Rischio fratturativo nella terapia con deprivazione ormonale

A F Scinto

Oncologia

ASL Roma 4

Introduzione

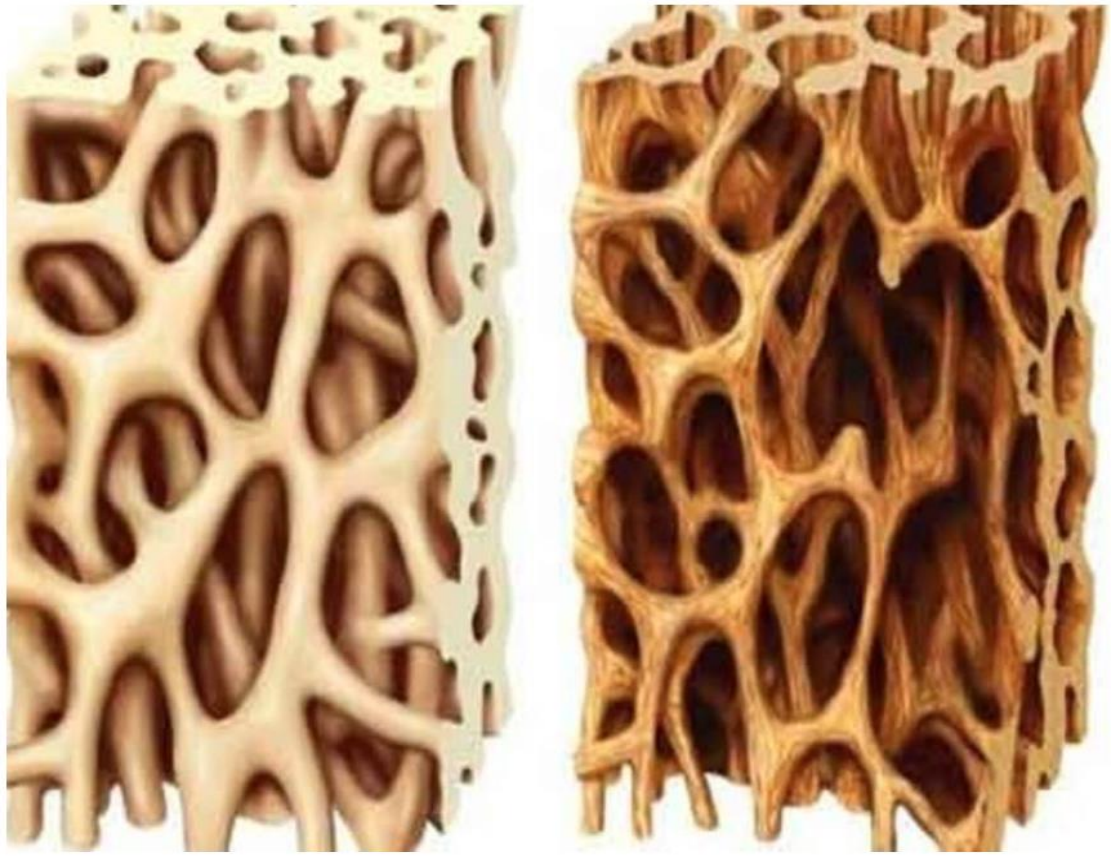
I trattamenti ormonali adiuvanti (IA, Tam, LH-RH – Gn-LH e/o A) inducono ipoestrogenismo

=>

un’accelerazione della perdita di massa ossea e aumentato rischio di fratture ossee

definizione

L'osteoporosi è una malattia sistemica dello scheletro caratterizzata da una ***ridotta massa ossea*** e da ***alterazioni qualitative*** (macro e microarchitettura, proprietà materiali) che si accompagnano ad aumento del rischio di frattura.



