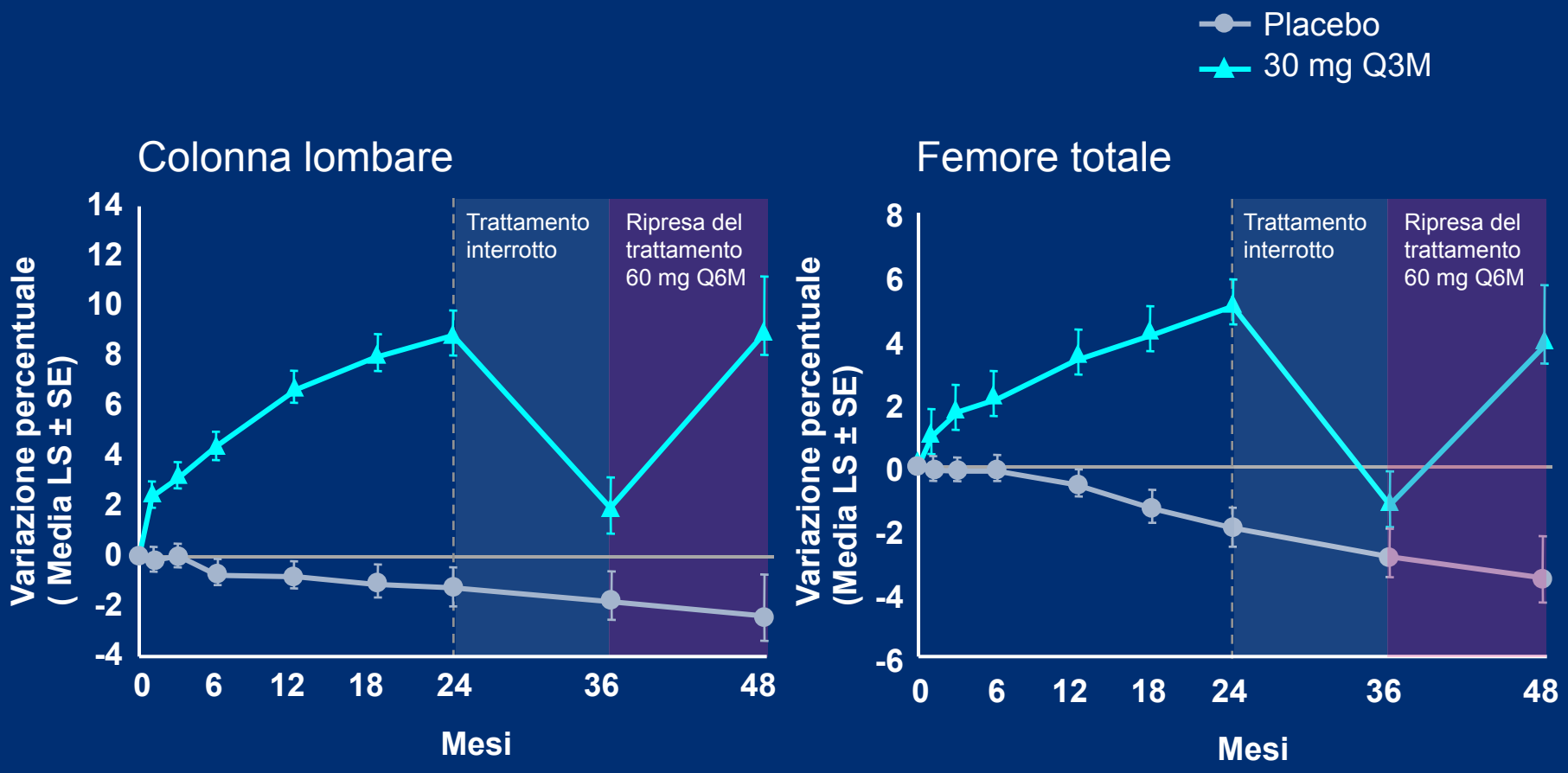
Ripresa del trattamento con denosumab: variazioni della BMD della colonna lombare e del femore totale



Adattato da m Miller PD, et al. *Bone*. 2008;43:222-229.

DECIDE Determining Efficacy: Comparison of Initiating Denosumab versus AlEndronate

STAND Study of Transitioning from AleNdronate to Denosumab

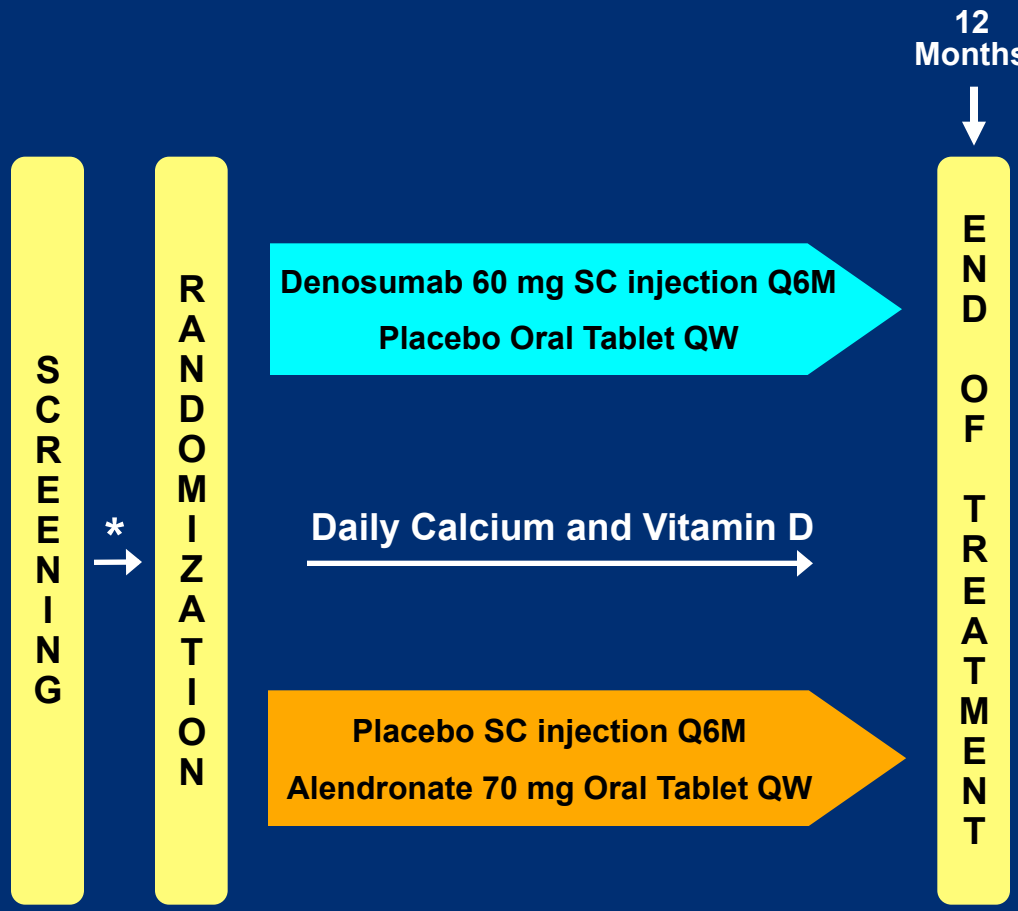
Multi-center, randomized, double-blind, active-controlled, double-dummy, parallel studies

DECIDE

- Postmenopausal women naïve to osteoporosis treatment
- T-score ≤ –2.0 at the lumbar spine or total hip

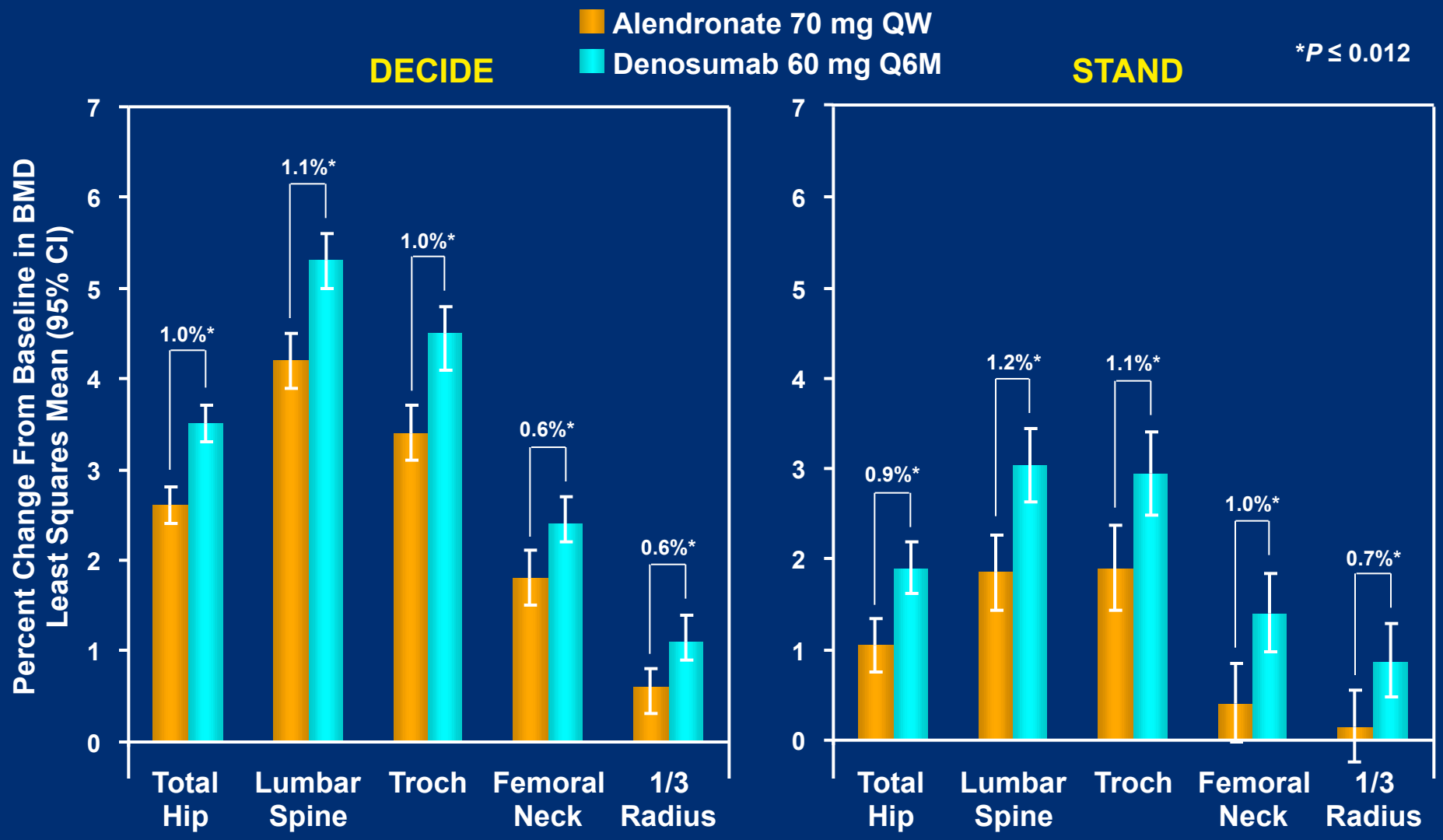
STAND

- Postmenopausal women who had been receiving alendronate treatment equivalent to 70 mg/week for ≥ 6 months immediately prior to screening
- T-score ≤ –2.0 and ≥ –4.0 at the lumbar spine or total hip



* In the STAND trial, all subjects received branded alendronate 70 mg QW during a 1-month run-in period before randomization.

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

Denosumab e bisfosfonati: differenze

- Differente farmacocinetica: meccanismo on-off
- Differente efficacia sulla riduzione del turnover
- Effettto diverso su osso trabecolare e corticale e sulla microstruttura

Denosumab e bisfosfonati: diverso meccanismo d'azione sugli osteoclasti

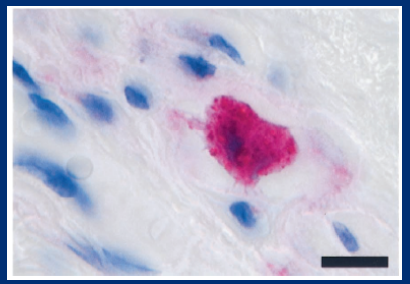
RANKL
RANK
OPG
Denosumab

Denosumab inibisce il RANKL

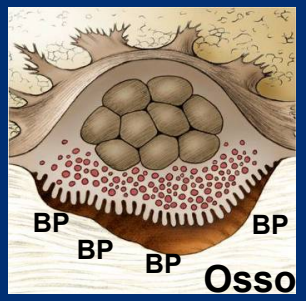
Precursori degli osteoclasti

Denosumab inibisce la formazione degli osteoclasti

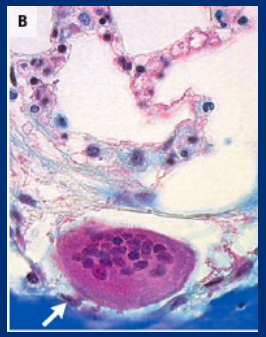
Denosumab inibisce la funzione e la sopravvivenza degli osteoclasti

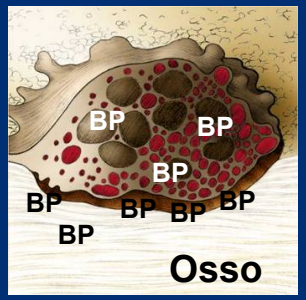


BP = bisfosfonati



I BP si legano alla matrice ossea a livello dei siti attivi di riassorbimento



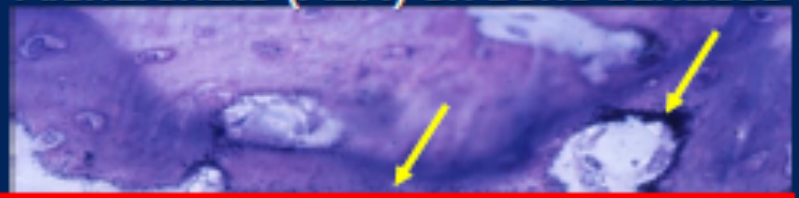


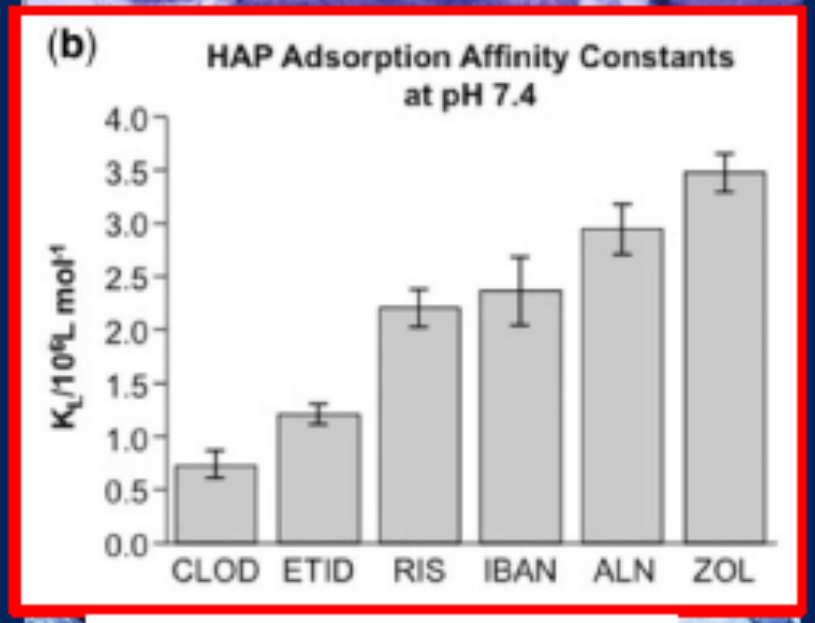
I BP sono citotossici e provocano la perdita della funzione riassorbitiva degli osteoclasti, anche se possono permanere degli osteoclasti inattivi

Adattato da Boyle WJ, et al. *Nature.* 2003;423:337-42
Adattato da Russell RGG, et al. *Ann NY Acad Sci.* 2007;1117:209-257

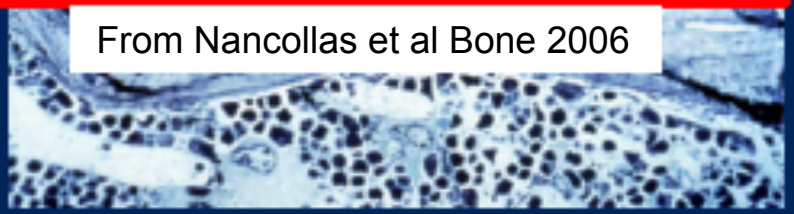
Different distribution of denosumab and bisphosphonates

