Azienda Ospedaliero-Universitaria Senese
Dip. di Scienze Mediche, Chirurgiche e Neuroscienze
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ROMOSOZUMAB: NUOVO PROTAGONISTA NELLA TERAPIA SEQUENZIALE

BRUNO FREDIANI
Presidente SIOMMMS

TRATTAMENTI SEQUENZIALI

Frost HM: Activation, Depression, Free, Ripetition (1979).

Seyle H, Burrows R: Estratti di Paratiroide stimolano la neoformazione (1932. 1938).

Riggs BL: il Fluoruro di Sodio aumenta le fratture non vertebrali, non modifica quelle vertebrali, riduce la BMD corticale aumenta la BMD vertebrale (1990).

Canalis E: Differente comportamento del PTH somministrato continuamente od intermittente sulla produzione di collagene osseo (1990).

Sone T: Teriparatide aumenta la massa ossea spongiosa e corticale (1995)

Black DM: Alendronato previene le fratture in pazienti con fratture vertebrali (1996)

Cummings SR: Alendronato previene le fratture in pazienti con bassa massa ossea non fratturate (1998)

Neer RM: Teriparatide previene le fratture vertebrali e non vertebrali in pazienti già fratturati (2001)

Finkelstein JS: L'Alendronato riduce l'efficacia del PTH sulla massa ossea (2003)

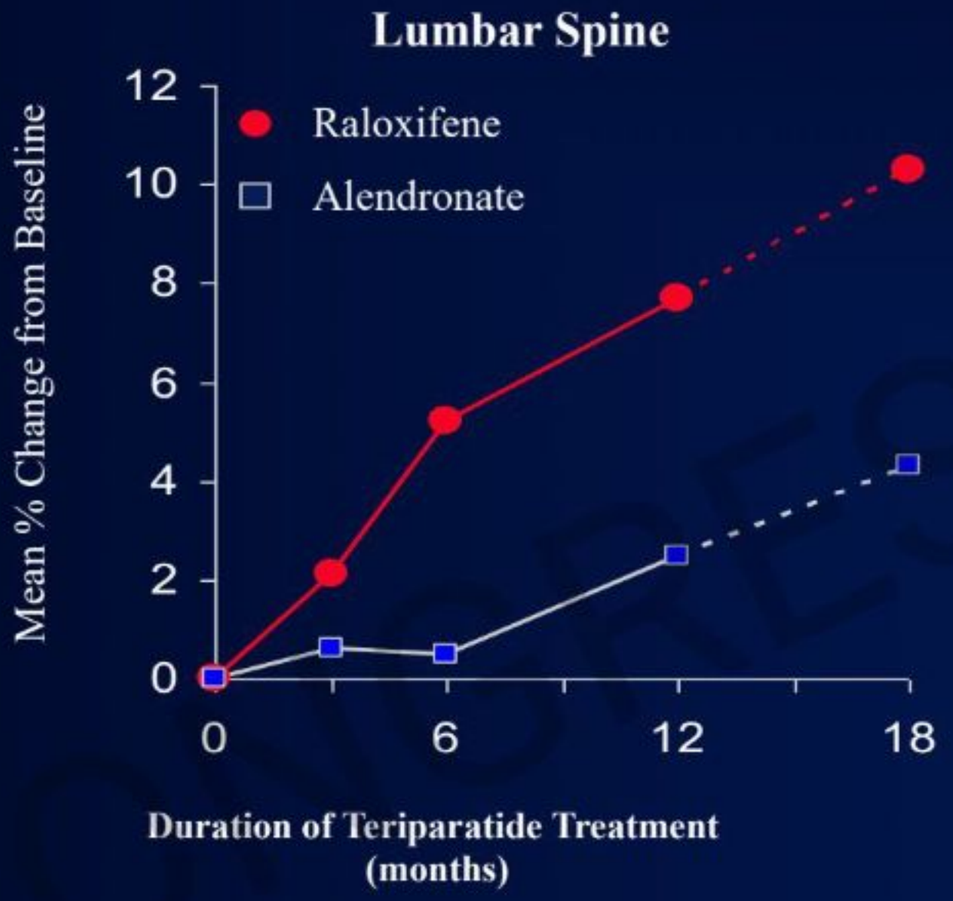
Ettinger B: Teriparatide più efficace sulla massa ossea dopo raloxifene che dopo alendronato (2004).

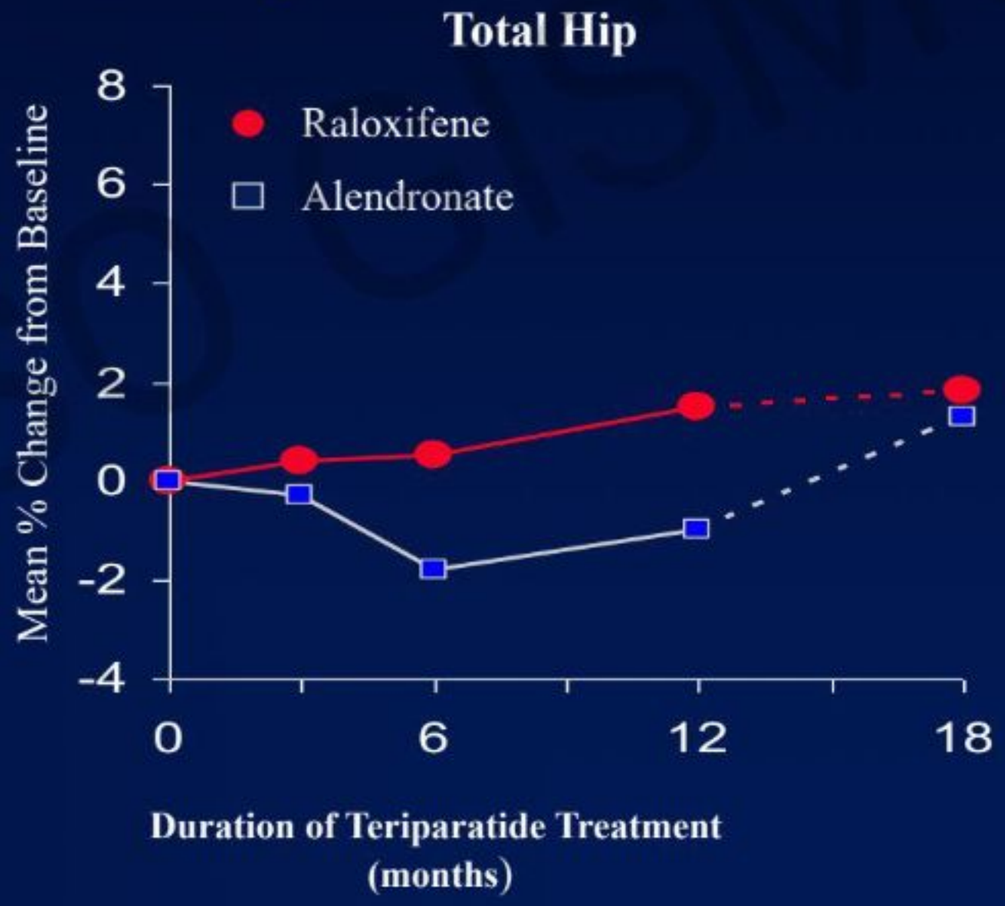
Miller PD: Teriparatide è più efficace sulla massa ossea e sul turnover dopo risedronato piuttosto che dopo alendronato (2008).

Black DM: Alendronato somministrato dopo Teriparatide incrementa ulteriormente la massa ossea (2005).

