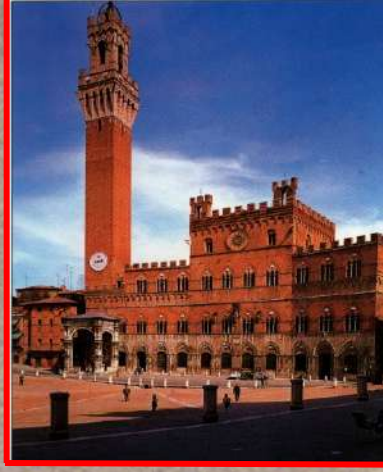
Azienda Ospedaliero-Universitaria Senese
Dipartimento Di Scienze Mediche
Dir. B. Frediani
U.O.C. REUMATOLOGIA
Dir. B. Frediani



LA GESTIONE DELLA NON RESPONSIVITA' TERAPEUTICA NELL'OSTEOPOROSI

BRUNO FREDIANI

Valutazione dell'insuccesso terapeutico

3 possibili parametri da valutare:

- ✓ Insorgenza di un frattura (basta 1? Rx annuale?)
- ✓Riduzione della BMD (tutte le sedi? >2% o Tscore >-2)
- ✓Variazione dei marcatori di turnover osseo (solo in alcuni casi?)

Pseudo Insuccesso terapeutico?

- ***Erronea identificazione di una frattura***

- ***Esecuzione non corretta dell'esame densitometrico o non corretta interpretazione dei risultati***

- ***Non sufficiente tempo di follow up***

- ***Impossibilità di comparazione dell'esame densitometrico***

- ***Discrepanza dei valori di BMD ottenuti nei diversi distretti scheletrici (in particolare BMDlombare/ femorale)***

Valutazione dell'insuccesso terapeutico

Reference	Year	BMD Decline	Incident Fracture	Minimum treatment (months)
Del Puente et al	2000	Yes	-----	12
Heckman et al	2002	Yes	Yes	12
Sawka et al	2003	Yes	Yes	<24
Lewiecki et al	2003	Yes	----	-----
Nice	2004	Yes	Yes	12
Jakob et al (OSSO study)	2006	-----	Yes	12
Obermayer-Pietsch BM, et al EUROFORS Study	2006	-----	Yes	12
Adami et al, ICARO study	2006	-----	Yes	6
Diez-Perez et al	2007	Yes	Yes	12
Diez-Perez et al*	2012	Yes	Yes	12

* Utilizzo dei marcatori di turnover osseo

Valutazione dell'insuccesso terapeutico

Fracture Incidence and Characterization in Patients on Osteoporosis Treatment: The ICARO Study

Silvano Adami,[1] Giancarlo Isaia,[2] Giovanni Luisetto,[3] Salvatore Minisola,[4] Luigi Sinigaglia,[5] Raffaella Gentilella,[6] Donato Agnusdei,[7] Nicoletta Iori,[6] and Ranuccio Nuti,[8] on behalf of ICARO Study Group

ABSTRACT: None of the available osteoporosis therapies have been shown to completely abolish the risk of fractures. In clinical practice, the outcome may be even poorer. In 880 patients prescribed with antiresorptives (alendronate, risedronate, and raloxifene) for >1 year, a fragility fracture was recorded in 8.9%/year of them. This incidence is considerably higher than that observed in randomized clinical trials, and it was significantly related to poor compliance and lack of supplementation with calcium and vitamin D.

Introduction: Osteoporotic fracture is one of the most important public health concerns among the elderly. Currently available therapies have been shown to significantly decrease the risk of fracture, although none of them completely abolishes this risk. In clinical practice, poor treatment response may also result from a number of other factors.

Materials and Methods: The Incidence and ChAracterization of inadequate clinical Responders in Osteoporosis (ICARO) is a multicenter, observational study carried out in Italy. It aimed to analyze, in postmenopausal women with established osteoporosis, the risk factors for an "inadequate clinical response" to drug therapy, defined as the occurrence of new vertebral or nonvertebral fragility fractures in patients prescribed for at least 1 year, alendronate, risedronate, or raloxifene, with a compliance >50%.

Results: In 880 patients treated with antiresorptive agents for a median of 2.0 years (95% CI: 1.0–4.5) years, the "inadequate clinical responder (ICR)" subjects over the observation period were 220 (25%), with an annual incidence of 8.9%. ICRs, compared with "adequate clinical responders (ACRs)," had more pretreatment fractures and were treated longer (2.8 versus 1.8 years; $p < 0.001$). After multiple adjustment for these confounding factors, significant determinants of inadequate clinical response were a poorer treatment compliance and a less frequent co-administration of calcium and vitamin D supplements.

Conclusions: The incidence of fractures during treatment with antiresorptive agents in a clinical setting is considerably higher than that observed in randomized clinical trials. Inadequate compliance to treatment and lack of supplementation of calcium and vitamin D are major determinants of this poor response.

Journal of Bone and Mineral Research 2006

Inadequate responders to osteoporosis treatment: proposal for an operational definition

A. Díez-Pérez · J. González-Macías

1. Inadequate response—incident fracture *and* a decrease in BMD greater than 2%, defined as a significant change according to the concept of the Trend Assessment Margin (TAM).
2. Possible inadequate response—incident fracture *or* a decrease in BMD greater than 2% (TAM).
3. Adequate response—no fracture *and* no decrease in BMD greater than 2% (TAM).

All these outcomes are based on patients with good compliance who have been under treatment for a minimum of 1 year.

Osteoporosis Int 2008

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

POSITION PAPER

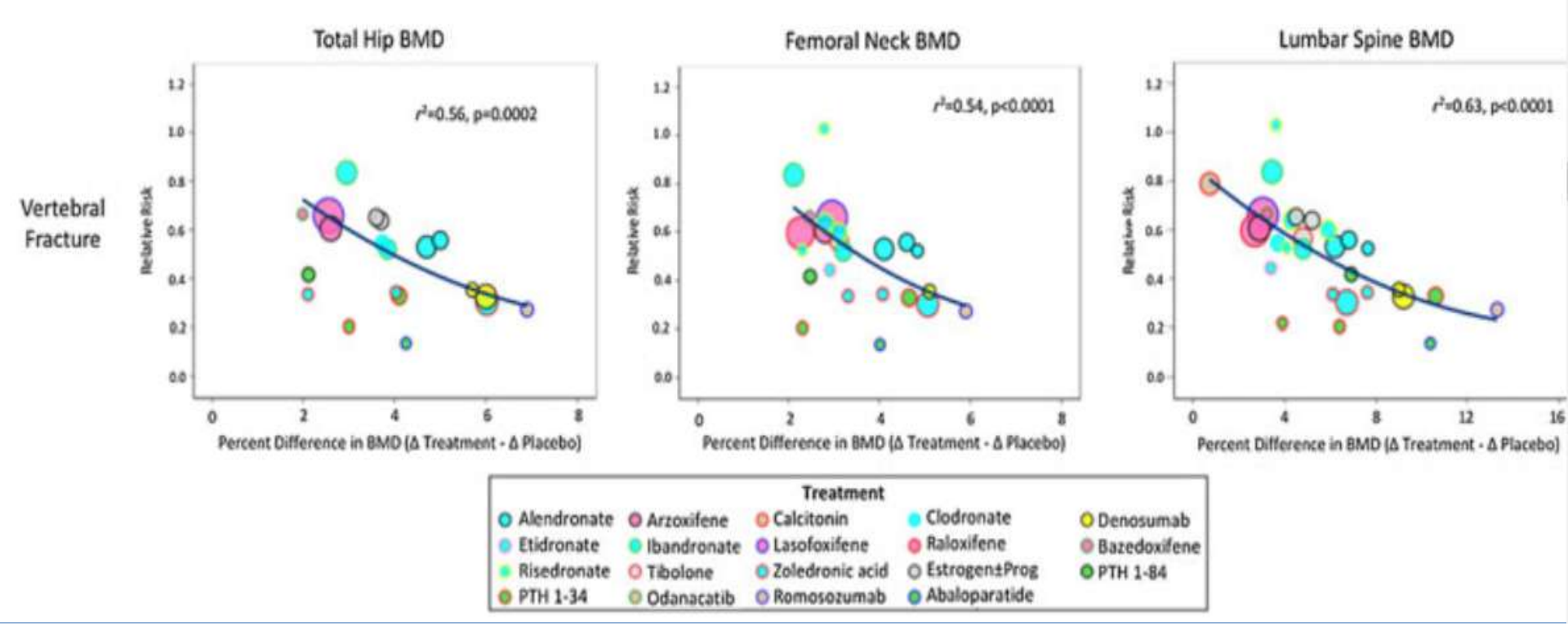
Treatment failure in osteoporosis

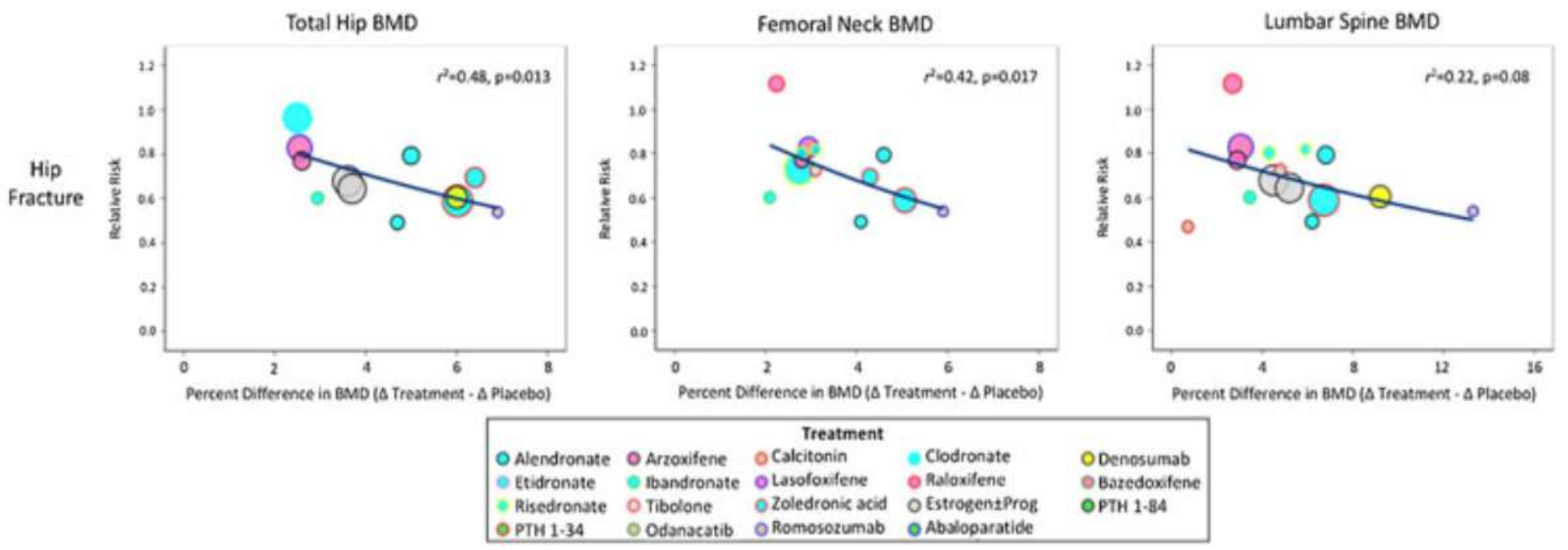
A. Diez-Perez · J. D. Adachi · D. Agnusdei · J. P. Bilezikian · J. E. Compston · S. R. Cummings · R. Eastell · E. F. Eriksen · J. Gonzalez-Macias · U. A. Liberman · D. A. Wahl · E. Seeman · J. A. Kanis · C. Cooper
for the IOF CSA Inadequate Responders Working Group