Alendronate (ALN) on bone surfaces at 24 hrs

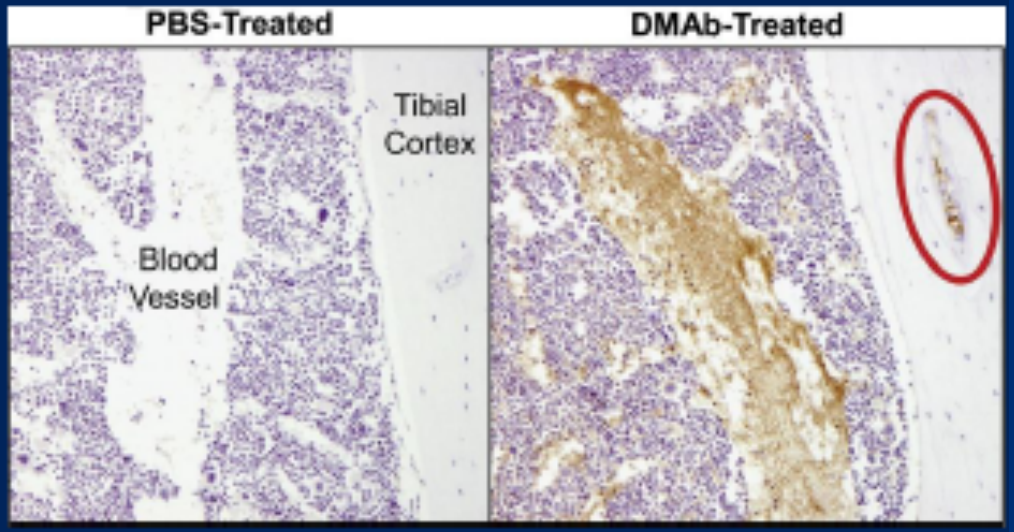




From Nancollas et al Bone 2006



Denosumab in blood vessels

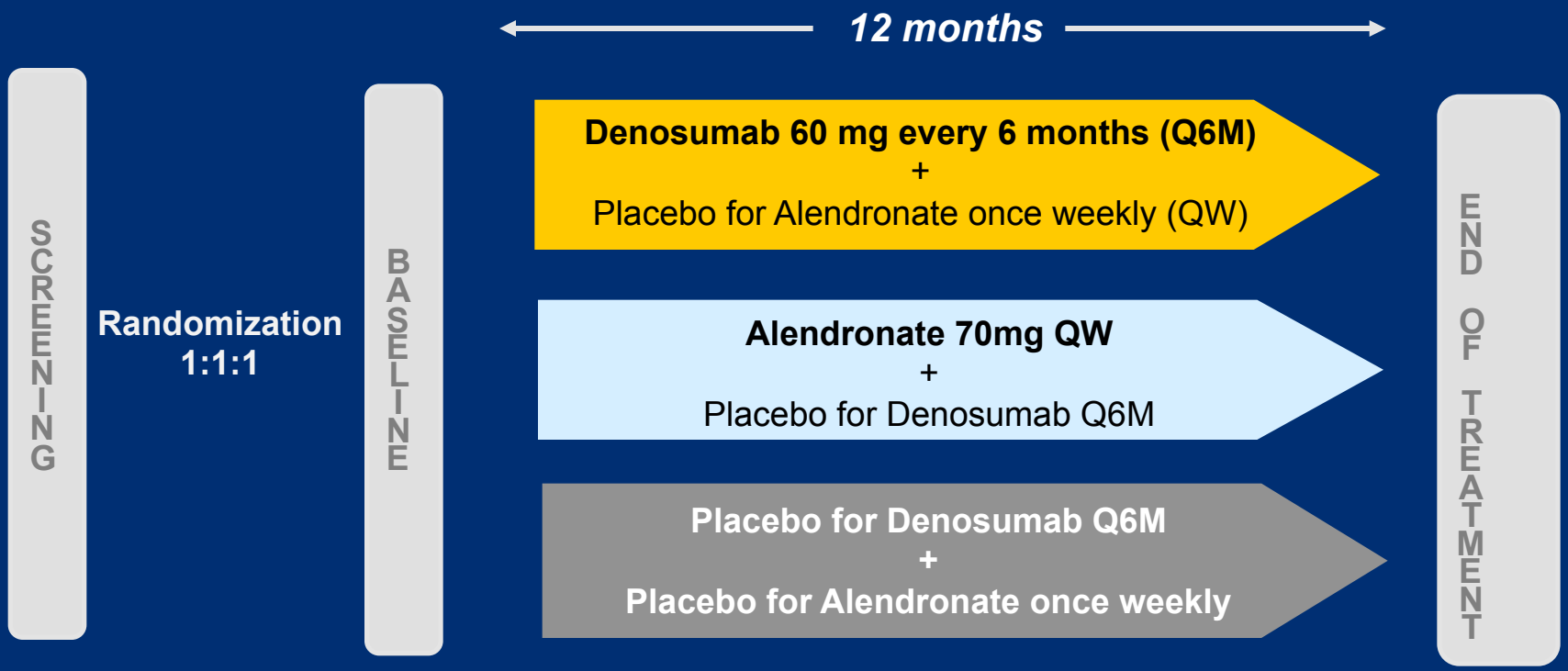


Masarachia P et al. *Bone* 1996;19:281–290;
Kostenuik PJ et al. *JBMR* 2009;24:182-95.

Study Design: Denosumab or Alendronate and Bone Architecture

Bone architecture pilot study

Multicenter, double-blind, active-controlled study



Study population

- 247 postmenopausal women
- T-score at the lumbar spine or total hip between -2.0 and -3.0

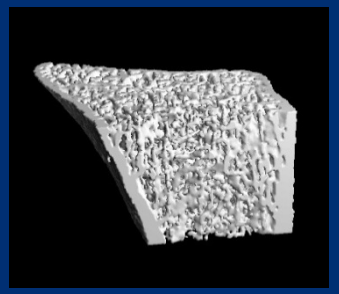
Endpoints

- % change from baseline in cortical thickness
- % changes in total, cortical, and trabecular vBMD
- Trabecular number, thickness, and separation
- Safety

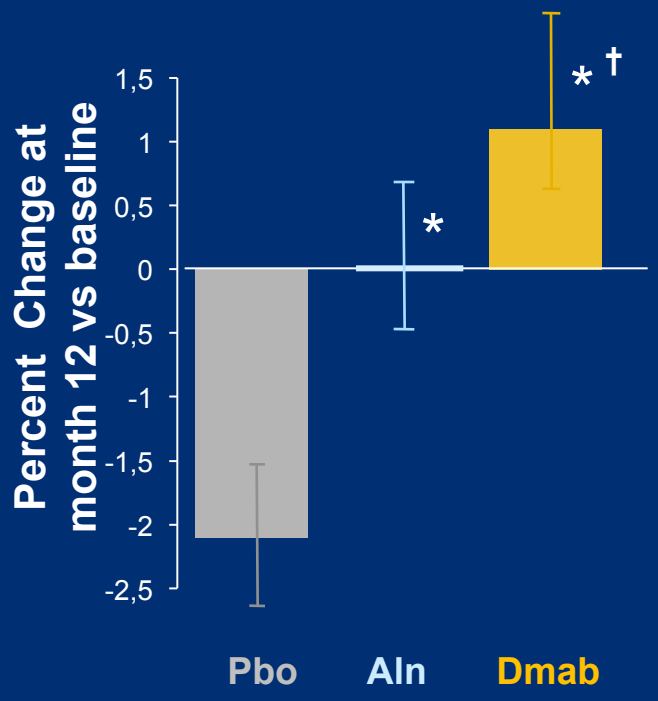
Adapted from Seeman E. et al *J Bone Miner Res* (2010) ;25:1886-1894

Greater increases in cortical BMD at the radius (HR-pQCT)

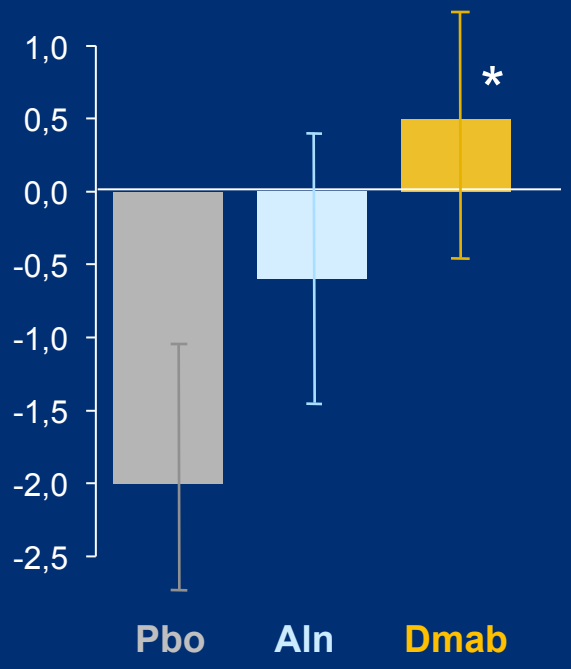
Bone architecture pilot study



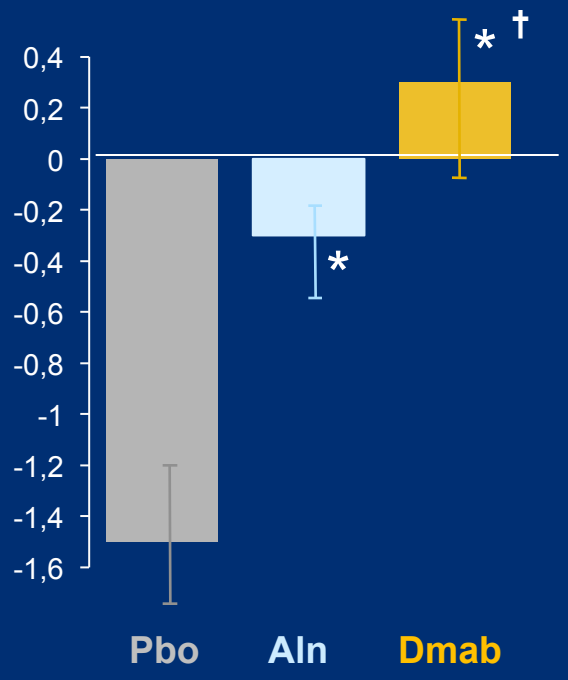
Total vBMD



Trabecular vBMD



Cortical vBMD



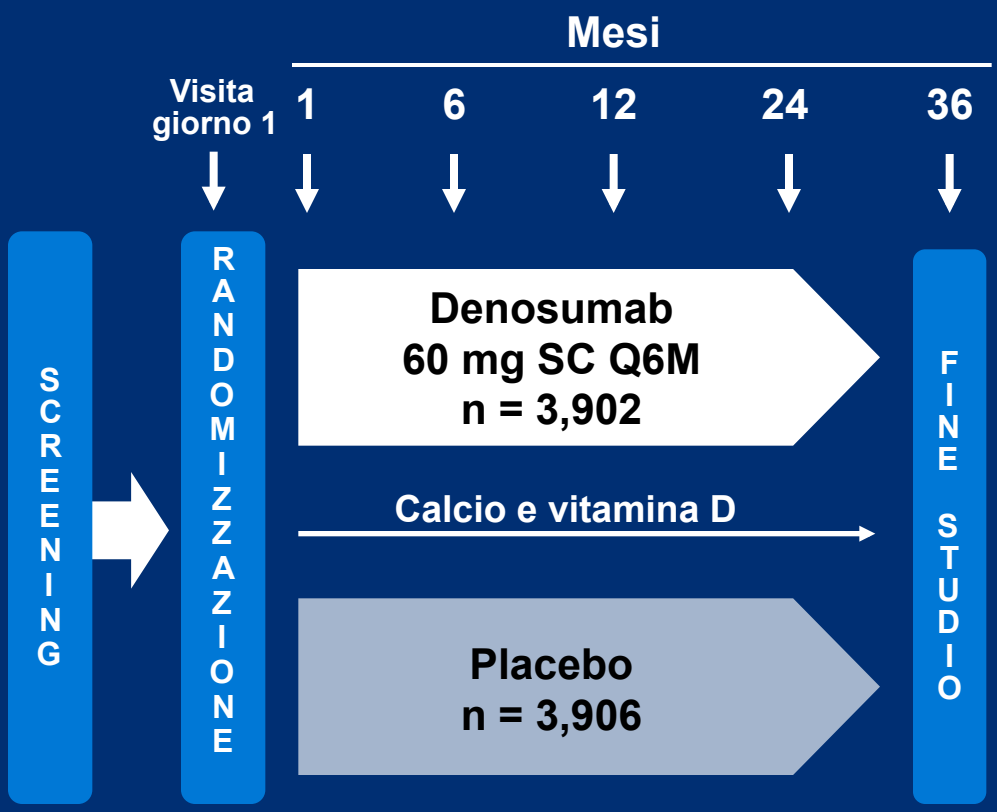
***P* < 0.001 vs placebo**
†*P* < 0.02 vs alendronate

Values shown are LS Mean (95% CI)

Adapted from Seeman E. et al *JBMR* (2010) ;25:1886-1894

Effetto sul rischio di frattura

Studio *FREEDOM*
Disegno dello studio



- **Internazionale, multicentrico, randomizzato, in doppio cieco e controllato con placebo**

Popolazione in studio

- 7,808 donne in postmenopausa
- T-score della colonna lombare o del femore totale < –2.5, ma non inferiore a –4.0 in ciascun sito
- Esclusione dei soggetti che presentavano una frattura vertebrale prevalente di grado severo (o più di 2 fratture di grado moderato)

End point primario

- Nuove fratture vertebrali a 36 mesi

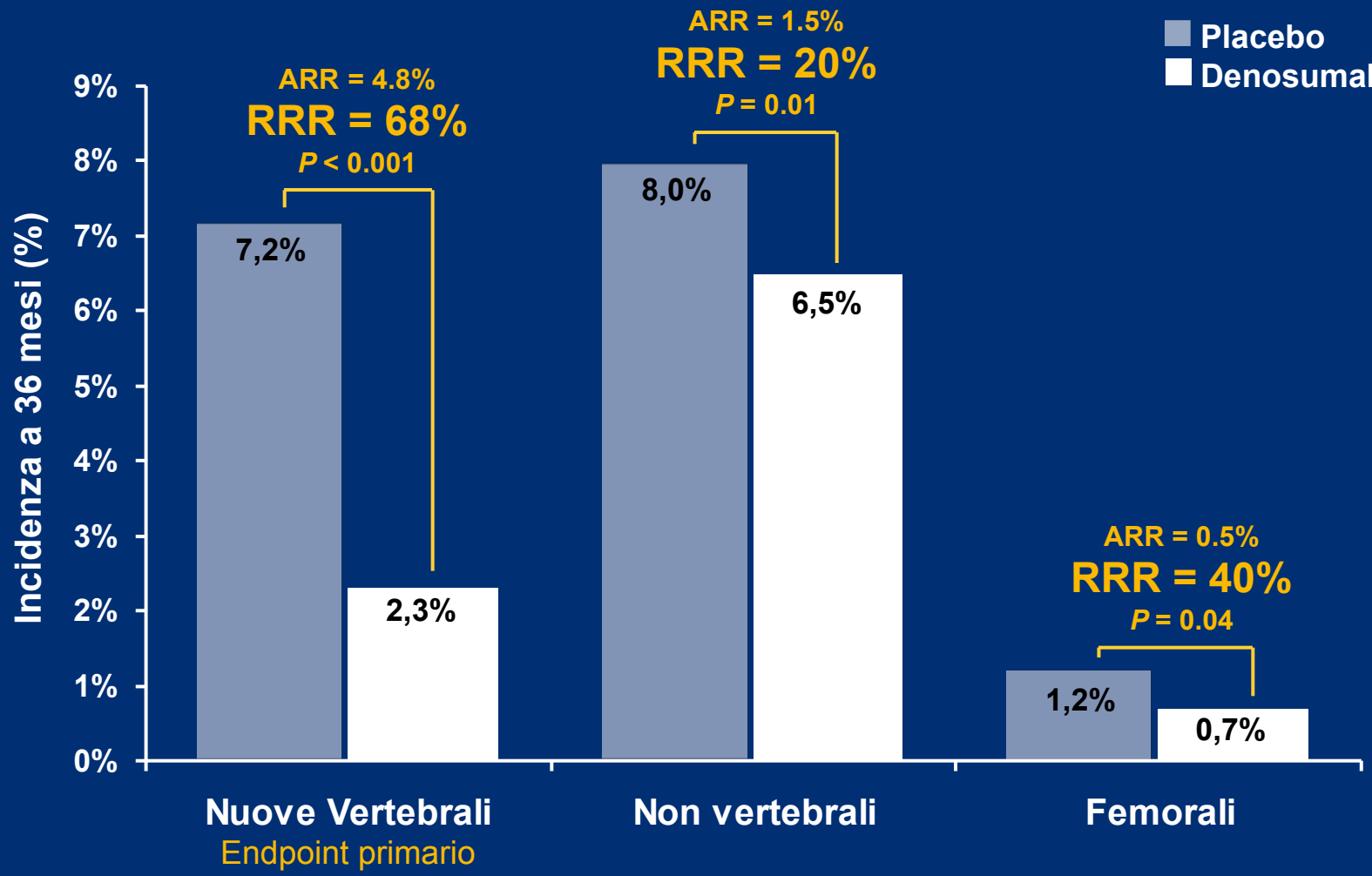
End point secondari

- Tempo alla prima frattura non vertebrale
- Tempo alla prima frattura di femore

SC = sottocutaneo; Q6M = una volta ogni 6 mesi

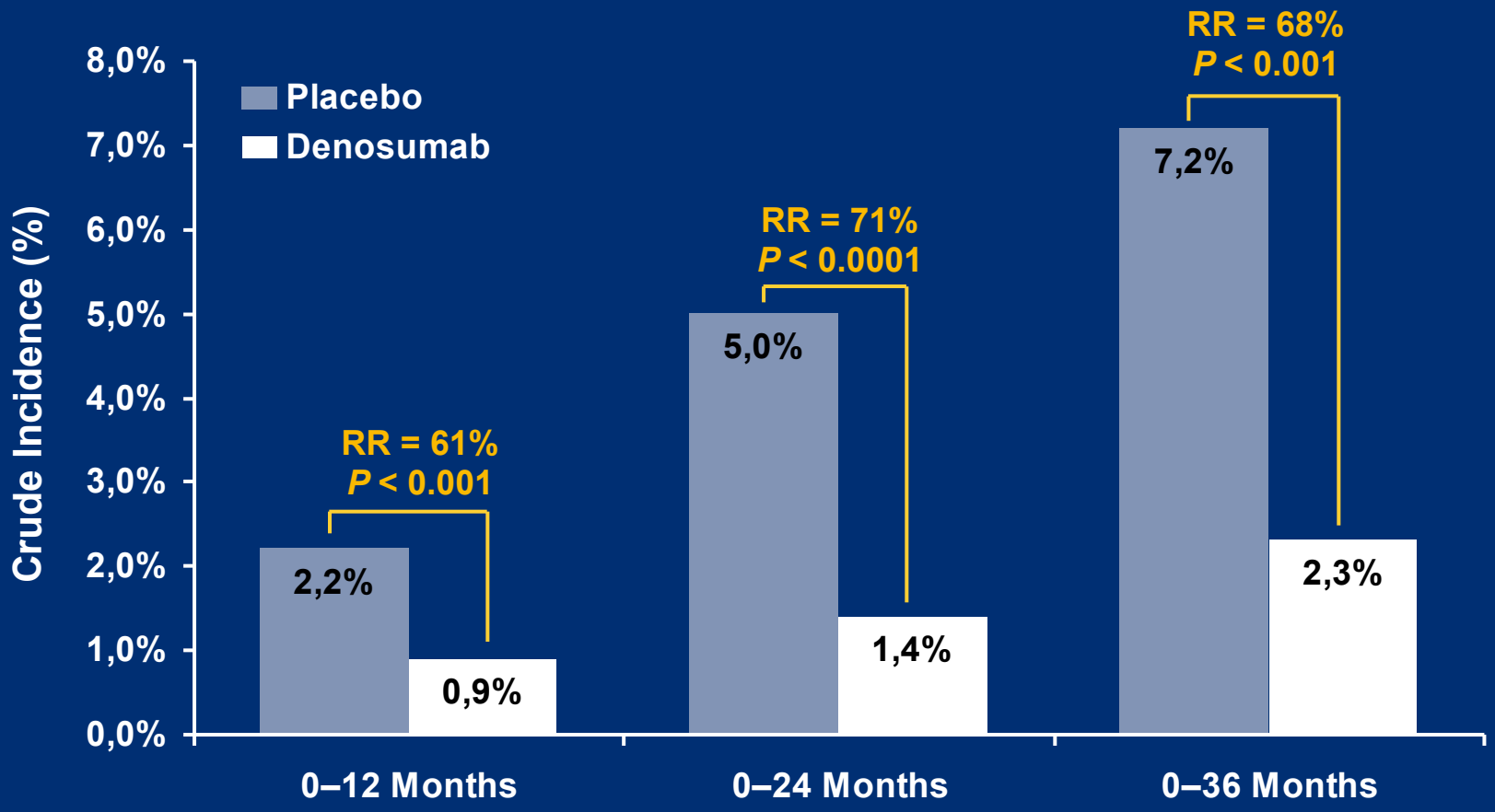
Cummings SR, et al. *N Engl J Med*. 2009;361:756-765.

