Denosumab per la prevenzione del danno osseo secondario alla terapia ormonale adiuvante

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Bone Metabolism and Osteoncology
Department of Medicine-School of Medicine
University of Verona

Conflitti di interesse

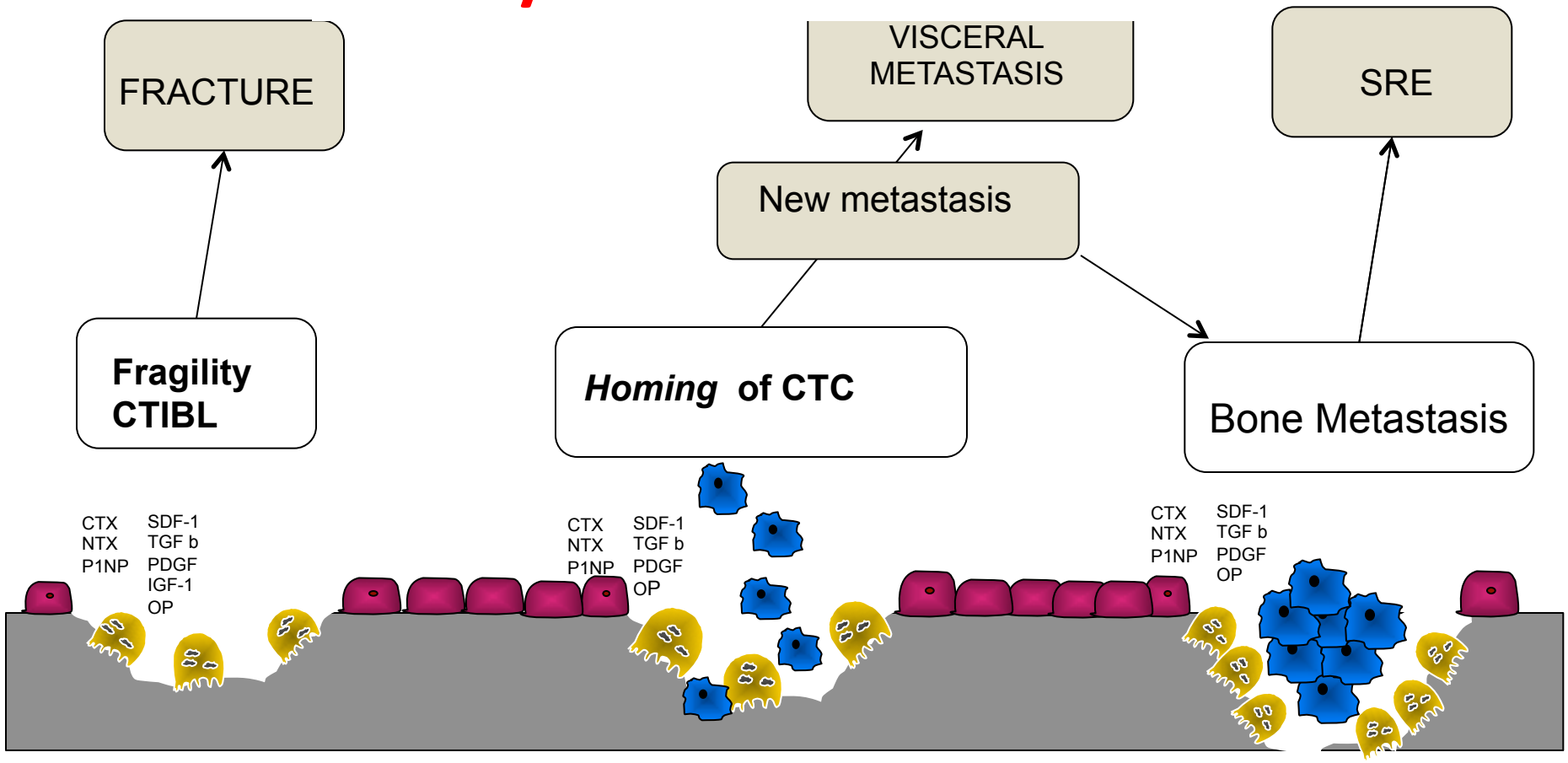
- Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Amgen
- Abiogen
- Astellas
- Bayer
- Chiesi
- Lilly
- Sandoz
- Roche

BONE HEALTH CONCEPT IN CANCER PATIENTS

(Age- VIT D levels- Hormonal Adj Therapy-Cancer)

RANK/RANKL PATHWAY



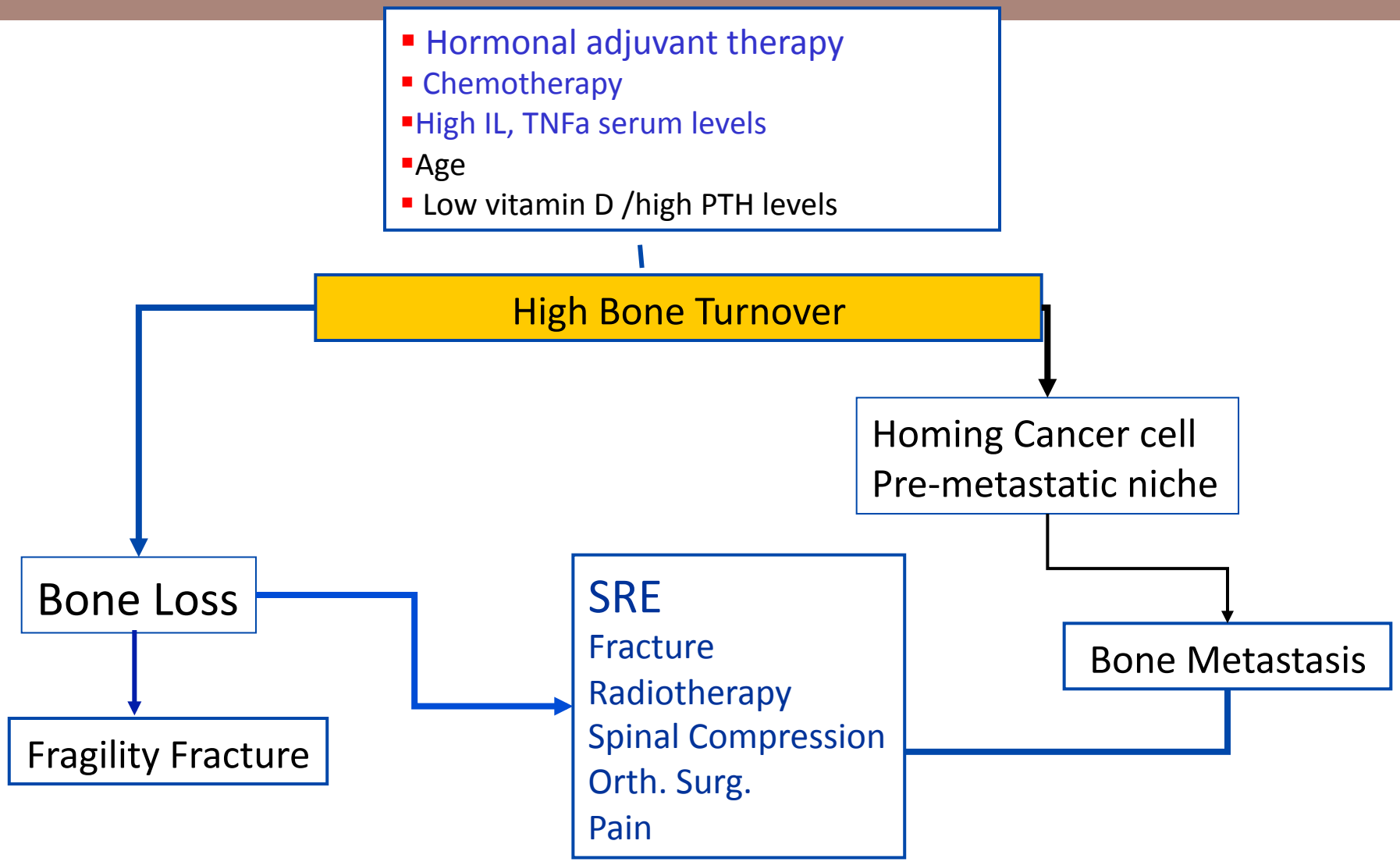
NON METASTATIC BONE

PREMETASTATIC NICHE

BONE MET.

Bertoldo F

The “Bone Health” concept in Cancer Patients



Bertoldo F 2006

TREATMENT/PREVENTION OF CTIBL IN BREAST AND PROSTATE CANCER PATIENTS

1) WHY
2) WHO
3) WHEN START
4) HOW
5) WHEN STOP

NUOVA NOTA 79 G.U. 20/5/15 n 115

- **Prevenzione primaria in donne in menopausa o uomini di età ≥ 50 anni a rischio elevato di frattura a causa di almeno una delle condizioni sottoelencate:**

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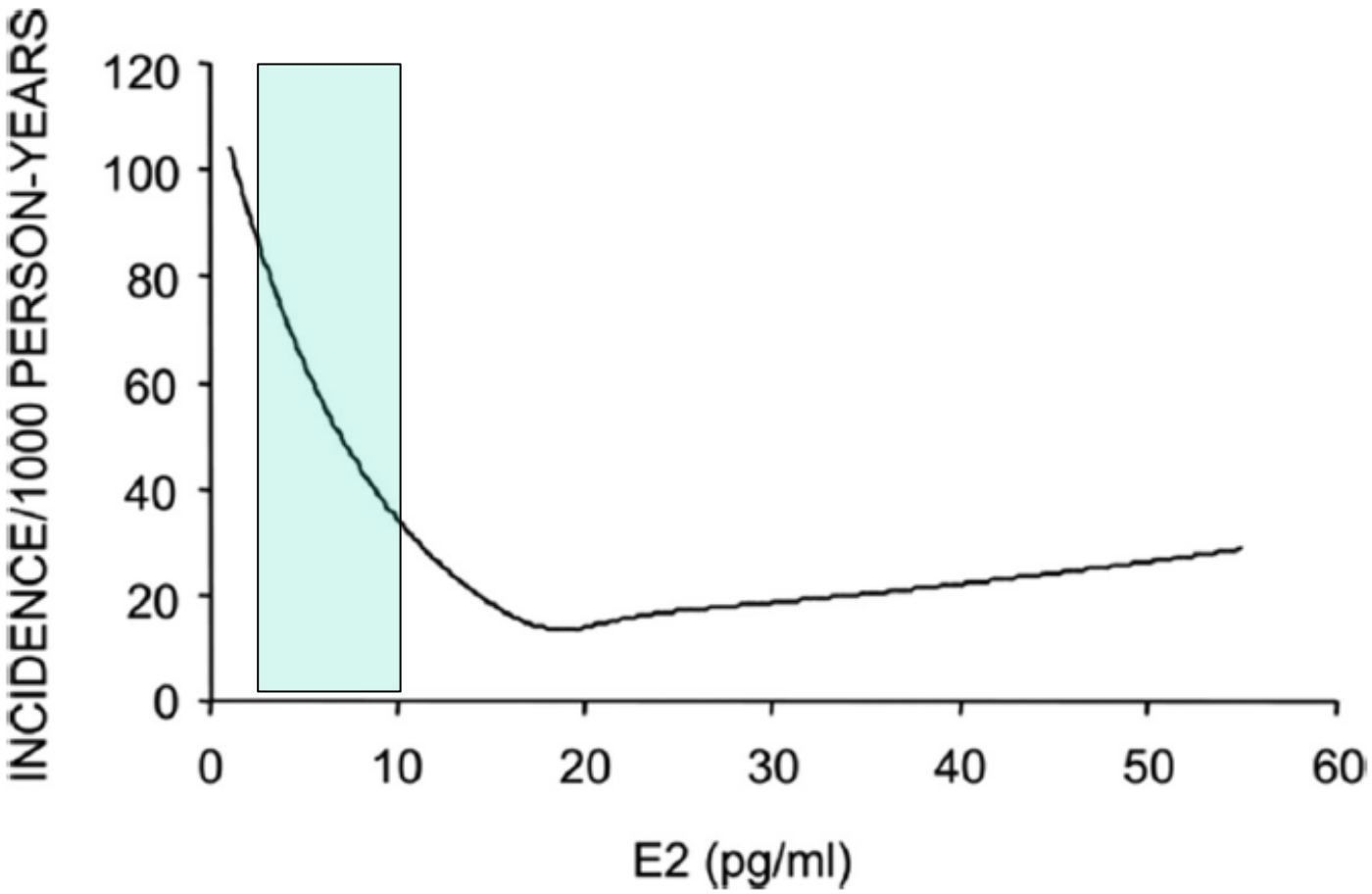
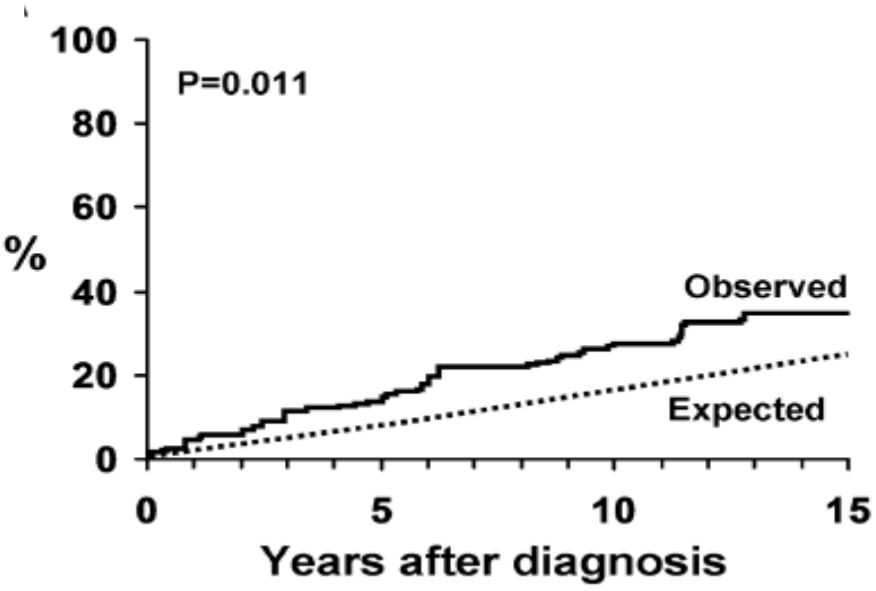
Trattamento in corso di blocco ormonale adiuvante in donne con carcinoma mammario o uomini con carcinoma prostatico	Alendronato (± vitD), Risedronato, Zoledronato [d], Denosumab [e]	----------	----------
T-score colonna o femore [c] ≤ -4	Alendronato (± vit.D), Risedronato,	Denosumab [e], Zoledronato [d], Ibandronato Raloxifene, Bazedoxifene	Stronzio ranelato [f]
T-score colonna o femore [c] ≤ -3 + almeno una delle seguenti condizioni: 1) Familiarità per fratture di vertebre o femore 2) Comorbilità a rischio di frattura (artrite reumatoide o altre connettiviti, diabete, broncopneumopatia cronica			

Annual Incidence of Fractures in Relation to Serum E2 levels

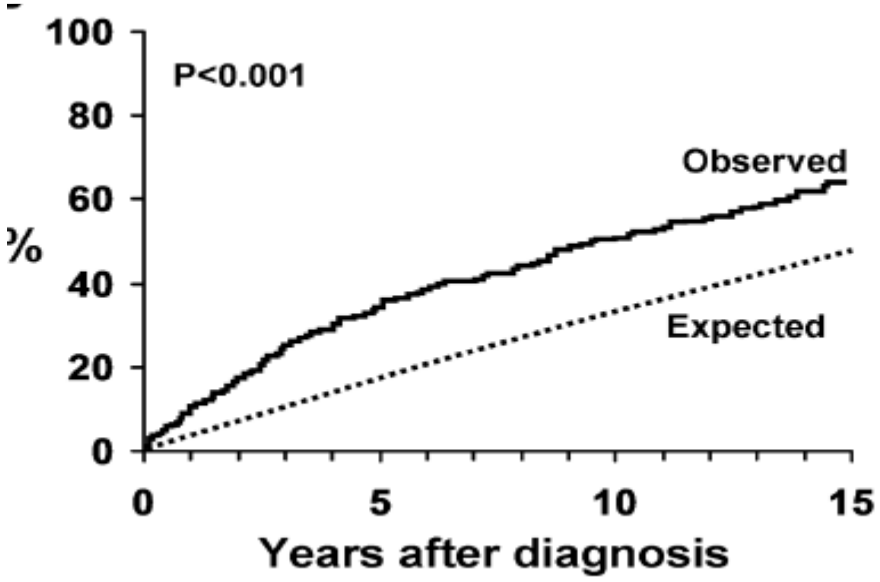


(*Endocrine Reviews* 35: 906–960, 2014)

Expected Cumulative Incidence of Fractures in Breast Cancer Patients



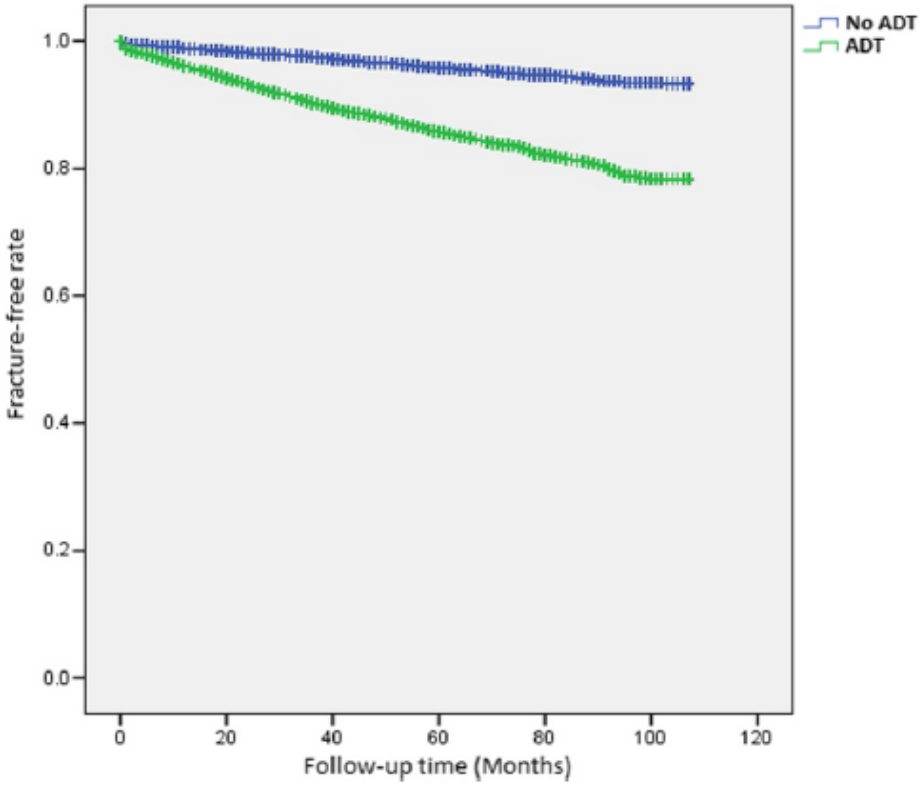
Premenopausal at diagnosis (CIOF)