PRIMA ANTIRIASSORBITORE

AAA Study: 12 and 18 month analyses
Bone Mineral Density





Ettinger B. et al., JBMR, 2004

PRIMA ANTIRIASSORBITORE

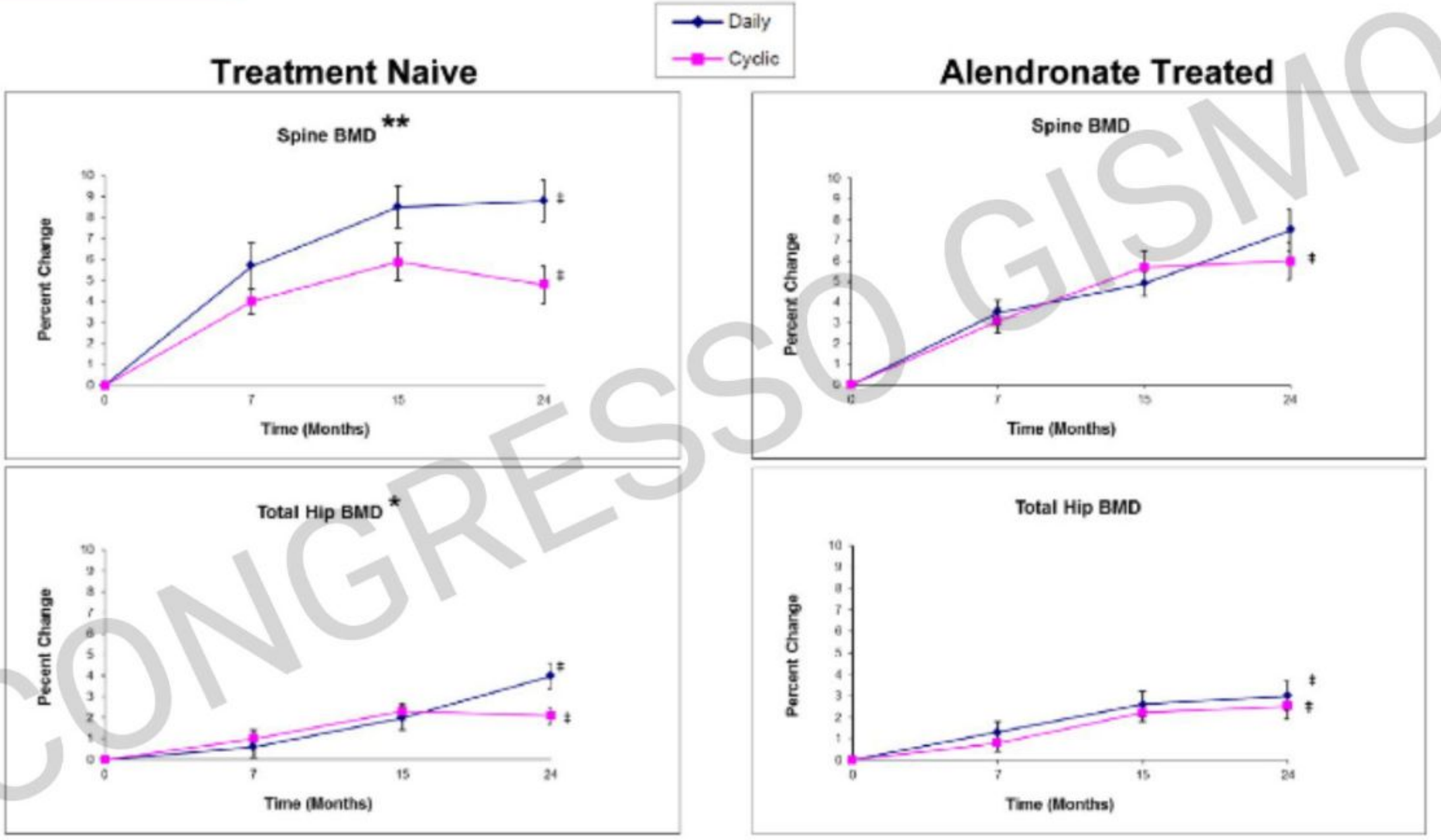
ORIGINAL ARTICLE

Daily or Cyclical Teriparatide Treatment in Women With Osteoporosis on no Prior Therapy and Women on Alendronate

Felicia Cosman, Jeri W. Nieves, Marsha Zion, Patricia Garrett, Simon Neubort, David Dempster, and Robert Lindsay

J Clin Endocrinol Metab, July 2015,

PRIMA ANTIRIASSORBITORE



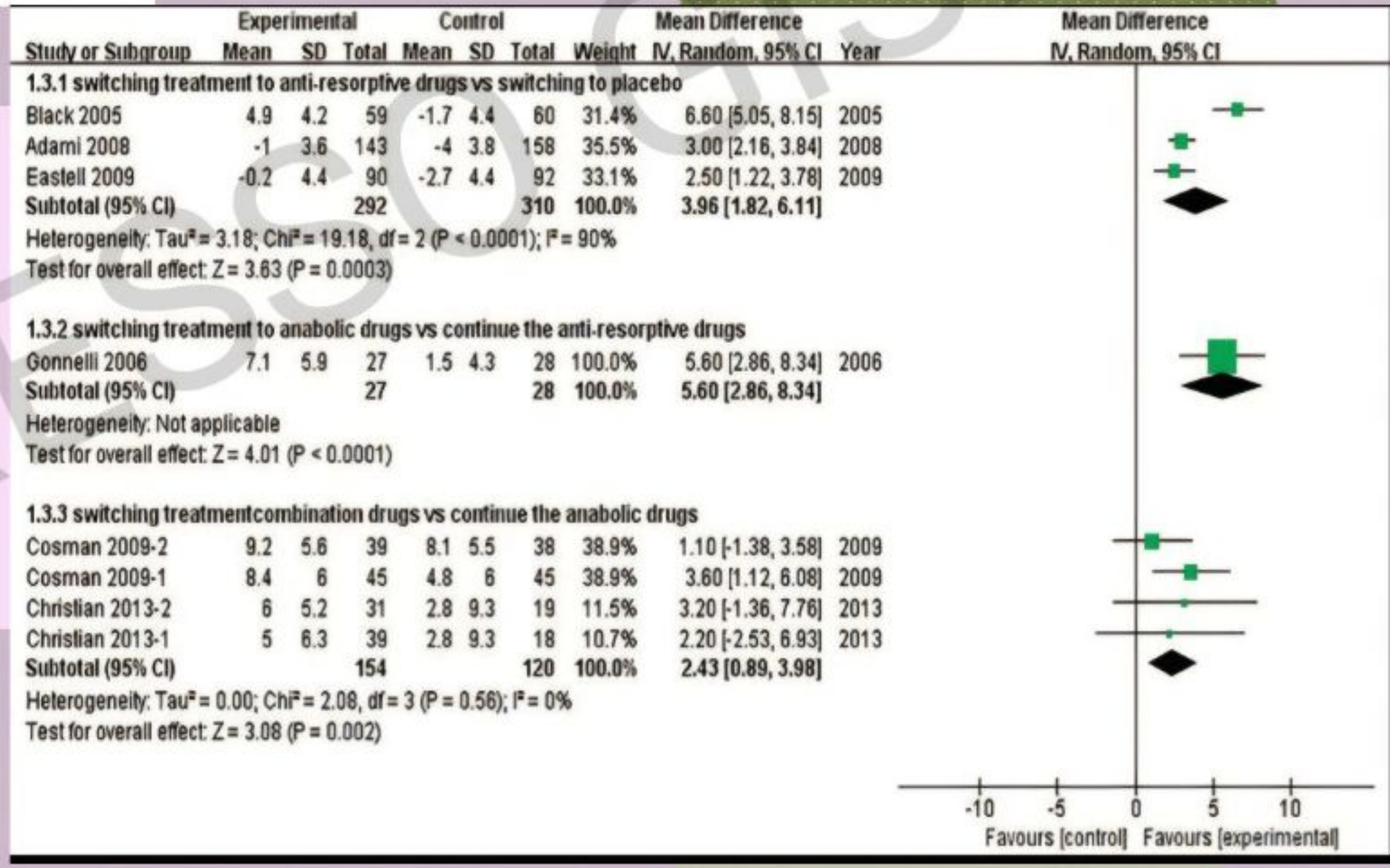
Medicine (2016) 95:49(e5496)
Systematic Review and Meta-Analysis
Medicine
OPEN

The effect of sequential therapy for postmenopausal women with osteoporosis

A PRISMA-compliant meta-analysis of randomized controlled trials

Shenghan Lou, MD, Houchen Lv, PhD, Guoqi Wang, PhD, Zhirui Li, PhD, Ming Li, PhD, Licheng Zhang, PhD, Peifu Tang, PhD*

- 8 trials for a sum of 1509 patients.
- After the change in the treatment, **in all cases the** second-line treatment led to a **statistically-significant increase in BMD** in both hip and lumbar spine.
- **Sequential treatment was superior to monotherapy** with any anti-resorptive drug and non-inferior to **monotherapy with anabolic agents.**



