Associazione Medici Endocrinologi

16° Congresso Nazionale AME

Joint Meeting with AACE Italian Chapter

Update in Endocrinologia Clinica

Roma, 9 - 12 novembre 2017

ITALIAN CHAPTER

Comitato Scientifico
Vincenzo Toscano, Rinaldo Guglielmi, Edoardo Guastamacchia, Franco Grimaldi

Coordinamento Centrale
Enrico Papini, Andrea Frasoldati, Roberto Attanasio, Giorgio Borretta, Nadia Cremonini

Comitato Organizzatore Locale
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Minicorso 2

Osteoporosi: come individualizzare il trattamento

Moderatori:
S. Cassibba, B. Madeo

1. Real clinical practice
   B. Madeo
2. I farmaci disponibili
   C.M. Francucci
3. Valutazione della risposta al trattamento
   G. Guabello
4. Denosumab per la prevenzione del danno osseo secondario alla terapia ormonale adiuvante
   F. Bertoldo
5. La terapia nei poor responders
   I. Chiodini
6. Take home messages
   S. Cassibba

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Italfarmaco
- Abiogen

AGENDA

Poor-responders

- Define
- **Diagnose**
- Treat

WHO HAS TO BE SCREENED FOR SECONDARY OSTEOPOROSIS ?

Secondary causes of osteoporosis should especially be excluded when:

- **Suggestive symptoms or signs of a secondary process are present.**
- **BMD is low relative to age- and weight-matched controls (Z-score < –2).**
- **BMD declines at a more rapid rate than expected for age or fails to respond to appropriate therapy.**
- **Fragility fractures in eugonadal females or young males**

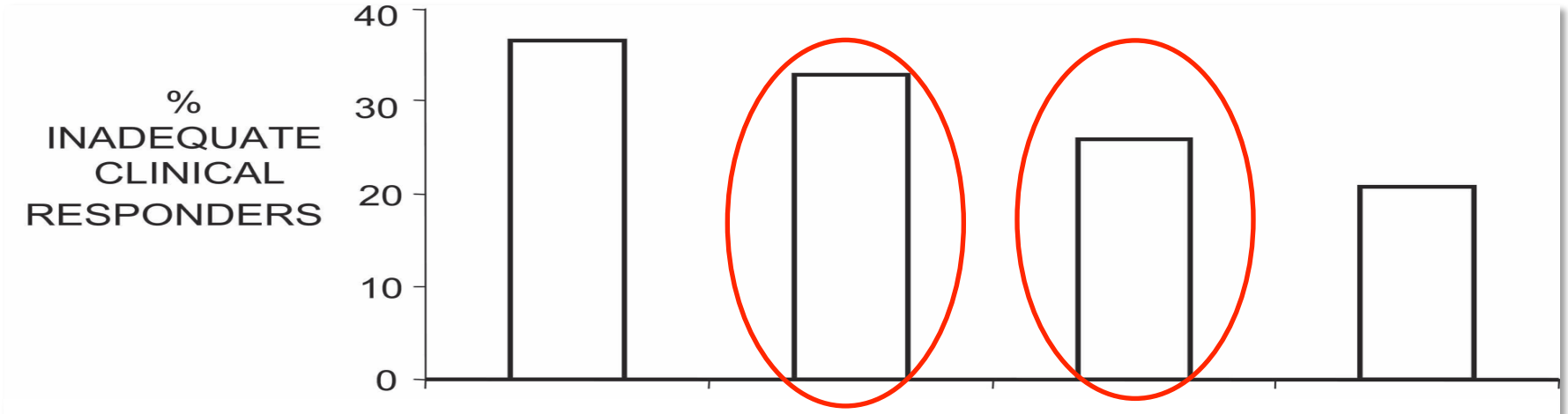
Hofbauer LC, Eur J Endocrinol 2010
Kok C and Sambrook PN, Best Pract Res Clin Rheumatol 2009

ESTABLISHED CAUSES OF SUBOPTIMAL RESPONSE TO BISPHOSPHONATES

Poor adherence	
Scarce intake of calcium and vitamin D	
Secondary osteoporosis	*Endocrine diseases* Acromegaly, diabetes mellitus, growth hormone deficit, hypogonadism, hypercortisolism, hyperparathyroidism, hyperthyroidism *Gastrointestinal diseases* Celiac disease, chronic liver disease, inflammatory bowel disease, malabsorption syndromes *Hematologic diseases* Lymphoproliferative and myeloproliferative disorders, multiple myeloma, systemic mastocytosis *Renal diseases* Chronic kidney disease, idiopathic hypercalciuria, renal tubular acidosis *Rheumatologic diseases* Ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus *Organ transplantation* Bone marrow, heart, kidney, liver, lung *Drugs* Anticonvulsants, aromatase inhibitors, chemotherapy, glucocorticoids, gonadotropin-releasing hormone agonists, immunosuppressants, thiazolidinediones *Miscellaneous conditions* Chronic obstructive pulmonary disease, eating disorders, prolonged immobilization, severe disability

Cairoli E & Chiodini I, Biomarkers of Bisphosphonate Failure in Osteoporosis, Springer 2016

POOR RESPONDERS TO BISPHOSPHONATES: CAUSES



Adami S, J Bone Miner Res 2006

Low adherence to therapies, low calcium intake and hypovitaminosis D are main causes of a poor response to anti-osteoporotic

Chiodini I. Unit of Endocrinology and Metabolic Diseases, Fondazione IRCCS Cà Granda – Dpt. of Medical Sciences and Community Health, University of Milan, Milan, Italy