Studio *FREEDOM*
Efficacia antifratturativa di denosumab a 36 mesi



ARR = riduzione rischio assoluto; RRR = riduzione rischio relativo
Adattato da: Cummings SR, et al. *N Engl J Med*. 2009;361:756-765.

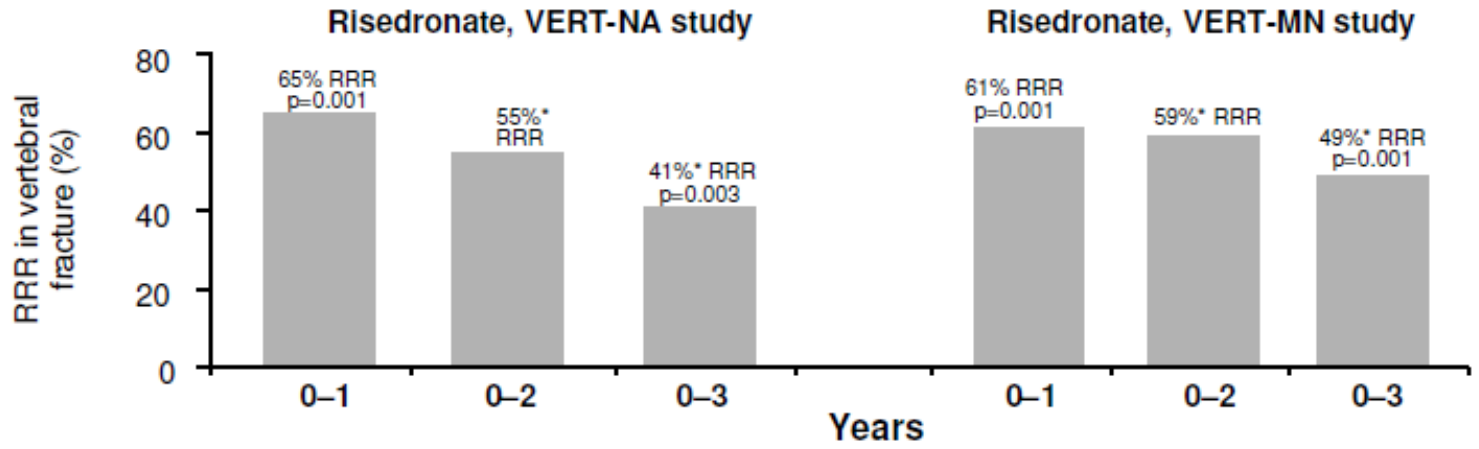
The Effect of Denosumab on New Vertebral Fractures At Month 12, 24, and 36

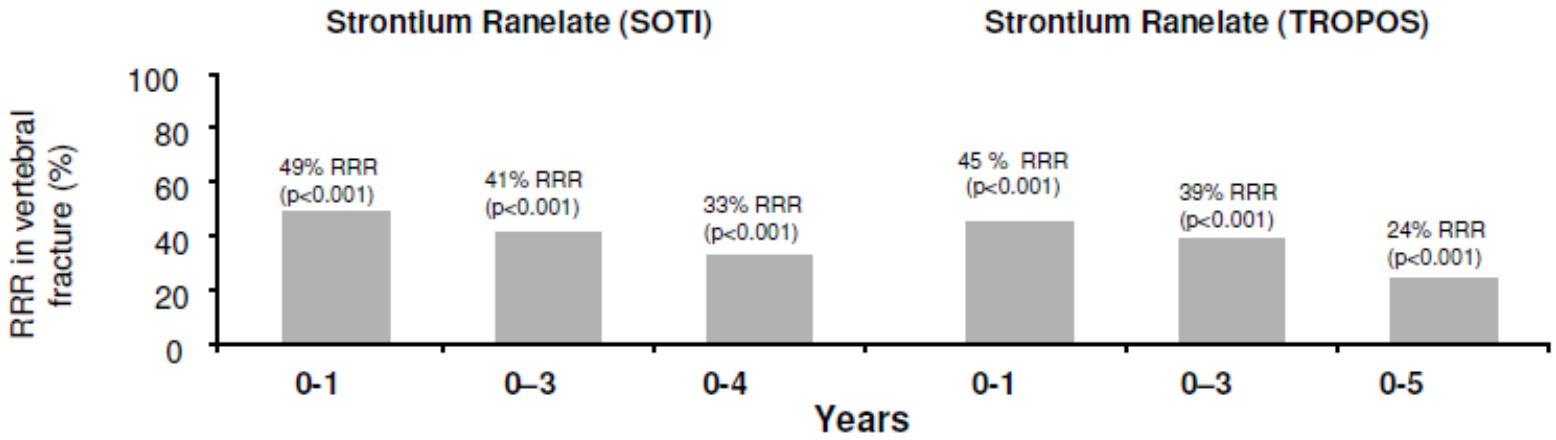


Intent-to-treat, last observation carried forward analysis
Denosumab Summary of Product Characteristics, 2010

Riduzione del rischio di fratture nel tempo

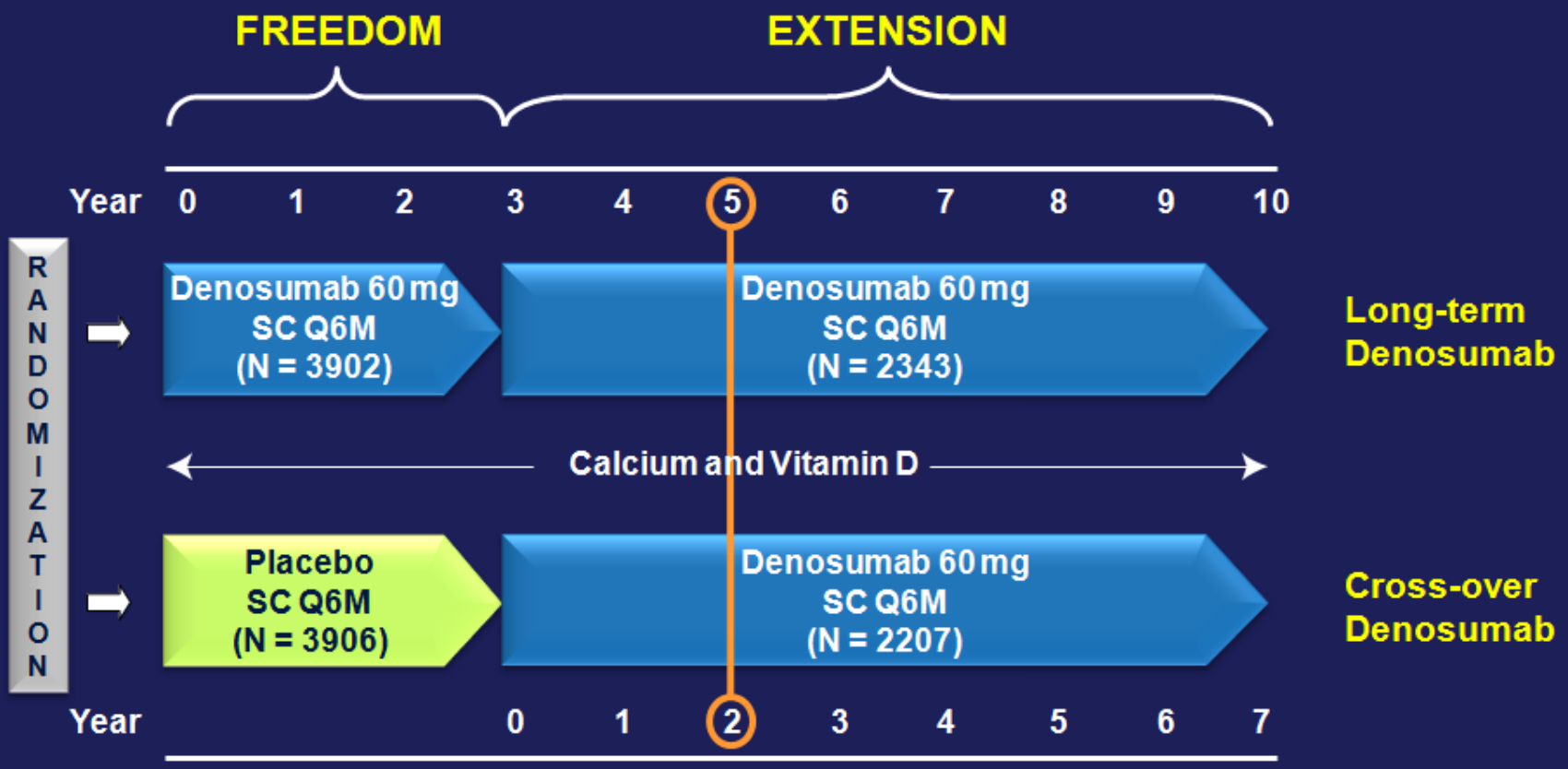
La RRR di frattura non è costante nel tempo per tutti i farmaci





FREEDOM Extension Study Design

International, multicenter, open-label, single-arm study

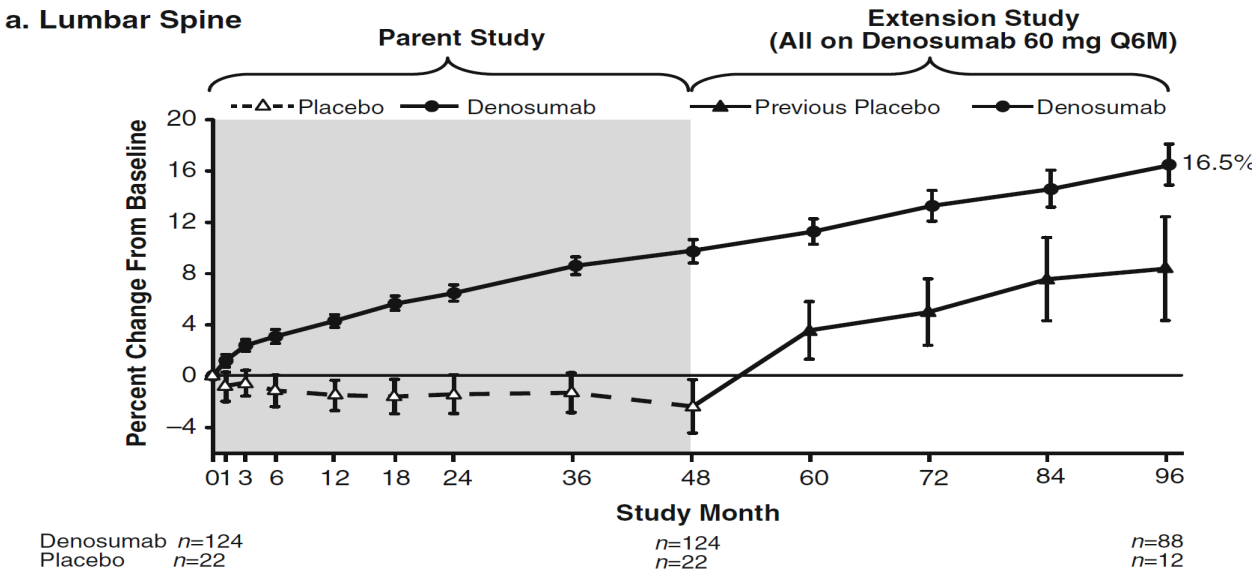


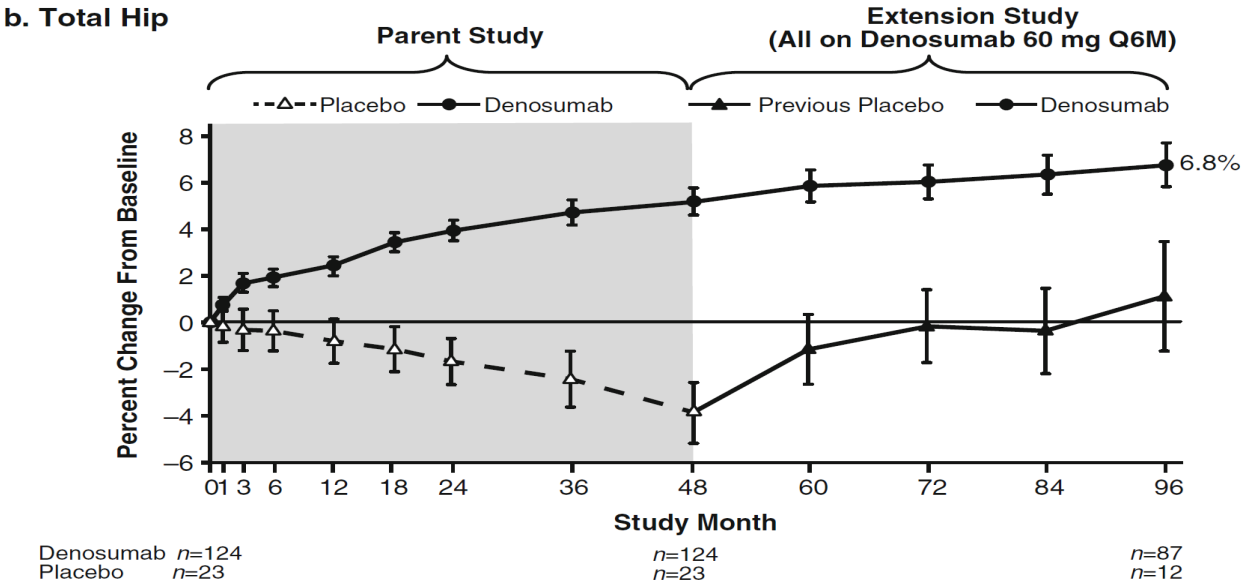
Key Inclusion Criteria:

- Must have completed the FREEDOM study (received denosumab or placebo)
- Not receiving any other osteoporosis medications

