Sequenztherapie der Osteoporose
mit Fokus auf
Teriparatid und Denosumab
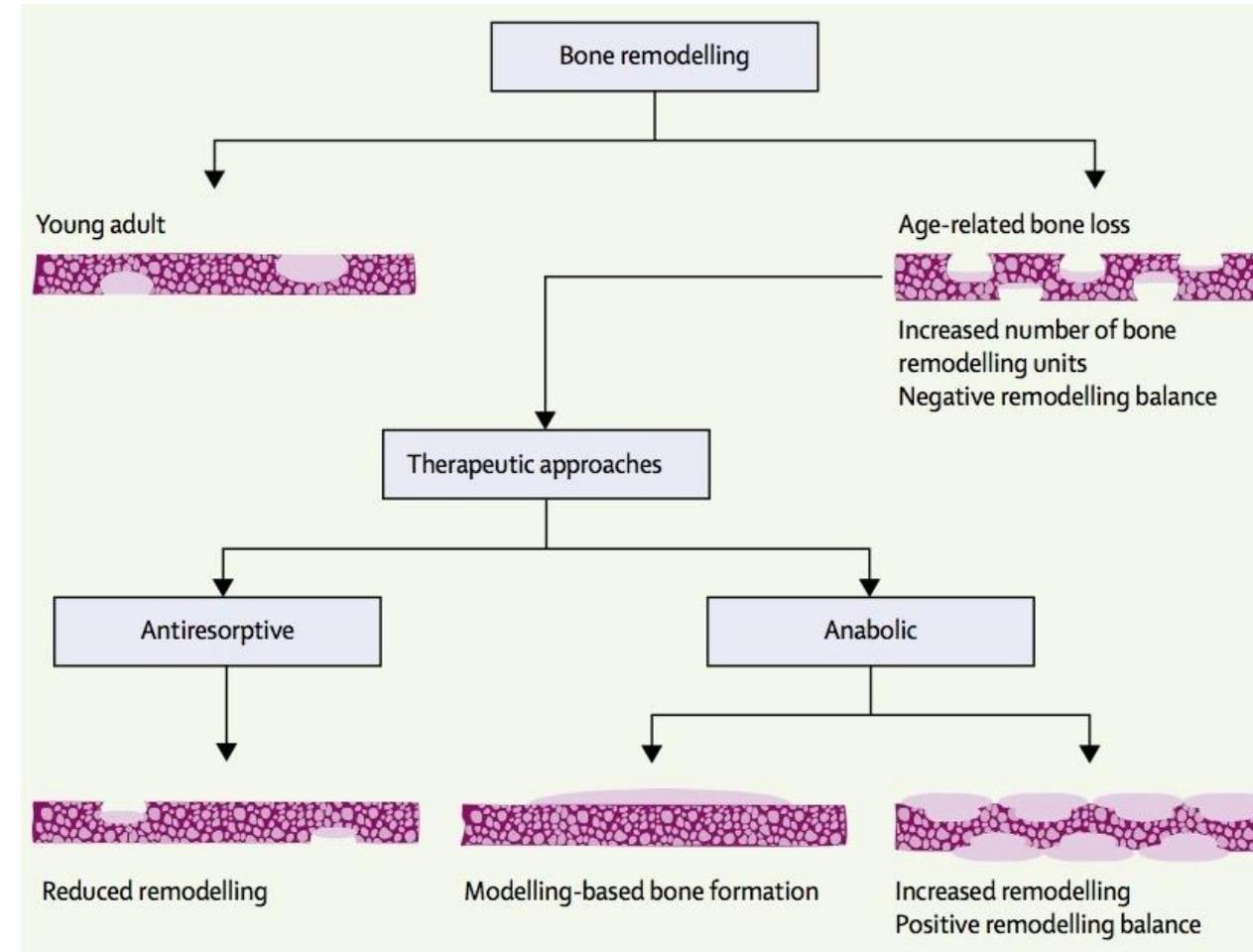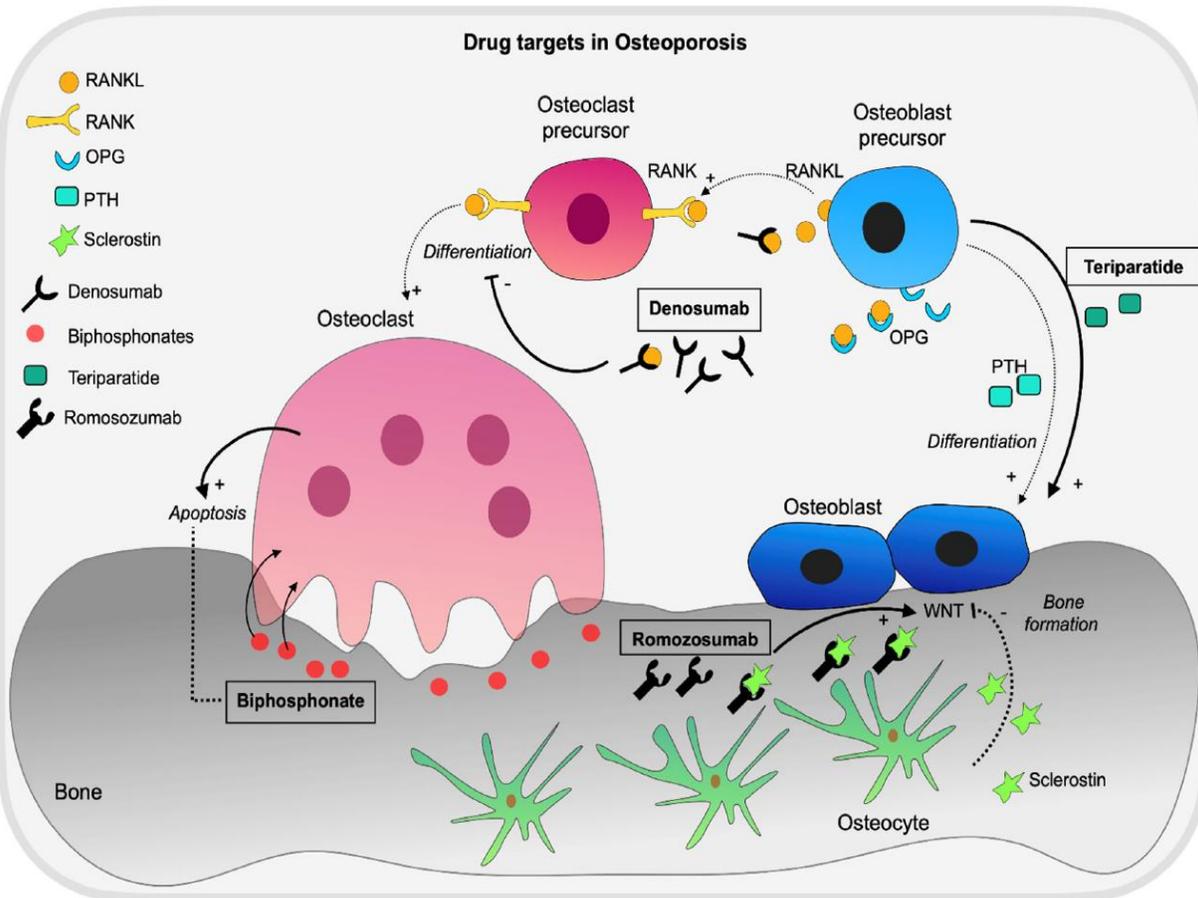
Lothar Seefried
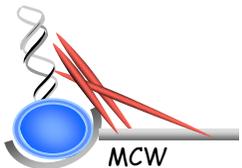
Treating osteoporosis

Drug targets in Osteoporosis

Treatment Objective: Fracture Prevention…

.… by improving Bone Resilience.

Kague et al., Genes 2022, Functional Validation of Osteoporosis Genetic Findings Using Small Fish Models

Compston et al, Osteoporosis, Lancet 2019

How to start?
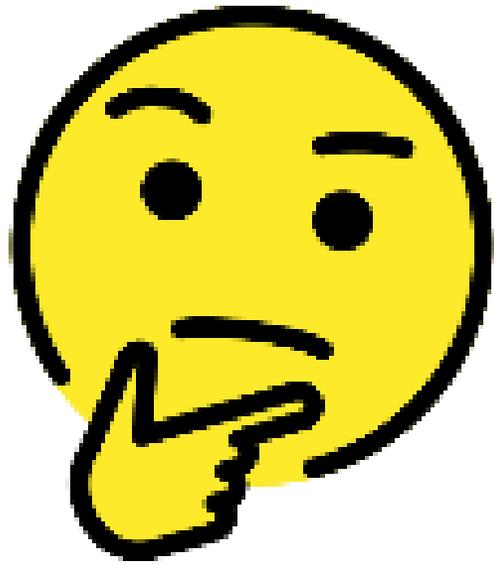
Opening matters…

Management of patients at very high risk of fractures and sequential treatment

Curtis et al., Aging Clin Experimental Res 2022, Management of patients at very high risk of osteoporotic fractures through sequential treatments
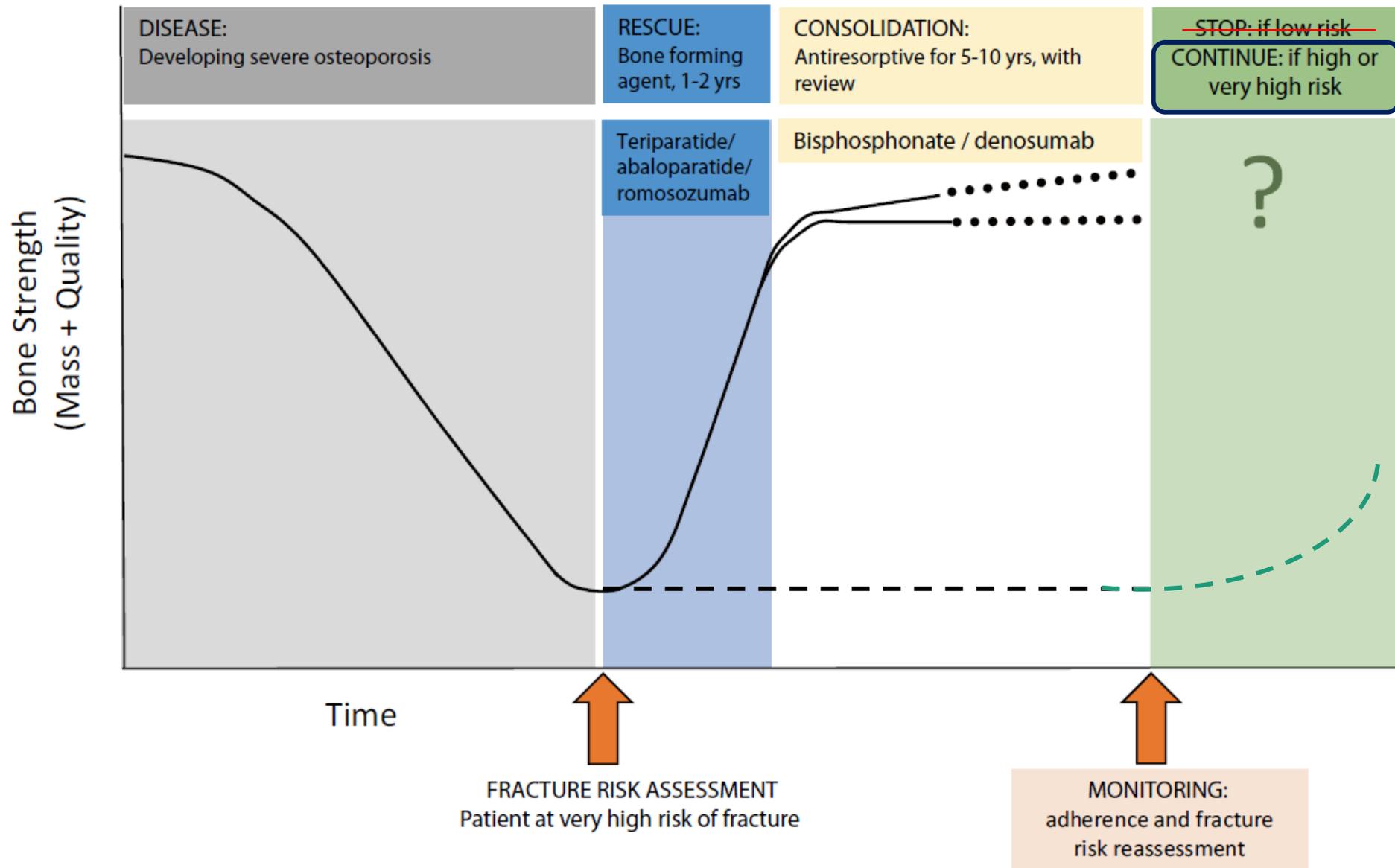
Therapieempfehlungen der DVO-Leilinie 2023

Risiko/3 Jahre	3 bis <5%	5 bis <10%	Ab 10%
Eine spezifische medikamentöse Therapie	**sollte in Betracht gezogen werden (B),** **wenn** starke oder irreversible Risikofaktoren oder ein sehr hohes Risiko einer unmittelbar bevorstehenden Fraktur („*imminent frocture risk*") vorliegen.	**soll empfohlen werden** (A) differenzialtherapeutisch **kann** der Einsatz einer osteoanabol wirksamen Substanz (Teriparatid oder Romosozumab) unter Beachtung des Zulassungsstatus und der Kontraindikationen **erwogen werden (0)**	**soll mit osteoanabol wirksamen Substanzen** (Romosozumab oder Teriparatid) **empfohlen werden (A)** SV: Sondervotum DEGAM: sollte empfohlen werden **(B)**

.... bei der Entscheidung für oder gegen eine osteoanabole Therapie sollen das Risiko für eine imminente Fraktur... Gebrechlichkeit, Komorbiditäten, Allgemeinzustand und Lebenserwartung berücksichtigt werden....

Imminente Frakturrisikoerhöhung bei
- ✓ Hüftfraktur im letzten Jahr
- ✓ Wirbelkörperfraktur(en) im letzten Jahr
- ✓ 2 oder mehr Stürze im letzten Jahr
- ✓ Neu begonnene GC-Therapie >5 mg/Tag über >3 Monate

Which treatment to prevent an imminent fracture

Minimal duration of treatment before obtaining a significant risk reduction for a) vertebral fractures; b) hip fractures and c) non-vertebral fractures according to the included studies. (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, NS – not significant, NA - not analysed).

In patients at high risk of imminent fracture, starting with a potent antiresorptive or an anabolic agent seems most appropriate to promptly reduce the fracture risk.

a) For vertebral fractures

	Before 12 months	After 12 months
Oral bisphosphonates (Black et al., 2000; Chesnut et al., 2004; Harris et al., 1999; Liberman et al., 1995): Alendronate Risedronate Ibandronate	NS	***
Zoledronate		***
Denosumab (...nen et al., 2011)	***	***
Teriparatide (Body et al., 2020; Lindsay et al., 2009)	**	**
Abaloparatide (Cosman et al., 2017; Miller et al., 2016a)	NA	***
Romosozumab (Cosman et al., 2016; Saag et al., 2017)	**	**

b) For non-vertebral fractures

	Before 12 months	After 12 months
Oral bisphosphonates (Black et al., 2000; Harris et al., 1999; Liberman et al., 1995): Alendronate Risedronate	NS	* *
Zoledronate (Dennis et al., 2007)	***	***
Denosumab (Steven et al., 2007)	*	*
Teriparatide (Body et al., 2020)	**	**
Abaloparatide (Cosman et al., 2017; Miller et al., 2016a)	*	*
Romosozumab (Cosman et al., 2016; Saag et al., 2017)		

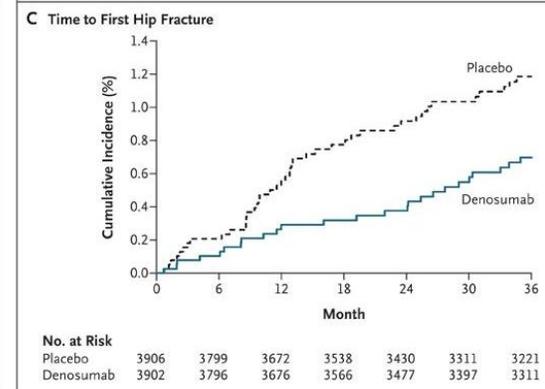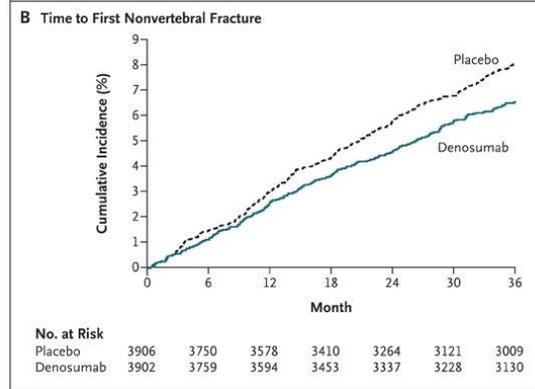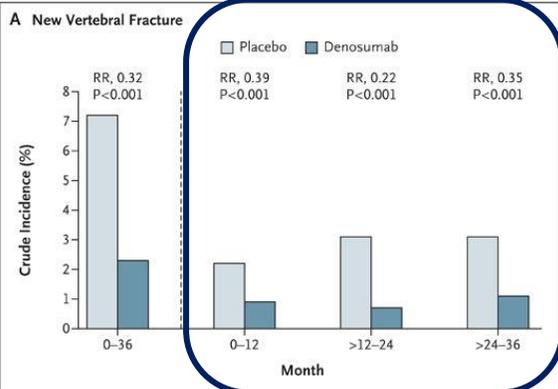|	Before 12 months	After 12 months
Oral bisphosphonates (Black et al., 2000; Liberman et al., 1995): Alendronate	NS	*
Zoledronate (Dennis et al., 2007)	***	***
Denosumab (Steven et al., 2007; Boonen et al., 2011)	*	*
Teriparatide (Eriksen et al., 2014; Lindsay et al., 2009)	*	*
Romosozumab (Saag et al., 2017)	NS	*

Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis

Table 2. Effect of Denosumab on the Risk of Fracture at 36 Months.*

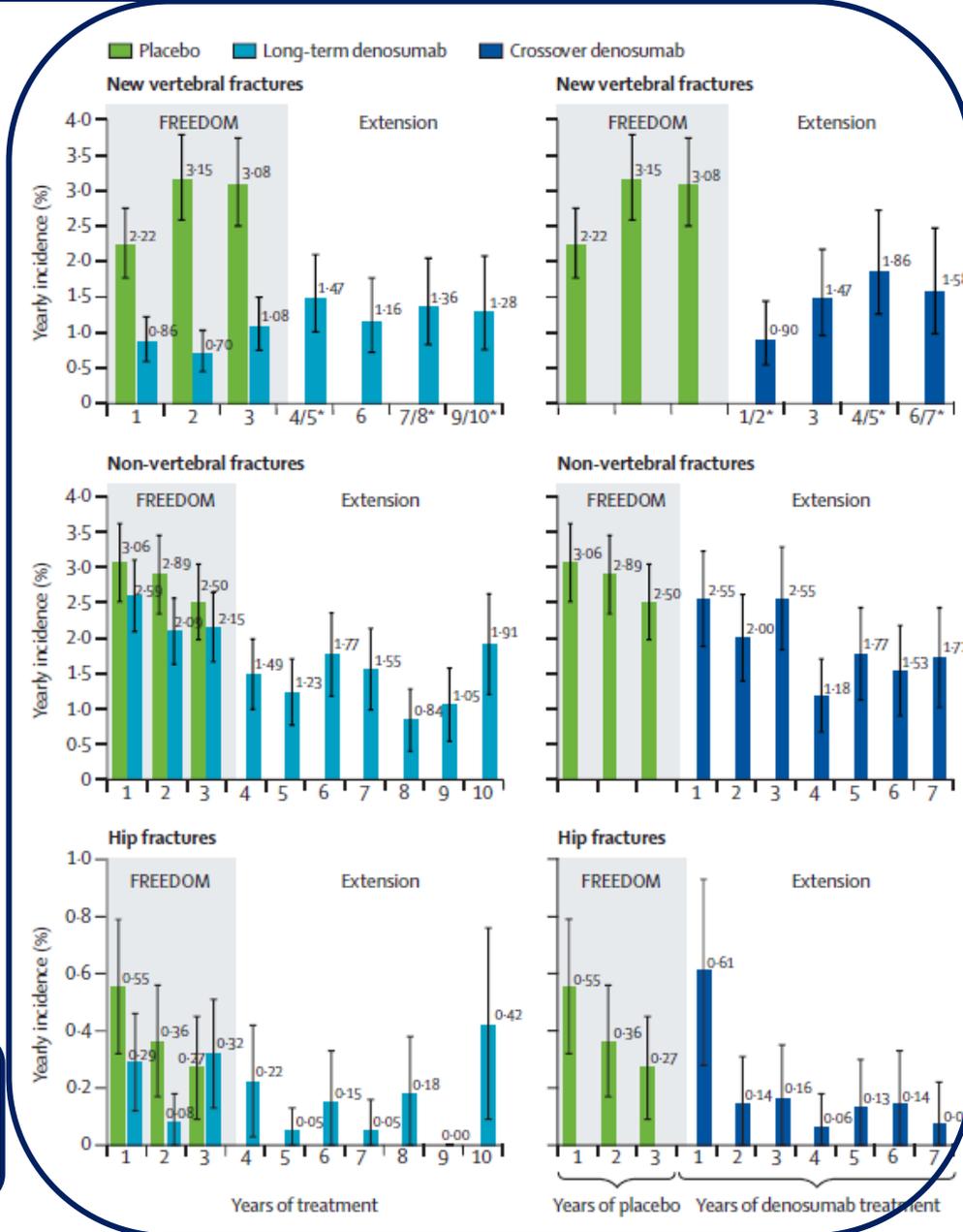| Outcome	Denosumab	Placebo	Difference in Rates (95% CI)	Relative Risk or Hazard Ratio (95% CI)†	P Value
	no. (%)				
Primary end point					
New vertebral fracture	86 (2.3)	264 (7.2)	4.8 (3.9 to 5.8)	0.32 (0.26 to 0.41)	<0.001
Secondary end points					
Nonvertebral fracture‡	238 (6.5)	293 (8.0)	1.5 (0.3 to 2.7)	0.80 (0.67 to 0.95)	0.01
Hip fracture	26 (0.7)	43 (1.2)	0.3 (−0.1 to 0.7)	0.60 (0.37 to 0.97)	0.04
Other fracture end points					
New clinical vertebral fracture	29 (0.8)	92 (2.6)	1.7 (1.1 to 2.3)	0.31 (0.20 to 0.47)	<0.001
Multiple (≥2) new vertebral fractures	23 (0.6)	59 (1.6)	1.0 (0.5 to 1.5)	0.39 (0.24 to 0.63)	<0.001