IA e perdita ossea

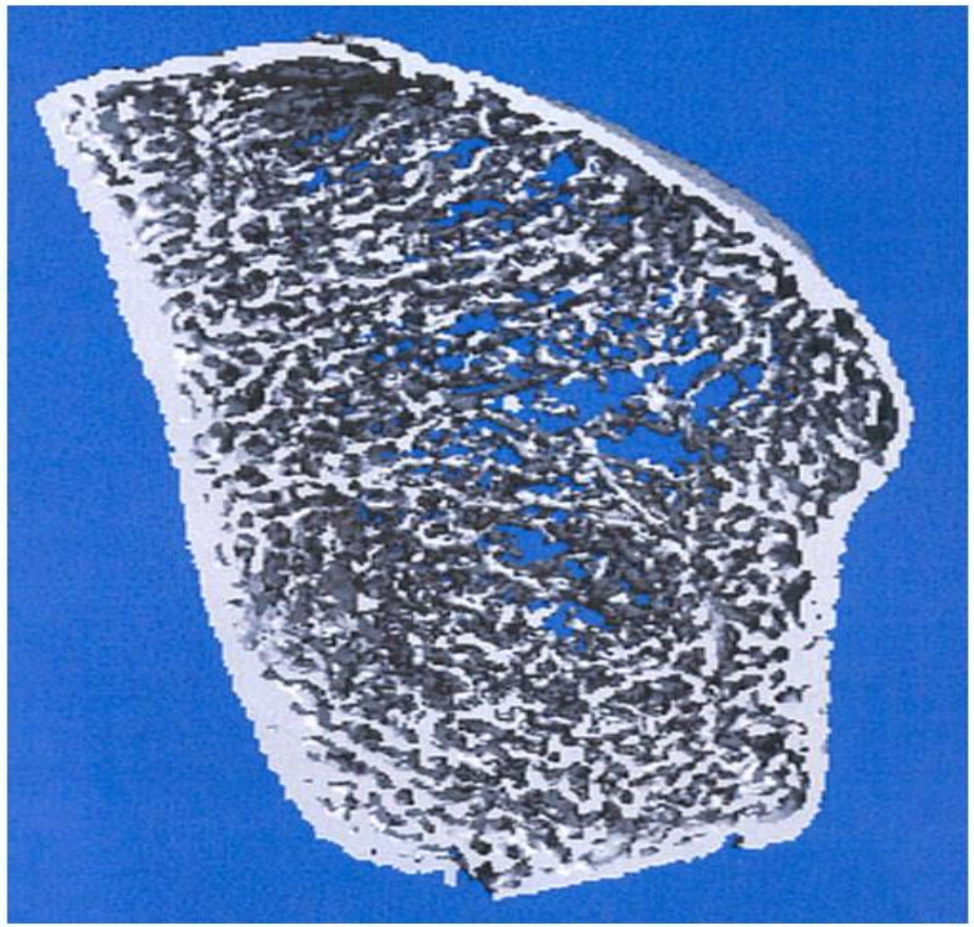
Nelle pazienti in trattamento con IA si ha perdita ossea doppia vs fisiologica

1-2 aa	-3%
3-4-5 aa	-1%

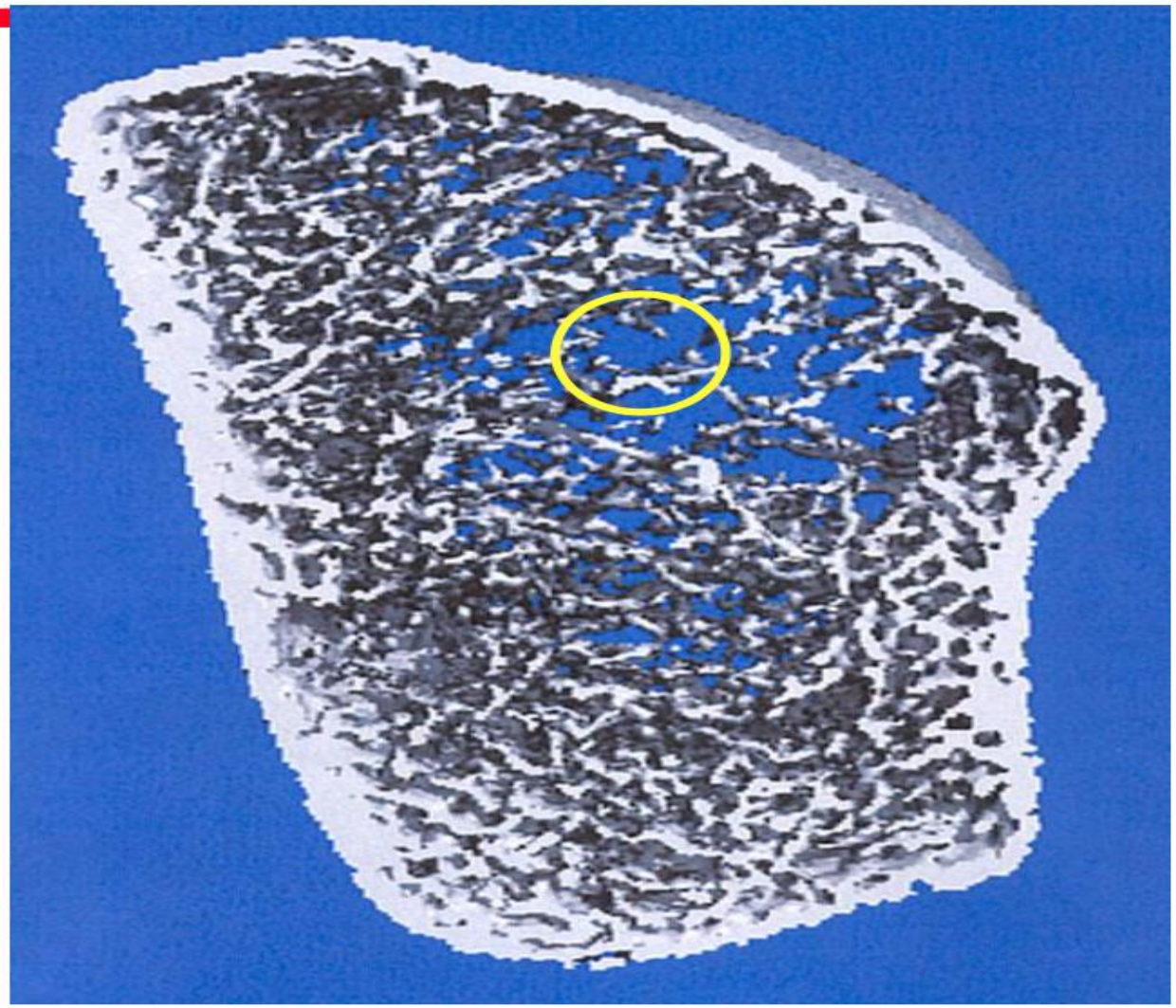
Dopo 5 aa di IA circa il 30% svilupperà osteoporosi