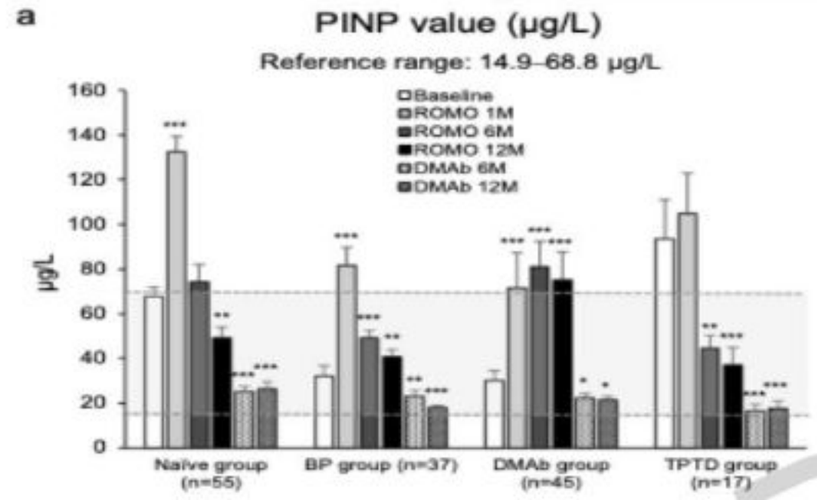
PRIMA ANTIRIASSORBITORE

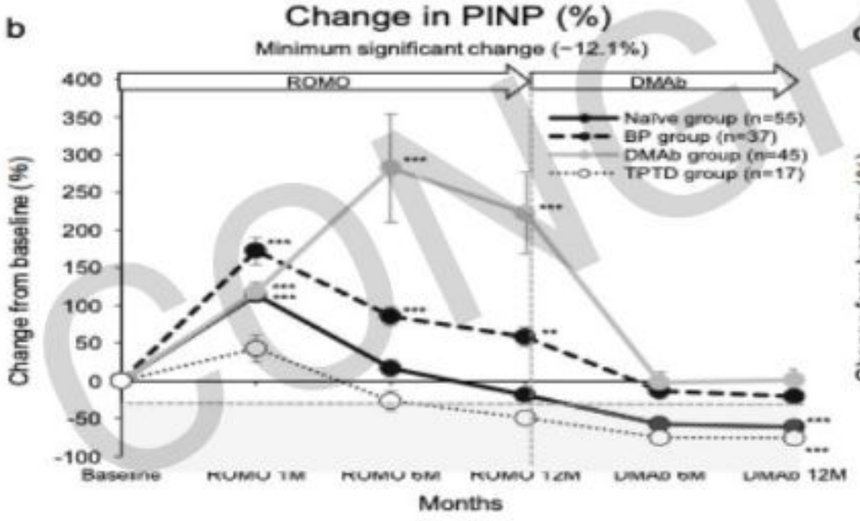
Osteoporosis International (2022) 33:1807–1813
https://doi.org/10.1007/s00198-022-06386-y

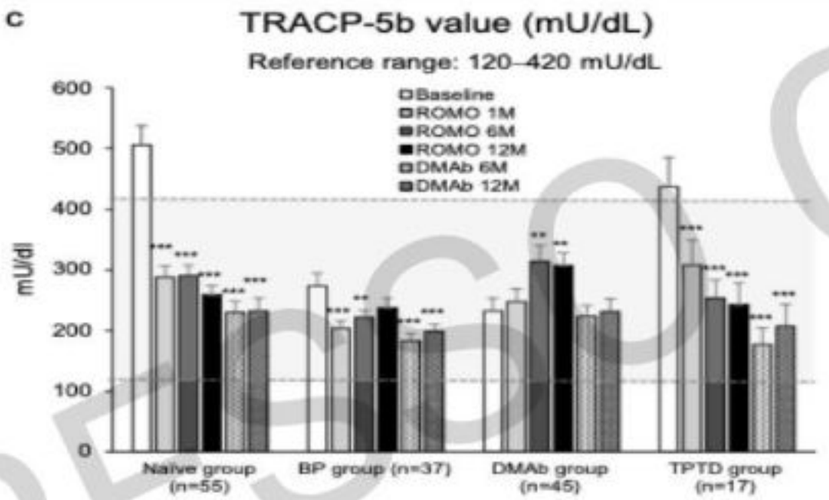
SHORT COMMUNICATION

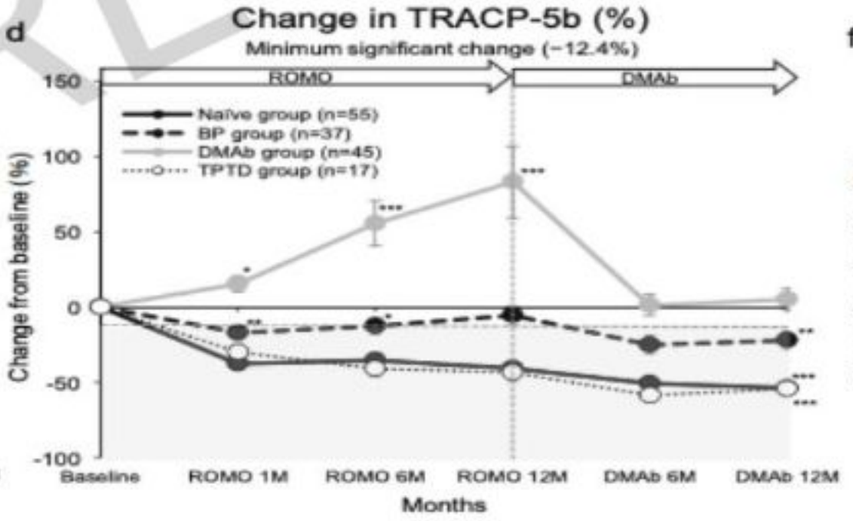
Effects of prior osteoporosis treatment on the treatment response of romosozumab followed by denosumab in patients with postmenopausal osteoporosis

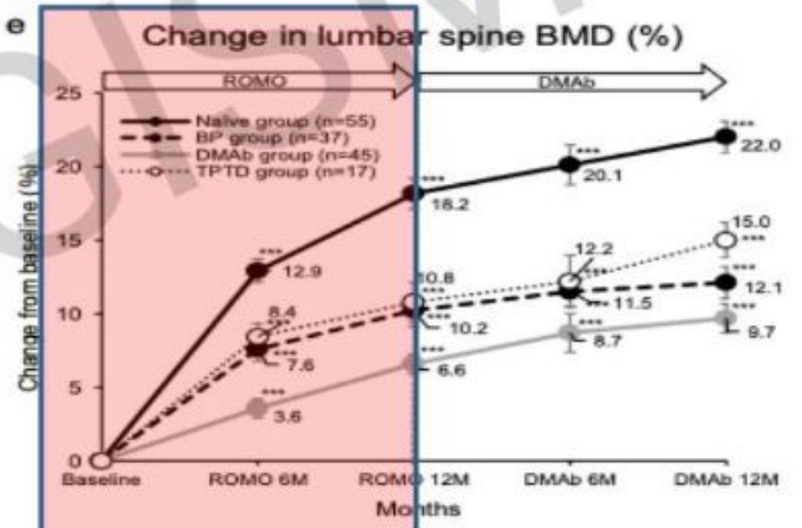
K. Ebina[1,2] · Y. Etani[2] · H. Tsuboi[3] · Y. Nagayama[4] · M. Kashii[5] · A. Miyama[6] · Y. Kunugiza[7] · M. Hirao[2] · G. Okamura[3] · T. Noguchi[8] · K. Takami[2] · A. Goshima[2] · T. Miura[2] · Y. Fukuda[2] · T. Kurihara[2] · S. Okada[2] · K. Nakata[9]