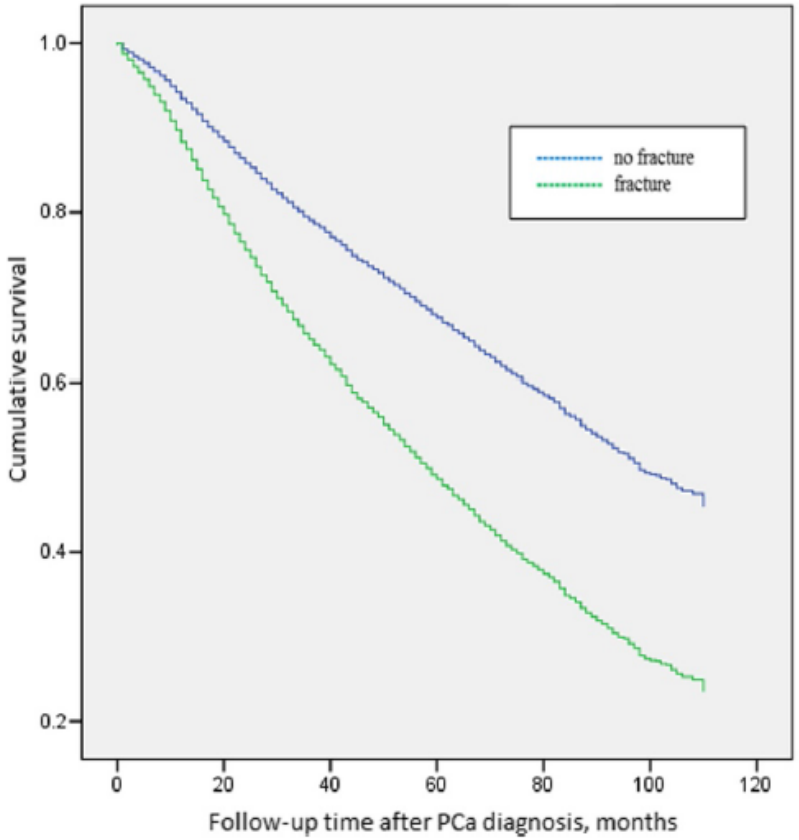


Postmenopausal at diagnosis

Melton III LJ J Bone Min Res 2012

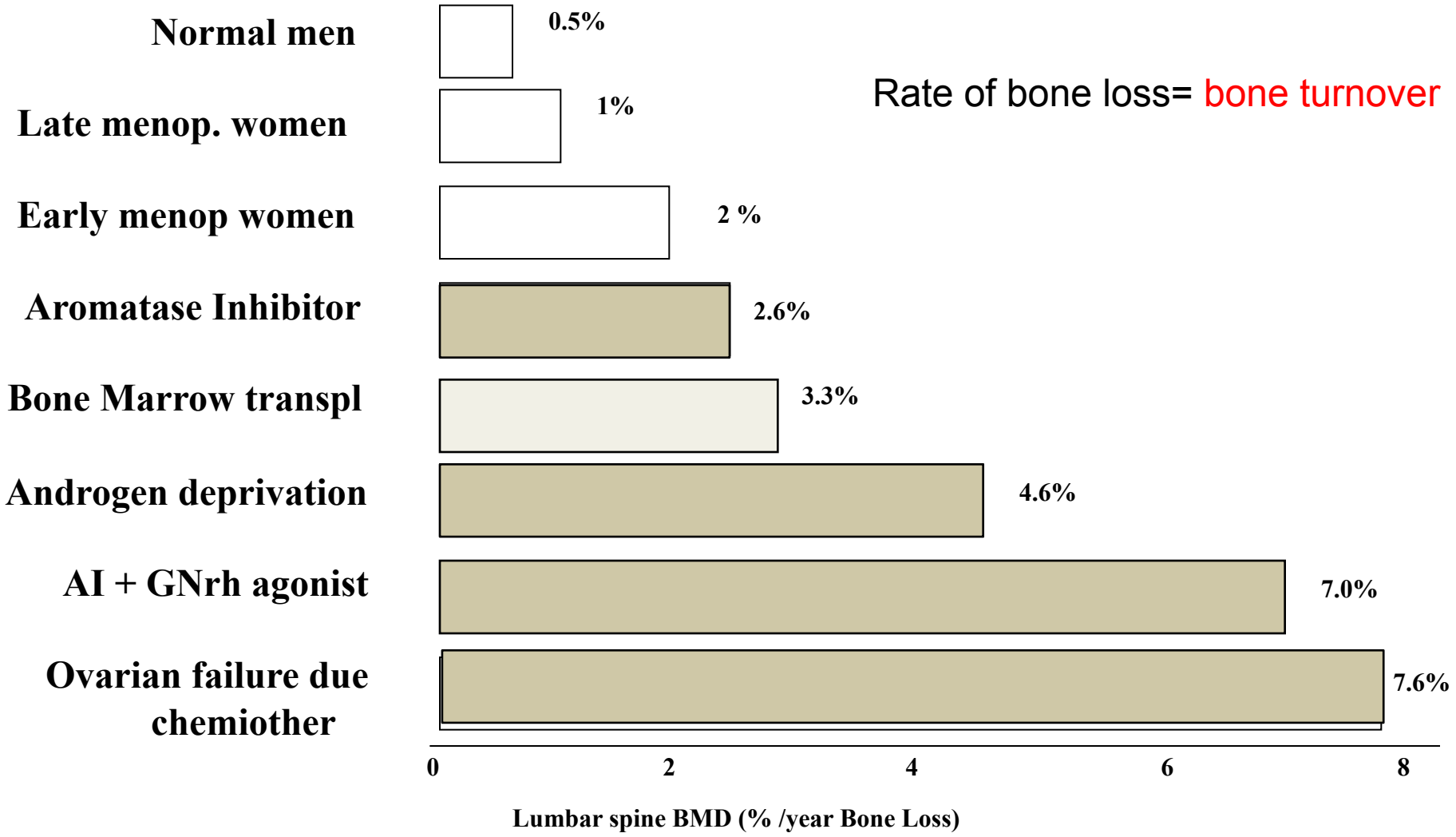
SURVIVAL AFTER A FRACTURE AND FRACTURE-FREE SURVIVAL IN ADT USERS VERSUS NONUSERS





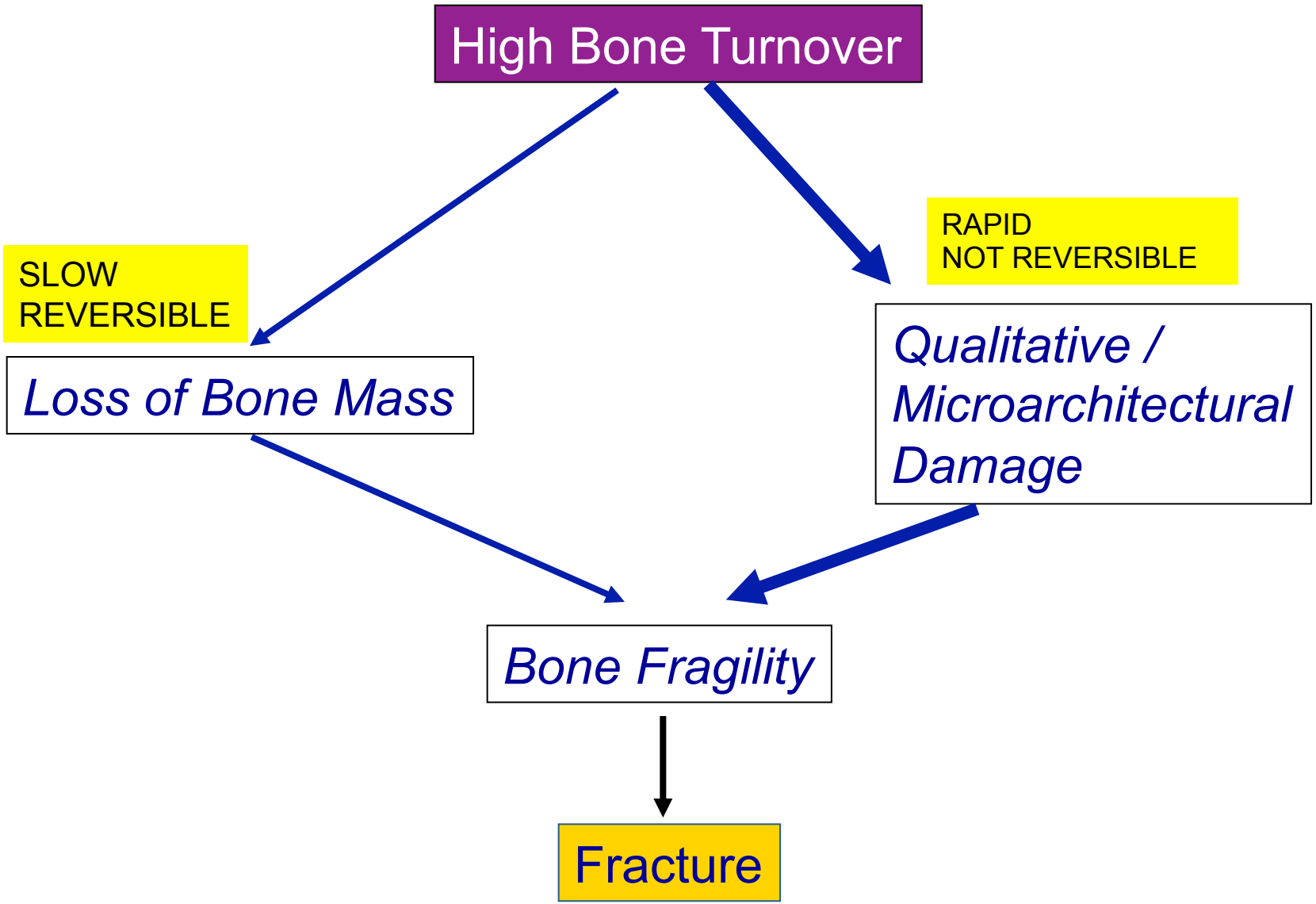
Wang *et al. BMC Cancer* (2015) 15:837

CANCER TREATMENT INDUCED BONE LOSS
Rate of BMD Loss

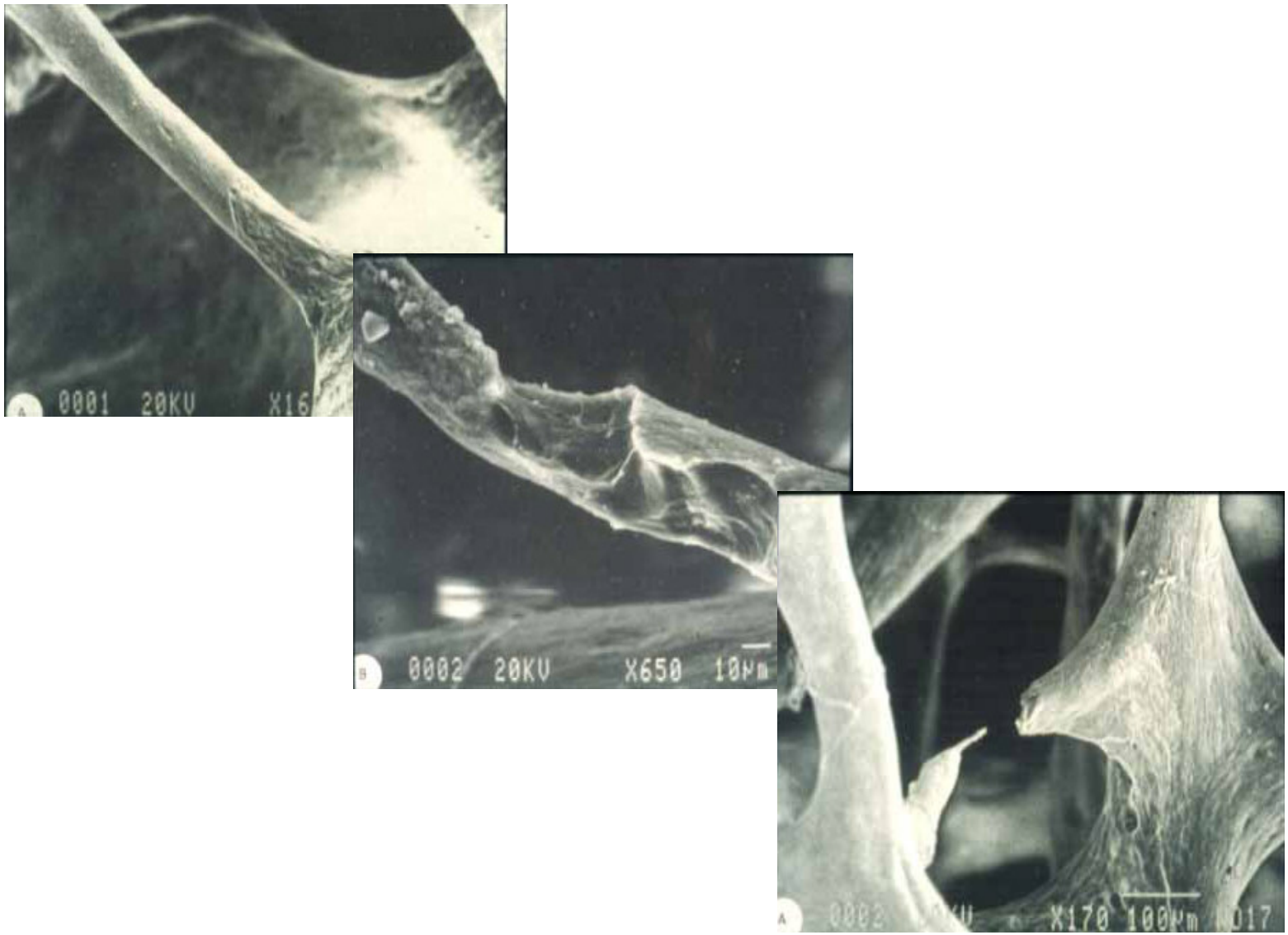


Rate of bone loss= bone turnover

Hirbe A et al Clin Cancer Res 2006

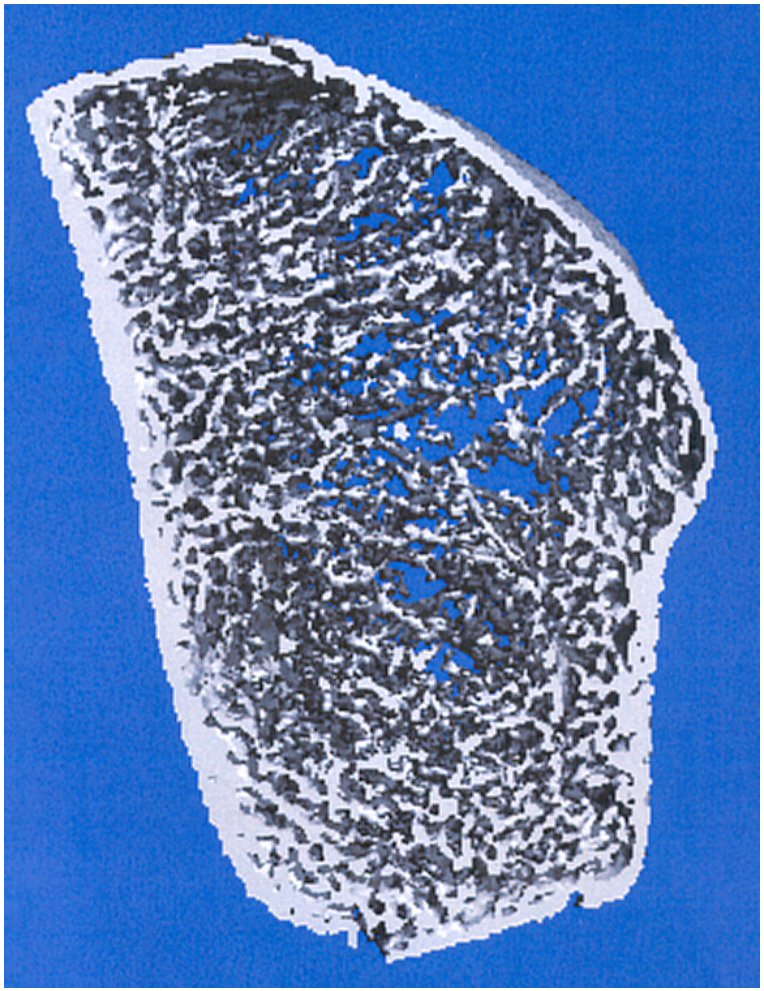


Boivin G et al. *Connect Tissue Res.* 2002;43:535-537.