Nelle pazienti con IA incremento del 33-43% rischio di frattura osteoporotica vs Tam e questo incremento permane per tutta la durata di IA

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

RISCHIO FRATTURATIVO NEI PAZIENTI IN BLOCCO ANDROGENICO

- Blocco ormonale marcata soppressione dei livelli circolanti di testosterone (circa 80 %) ma soprattutto marcato ipoestrogenismo tissutale (fino al 90 %)

- Perdita massa ossea: 3-7 % / anno a livello della colonna (4 volte rispetto alla menopausa e doppia da quella indotta da inibitori delle aromatasi)

- Rischio di frattura 4 x rispetto a soggetti sani (almeno un anno di terapia)

ADT e rischio fratturativo

Il rischio fratturativo correla con:

Età del paziente
Durata ADT
Stadio tumorale

Shahinian VB et al. NEJM 2005

Perdita ossea e rischio frattura in CTBIL

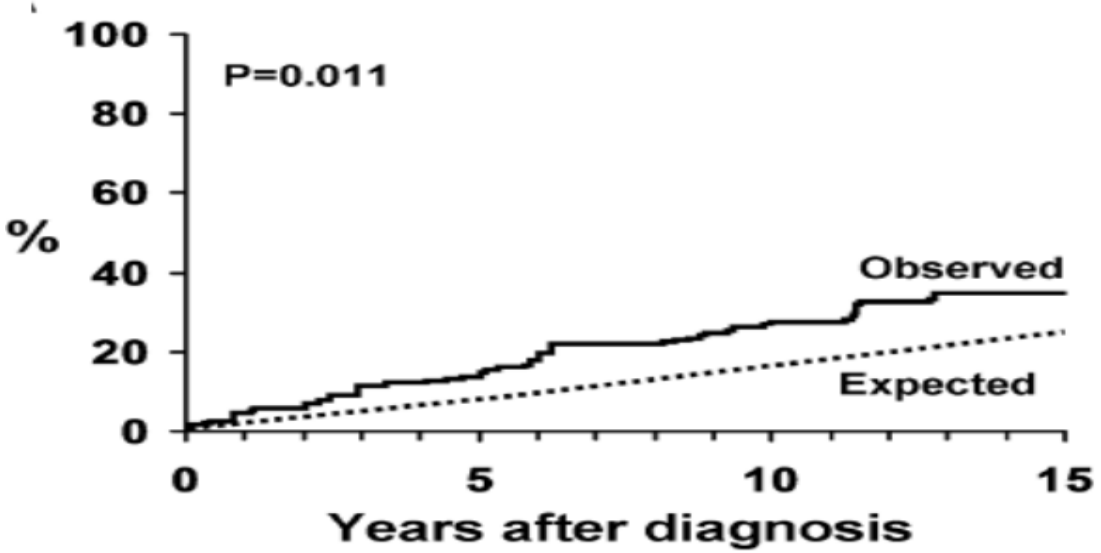
Effetto precoce e rapido – già nel 1° anno terapia

Paragonabile a osteoporosi indotta da steroidi

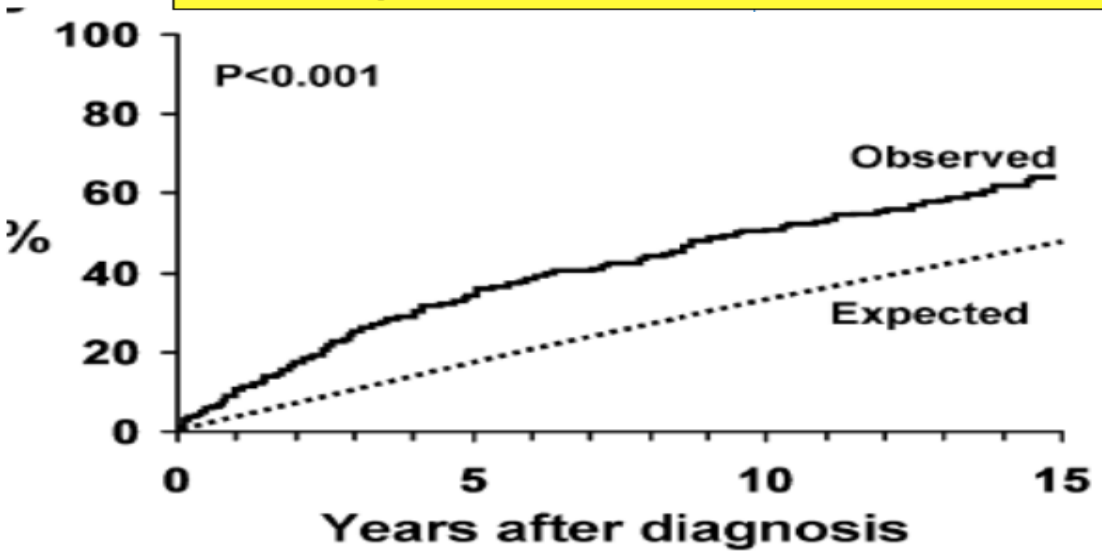
Il rischio di frattura è indipendente dai valori di BMD

