)	4 / 137	13 / 137	0.31	0.10	0.92	0.03
VS ANTI	Fogelman 2008	3 / 90	3 / 90	1.00	0.21	4.82	1.00
VS ANTI	Lane 1998	2 / 28	3 / 23	0.55	0.10	3.00	0.49
VS ANTI	Walker 2013(2)	2 / 10	1 / 10	2.00	0.21	18.69	0.54
VS ANTI		18 / 389	35 / 381	0.59	0.33	1.05	0.07
Overall		36 / 774	59 / 782	0.64	0.42	0.98	0.04



ANA, anabolic agents; ANTI, antiresorptive agents

Lou S et al Osteoporos Int 2019

COMBINATION THERAPY OF ANABOLIC AGENTS AND BISPHOSPHONATES ON BONE MINERAL DENSITY IN OSTEOPOROSIS: RCTS

Combination	Comparators	Participants	Osteoporosis status	Trial duration
PTH + ALN	PTH/ALN	238 postm women	T < −2.5 or T < −2 and risk factor	12 mo
TPTD + ZOL	TPTD/ZOL	412 postm women	T < −2.5 or T < −2 and prior fx	1 yr
TPTD + DMAB	TPTD/DMAB	94 postm women	T < −2.5 or T < −2 and risk factor	2 yrs

Combination	Comparators	Trial duration	Δ BMD LS (%)	Δ BMD TH (%)
PTH + ALN	PTH/ALN	12 mo	6.3 vs. 6.1/4.6	0.3 vs. 1.9/NA
TPTD + ZOL	TPTD/ZOL	1 yr	7.5 vs. 7.0/4.4[a]	2.3 vs. 1.1/2.2[a]
TPTD + DMAB	TPTD/DMAB	2 yrs	12.9 vs. 9.5/8.3[a]	6.3 vs. 2.0/3.2[a]