Table 3. Adverse Events.*

Event	Denosumab (N=3886)	Placebo (N=3876)	P Value†
	no. (%)		
All	3605 (92.8)	3607 (93.1)	0.91
Serious	1004 (25.8)	972 (25.1)	0.61
Fatal	70 (1.8)	90 (2.3)	0.08
Leading to study discontinuation	93 (2.4)	81 (2.1)	0.39
Leading to discontinuation of a study drug	192 (4.9)	202 (5.2)	0.55
Adverse events			
Infection	2055 (52.9)	2108 (54.4)	0.17
Cancer	187 (4.8)	166 (4.3)	0.31
Hypocalcemia	0	3 (0.1)	0.08
Osteonecrosis of the jaw	0	0	NA
Serious adverse events			
Cancer	144 (3.7)	125 (3.2)	0.28
Infection	159 (4.1)	133 (3.4)	0.14
Cardiovascular event	186 (4.8)	178 (4.6)	0.74
Stroke	56 (1.4)	54 (1.4)	0.89
Coronary heart disease	47 (1.2)	39 (1.0)	0.41
Peripheral vascular disease	31 (0.8)	30 (0.8)	0.93
Atrial fibrillation	29 (0.7)	29 (0.7)	0.98
Adverse events occurring in at least 2% of subjects‡			
Eczema	118 (3.0)	65 (1.7)	<0.001
Falling§	175 (4.5)	219 (5.7)	0.02
Flatulence	84 (2.2)	53 (1.4)	0.008
Serious adverse events occurring in at least 0.1% of subjects¶			
Cellulitis (including erysipelas)	12 (0.3)	1 (<0.1)	0.002
Concussion	1 (<0.1)	11 (0.3)	0.004

A New Vertebral Fracture — RR, 0.32 P<0.001; RR, 0.39 P<0.001; RR, 0.22 P<0.001; RR, 0.35 P<0.001

B Time to First Nonvertebral Fracture

C Time to First Hip Fracture

Cummings et al., NEJM 2009, Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis

10 years of Denosumab treatment in postmenopausal women, FREEDOM Trial, Extension

	Long-term denosumab (n=2343)		Crossover denosumab (n=2207)	
	FREEDOM baseline	Extension baseline	FREEDOM baseline	Extension baseline
Age (years)	71·9 (5·0)	74·9 (5·0)	71·8 (5·1)	74·8 (5·1)
Age groups, n (%)				
≥65 years	2209 (94%)	2294 (98%)	2067 (94%)	2149 (97%)
≥75 years	662 (28%)	1258 (54%)	624 (28%)	1151 (52%)
Years since menopause	23·7 (7·3)	26·7 (7·3)	23·7 (7·4)	26·7 (7·4)
Prevalent vertebral fractures, n (%)	559 (24%)	573 (24%)	485 (22%)	551 (25%)
Lumbar spine BMD T-score	−2·83 (0·67)	−2·14 (0·80)	−2·84 (0·68)	−2·81 (0·75)
Total hip BMD T-score	−1·85 (0·79)	−1·50 (0·79)	−1·85 (0·79)	−1·93 (0·80)
CTx (ng/mL), median (IQR)*	0·505 (0·357–0·700)	0·182 (0·086–0·555)	0·555 (0·420–0·661)	0·568 (0·426–0·728)
P1NP (µg/L), median (IQR)*	46·17 (31·45–56·79)	17·25 (10·31–25·98)	55·81 (42·52–65·60)	48·80 (35·04–67·58)

	Placebo			Combined denosumab groups									
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Number of participants	3883	3687	3454	6085	5787	5452	4099	3890	3582	3261	1743	1585	1451
All adverse events	189·5	156·3	132·8	165·3	137·8	124·6	129·9	110·9	110·0	108·4	107·6	109·5	95·9
Infections	38·6	33·9	31·7	35·1	30·3	29·5	29·1	26·0	27·2	26·5	27·0	27·0	23·0
Malignancies	1·8	1·6	1·5	1·9	1·5	2·2	2·3	2·4	2·2	2·7	1·7	2·6	1·6
Eczema	0·8	0·5	0·6	1·4	1·1	1·0	1·1	1·2	0·9	0·7	0·8	0·9	1·3
Hypocalcaemia	<0·1	0	<0·1	<0·1	<0·1	0	<0·1	0·1	0	<0·1	<0·1	0	0·1
Pancreatitis	<0·1	<0·1	0	<0·1	<0·1	<0·1	0	<0·1	0·1	<0·1	0·1	<0·1	0
Serious adverse events	11·7	11·9	10·8	12·0	11·5	12·3	11·5	12·9	12·6	14·4	11·5	13·1	12·3
Infections	1·1	1·4	1·4	1·5	1·6	1·4	1·4	1·3	1·9	2·3	1·2	1·5	2·6
Cellulitis or erysipelas	0	0	<0·1	<0·1	<0·1	0·2	<0·1	<0·1	0·1	<0·1	0·2	<0·1	0·1
Fatal adverse events	0·8	0·8	1·0	0·7	0·6	0·7	0·5	0·8	0·9	1·5	0·7	1·0	0·9
Osteonecrosis of the jaw	0	0	0	0	<0·1	0	<0·1	0	0·2	<0·1	0	<0·1	<0·1
Atypical femoral fracture	0	0	0	0	0	<0·1	0	0	0	<0·1	0	0	0

Bone, Lancet Diabetes Endocrinol 2017, 10 years of denosumab treatment in postmenopausal women, FREEDOM Trial, Extension

Comparative Effectiveness of Denosumab versus Bisphosphonates among Treatment-Experienced Postmenopausal Women with Osteoporosis in the U.S. Medicare Program

Retrospective cohort study, females ≥ 66 years with **prior history of treatment with an oral BP, who newly initiated Dmab (n~108,000), a different oral BP (alendronate, ibandronate, or risedronate; n=100,649), alendronate (Aln; n=53,165), or zoledronic acid (ZA; n=35,100)** between Jan 1, 2012 to Dec 31, 2018

Followed from treatment initiation (index date) until the first instance of
- fracture outcome
- treatment discontinuation
- Treatment switch
- Medicare disenrollment
- Death
- End of available data (Dec 31, 2019)
- 5 years post-index date

	Alendronat (n = 53.165) RR (95% KI)	Orale Bisphosphonate (n = 100.649) RR (95% KI)	Zoledronsäure (n = 35.100) RR (95% KI)
MOFs			
1 Jahr	0,91 (0,83, 0,99)	0,90 (0,84, 0,96)	0,91 (0,83, 0,98)
2 Jahre	0,85 (0,77, 0,93)	0,83 (0,78, 0,89)	0,88 (0,81, 0,95)
3 Jahre	0,81 (0,73, 0,88)	0,78 (0,72, 0,84)	0,85 (0,78, 0,93)
5 Jahre	0,75 (0,67, 0,82)	0,69 (0,61, 0,76)	0,69 (0,57, 0,82)
Hüfte			
1 Jahr	0,86 (0,74, 0,99)	0,90 (0,79, 1,01)	0,86 (0,74, 0,98)
2 Jahre	0,87 (0,74, 1,01)	0,87 (0,77, 0,97)	0,89 (0,77, 1,02)
3 Jahre	0,86 (0,72, 0,99)	0,78 (0,69, 0,88)	0,90 (0,77, 1,03)
5 Jahre	0,63 (0,51, 0,75)	0,55 (0,42, 0,68)	0,62 (0,32, 0,91)
Nichtvertebrale			
1 Jahr	0,91 (0,82, 1,00)	0,93 (0,86, 1,00)	0,94 (0,86, 1,02)
2 Jahre	0,86 (0,77, 0,95)	0,86 (0,80, 0,93)	0,91 (0,83, 0,98)
3 Jahre	0,78 (0,70, 0,86)	0,78 (0,71, 0,84)	0,87 (0,79, 0,95)
5 Jahre	0,72 (0,64, 0,81)	0,67 (0,58, 0,76)	0,69 (0,53, 0,85)
NHNV			
1 Jahr	0,91 (0,80, 1,03)	0,94 (0,85, 1,02)	0,97 (0,87, 1,08)
2 Jahre	0,84 (0,74, 0,94)	0,84 (0,77, 0,92)	0,91 (0,81, 1,00)
3 Jahre	0,74 (0,65, 0,83)	0,77 (0,69, 0,85)	0,88 (0,77, 0,98)
5 Jahre	0,74 (0,64, 0,85)	0,74 (0,66, 0,83)	0,62 (0,44, 0,81)
SBWF			
1 Jahr	0,92 (0,73, 1,12)	0,79 (0,67, 0,91)	0,82 (0,68, 0,97)
2 Jahre	0,80 (0,65, 0,95)	0,72 (0,62, 0,82)	0,82 (0,67, 0,96)
3 Jahre	0,85 (0,69, 1,01)	0,74 (0,64, 0,85)	0,81 (0,66, 0,97)
5 Jahre	0,77 (0,59, 0,95)	0,63 (0,49, 0,77)	0,67 (0,50, 0,84)

0,25 0,5 0,75 1 1,25
Begünstigt Denosumab — Begünstigt Alendronat
Begünstigt Denosumab — Begünstigt Orale Bisphosphonate
Begünstigt Denosumab — Begünstigt Zoledronsäure

Dmab reduced the risk of hip fracture by 45% (RR=0.55;68), 37% (RR 0.63) and 38% (RR 0.62) and reduced the risk of MOF by 31% (RR 0.69), 25% (RR 0.75 and 31% (RRR 0.69) compared with oral BP, Aln, and ZA respectively. Similar results were observed for NV, NHNV, and HV fractures

Curtis et al., ASBMR 2023, Abstract FRI-434

Switching from BPs to Denosumab or continuing

Efficacy and safety of transitioning to denosumab vs. continuing bisphosphonate treatment in postmenopausal women who previously received oral bisphosphonates

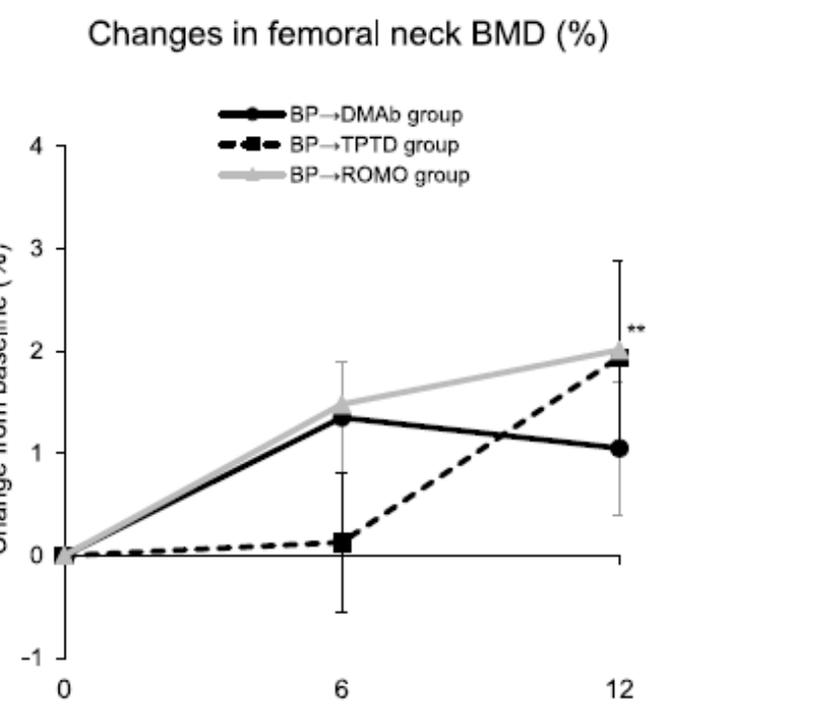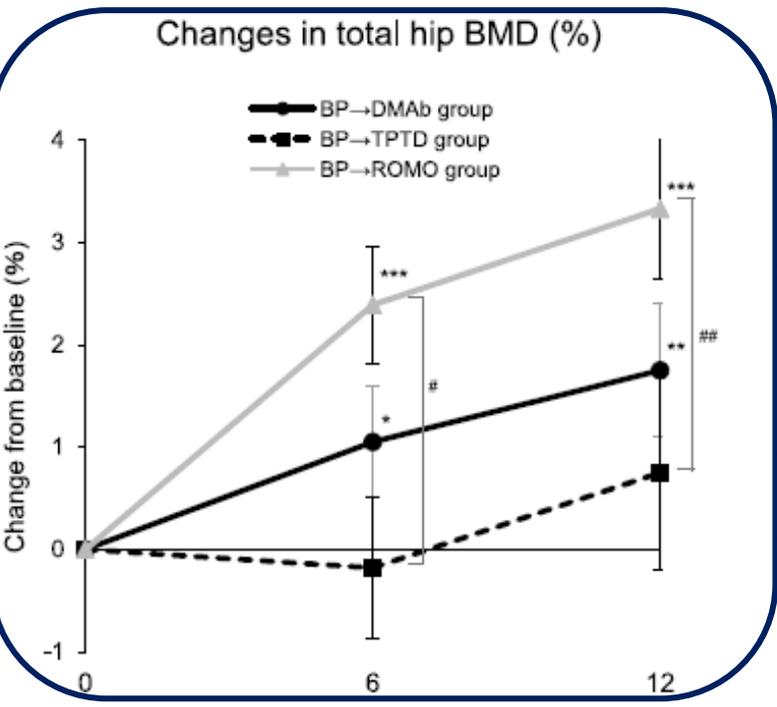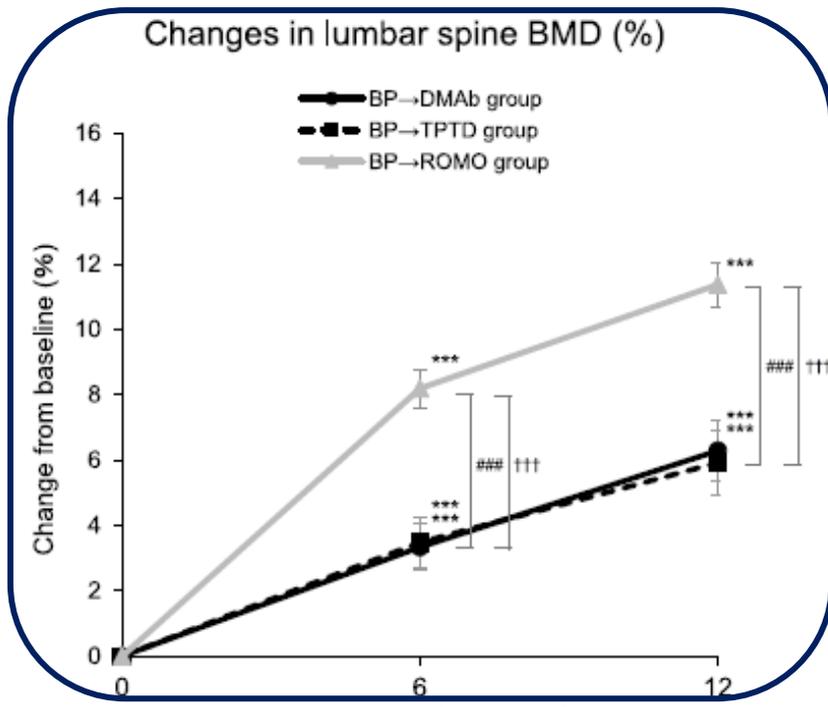|	Kendler et al. [20] NCT00377819	Roux et al. [23] NCT00919711	Recknor et al. [22] NCT00936897	Miller et al. [21] NCT01732770
Study design	Phase 3, multicenter, double-blind, double-dummy RCT	Phase 3, multicenter, randomized, open-label study	Phase 3, multicenter, randomized, open-label study	Phase 4, multicenter, double-blind, double-dummy RCT
Eligibility	Postmenopausal women ≥ 55 years old	Postmenopausal women ≥ 55 years old	Postmenopausal women ≥ 55 years old	Postmenopausal women ≥ 55 years old
	BMD T-score ≤ − 2.0 and ≥ − 4.0 at total hip or lumbar spine		BMD T-score ≤ − 2.0 and ≥ − 4.0 at total hip or lumbar spine	BMD T-score ≤ − 2.5 at the lumbar spine, total hip, or femoral neck
	Adherence to prior BP treatment, not specified	Suboptimally adherent to BP treatment[a]	Suboptimally adherent to BP treatment[b]	Adherent to BP treatment[c]
Prior oral BP	Alendronate for ≥ 6 months	Alendronate daily or weekly; first prescription ≥ 1 month before screening; no limitation on treatment duration	Daily or weekly oral BP; first prescription ≥ 1 month before screening	Oral BP for ≥ 2 years
BP dosing	Alendronate PO 70 mg QW	Risedronate PO 150 mg QM (one 75 mg tablet on each of 2 consecutive days)	Ibandronate PO 150 mg QM	Zoledronic acid IV 5 mg Q12M
Total randomized (1:1) (n)	504	870	833	643
Denosumab	253	435	417	321
BP	251	435	416	322
Sample size for BTM analysis	253 denosumab	88 denosumab	147 denosumab	61 denosumab
	251 alendronate	69 risedronate	133 ibandronate	56 zoledronic acid
Primary endpoint	% change from BL in total hip BMD at month 12	% change from BL in total hip BMD at month 12	% change from BL in total hip BMD at month 12	% change from BL in lumbar spine BMD at month 12
Secondary endpoints	% change from BL in serum CTX-1 at month 3; % change from BL in lumbar spine BMD at month 12	% change from BL in serum CTX-1 at month 1; % change from BL in lumbar spine and femoral neck BMD at month 12	% change from BL in serum CTX-1 at month 1; % change from BL in lumbar spine and femoral neck BMD at month 12	% decrease from BL in serum CTX-1 at various time points; % change from BL in total hip BMD at month 12
Results for primary endpoint	Among patients who transitioned to denosumab vs. continued alendronate use, total hip BMD increased by 1.90 vs. 1.05% (p < 0.0001)	Among patients who transitioned to denosumab vs. risedronate, total hip BMD increased by 2.0 vs. 0.5% (p < 0.0001)	Among patients who transitioned to denosumab vs. ibandronate, total hip BMD increased by 2.3 vs. 1.1% (p < 0.001)	Among patients who transitions to denosumab vs. zoledronic acid, lumbar spine BMD increased by 3.2 vs. 1.1% (p < 0.0001)