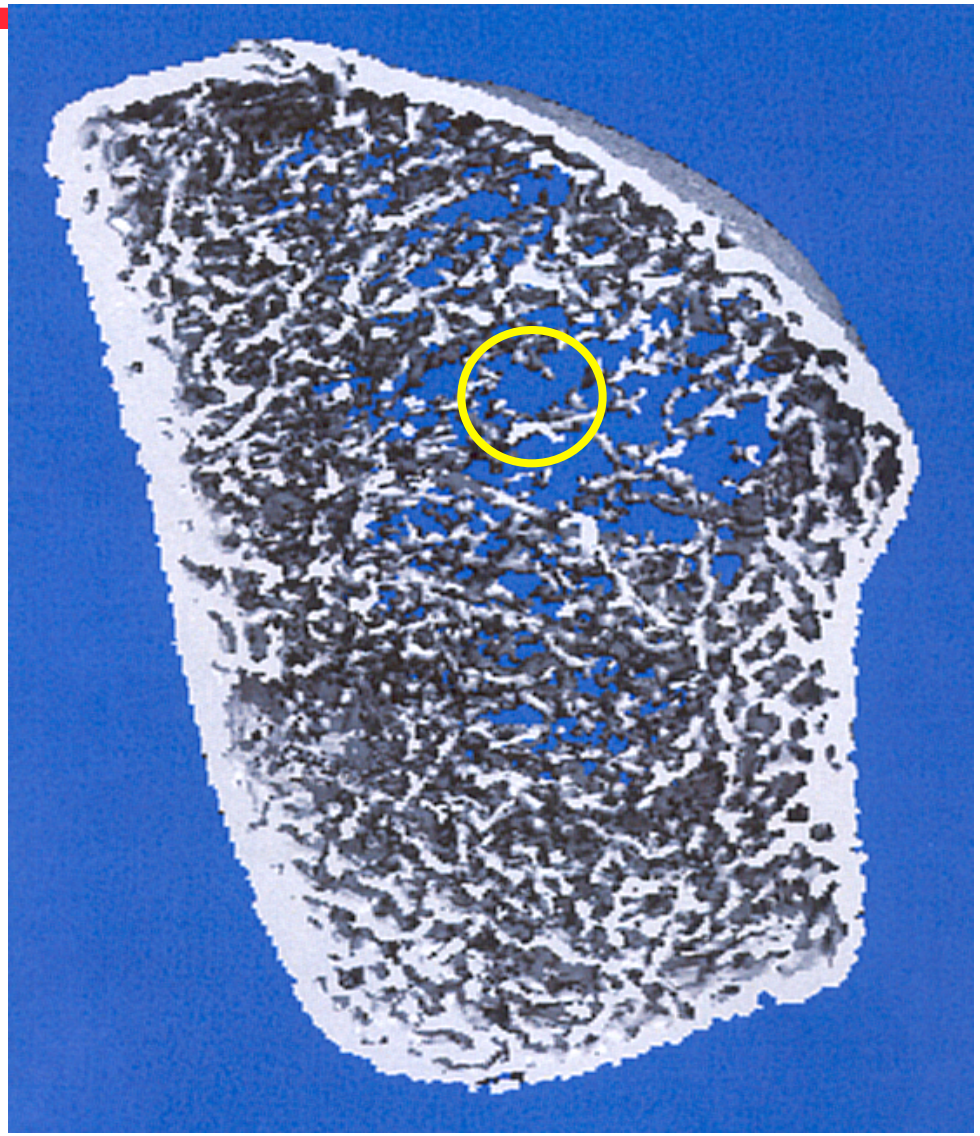


Mosekilde, Bone Miner 10: 13-35 (1990)

Influence of Anastrozole on Trabecular Microstructure After 3 Months (Xtreme-CT)



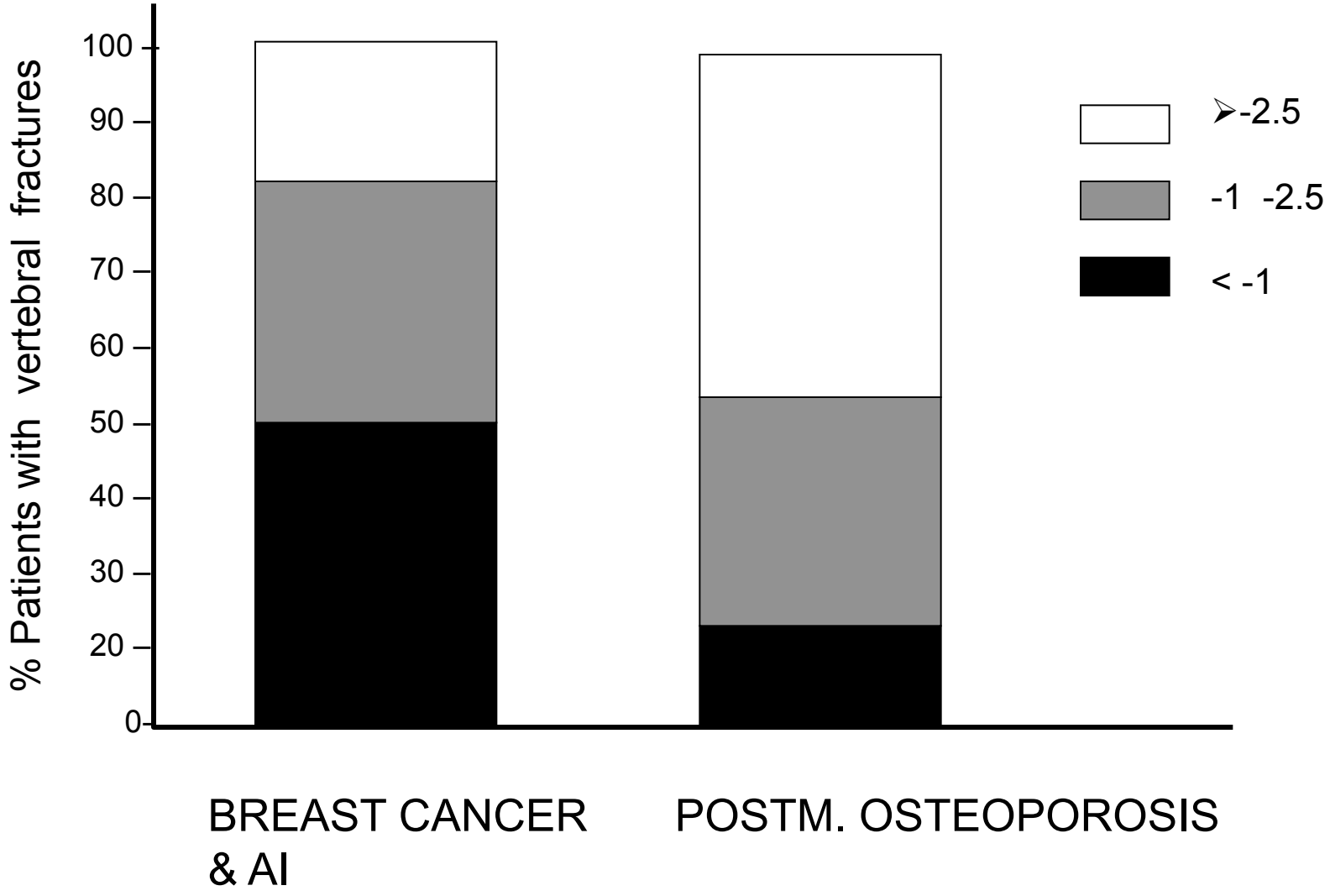
Dist. Radius 09.11.2005



Dist. Radius 16.02.2006

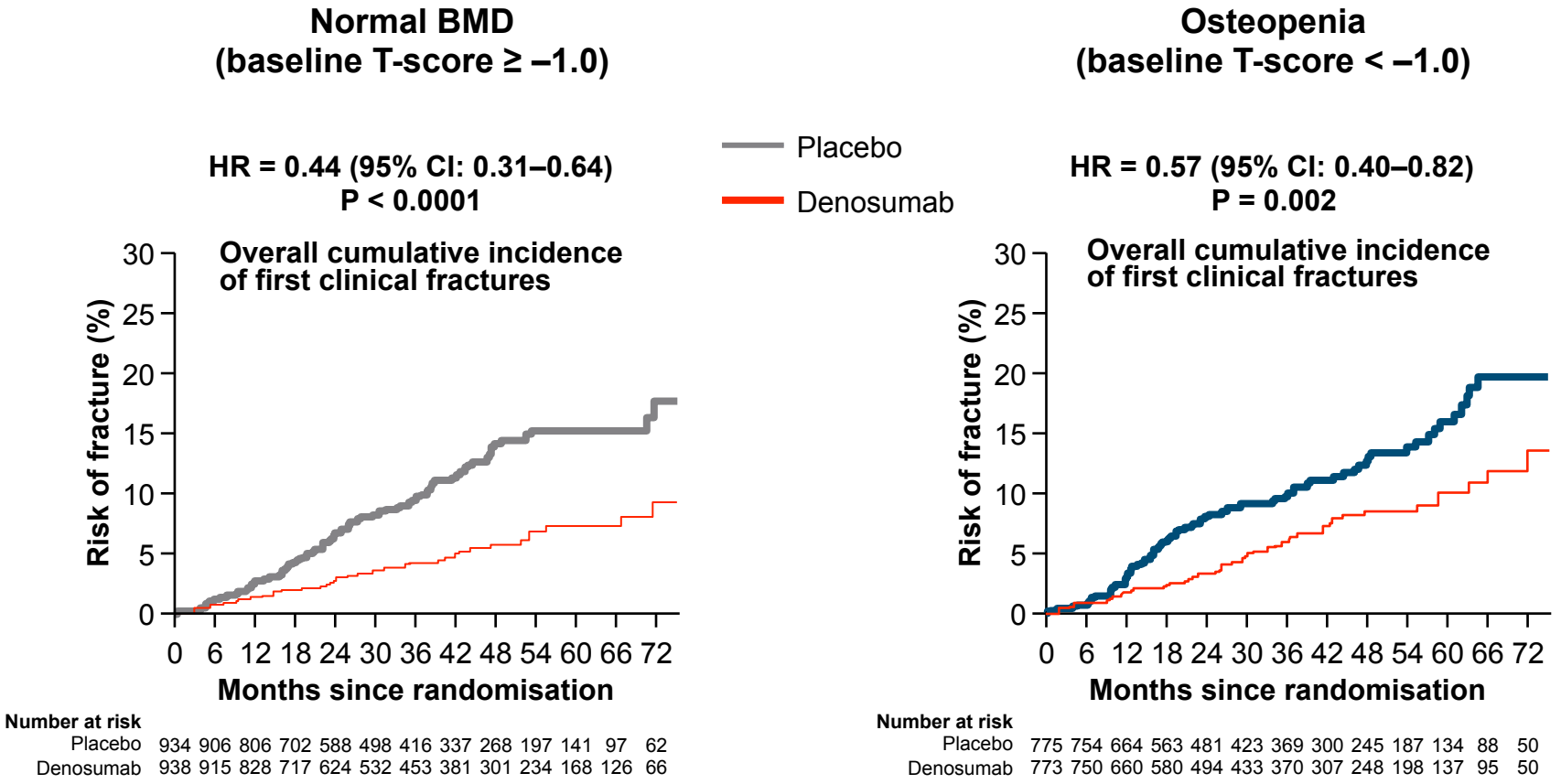
H. Radspieler, Center for Osteoporosis Munich, Germany

LUMBAR SPINE T-SCORE IN AI BC WOMEN AND IN POSTMENOPAUSAL OSTEOPOROSIS WITH VERTEBRAL FRACTURES



Bertoldo F et al J Bone iMn Res abst s345; 2009 ASBMR ; Bertoldo F et al abst. J Bone Oncol 2012

ABCSG-18: denosumab significantly reduced the incidence of clinical fractures vs placebo regardless of baseline BMD

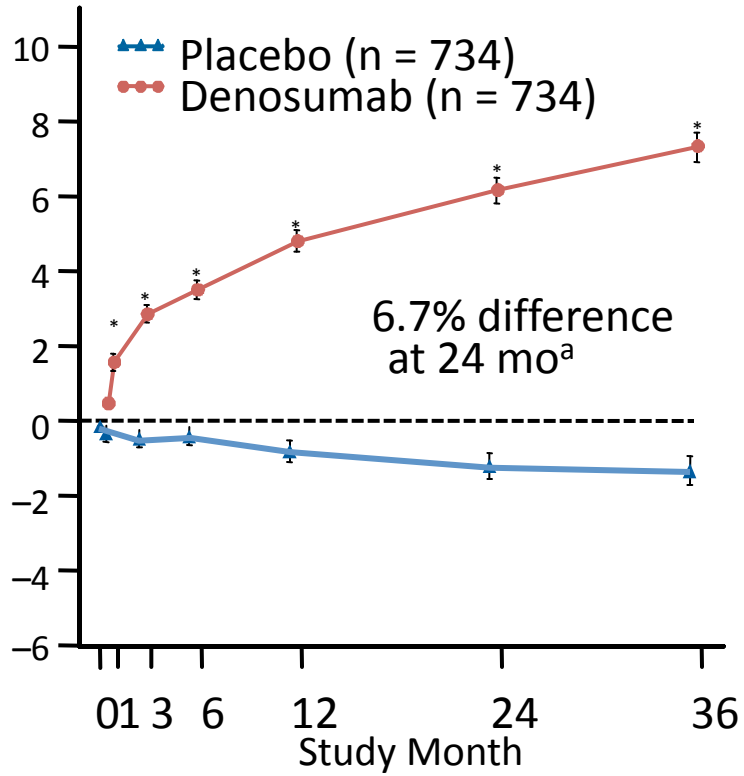


Adapted from Gnant M, et al. Lancet 2015;386:433–43 (and supplementary appendix).

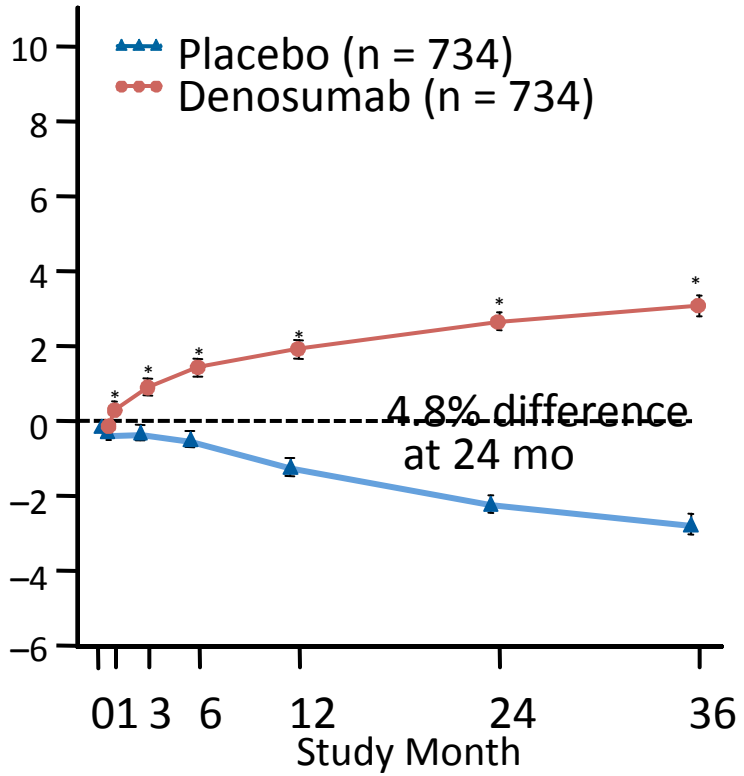
Prevention of Cancer Treatment Induced Bone Loss (CTIBL)

HALT-PC (20040138): Denosumab in ADT-Treated Prostate Cancer

Lumbar Spine



Total Hip

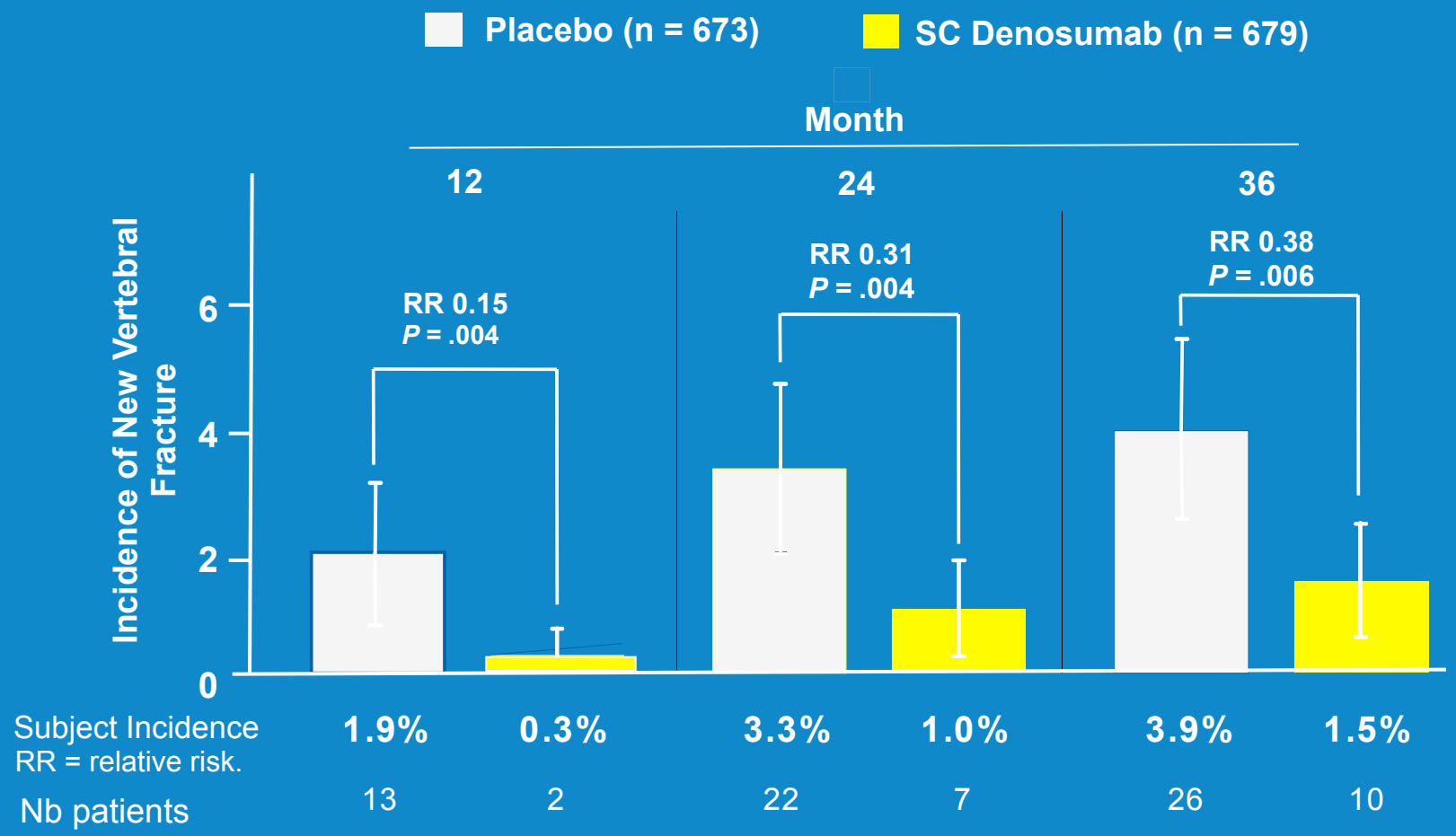


*$P \leq .001$ at all measured sites

[a]Primary end point

Smith MR, Egerdie B, Toriz NH, et al. *N Engl J Med.* 2009;361:745-755.

Denosumab reduces the Risk of New Vertebral Fractures



Smith MR, Egerdie B, Toriz NH, et al. *N Engl J Med.* 2009;361:745-755.