(1) two or more incident fragility fractures;
(2) one incident fracture and elevated serum βCTX or PINP at baseline with no significant reduction during treatment, a significant decrease in BMD, or both; and
(3) both no significant decrease in serum βCTX or PINP and a significant decrease in BMD.

1. Fractures of the hand, skull, digits, feet and ankle are not considered as fragility fractures.
2. The overall decline in BMD should be in the order of 5 % or more in at least two serial BMD measurements at the lumbar spine or 4 % at the proximal femur.
3. Sequential measurement of markers of bone turnover should use the same assay. A significant response is a decline of 25 % from baseline levels for anti-resorptive treatments, and 25 % increase for anabolic agents (PTH) after 6 months. For anti-resorptive treatments, if baseline levels are not known, a positive response is a decrease below the average value of young healthy adults. It is assumed that the response is similar between men and women.
4. Falls are an important driver of fracture. Therefore this problem should be considered when analysing response to treatments.

Osteoporosis Int 2012


Vertebral Fracture
Total Hip BMD
Femoral Neck BMD
Lumbar Spine BMD
r^2=0.56, p=0.0002
r^2=0.54, p<0.0001
r^2=0.63, p<0.0001
Relative Risk
Percent Difference in BMD (Δ Treatment - Δ Placebo)
Treatment
Alendronate
Arzoxifene
Calcitonin
Clodronate
Denosumab
Etidronate
Ibandronate
Lasofoxifene
Raloxifene
Bazedoxifene
Risedronate
Tibolone
Zoledronic acid
Estrogen±Prog
PTH 1-84
PTH 1-34
Odanacatib
Romosozumab
Abaloparatide


Hip Fracture
Total Hip BMD
Femoral Neck BMD
Lumbar Spine BMD
r^2=0.48, p=0.013
r^2=0.42, p=0.017
r^2=0.22, p=0.08
Relative Risk
Percent Difference in BMD (Δ Treatment - Δ Placebo)
Treatment
Alendronate
Arzoxifene
Calcitonin
Clodronate
Denosumab
Etidronate
Ibandronate
Lasofoxifene
Raloxifene
Bazedoxifene
Risedronate
Tibolone
Zoledronic acid
Estrogen±Prog
PTH 1-84
PTH 1-34
Odanacatib
Romosozumab
Abaloparatide

REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Western Osteoporosis Alliance Clinical Practice Series: Treat-to-Target for Osteoporosis

E. Michael Lewiecki, MD,[a] David L. Kendler, MD,[b] K. Shawn Davison, PhD,[c] David A. Hanley, MD,[d] Steven T. Harris, MD,[e] Michael R. McClung, MD,[f,g] Paul D. Miller, MD[h]

[a]New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM; [b]Department of Medicine (Endocrinology), University of British Columbia, Vancouver, Canada; [c]A Priori Medical Sciences, Inc., Victoria, British Columbia, Canada; [d]Departments of Medicine, Community Health Sciences, and Oncology, Cumming School of Medicine and McCaig Institute for Bone and Joint Health Cumming School of Medicine, The University of Calgary, Calgary, Alberta, Canada; [e]University of California, San Francisco, CA; [f]Oregon Osteoporosis Center and Oregon Health & Science University, Portland, OR; [g]Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Victoria, Australia; [h]Colorado Center for Bone Research, Lakewood, CO.

- **TARGET: T-score > -2**

  T-score ≥ - 1

  Se T-score di partenza è < -3 ?

Insuccesso terapeutico:Quali Cause ?

- **Scarsa aderenza alla terapia**
- **Inadeguata durata del trattamento**
- **Insufficiente apporto di calcio e Vitamina D**
- **Fattori legati alla scelta del farmaco per quel paziente:**

errore di diagnosi, eventuali comorbidità (patologie autoimmunitarie insufficienza renale, demenza, morbo di Parkinson), assunzione di altre terapie (corticosteroidi, PPI, anticoagulanti), abitudini di vita (fumo, alcool, non attività fisica, frequenti cadute, una basso BMI), pregresse fratture

Perchè scarsa Aderenza alla terapia?

- ***Problematiche legate alla terapia*: comparsa di effetti collaterali, (ad esempio eventi avversi GI in corso di terapia con bifosfonati), costo della terapia, modalità di somministrazione ed interferenza con la vita quotidiana del paziente**

- ***Problematiche legate al paziente*: Mancata consapevolezza della patologia e in particolare delle sue conseguenze, scetticismo circa l'efficacia della terapia in atto**

- ***Problematiche legate al rapporto medico-paziente***

Silvermann S, Gold D.T., Rev Endocr Metab Disord 2010

Fracture Incidence and Characterization in Patients on Osteoporosis Treatment: The ICARO Study

Silvano Adami,[1] Giancarlo Isaia,[2] Giovanni Luisetto,[3] Salvatore Minisola,[4] Luigi Sinigaglia,[5] Raffaella Gentilella,[6] Donato Agnusdei,[7] Nicoletta Iori,[6] and Ranuccio Nuti,[8] on behalf of ICARO Study Group

TABLE 1. BASELINE CHARACTERISTICS OF STUDY POPULATION

	All patients (N = 880)	*ICRs (N = 220)*	*ACRs (N = 660)*	*ACRs vs. ICRs p*
Age (years)	68 (53–79)	69 (52–79)	67 (53–79)	NS
Body mass index (kg/m^2)	25.2 (19.5–33.3)	25.3 (19.2–35.2)	25.1 (19.5–32.8)	NS
Disease duration (years)*	2.8 (1.1–1.2)	3.8 (1.1–12.8)	2.6 (1.1–10.3)	<0.001
Treatment duration (years)†	2.0 (1.0–4.5)	2.8 (1.1–4.7)	1.8 (1.0–4.4)	<0.001
Prevalent fractures:				
1 vertebral	366 (41.6%)	66 (30.0%)	300 (45.4%)	<0.001
>1 vertebral	415 (47.1%)	121 (55.0%)	294 (44.5%)	<0.001
Hip	40 (4.5%)	9 (4.1%)	31 (4.7%)	<0.001
Vertebral + nonvertebral	59 (6.7%)	24 (10.9%)	35 (5.3%)	<0.001
Prevalent traumatic fractures	95 (10.8%)	26 (11.8%)	69 (10.4%)	NS
Treatment distribution:				NS
Alendronate	468 (53.2%)	128 (58.2%)	340 (51.5%)	
Risedronate	139 (15.8%)	19 (8.6%)	120 (18.2%)	
Raloxifene	99 (11.2%)	17 (7.7%)	82 (12.4%)	
Mixture	174 (19.8%)	56 (25.4%)	118 (17.9%)	
Co-administration of calcium and vitamin D				
No	332 (37.7%)	100 (45.5%)	232 (35.2%)	0.02
Yes, compliance < 50%	109 (12.4%)	22 (10.0%)	87 (13.2%)	
Yes, compliance > 50%	439 (49.9%)	98 (44.5%)	341 (51.7%)	
Compliance to treatment:				
50–75%	55 (6.2%)	21 (9.5%)	34 (5.1%)	0.004
>75%	748 (85.0%)	174 (79.1%)	574 (87.0%)	
Not determined	77 (8.7%)	25 (11.4%)	52 (7.9%)	