Expected Cumulative Incidence of Fractures in Breast Cancer Patients

Il **rischio di frattura vertebrale** a 3 anni in donne con carcinoma mammella è **5 volte superiore** rispetto a donne controllo



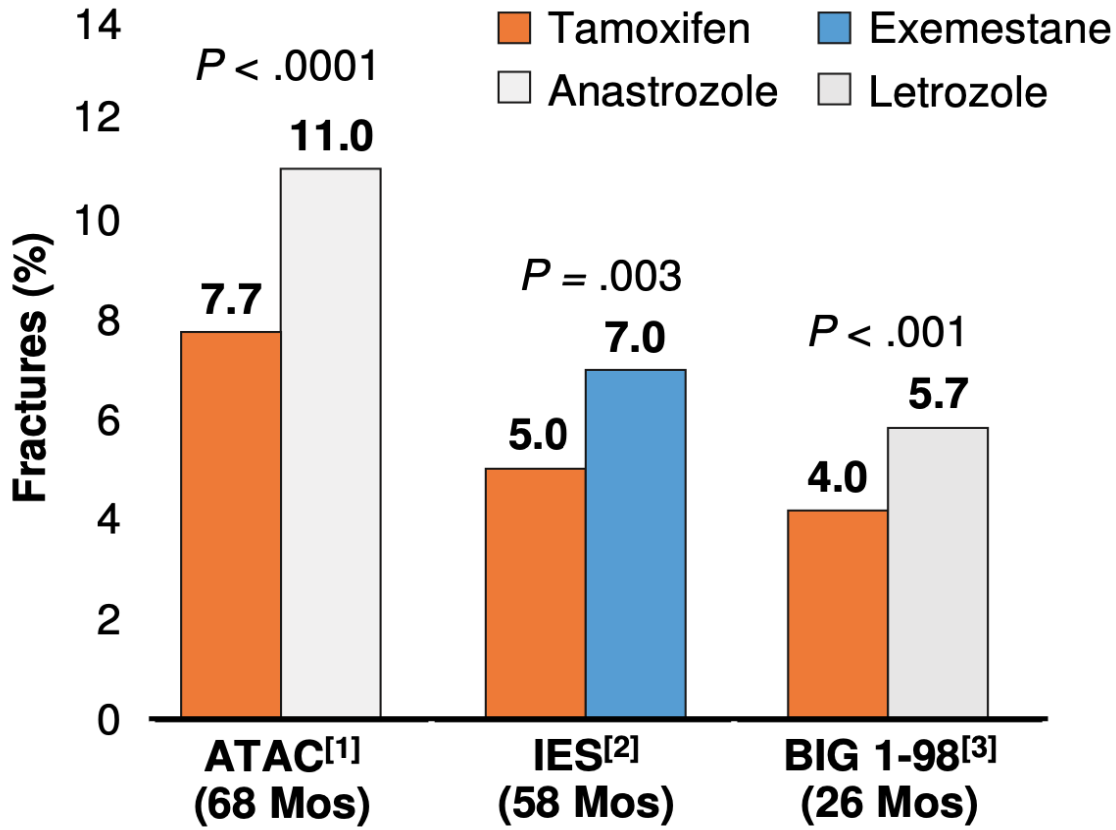
Premenopausal at diagnosis (CIOF)



Postmenopausal at diagnosis

Melton III LJ J Bone Min Res 2012

Prevalenza % di fratture durante terapia adiuvante in donne con ca mammella



1. Howell A, et al. Lancet. 2005;365:60-62. 2. Coleman RE, et al. Lancet Oncol. 2007;8:119-127.
3. Thürlimann B, et al. N Engl J Med. 2005;353:2747-2757.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk of Fracture after Androgen Deprivation for Prostate Cancer

Vahakn B. Shahinian, M.D., Yong-Fang Kuo, Ph.D., Jean L. Freeman, Ph.D., and James S. Goodwin, M.D.