Papapoulos S et al. JBMR 2012; 27 (3):694-701

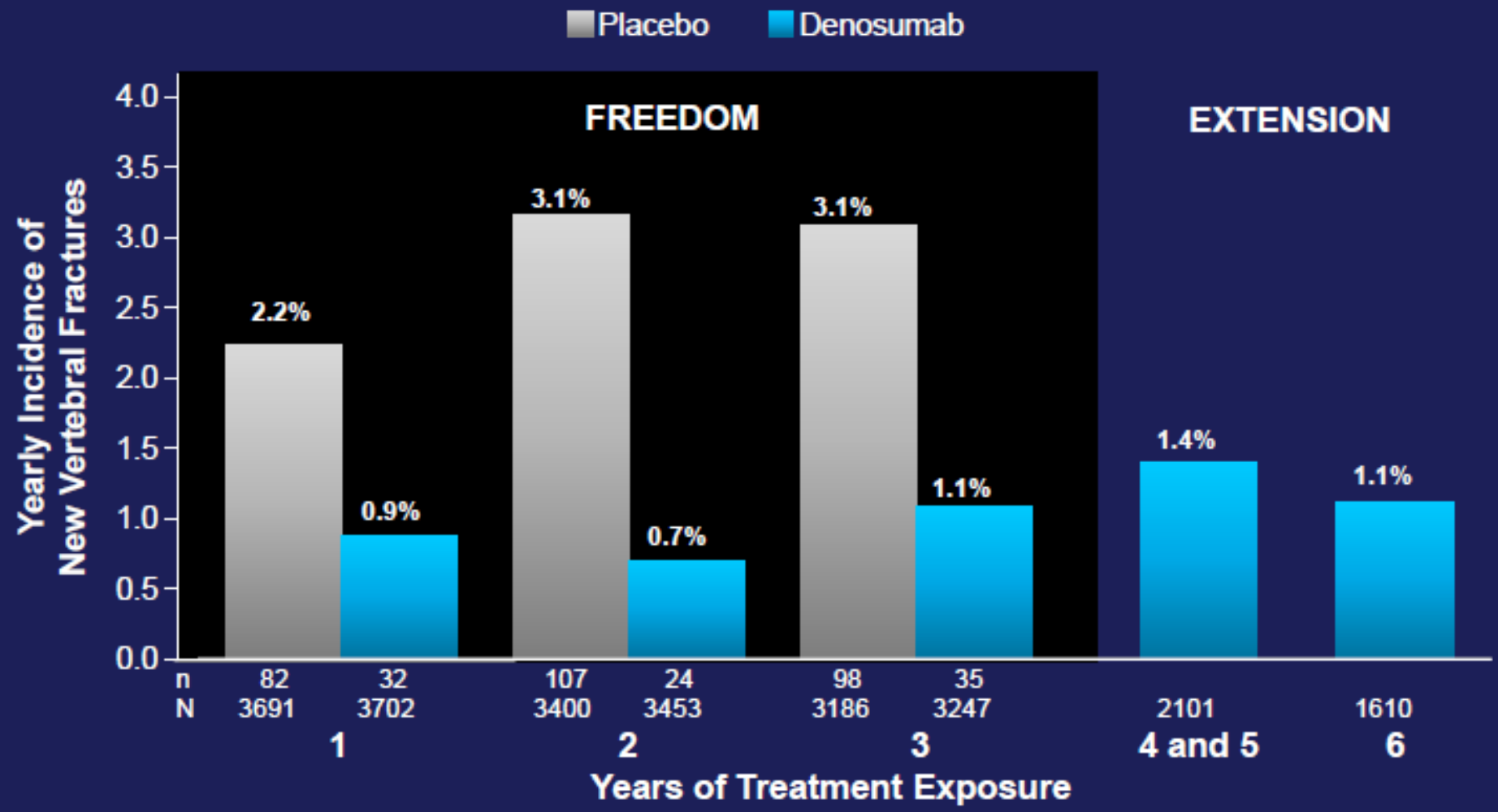
EFFECT OF DENOSUMAB ON BONE MINERAL DENSITY AND BIOCHEMICAL MARKERS OF BONE TURNOVER: 8-YEAR RESULTS OF A PHASE 2 CLINICAL TRIAL





McClung MR et al, Osteoporos Int 2012

Yearly Incidence of New Vertebral Fractures Through 6 Years: Long-term Denosumab Group

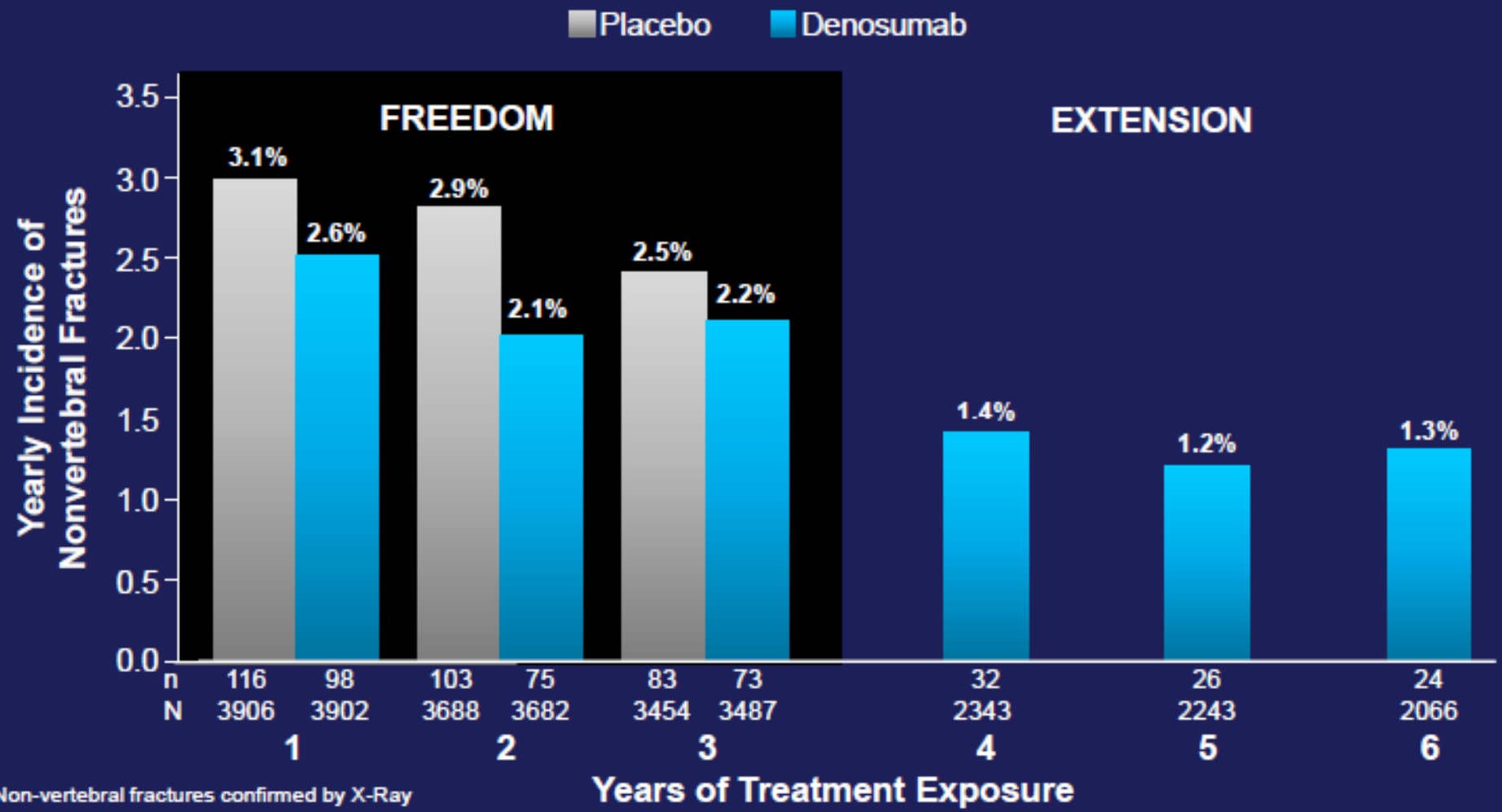


N = number of subjects in the primary efficacy analysis set who are still on study at the beginning of each period

Data on file, Amgen.

Papapoulos S et al. JBMR 2012; 27 (3):694-701

Yearly Incidence of Nonvertebral Fractures Through 6 Years: Long-term Group



Non-vertebral fractures confirmed by X-Ray
n = number of subjects with ≥ 1 fracture
N = number of randomized subjects who remained on study at the beginning of each period
*Percentages for nonvertebral fractures are Kaplan-Meier estimates

Data on file, Amgen.

Papapoulos S et al. JBMR 2012; 27 (3):694-701

Caratteristiche dei pazienti arruolati negli studi registrativi di efficacia antifratturativa

	FREEDOM Denosumab	HORIZON Acido zoledronico	FIT-1 Alendronato
Caratteristiche basali			
Pazienti arruolate, n	7,868	7,765	2,027
Età media, anni	72	73	71
Pazienti con T-score del collo femorale < –2.5	30%	72%	Non riportato
Pazienti con frattura vertebrale prevalente	24%	63%	100%
Rischio di frattura a 3 anni nel braccio placebo			
Nuova frattura vertebrale	7.2%	10.9%	15.0%
Frattura di femore	1.2%	2.5%	2.2%
Frattura non vertebrale	8.0%	10.7%	14.7%

HORIZON = The Health Outcomes and Reduced Incidence with Zoledronic Acid ONce Yearly; FIT = Fracture Intervention Trial

Boonen S, et al. *J Clin Endocrinol Metab*. 2011;96(6): 1727-1736
Cummings SR, et al. *N Engl J Med*. 2009;361:756-765.
Black DM, et al. *New Engl J Med.* 2007;356:1809-1822.
Black DM, et al. *Lancet.* 1996;348:1535-1541.

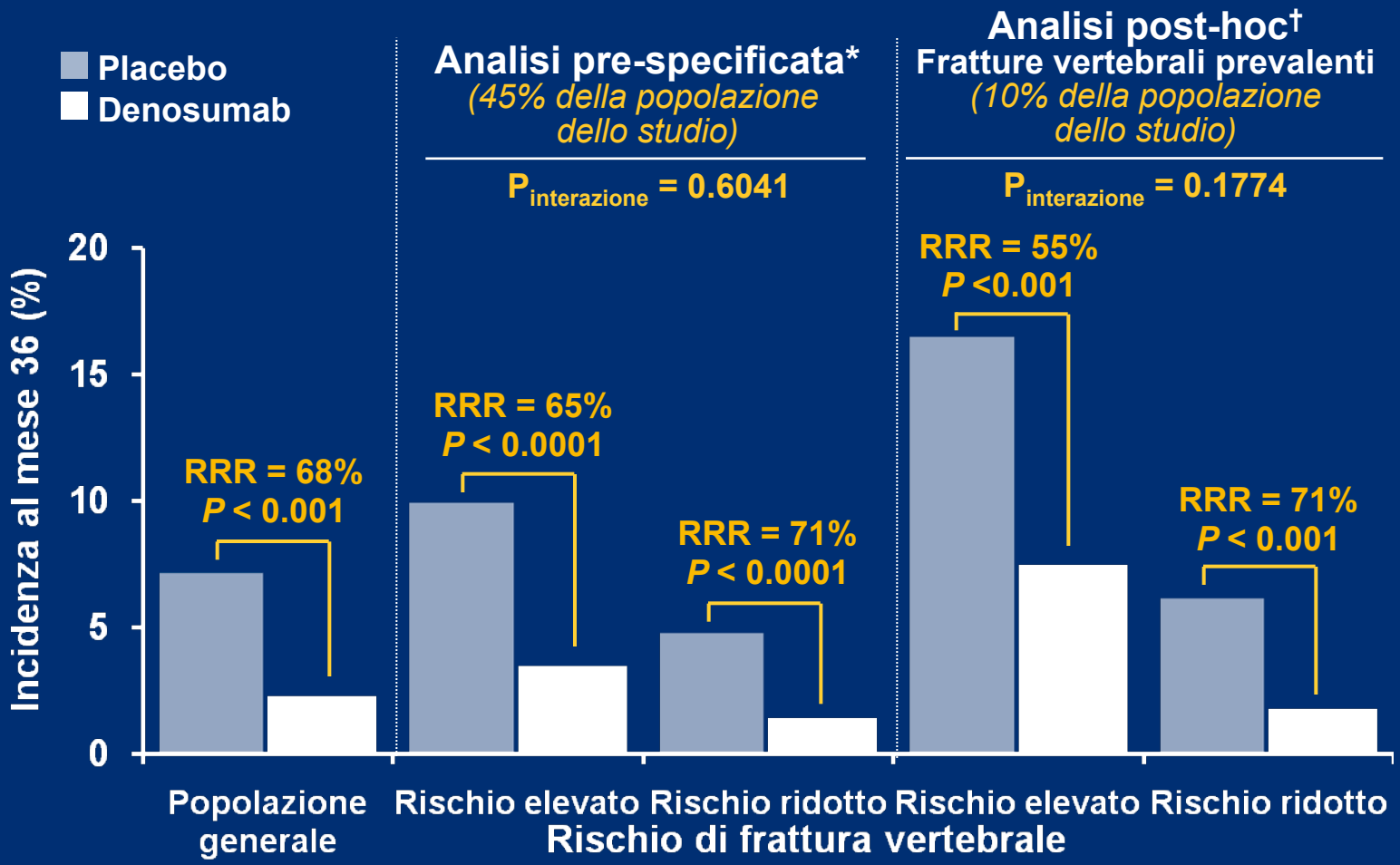
Definizione dei soggetti a più elevato rischio fratturativo nelle analisi per sottogruppi

Tipo di frattura	Analisi pre-specificate	Analisi post-hoc
Frattura vertebrale	Soggetti con ≥ 2 dei seguenti criteri: ▪ Età > 70 anni ▪ T-score della BMD basale ≤ –3.0 alla colonna lombare, al femore totale o al collo femorale ▪ Una frattura vertebrale prevalente al basale *(45% della popolazione dello studio)*	Soggetti con ≥ 2 fratture vertebrali prevalenti o ≥ 1 fratture vertebrali prevalenti di grado moderato o severo *(10% della popolazione dello studio)*
Frattura di femore		Soggetti con T-score della BMD basale del collo femorale ≤ –2.5 *(36% della popolazione dello studio)*
		Soggetti di età ≥ 75 anni *(32% della popolazione dello studio)*

BMD = densità minerale ossea

Boonen S, et al. *J Clin Endocrinol Metab*. 2011;96(6): 1727-1736

Efficacia di denosumab sulle nuove fratture vertebrali nei soggetti a più elevato rischio fratturativo

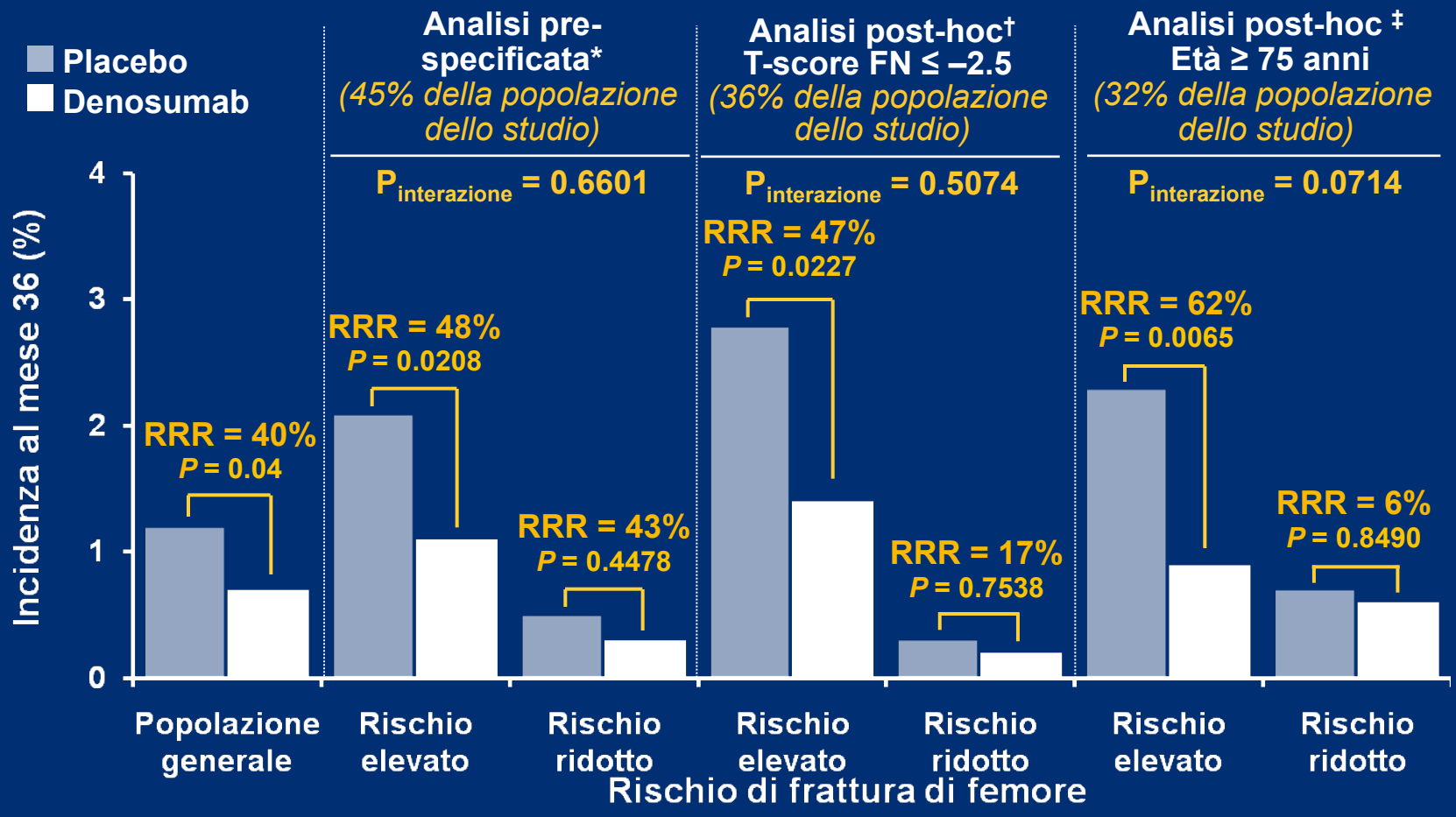


*In un sottogruppo di pazienti a rischio elevato con ≥ 2 dei seguenti criteri: (a) età > 70 anni, (b) T-score della BMD basale ≤ –3.0 alla colonna lombare, al femore totale o al collo femorale, (c) una frattura vertebrale prevalente al basale

†In un sottogruppo di pazienti a rischio elevato con ≥ 2 fratture vertebrali prevalenti e/o ≥ 1 fratture vertebrali prevalenti di grado moderato o severo

Boonen S, et al. *J Clin Endocrinol Metab*. 2011;96(6): 1727-1736

Efficacia di denosumab sulle nuove fratture di femore nei soggetti a più elevato rischio fratturativo



*In un sottogruppo di pazienti a rischio elevato con ≥ 2 dei seguenti criteri: (a) età > 70 anni, (b) T-score della BMD basale ≤ –3.0 alla colonna lombare, al femore totale o al collo femorale, (c) una frattura vertebrale prevalente al basale

†In un sottogruppo di pazienti a rischio elevato con T-score della BMD basale del collo femorale **≤ –2.5**