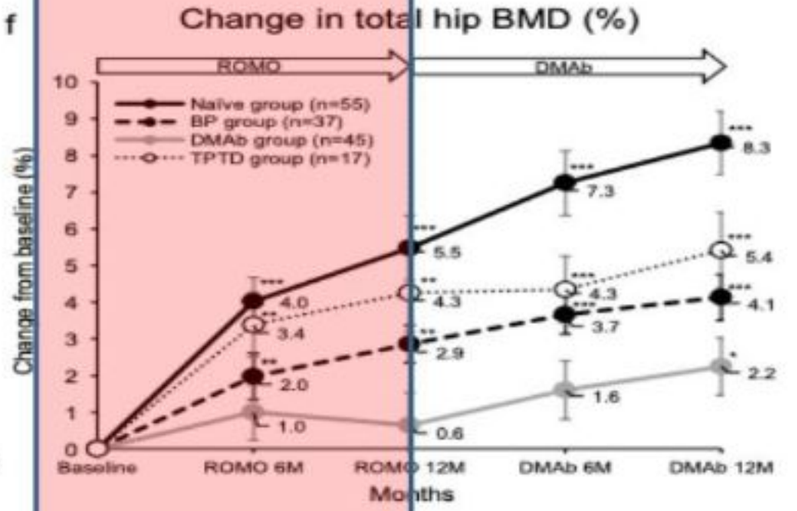


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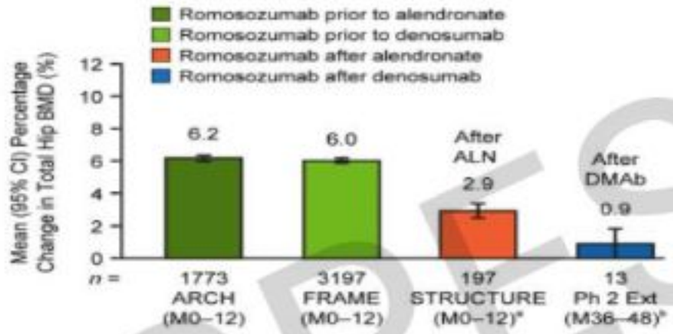
Table 1 Baseline characteristics of patients included in the four studies

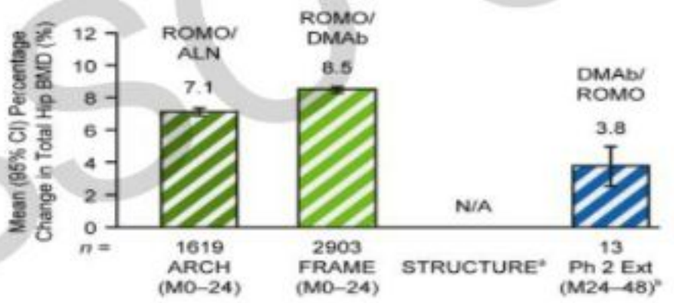
	ARCH Romosozumab to alendronate $n=2046$	FRAME Romosozumab to denosumab $n=3589$	STRUCTURE[a] Alendronate to romosozumab $n=218$	Phase 2 Extension[b] Denosumab to romosozumab $n=16$
Age, mean (SD), years	74.4 (7.5)	70.9 (7.0)	71.8 (7.4)	67.1 (4.1)
BMD T-score, mean (SD)				
Lumbar spine	−2.9 (1.3)	−2.7 (1.0)	−2.8 (1.1)	−2.01 (0.5)
Total hip	−2.8 (0.7)	−2.5 (0.5)	−2.3 (0.8)	−1.04 (0.6)
Femoral neck	−2.9 (0.5)	−2.8 (0.3)	−2.5 (0.7)	−1.59 (0.5)
Prevalent vertebral fracture, *n* (%)	1969 (96.2)	672 (18.7)	218 (100)[c]	ND
Previous nonvertebral fracture, *n* (%)	767 (37.5)	778 (21.7)	218 (100)[c]	ND
PINP, median (Q1, Q3), µg/L	50.6 (37.5, 64.7)[d]	50.3 (36.2, 65.9)[e]	25.0 (18.0, 34.0)	17.4 (11.2, 21.4)
β-CTX, median (Q1, Q3), ng/L	276 (166, 407)[d]	551 (338, 706)[e]	229 (150, 318)	163 (96, 268)