NUOVA NOTA 79 G.U. 20/5/15 n 115

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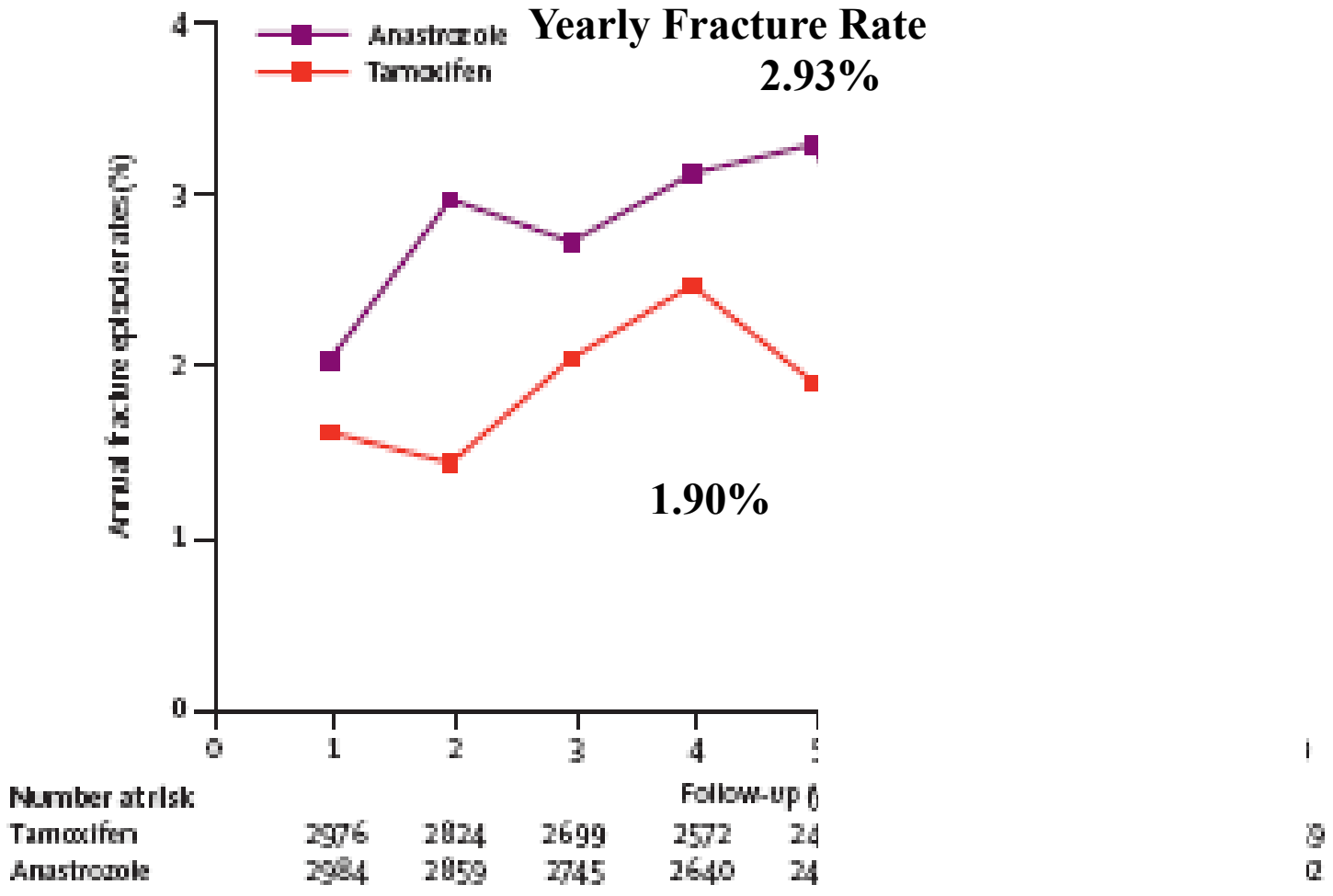
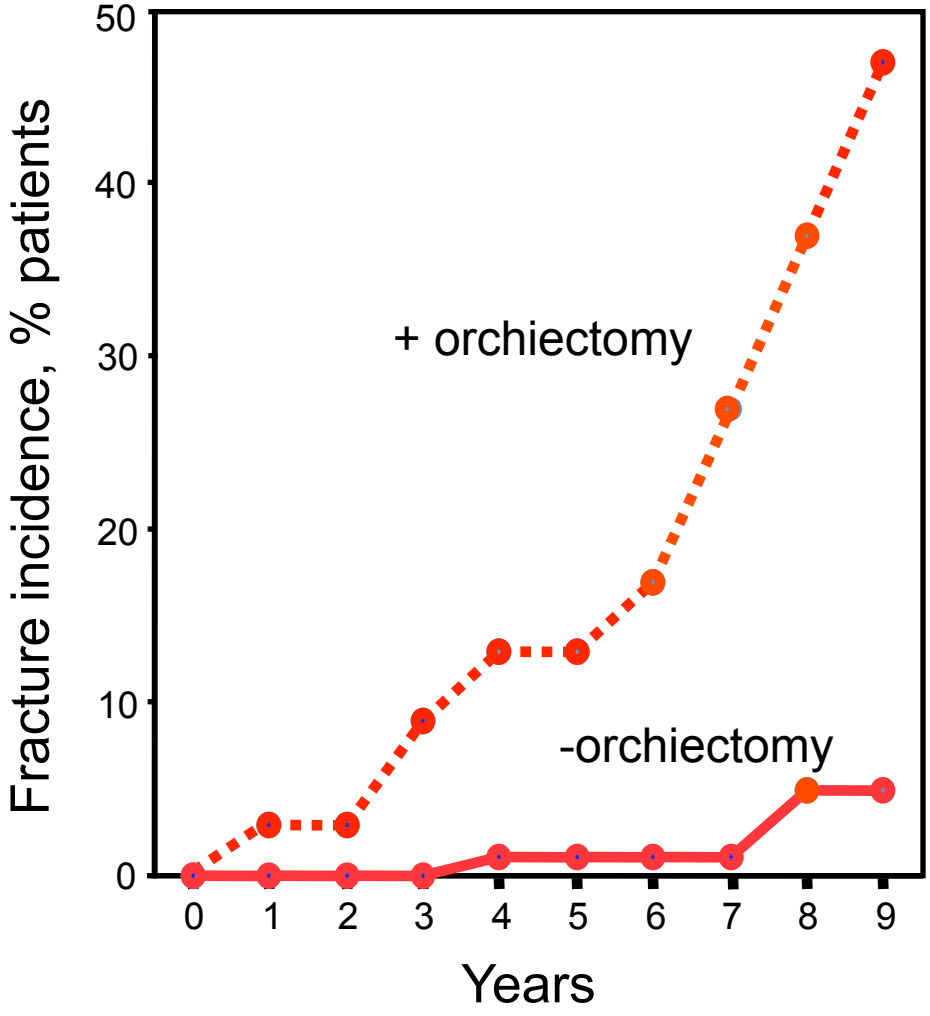
10 yrs Analysis of the ATAC Trial



Lancet Oncol 2008

Androgen Deprivation Therapy Increases Fracture Risk



Daniell HW, et al. *J Urol.* 1997;157:439-444.

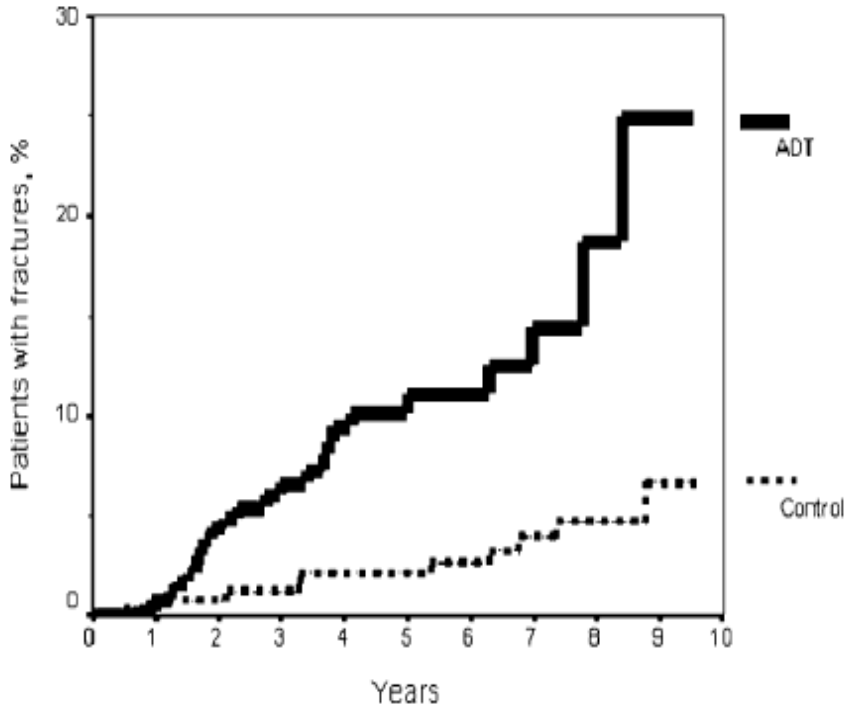


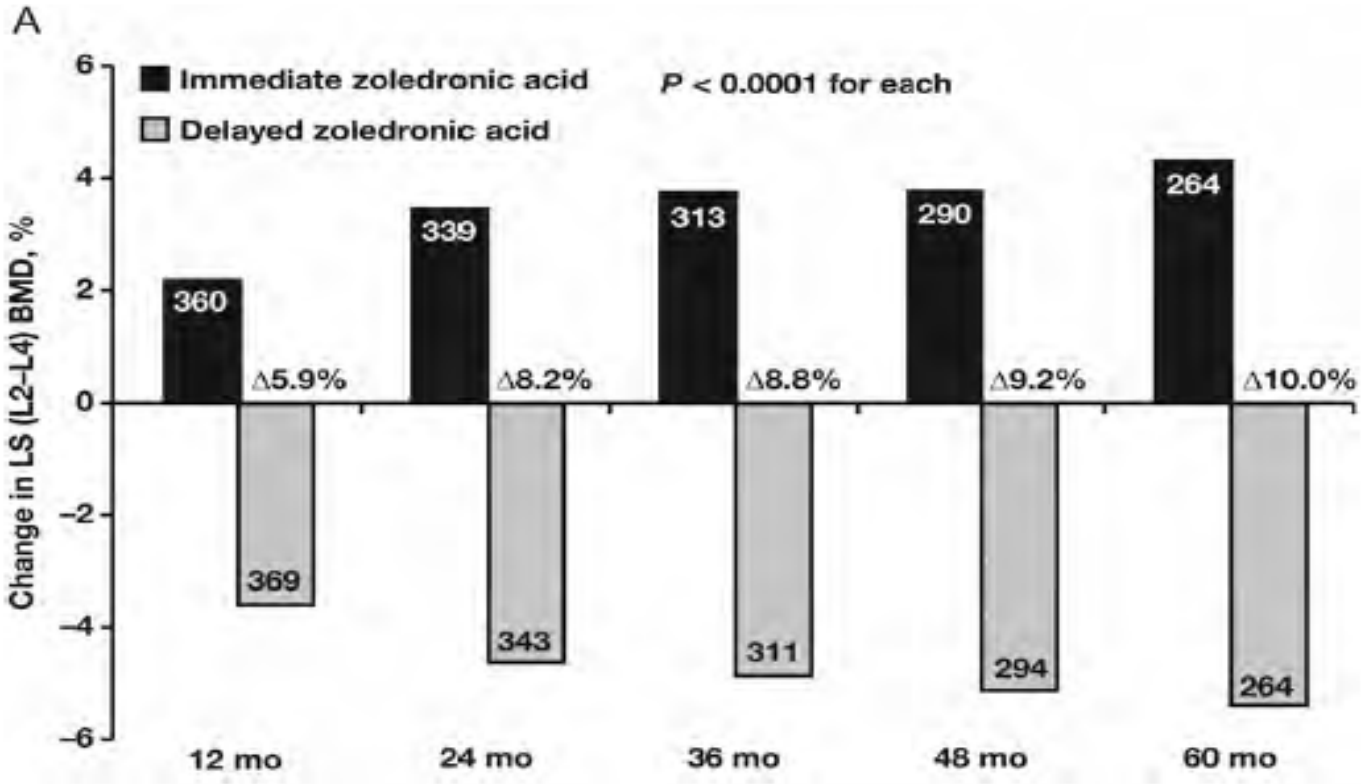
Fig. 1 Kaplan–Meier plots of patients with fractures after ADT (patient group) or diagnosis (control group)

Fracture risk in patients with prostate cancer on androgen deprivation therapy

Ana M. López · María A. Pena · Rafael Hernández
Fernando Val · Bernardo Martín · José A. Riancho

Zoledronic acid for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results

UP –FRONT: at the start of aromatase inhibitors
DELAYED: >3% BMD reduction, Fracture, BMD -2.5 T score



Coleman R et al Annals of Oncology 24: 398–405, 2013

Zoledronic acid preserves bone mineral density in premenopausal women who develop ovarian failure due to adjuvant chemotherapy: Final results from CALGB trial 79809

Zol 4 mg/ 3 mo.
Arm A: UpFront **Arm B : after 1 y of CIOF**

Median (interquartile range) Percent Difference in BMD from Baseline to 1 or 3 years

	ZA-Arm A	Control-Arm B	p
Total with CIOF at 1 year (n=150)	1.2 (−0.5 to +2.8)	−6.7 (−2.9 to −9.7)	<0.001
Total women at 1 year (n=302)	1.4 (−0.7 to +3.9)	−5.5 (−2.3 to −8.8)	<0.001
Total women at 3 years mos (n=177)	1.0 (−1.6 to +5.20)	−0.5 (−3.7 to +3.2)	0.019

Abbreviations: Bone mineral density (BMD); chemotherapy-induced ovarian failure (CIOF); zoledronic acid (ZA).

Shapiro L et al *Eur J Cancer*. 2011

NUOVA NOTA 79 G.U. 20/5/15 n 115

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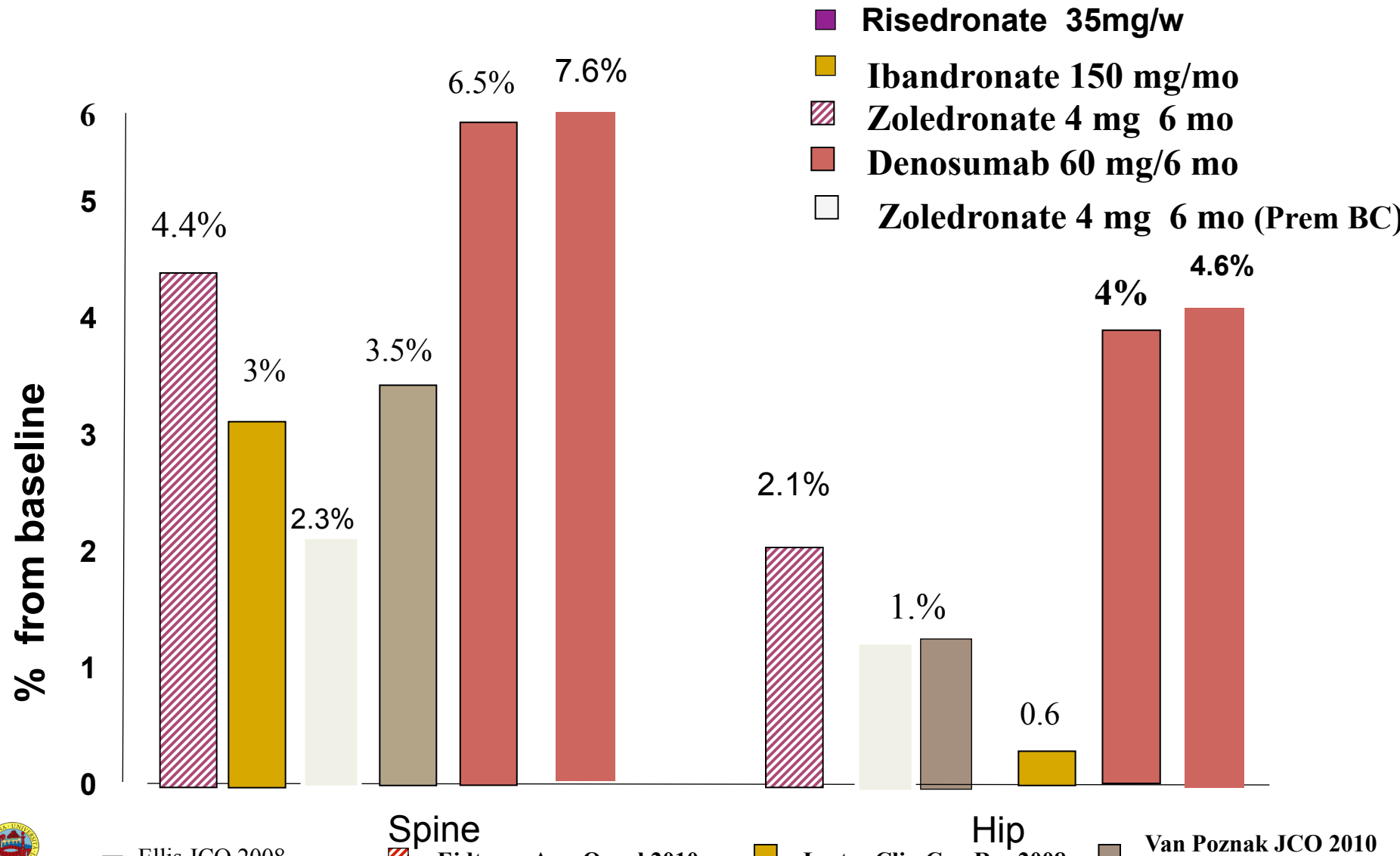
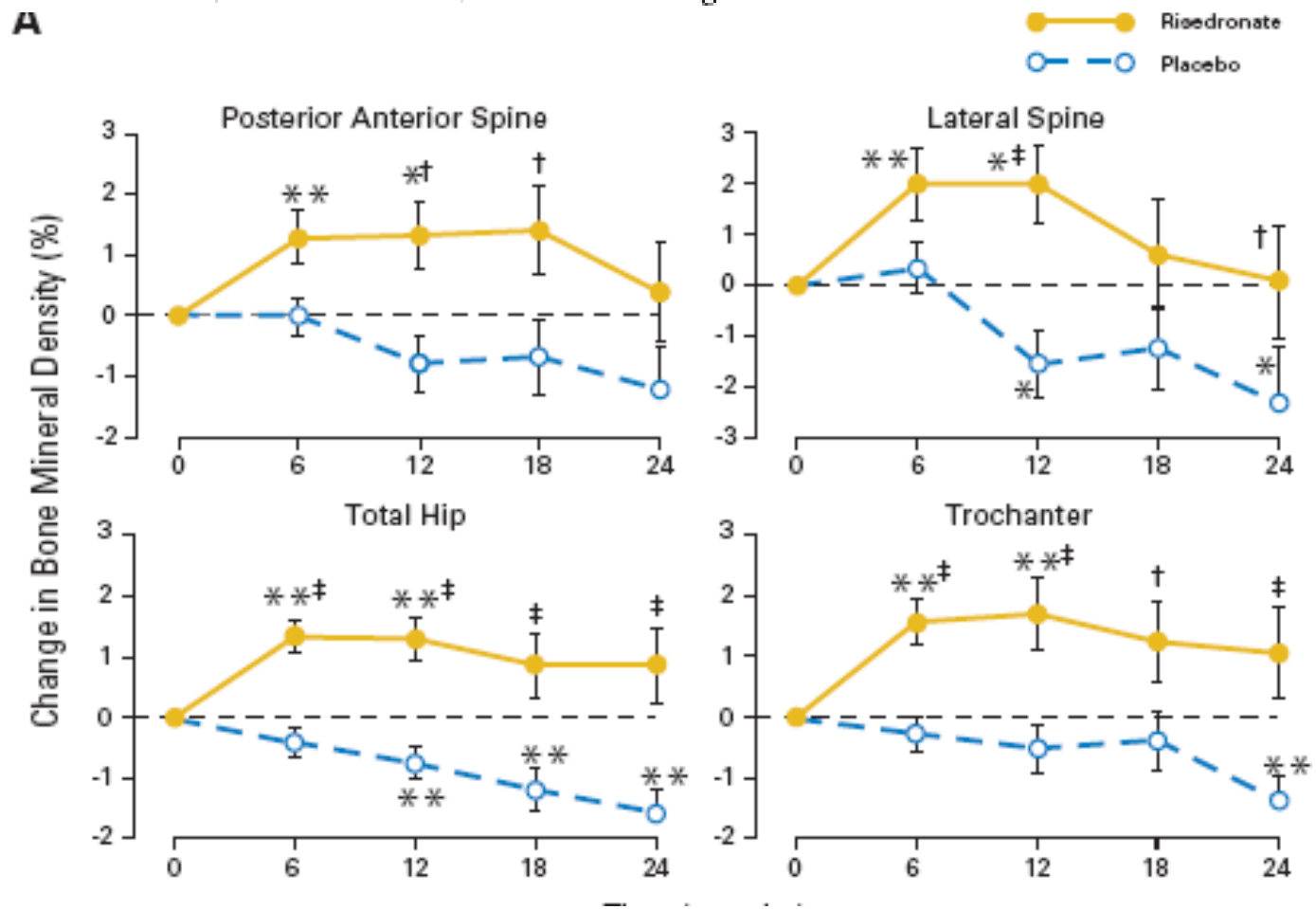
Effects of Antiresorptive therapy on BMD in BC Women treated with AI