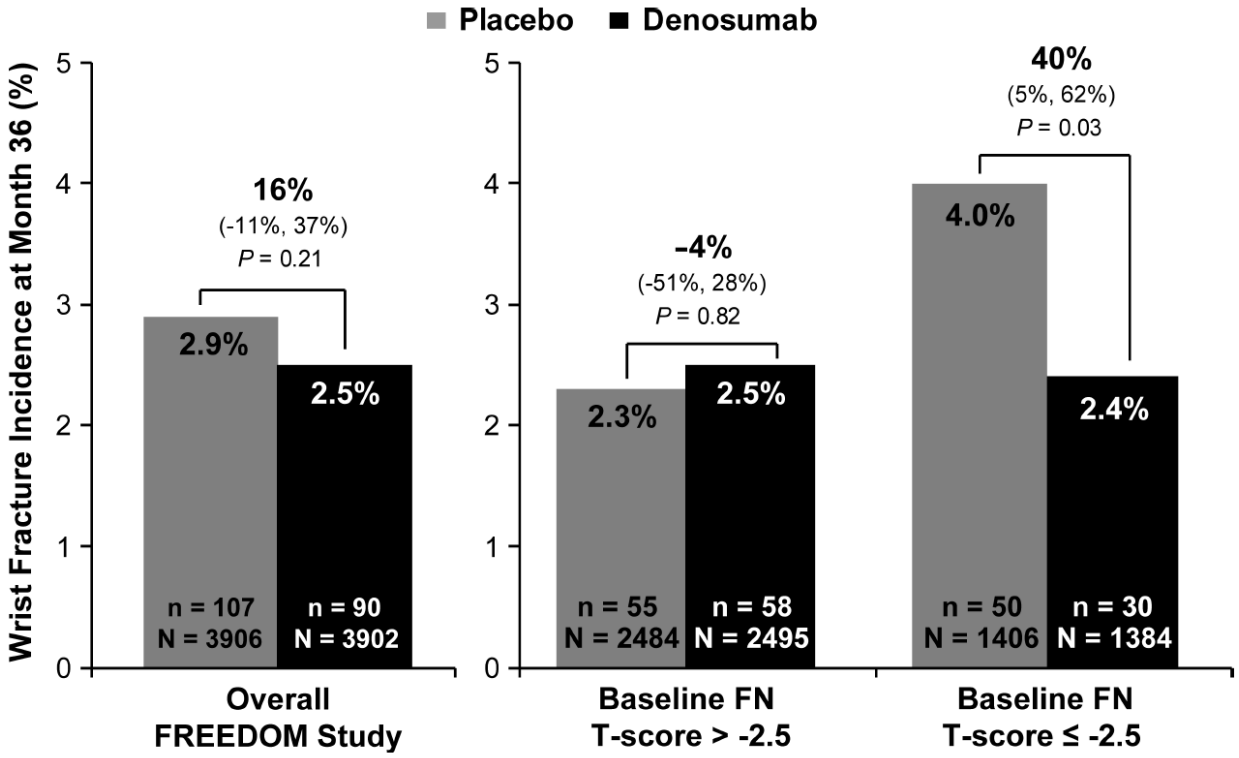
‡In un sottogruppo di pazienti a rischio elevato di età ≥ 75 anni

FN = collo femorale

Boonen S, et al. *J Clin Endocrinol Metab*. 2011;96(6): 1727-1736

IMPACT OF DENOSUMAB ON THE PERIPHERAL SKELETON OF POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS: BONE DENSITY, MASS, AND STRENGTH OF THE RADIUS, AND WRIST FRACTURE

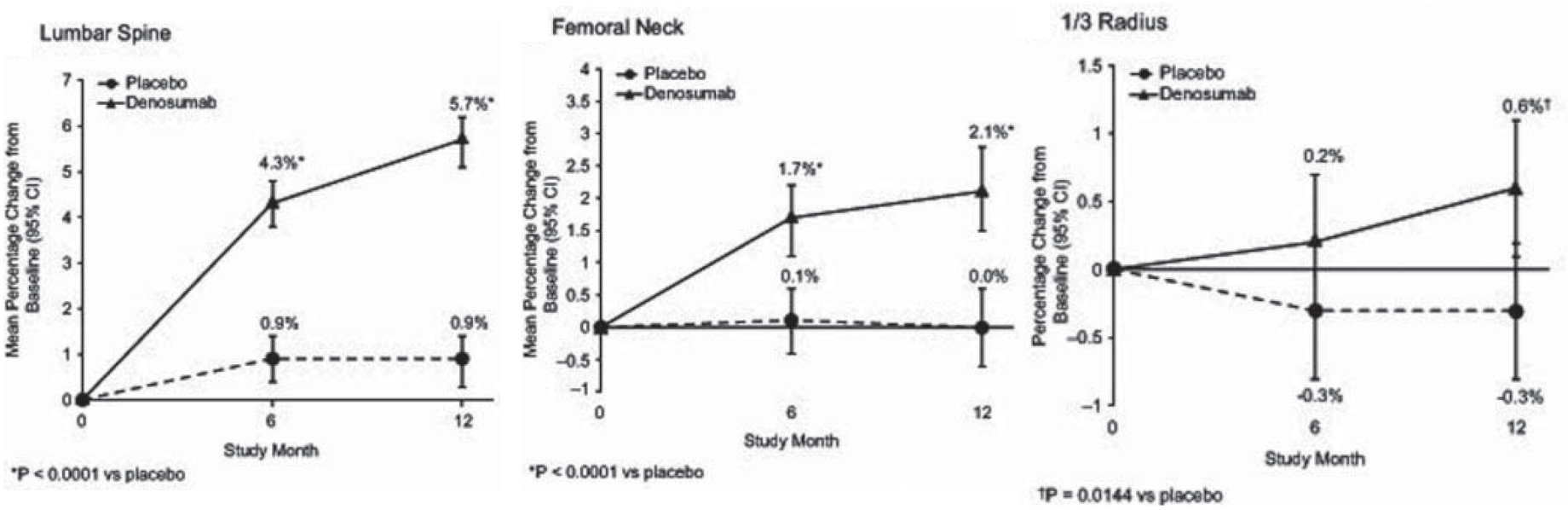
Two separate prespecified substudies of FREEDOM ,the DXA substudy (n = 441) and the QCT radius substudy (n =182, of which 110 had one or more evaluable forearm scans), and on wrist fracture incidence in the overall FREEDOM study (N = 7,808).



Simon JA et al, Menopause 2012

A RANDOMIZED, PLACEBO-CONTROLLED STUDY OF THE EFFECTS OF DENOSUMAB FOR THE TREATMENT OF MEN WITH LOW BONE MINERAL DENSITY

242 randomized subjects (mean age 65 yr)



One year of denosumab therapy in men with low BMD was well tolerated and resulted in a reduction in bone resorption and significant increases in BMD at all skeletal sites assessed

Orwoll E et al, J Clin Endocrinol Metab 97: 3161–3169, 2012

Eventi avversi

Studio *FREEDOM*
Eventi avversi a 36 mesi

Eventi avversi, n (%)	Placebo (n = 3,876)	Denosumab 60 mg Q6M (n = 3,886)
Eventi avversi		
Infezioni	2,108 (54.4)	2,055 (52.9)
Neoplasie	166 (4.3)	187 (4.8)
Reazioni nel sito di iniezione	26 (0.7)	33 (0.8)
Ipocalcemia	3 (0.1)	0 (0)
Ritardata riparazione della frattura	4 (0.1)	2 (0.05)
Fratture femorali atipiche	3 (0.1)	0 (0)
Mancata saldatura fratture dell'omero	1 (0.03)	0 (0)
Osteonecrosi della mandibola	0 (0)	0 (0)
Eventi avversi presenti in almeno il 2% dei soggetti e $P \leq 0.05$		
Eczema	65 (1.7)	118 (3.0)
Cadute*	219 (5.7)	175 (4.5)
Flatulenza	53 (1.4)	84 (2.2)

* Escluse cadute avvenute nello stesso giorno di una frattura

Adattato da: Cummings SR, et al. *N Engl J Med*. 2009;361:756-765.

Studio *FREEDOM*
Eventi avversi gravi a 36 mesi (continuazione)

Eventi avversi, n (%)	Placebo (n = 3,876)	Denosumab 60 mg Q6M (n = 3,886)	*P*
Eventi avversi gravi			
Neoplasie	125 (3.2)	144 (3.7)	0.28
Infezioni	133 (3.4)	159 (4.1)	0.14
Eventi cardiovascolari	178 (4.6)	186 (4.8)	0.74
Ictus	54 (1.4)	56 (1.4)	0.89
Cardiopatia ischemica	39 (1.0)	47 (1.2)	0.41
Vasculopatia periferica	30 (0.8)	31 (0.8)	0.93
Fibrillazione atriale	29 (0.7)	29 (0.7)	0.98
Eventi avversi gravi presenti in almeno lo 0.1% dei soggetti e $P \leq 0.01$			
Cellulite (inclusa erisipela)	1 (< 0.1)	12 (0.3)	0.002
Commozione cerebrale	11 (0.3)	1 (< 0.1)	0.004

Adattata da Cummings SR, et al. *N Engl J Med*. 2009;361:756-765.

Exposure-adjusted Subject Incidence of Adverse Events (Rates per 100 Patient-years)

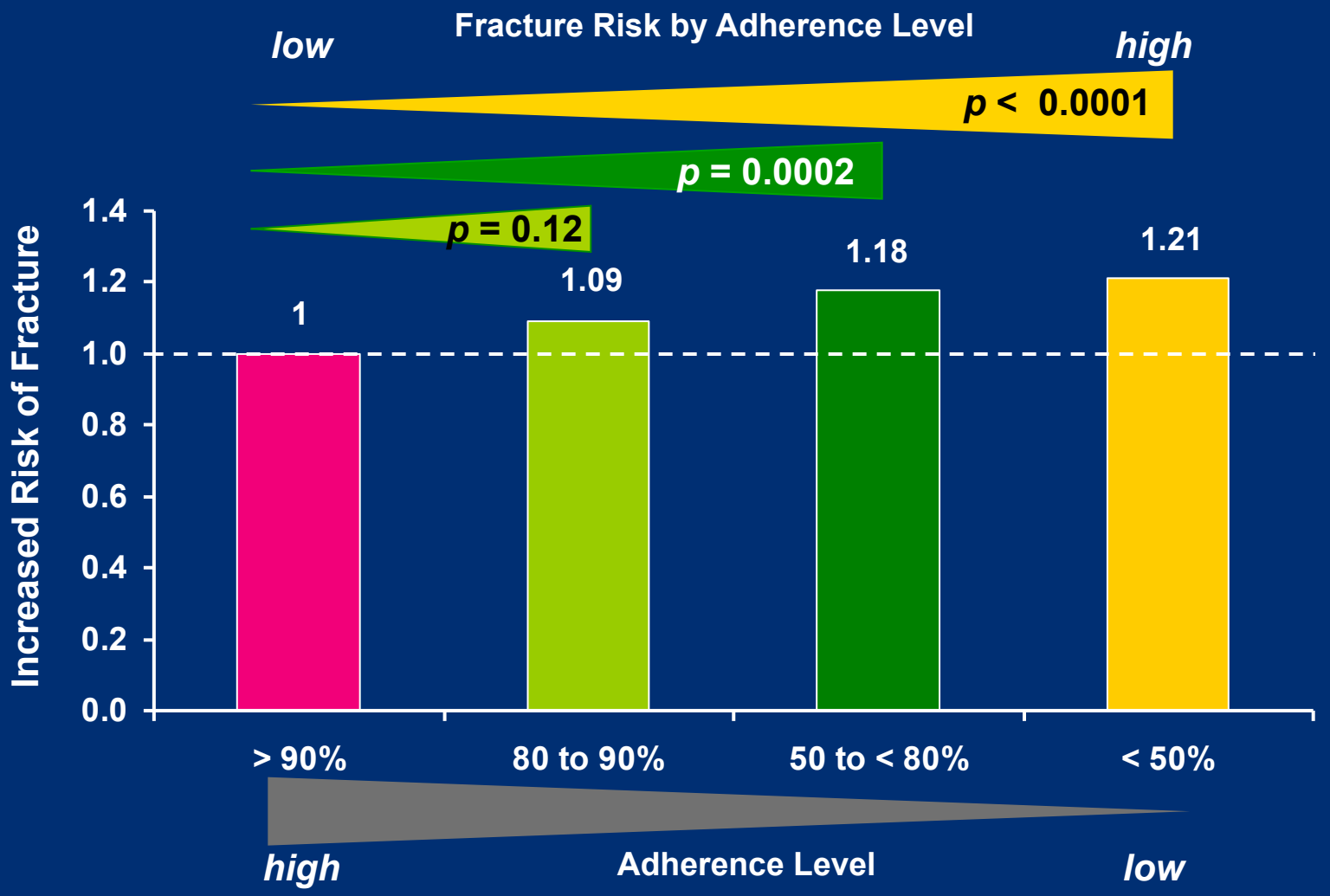
Rate (n)	Placebo	Denosumab		
	FREEDOM Years 1-3 N = 3883	FREEDOM Years 1-3 N = 3879	EXT Long-term Years 4-6 N = 2343	EXT Cross-over Years 1-3 N = 2206
All AEs	156.1 (3614)	154.3 (3598)	106.2 (2067)	104.2 (1944)
Infections	30.7 (2113)	29.3 (2052)	23.4 (1070)	25.0 (1054)
Malignancies	1.6 (167)	1.8 (187)	1.9 (120)	1.8 (108)
Eczema	0.6 (67)	1.1 (119)	1.0 (65)	1.0 (57)
Hypocalcemia	< 0.1 (3)	0	< 0.1 (1)	< 0.1 (6)
Pancreatitis	< 0.1 (3)	< 0.1 (7)	< 0.1 (5)	< 0.1 (2)
Serious AEs	10.4 (974)	10.6 (1002)	10.6 (597)	10.9 (573)
Infections	1.3 (134)	1.5 (160)	1.3 (82)	1.4 (81)
Cellulitis or Erysipelas	< 0.1 (1)	0.1 (12)	< 0.1 (5)	< 0.1 (1)
Fatal AEs	0.8 (90)	0.6 (70)	0.7 (45)	0.7 (41)
ONJ	0	0	< 0.1 (2)	< 0.1 (2)
Atypical Femur Fracture	0	0	0	0

Data on File, Amgen.

Papapoulos S et al. JBMR 2012; 27 (3):694-701

Aderenza

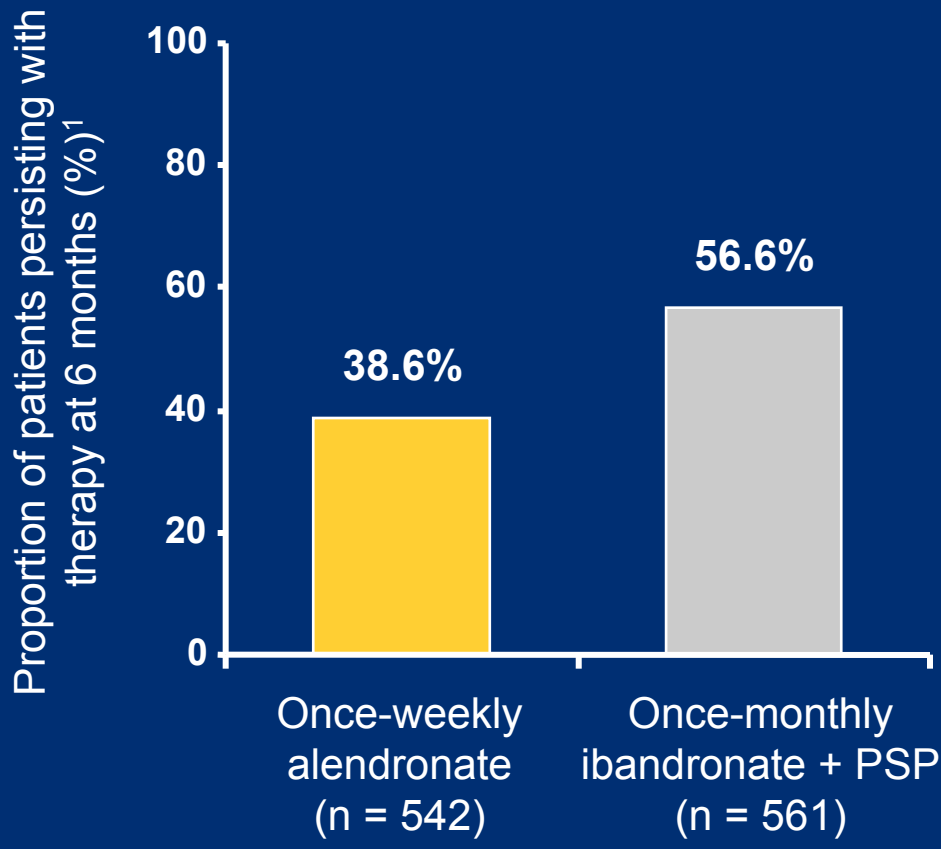
Poor Adherence is Associated with Increased Fracture Risk

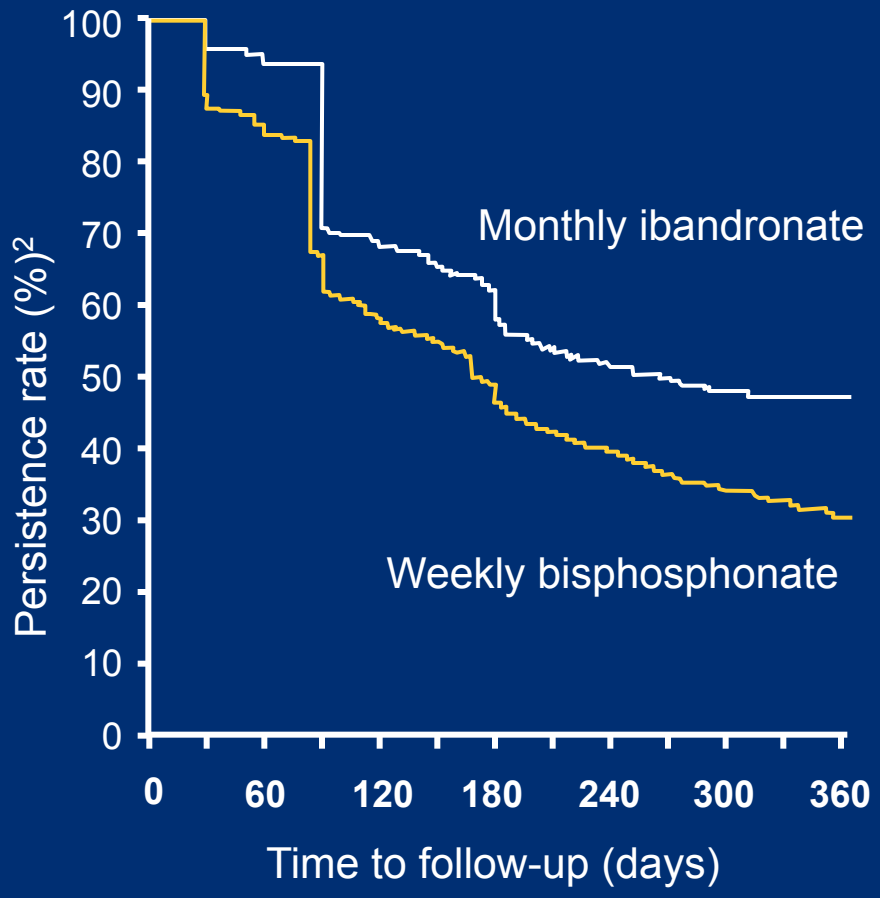


Huybrechts KF, et al. *Bone*. 2006;38:922-928.