Adverse Events, n (%)	Transitioned to DMAb N = 1,413	Continued BP N = 1,408
Any	910 (64.4)	918 (65.2)
Serious	112 (7.9)	102 (7.2)
Fatal	1 (0.1)	3 (0.2)
Leading to study discontinuation	26 (1.8)	57 (4.0)
Osteoporosis-related fractures	47 (3.3)	43 (3.1)
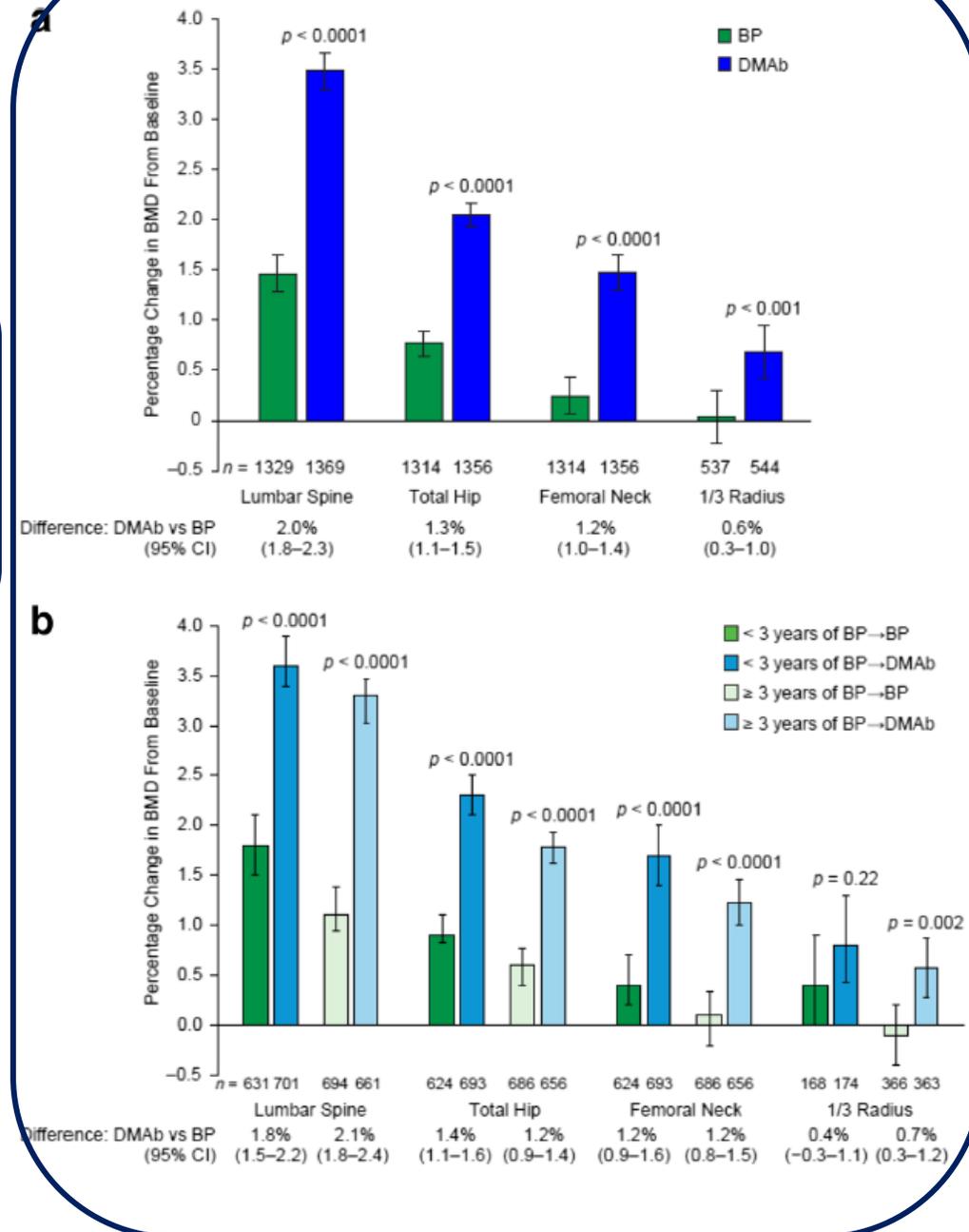
Miller et al., Osteoporos Int 2020, Efficacy and safety of denosumab vs. bisphosphonates in postmenopausal women previously treated with oral bisphosphonates

# Switching from BPs to Denosumab, Teriparatide, or Romosozumab

Variable	DMAb group (n = 45)	TPTD group (n = 45)	ROMO group (n = 45)	P-value
Age (years)	73.3 ± 10.6	73.2 ± 10.0	74.9 ± 9.4	0.67
Body mass index (kg/m^2)	20.5 ± 2.9	20.8 ± 2.8	20.9 ± 3.4	0.82
Prior vertebral fracture (%)	48.8	72.7	53.3	0.054
Prior nonvertebral fracture (%)	15.6	20.5	20.0	0.16
Duration of prior BP treatment (months)	46.1 ± 34.3	40.2 ± 35.6	25.2 ± 20.7	0.007
Prior BP usage (%)	MIN: 46.7 ALN: 33.3 RIS: 17.8 IBN: 2.2	RIS: 38.1 ALN: 23.8 MIN: 19.1 IBN: 14.3 ZLD: 4.8	ALN: 44.4 RIS: 40.0 MIN: 15.6	NA
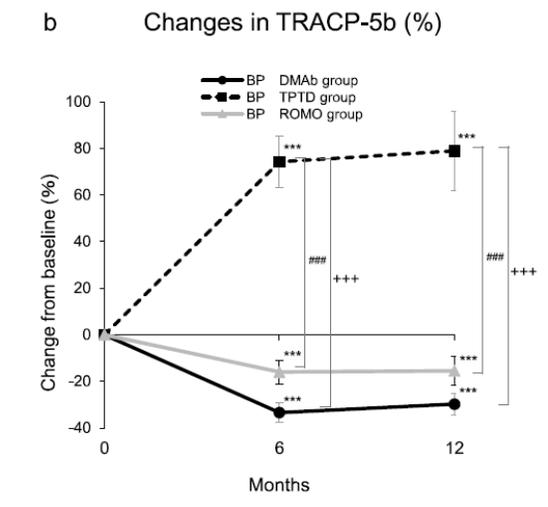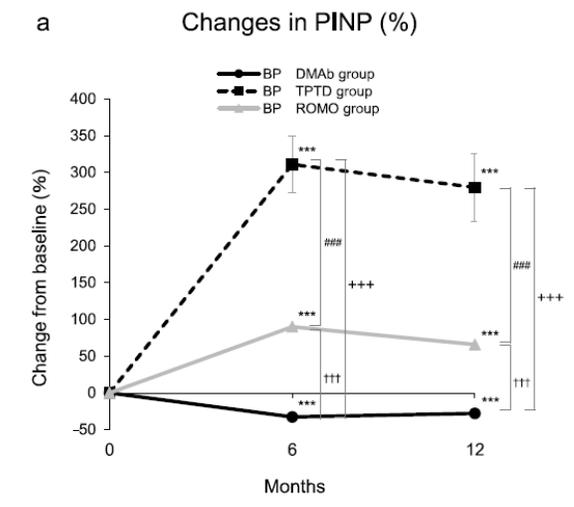
a — Changes in PINP (%)

b — Changes in TRACP-5b (%)

Changes in lumbar spine BMD (%)

Changes in total hip BMD (%)

Changes in femoral neck BMD (%)

Yukishima et al., Osteoporos Int 2024, Impact of switching from bisphosphonates to denosumab, teriparatide, or romosozumab in patients with postmenopausal osteoporosis - a case-control study

✓ Levels of BTM increased upon discontinuation and decreased with retreatment.

✓ Discontinuation of denosumab was associated with a BMD decrease of 6.6% at the lumbar spine and 5.3% at the total hip within the first 12 months

Conclusions: …long-term denosumab treatment led to gains in BMD and reduction of BTM throughout the course of the study. The effects on bone turnover were fully reversible with discontinuation
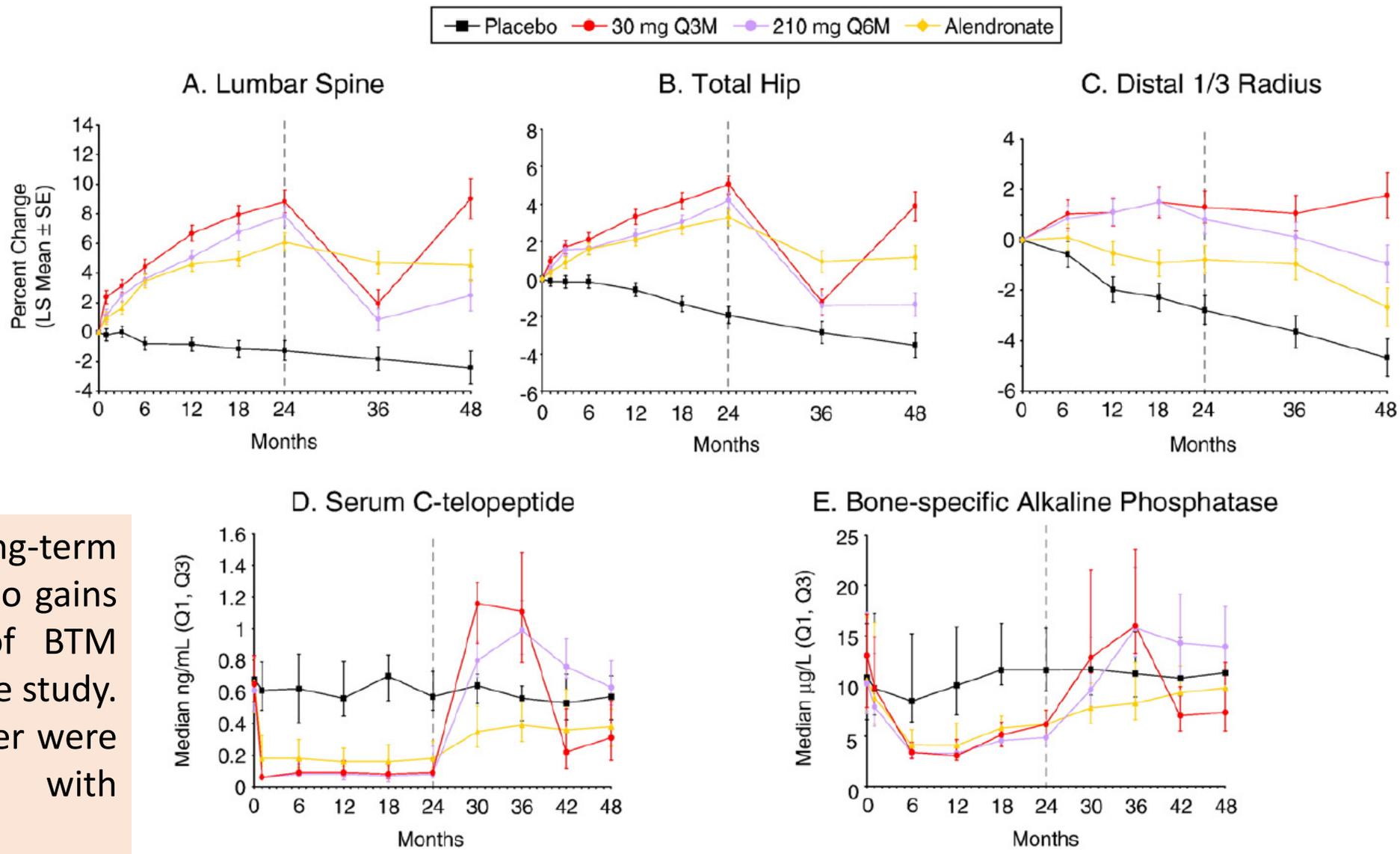
Number of Dmab injections before discontinuation and changes in BMD 1 year after subsequent i.v. ZOL 5mg

47 postmenopausal women who received a single zoledronate infusion 6 months after the last denosumab injection and then were followed for 1 year. Twenty-seven women received ≤ 6 denosumab injections (≤ 6 Group) and 20 received > 6 denosumab injections (> 6 Group).
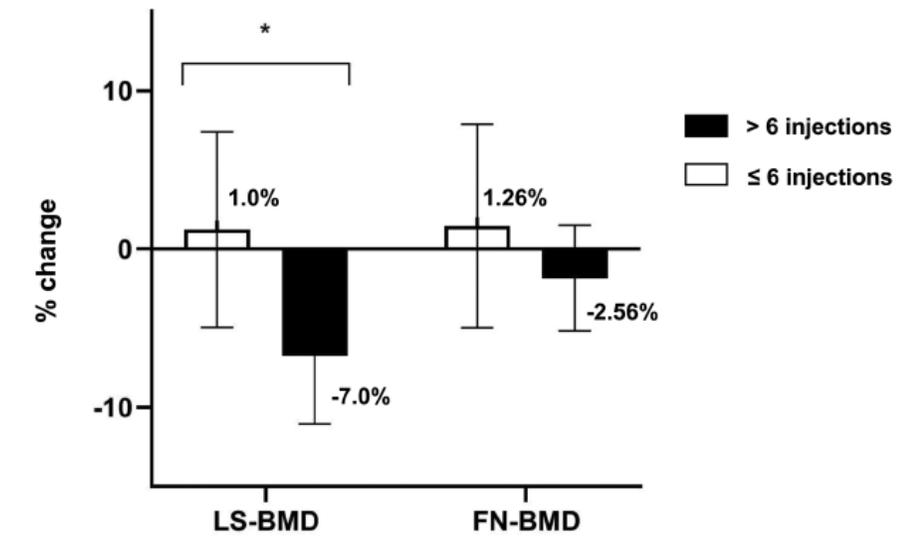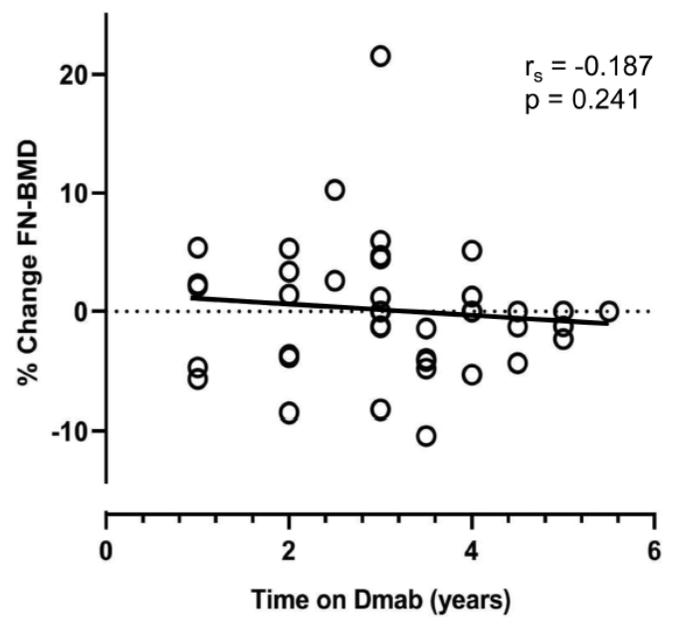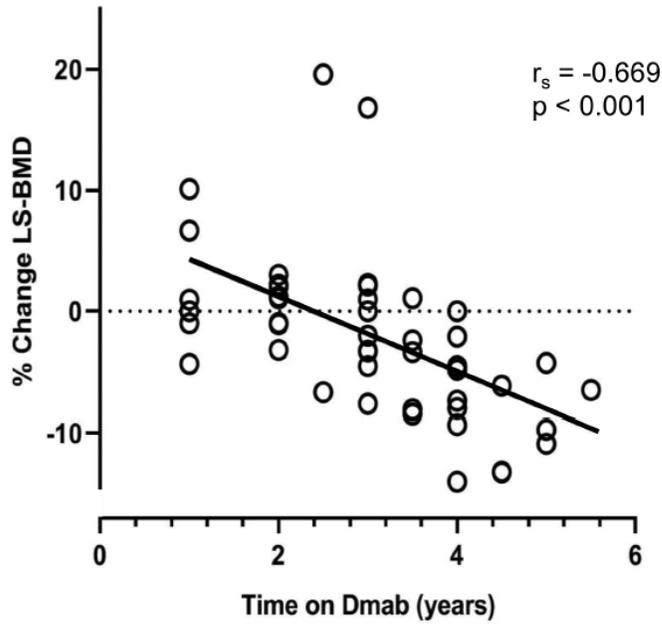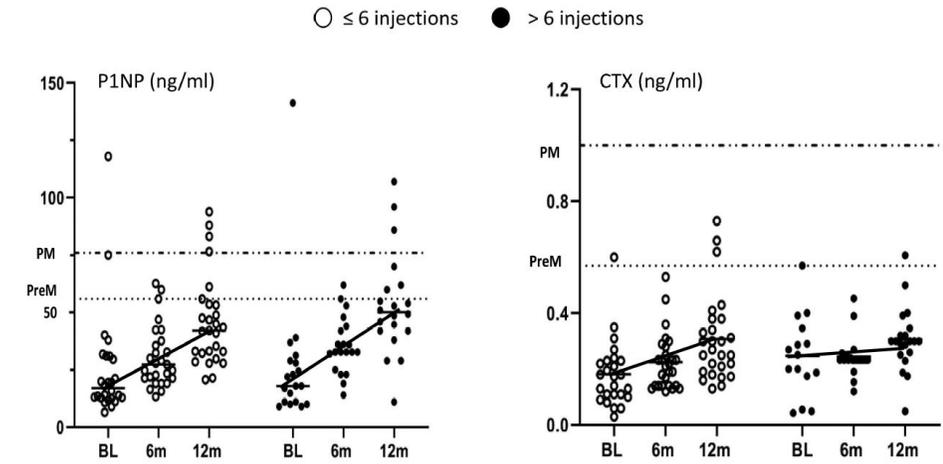
The duration of denosumab treatment significantly affects the efficacy of subsequent zoledronate infusion to maintain BMD gains. Frequent follow-up of patients treated with denosumab longer than 3 years is advisable as additional therapeutic interventions may be needed.

Kumar et al., JBMR 2025, Denosumab discontinuation in the clinic - implications of rebound bone turnover and emerging strategies to prevent bone loss and fractures
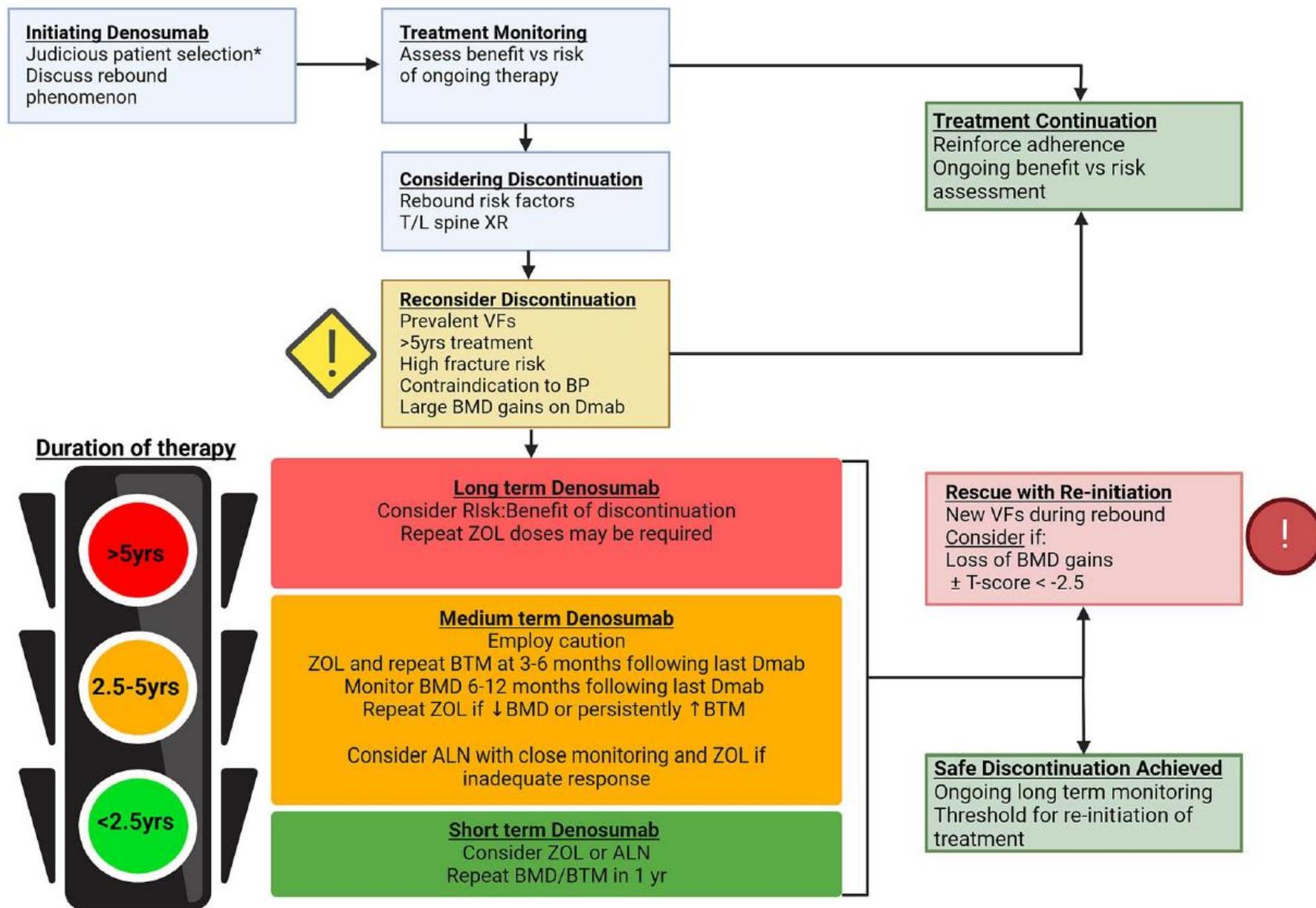
Differential structural effects of antiresorptives vs PTH analogues

Table 1 Summary of treatment-related changes in human skeletal architecture. Only published studies that reported defined skeletal architectural indices were included in the Table

Location	Areal BMD		HR-pQCT, QCT Radius/Tibia				QCT Spine			Bone biopsy/QCT Hip		
	Spine	Hip	Per.Diam	CoPo	CtTh	Tb	CoPo	CtTh	BV/TV	CoPo	CtTh	BV/TV
Measure	BMD (Approx. % increase)											
Bisphosphonates	4[a]	2-2.5[a]		↓,NS[g]	↑[g]	↑,NS[g]				↓[m]		NS[m]
Denosumab	5.5[b]	3[b]		↓,NS[h]	↑[h]	↑[h]				↓[n]		
Teriparatide	9[c]	3[c]	↑[f]	↑,NS[i]	↑,NS[i]	↑,↓[i]	NS[j]	↑[k]		↑[o]	↑[p]	↑[p]
Abaloparatide	11[d]	4[d]										
Romosozumab	13.5[e]	6.5[e]					↑[l]	↑[l]				↑[l]

Bisphosphonates / Denosumab

NC Periosteal diameter
↓ Endocortical diameter
↓ Cortical porosity
↑ Trabecular indices

Teriparatide (Abaloparatide?)