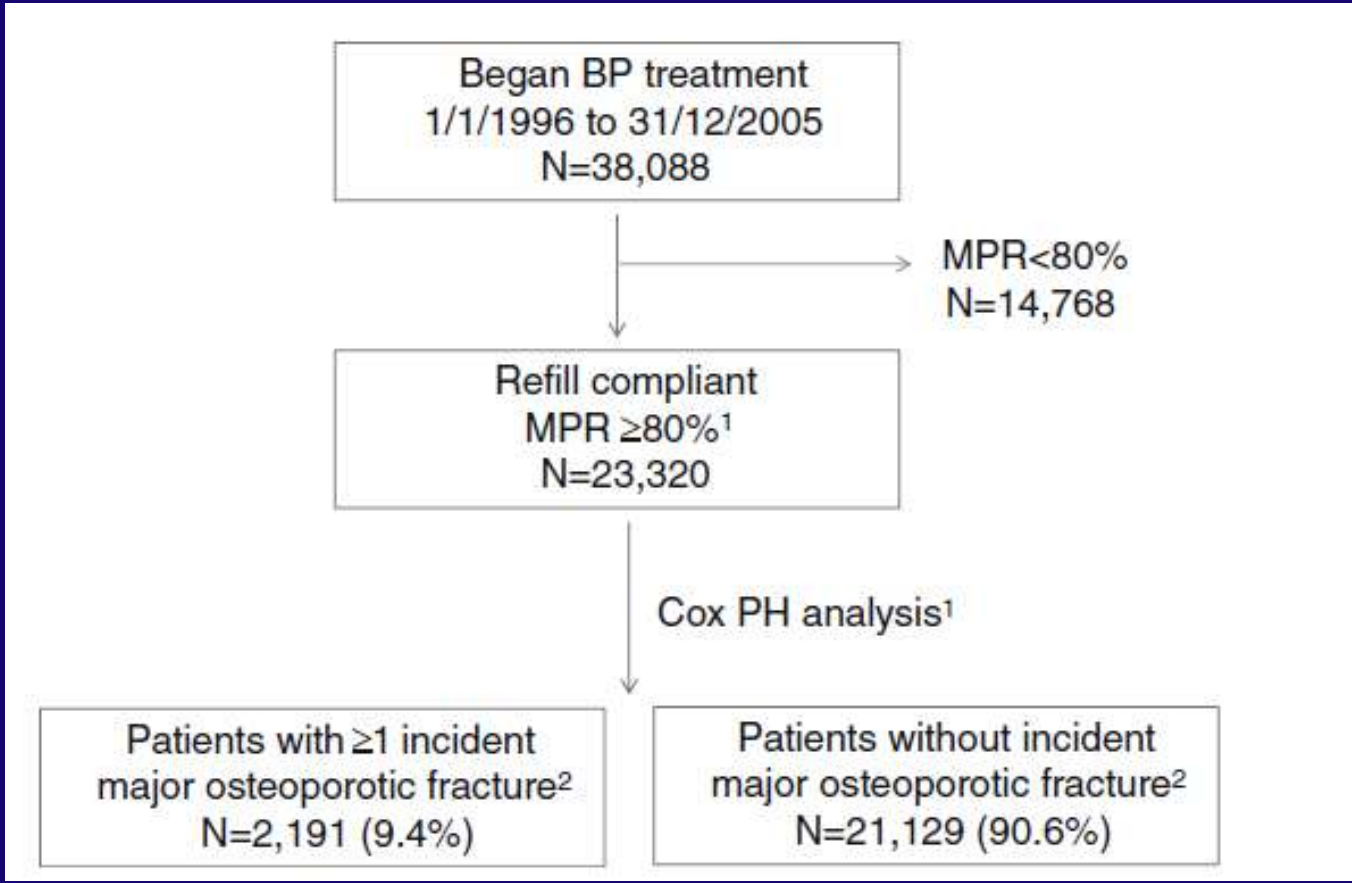
Journal of Bone and Mineral Research 2006

Insuccesso terapeutico:Quali Cause ?

- **Scarsa aderenza alla terapia**
- **Inadeguata durata del trattamento**
- **Insufficiente apporto di calcio e Vitamina D**
- **Fattori legati alla scelta del farmaco per quel paziente: errore di diagnosi, eventuali comorbidità (patologie autoimmunitarie insufficienza renale, dolore, demenza, morbo di Parkinson), assunzione di altre terapie (corticosteroidi, PPI, anticoagulanti), abitudini di vita (fumo, alcool, non attività fisica, frequenti cadute, un basso BMI), pregresse fratture e grado di severità**

Characteristics of patients who suffer major osteoporotic fractures despite adhering to alendronate treatment: a National Prescription registry study

B. Abrahamsen · K. H. Rubin · P. A. Eiken · R. Eastell



Osteoporosis Int 2013

Characteristics of patients who suffer major osteoporotic fractures despite adhering to alendronate treatment: a National Prescription registry study

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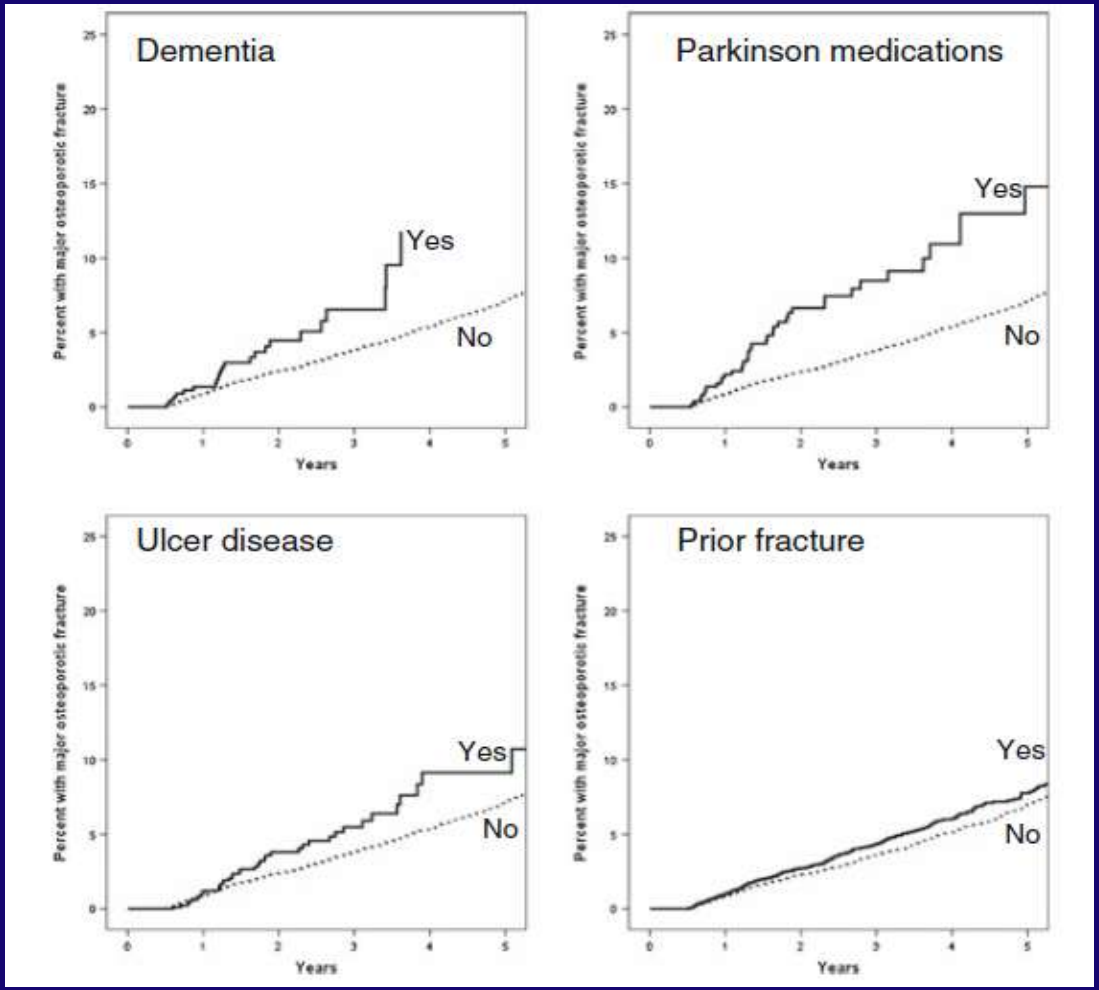


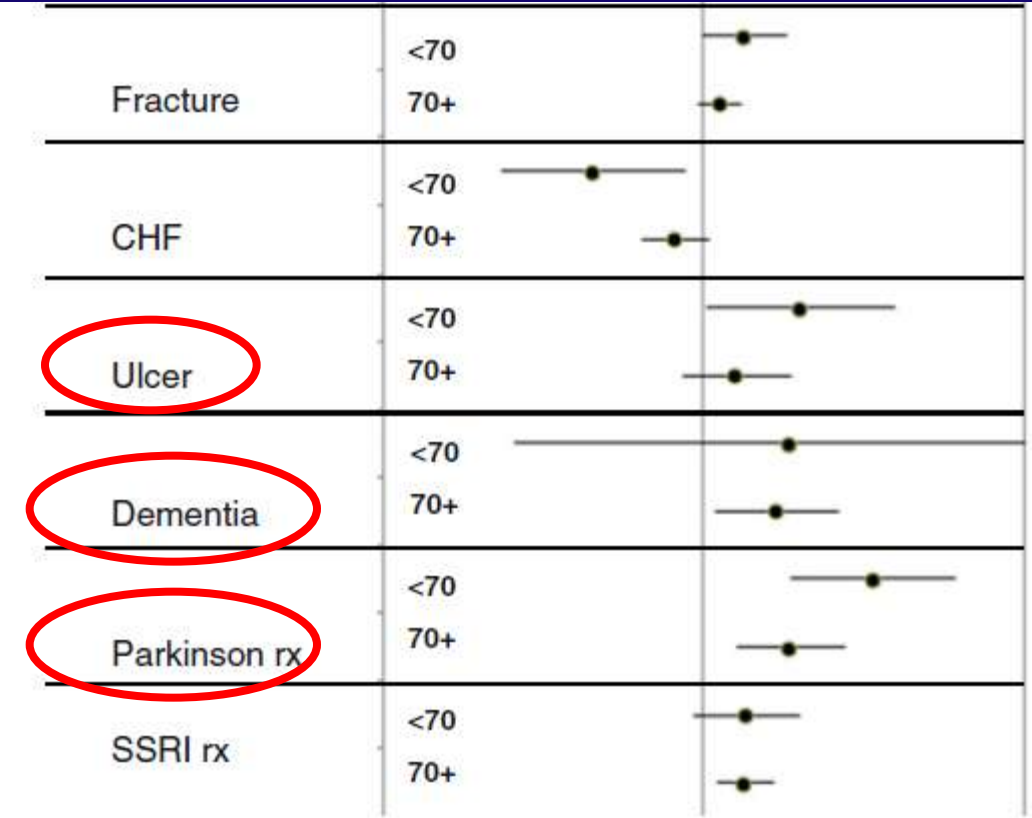
Osteoporosis Int 2013

Characteristics of patients who suffer major osteoporotic fractures despite adhering to alendronate treatment: a National Prescription registry study

B. Abrahamsen · K. H. Rubin · P. A. Eiken · R. Eastell

Maggior rischio legato sia all' assunzione di PPI, alla difficoltà nell'assunzione di BF e alla stessa infezione da HP

Immobilizzazione, maggiore facilità alle cadute, concomitante assunzione di altri farmaci, difficoltà nell'assunzione della tp secondo le modalità prescritte



Questo studio evidenzia la presenza di condizioni cliniche che identificano un sottogruppo di pz ad elevato rischio di risposta insoddisfacente alla terapia in corso