AGENDA

Poor-responders

- Define
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- **Treat**

INADEQUATE RESPONDERS (IOF WORKING GROUP)
GENERAL RULES

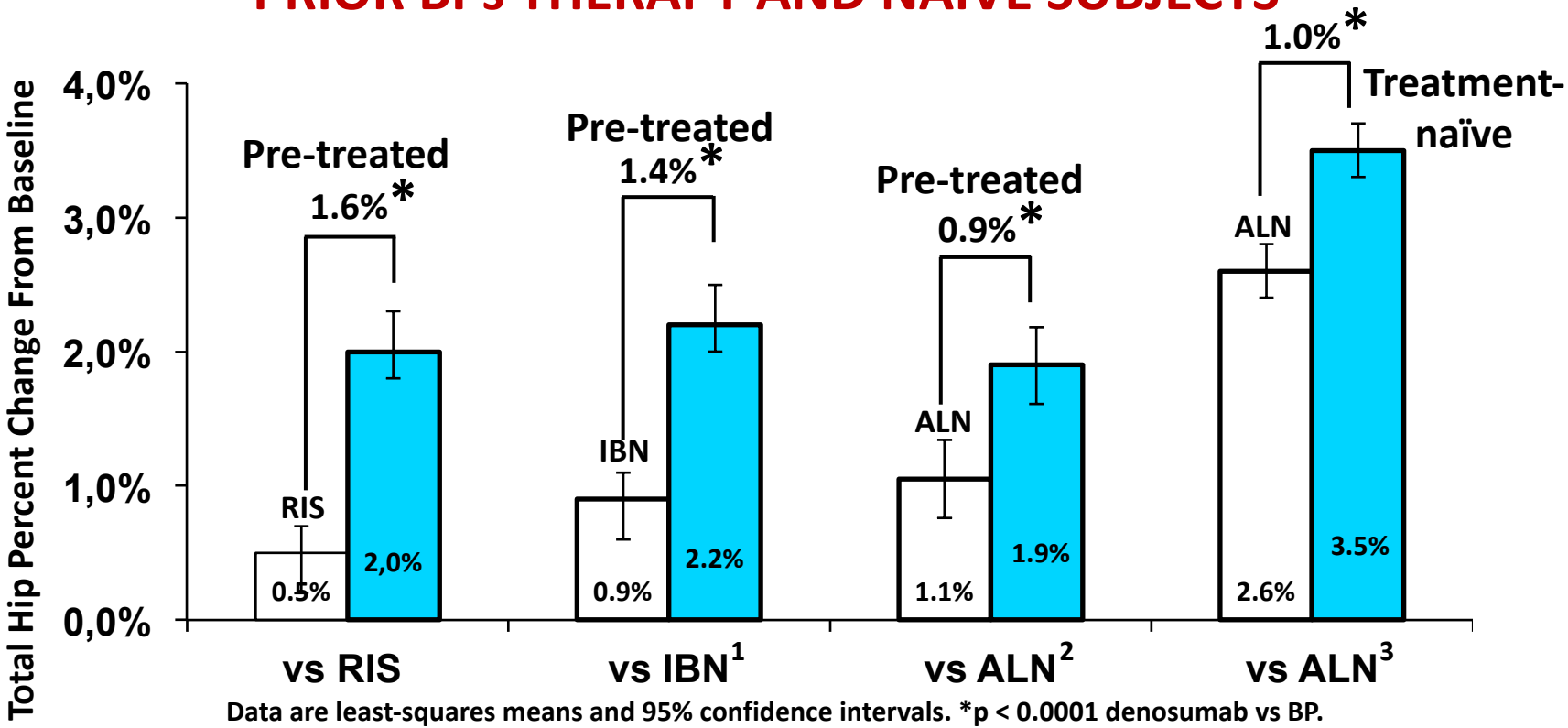
Some data based on indirect comparisons or surrogate end points can be of help

Three general rules are recommended:

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

Diez-Perez A. IOF Guidelines Osteoporos Int 2012

"HEAD TO HEAD" STUDIES DENOSUMAB VS BPS IN SUBJECTS WITH PRIOR BPs THERAPY AND NAÏVE SUBJECTS



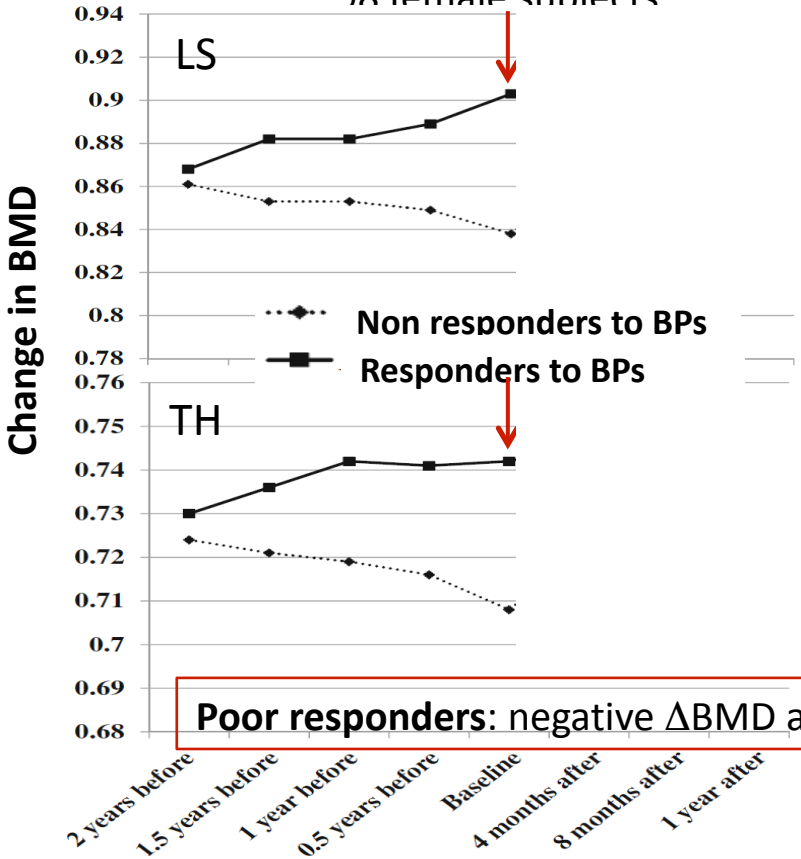
Data are least-squares means and 95% confidence intervals. *p < 0.0001 denosumab vs BP.