PaTH Study, Black DM et al, NEJM 2003

Cosman F et al, JBMR 2011*

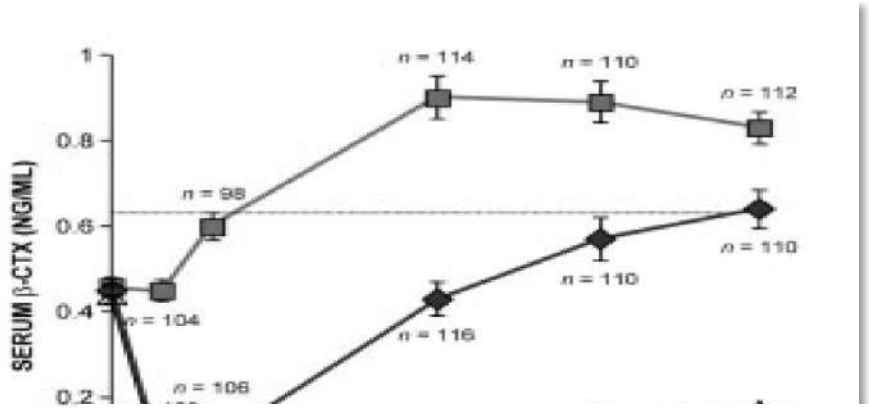
DATA Study, Leder BZ et al, JCEM 2014**

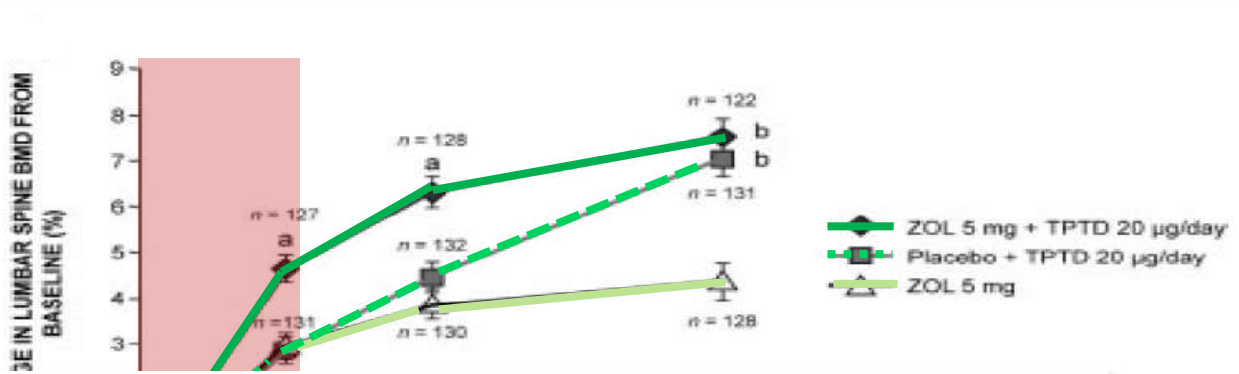
*In the combination group, spine BMD increased more rapidly than with either agent alone ($p < .001$ versus both teriparatide and zoledronic acid at 13 and 26 weeks). Combination therapy increased total-hip BMD more than teriparatide alone at all times (all $p < .01$) and more than zoledronic acid at 13 weeks ($p < .05$), with final 52-week increments of 2.3%, 1.1%, and 2.2% in the combination, teriparatide, and zoledronic acid groups, respectively

**The bone turnover markers in the combination groups were more similar to the markers in the denosumab treated women than to the markers in the teriparatide treated women, suggesting that the combination may blunt at least partly the bone forming effect of teriparatide