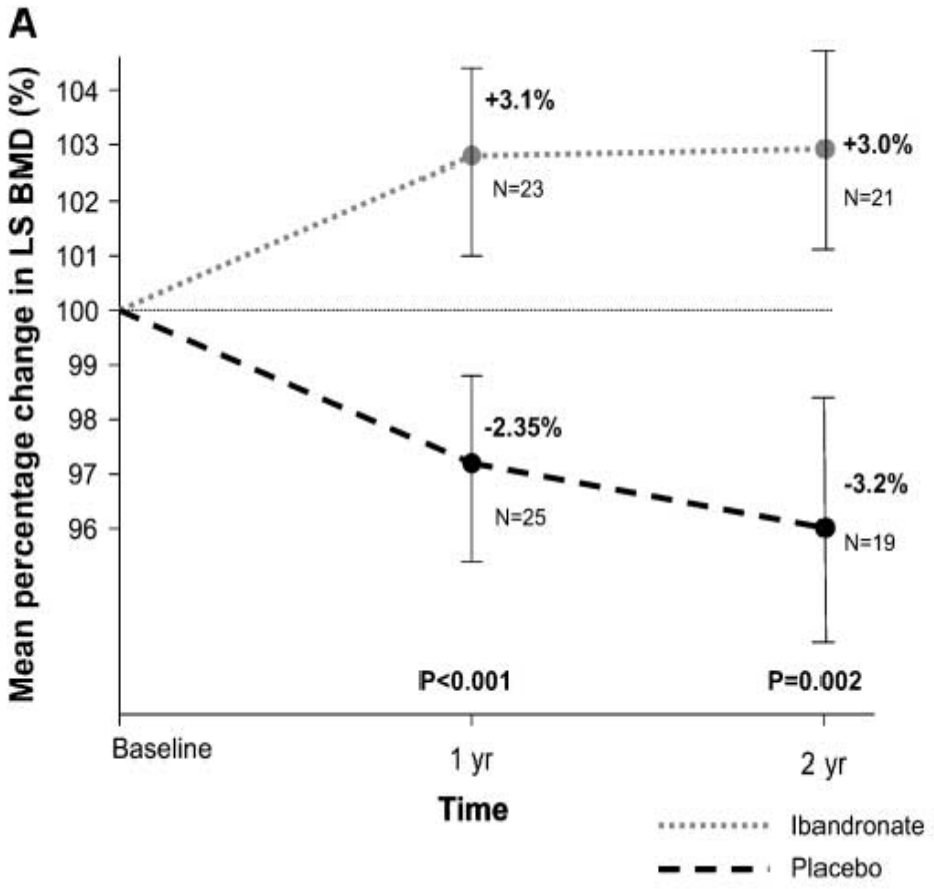
Risedronate Prevents Bone Loss in Breast Cancer Survivors: A 2-Year, Randomized, Double-Blind, Placebo-Controlled Clinical Trial

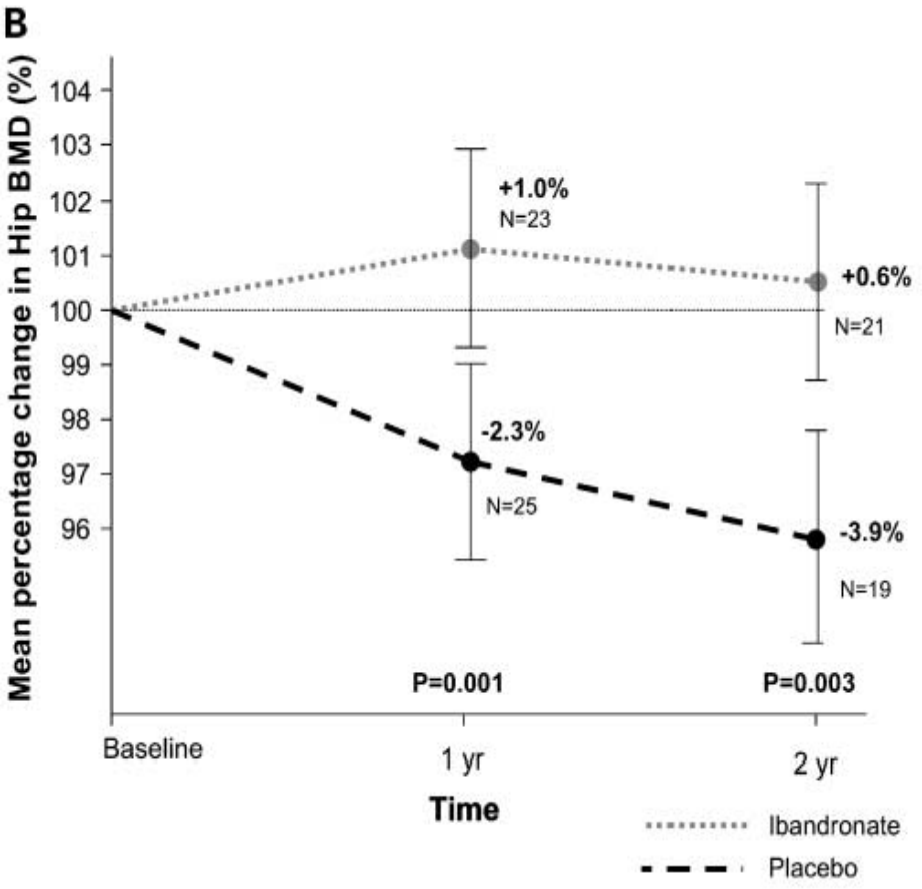
Susan L. Greenspan, Adam Brufsky, Barry C. Lembersky, Rajib Bhattacharya, Karen T. Vujevich, Subashan Perera, Susan M. Sereika, and Victor G. Vogel



J Clin Oncol 2008

Prevention of Anastrozole-Induced Bone Loss with Monthly Oral Ibandronate during Adjuvant Aromatase Inhibitor Therapy for Breast Cancer





Lester JE *Clin Canc Res 2008*

Zoledronic acid for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results

UP –FRONT: at the start of aromatse inhibitors
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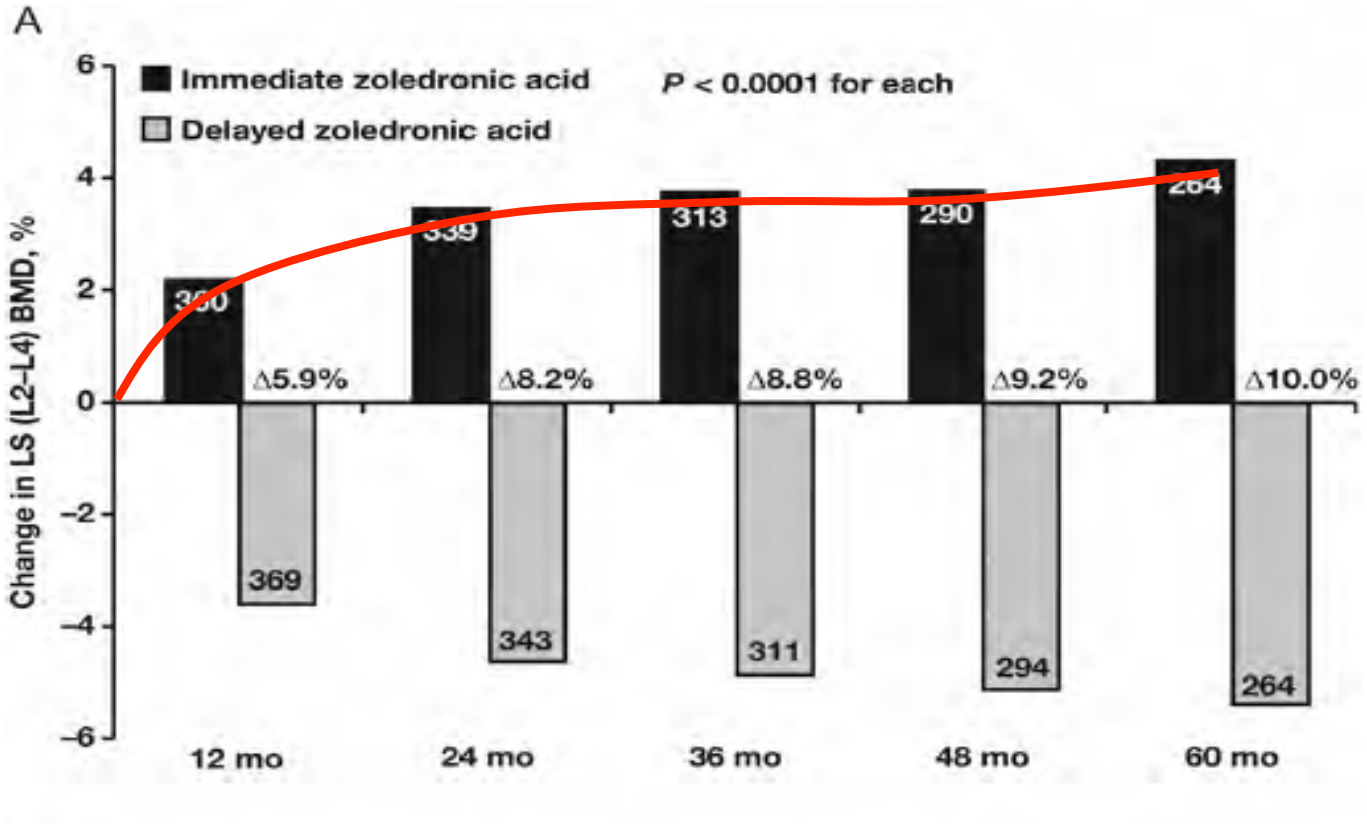
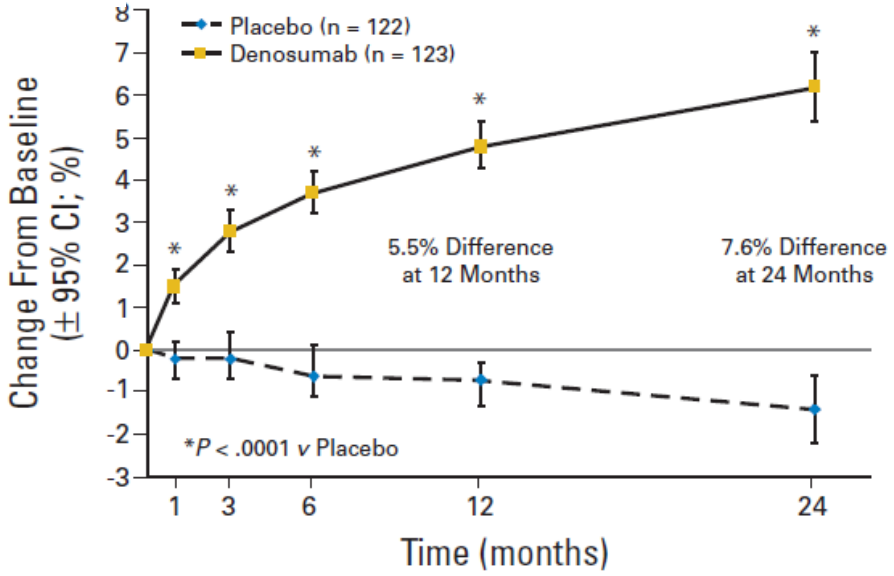


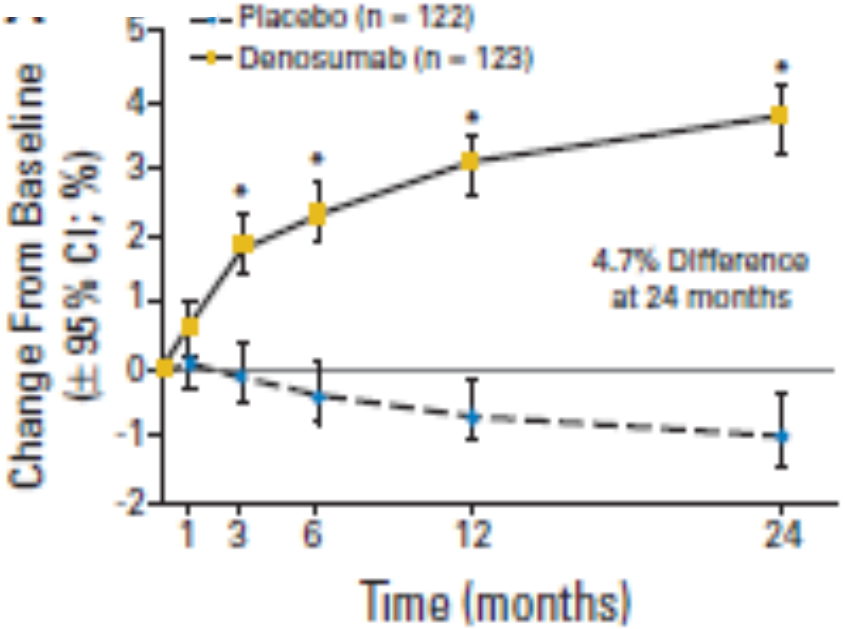
Coleman R et al Annals of Oncology 24: 398–405, 2013

Randomized Trial of Denosumab in Patients Receiving Adjuvant Aromatase Inhibitors for Nonmetastatic Breast Cancer

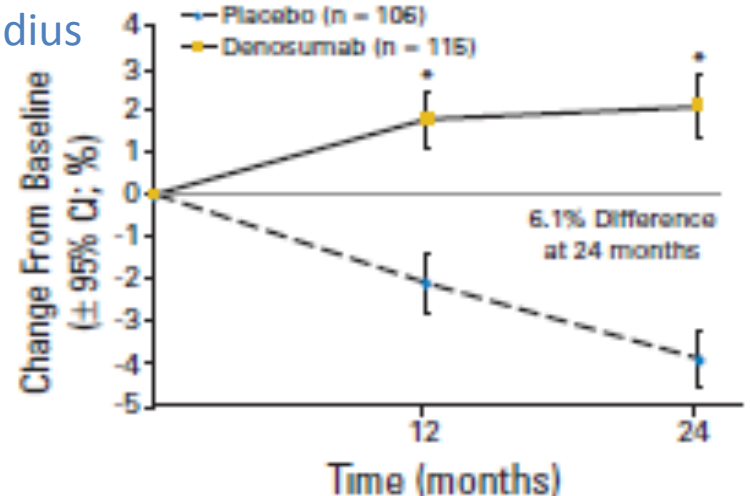
SPINE



Femoral Neck



Radius

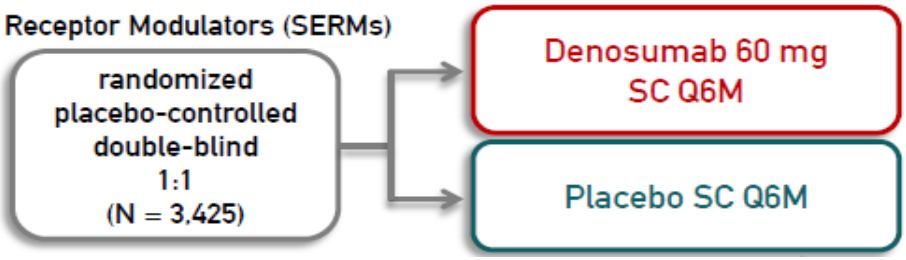


Ellis GK J Clin Oncol 2008

Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial

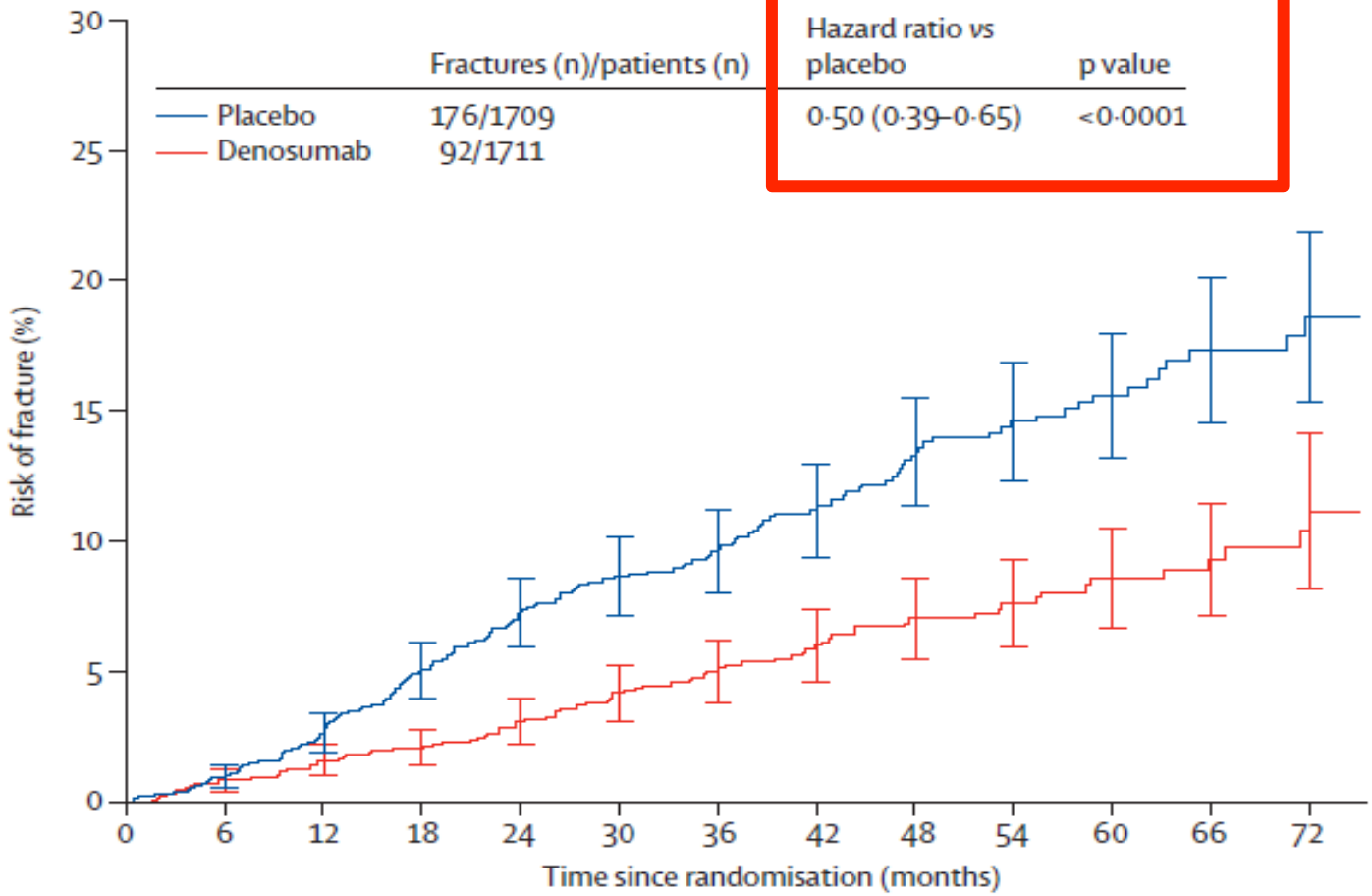
Trial Design ABCSG 18

- Prospective randomized placebo-controlled double-blind multicenter phase-3 trial
- Recruitment 2006 – 2013 (3,425 postmenopausal patients)
- Primary endpoint: Time to first clinical fracture
- Inclusion criteria:
  - Postmenopausal women with non-metastatic adenocarcinoma of the breast
  - ER+ and/ or PR+; adjuvant non-steroidal aromatase inhibitor therapy
- Exclusion criteria:
  - Prior or concurrent treatment with Selective Estrogen Receptor Modulators (SERMs)
  - Current or prior IV bisphosphonate administration
  - Known history of:
    - Paget's disease
    - Cushing's disease
    - hyperprolactinemia
    - hypercalcaemia or hypocalcaemia
    - other active metabolic bone disease