Total Hip

a. 1 Year Gains With Romosozumab

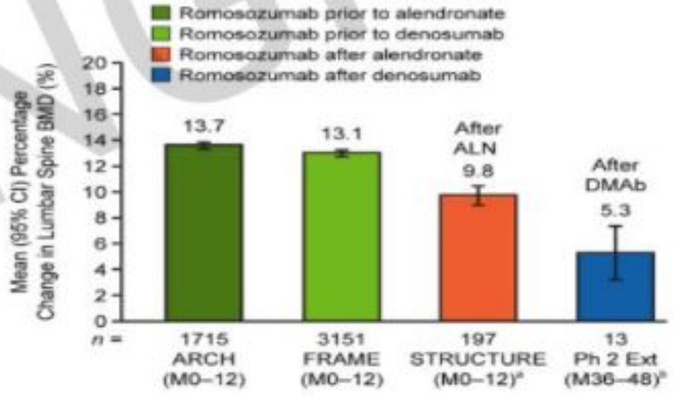


b. Cumulative 2 Year Gains After Sequential Treatment

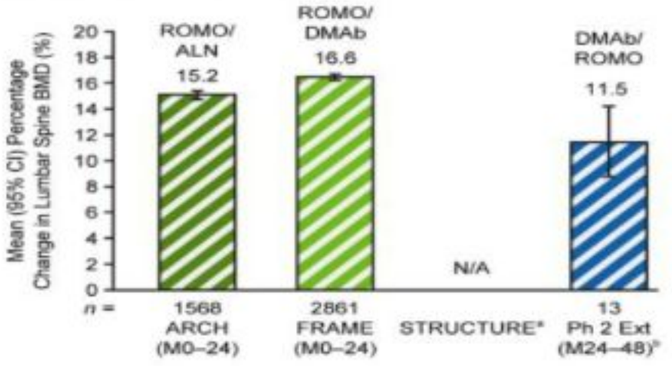


Lumbar Spine

c. 1 Year Gains With Romosozumab



d. Cumulative 2 Year Gains After Sequential Treatment



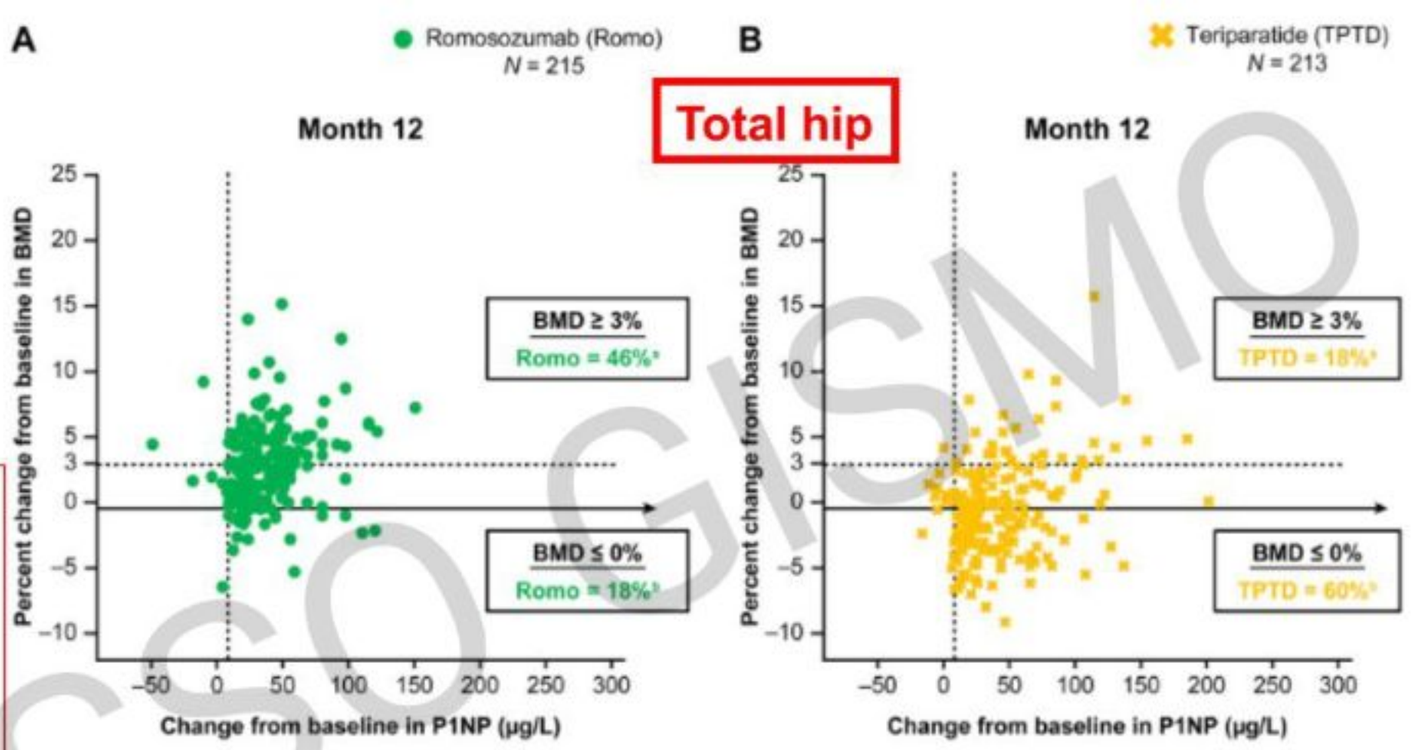
PRIMA ANTIRIASSORBITORE

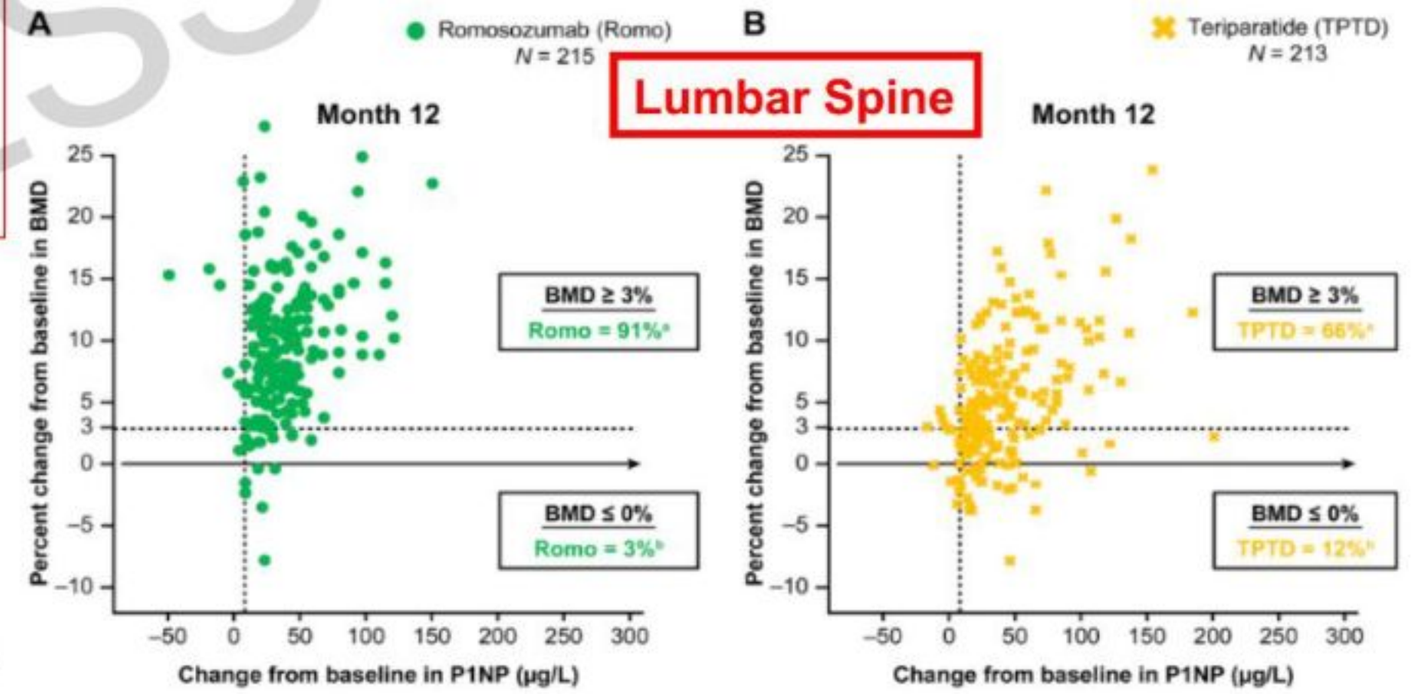
Journal of Bone and Mineral Metabolism (2020) 38:310–315
https://doi.org/10.1007/s00774-019-01057-1

ORIGINAL ARTICLE

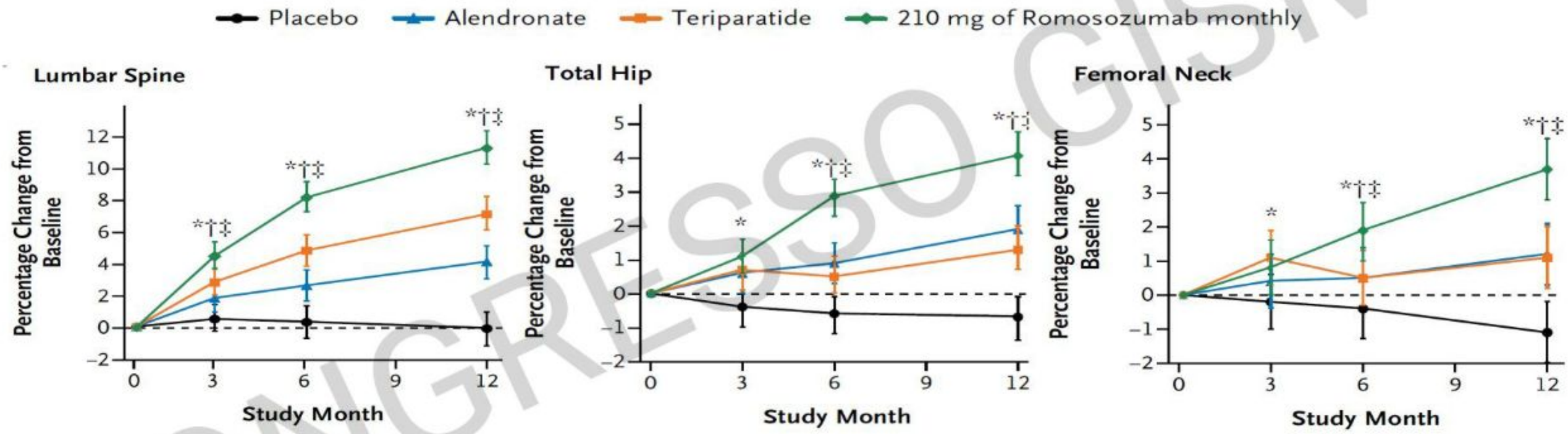
Relationship between P1NP, a biochemical marker of bone turnover, and bone mineral density in patients transitioned from alendronate to romosozumab or teriparatide: a post hoc analysis of the STRUCTURE trial

Junichi Takada[1] · Rajani Dinavahi[2] · Akimitsu Miyauchi[3] · Etsuro Hamaya[4] · Toshiyasu Hirama[4] · Cesar Libanati[5] · Yoichi Nakamura[4] · Cassandra E. Milmont[2] · Andreas Grauer[2]





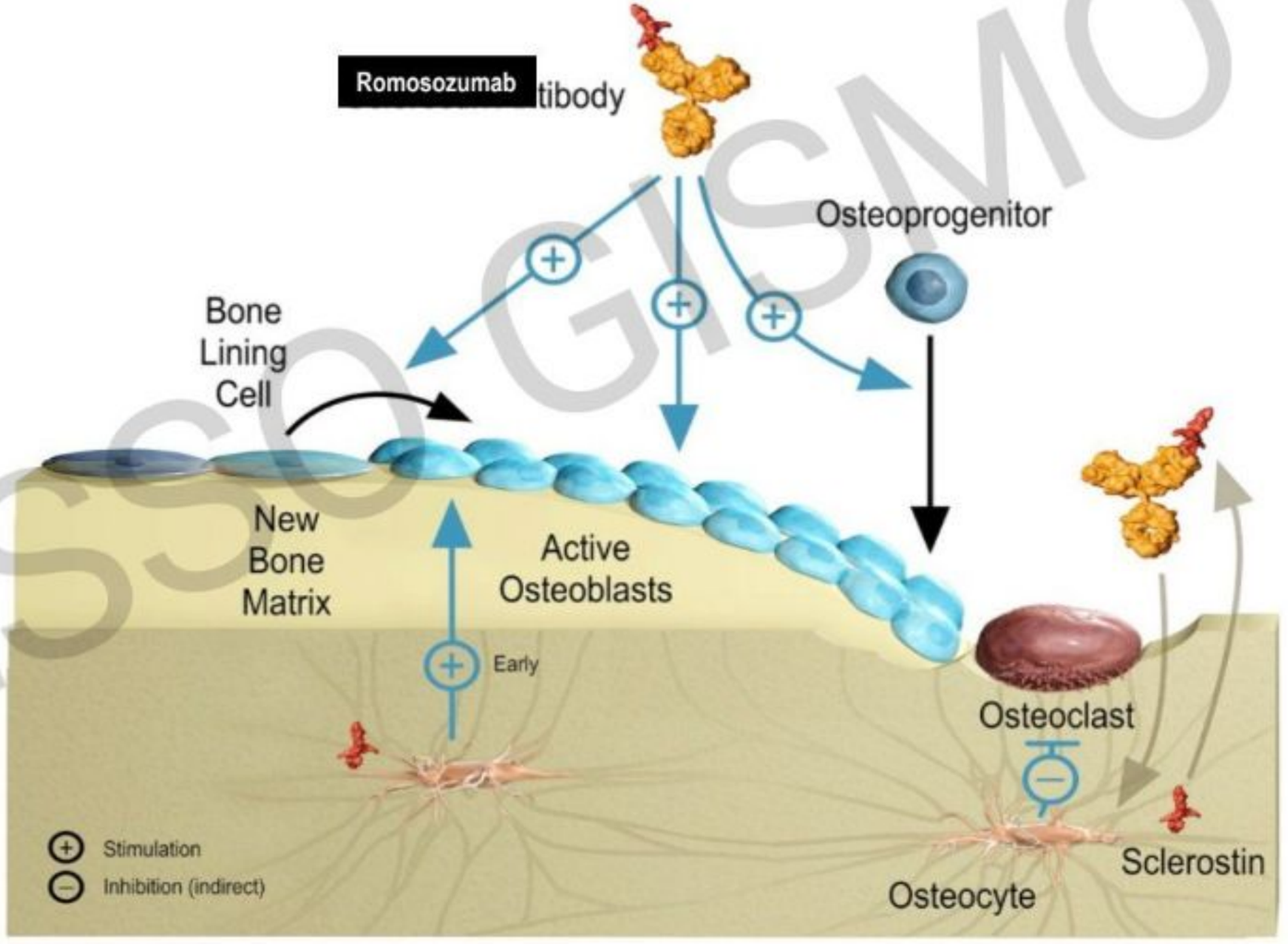
Percentage Change from Baseline in Bone Mineral Density