↑ Periosteal diameter
↑ Endocortical diameter
↑ Cortical porosity
↑ Trabecular indices

Age → Genetics → Sex steroids → **Size**

Habitual loads → Genetics → **Shape**

Diameter → Thickness → Porosity → Cortical → **Architecture**

Number → Thickness → Connectivity → Trabecular → **Architecture**

Collagen crosslinking → Collagen density → Matrix → **Composition**

Hydroxyapatite arrangement → Mineralization → Mineral → **Composition**

Size, Shape, Architecture, Composition → **Bone Strength**

Choksi et al., Clin Diab Endocrinol 2018, The challenges of diagnosing osteoporosis and the limitations of currently available tools
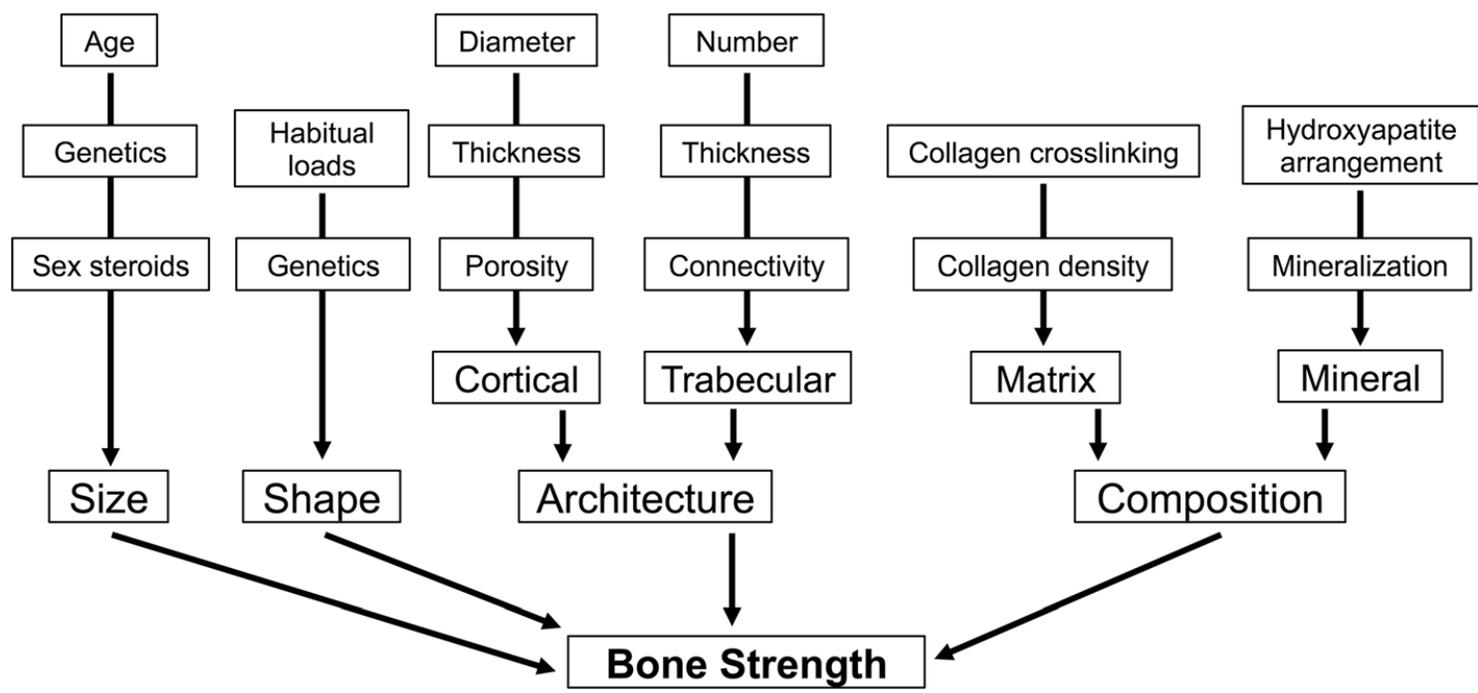
Remodeling- and Modeling-Based Bone Formation

Open-label Teriparatide s.c. 20µg/d (n=33) vs. Denosumab 60mg/6mo (n=36, 60mg) in treatment – naïve postmenopausal osteoporosis. Histomorphometry before and after 3 mo of treatment
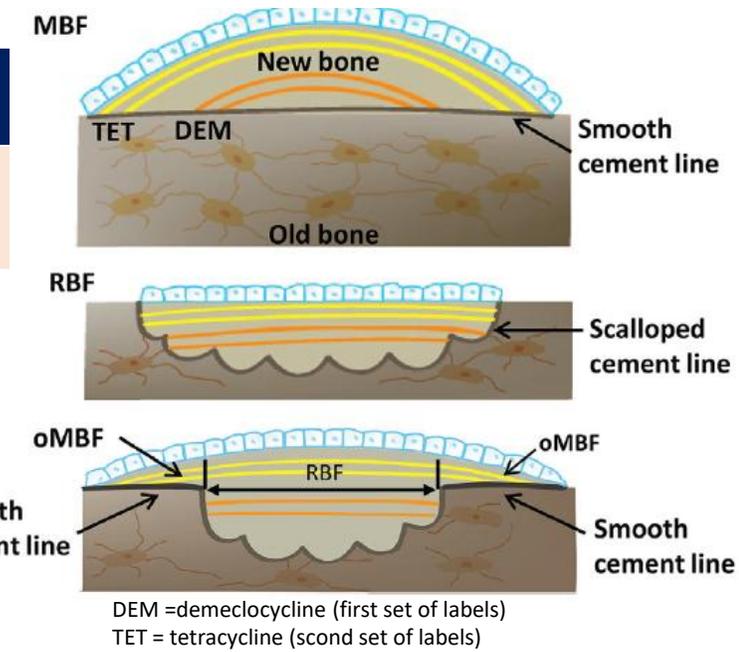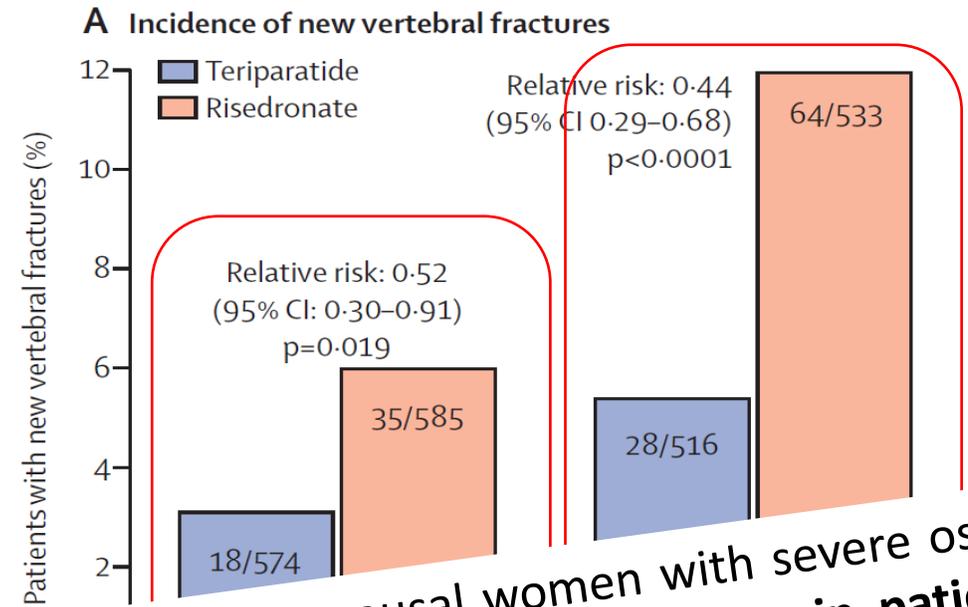

Dempster et al., JBMR 2017, Remodeling- and Modeling-Based Bone Formation With Teriparatide Versus Denosumb - A Longitudinal Analysis From Baseline to 3 Months in the AVA Study

DEM =demeclocycline (first set of labels)
TET = tetracycline (scond set of labels)
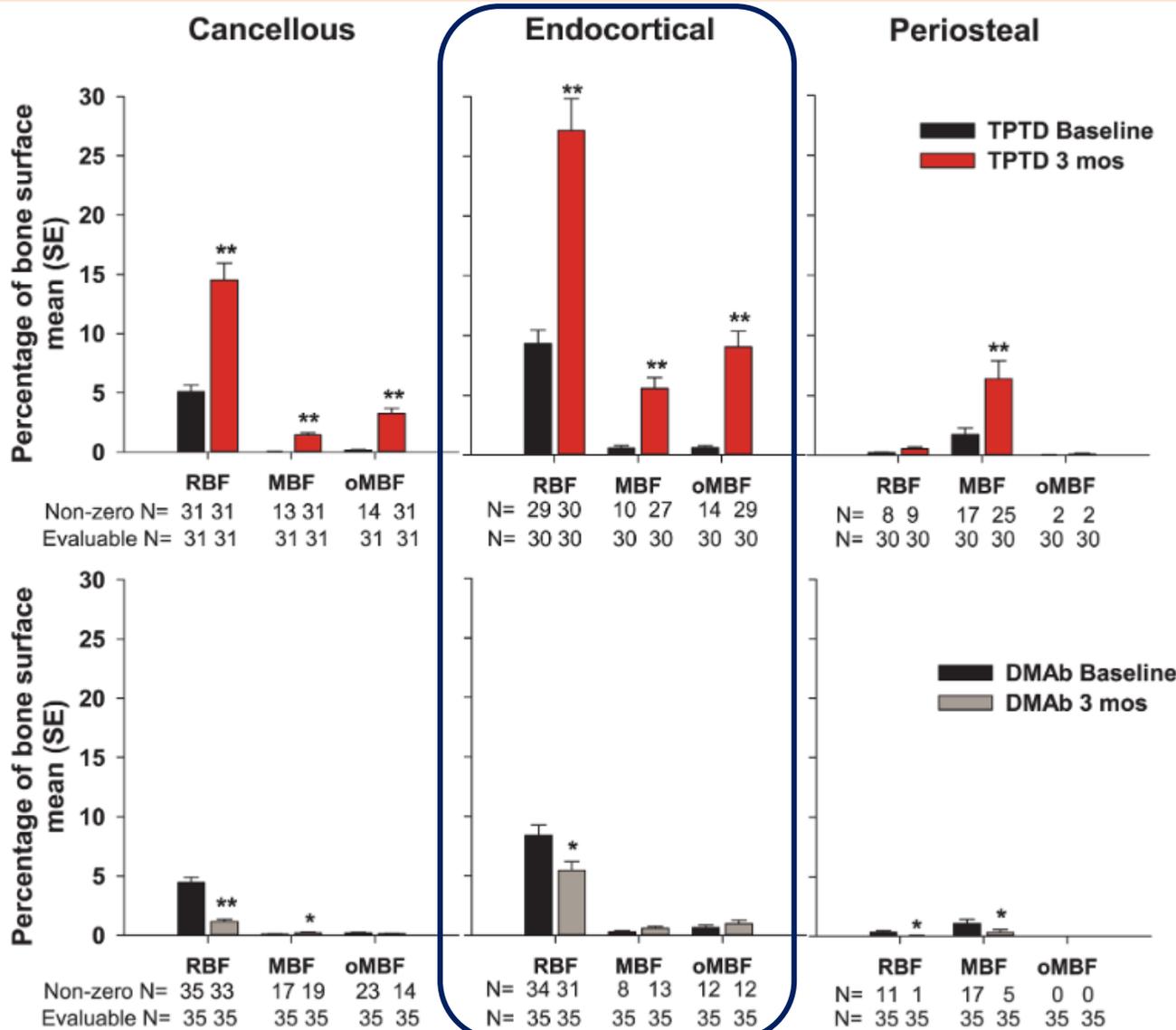
- ✓ MBF = modeling-based formation
- ✓ RBF = remodeling-based formation
- ✓ oMBG = overflow modeling-based formation
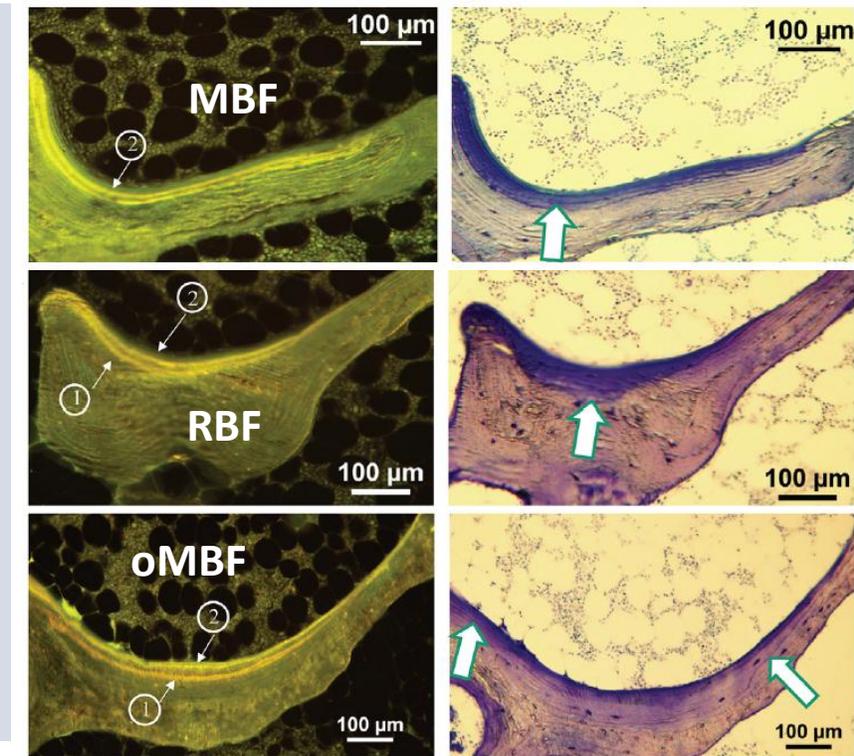
Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO)

A Incidence of new vertebral fractures

	Teriparatide group (n=680)	Risedronate group (n=680)
(Continued from previous column)		
Previous osteoporosis medication use		
Patients with ≥1 previous osteoporosis therapy¶	496 (73%)	485 (71%)
Prevalent fractures		
Vertebral fractures‡		
≥1	679 (100%)	679 (100%)
1	231 (34%)	240 (35%)
2	178 (26%)	174 (26%)
3	104 (15%)	101 (15%)
4		62 (9%)
		102 (15%)

Among post-menopausal women with severe osteoporosis, the risk of **new vertebral and clinical fractures is significantly lower in patients receiving teriparatide** than in those receiving risedronate

	group	Risedronate group	Effect size (95% CI)*	p value
Primary endpoint				
New vertebral fracture†	28 (5%)	64 (12%)	0·44 (0·29–0·68)	<0·0001
Secondary gated endpoints				
New and worsened vertebral fracture†	31 (6%)	69 (13%)	0·46 (0·31–0·68)	<0·0001
Pooled clinical fracture‡§	30 (5%)	61 (10%)	0·48 (0·32–0·74)	0·0009
Non-vertebral fragility fracture§	25 (4%)	38 (6%)	0·66 (0·39–1·10)	0·10
Major non-vertebral fragility fracture§	18 (3%)	31 (5%)	0·58 (0·32–1·05)	0·06

Kendler, Lancet 2017

Number at risk
Teriparatide 680 | 623 | 589 | 561 | 508
Risedronate 680 | 616 | 584 | 553 | 502

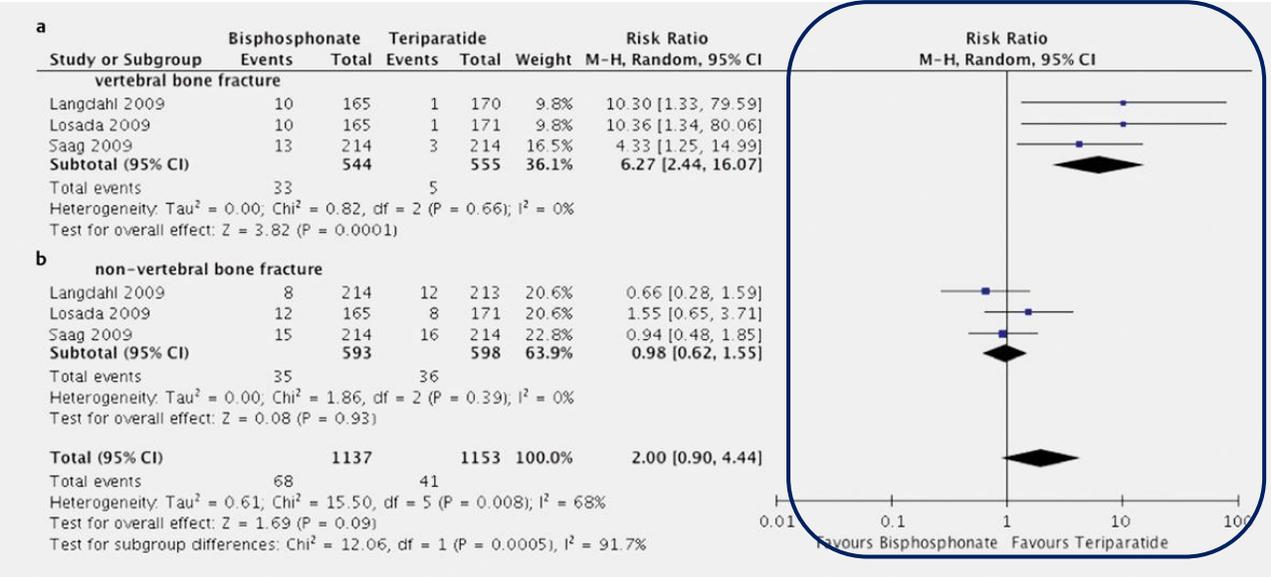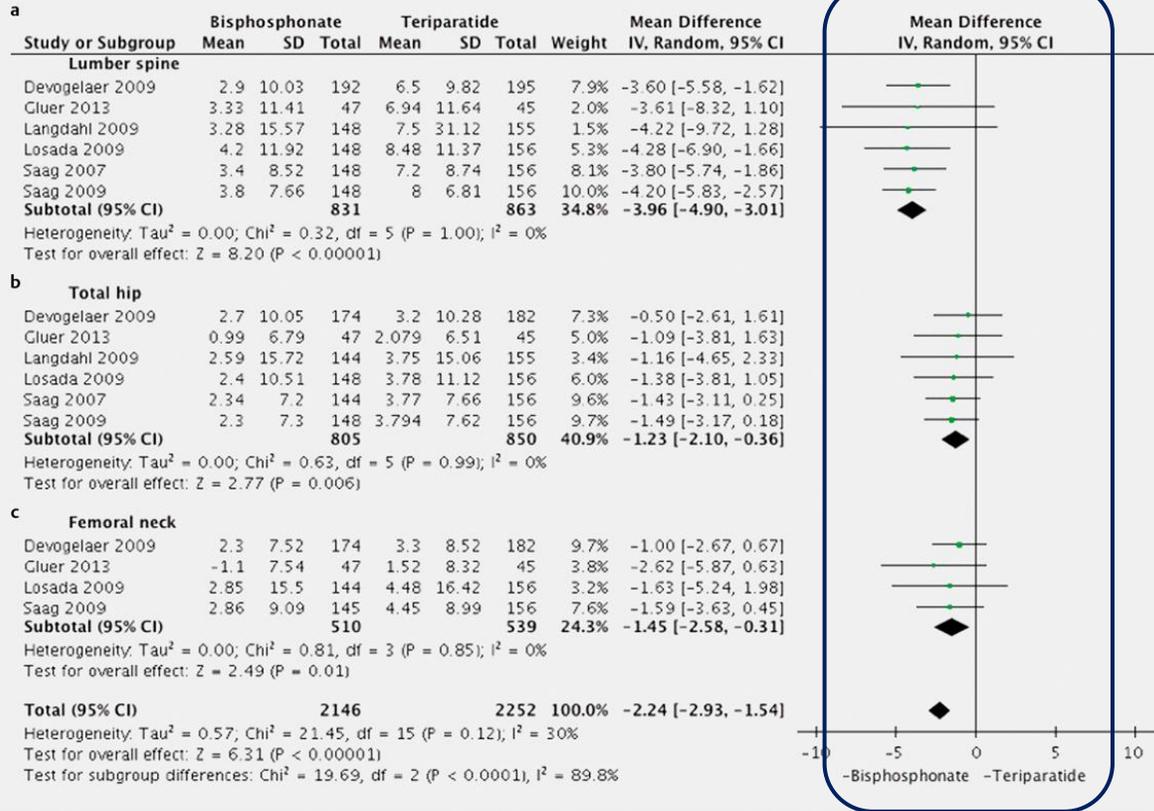# The VERO Trial - Risk of Fractures in Subgroups with Severe Osteoporosis
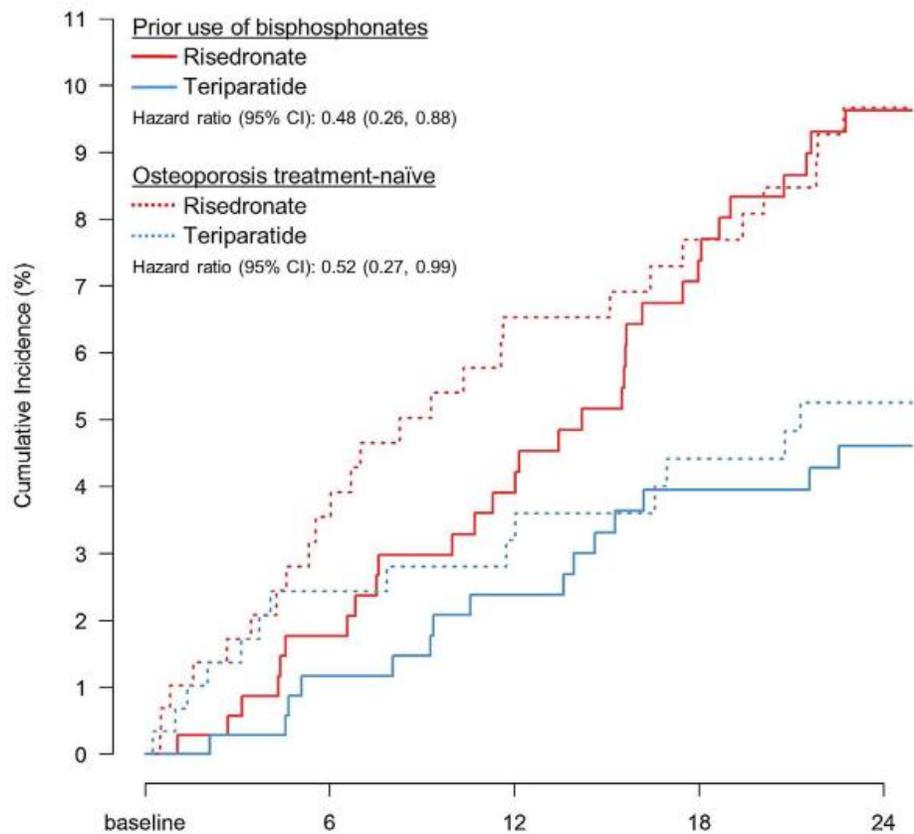
In postmenopausal women with severe osteoporosis, risk reduction of TPTD vs RIS for new VFx, clinical fractures, and NVFFx was confirmed across different subgroups including patients pretreated with BPs.