Langdahl B, Bone 2020

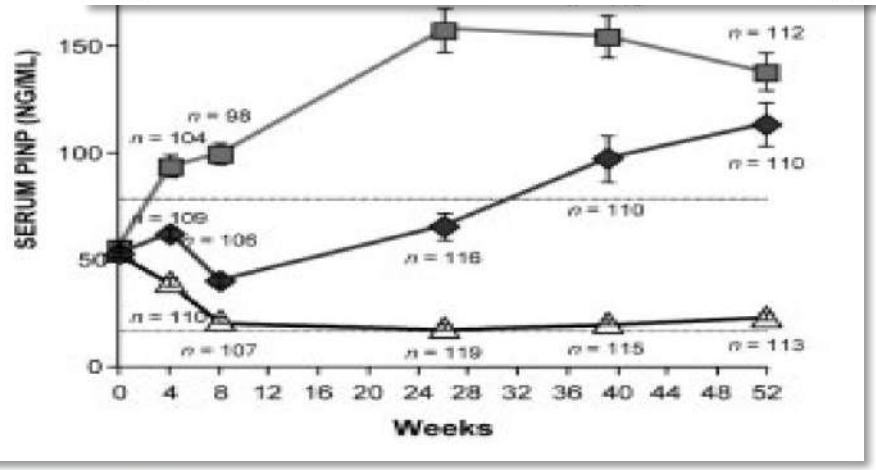
COMBINATION THERAPY: TPT+ZOL

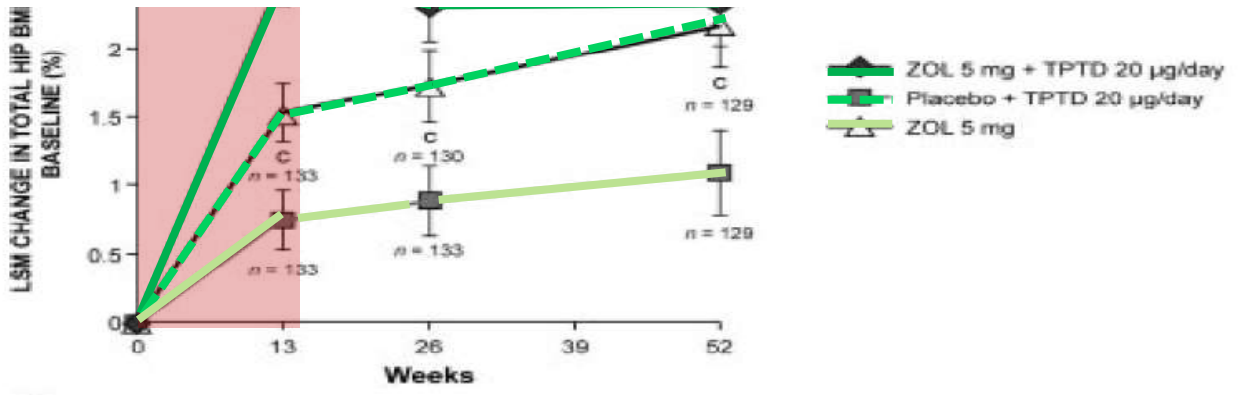




Clinical fracture type	ZOL 5 mg IV + TPTD 20 µg/day (*n* = 137), *n* (%)	Placebo + TPTD 20 µg/day (*n* = 137), *n* (%)	ZOL 5 mg IV (*n* = 137), *n* (%)
Total	4 (2.9)	8 (5.8)[a]	13 (9.5)[b]

[a]not significant versus combination therapy; [B]p=0.04 versus combination therapy





Cosman F et al, JBMR 2011

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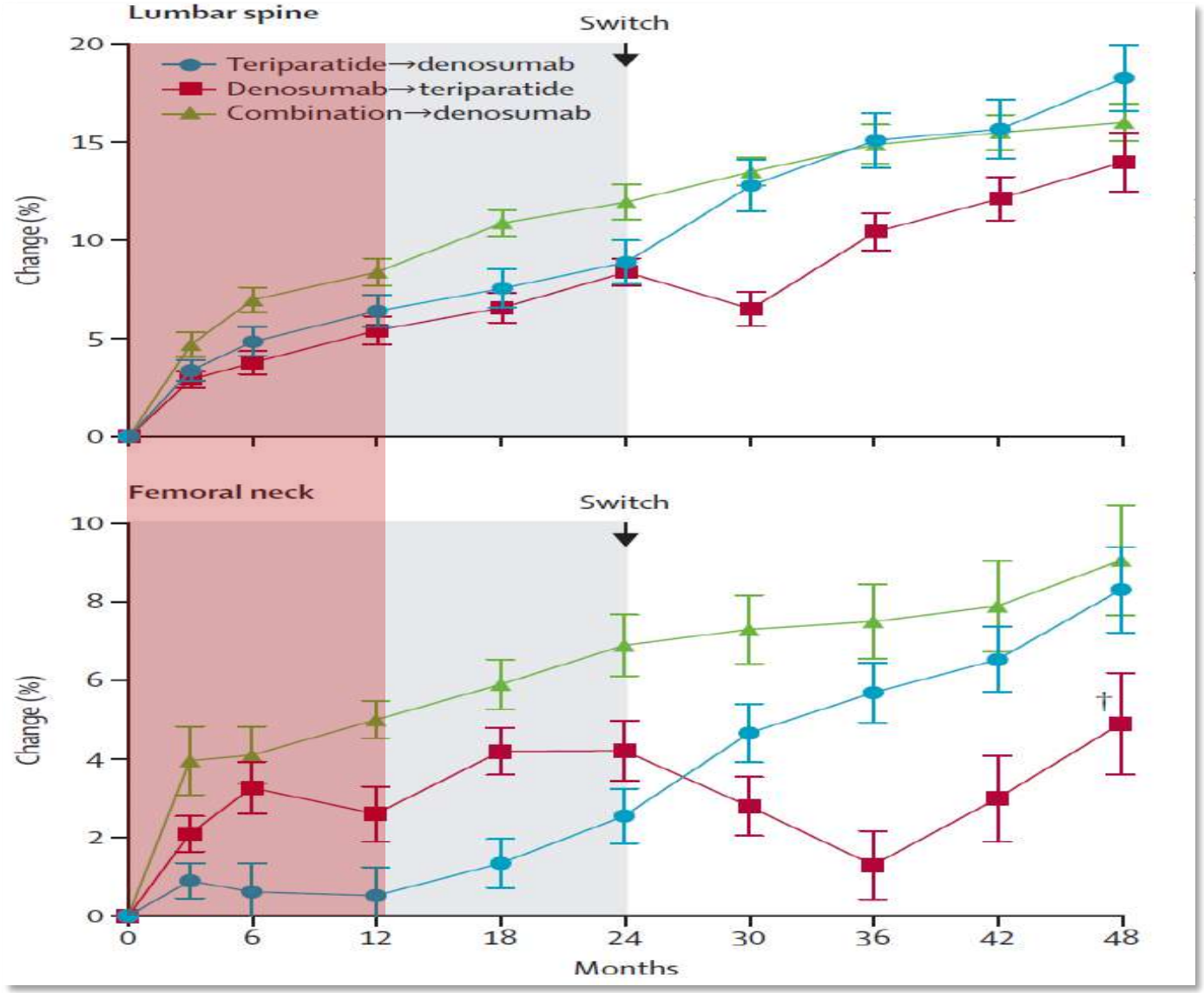
Langdahl B, Bone 2020