Osteoporosis Int 2013

Drug class	Active substance	Possible mechanism of action
Glucocorticoids*	Hydrocortisone, prednisone, dexamethasone	Inhibition of osteoblast activity/osteocyte apoptosis
Aromatase inhibitors*	Letrozole, anastrozole, examestane	Hypogonadism with high turnover
SSRIss*	Citalopram, fluoxetine, paroxetine	Inhibition of osteoblast proliferation, RANKL activation
Proton pump inhibitors*	Esomeprazole, omeprazole, lansoprazole	Reduced calcium intestinal absorption
H2-inhibitors	Ranitidine, cimetidine	Reduced calcium absorption
Thiazolidinediones*	Rosiglitazone, pioglitazone	Inhibition of bone formation and osteoblast differentiation
Thyroid hormone (excess)*	Levothyroxine	Increased bone turnover
Anticoagulants*	Heparin, warfarin	Reduced osteocalcin activity
Anticonvulsants*	Phenobarbital, valproic acid, oxcarbazepine, phenytoin	Altered vitamin D metabolism
GnRH*	Leuprolide, goserelin	Hypogonadism with high turnover
Loop diuretics	Furosemide	Calciuric effect
Antiretroviral agents	Efavirenz, nevirapine Tenofovir Protease inhibitors	Altered vitamin D metabolism Increased urinary phosphate excretion Inhibition of osteoblastogenesis/increased RANKL
Calcineurin inhibitors*	Ciclosporin A (high doses), tacrolimus	Increased bone turnover. Increased RANKL expression
Parenteral nutrition		Unclear

*Evidence for an association with fracture risk. SSRI, selective serotonin reuptake inhibitors; GnRH, gonadotropin-releasing hormones.

PREFERIBILMENTE QUANDO….
(in assenza di controindicazioni)

- AminoBisfosfonati: Alto Turnover, Inizio Menopausa in Sequenziale, Cortisonati (Ale, Ris, Zol), Maschio (Ale, Ris, Zol), Tumori
- NonAminobisfosfonati (Clodronato): **in** +Dolore, Edema Osseo, Artrosi, Flogosi
- Denosumab: Insuff. Renale, Alto Turnover, Alto Rischio (>20%)
- SERMS: Inizio menopausa in sequenziale (senza S. Climaterica), Tumore Seno
- HRT: Inizio menopausa in sequenziale (presenza di S. Climaterica)
- Calcitonina: Dolore non responsivo, impossibilità di terapia orale
- Teriparatide: alto rischio (>20%), Cortisonati, Dolore, Basso turnover
- Romosozumab: alto rischio (>30%),
-
- Stronzio Ranelato: Basso turnover , Artrosi.

TERAPIE SEQUENZIALI

- BISFOSF. (os)
  - ANTIRIASSORBITORE
    - BISFOSFONATO (via somm. Es ZOL)
    - DENOSUMAB
  - TERIPARATIDE
  - ROMOSOZUMAB
- DENOSUMAB
  - SI' BISFOSFONATO
  - NO TERIPARATIDE
  - SI' ROMOSOZUMAB
- TERIPARATIDE → BISFOSF. (os), DENOSUMAB
- ROMOSOZUMAB → BISFOSF. (os), DENOSUMAB

TERAPIE SEQUENZIALI

- BISFOSF. (os)
  - ANTIRIASSORBITORE
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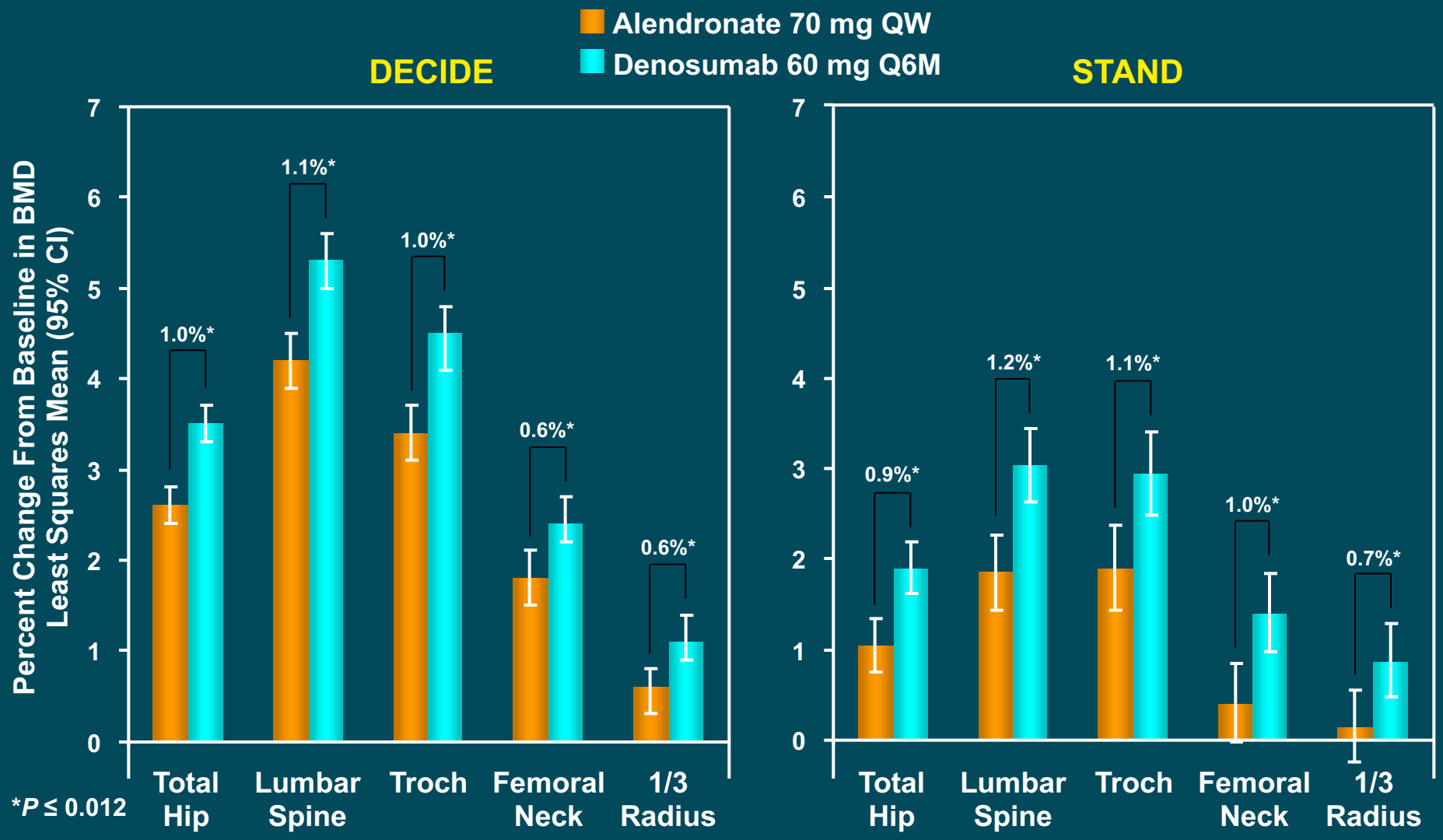
- TERIPARATIDE
  - BISFOSF. (os)
  - DENOSUMAB
- ROMOSOZUMAB
  - BISFOSF. (os)
  - DENOSUMAB

Different Percent Changes in BMD for All Evaluated Skeletal Sites at Month 12



Adapted from: Brown JP, et al. *J Bone Miner Res.* 2009;24:153-161; Kendler DL, et al. *J Bone Miner Res.* 2010;25:72-81