Gnant M et al www.thelancet.com Published online June 1, 2015 http://dx.doi.org/10.1016/S0140-6736(15)60995-3

Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial (primary end point)

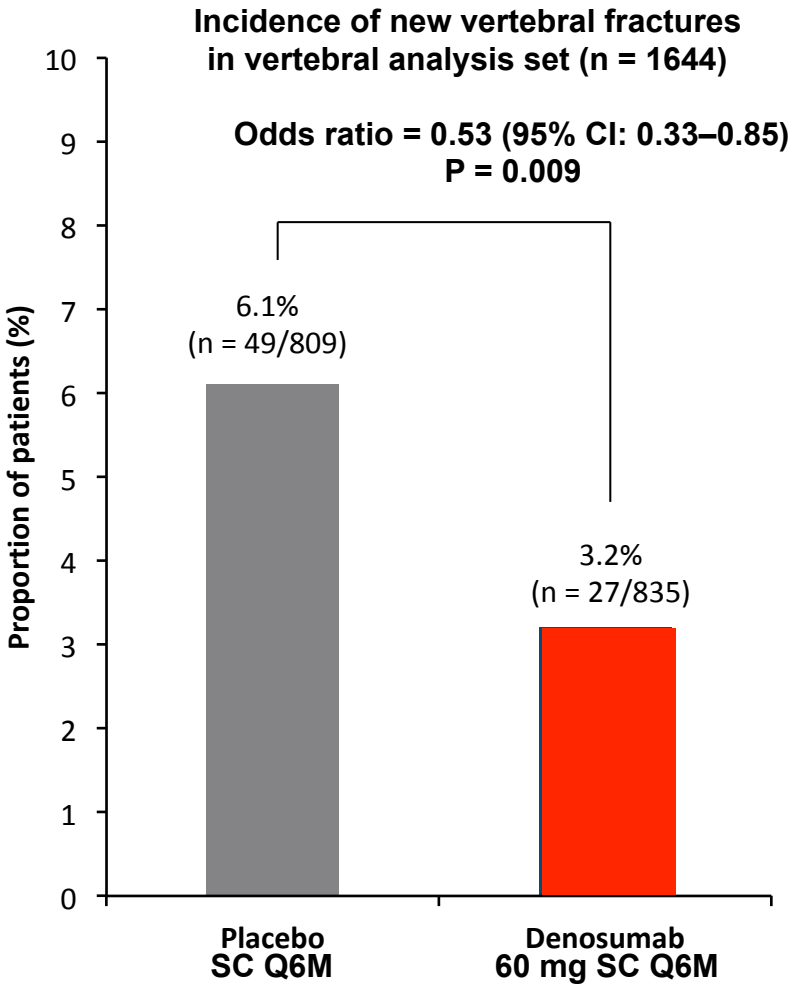


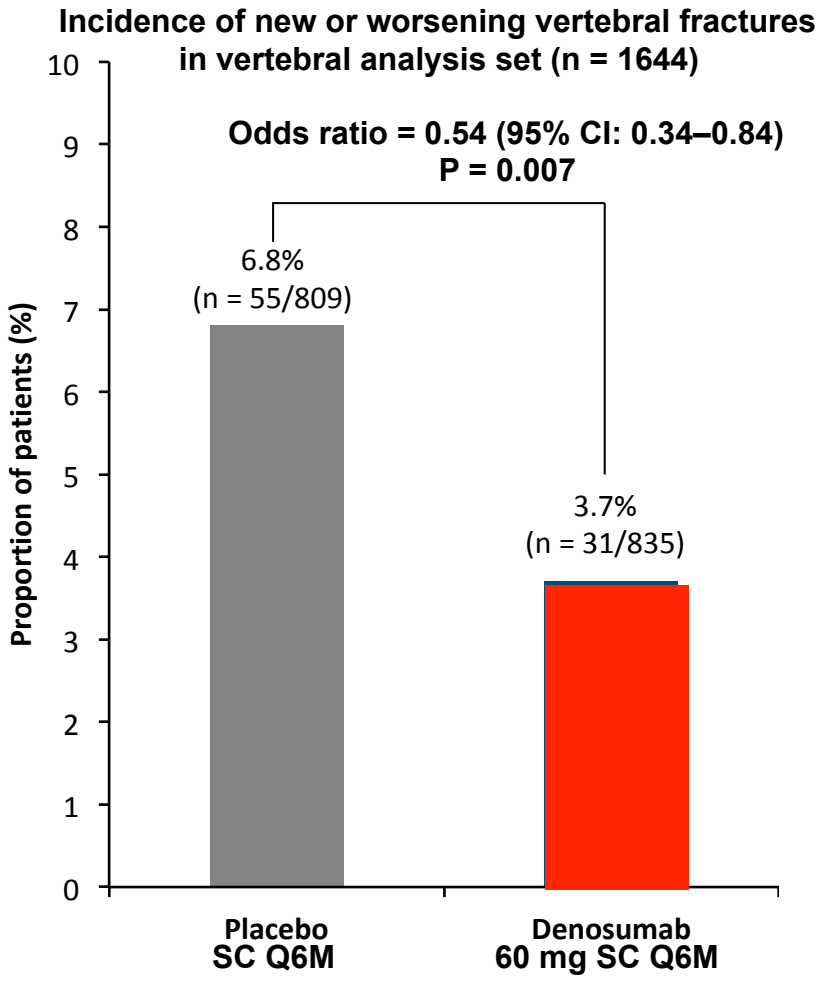
Number at risk

Placebo	1709	1660	1470	1265	1069	921	785	637	513	384	275	185	112
Denosumab	1711	1665	1488	1297	1118	965	823	688	549	432	305	221	116

www.thelancet.com **Published online June 1, 2015** http://dx.doi.org/10.1016/S0140-6736(15)60995-3

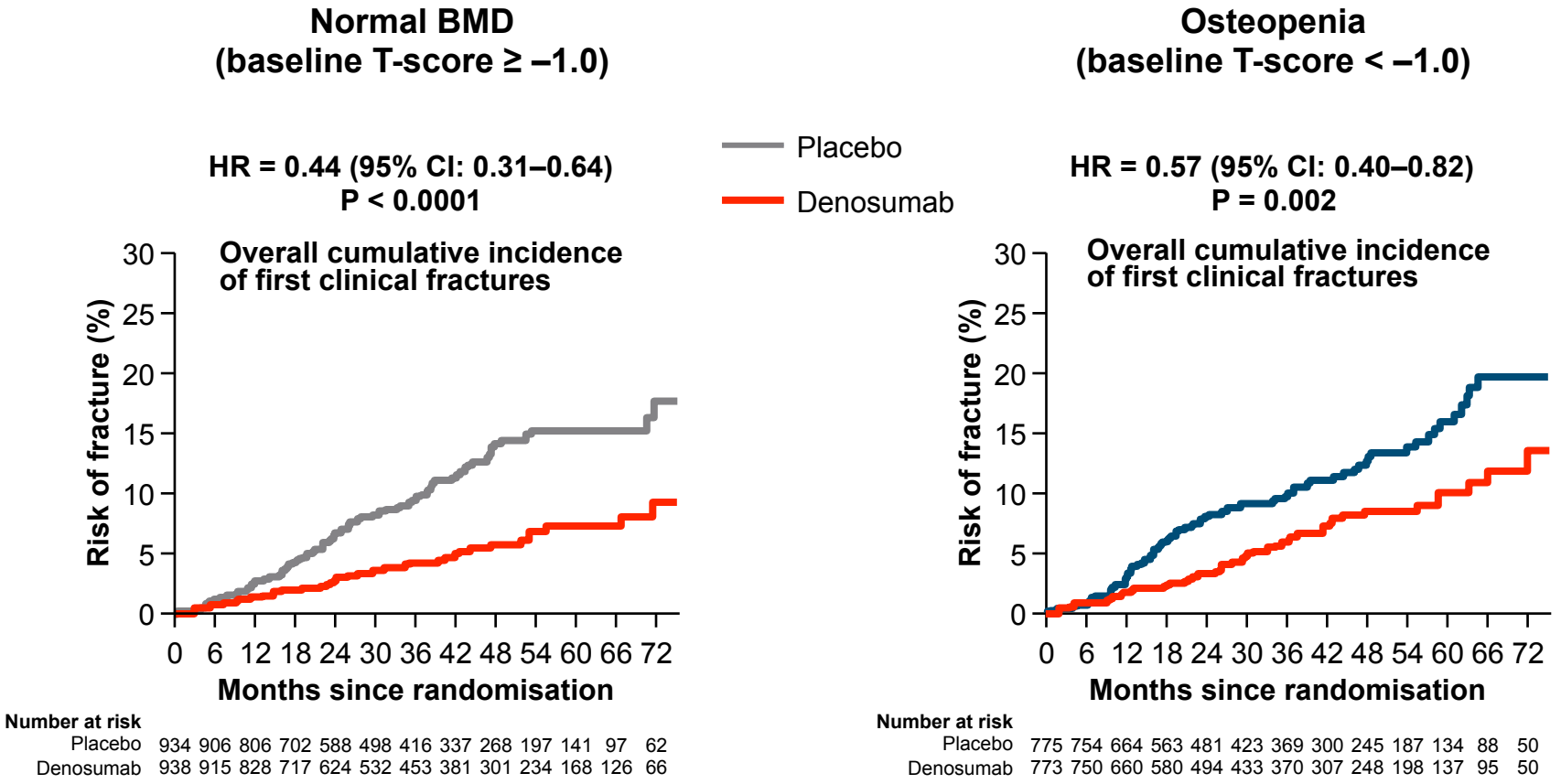
ABCSG-18: denosumab significantly reduced the incidence of new and new or worsening vertebral fractures at Month 36 vs placebo





Elaborated from Gnant M, et al. Lancet 2015;386:433–43.

ABCSG-18: denosumab significantly reduced the incidence of clinical fractures vs placebo regardless of baseline BMD



Adapted from Gnant M, et al. Lancet 2015;386:433–43 (and supplementary appendix).

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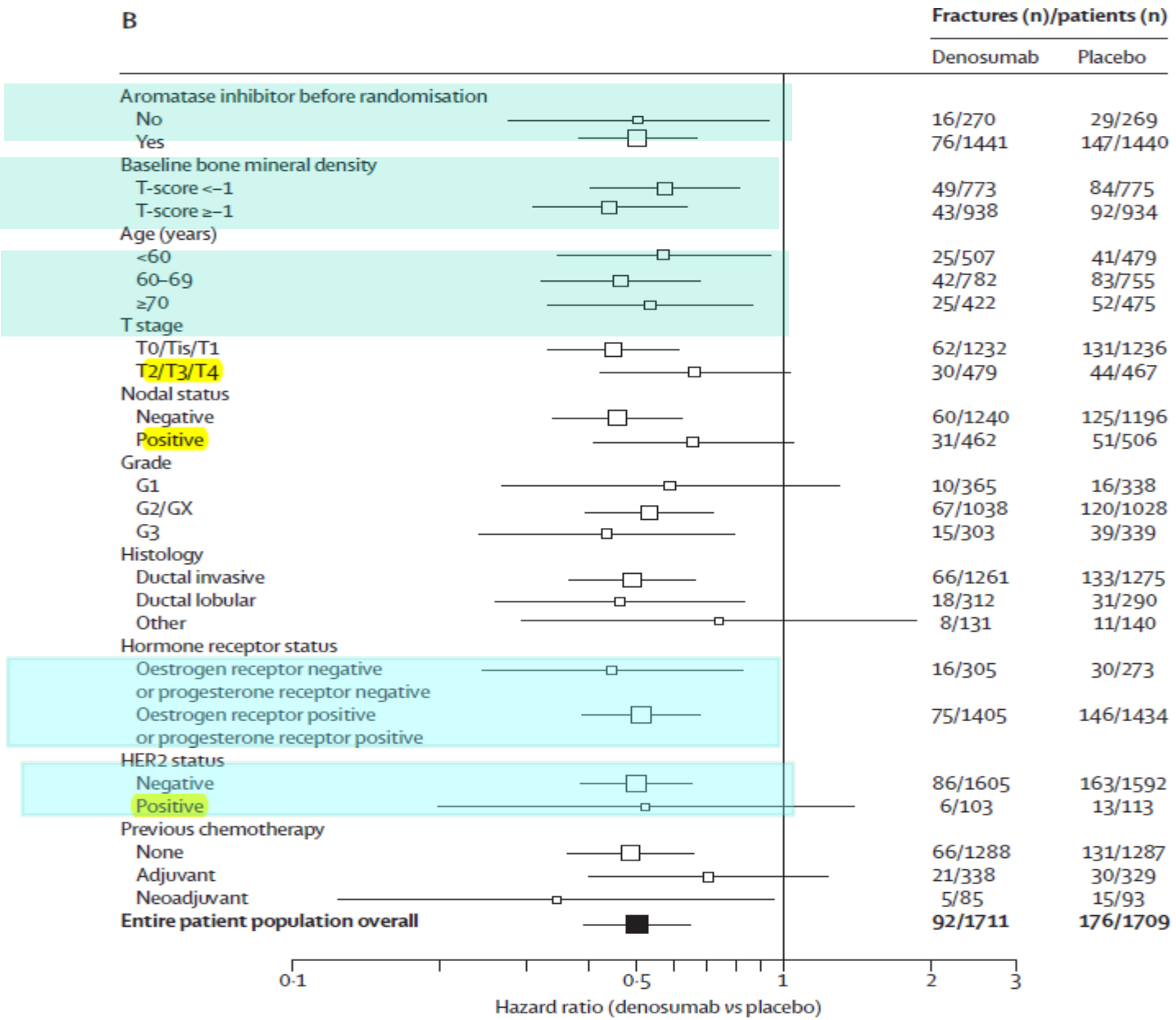
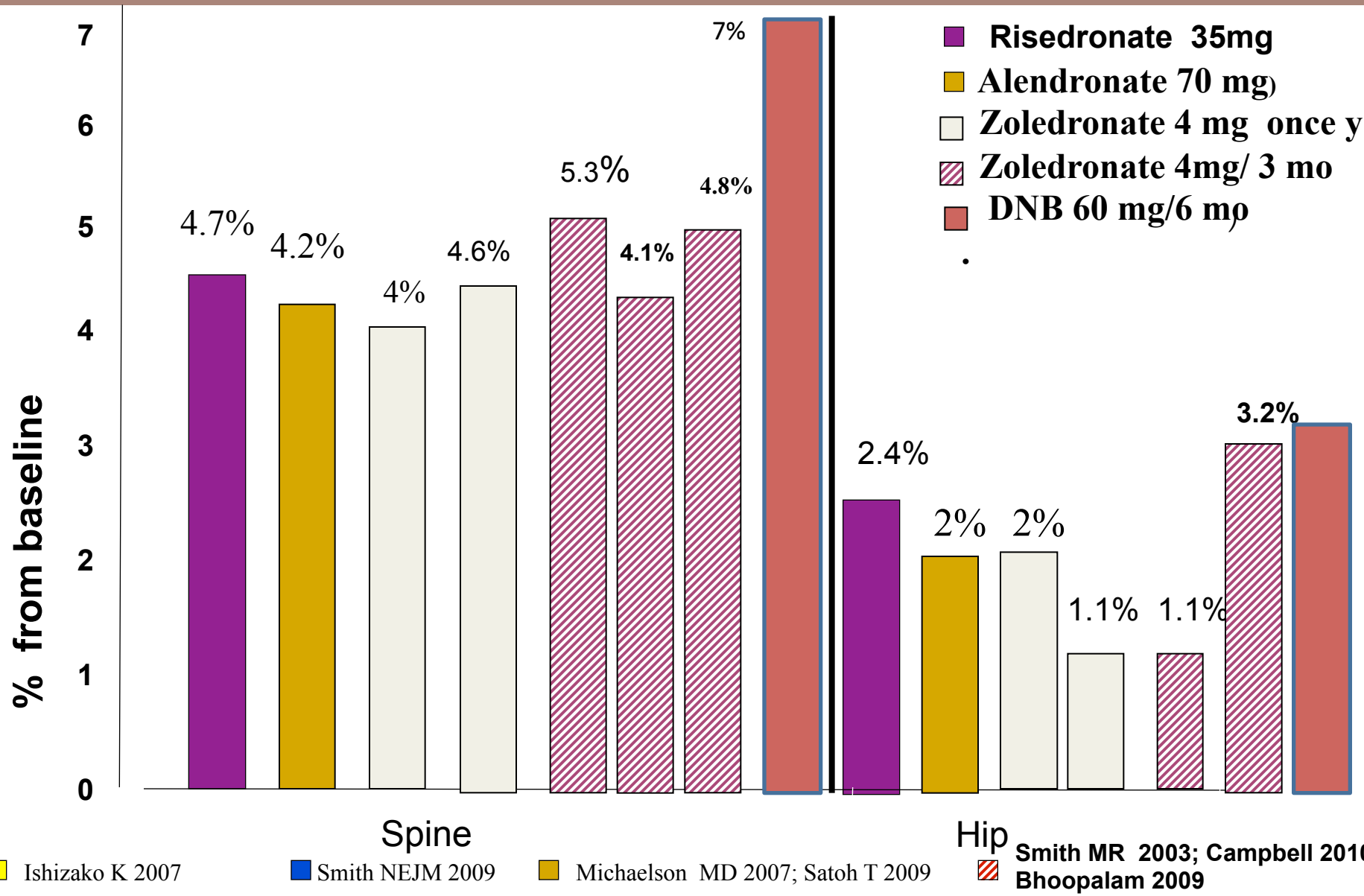