COMBINATION THERAPY: TPT+DMAB



Leder BZ et al, Lancet 2015

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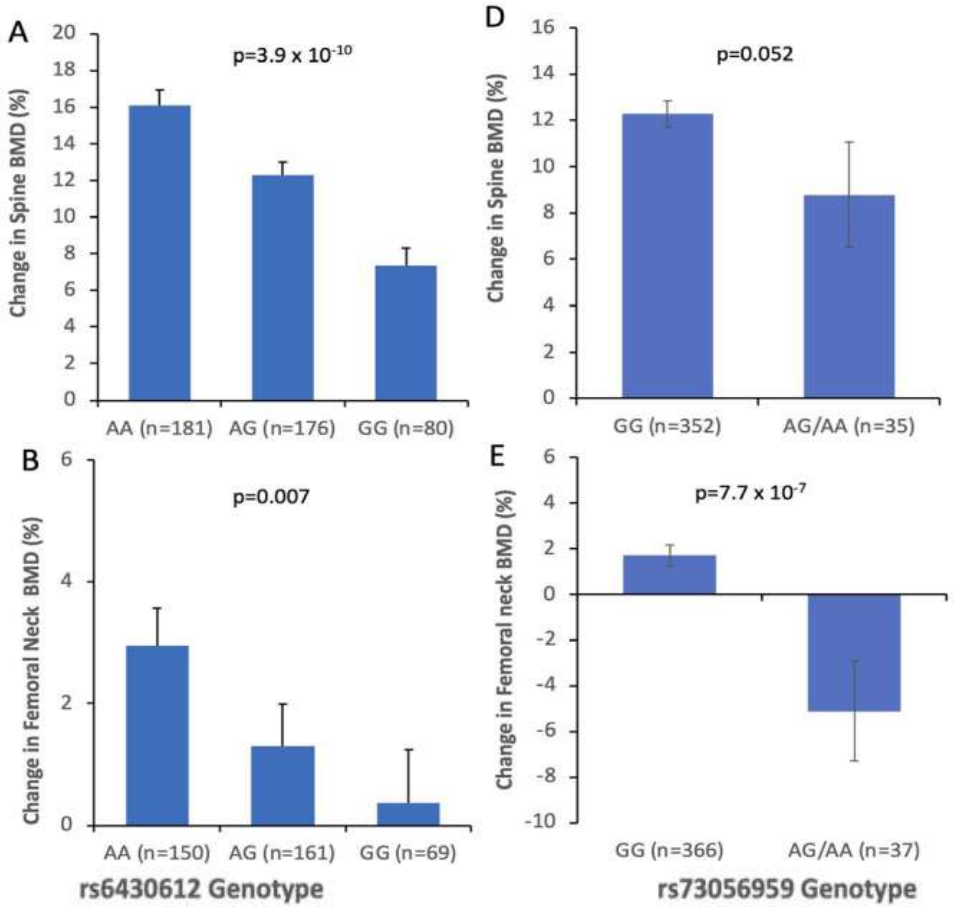
Genome-wide association study identifies genetic variants which predict the response of bone mineral density to teriparatide therapy

Nerea Alonso [1,2] Omar M E Albagha,[1,3] Asim Azfer,[1] Beatriz Larraz-Prieto,[1] Kathryn Berg,[1] Philip L Riches,[1,4] Barbara Ostanek,[5] Tomaz Kocjan,[6,7] Janja Marc,[5] Bente L Langdahl,[8] Stuart H Ralston [1,4]