TERAPIE SEQUENZIALI

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- TERIPARATIDE → BISFOSF. (os), DENOSUMAB
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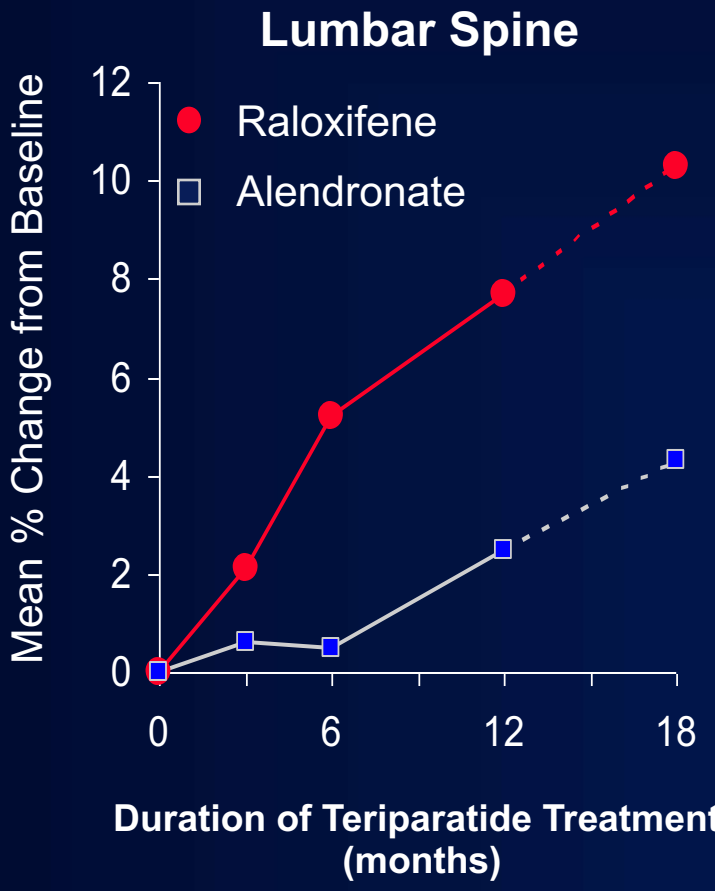
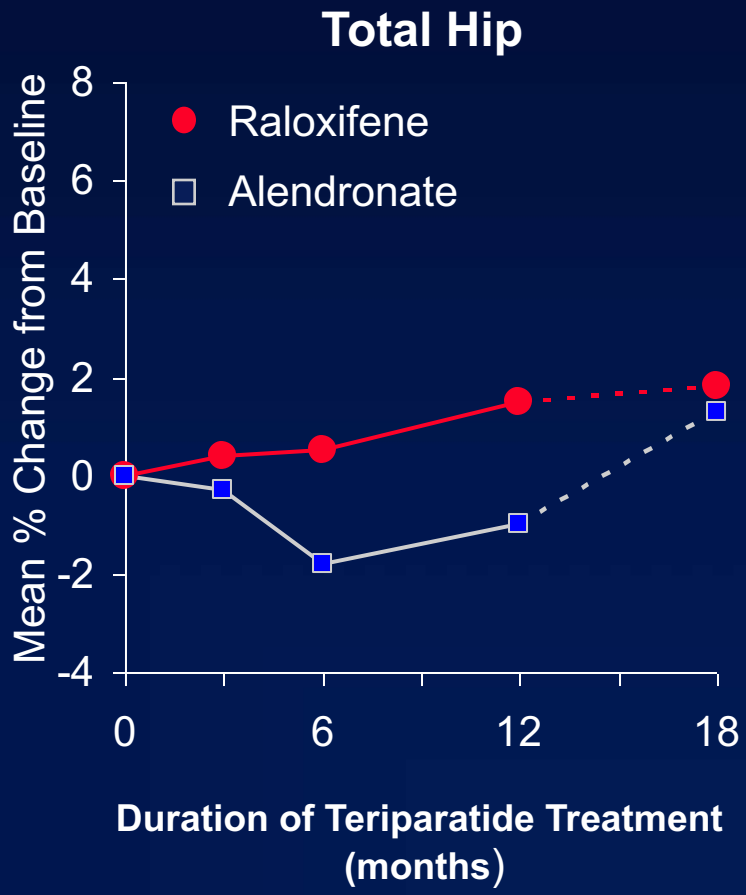
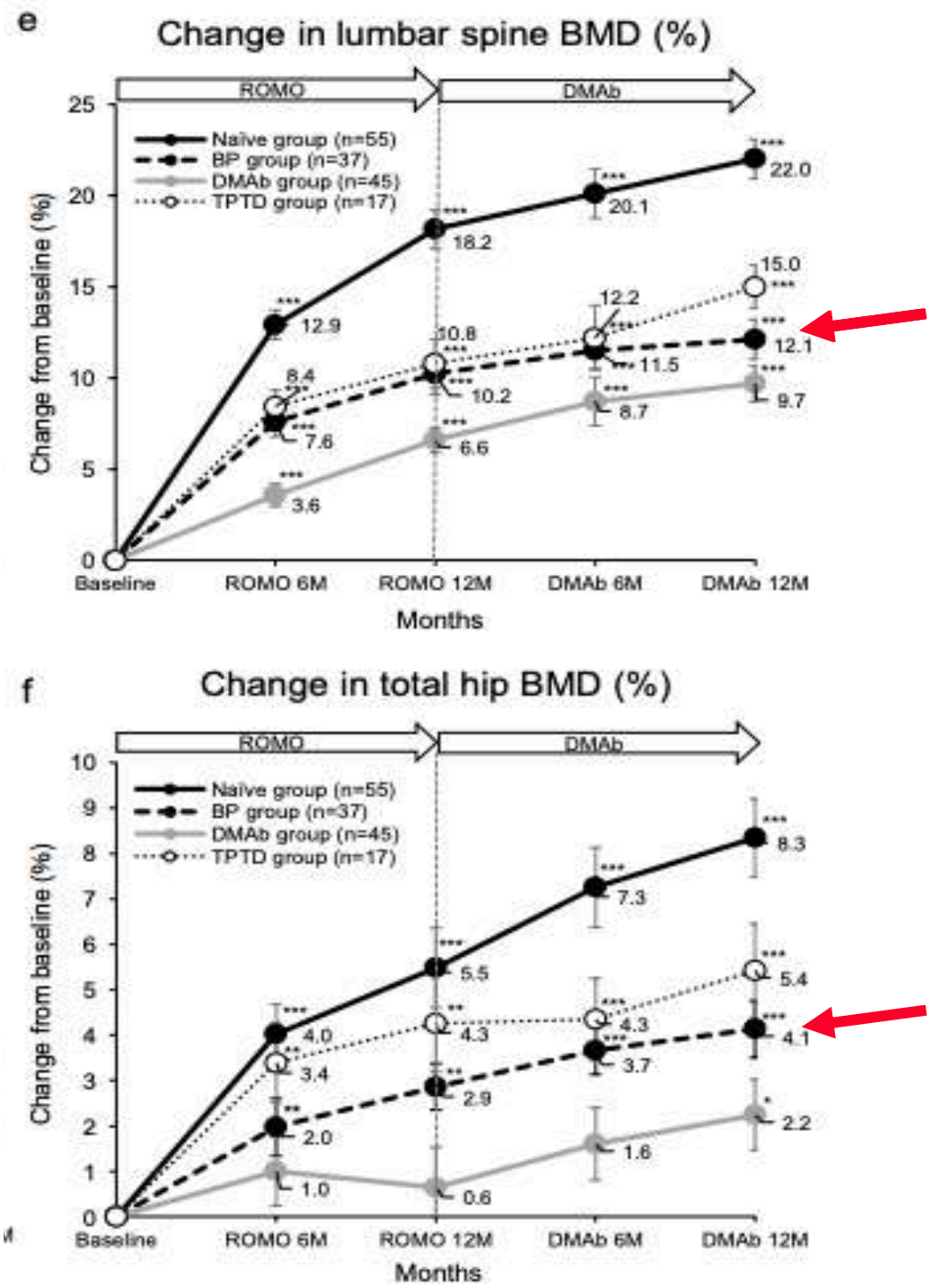
AAA Study: 12 and 18 month analyses
Bone Mineral Density





Ettinger B. et al., JBMR, 2004

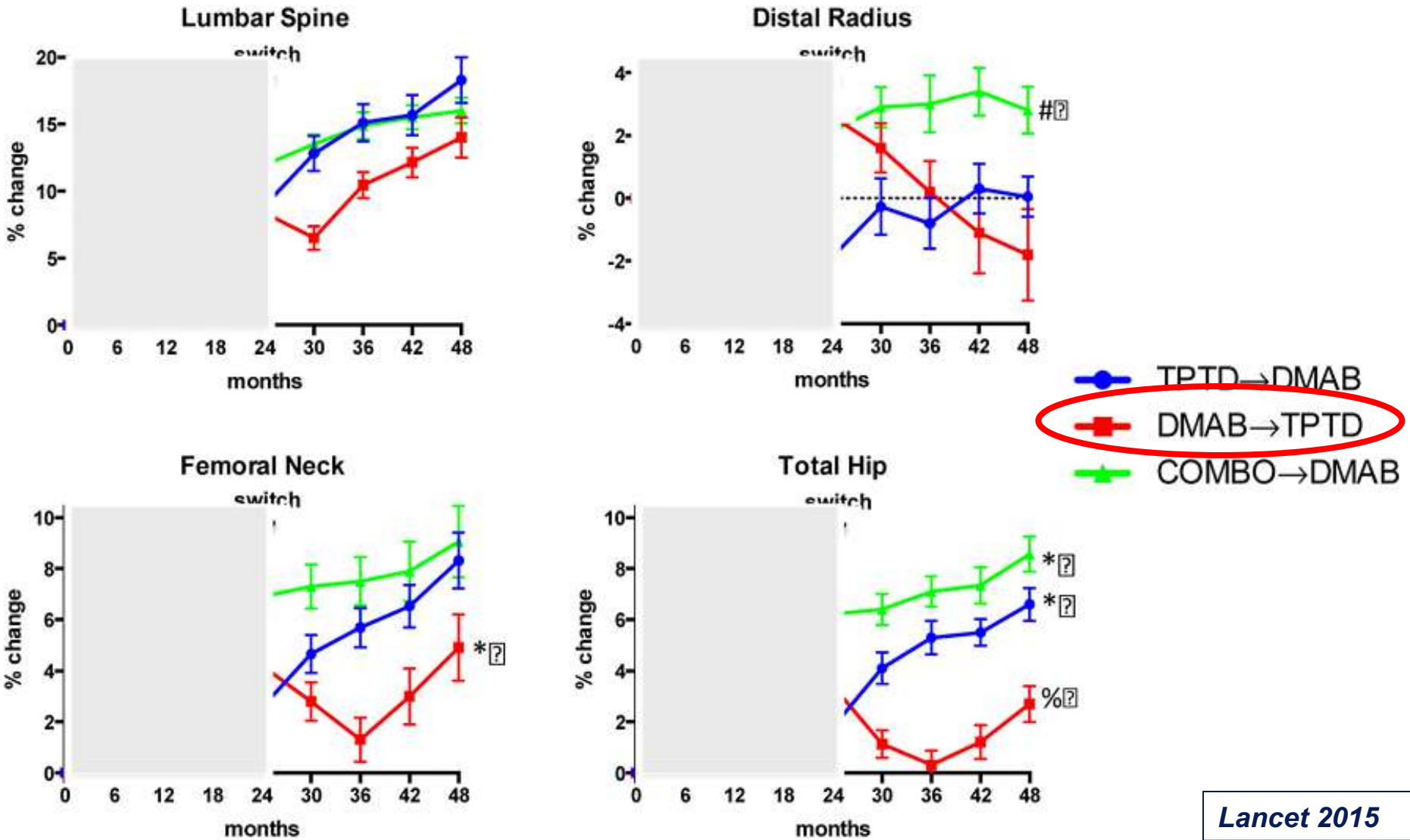

e
Change in lumbar spine BMD (%)
ROMO
DMAb
Naive group (n=55)
BP group (n=37)
DMAb group (n=45)
TPTD group (n=17)
Change from baseline (%)
25
20
15
10
5
0
12.9
18.2
20.1
22.0
8.4
10.8
12.2
15.0
7.6
10.2
11.5
12.1
3.6
6.6
8.7
9.7
Baseline
ROMO 6M
ROMO 12M
DMAb 6M
DMAb 12M
Months
f
Change in total hip BMD (%)
ROMO
DMAb
Naive group (n=55)
BP group (n=37)
DMAb group (n=45)
TPTD group (n=17)
Change from baseline (%)
10
9
8
7
6
5
4
3
2
1
0
4.0
5.5
7.3
8.3
3.4
4.3
4.3
5.4
2.0
2.9
3.7
4.1
1.0
0.6
1.6
2.2
Baseline
ROMO 6M
ROMO 12M
DMAb 6M
DMAb 12M
Months

TERAPIE SEQUENZIALI

- BISFOSF. (os)
  - ANTIRIASSORBITORE
    - BISFOSFONATO (via somm. Es ZOL)
    - DENOSUMAB
  - TERIPARATIDE
  - ROMOSOZUMAB
- DENOSUMAB
  - SI' BISFOSFONATO
  - NO TERIPARATIDE
  - SI' ROMOSOZUMAB
- TERIPARATIDE → BISFOSF. (os)
- ROMOSOZUMAB → DENOSUMAB

Denosumab and Teriparatide Transitions in Postmenopausal Osteoporosis (The DATA-Switch Study): a Randomised Controlled Trial

Benjamin Z. Leder, MD, Joy N. Tsai et al.