Gnant M et a lLancet 2015

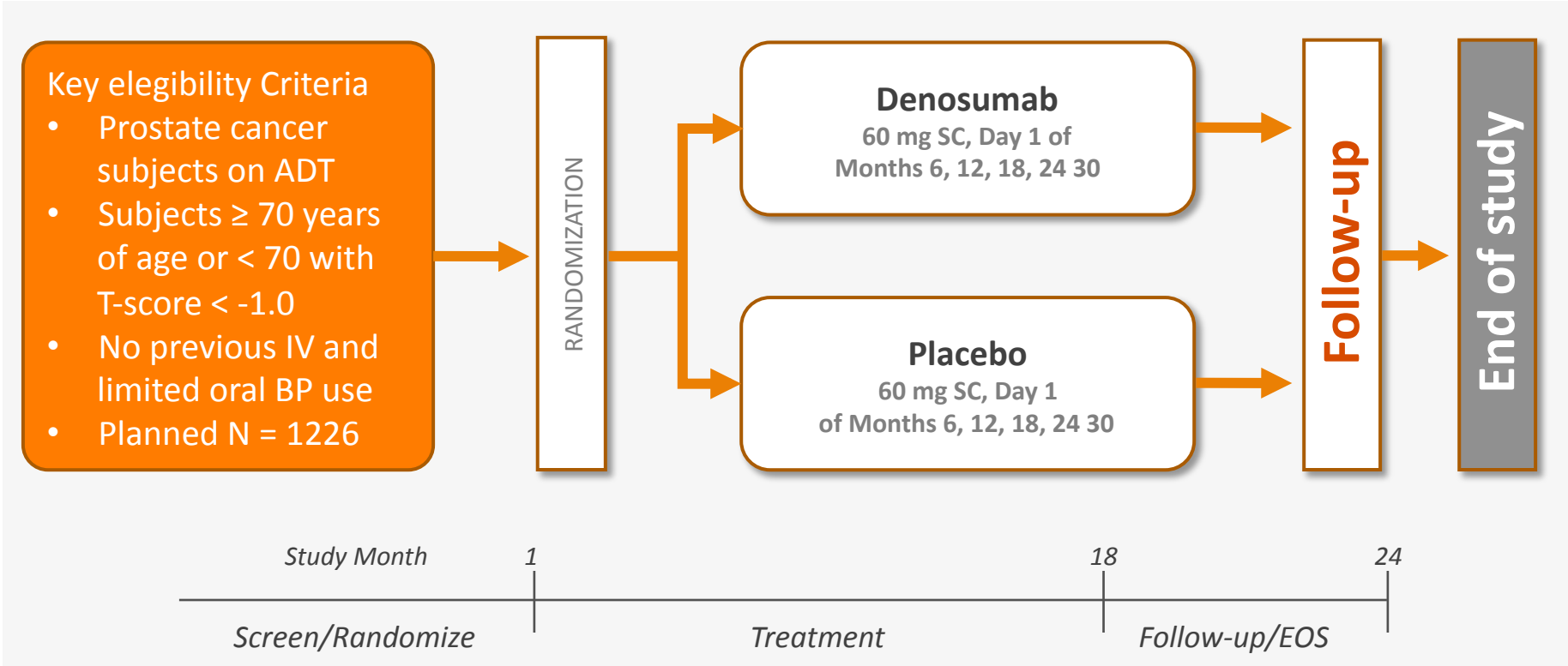
Bone target agents: effects on BMD in Men with ADT Induced Bone Loss

by Bertoldo



Prevention of Cancer Treatment Induced Bone Loss (CTIBL)

HALT-PC (20040138): Denosumab in ADT-Treated Prostate Cancer



Primary Endpoint: Percentage Change in Lumbar Spine BMD at Month 24

Secondary Objectives: Efficacy of denosumab compared with placebo on: Fractures and BMD at nonvertebral sites

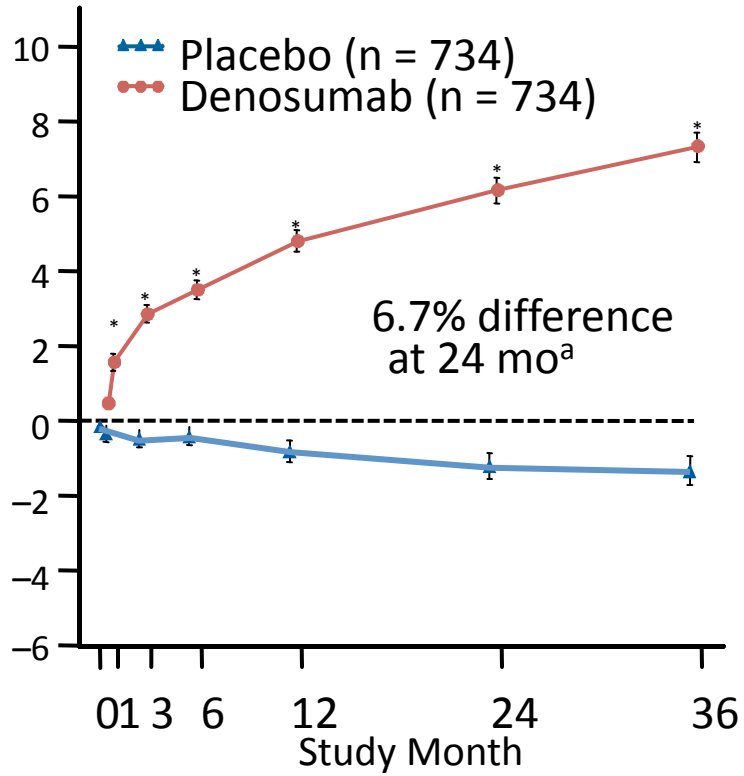
Smith M et al. N Engl J Med, 361:745-55, 2009.

Enrico Cortesi

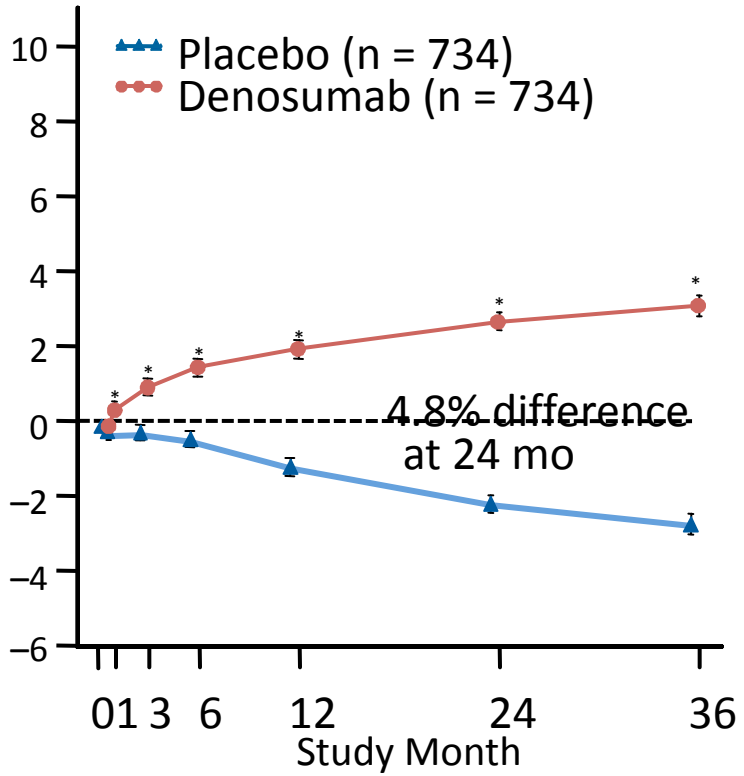
Prevention of Cancer Treatment Induced Bone Loss (CTIBL)

HALT-PC (20040138): Denosumab in ADT-Treated Prostate Cancer

Lumbar Spine



Total Hip

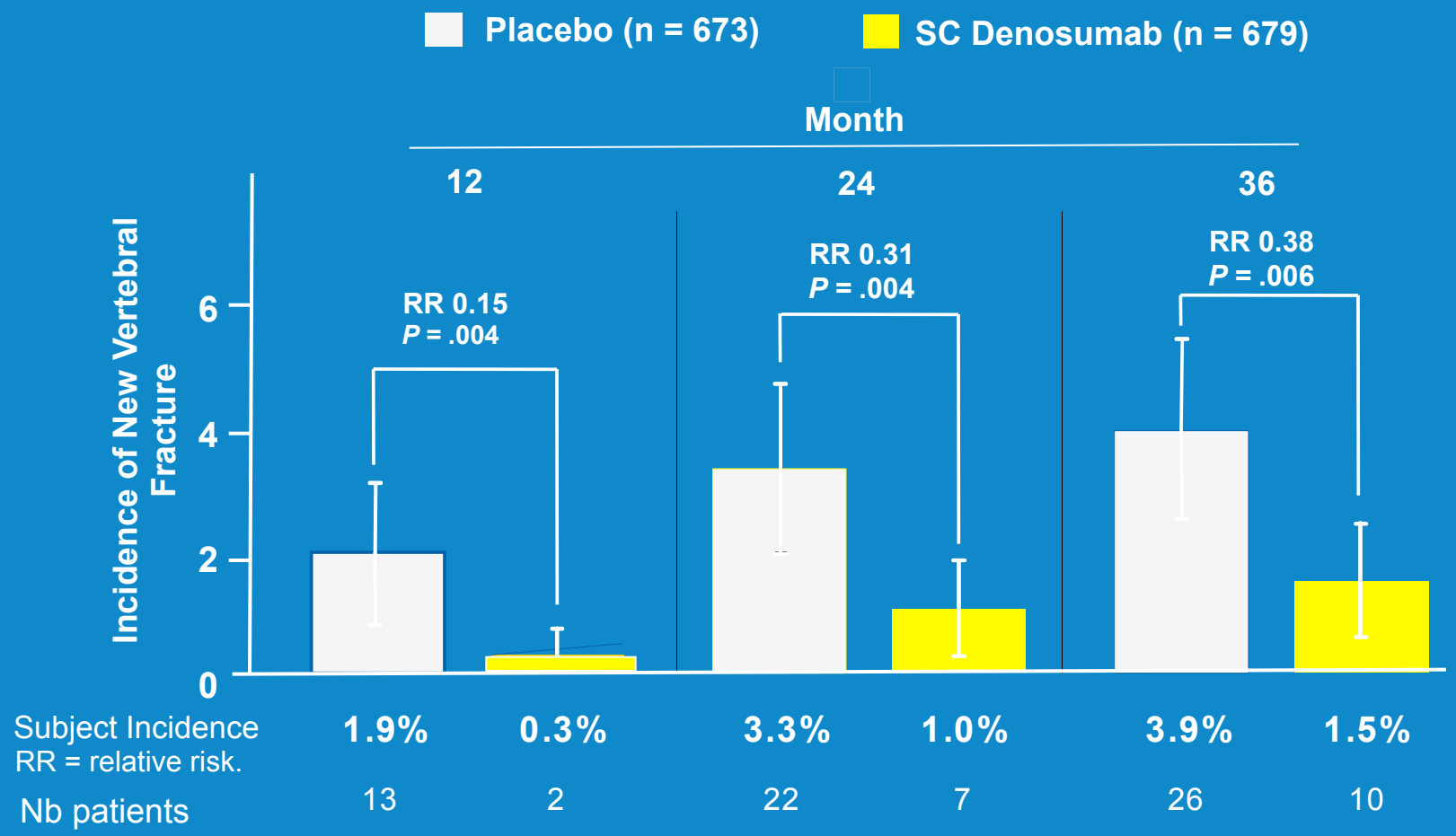


*$P \leq .001$ at all measured sites

[a]Primary end point

Smith MR, Egerdie B, Toriz NH, et al. *N Engl J Med.* 2009;361:745-755.

Denosumab reduces the Risk of New Vertebral Fractures



Smith MR, Egerdie B, Toriz NH, et al. *N Engl J Med.* 2009;361:745-755.

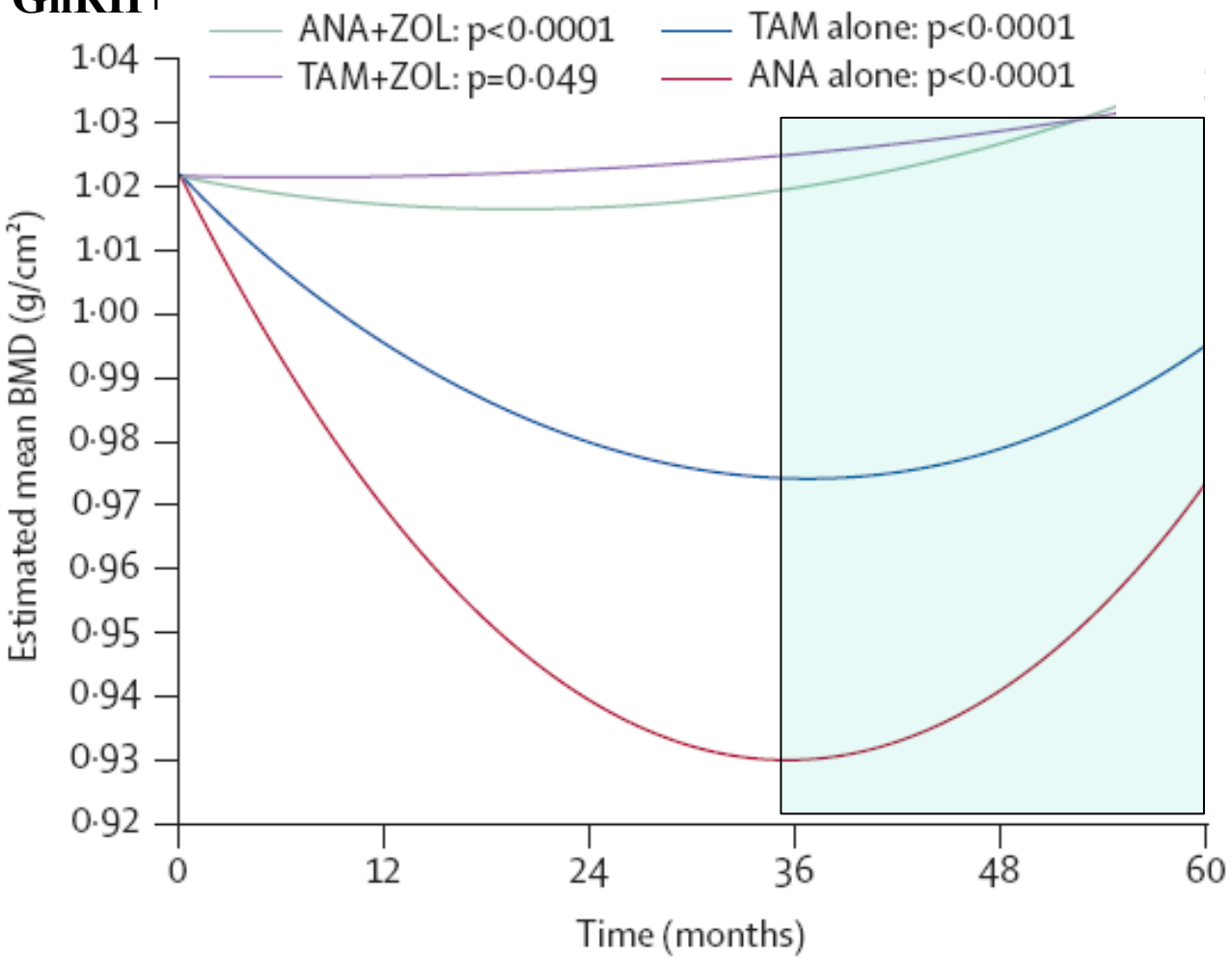
NUOVA NOTA 79 G.U. 20/5/15 n 115

- **Prevenzione primaria in donne in menopausa o uomini di età ≥ 50 anni a rischio elevato di frattura a causa di almeno una delle condizioni sottoelencate:**

Condizione	I scelta [a]	II scelta	III scelta
Trattamento in atto o previsto per > 3 mesi con prednisone equivalente ≥ 5 mg/die	Alendronato (± vitD), Risedronato, Zoledronato [d],	denosumab	----------
Trattamento in corso di blocco ormonale adiuvante in donne con carcinoma mammario o uomini con carcinoma prostatico	Alendronato (± vitD), Risedronato, Zoledronato [d], Denosumab [e]	----------	----------
T-score colonna o femore [c] ≤ -4	Alendronato (± vit.D), Risedronato,	Denosumab [e], Zoledronato [d], Ibandronato Raloxifene, Bazedoxifene	Stronzio ranelato [f]
T-score colonna o femore [c] ≤ -3 + almeno una delle seguenti condizioni: 1) Familiarità per fratture di vertebre o femore 2) Comorbilità a rischio di frattura (artrite reumatoide o altre connettiviti, diabete, broncopneumopatia cronica			