McClung MR et al. N Engl J Med 2014

Romosozumab

- (AMG 785/CDP7851) è un anticorpo monoclonale che si lega alla sclerostina
- L'inibizione della sclerostina consente l'attivazione della segnalazione Wnt che porta ad un aumento della formazione ossea e della densità minerale ossea (BMD), diminuendo anche il riassorbimento osseo
- Romosozumab è il primo Scl-Ab ad essere testato su soggetti umani



TERAPIE SEQUENZIALI: SONO TUTTE UGUALI?

THERAPEUTIC ADVANCES in *Musculoskeletal Disease*

Meta-analysis

The sequential antifracturative treatment: a meta-analysis of randomized clinical trials

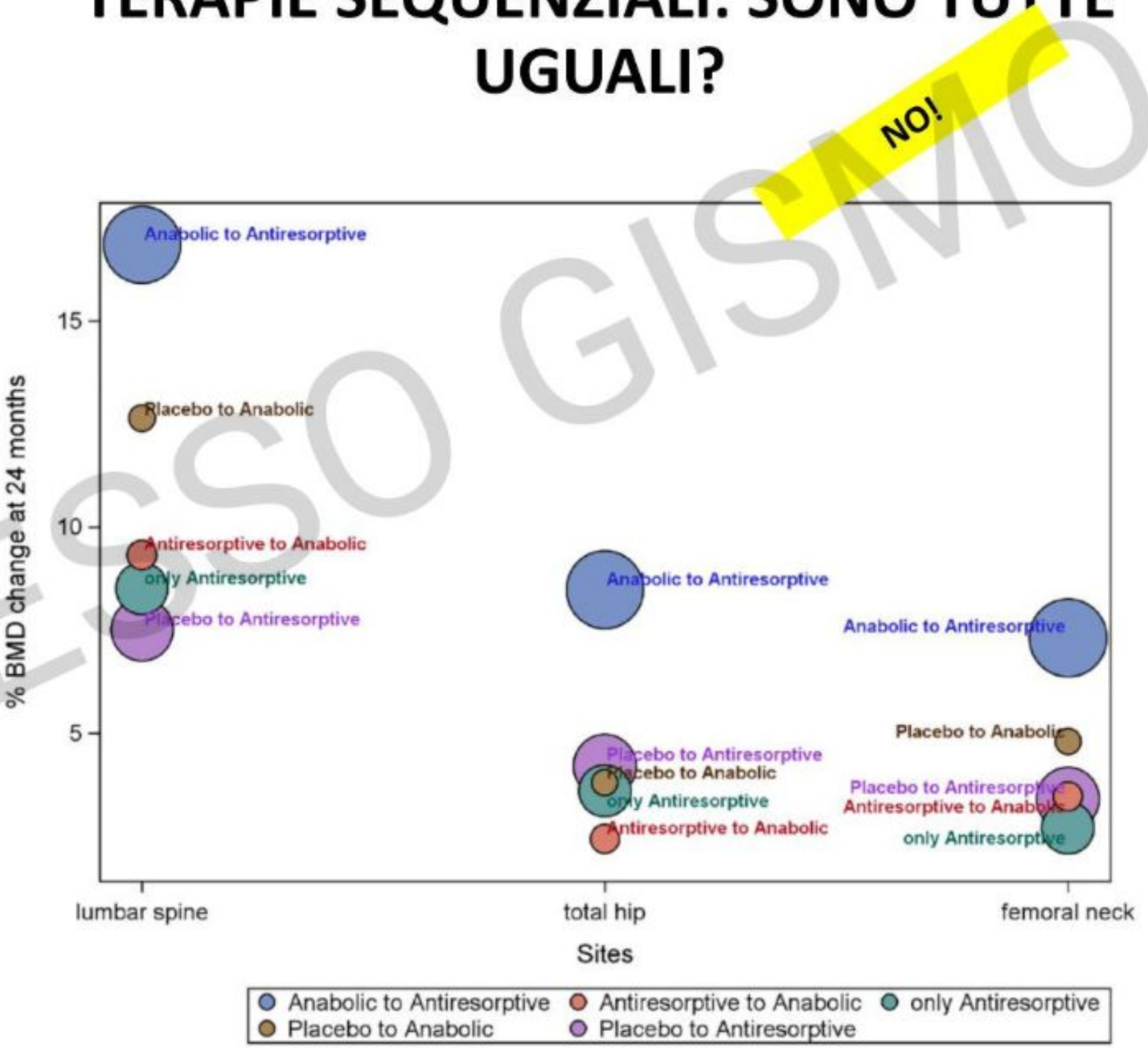
Angelo Fassio, Davide Gatti, Annalisa Biffi, Raffaella Ronco, Gloria Porcu, Giovanni Adami, Rosaria Alvaro, Riccardo Bogini, Achille P. Caputi, Luisella Cianferotti, Bruno Frediani, Stefano Gonnelli, Giovanni Iolascon, Andrea Lenzi, Salvatore Leone, Raffaella Michieli, Silvia Migliaccio, Tiziana Nicoletti, Marco Paoletta, Annalisa Pennini, Eleonora Piccirilli, Maurizio Rossini, Maria Luisa Brandi, Giovanni Corrao and Umberto Tarantino

Ther Adv Musculoskelet Dis
2024, Vol. 16: 1–15
DOI: 10.1177/
17589720241234586

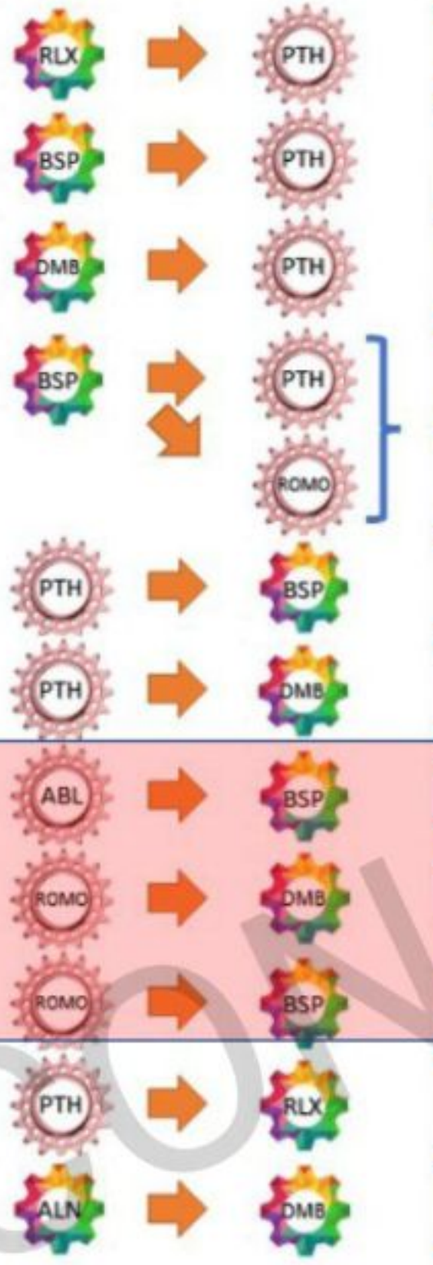
L'uso di una **terapia sequenziale è sempre efficace** in ogni distretto esaminato.