Lancet 2015

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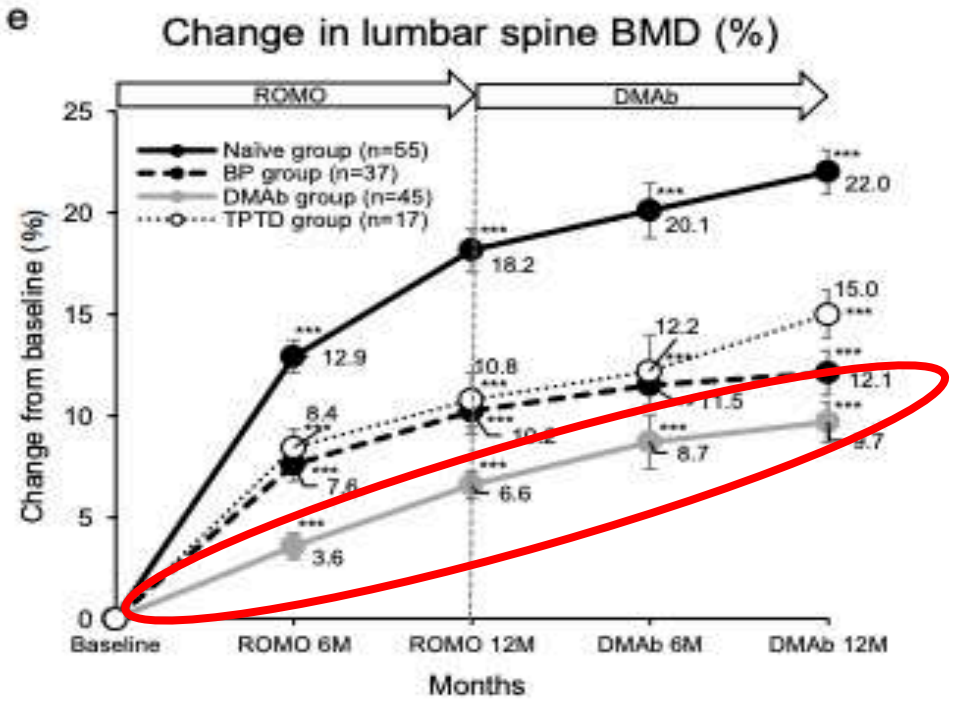
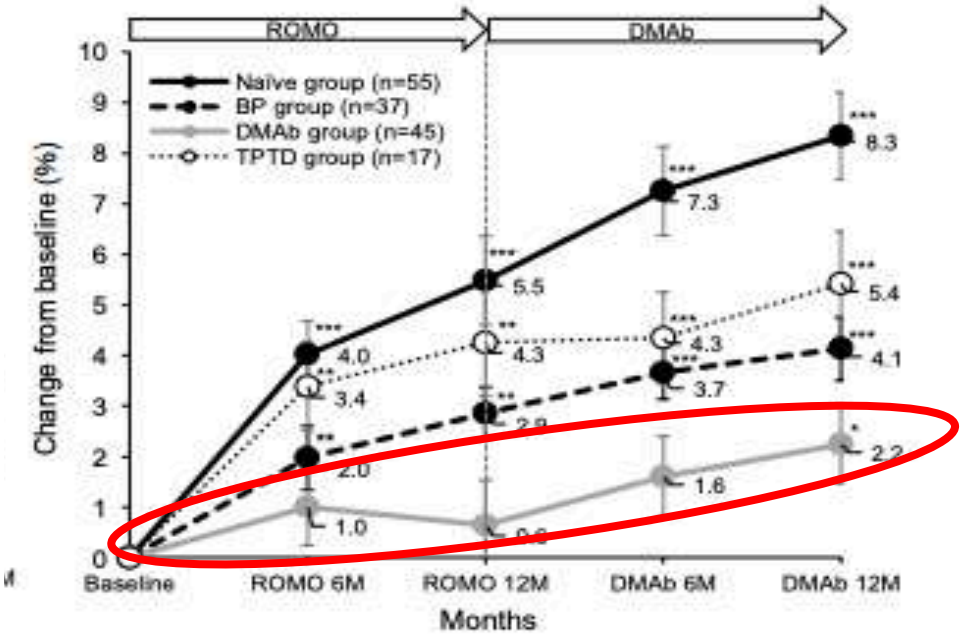

Change in lumbar spine BMD (%)
ROMO
DMAb
Naive group (n=55)
BP group (n=37)
DMAb group (n=45)
TPTD group (n=17)
Change from baseline (%)
25
20
15
10
5
0
12.9
18.2
20.1
22.0
8.4
10.8
12.2
15.0
7.6
11.5
12.1
6.6
8.7
9.7
3.6
Baseline
ROMO 6M
ROMO 12M
DMAb 6M
DMAb 12M
Months

f

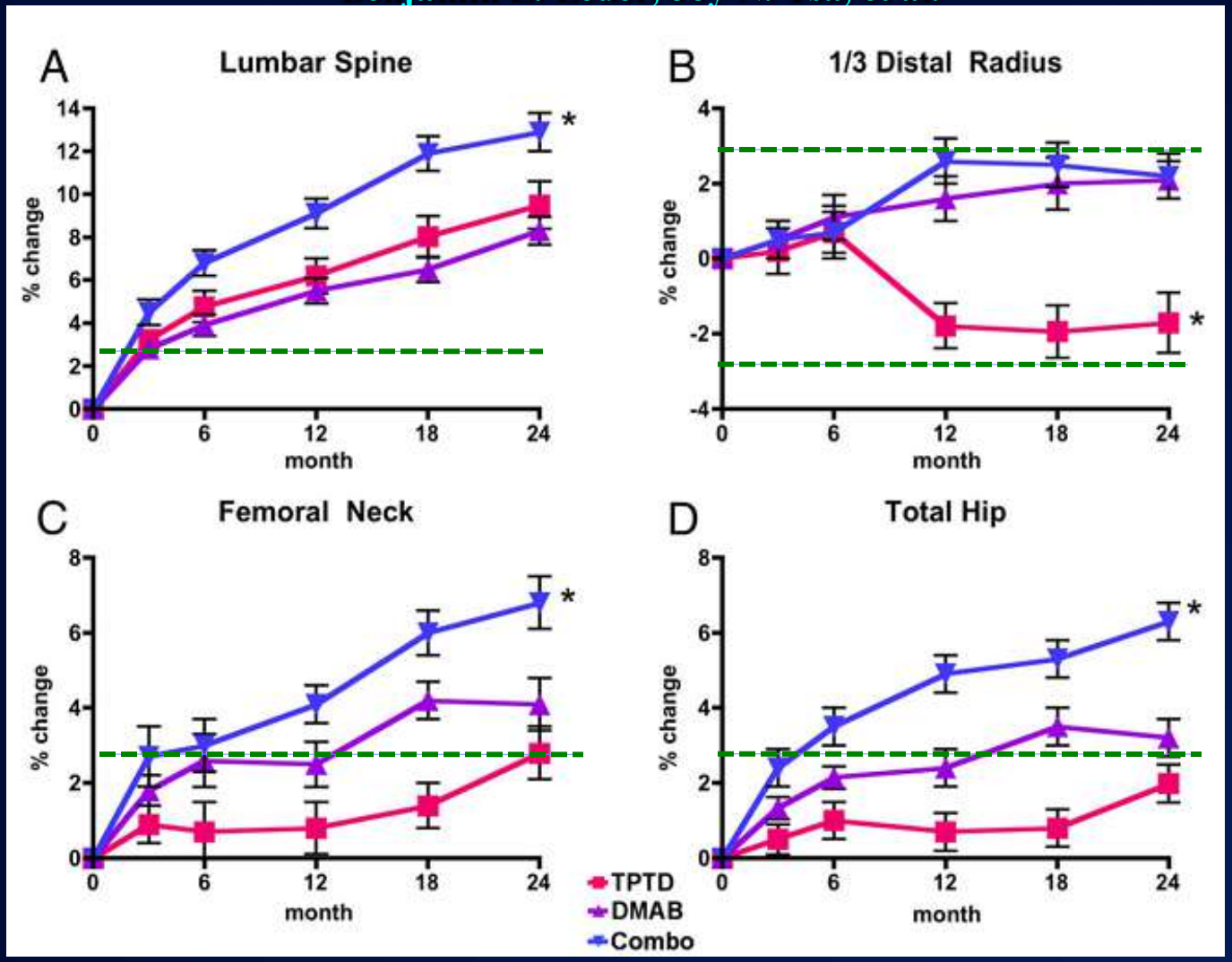

Change in total hip BMD (%)
ROMO
DMAb
Naive group (n=55)
BP group (n=37)
DMAb group (n=45)
TPTD group (n=17)
Change from baseline (%)
10
9
8
7
6
5
4
3
2
1
0
4.0
5.5
7.3
8.3
3.4
4.3
4.3
5.4
2.0
2.9
3.7
4.1
1.0
1.6
2.2
Baseline
ROMO 6M
ROMO 12M
DMAb 6M
DMAb 12M
Months

TERAPIE SEQUENZIALI

- BISFOSF. (os)
  - ANTIRIASSORBITORE
    - BISFOSFONATO (via somm. Es ZOL)
    - DENOSUMAB
  - TERIPARATIDE
  - ROMOSOZUMAB
- DENOSUMAB
  - SI' BISFOSFONATO
  - NO TERIPARATIDE
  - SI' ROMOSOZUMAB
- TERIPARATIDE → BISFOSF. (os)
- ROMOSOZUMAB → DENOSUMAB