Data from 38,000 women in a managed care database

Patient Adherence with Oral Bisphosphonates is Low with Both Weekly and Monthly Dosing

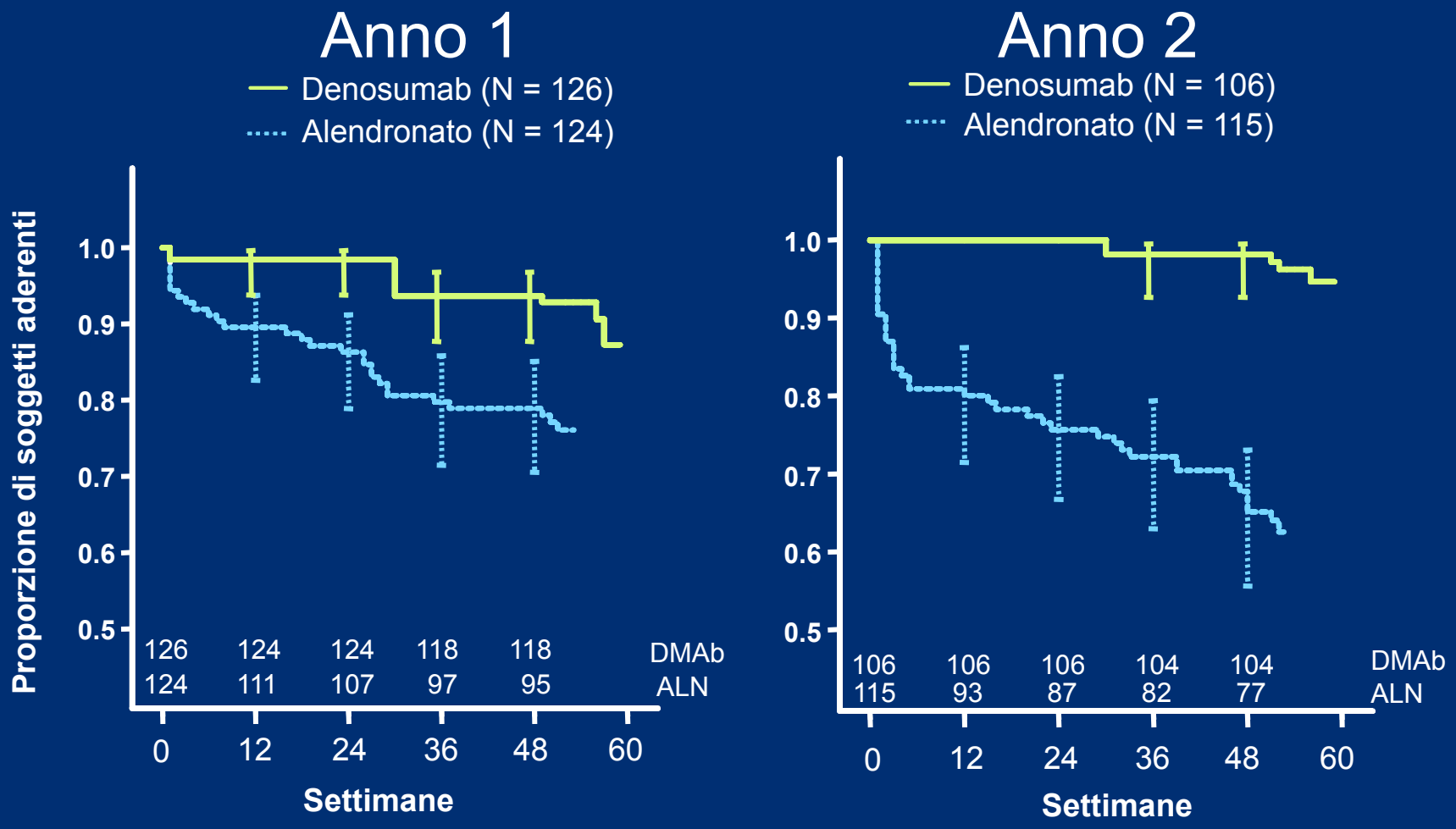




PSP: patient support programme

1.Cooper A, et al. *Int J Clin Pract* 2006;60:896-905;
2.Cotte FE et al. *Osteoporos Int* 2008 DOI 10.1007/S00198-009-0930-1

Precoce riduzione dell'aderenza al trattamento con alendronato rispetto a denosumab



Kendler DL et al. Osteoporos Int 2011; 22: 1725-1735
Freemantle N et al. Osteoporos Int 2012;23: 317-326

AGENDA

- ✓ Rimodellamento osseo e ruolo del sistema RANK-RANKL-OPG
- ✓ Controllo farmacologico del sistema RANK-RANKL-OPG: dati preclinici
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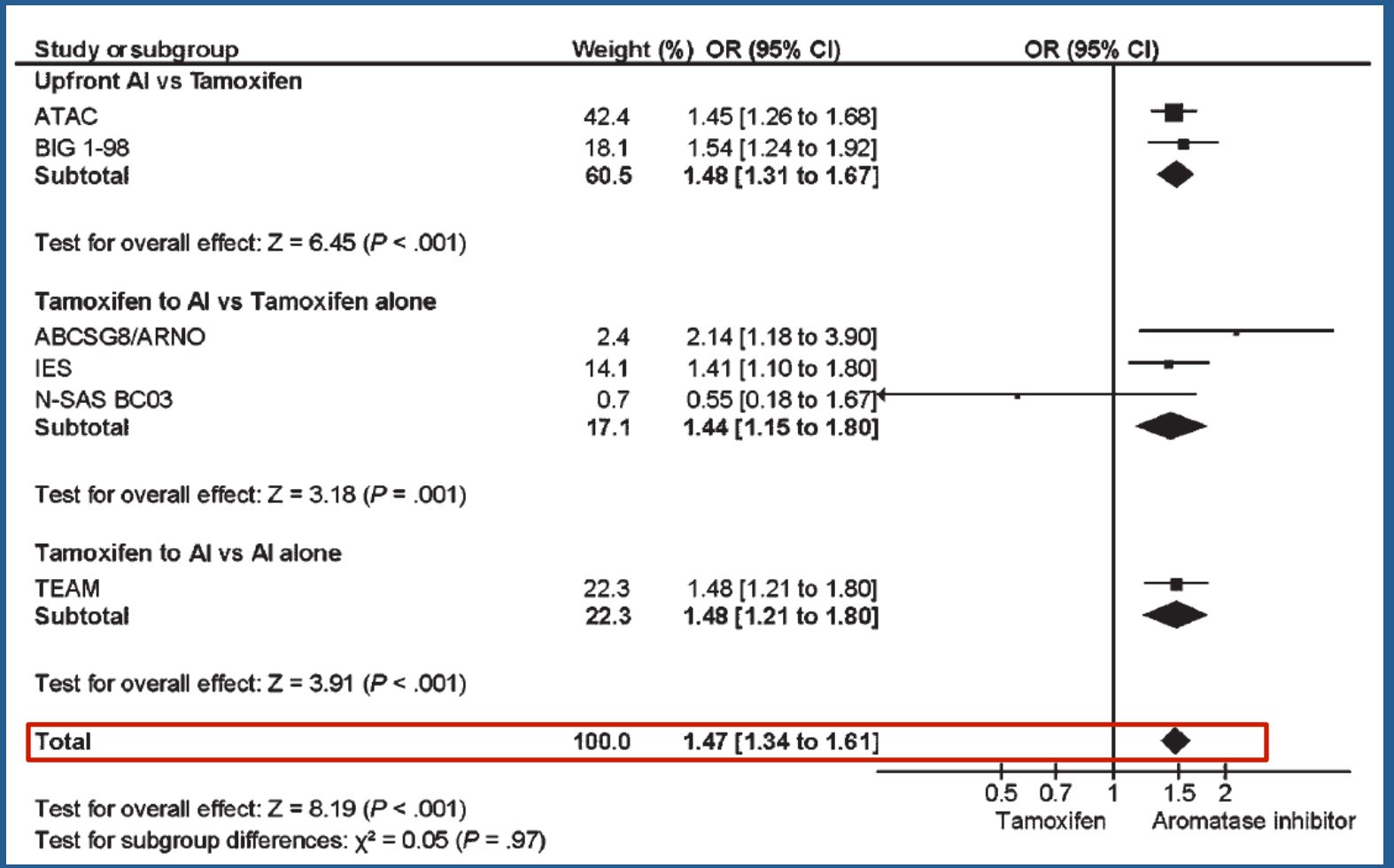
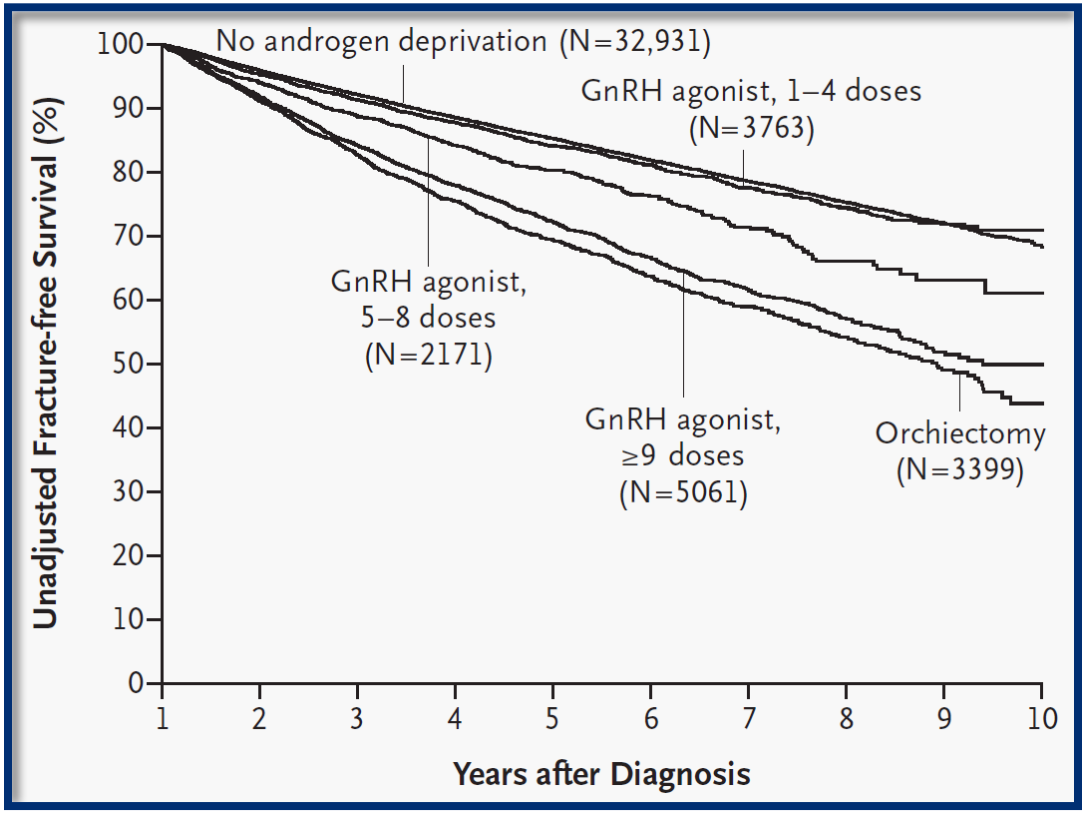
- ✓ Possibile ruolo di Denosumab nel'osteoporosi da glucocorticoidi.

ODDS RATIO FOR FRACTURES IN PATIENTS TREATED WITH AI AND/OR TAMOXIFEN



Amir E et al, J Natl Cancer Inst 2011

UNADJUSTED FRACTURE-FREE SURVIVAL AMONG PATIENTS WITH PROSTATE CANCER, ACCORDING TO ANDROGEN-DEPRIVATION THERAPY

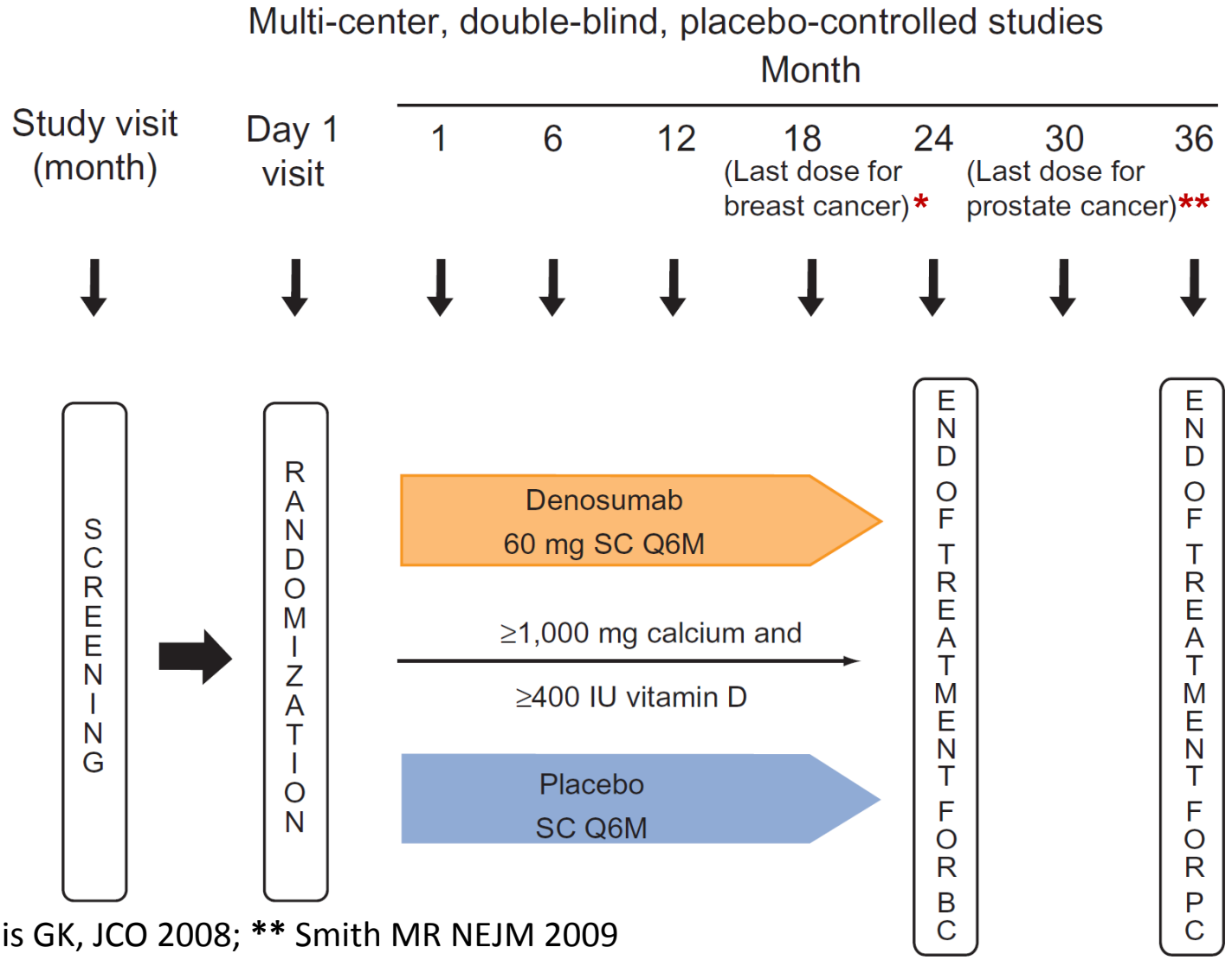


Age	Gonadotropin-Releasing Hormone Agonist			Orchiectomy
	1–4 doses	5–8 doses	≥9 doses	
	no. needed to harm (95% CI)			
66–69 yr	74 (50–146)	42 (29–73)	18 (16–24)	15 (13–18)
70–74 yr	69 (46–146)	39 (27–71)	17 (15–20)	14 (12–17)
75–79 yr	61 (41–125)	34 (24–61)	15 (14–17)	13 (11–15)
≥80 yr	46 (32–91)	26 (19–45)	12 (11–13)	10 (9–11)

Within 12 months of diagnosis, men treated with ADT or with bilateral orchiectomy have a 5-year fracture risk of 19% vs 12% in matched controls