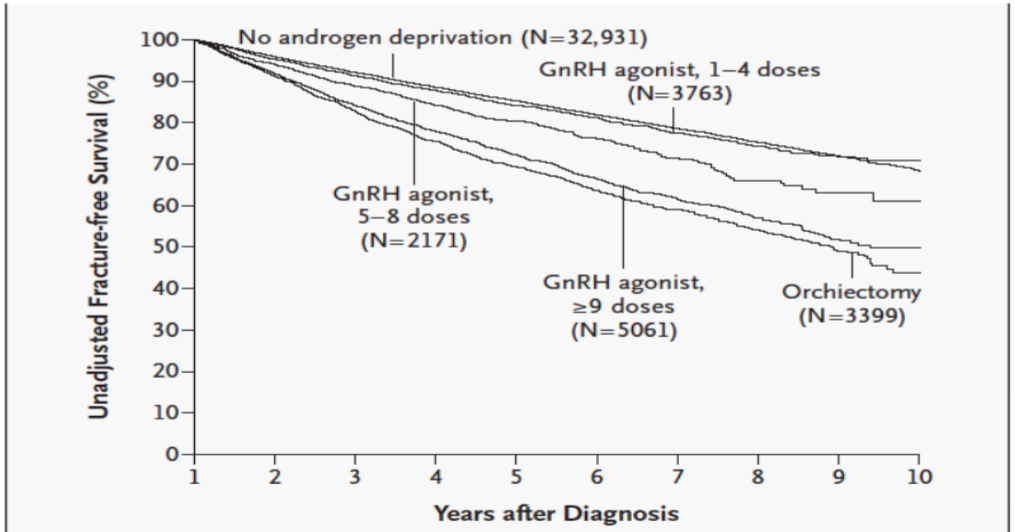


Figure 1. Unadjusted Fracture-free Survival among Patients with Prostate Cancer, According to Androgen-Deprivation Therapy.

The survival curves start at 12 months after diagnosis, and androgen deprivation was initiated within 6 months after diagnosis. GnRH denotes gonadotropin-releasing hormone. The number of doses is the number administered within 12 months after diagnosis.

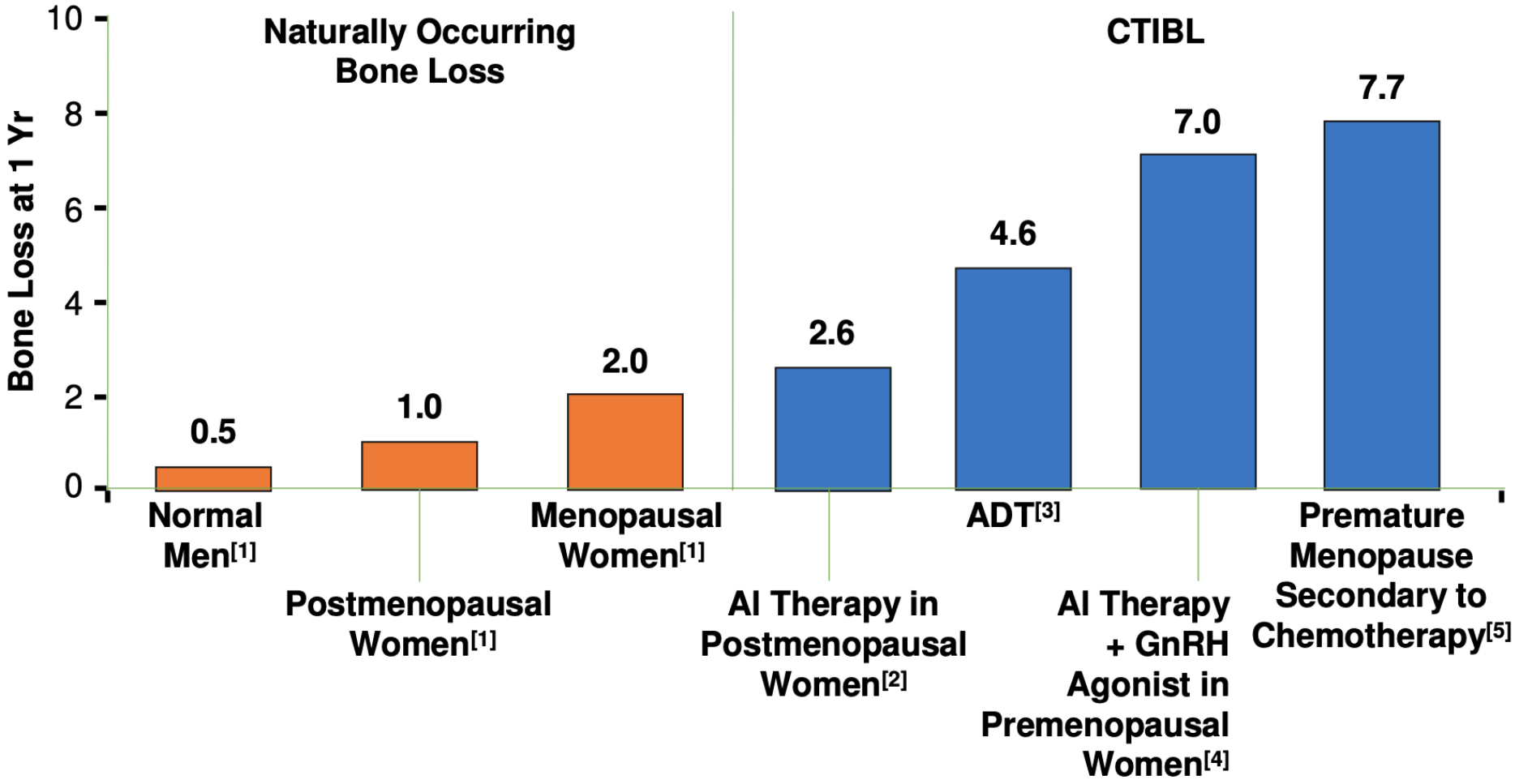
In conclusion, our study shows that androgen deprivation in the form of orchiectomy or treatment with gonadotropin-releasing hormone agonists is associated with an increased risk of fracture in patients with prostate cancer. This finding under-

N Engl J Med 2005;352:154-64.