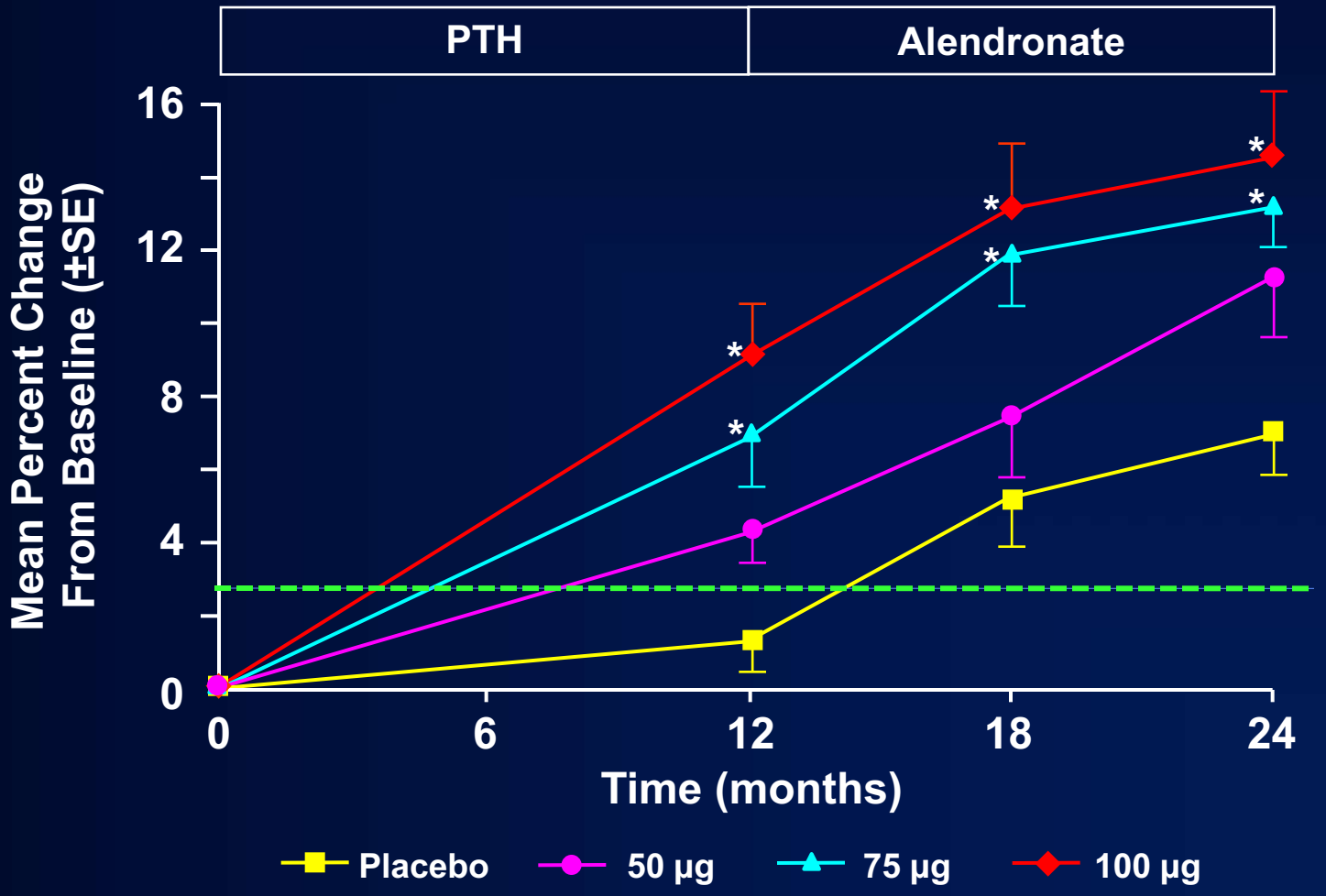
Two Years of Denosumab and Teriparatide Administration inPostmenopausal Women With Osteoporosis (The DATAExtension Study): A Randomized Controlled Trial

Benjamin Z. Leder, Joy N. Tsa, et al.



Lancet 2013

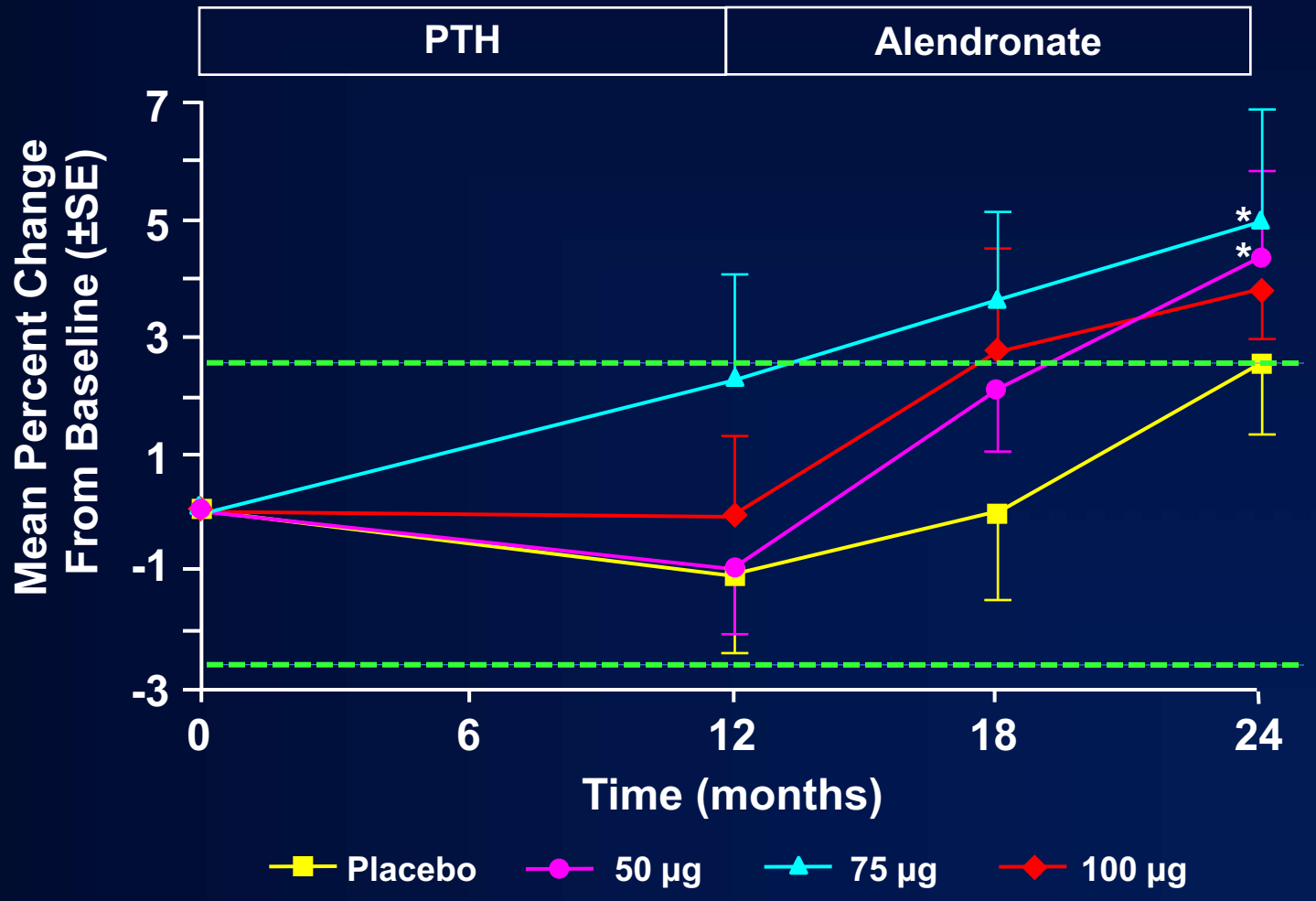
PTH(1-84) followed by Alendronate
Lumbar Spine BMD



***P*<0.05 vs placebo/alendronate group.**

Rittmaster R, et al. *J Clin Endocrinol Metab*. 2000;85:2129-2134.