Geusens, JBMR 2018, Effects of Teriparatide Compared with Risedronate on the Risk of Fractures in Subgroups with Severe Osteoporosis - The VERO Trial

Bisphosphonates vs Teriparatide in Glucocorticoid induced Osteoporosis

## Subgroup analysis of the efficiency of BMD change (%)

The increases in BMD were sign. greater with Teriparatide vs BPs:
- Lumbar Spine + 3.96% (p<0.00001)
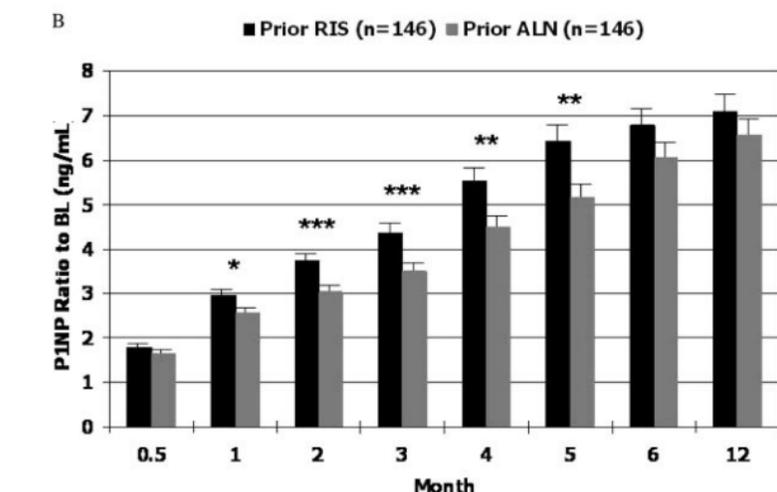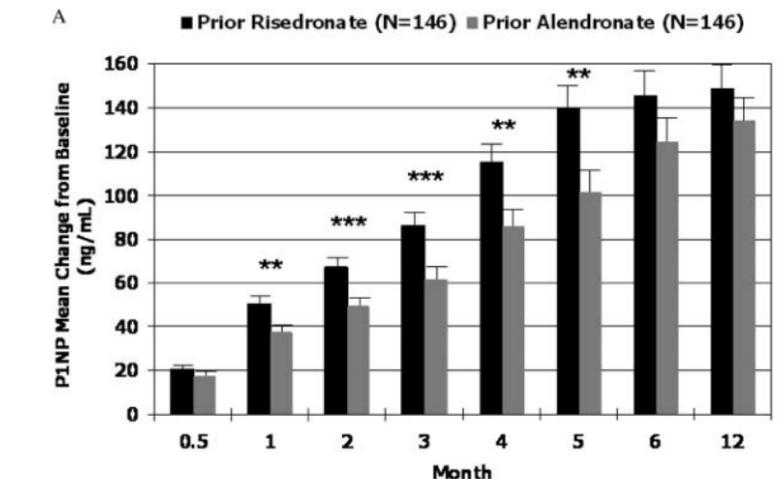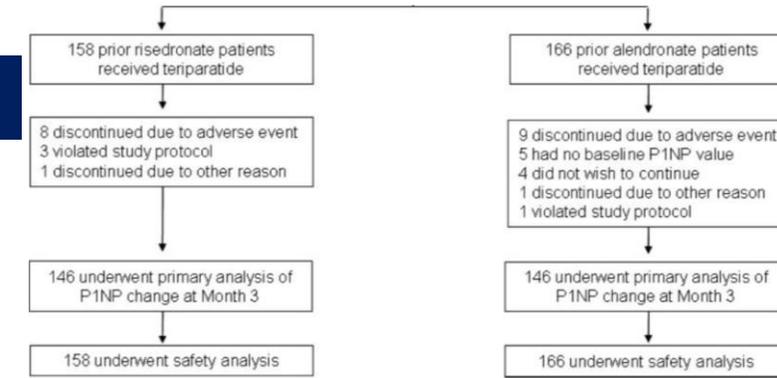- Total Hip + 1.23% (p=0.006) a
- Femoral Neck + 1.45% (p=0.01)

Dong et al., Horm Metab Res 2023, Comparison of Bisphosphonates versus Teriparatide in Therapy of Glucocorticoid induced Osteoporosis - Meta Analysis

Bone fracture risk by bisphosphonate and teriparatide treatment at vertebral (**a**) and non-vertebral (**b**) fracture at 18 months.

Meta-regression analysis shows that factors including age, sex, menopausal status, steroid dosage, steroid duration, underlying diseases and previous rheumatic diseases, and previous bone fracture are not associated with the incidence of vertebral bone fracture

▶ **Table 1** Meta-regression analysis of the demographic and clinical variables concerning the risk of vertebral bone fracture in GIOP.

Characteristics	Coefficient, 95% CI	p-Value	Tau²	Adj R-squared (%)
Age	1.395 (0.146–13.361)	0.671	1.436	−18.69
Female (%)	2.349 (0.062–88.767)	0.509	1.267	−4.74
Menopausal female	1.089 (0.658–1.803)	0.541	1.483	−11.24
Steroid dosage	2.356 (0.524–10.595)	0.167	0.599	50.42
Steroid duration	1.582 (0.472–5.299)	0.314	0.944	21.98
Underlying disease (previous rheumatic disease)	0.387 (0.00–25.483)	0.433	1.24	6.79
Previous fracture	1.342 (0.235–7.664)	0.543	1.487	−11.55
Previous vertebral fracture	1.348 (0.197–9.208)	0.655	1.431	−18.27

All are univariate meta-regression analyses, with the exception of teriparatide compared with bisphosphonate as a reference. Proportion between study variance was explained with Hartung–Knapp modification.
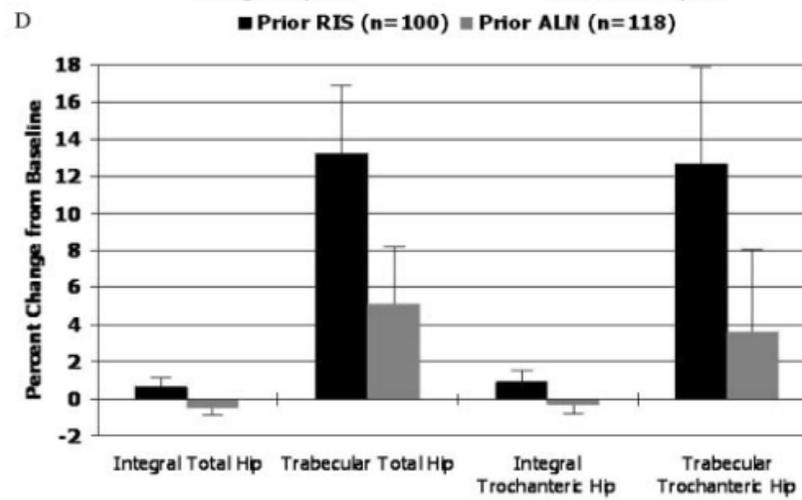
Teriparatide in GC-induced Osteoporosis
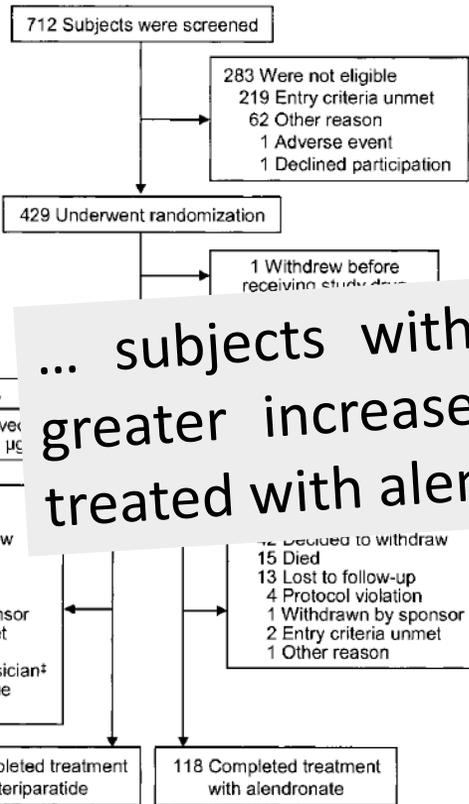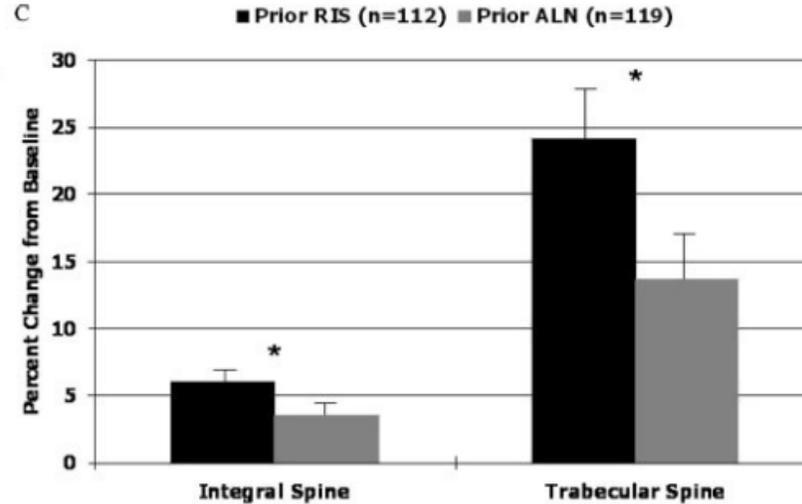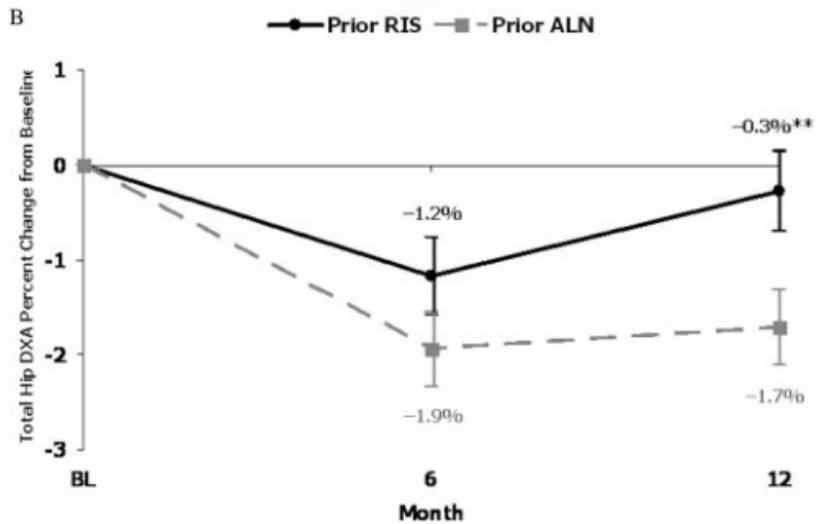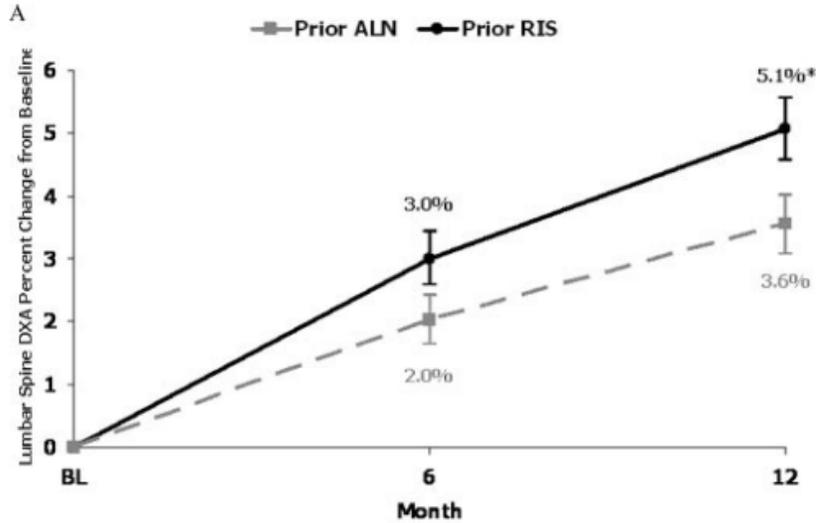

… subjects with GC-induced osteoporosis treated with teriparatide […] had greater increases in BMD and fewer new vertebral fractures than subjects treated with alendronate.
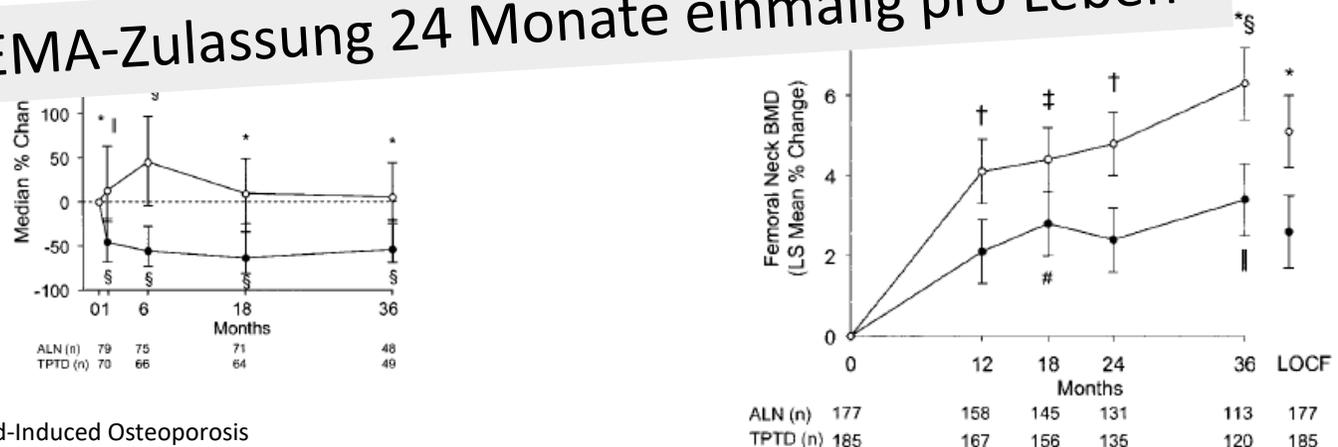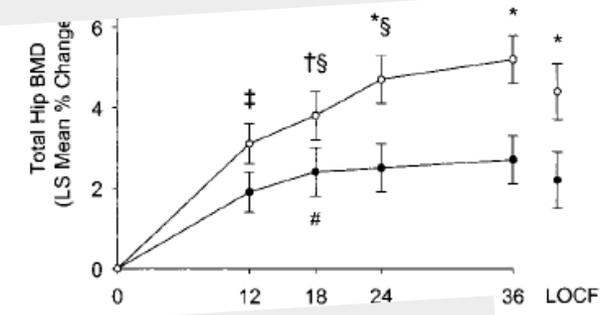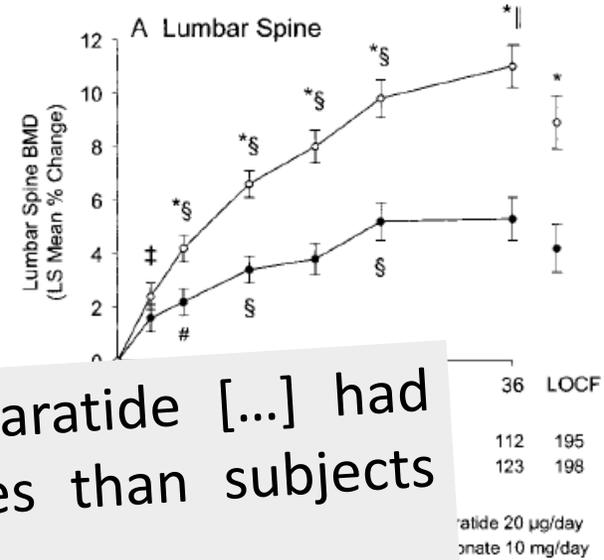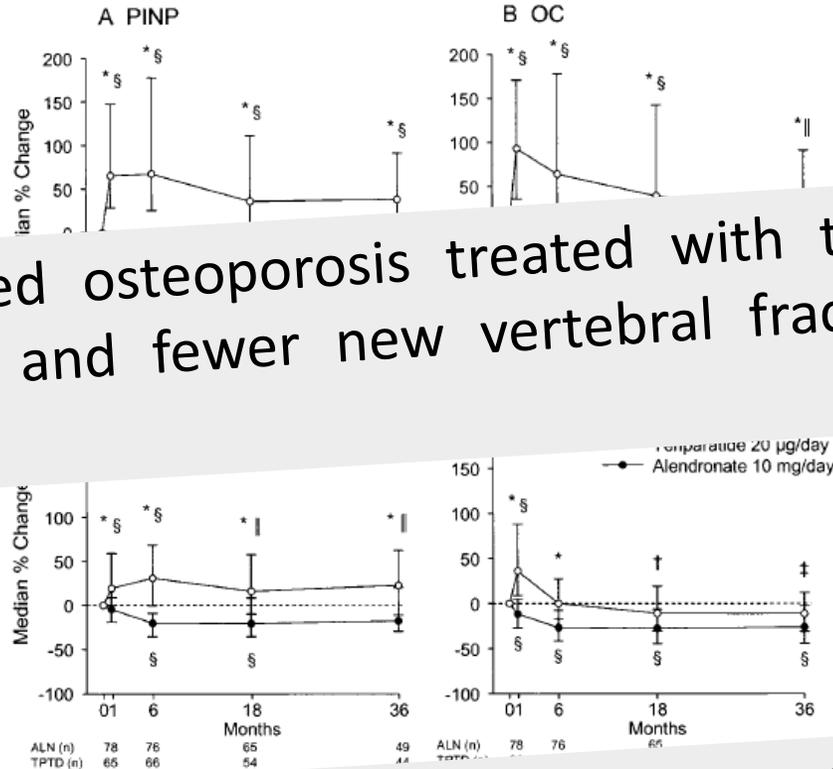
Therapiedauer für Teriparatid gemäß EMA-Zulassung 24 Monate einmalig pro Leben
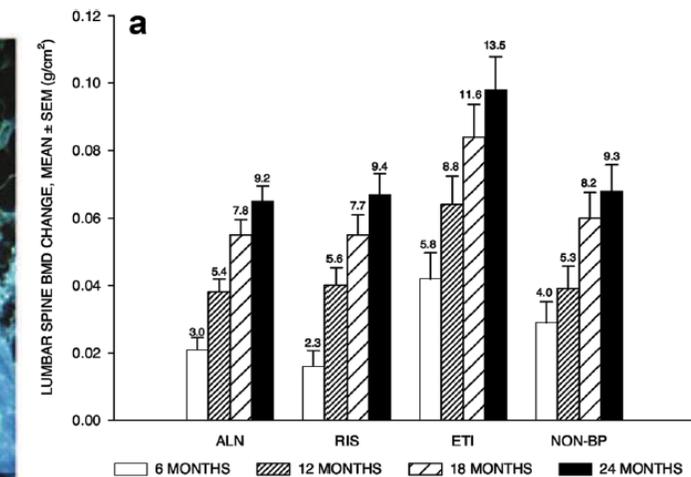
Fracture type	alendronate (n = 214)	teriparatide (n = 214)	P
≥1 radiographic vertebral†	13 (7.7)	3 (1.7)	0.007
≥1 clinical vertebral‡	4 (2.4)	0	0.037
≥1 nonvertebral	15 (7.0)	16 (7.5)	0.843
≥1 nonvertebral fragility	5 (2.3)	9 (4.2)	0.256

Saag et al., Arthritis Rheumatism 2009, Effects of Teriparatide versus Alendronate for Treating Glucocorticoid-Induced Osteoporosis

Teriparatide following Alendronate vs. Risedronate – OPTAMISE-Study

This non-randomized but prospective study suggests that there may be differences in anabolic responsiveness to teriparatide as a function of the type of prior bisphosphonate exposure.