Cancer Treatment–Induced Bone Loss

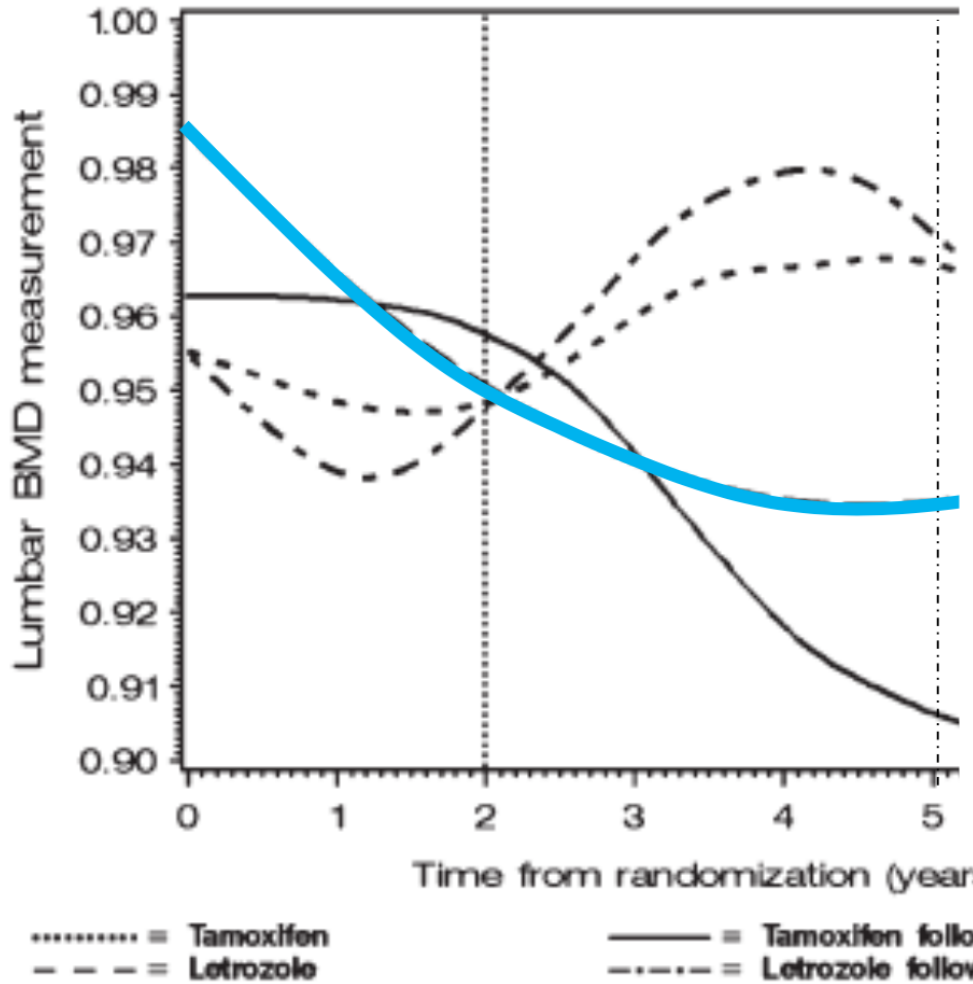
- **Rapid and severe bone loss** resulting from cancer therapies that lead to estrogen or androgen deprivation
- Various **cancer therapies decrease BMD and increase fracture risk**
  - **Androgen-deprivation therapy**
  - **Estrogen-deprivation therapy**
  - Chemotherapy
  - Surgical (castration)
- CTIBL has significant clinical, social, and economic consequences
- Related **fractures are associated** with **decreased quality of life** and **shorter survival**

Bone Loss With Cancer Therapies



1. Kanis JA. Osteoporosis. 1997:22-55. 2. Eastell R, et al. J Bone Mineral Res. 2002. 3. Maillefert JF, et al. J Urol. 1999;161:1219-1222. 4. Gnant M, et al. Lancet Oncol. 2008;9:840-849. 5. Shapiro CL, et al. J Clin Oncol. 2001;19:3306-3311.