Roux C, Bone 2014; [1]Recknor C et al, Obs Gyn 2013 ; [2]Kendler DL et al. J Bone Miner Res 2010; [3]Brown JP et al. J Bone Miner Res 2009

Chiodini I. Unit of Endocrinology and Metabolic Diseases, Fondazione IRCCS Cà Granda – Dpt. of Medical Sciences and Community Health, University of Milan, Milan, Italy

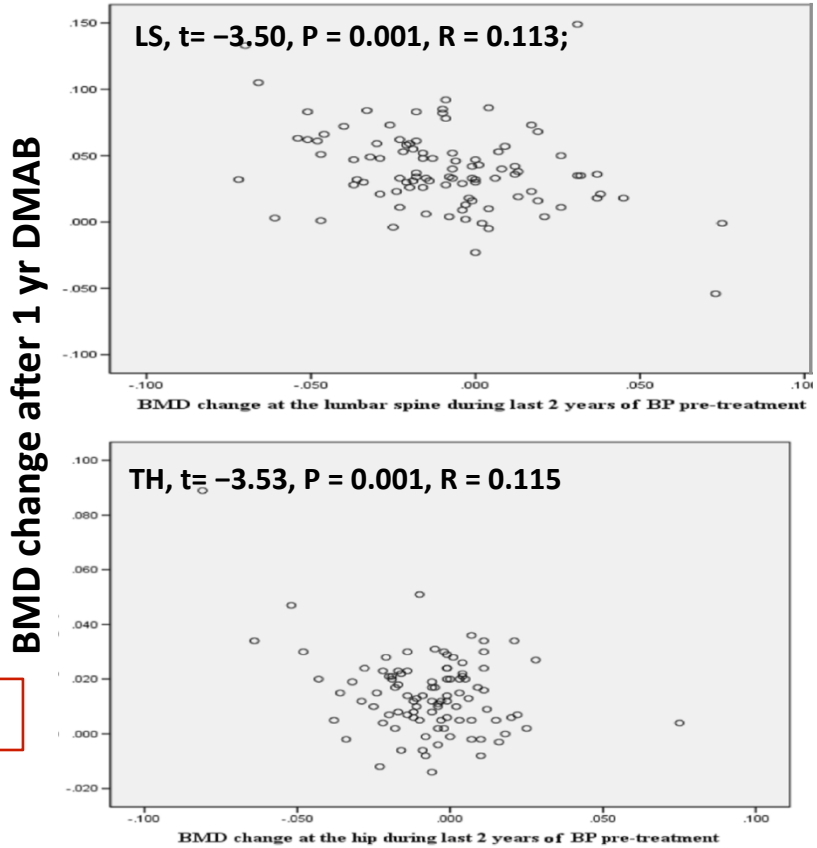
SIGNIFICANT IMPROVEMENT OF BONE MINERAL DENSITY BY DENOSUMAB THERAPY IN BISPHOSPHONATE-UNRESPONSIVE PATIENTS

98 female subjects



Poor responders: negative ΔBMD after BPs

Kamimura M. et al, Osteoporos Int 2017



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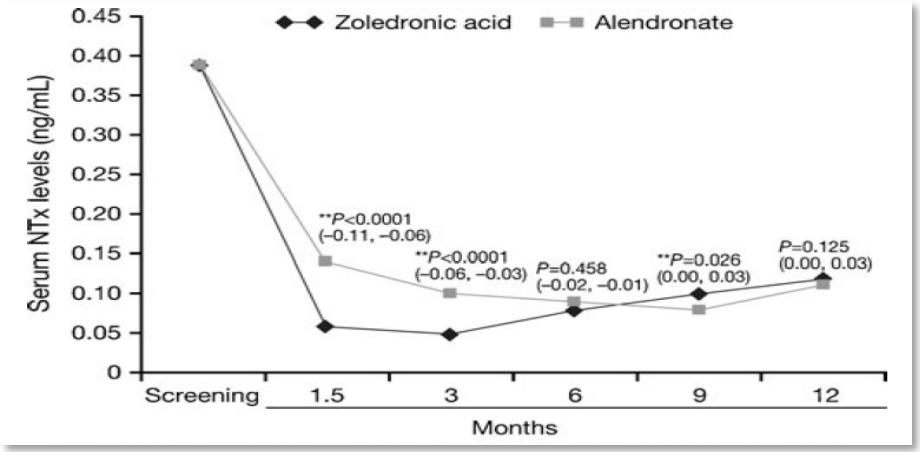
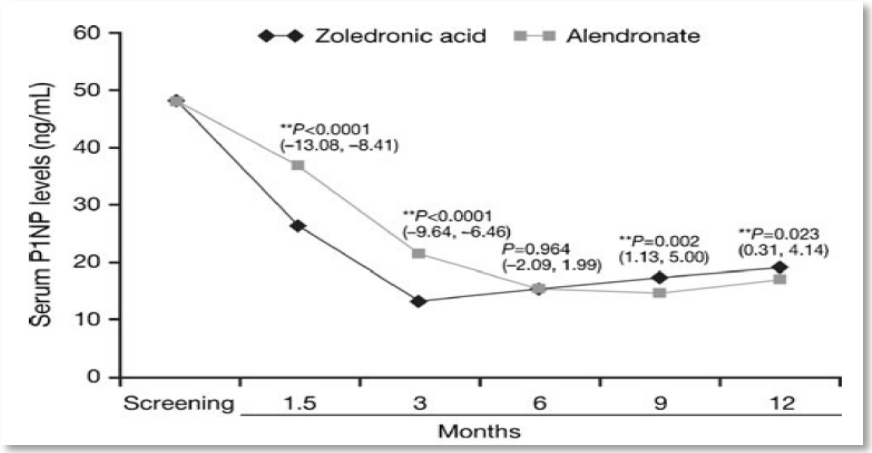
Diez-Perez A. IOF Guidelines Osteoporos Int 2012

ONCE-YEARLY IV ZOLEDRONIC ACID PROVIDES A GREATER AND FASTER REDUCTION IN NTX AND P1NP LEVELS THAN ONCE-WEEKLY ORAL ALENDRONATE: THE ROSE STUDY