Shahinian VB et al. NEJM, 2005

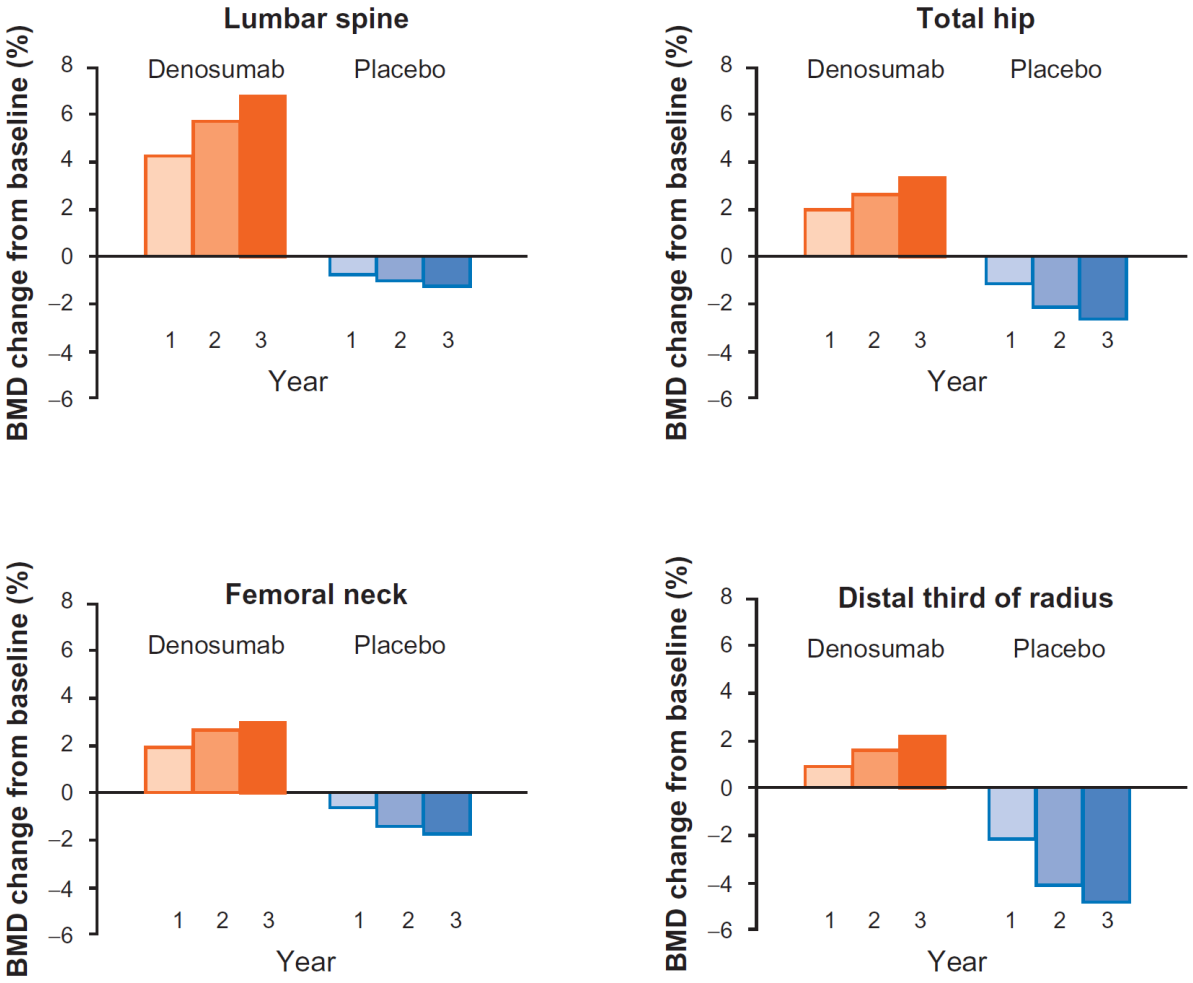
DENOSUMAB IN WOMEN WITH BREAST CANCER OR IN MEN WITH PROSTATE CANCER RECEIVING HORMONE ABLATION THERAPY



* Ellis GK, JCO 2008; ** Smith MR NEJM 2009

Lipton A et al, Clinical Medicine Insights: Oncology 2012

CUMULATIVE PERCENT CHANGE IN BMD FROM BASELINE, DENOSUMAB VS. PLACEBO IN MEN WITH PROSTATE CANCER RECEIVING ADT



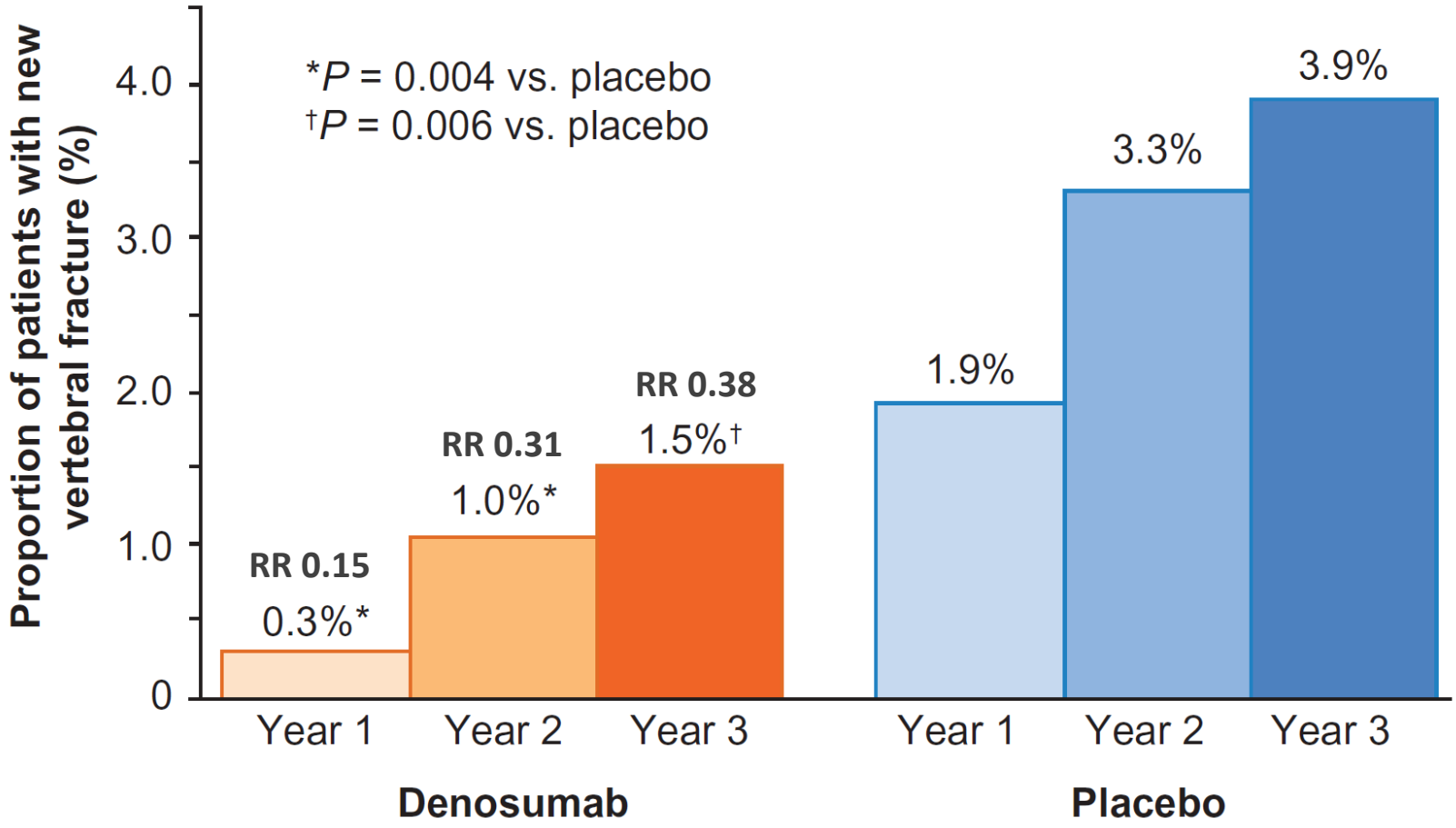
HALT study: a randomized, doubleblind, placebo-controlled phase 3 study in 1,468 men with nonmetastatic prostate cancer receiving ADT ≥12 months.

They had either a low baseline BMD (T-score , −1.0 at the lumbar spine, total hip, or femoral neck) or history of an osteoporotic fracture

At 24 months (the primary endpoint), the difference between Denosumab and placebo was 6.7% at the lumbar spine, 4.8% at the total hip, 3.9% at the femoral neck, and 5.5% at the distal third of the radius

Smith MR NEJM 2009

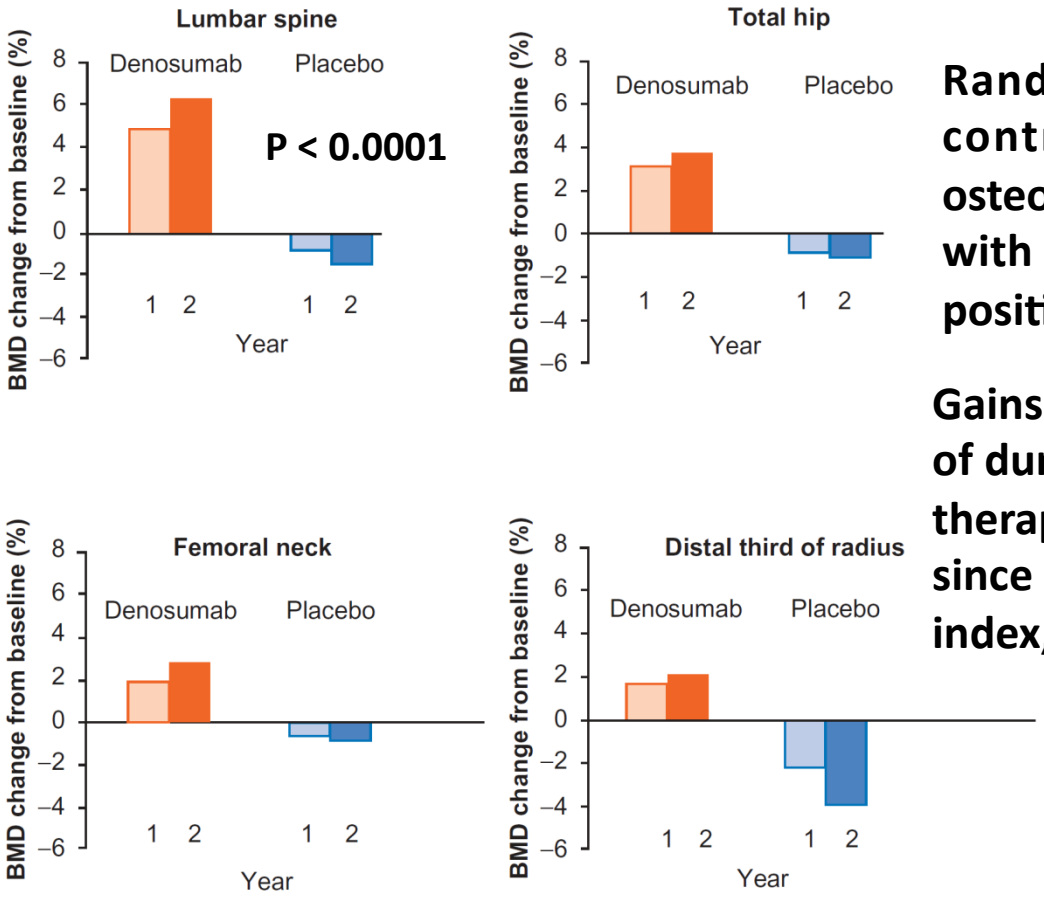
DENOSUMAB REDUCED THE RISK OF VERTEBRAL FRACTURES OVER 3 YEARS IN MEN WITH PROSTATE CANCER RECEIVING ADT



HALT study: randomized, double-blind, placebo-controlled phase 3 study in 1,468 men with nonmetastatic prostate cancer and low bone mineral density or history of an osteoporotic fracture, receiving ADT (orchiectomy or GnRH agonist ≥12 months).

Smith MR NEJM 2009

CUMULATIVE PERCENT CHANGE IN BMD FROM BASELINE, DENOSUMAB VS. PLACEBO IN WOMEN WITH BREAST CANCER RECEIVING AROMATASE INHIBITORS



Randomized, double-blind, placebo-controlled phase 3 study on 252 osteopenic women (>18 years of age) with nonmetastatic hormone-receptor positive breast cancer receiving AI.

Gains in BMD were consistent regardless of duration or type of aromatase inhibitor therapy, prior use of tamoxifen, age, time since the onset of menopause, body mass index, and baseline T-score .

No vertebral fractures were reported in either treatment group during the study. Major nonvertebral fractures (defined as fractures in the pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm and hip) occurred in 3 patients (2%) in the denosumab group and 5 patients (4%) in the placebo group.

Ellis GK et al, JCO 2008

DENOSUMAB IN WOMEN WITH BREAST CANCER OR IN MEN WITH PROSTATE CANCER RECEIVING HORMONE ABLATION THERAPY

Adverse events

	Breast cancer study		Prostate cancer study	
	Placebo N = 120	Denosumab N = 120	Placebo N = 725	Denosumab N = 731
Any adverse event, n (%)	108 (90.0)	117 (90.7)	627 (86.5)	638 (87.3)
Serious adverse events, n (%)	11 (9.2)	19 (14.7)	222 (30.6)	253 (34.6)
Adverse events related to investigational product,* n (%)	31 (25.8)	32 (24.8)	65 (9.0)	62 (8.5)
Any fatal adverse event, n (%)	1 (0.8)	1 (0.8)	46 (6.3)	44 (6.0)
Adverse events reported by > 10% of patients receiving denosumab in either study				
Arthralgia	30 (25.0)	31 (24.0)	80 (11.0)	92 (12.6)
Pain in extremity	14 (11.7)	19 (14.7)	51 (7.0)	66 (9.0)
Back pain	15 (12.5)	18 (14.0)	74 (10.2)	81 (11.1)
Fatigue	17 (14.2)	17 (13.2)	45 (6.2)	44 (6.0)
Constipation	11 (9.2)	15 (11.6)	75 (10.3)	73 (10.0)
Cough	5 (4.2)	13 (10.1)	27 (3.7)	33 (4.5)
Insomnia	14 (11.7)	12 (9.3)	16 (2.2)	23 (3.1)

Notes: N = the number of patients randomized in each group. *Adverse events assessed by investigators as potentially related during the blinded clinical trials.