Miller et al., JCEM 2008, Early Responsiveness of Women with Osteoporosis to Teriparatide After Therapy with Alendronate or Risedronate

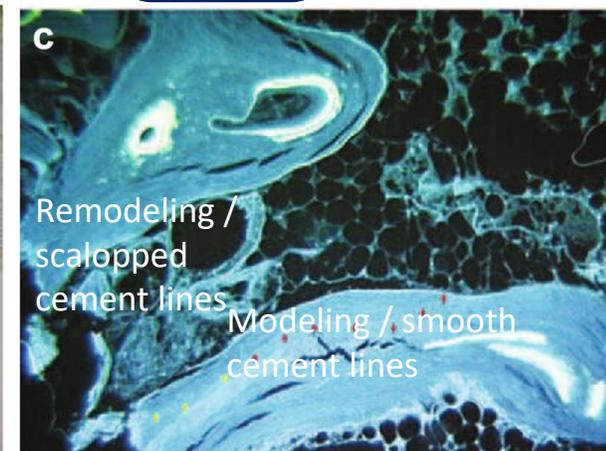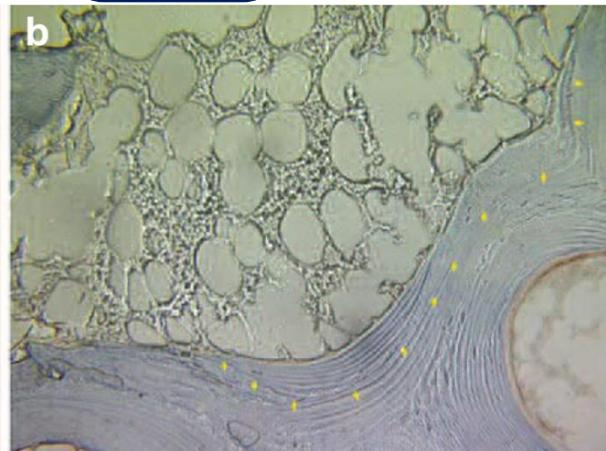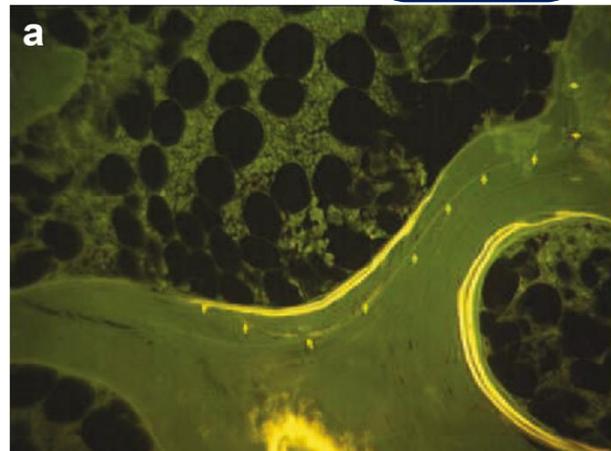# Teriparatide Treatment Effect and Significance of Pretreatment
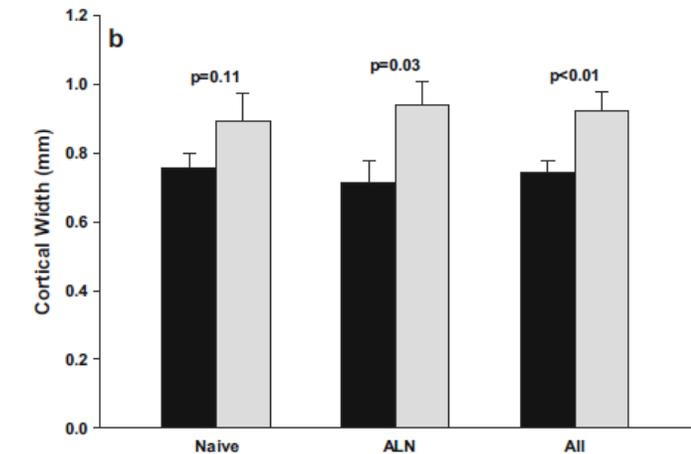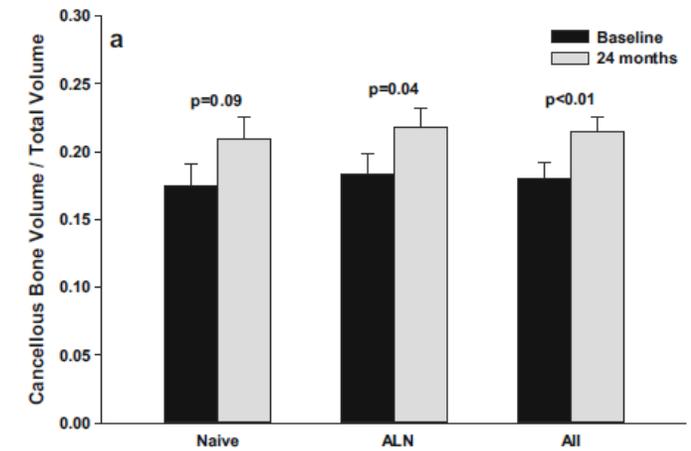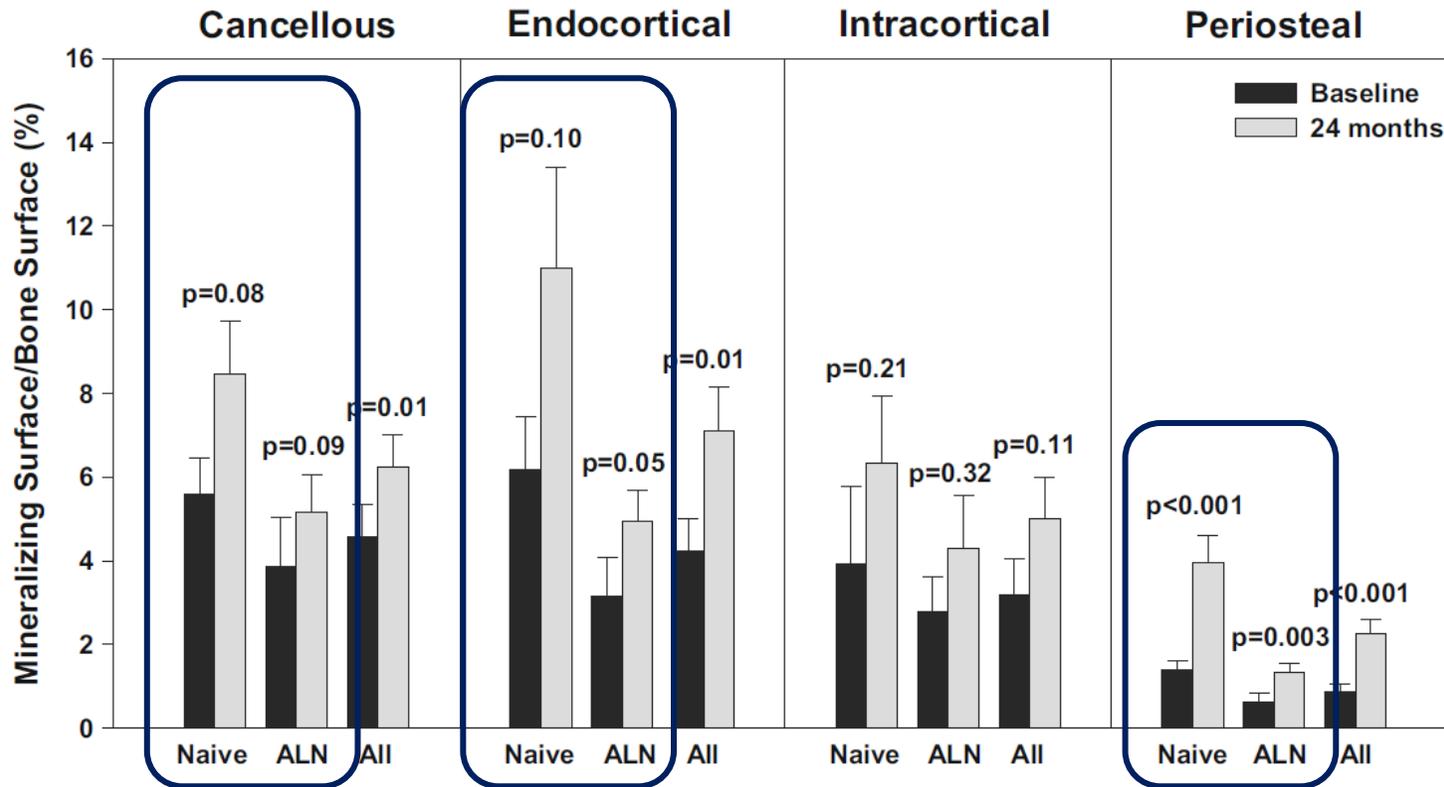
Lindsay et al., Osteoporos Int (2016)

Pre-treatement effect on Teriparatide-Efficacy

Exploratory analysis to investigate the effects of teriparatide on cancellous bone microstructure in postmenopausal women with osteoporosis who were either treatment-naïve (TN, n = 16) or alendronate-pretreated (ALN, n = 29) at teriparatide initiation.
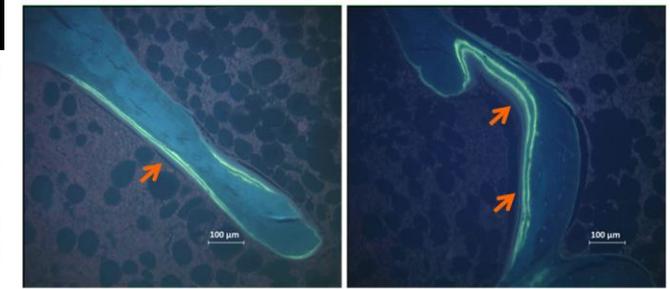
Teriparatide (20 µg/day) was given for 24 months

Fahrleitner-Pammer et al., Bone 2016, Improvement of cancellous bone microstructure in patients on teriparatide following alendronat pretreatment

Teriparatide induced trabecular connectivity

Treatment-naïve
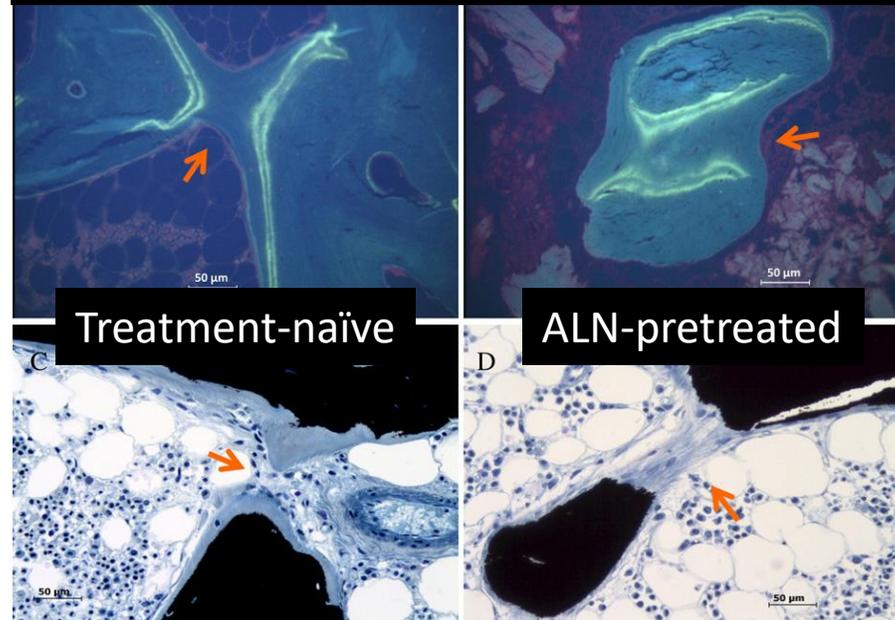
ALN-pretreated

A. Treatment-naïve patient

Baseline — 24 Months of Teriparatide

B. Alendronate-pretreated patient

Baseline — 24 Months of Teriparatide

	Treatment-naïve (n = 16)			Alendronate pretreated (n = 29)			All (n = 45)		
	Baseline	24 Months		Baseline	24 Months		Baseline	24 Months	
	Mean (SD)	% Change (SD)	P-value	Mean (SD)	% Change (SD)	P-value	Mean (SD)	% Change (SD)	P-value
Two dimensional (2D)									
Bone area/total area (B·Ar/Tt. Ar, %)	20.1 (5)	−3.6 (30)	0.273	19.0 (6)	33.2 (66)	0.016	19.5 (5)	19.6 (58)	0.138
Trabecular width (Tb·Wi, µm)	0.14 (0.03)	7.0 (24)	0.273	0.14 (0.03)	19.6 (35)	0.033	0.14 (0.03)	14.9 (32)	0.018
Trabecular number (Tb·N, mm^{-1})	1.4 (0.3)	−9.9 (14)	0.068	1.3 (0.3)	8.0 (28)	0.163	1.4 (0.3)	1.3 (25)	0.810
Trabecular separation (Tb·Sp, µm)	0.58 (0.12)	15.2 (20)	0.017	0.64 (0.20)	−3.4 (39)	0.126	0.62 (0.17)	3.5 (34)	0.798
Three dimensional (3D)									
Bone volume/tissue volume (BV/TV, %)	17 (6)	105 (356)	0.039	18 (8)	55 (139)	0.005	18 (7)	73 (237)	<0.001
Trabecular thickness (Tb·Th, µm)	0.12 (0.03)	30.4 (30)	<0.001	0.13 (0.03)	30.8 (53)	<0.001	0.12 (0.03)	30.7 (46)	<0.001
Trabecular number (Tb·N, mm^{-1})	1.47 (0.43)	36.7 (179)	0.298	1.44 (0.55)	12.7 (54)	0.254	1.45 (0.51)	21.2 (114)	0.637
Trabecular separation (Tb·Sp, µm)	0.89 (1.40)	3.1 (36)	0.706	0.71 (0.49)	10.4 (75)	0.237	0.77 (0.91)	7.8 (64)	0.439

Teriparatide in men

Bone ALP, PICP, NTX/CR, fDPD/CR graphs:
- *P < 0.001 versus placebo
- †P = 0.06 versus placebo
- †P = 0.04 versus placebo
- †P = 0.021 versus placebo
- Placebo
- TPTD20
- TPTD40
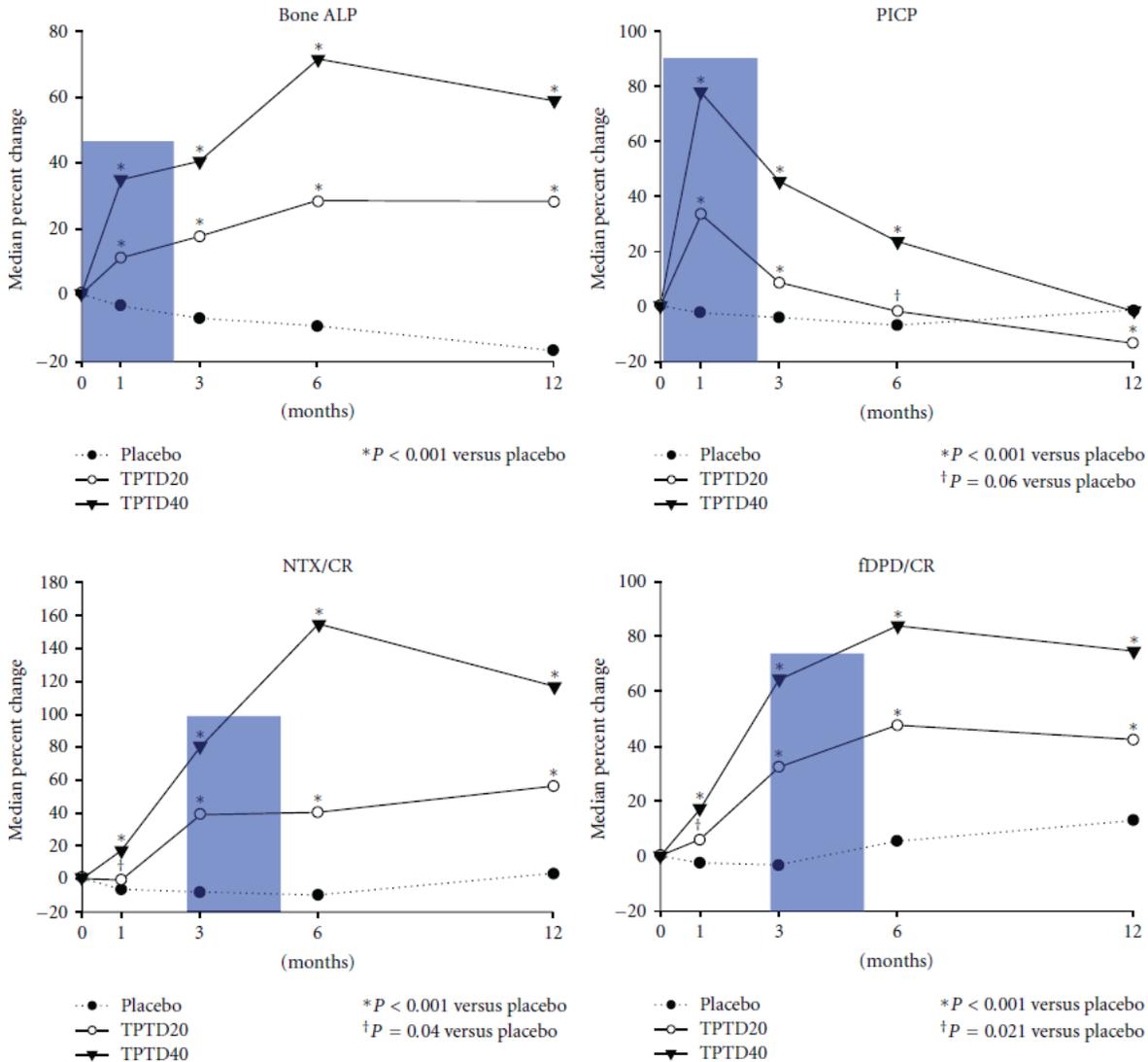
Effect of PTH on BMD: women versus men (not head to head)
- Women
- Men
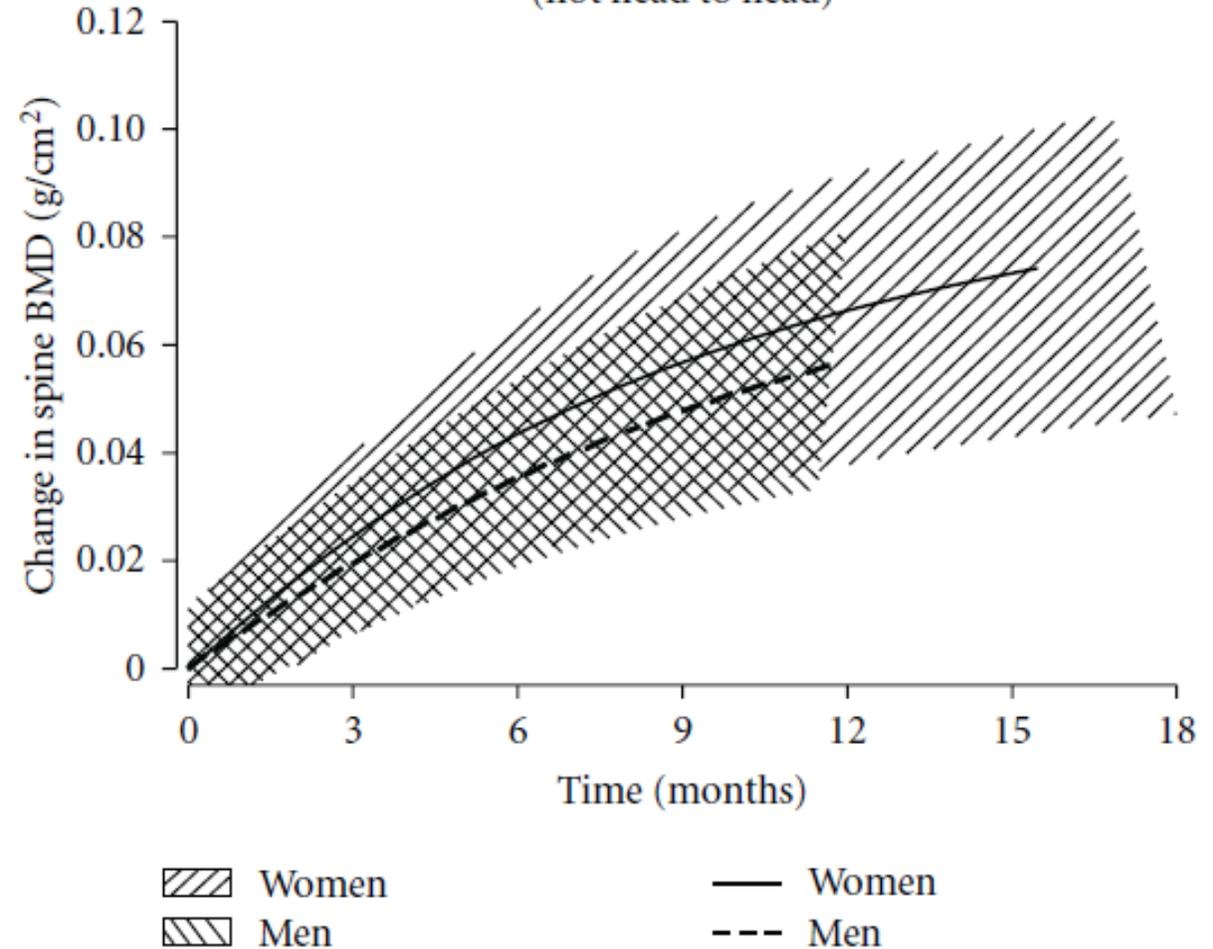
Changes in lumbar spine bone mineral density with teriparatide 20 μg daily. Although the figure does not show a head-to-head comparison, the increase in bone mineral density in men over the 11 months of the trial by Orwoll et al. tracks closely along the trajectory in bone mineral density women over the same period of time in the trial of Neer et al.