In particolare, la massima efficacia si ha per (in ordine decrescente):

1. **romosozumab->denosumab** vs PBO ->denosumab e romosozumab->PBO
2. **Teriparatide->denosumab** vs teriparatide->BF
3. **Romosozumab -> alendronato** vs PBO->alendronato



PRIMA ANABOLIZZANTE

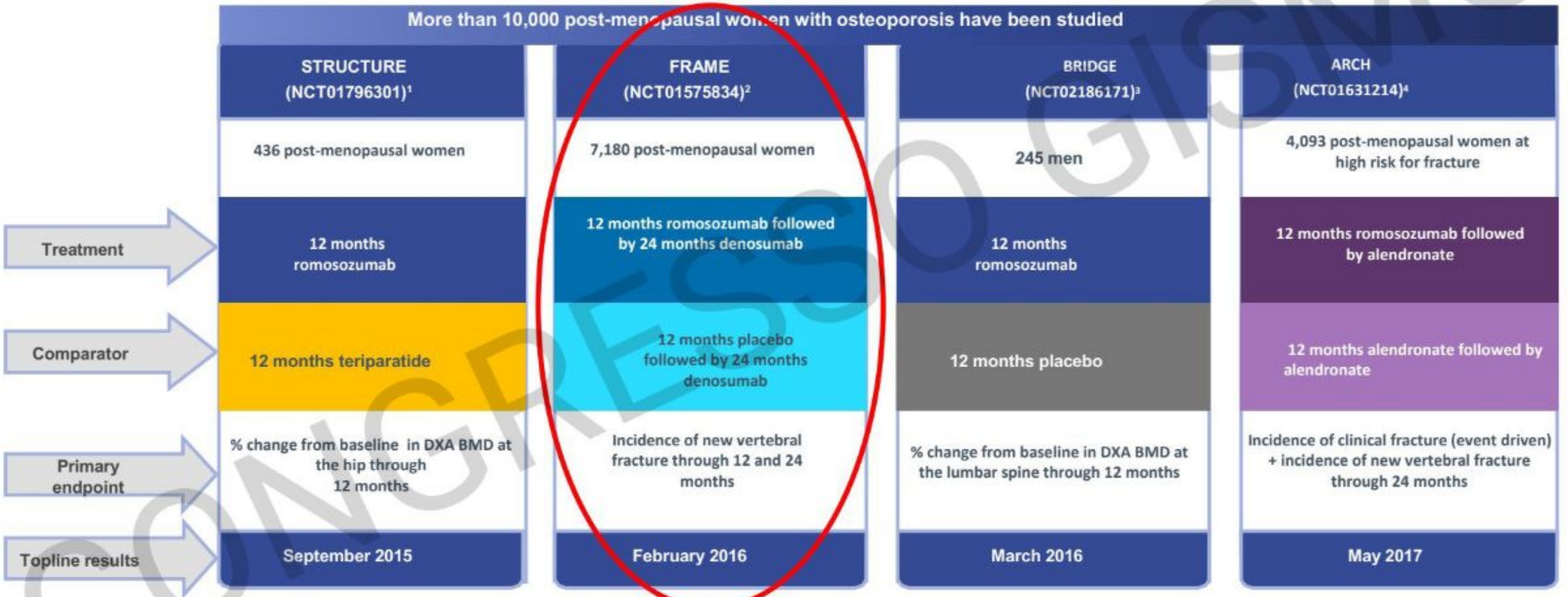


Sequential Therapy

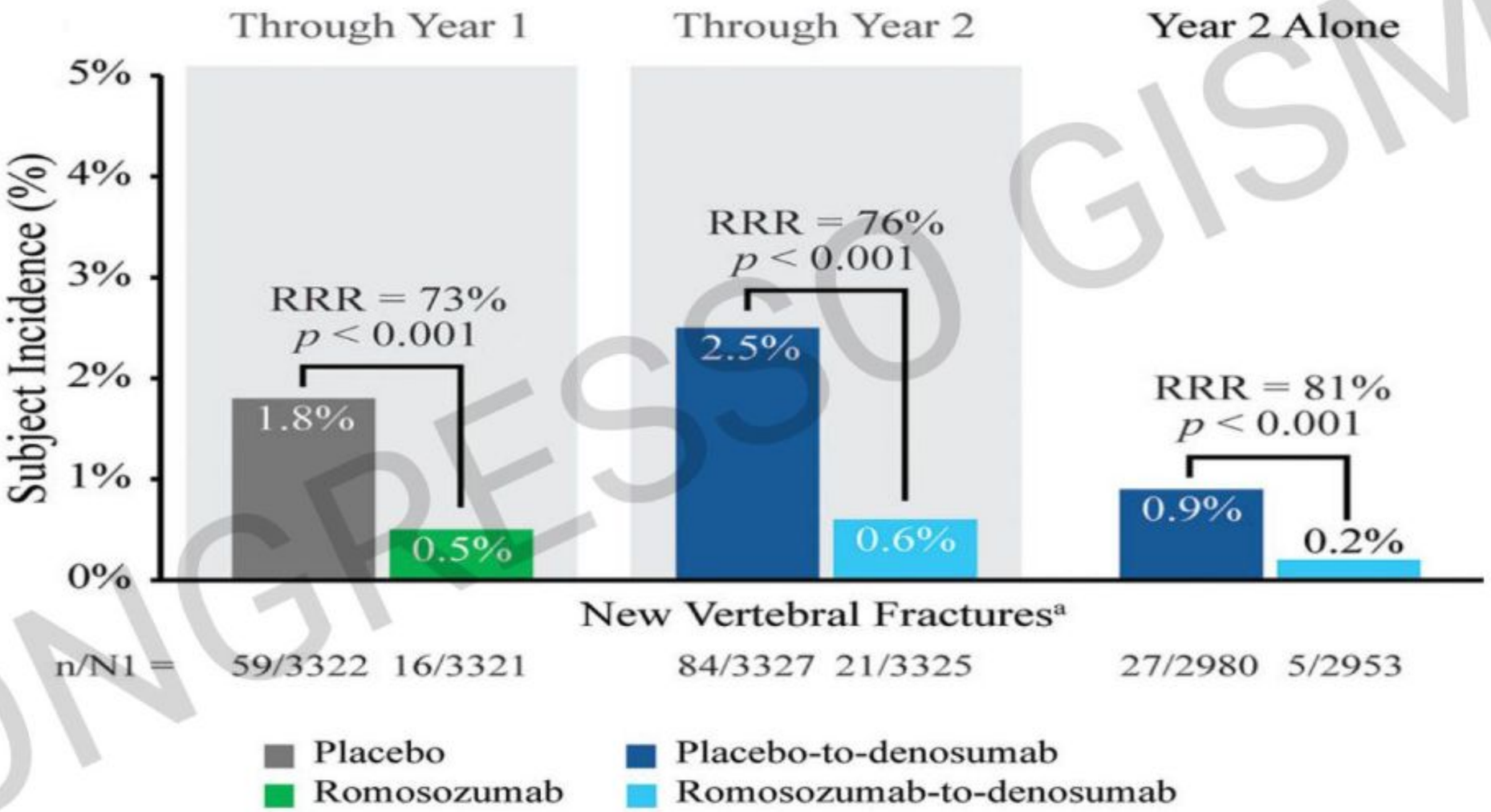
Spine BMD – Benefit Hip BMD – Benefit	*"Switch to or ADD" Cosman F et al. JCEM 2009;94(10); 3772*
Spine BMD – Benefit Hip BMD – No benefit	
Spine BMD – Benefit Hip BMD – No benefit. Loss x 18 months	*DATA Switch - Leder BZ et al. Lancet 2015;386(9999);1147*
Spine BMD – No benefit Hip BMD – No benefit. Loss x 18 months also Loss of Cortical BMD and Hip strength x 18 months	*STRUCTURE Langdahl BL et al. Lancet 2017;390*
Spine BMD – Benefit Hip BMD – Benefit. Cortical BMD and Hip Strength benefit	
Spine BMD – Benefit Hip BMD – Benefit	*PaTH Black DM et al. NEJM 2005;353*
Spine BMD – Benefit Hip BMD – Benefit	*DATA Switch - Leder BZ et al. Lancet 2015;386(9999);1147*
Vertebral and Non-Vertebral # Risk Reduction in ABL → ALN x 2 years	*ACTIVEXTEND Bone HG et al. JCEM 2018;103*
Vertebral, Clinical and Non-Vertebral # Risk Reduction in Romo → DMB x 1 year	*FRAME Cosman F et al. NEJM 2016;375*
Vertebral and Non-Vertebral # Risk Reduction in Romo → ALN X 1 year	*ARCH Saag KG et al. NEJM 2017;377*
Spine BMD – Maintained Hip BMD – Benefit	*EUROFORS Eastell R et al. JBMR 2009; 726*
Spine BMD – Benefit Hip BMD – Benefit	*Kendler DL et al. JBMR 2010; 72*