P. Hadji at al, Osteoporos Int 2012

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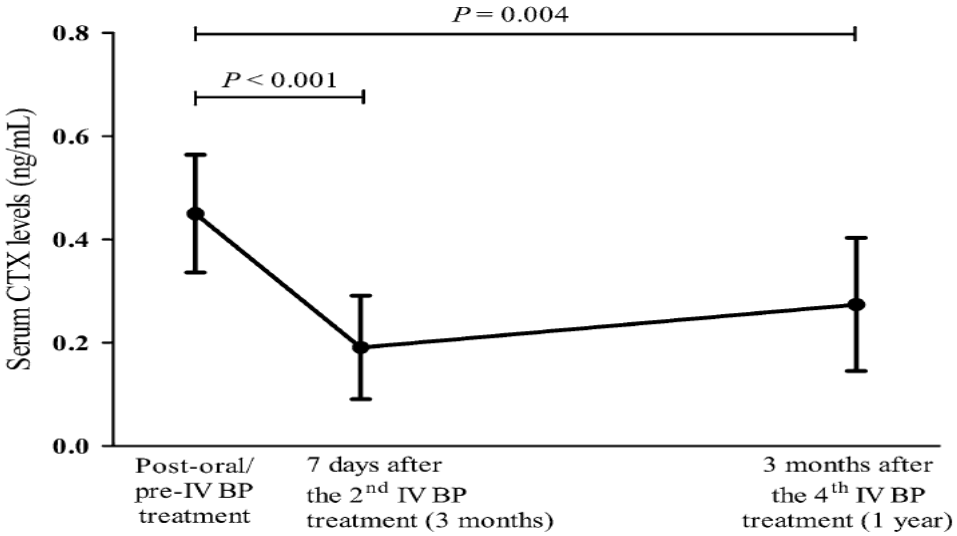
INTRAVENOUSLY IBANDRONATE IN POSTMENOPAUSAL KOREAN WOMEN POOR RESPONDERS TO ORALLY ADMINISTERED BISPHOSPHONATES

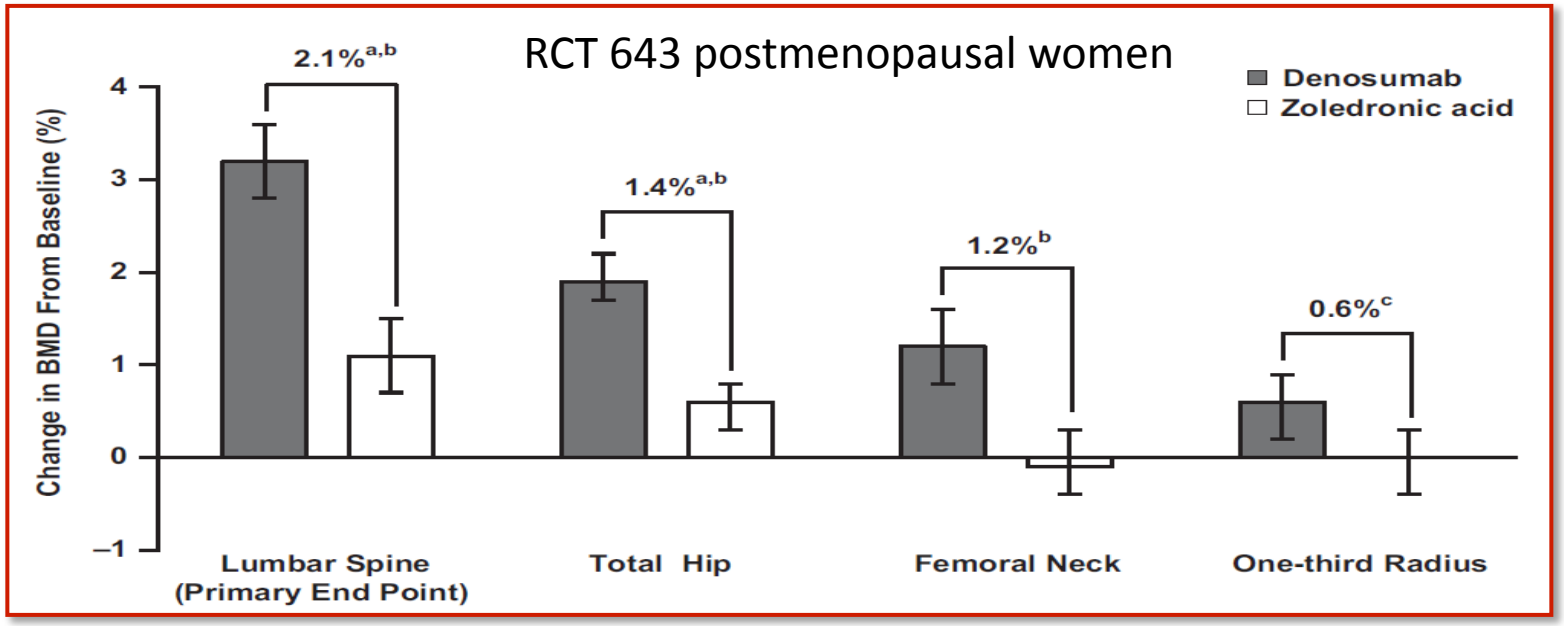
Sung Jin Bae SJ et al, J Bone Miner Metab 2012



Poor responders: <50% of inhibition of BTM

	ΔLS BMD (g/cm²/year)			ΔFN BMD (g/cm²/year)		
	Oral BP (n = 19)	IV BP (n = 13)	P	Oral BP (n = 19)	IV BP (n = 13)	P
Unadjusted	0.031 ± 0.023	0.037 ± 0.037	0.202	0.008 ± 0.026	0.008 ± 0.031	0.998
Adjusted	0.033± 0.031	0.036 ± 0.032	0.177	0.005 ± 0.026	0.011 ± 0.025	0.536

DENOSUMAB OR ZOLEDRONIC ACID IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS PREVIOUSLY TREATED WITH ORAL BISPHOSPHONATES