Cusano et al., J Osteoporos 2011, Therapy of Osteoporosis in Men with Teriparatide

Teriparatide and Risedronate in GIO in Men

Glüer, JBMR 2013, Comparative Effects of Teriparatide and Risedronate in GIO in Men, 18-month Results of the EUROGIOPs Trial

BMD: bone mineral density
TMD: tissue mineral density
BV/TV: bone volume fraction

Teriparatide

Time	0 mo	6 mo	18 mo
BMD [mg/cm³]	67	81	90
BV/TV	9.8%	12.8%	14.7%
relative TMD	100%	93%	90%

Risedronate

0 mo	6 mo	18 mo
69.8	73.1	83.5
9.3%	8.7%	10.4%
100%	112%	107%
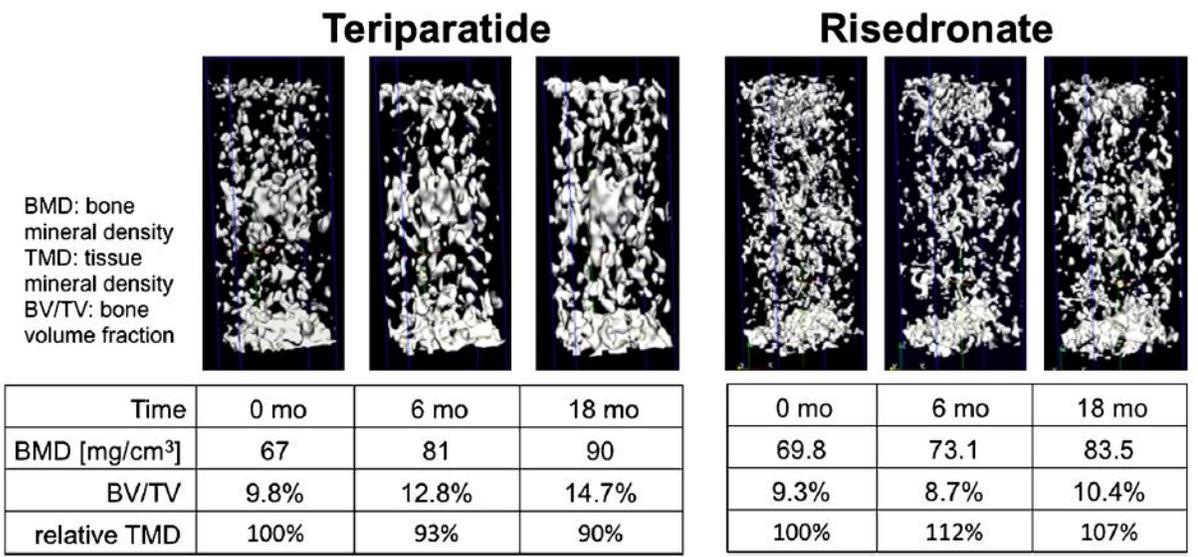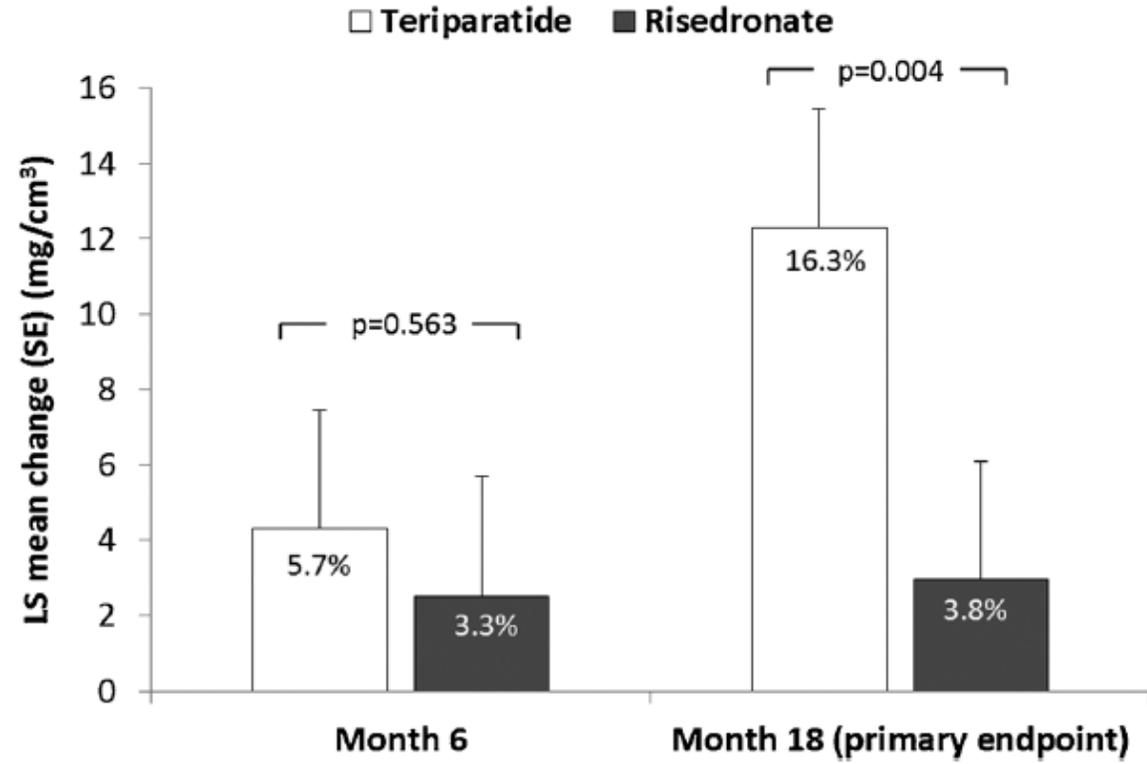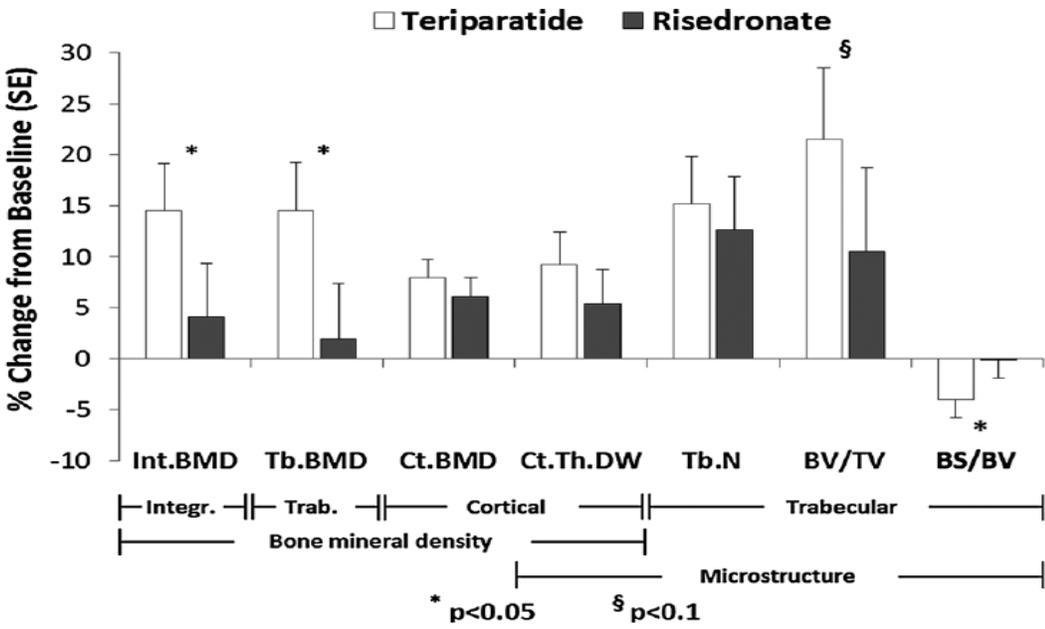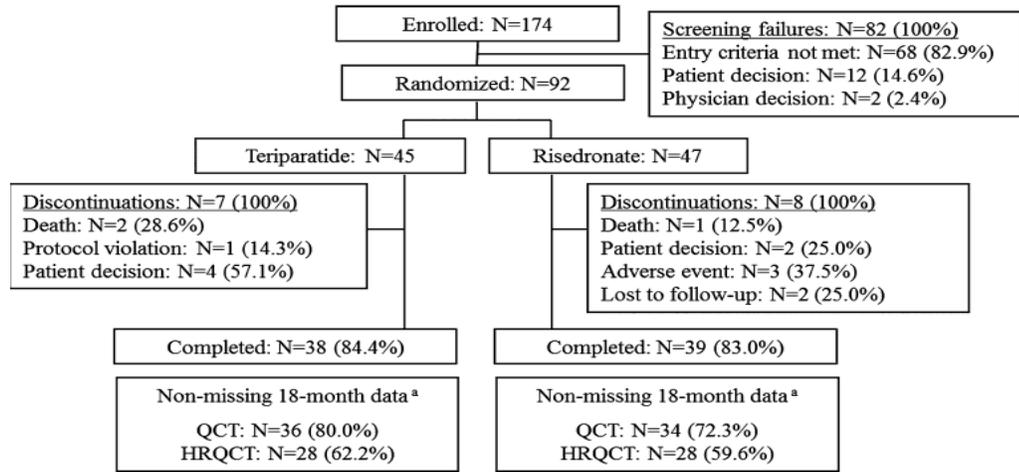
First author/ reference/date/ country	Patients (n)	TPTD therapy (n)	Age/ mean age	Gender	BP duration/ mean time	Fractures (n)	Location	Initiation of TPTD	Treatment dose	Duration of treatment	surgery (n)	Union rate (%)	Time to union/ mean time
Anas Saleh, 2012, USA (57)	10	9	50–85 years/67 years	F	4–17 years/10 years	IF	ST (4)/FD (11)	NS	NS	24 months	NS	50	3 months
Paul D. Miller, 2015, USA (21)	15	13	57–87 years/67 years	F	6–11 years/7 years	CF	B, FD (n = 6)/l or R FD (n = 9)	After the first bone biopsy	20 µg/d	12 months			NS
Naohisa Miyakoshi, 2015, Japan (58)	34	NS	66–88 years	F	1–11.6 years/								2–7 months/ 5.4 months
Basmah K. Alwah Saudi An													NS
Wen-Ling 2017, Taiv													2.3–8.2 months/4.4 months
H. Tsuchie Japan (61)													6.1 ± 4.1 months (daily)/ 10.1 ± 4.2 months (weekly)
HiroyukiTsu 2021, Japan						(12)	NS	Postoperation immediately (n = 7)/6 months (n = 6)	20 µg/d	12 months	NS	NS	NS
Cherie Ying Chiang, 2013, Australia (63)	14	5	76 years	F (13)/M (1)	4–10 years	IF (8)/CF (6)	NS	NS	20 µg/d	6 months	NS	NS	NS
Nelson B Watts, 2017, USA (64)	14	14	52–83 years/68.3 years	F	3–14.5 years/ 8.8 years	IF (5)/CF (9)	NS	NS	NS	24 months	NS	64.3	NS
S. L. Greenspan, 2017, USA (65)	13	13	74.2 years	F	NS	IF (1)/CF (12)	NS	Postoperation immediately (n = 7)/6 months (n = 6)	20 µg/d	12 months	NS	NS	NS

✓TPTD may promote the healing of AFFs by reducing the time to bone union and likelihood of non-union

✓TPTD should be considered for treating osteoporosis complicated by AFFs

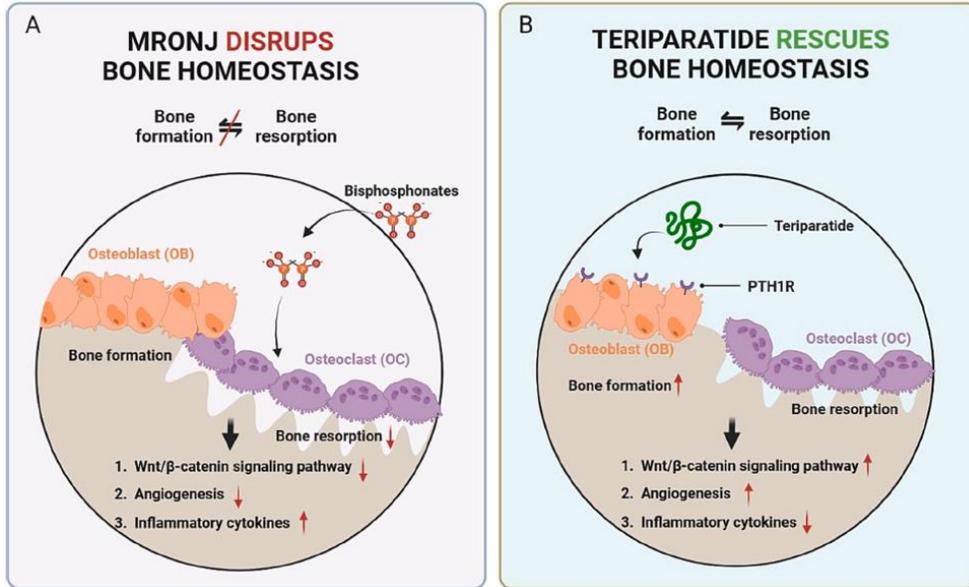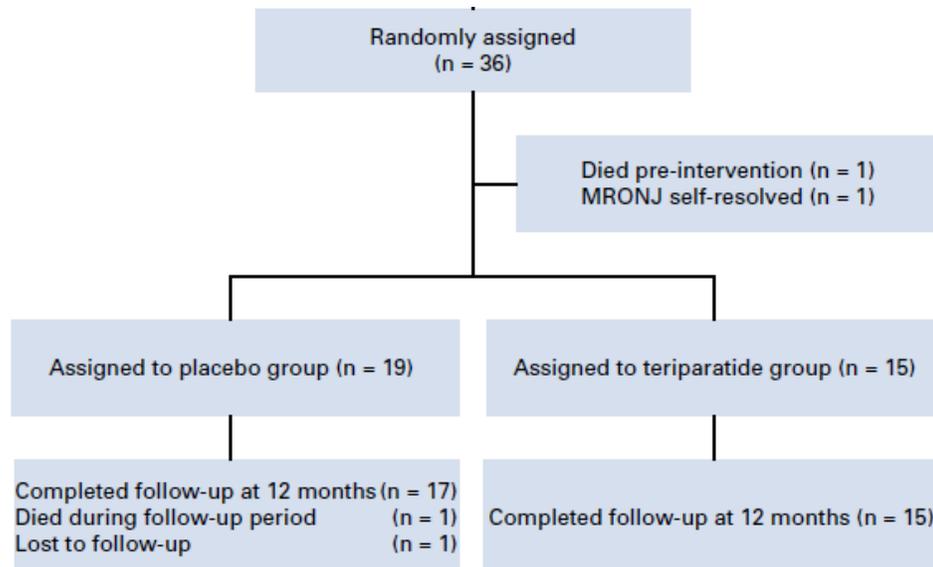Gao et al., Front Surg 2023., A brief review and clinical evidences of teriparatide therapy for atypical femoral fractures associated with long-term bisphosphonate treatment

Teriparatide in ONJ

Yu et al., Medical Hypotheses 2023, Teriparatide-induced alleviation of medication-related osteonecrosis of the jaw - Potential molecular mechanisms

Teriparatide was significantly associated with a greater rate of resolution of MRONJ lesions compared with placebo (OR for change over time in the control group, 0.40 v 0.15 in the teriparaide group; p= .013).
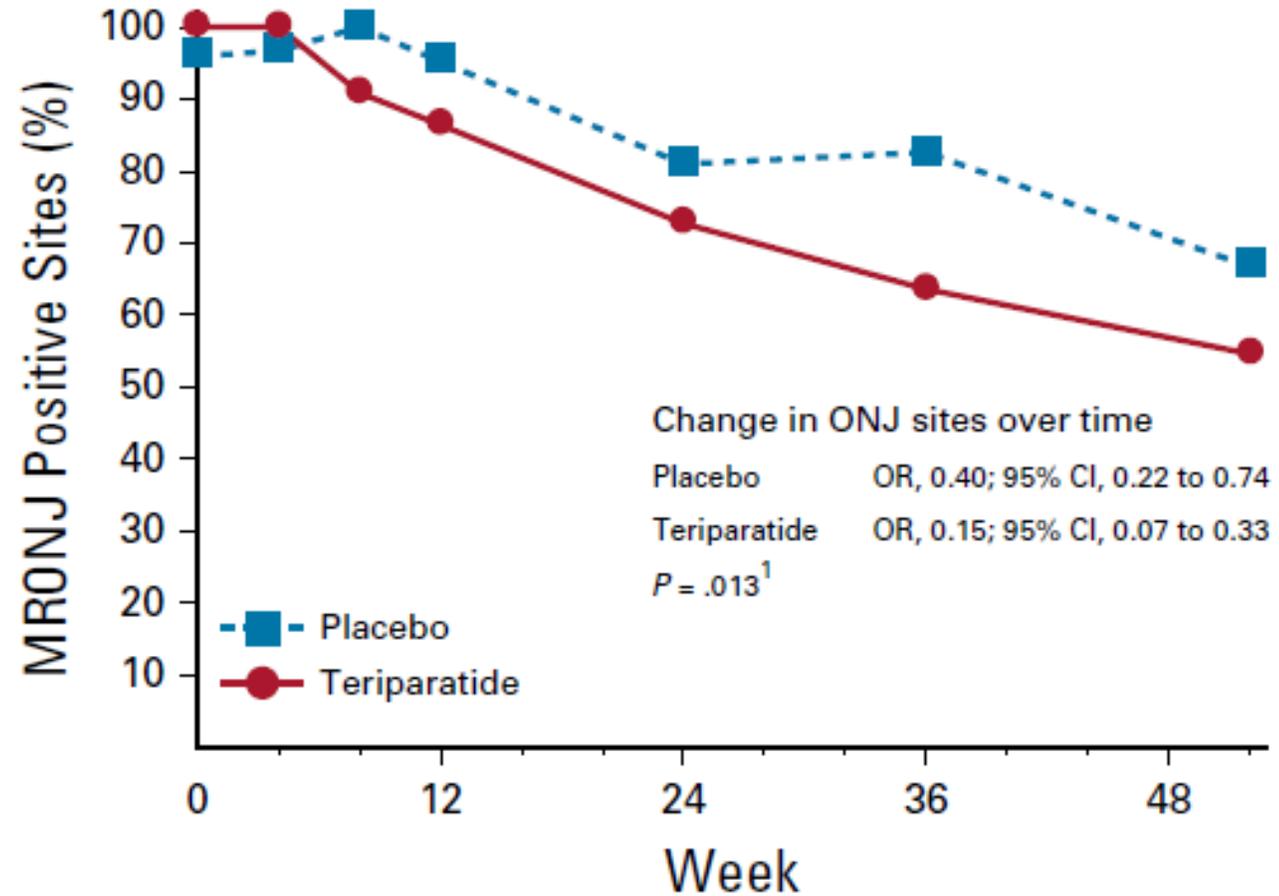
The only significant predictor of MRONJ resolution was low gingival index, which is an indicator of good oral hygiene