PRIMA ANABOLIZZANTE

Overview of the Romosozumab Phase 3 Clinical Programme



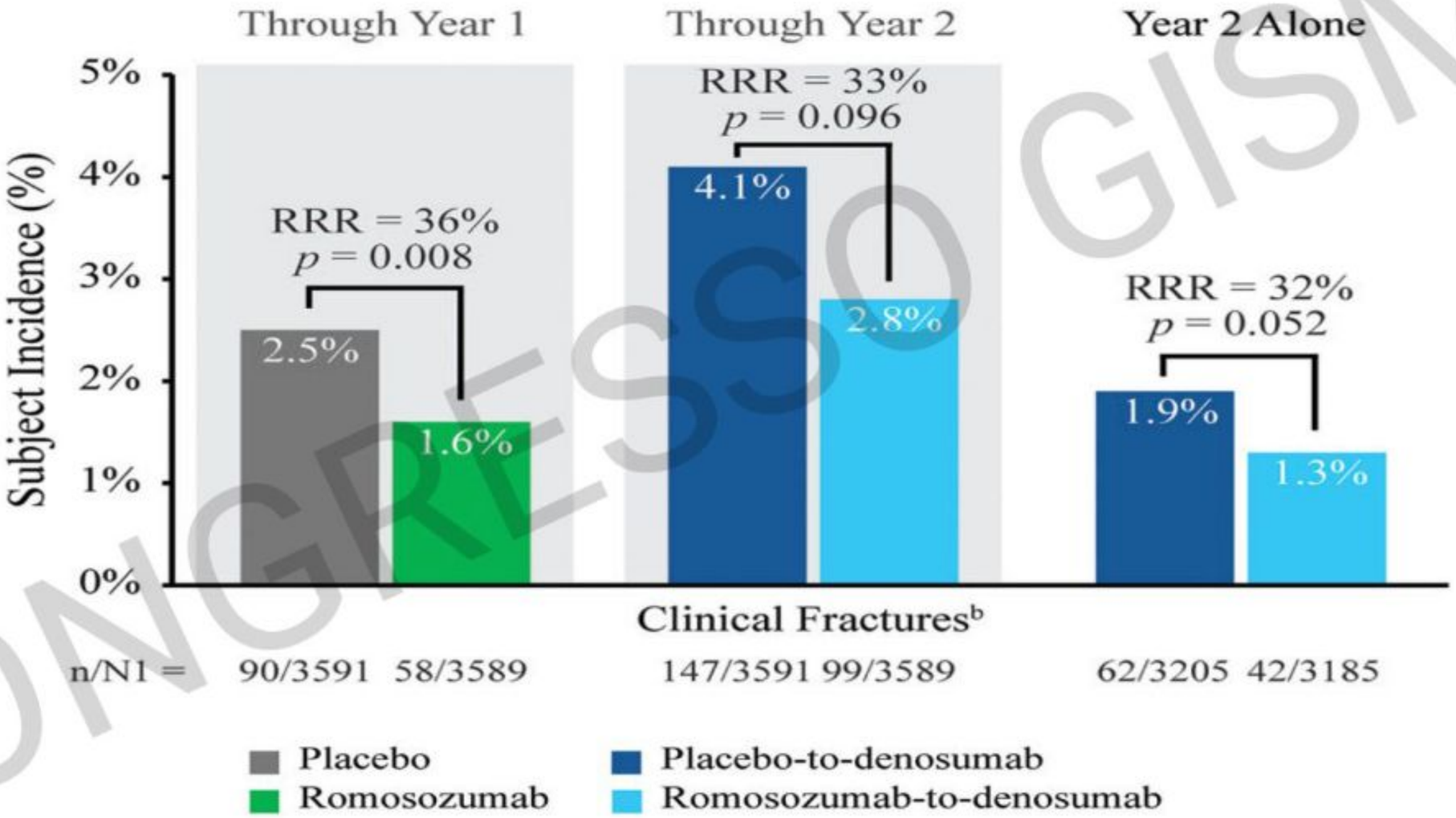
Fracture Incidence in FRAME: New Vertebral Fractures



Cosman F et al. J Bone Miner Res 2018

PRIMA ANABOLIZZANTE

Fracture Incidence in FRAME: Clinical Fractures

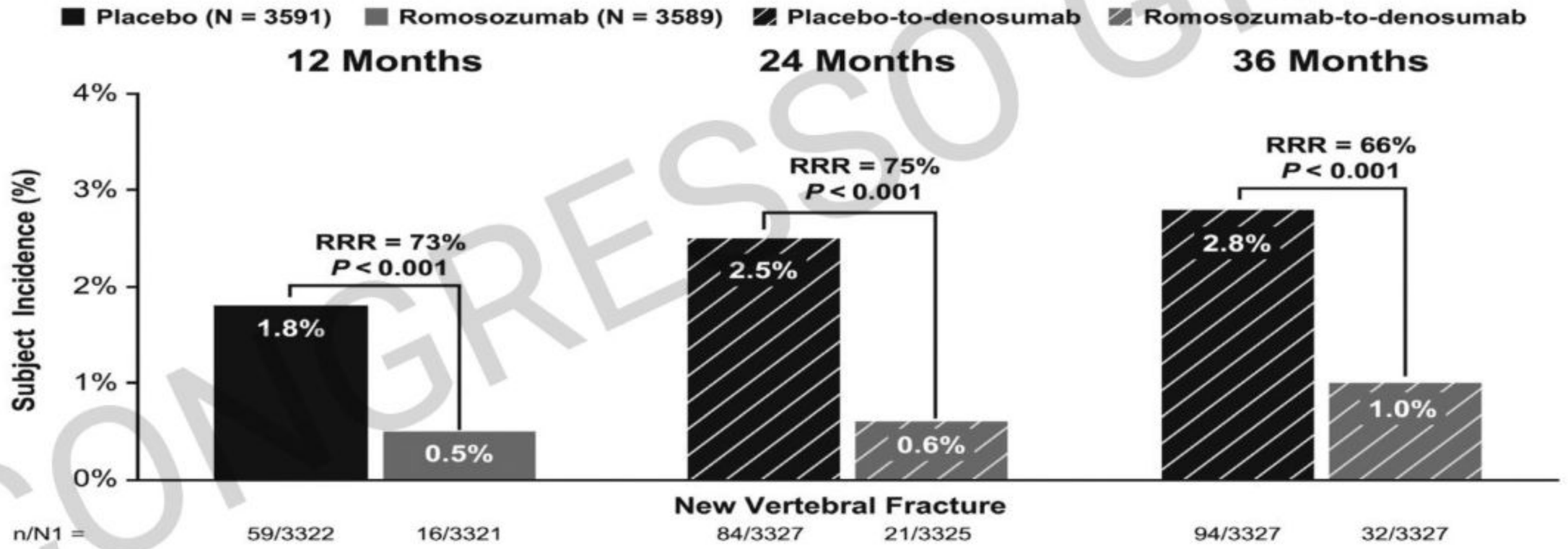


Cosman F et al. J Bone Miner Res 2018

ORIGINAL ARTICLE

JBMR®

One Year of Romosozumab Followed by Two Years of Denosumab Maintains Fracture Risk Reductions: Results of the FRAME Extension Study



Lewiecki EM al. J Bone Miner Res 2019