Ann Rheum Dis 2023;0:1–7. doi:10.1136/ard-2022-223618

GWA in 347 treated with TPT for at least 18 months

Relation between allelic variants and percentage changes in BMD following TPT at spine and femur



A **locus on chromosome 19 tagged by rs73056959** was associated with the response of femoral neck BMD to TPTD (p = 3.5x10-9 , beta = -1.61 [-2.14 - -1.07]

Allelic variation at **rs6430612 on chromosome 2, close to the CXCR4 gene** was associated with the response of spine BMD to TPTD at a genome wide significant level (p=9.2x10-9 beta= -0.35 [-0.47- -0.23]). **The increase in BMD was almost twice as great in AA homozygotes at rs6430612 as compared with GG homozygotes with intermediate values in heterozygotes**. The same variant was also associated with response of femoral neck and total hip BMD (p=0.007).

Genetic factors influence the response to TPTD at the lumbar spine and hip with a magnitude of effect that is clinically relevant

SEQUENTIAL REGIMENS

Anabolic *(or Dual Active)* to Antiresorptive

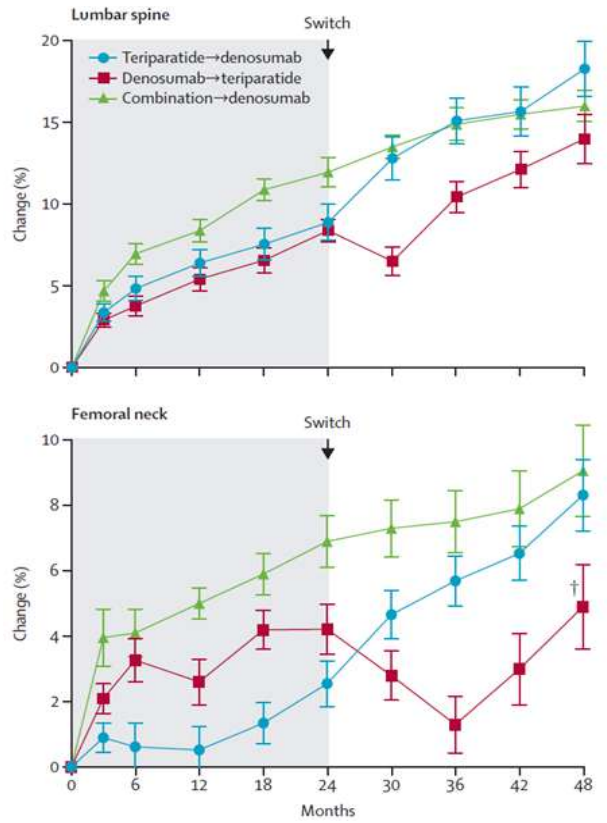
- ✓ Necessary, due to the limited duration of anabolic treatment (1 yr ROMO, 2yr PTH analogs)
- ✓ The best antiresorptive treatment following **TPT and ROMO** is **Dmab** (in terms of BMD gain)

Antiresorptive to Anabolic *(or Dual Active)*

- ✓ Transitioning from **NBPs to PTH analogs** leads to lower BMD gains than in treatment naive pts *(but the increase in BMD is generally higher than continuing the same NBP)*
- ✓ Transitioning from **Dmab to PTH analogs** may be problematic *(better ROMO?)*

Antiresorptive to Antiresorptive

- ✓ Transitioning from **NBPs to Dmab** leads to greater BMD gains vs continuing NBPs *(but the increase in BMD is generally lower than observed in treatment naive pts)*
- ✓ Transitioning from **Dmab to NBPs** is often required to maintain BMD gains and avoid the rebound increase in bone resorption



Leder BZ et al, Lancet 2015

- **Transitioning from one agent to another is common and often necessary in the long-term management.**
- **The use of either Dmab or PTH analogs after NBPs increases BMD, but to a lesser extent than in naive pts.**
- **When possible, preferentially start with bone anabolic drugs followed by antiresorptive treatment**

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THANK YOU

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