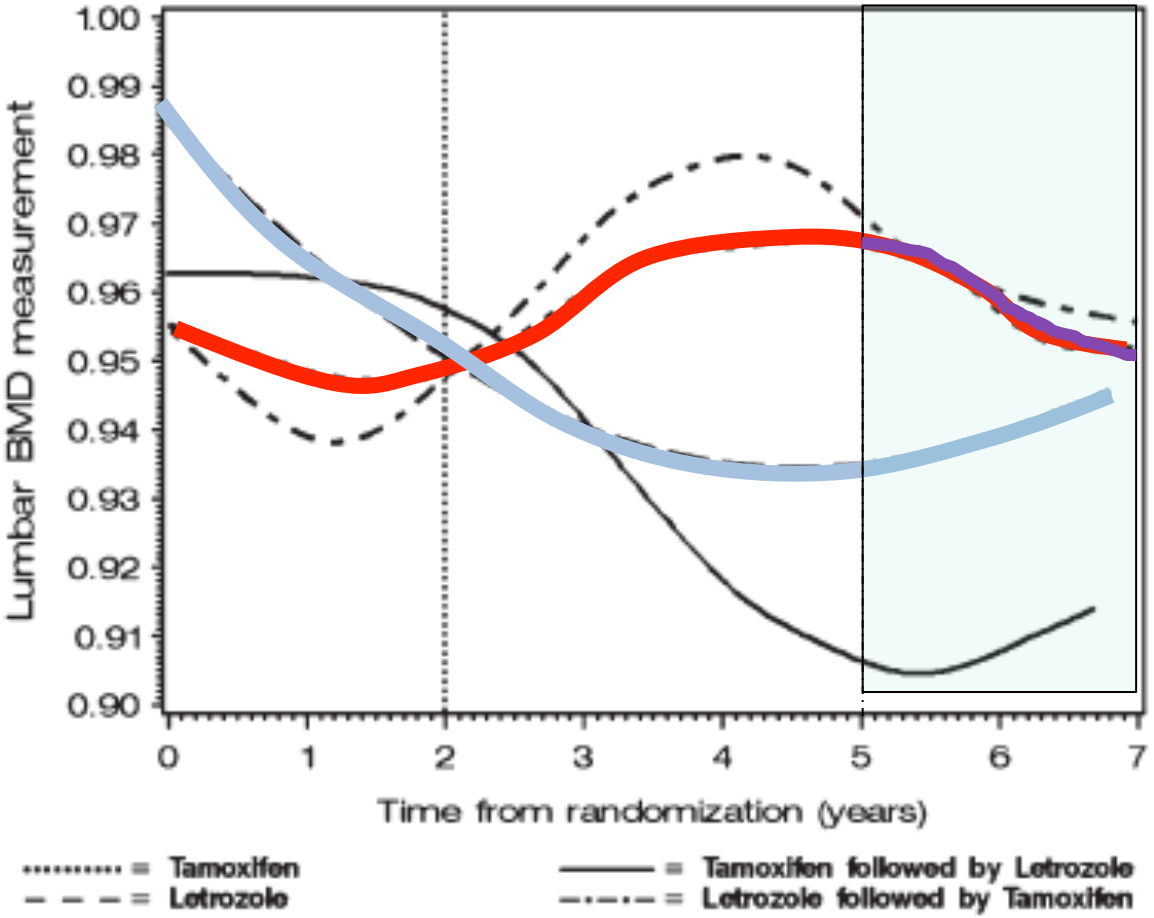
Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy

GnRH+



Gnant M *Lancet Oncol 2008*

Bone mineral density in breast cancer patients treated with adjuvant letrozole, tamoxifen, or sequences of letrozole and tamoxifen in the BIG 1-98 study (SAKK 21/07)

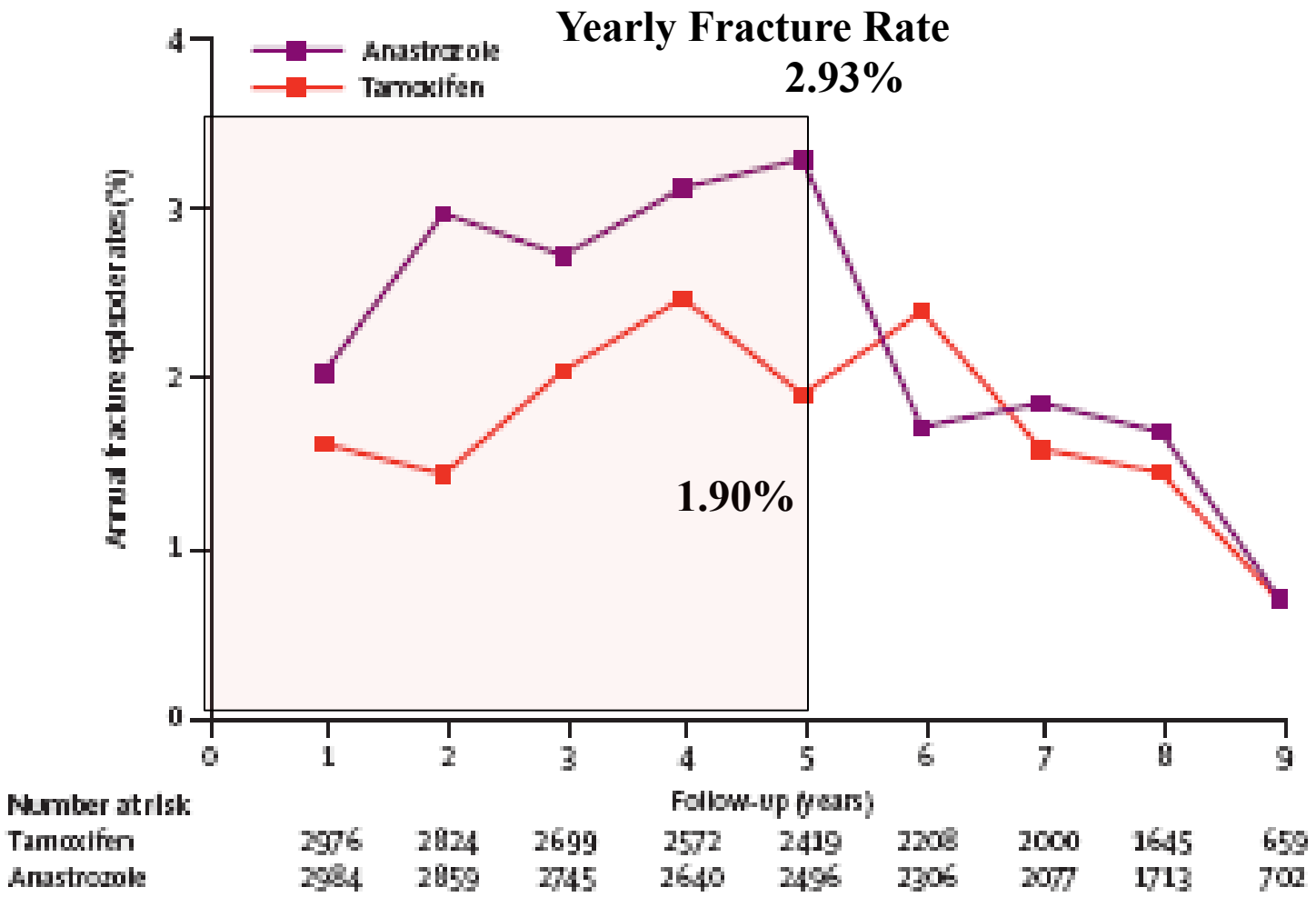


TAM

LETROZOLE

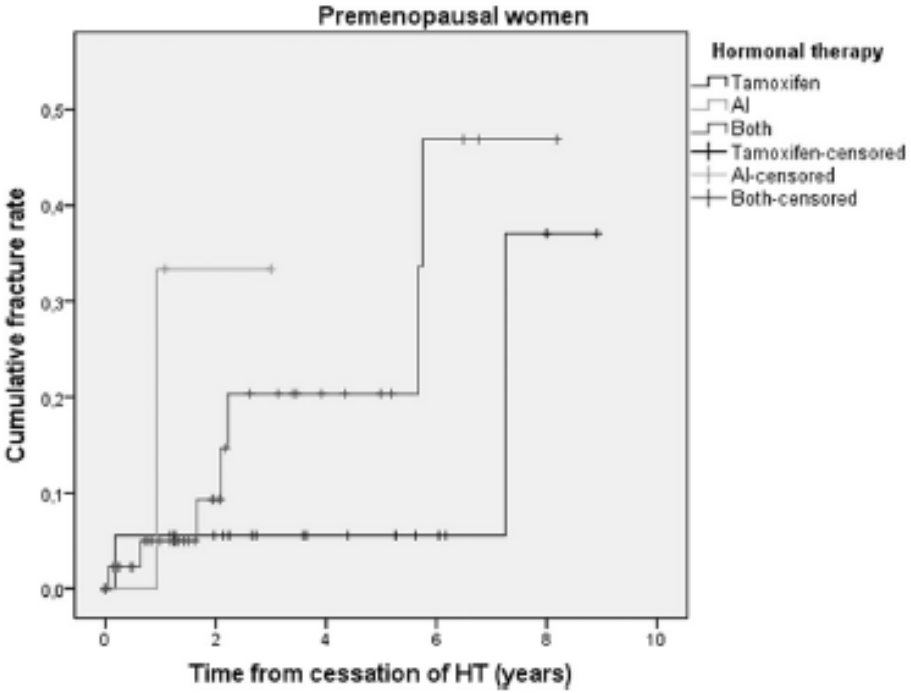
Zaman K et al. Annals of Oncology 23: 1474–1481, 2012

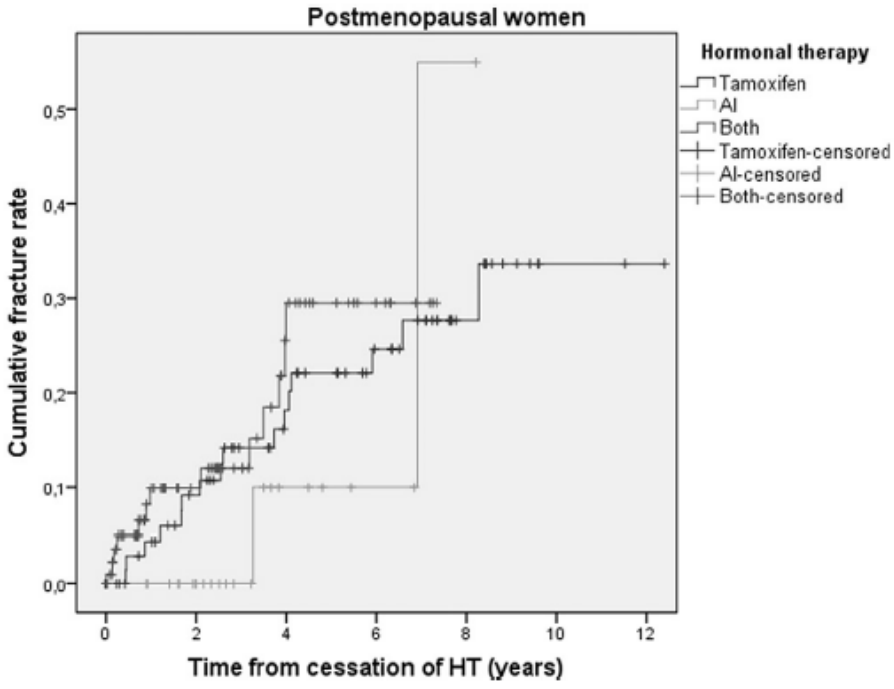
10 yrs Analysis of the ATAC Trial



Lancet Oncol 2008

Fracture incidence in pre- and postmenopausal women after completion of adjuvant hormonal therapy for breast cancer





Mean Fracture Rate: 12%
Mean Time to First Fx: 1.3 y

Koopal C et al .*The Breast 2015*

review

Annals of Oncology 00: 1–12, 2016
doi:10.1093/annonc/mdv617

Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel

P. Hadji[1,†], R. E. Coleman[2*,†], C. Wilson[2], T. J. Powles[3], P. Clézardin[4], M. Aapro[5], L. Costa[6], J.-J. Body[7], C. Markopoulos[8], D. Santini[9], I. Diel[10], A. Di Leo[11], D. Cameron[12], D. Dodwell[13], I. Smith[14], M. Gnant[15], R. Gray[16], N. Harbeck[17], B. Thurlimann[18], M. Untch[19], J. Cortes[20], M. Martin[21], U.-S. Albert[1], P.-F. Conte[22], B. Ejlertsen[23,24], J. Bergh[25], M. Kaufmann[26] & I. Holen[2]

Ann Oncol. 2016 Mar;27(3):379-90.

Prevention of metastases and improving disease outcomes

Premenopausal women on adjuvant ovarian suppression

- BPs should be considered to prevent CTIBL and metastases (I,A)
- Recommended BP is zoledronic acid (4 mg IV Q6 months) or clodronate (1600 mg PO daily) (I,A)
- BPs should be initiated at the start of adjuvant therapy (II,A)
- Duration of BP treatment should not exceed duration of ovarian suppression unless indicated for low T score (3–5 years) (II,A)

Postmenopausal women at intermediate or high risk of recurrence

- BPs should be considered to prevent metastases irrespective of fracture risk (I,A)
- Recommended BPs are zoledronic acid (4 mg IV Q6 months) or clodronate (1600 mg PO daily) (I,A) alongside vitamin D supplementation and adequate calcium intake
- BPs should be initiated at the start of adjuvant therapy (II,A)
- Duration of BP treatment should be 3–5 years and only continued after 5 years if indicated by fracture risk (II,A)

Clinical Features of 24 Patients With Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: Systematic Review and Additional Cases

Athanasios D Anastasilakis,[1] Stergios A Polyzos,[2] Polyzois Makras,[3] Berengere Aubry-Rozier,[4] Stella Kaouri,[5] and Olivier Lamy[4]

Journal of Bone and Mineral Research, Vol. 32, No. 6, June 2017, pp 1291–1296

Reference	Age (years) at VFxs	Time on Dmab (Yrs)	Last injection to VFx (months)	No. of VFxs	Site of VFxs	Prevalent VFxs	Prevalent non-VFxs	*T*-score_LS at Dmab initiation	*T*-score_LS at Dmab stop	Reason for Dmab discontinuation	Post VFxs management	Comments
Popp, Osteoporos Int 2016[6]	53	3	9	7	T8, T10, T12, L1–4	0	0	−2.0	−0.8	End of AI and normalization of BMD	NR	Breast cancer under AI
Polyzos, Endocrine 2016[7]	62	2	14	1	L3	T8	0	−2.8	−0.2	Normalization of BMD	Calcium/vitamin D–intention for TPTD	Secondary hyperparathyroidism
Polyzos, Endocrine 2016[7]	61	1	12	2	T12, L1	0	0	NR	NR	Became osteopenic	Dmab	Pretreated 1year with SR and 5 years with raloxifene
Anastasilakis, Osteoporos Int 2016[4]	55	3	8	3	T12, L1, L3	0	0	−2.5	−1.8	Became osteopenic	TPTD	—
Lamy, JCEM 2016[8]and Aybrie-Rozier, Osteoporos Int 2016[5]	55	2.5	9	5	T11, T12, L2–L4	0	0	−3.1	−2.3	Became osteopenic	TPTD	—
Lamy, JCEM 2016[8]	56	4	10	9 (7 + 2)	T7, T8, T10–12, L1, L2, L4, L5	0	0	−2.8	−2.2	Tx duration	Vertebroplasty – Dmab + TPTD	—
Lamy, JCEM 2016[8] and Aybrie-Rozier, Osteoporos Int 2016[5]	59	3.5	10	2	T11, T12	0	0	−3.1	−2.4	Became osteopenic	TPTD	Rheumatoid arthritis/never on glucocorticoids
Lamy, JCEM 2016[8]	58	1	11	8	T8–T11, L1, L3–L5 (T11 and L1: deterioration)	T11, L1	0	−3.9	−3.5	Patient's wish	TPTD	—
Lamy, JCEM 2016[8]	63	1	12	1	T10	0	0	−1.7	NR	Tx omission	Dmab	Breast cancer under AI
Lamy, JCEM 2016[8]	65	4	10	6	T5, T8, T12, L2–L4 (T12: deterioration)	T12	0	−3	−2.3	Tx duration	Dmab + TPTD	—
Lamy, JCEM 2016[8]	73	1	11	5	T12, L2–L5	L1	Hip	−4.5	−3.1	Patient's wish	No Rx	Bisphosphonate for 3 years, 11 years before Dmab initiation
Lamy, JCEM 2016[8]0	81	3	16	5 (3 + 2)	T9, T12, L1–L3	0	0	−3.9	−3.1	End of AI	Vertebroplasty – ZOL	Breast cancer under AI
Lamy, JCEM 2016[8] and Aybrie-Rozier, Osteoporos Int 2016[5]	80	2.5	16	9 (3 + 6)	T5–9, T11–L2	0	0	−4.1	−3.7	Patient's wish	Vertebroplasty – No Rx	—
New case	60	3.5	12	7	T5, T11, L1–L5	T7, T10, T12	0	−2.3	−2.1	Dental Tx	Dmab + TPTD	Glucocorticoids (inflammatory disease). Breast cancer under AI
New case	65	5	11	5	T8, T11–L2	0	0	−3.4	−2.6	Tx duration	ZOL + TPTD	
New case	62	5	11	5 (4 + 1)	T10–L2	0	0	−4.1	−2.8	Tx omission	Vertebroplasty – Dmab + TPTD	ALN before Dmab (short time, adverse effect)
New case	48	4.5	10	5	T4, T8, T9, T12, L2	0	0	−1.9	−1.3	End of AI and normalization of BMD	Dmab	Breast cancer under AI
New case	83	3	10	2	T12, L3	0	0	–	–	Patient's negligence	TPTD	Pretreated 1 year with TPTD
New case	82	2	16	2	T11, L1	L3, L5	0	−2.6	−2.0	Became osteopenic	TPTD	—

continued

Vertebral Fractures Following Discontinuation of Denosumab: a Post-hoc Analysis of the Randomized Placebo-controlled FREEDOM Trial and its Extension.

The vertebral fracture rate increased from 1.2 per 100 participant-years during the on-treatment period to 7.1

The vertebral fracture rate increased upon denosumab discontinuation to the level observed in untreated participants

A majority of participants who sustained a vertebral fracture after discontinuing denosumab had multiple vertebral fractures

The odds (95% CI) of developing multiple vertebral fractures after stopping denosumab were 3.9 (2.1-7. 2) times higher in those with prior vertebral fractures, sustained before or during treatment, than those without

Cummings SR et al. J Bone Min Res 2017 Nov 4 doi : 10.1002/jbmr.3337

Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS.

Patients considered at high fracture risk should either continue denosumab therapy for up to 10 years or be switched to an alternative treatment.

For patients at low risk, a decision to discontinue denosumab could be made after 5 years, but bisphosphonate therapy should be considered to reduce or prevent the rebound increase in bone turnover.

Optimal bisphosphonate regimen post-denosumab is currently unknown. Continuation of denosumab can also be considered until results from ongoing trials become available.

Bone. 2017 Dec;105:11-17. doi: 10.1016/j.bone.2017.08.003.

DENOSUMAB IN CTIBL: Personal opinion NO EBM

A..GENERAL RULES:

Always re-assess fracture risk at the end of the hormonal Adj therapy

Ensure that it is discontinued before suspending BPs or DNB.

B.

Patient with NO FRACTURE RISK BEFORE Hornonal Adjuvant therapy (Primary Prevention).

At discontinuation of AI, the DNB could be discontinued without the need for other treatment. **GUARANTEE FOLLOW UP !**

C.**Patient who has already osteoporosis (low BMD and / or fractures) before starting DNB**

Or

Patients who develops a new fracture or at high risk factor during DNB

At discontinution of AI, treatment should continue (with DNB or others Antiresorptive Ag)