Lipton A et al, Clinical Medicine Insights: Oncology 2012

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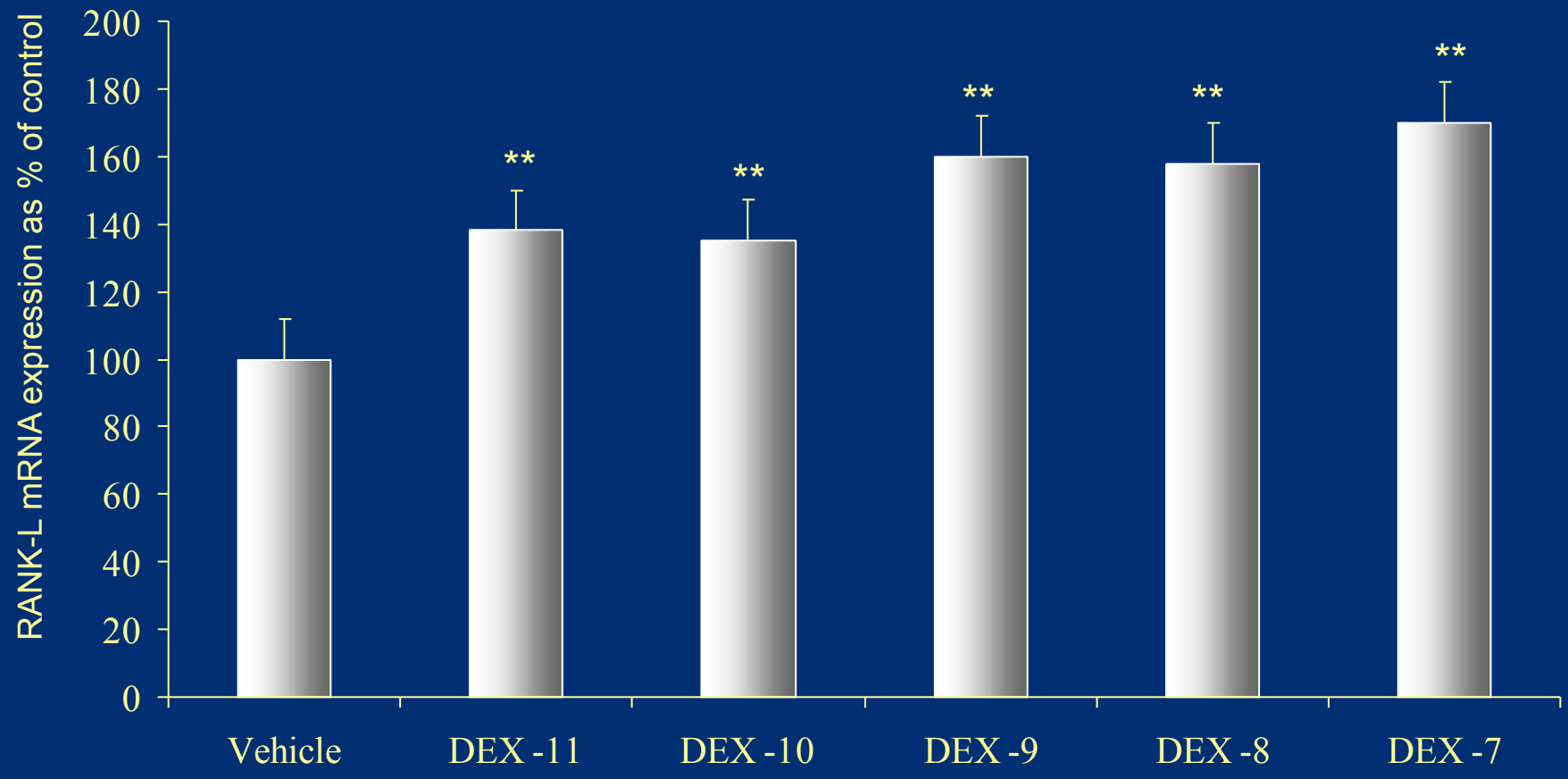
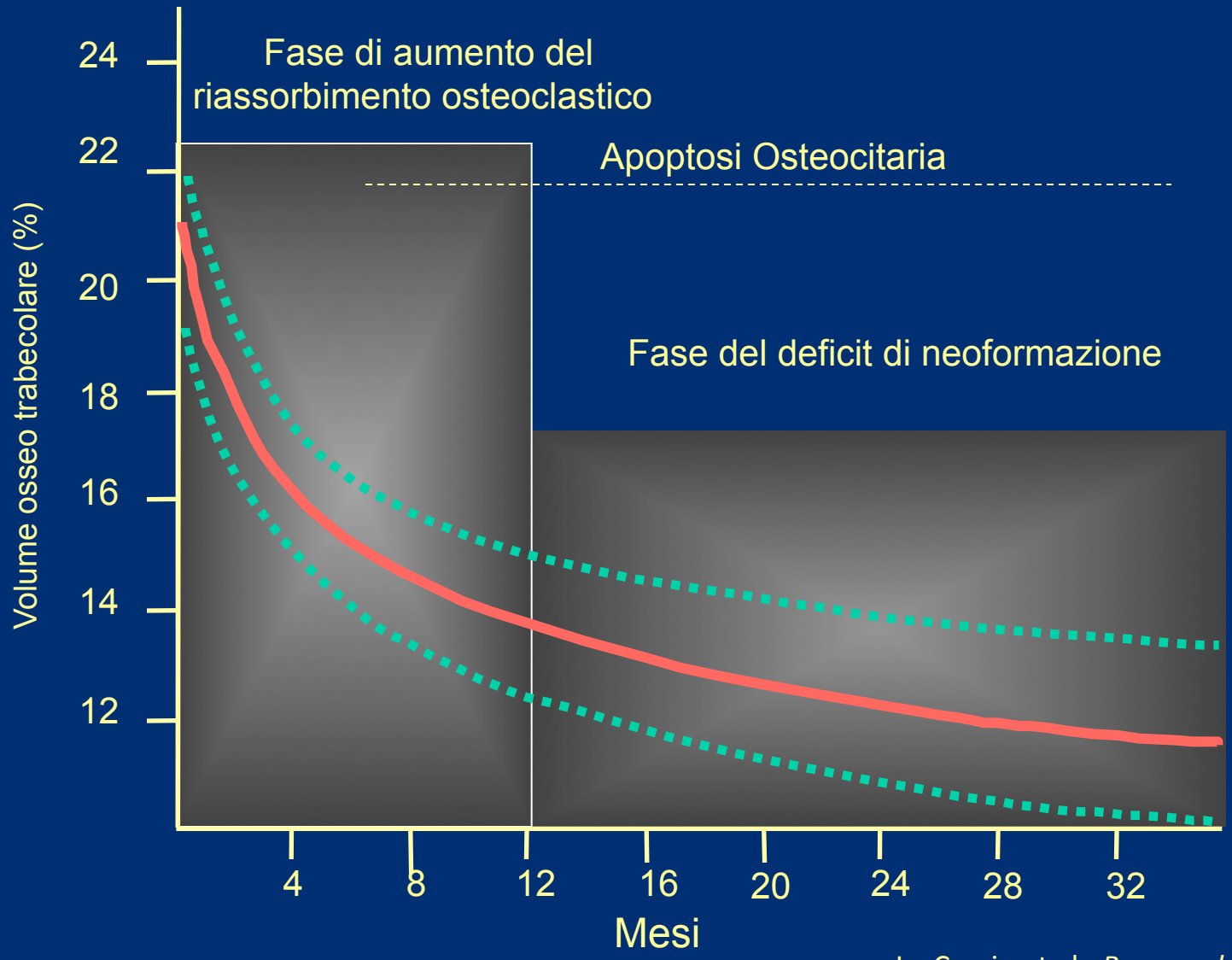
EFFECTS OF DEXAMETHASONE ON RANK-L GENE ESPRESSION IN HUMAN PRIMARY OSTEOBLASTS



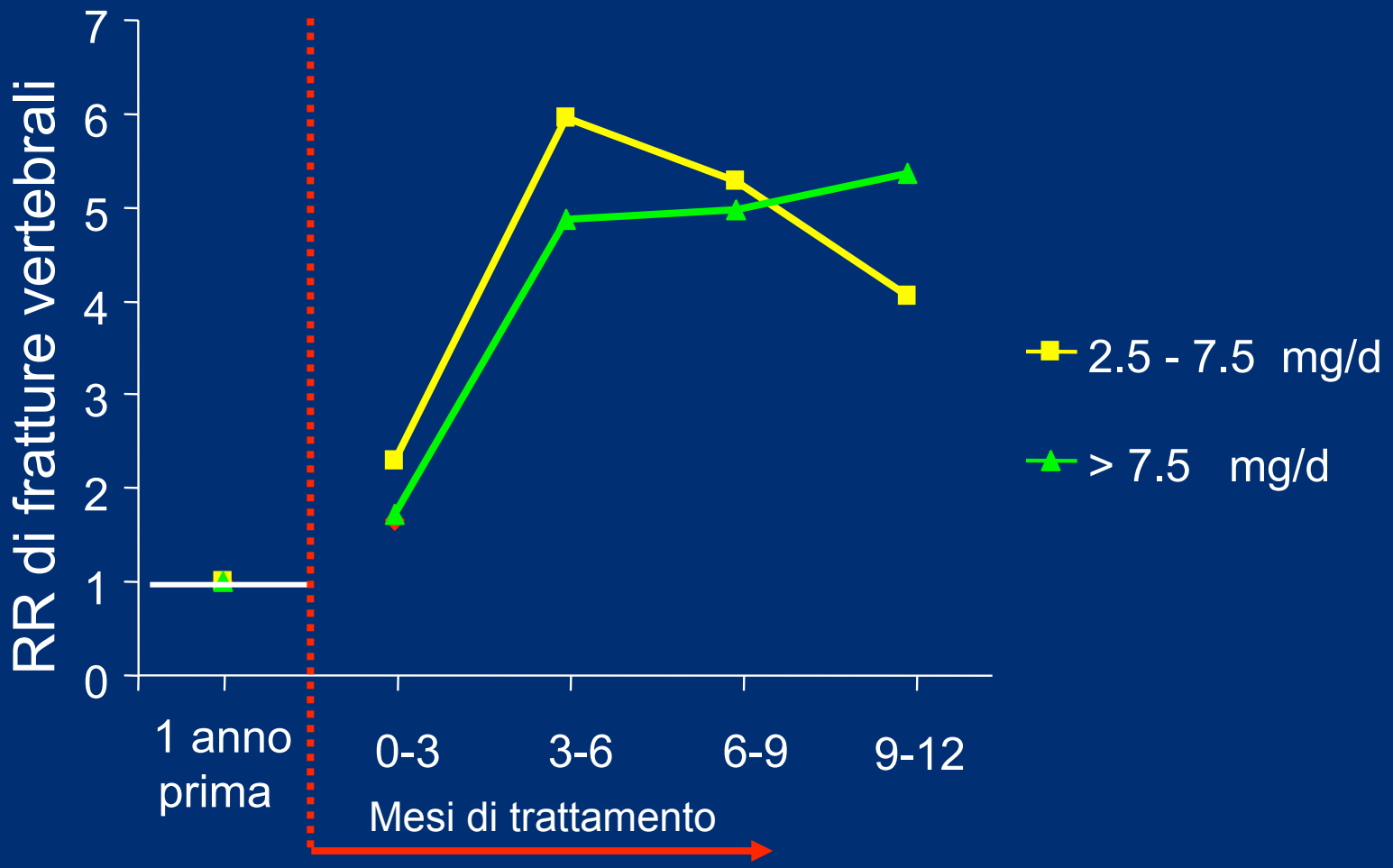
Sivagurunathan S. et al., *JBMR* 2005

VARIAZIONE NEL TEMPO DEL VOLUME TRABECOLARE OSSEO IN 19 PAZIENTI SENZA PRECEDENTE TRATTAMENTO CORTICOSTEROIDEO



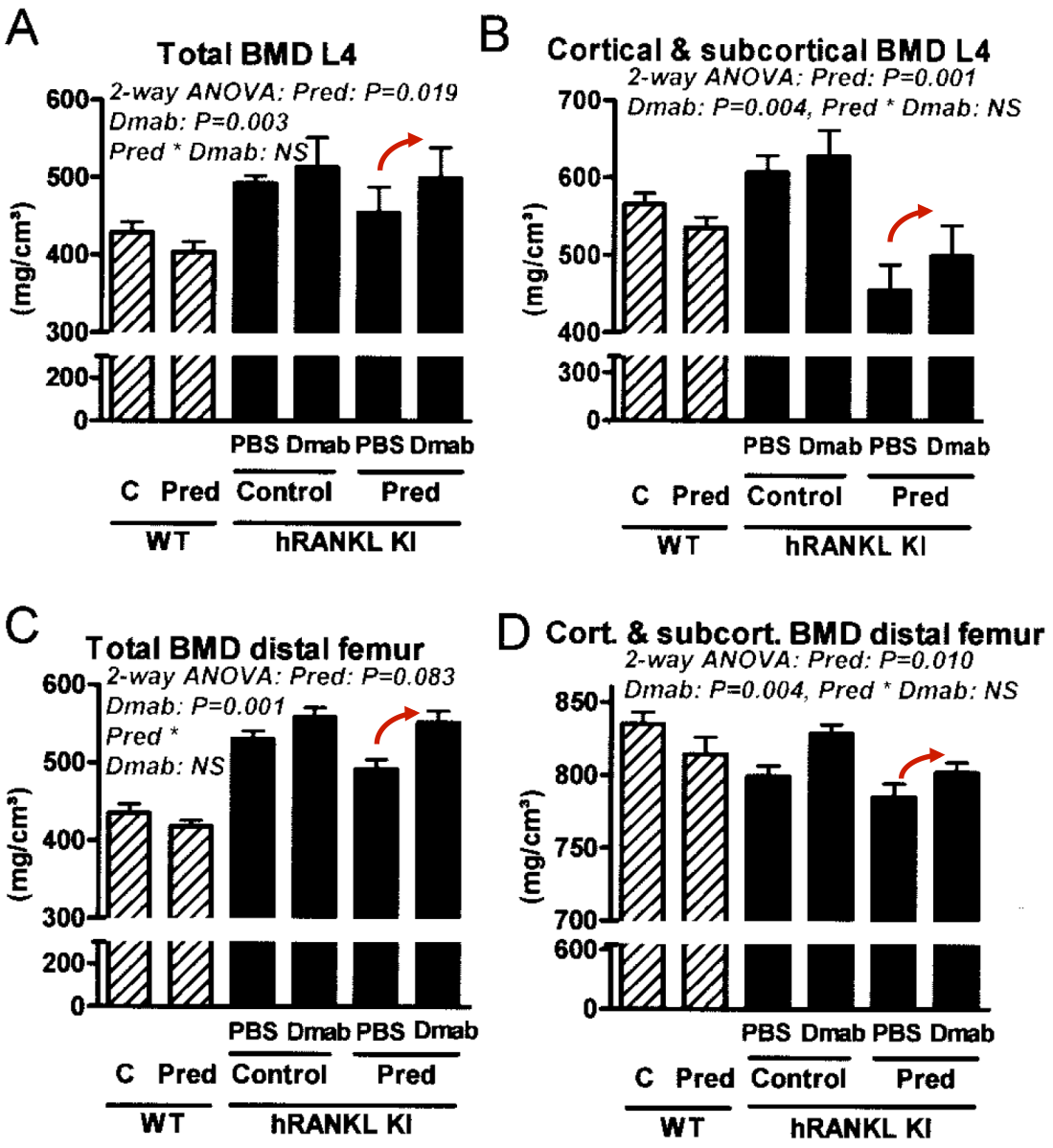
Lo Cascio et al., *Bone and Mineral* 1990

RAPIDO AUMENTO DEL RISCHIO FRATTURATIVO NELLA GIO



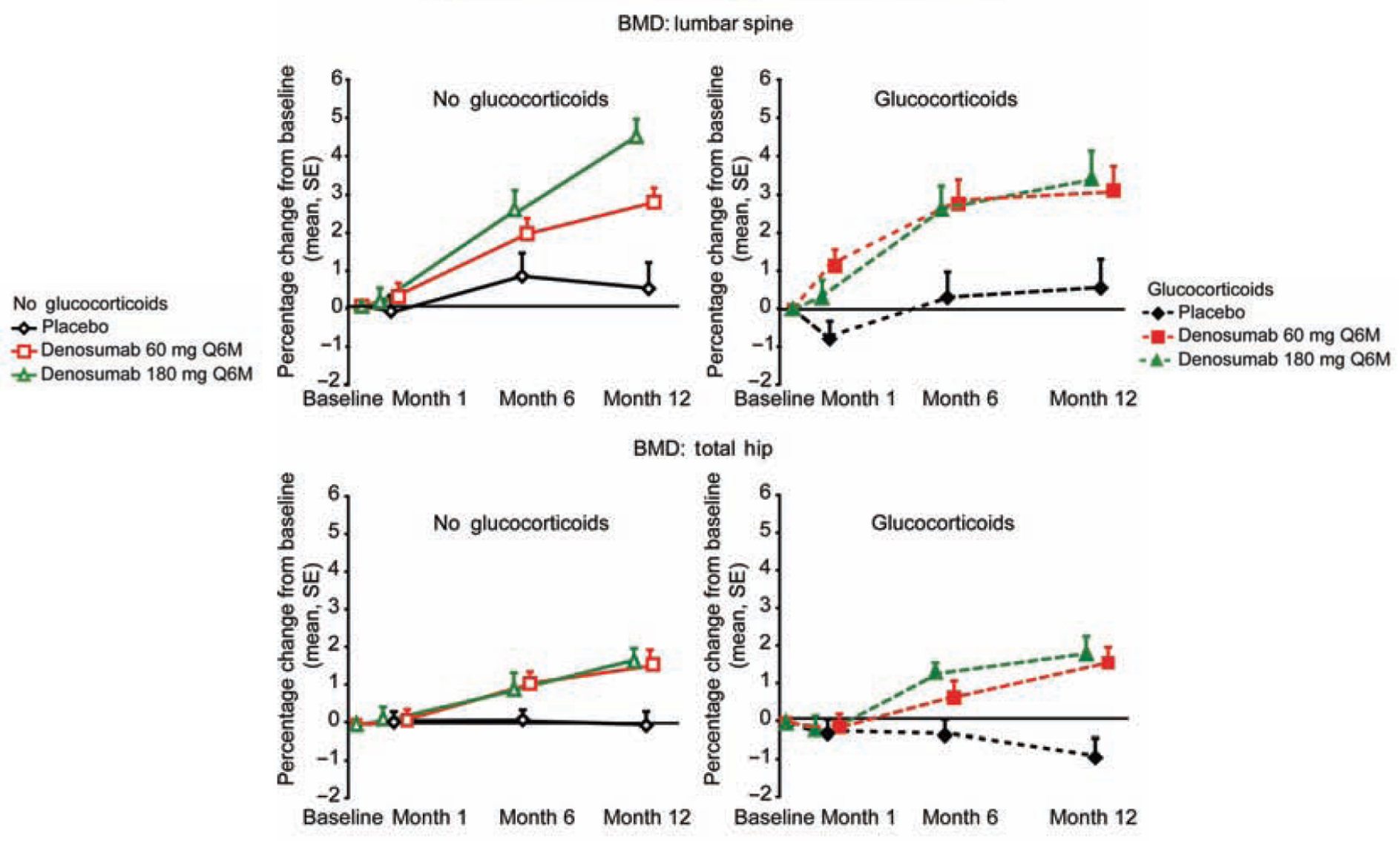
van Staa et al, Osteoporosis Int 2002

DENOSUMAB PREVENTS GLUCOCORTICOID-INDUCED LOSS OF BONE MINERAL DENSITY (BMD) IN HUMAN RANKL–KNOCKIN (hRANKL KI) MICE



Hofbauer LC et al, Arthr Rheum, 2009

EFFECTS OF DENOSUMAB ON BONE MINERAL DENSITY AND TURNOVER IN PATIENTS WITH RHEUMATOID ARTHRITIS RECEIVING CONCURRENT GLUCOCORTICOIDS OR BISPHOSPHONATES



Dore RK et al, Ann Rheum Dis 2010

TAKE HOME MESSAGES

- ✓ **RANKL è un mediatore essenziale per la formazione, funzione e sopravvivenza degli osteoclasti e dati preclinici e clinici dimostrano che la sua inibizione è una strategia possibile per la cura dell'osteoporosi**
- ✓ **Denosumab è un anticorpo monoclonale che lega specificamente RANKL, inibendo il riassorbimento osseo trabecolare e corticale, con effetto che scompare alla sospensione.**
- ✓ **Denosumab aumenta la densità minerale vertebrale e femorale e a 6 anni riduce costantemente il rischio di frattura vertebrale, non vertebrale e femorale in donne con osteoporosi post-menopausale.**
- ✓ **Gli eventi avversi associati sono eczema (3%) e cellulite (0.3%); ONJ ?.**
- ✓ **Denosumab riduce il rischio di frattura in donne in terapia con inibitori dell'aromatasi per k mammario ed in uomini in terapia da deprivazione androgenica per k prostatico.**
- ✓ **Denosumab potrebbe essere efficace nei pazienti con osteoporosi da glucococorticoidi.**

GRAZIE PER
L’ATTENZIONE