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)

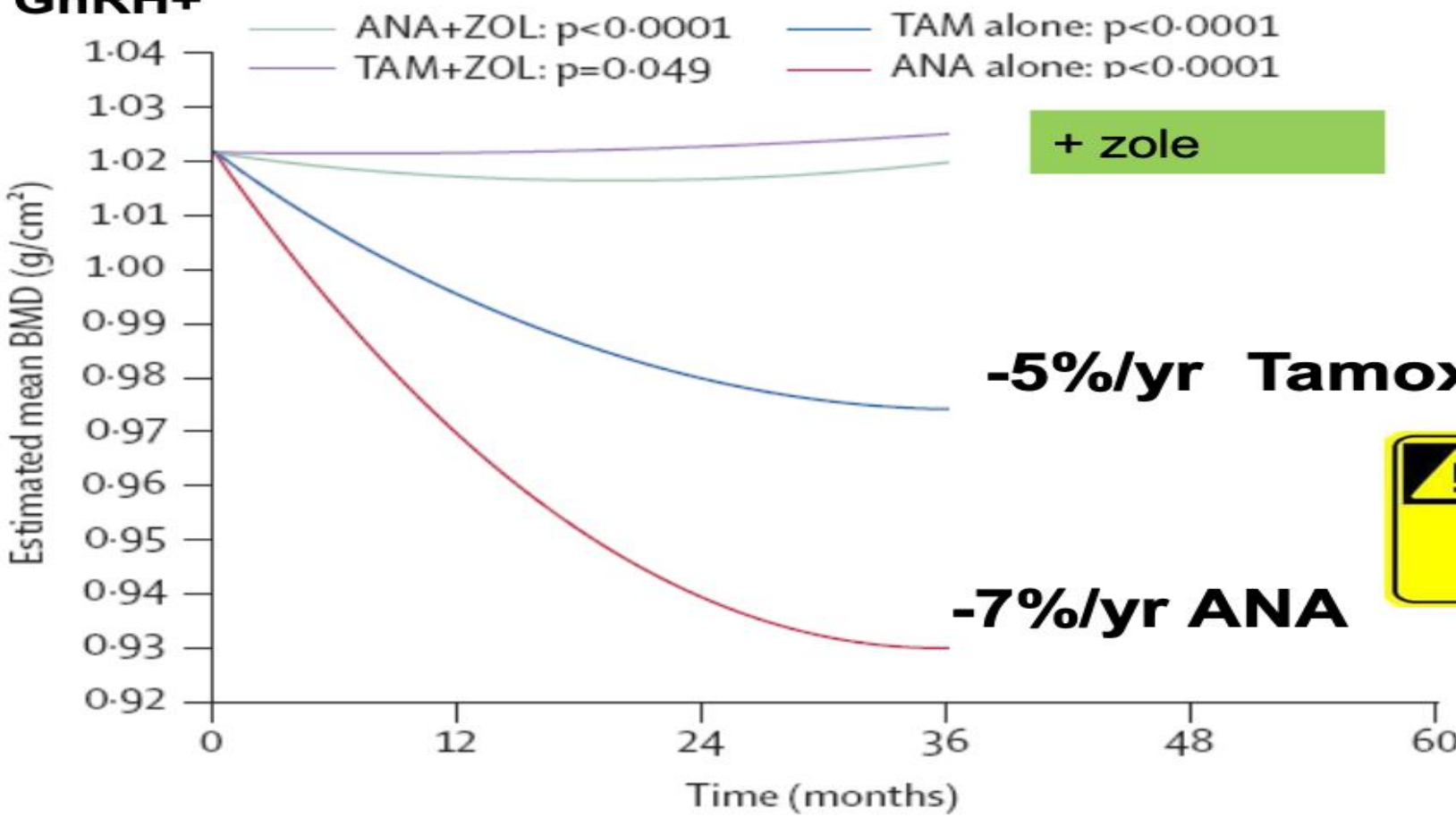


LETROZOLE

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

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+



+ zole

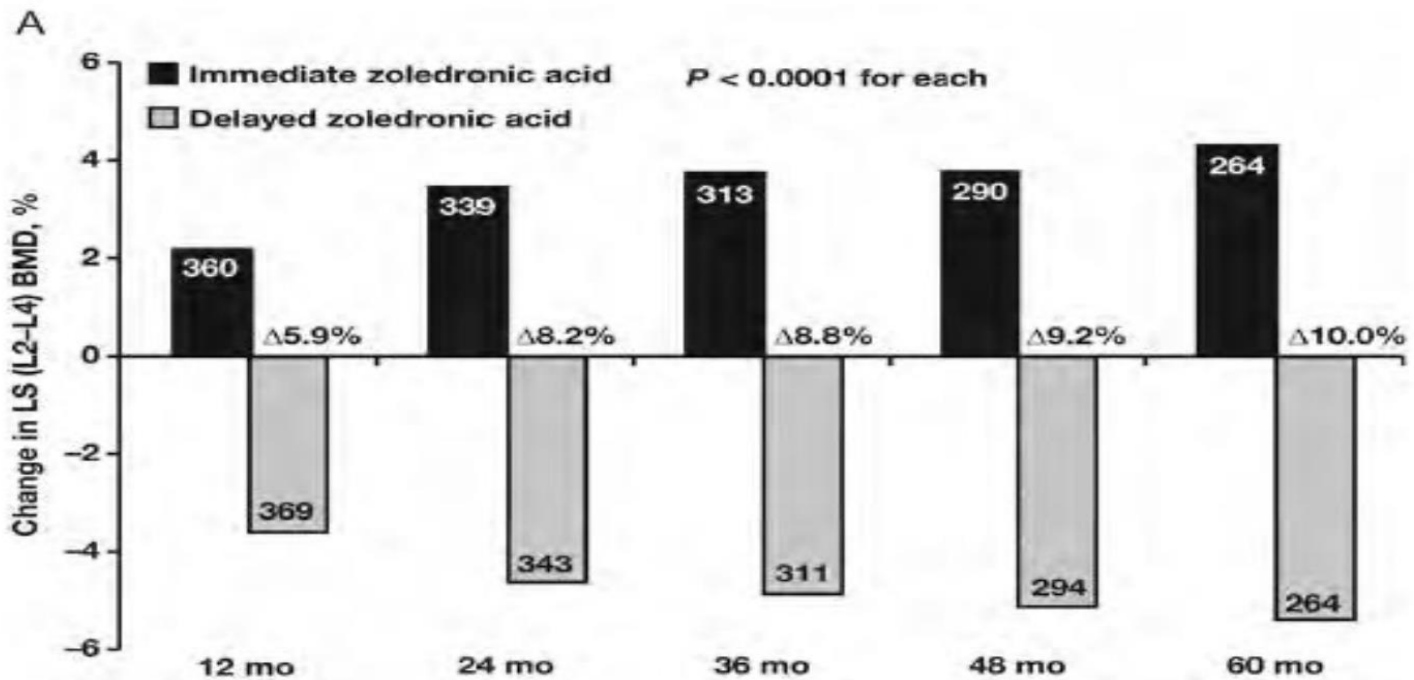
-5%/yr Tamoxifene

-7%/yr ANA