Sim et al., J Clin Oncol 2020, Teriparatide Promotes Bone Healing in Medication-Related Osteonecrosis of the Jaw - A Placebo-Controlled, Randomized Trial

Fracture Risk with Osteoanabolic Drugs

Study	Study population	Assigned treatment		Treatment time	Treatment effect		
	PM women with osteoporosis and	Romosozumab to alendronate	Alendronate to alendronate				
ARCH [83]	fragility fracture	(n = 2046)	(n = 2047)	(months)	ARR	RRR	P-value
	Fracture incidence						
	Vertebral	6.2%	11.9%	24	5.7%	48%	<0.001
	Nonvertebral	8.7%	10.6%	32.4[a]	1.9%	19%	0.04
	Clinical	9.7%	13.0%	32.4[a]	3.3%	27%	<0.001
	Hip	2.0%	3.2%	32.4[a]	1.2%	38%	0.02

Study	Study population	Assigned treatment			Treatment effect		
	PM women with ≥2 moderate or ≥1 severe vertebral fracture & a	Teriparatide	Risedronate	Treatment			
VERO [49]	BMD T-score ≤−1.50	(n = 680)	(n = 680)	time (months)	ARR	RRR	P-value
	Fracture incidence						
	Vertebral	5.4%	12.0%	24	6.6%	56%	<0.0001
	Nonvertebral	4.0%	6.1%	24	2.1%	34%	0.10
	Clinical	4.8%	9.8%	24	5.0%	52%	0.0009

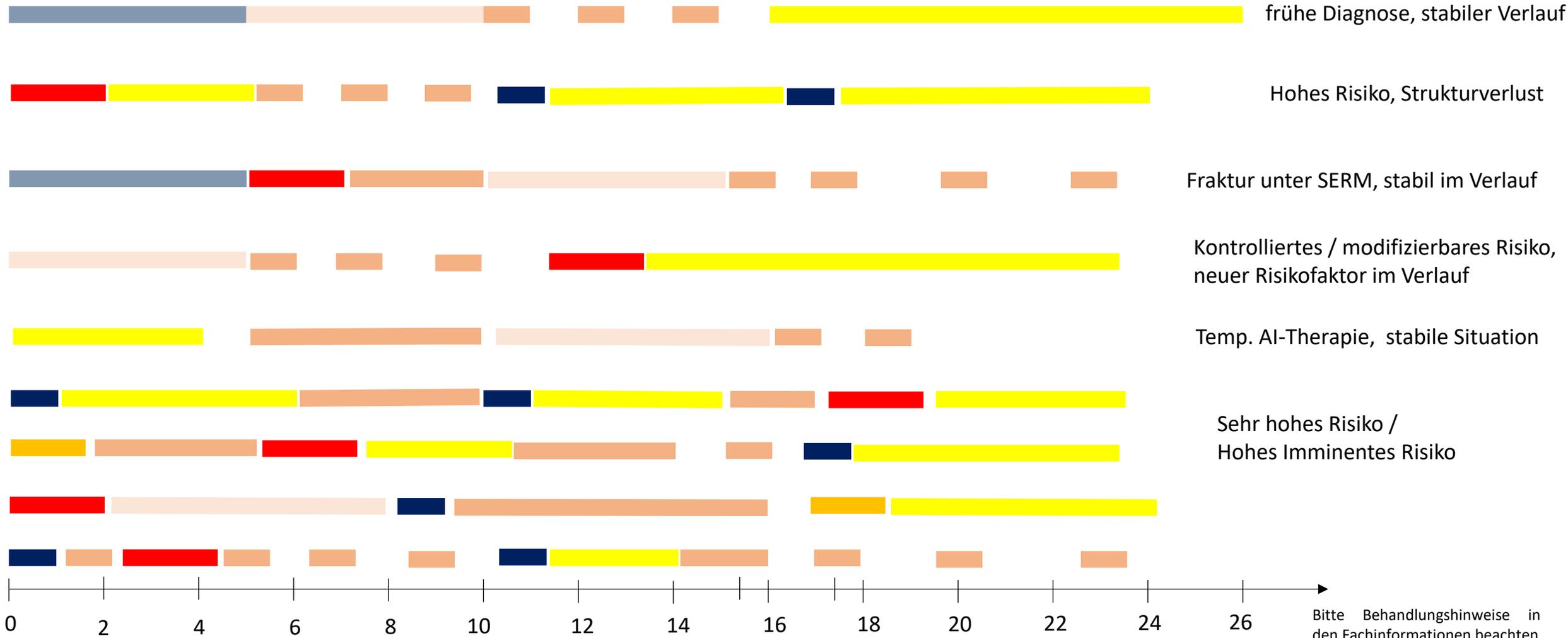ARR, Absolute risk reduction; BMD, Bone mineral density; PM, Postmenopausal; RRR, Relative risk reduction.
Adapted from [83] and [49].
[a]Denotes median ± interquartile range.

Lorentzon, J Int Med 2019, Treating osteoporosis to prevent fractures - current concepts and future developments

Optionen in der Sequenztherapie

Verfügbarkeit insbesondere von Teriparatid und Denosumab als Biosimilars erleichtert die wirtschaftliche Umsetzung individualisierter Sequenztherapien.

Legende:
- Niedrigaffines BP
- Hochaffines BP
- Teriparatid
- Abaloparatid
- Denosumab
- Raloxifen / HRT
- Romosozumab

Szenarien:
- frühe Diagnose, stabiler Verlauf
- Hohes Risiko, Strukturverlust
- Fraktur unter SERM, stabil im Verlauf
- Kontrolliertes / modifizierbares Risiko, neuer Risikofaktor im Verlauf
- Temp. AI-Therapie, stabile Situation
- Sehr hohes Risiko / Hohes Imminentes Risiko

Zeitachse: 0 2 4 6 8 10 12 14 16 18 20 22 24 26

Bitte Behandlungshinweise in den Fachinformationen beachten

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

Antoine de Saint-Exupéry

Denosumab discontinuation - emerging strategies to prevent bone loss and fractures
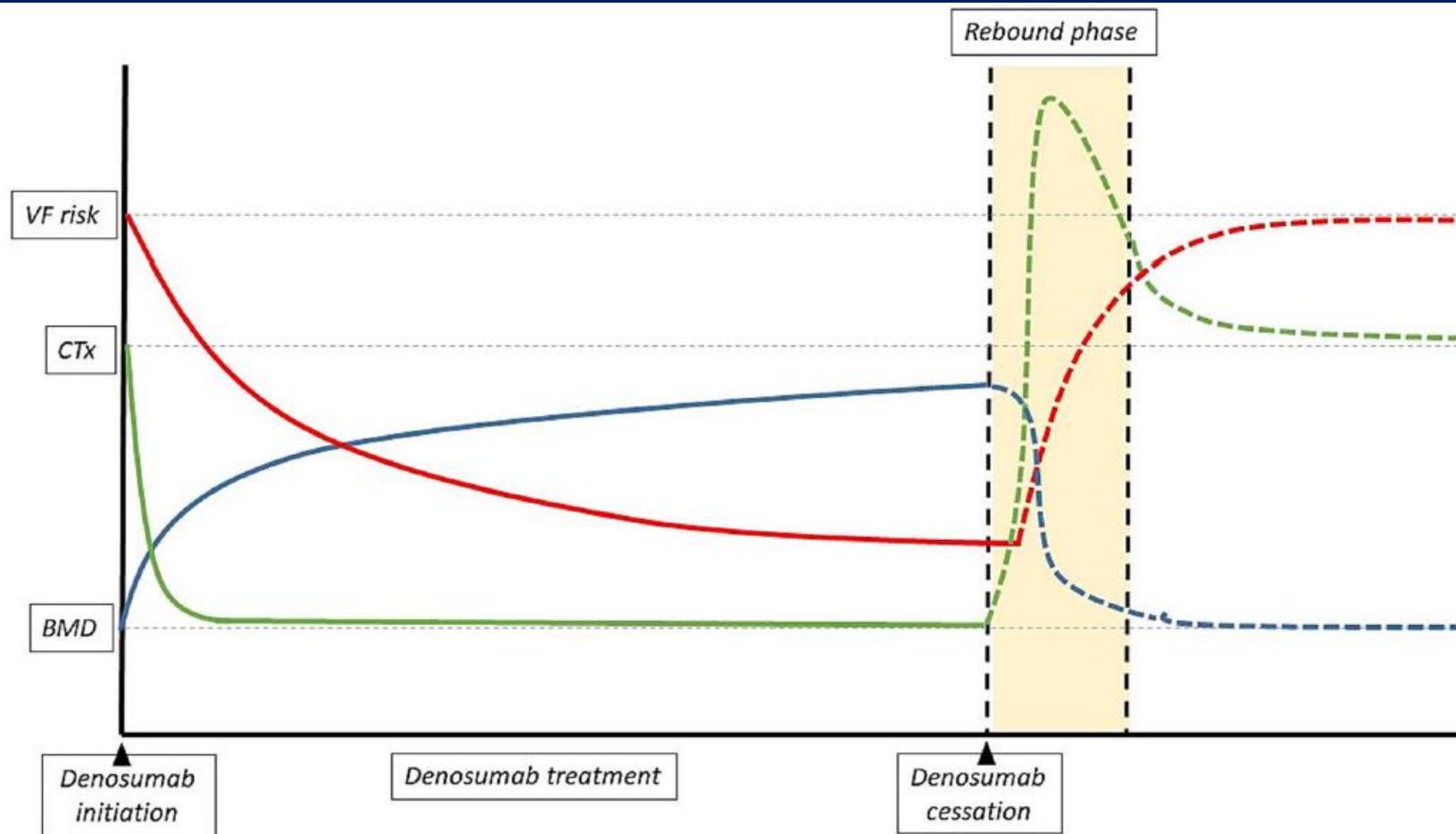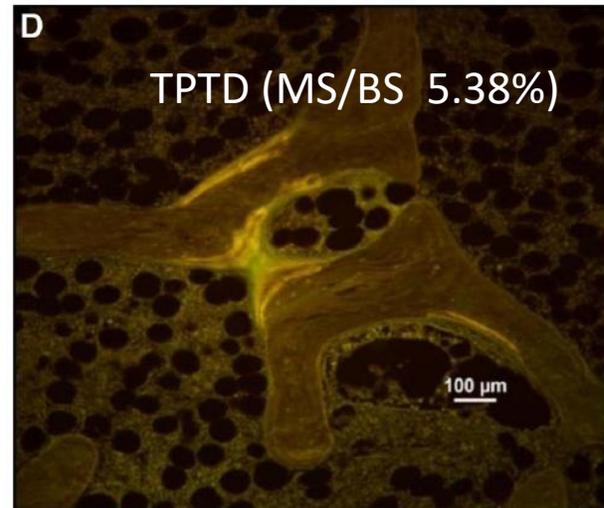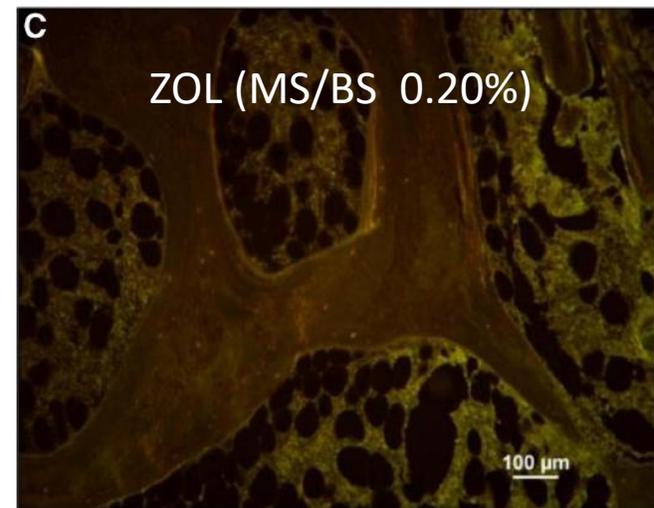

Table 2. Risk factors for developing vertebral fractures and/or BMD loss after denosumab withdrawal.

Prior to denosumab therapy	During denosumab therapy	After denosumab therapy
Prevalent VFs or other fragility fracture	Prevalent VFs or other fragility fracture	No bisphosphonate therapy
No bisphosphonate therapy	Longer treatment duration (>2-3 yr)	Longer duration off-therapy
Younger age	Greater BMD gain	Greater hip BMD loss
		Higher off-treatment CTx

Table summarized from references.[14–16,20,22,26,28–32] Abbreviations: CTx, C-telopeptide of type I collagen; VF, vertebral fractures.

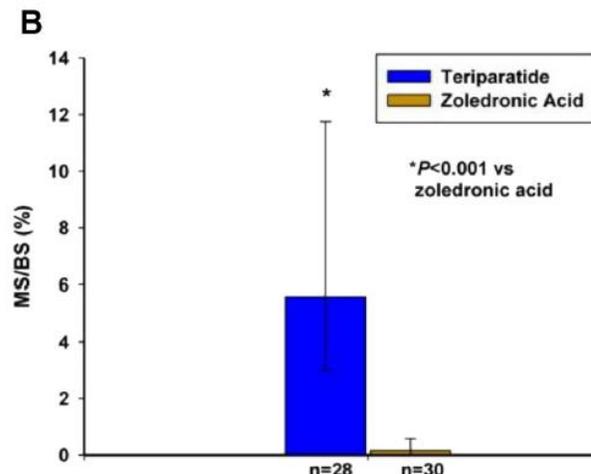Kumar et al., JBMR 2025, Denosumab discontinuation in the clinic - implications of rebound bone turnover and emerging strategies to prevent bone loss and fractures

Histomorphometry in Subjects on Teriparatide or Zoledronic Acid Therapiy (SHOTZ) Study
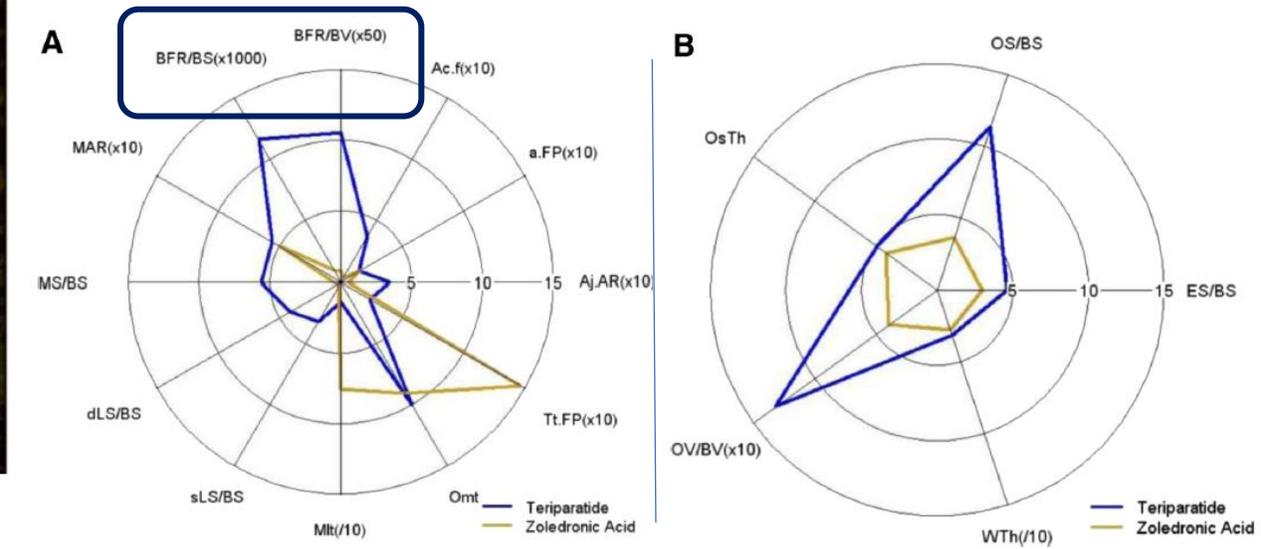
RCT, TPTD 20 μg/d sc (n=34) vs ZOL 5 mg i.v. (n=35), Histomorphometry at 6 months

A — *P<0.001 for between-group comparisons; Double or Single Label
Teriparatide / Zoledronic Acid

B — *P<0.001 vs zoledronic acid

C — ZOL (MS/BS 0.20%)   100 µm

D — TPTD (MS/BS 5.38%)   100 µm
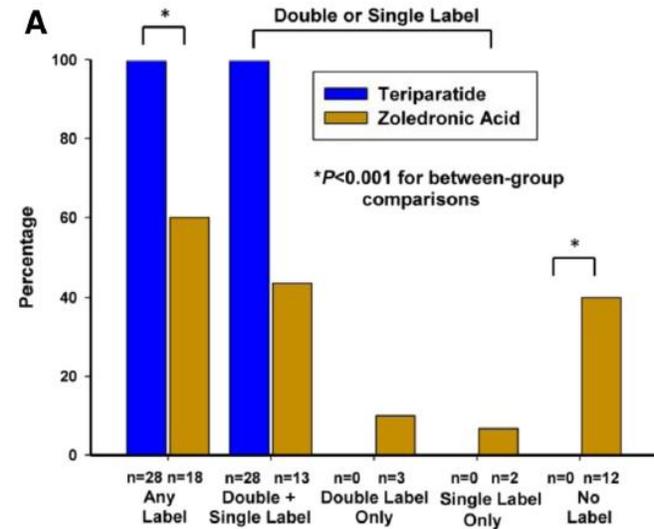
Dynamic parameters		Teriparatide, n		Zoledronic acid, n		Wilcoxon rank-sum P Value
Mineralizing surface/bone surface (MS/BS, %)	28	5.60 (3.00, 11.75)	30	0.16 (0.00, 0.58)		<0.001
Activation frequency (Ac.f, per year)[a]	28	0.37 (0.17, 0.82)	16	0.03 (0.01, 0.04)		<0.001
Bone formation rate/bone surface (BFR/BS, mm³/mm²/yr)[a]	28	0.0116 (0.0051, 0.0265)	16	0.0009 (0.0003, 0.0012)		<0.001
Bone formation rate/bone volume (BFR/BV, % per year)[a]	28	0.21 (0.10, 0.43)	16	0.01 (0.00, 0.03)		<0.001
Mineral apposition rate (MAR, μm/d)[a]	28	0.56 (0.48, 0.62)	16	0.50 (0.40, 0.52)		0.031
Adjusted apposition rate (Aj.AR, μm/d)[a]	28	0.34 (0.15, 0.51)	16	0.05 (0.02, 0.18)		<0.001
Mineralization lag time (Mlt, d)[a]	28	13.63 (11.22, 29.22)	16	75.72 (26.84, 193.78)		<0.001
Osteoid maturation time (Omt, d)[a]	28	9.99 (8.39, 10.74)	16	9.05 (7.83, 10.76)		0.502
Total formation period (Tt.FP, d)[a]	28	0.24 (0.16, 0.50)	16	1.46 (0.44, 3.10)		<0.001
Active formation period (a.FP, d)[a]	28	0.15 (0.14, 0.17)	16	0.16 (0.15, 0.19)		0.154
Double-label surface/bone surface (dLS/BS, %)	28	4.13 (2.14, 8.88)	30	0.07 (0.00, 0.30)		<0.001
Single-label surface/bone surface (sLS/BS, %)	28	3.19 (1.58, 4.86)	30	0.02 (0.00, 0.38)		<0.001
Double-label length (mm)	28	0.35 (0.28, 0.38)	16	0.24 (0.19, 0.30)		0.002
Static parameters, bone formation						
Osteoid volume/bone volume (OV/BV, %)	28	1.32 (0.81, 2.13)	30	0.24 (0.08, 0.49)		<0.001
Osteoid surface/bone surface (OS/BS, %)	28	11.34 (6.58, 16.52)	30	2.51 (1.27, 4.58)		<0.001
Osteoid thickness (OsTh, μm)	28	4.92 (4.29, 6.68)	30	3.77 (3.51, 4.22)		<0.001
Wall thickness (WTh, μm)	28	31.29 (28.80, 33.26)	30	28.63 (27.16, 30.43)		0.014
Static parameters, bone resorption						
Eroded surface/bone surface (ES/BS, %)	28	4.59 (3.14, 6.01)	30	2.71 (1.73, 3.21)		<0.001

A — BFR/BS(x1000), BFR/BV(x50), Ac.f(x10), a.FP(x10), Aj.AR(x10), Tt.FP(x10), Omt, Mlt(/10), sLS/BS, dLS/BS, MS/BS, MAR(x10); Teriparatide / Zoledronic Acid

B — OS/BS, OsTh, OV/BV(x10), WTh(/10), ES/BS; Teriparatide / Zoledronic Acid

Dempster et al., JCEM 2012, Skeletal Histomorphometry in Subjects on Teriparatide or Zoledronic Acid Therapiy (SHOTZ) Study - A Randomized Controlled Trial