Miller PD et al, J Clin Endocrinol Metab 2016

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GENERAL RULES

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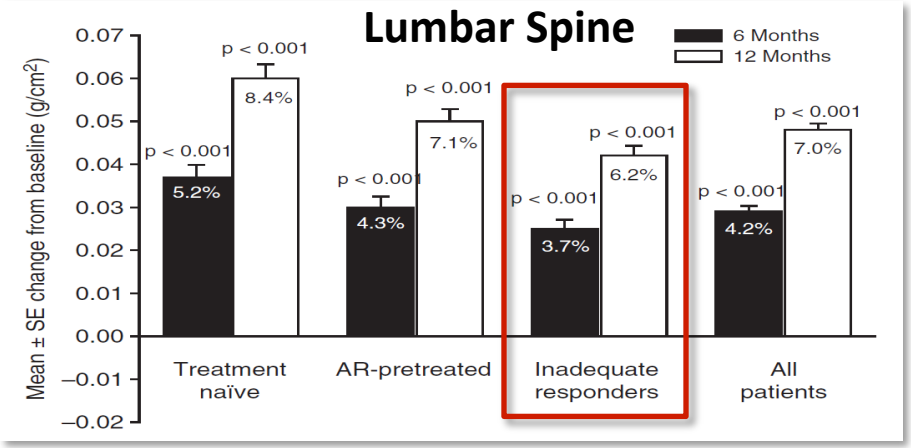
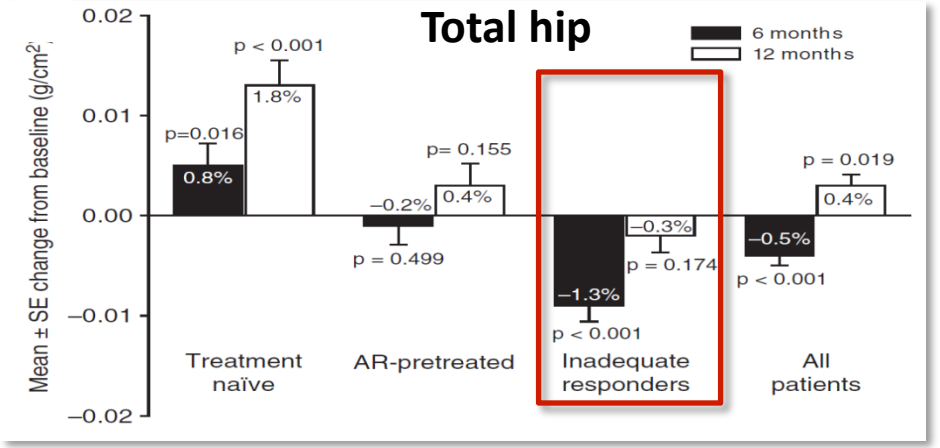
Diez-Perez A. IOF Guidelines Osteoporos Int 2012

BONE DENSITY AT SPINE BUT NOT AT FEMUR INCREASES AFTER TERIPARATIDE IN PATIENTS WITH PRIOR INADEQUATE RESPONSE TO ANTIRESORPTIVES





Naive=204, AR-pretreated=240, inadequate responders=421

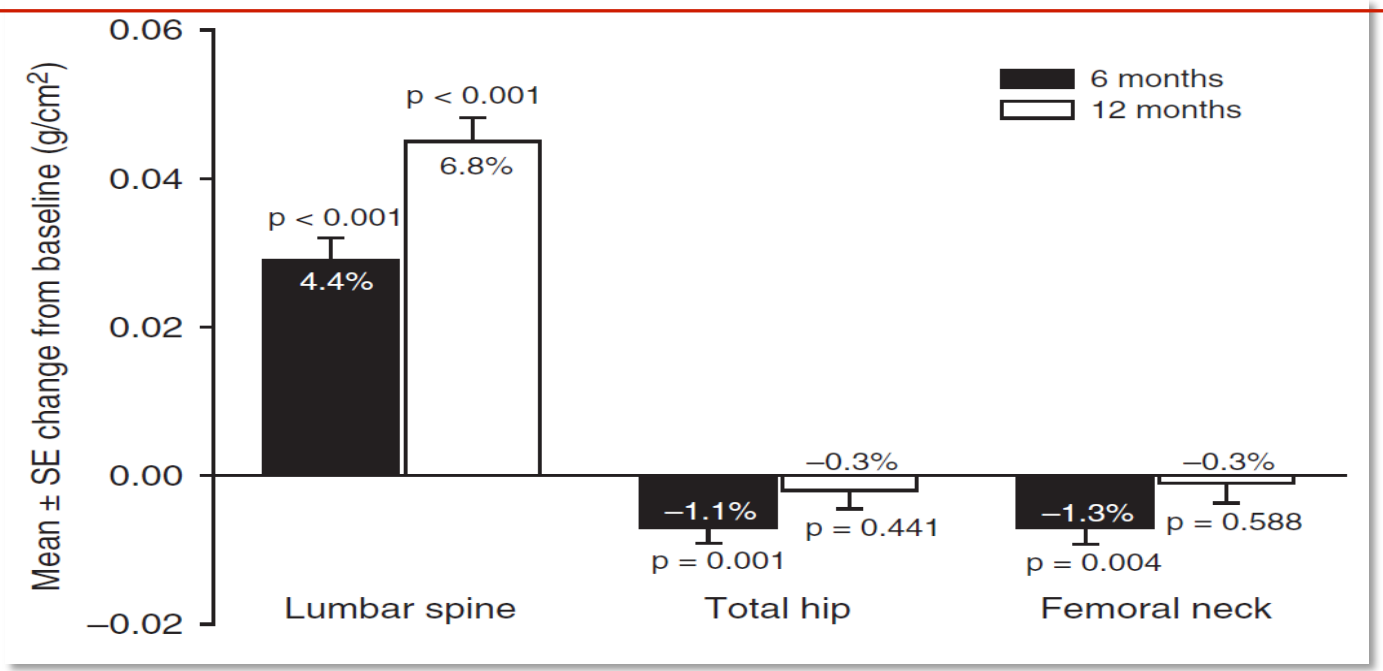
Minne H et al, Curr Med Res Op 2008

Poor responders:

- **≥1 new clinical fragility fracture or**
- **continued to have a lumbar spine, total hip, or femoral neck BMD T-score < -3.0 or**
- **experienced a decrease of 3.5% in BMD at any one of those skeletal sites**

BONE DENSITY AT SPINE BUT NOT AT FEMUR INCREASES AFTER TERIPARATIDE IN PATIENTS WITH PRIOR INADEQUATE RESPONSE TO ANTIRESORPTIVES

Poor responders:
Bone mineral density loss of > 3.5% and a new fragility fracture (=179)



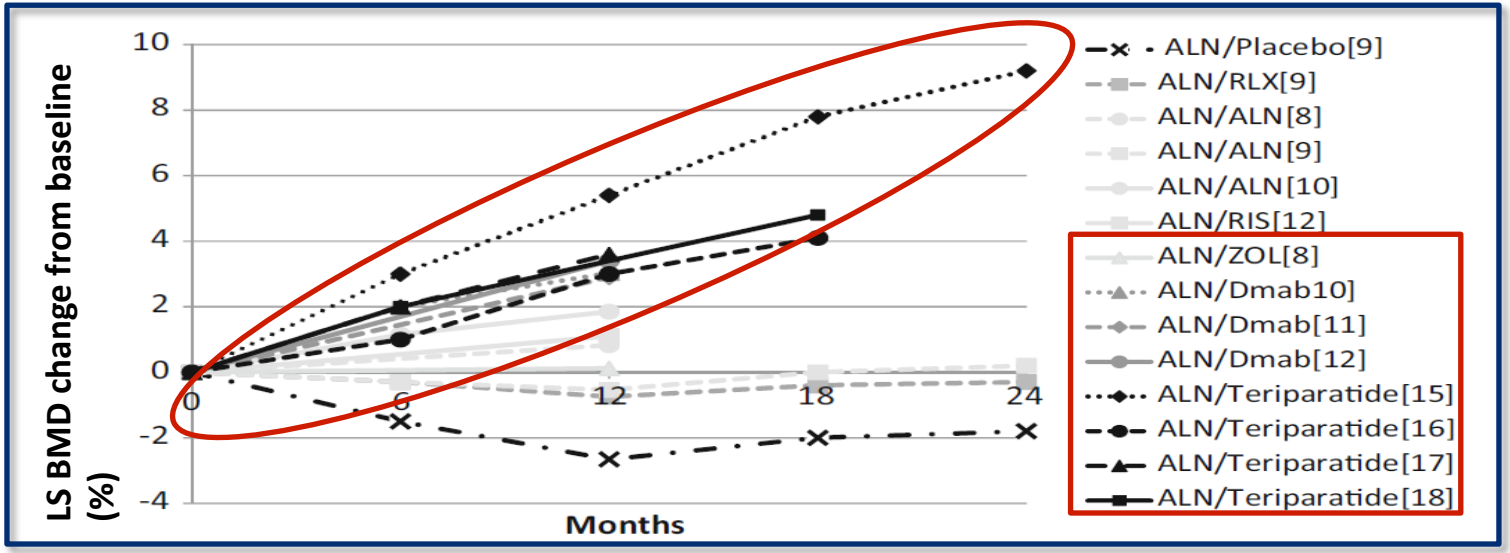
Minne H et al, Curr Med Res Op 2008

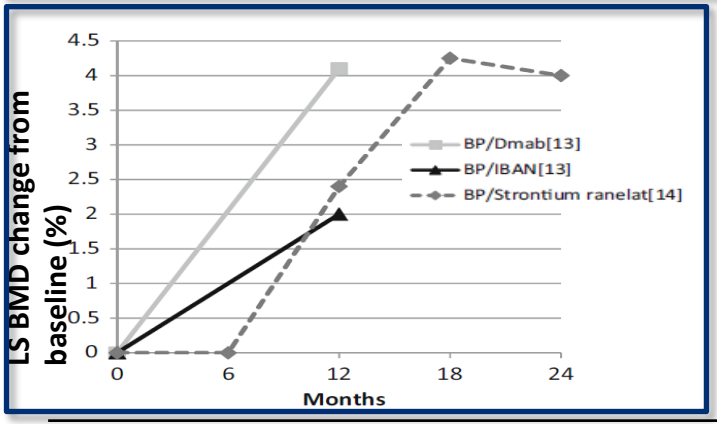
SEQUENTIAL THERAPY OF OSTEOPOROSIS

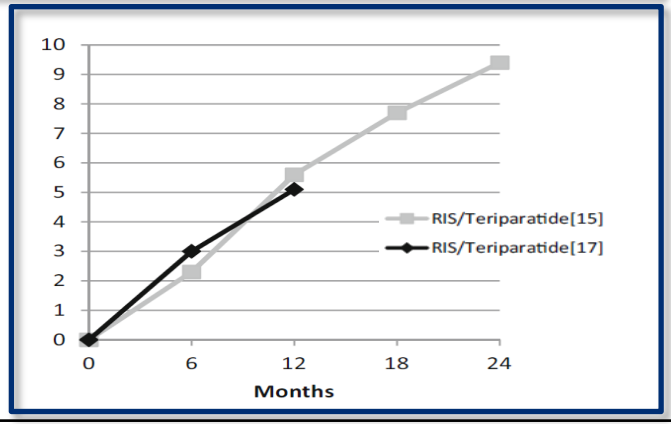
Drug	Reference [a]	12 MO	18 MO	24-25 MO	4 YR
PTH 1-84 12M to alendronate 12M	57	-	-	4.4% [g]	-
PTH 1-84 12M to alendronate 12M	58	-	-	3%	-
Teriparatide 24M to denosumab 24M	59	-	-	-	6.6%
Teriparatide + denosumab 24M to denosumab 24M	59	-	-	-	8.6%
Alendronate to teriparatide	28	-	0.9%	-	-
Alendronate to teriparatide	60	-	-1.7%	-	-
Risedronate to teriparatide	60	-	-0.3%	-	-
Alendronate to teriparatide	61	-0.6%	0.6%	2.1%	-
Risedronate to teriparatide	61	-0.4%	0.9%	2.9%	-
Alendronate to teriparatide	64	-	-	3.3% [g]	-