PTH(1-84) followed by Alendronate
Femoral Neck BMD

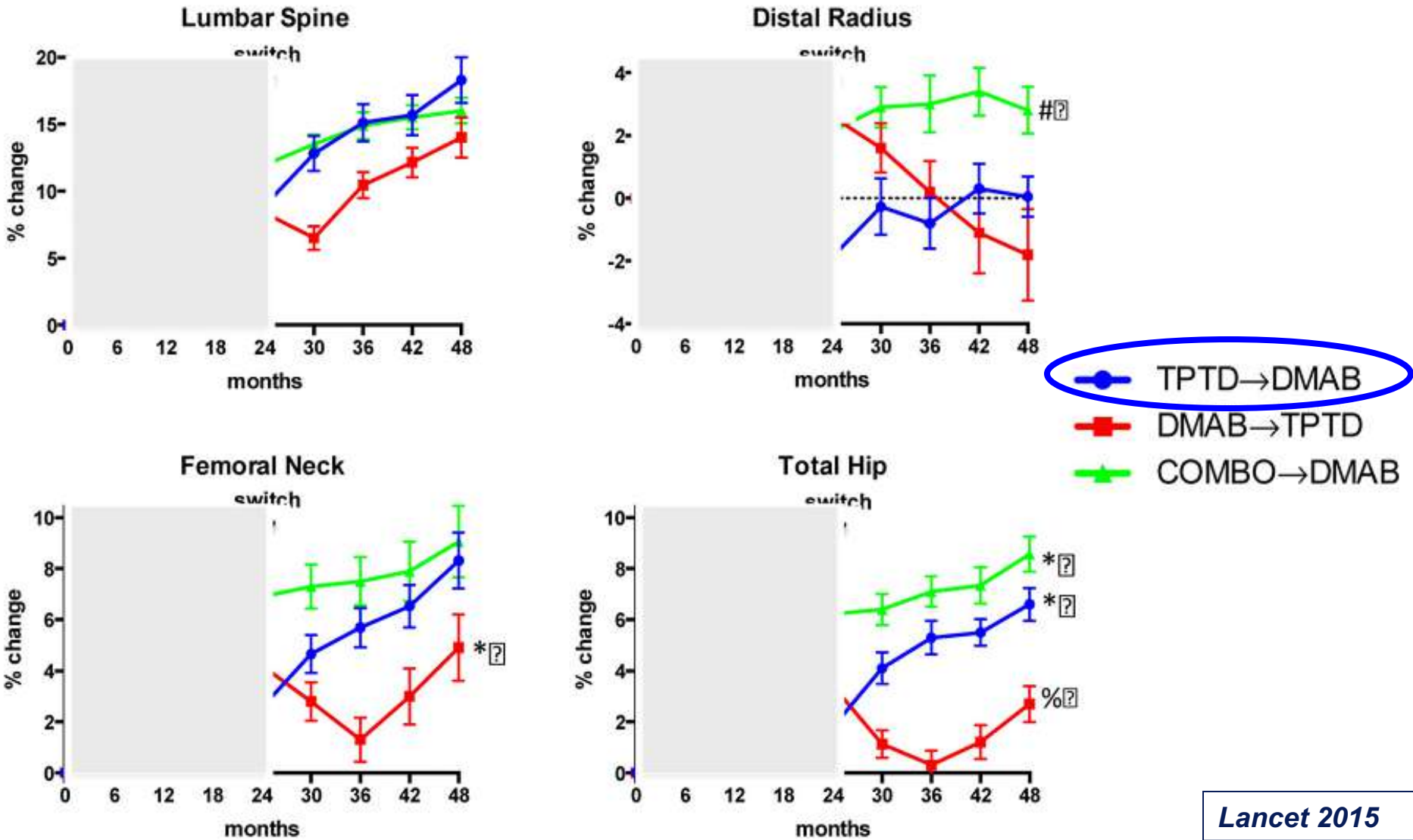


*$P<0.05$ vs baseline.

Rittmaster R, et al. *J Clin Endocrinol Metab*. 2000;85:2129-2134.

Denosumab and Teriparatide Transitions in Postmenopausal Osteoporosis (The DATA-Switch Study): a Randomised Controlled Trial

Benjamin Z. Leder, MD, Joy N. Tsai et al.

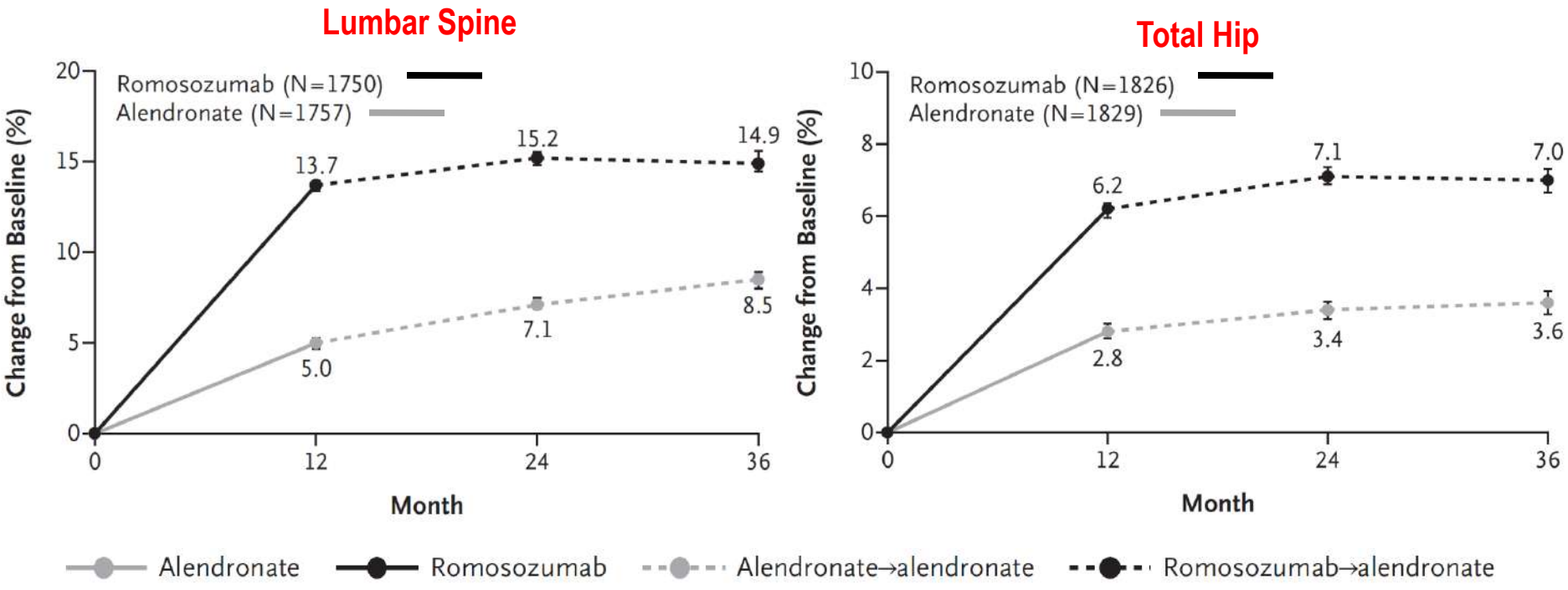


Lancet 2015

TERAPIE SEQUENZIALI

- BISFOSF. (os)
  - ANTIRIASSORBITORE
    - BISFOSFONATO (via somm. Es ZOL)
    - DENOSUMAB
  - TERIPARATIDE
  - ROMOSOZUMAB
- DENOSUMAB
  - SI' BISFOSFONATO
  - NO TERIPARATIDE
  - SI' ROMOSOZUMAB
- TERIPARATIDE
  - BISFOSF. (os)
  - DENOSUMAB
- ROMOSOZUMAB
  - BISFOSF. (os)
  - DENOSUMAB

Change in Bone Mineral Density



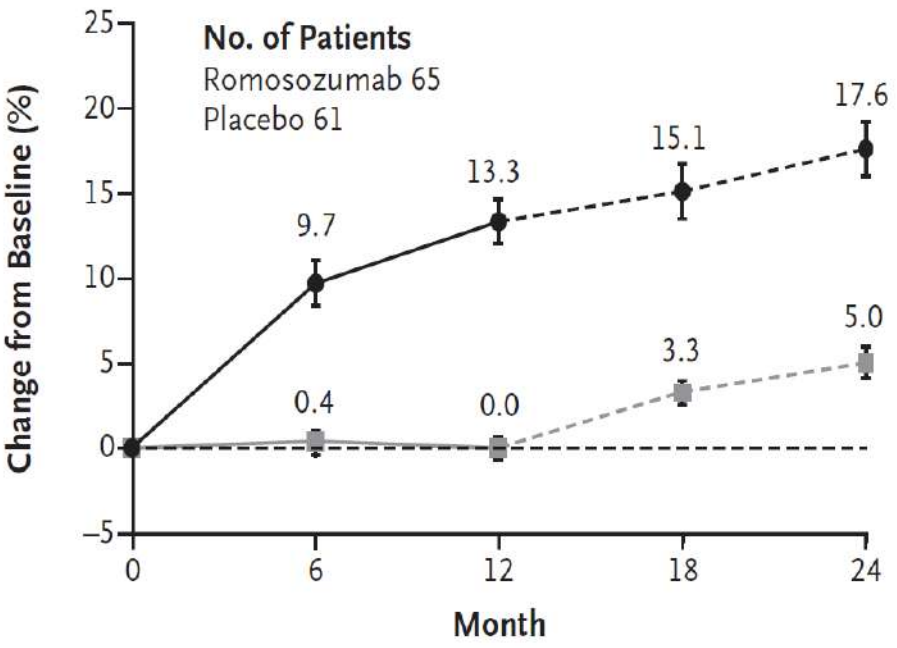
Saag KG et al. N Engl J Med 2017

The NEW ENGLAND JOURNAL of MEDICINE

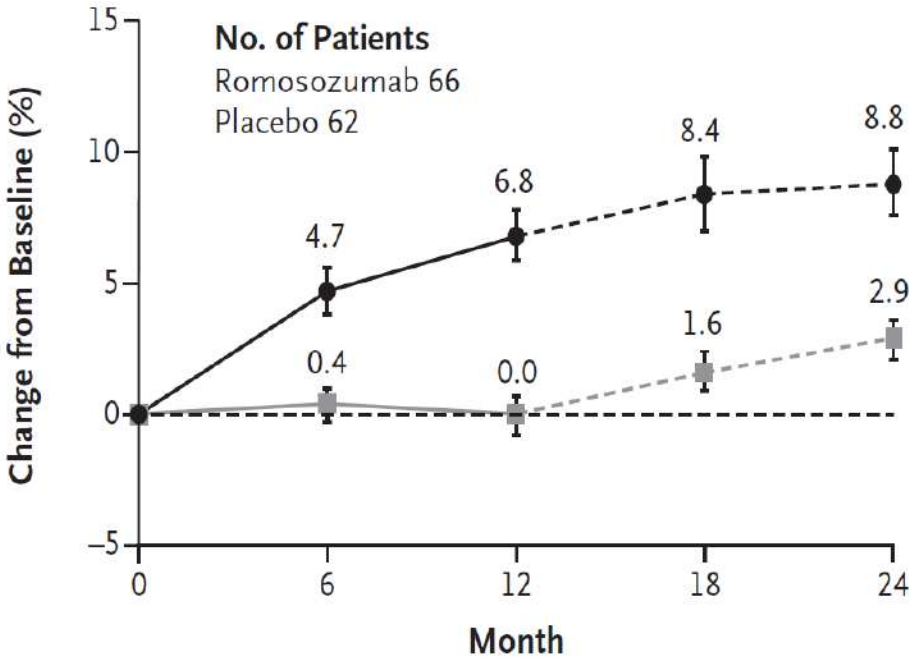
ORIGINAL ARTICLE

Romosozumab Treatment in Postmenopausal Women with Osteoporosis

Change in BMD at lumbar Spine



Change in BMD at Total Hip



Cosman F et al. N Engl J Med 2016

CONCLUSIONI sull' INSUCCESSO TERAPEUTICO

1) DEFINIZIONE del TARGET in base alla SEVERITA' e alle POTENZIALITA' del FARMACO

2) Valutazi[illegible] nelle varie

3) [illegible] prima e dopo il fallimento terapeutico

4) Terapia Sequenziale Pianificata

Grazie dell'Attenzione!

Grazie per l’attenzione