Mc Clung MR, Curr Osteoporos Rep 2017

SUMMARY: THERAPY OF OSTEOPOROSIS AFTER ALENDRONATE OR RISEDRONATE







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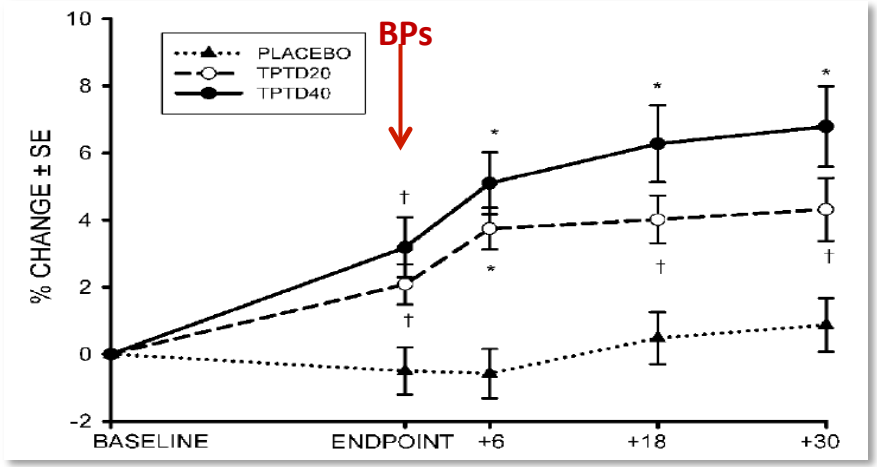
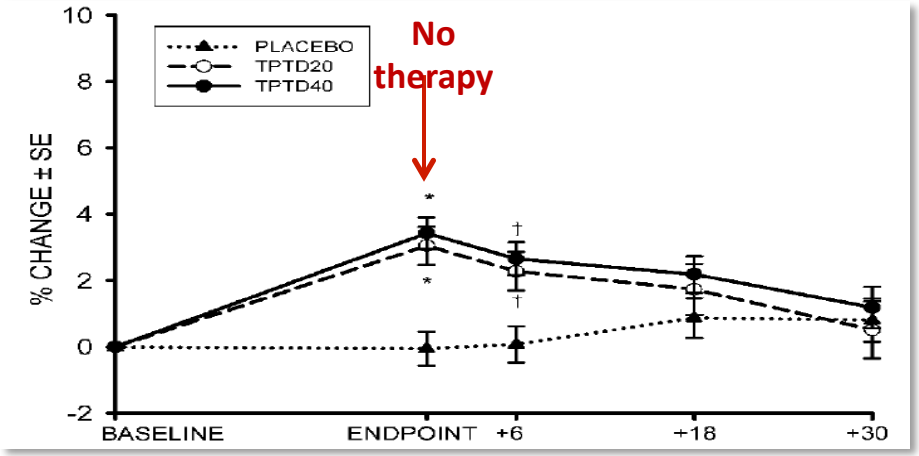
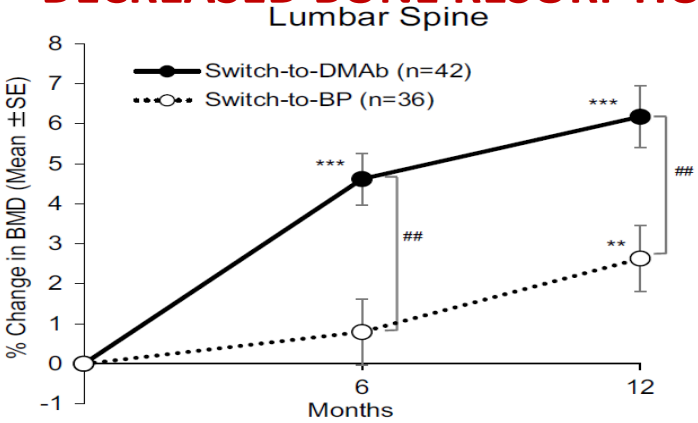
THERAPY OF OSTEOPOROSIS AFTER TERIPARATIDE

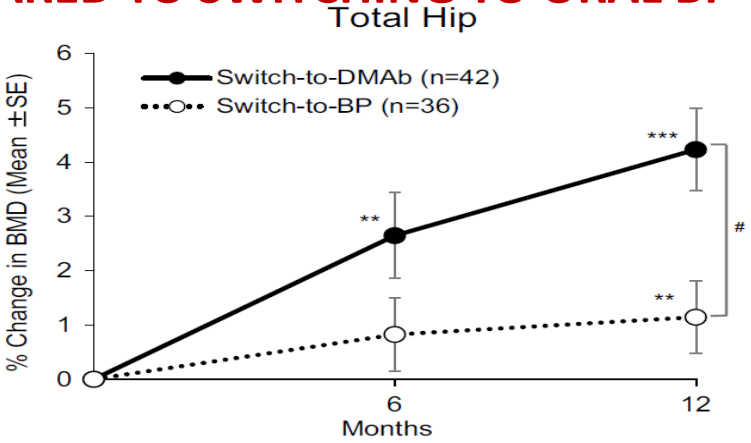


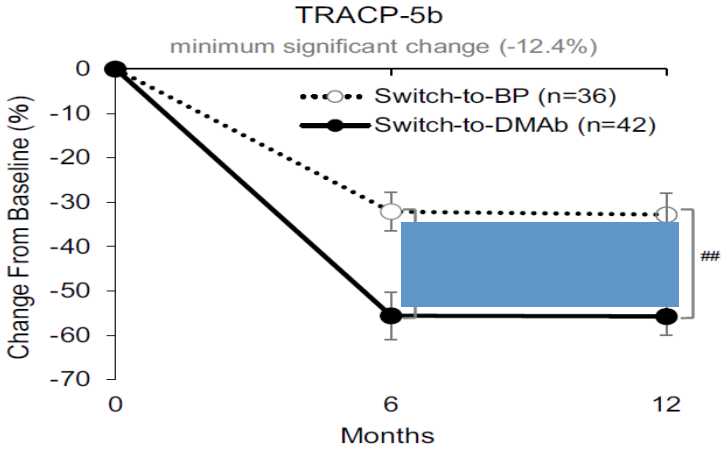


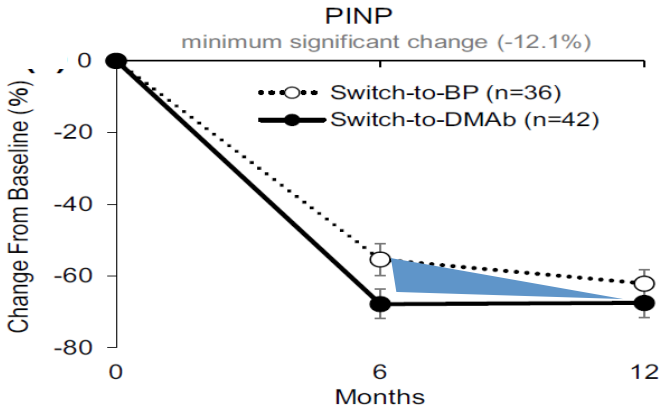
Prince R et al, J Bone Miner Res 2005

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









Ebina K et al, J Bone Miner Metab, 2017

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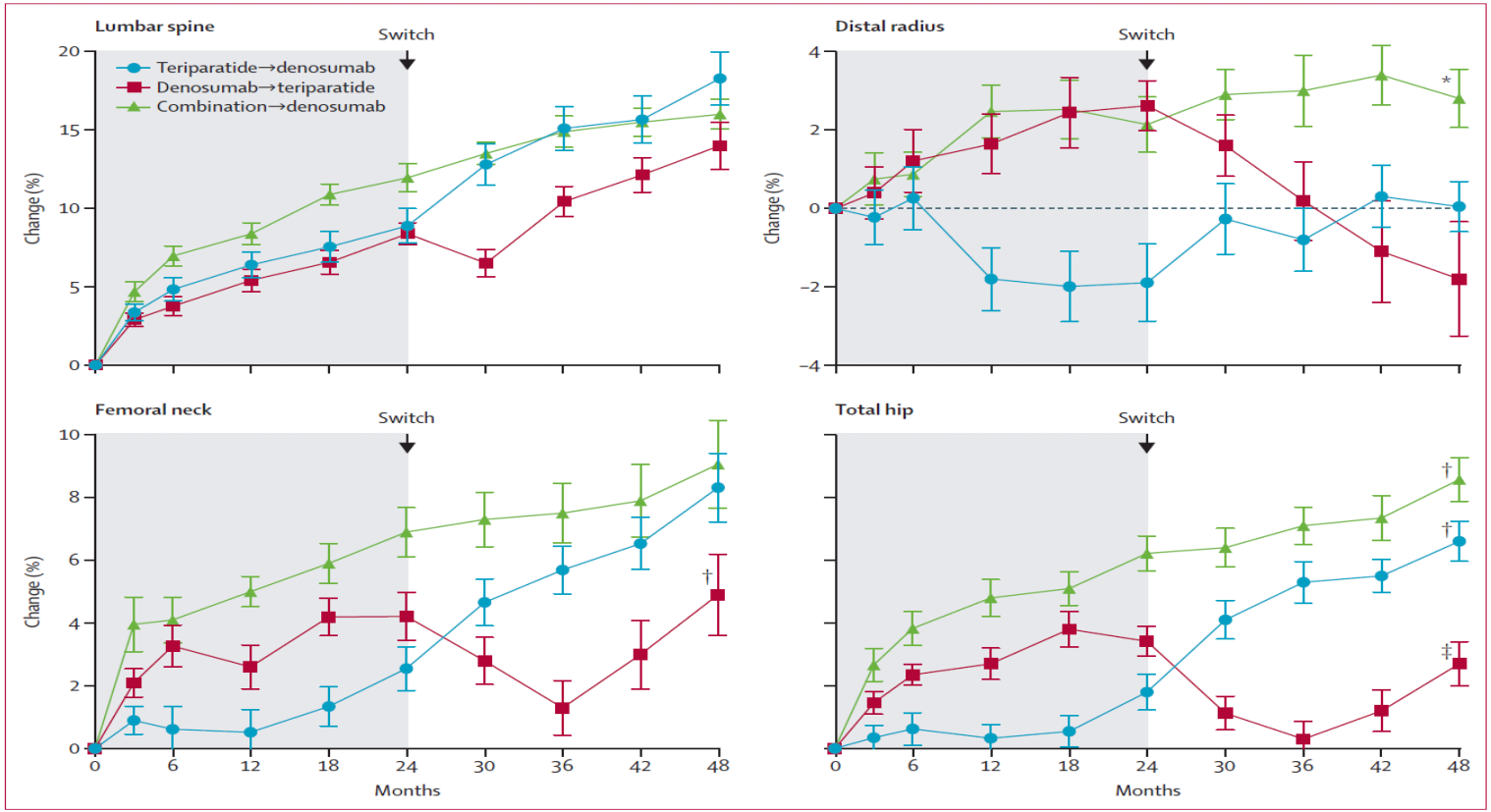
Mc Clung MR, Curr Osteoporos Rep 2017

DMAB AND TPT TRANSITIONS IN POSTMENOPAUSAL OSTEOPOROSIS (DATA-SWITCH STUDY)



Leder BZ et al, Lancet 2015

Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico

Sistema Socio Sanitario
Regione Lombardia

UNIVERSITÀ DEGLI STUDI DI MILANO

THANK YOU

Cristina Eller-Vainicher

Elisa Cairoli

Valentina Morelli

Serena Palmieri

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