Gnant M *Lancet Oncol 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
DELAYED: initiated for >3% BMD reduction, Fracture, BMD -2.5 T score

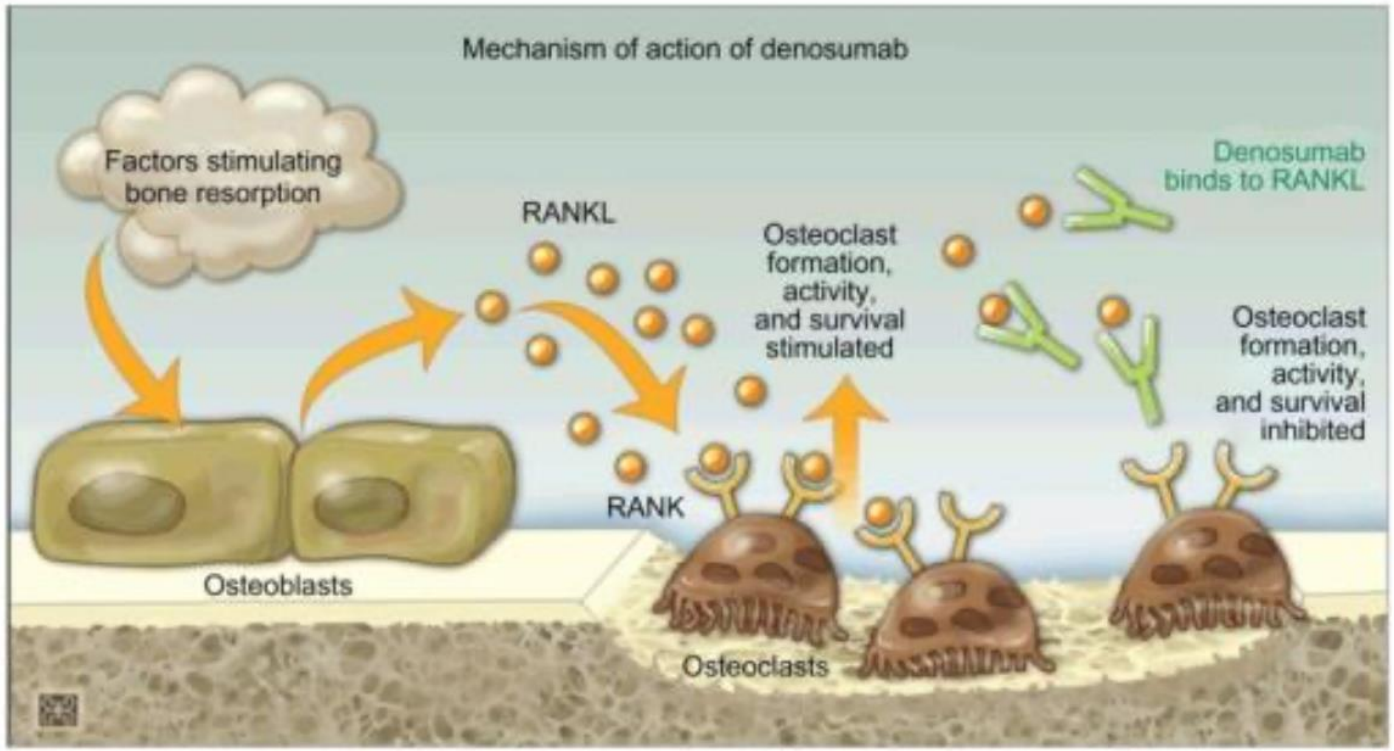


Coleman R et al Annals of Oncology 24: 398–405, 2013

Unico farmaco con evidenza di riduzione del rischio fratturativo in <u>questo specifico setting di pazienti</u>

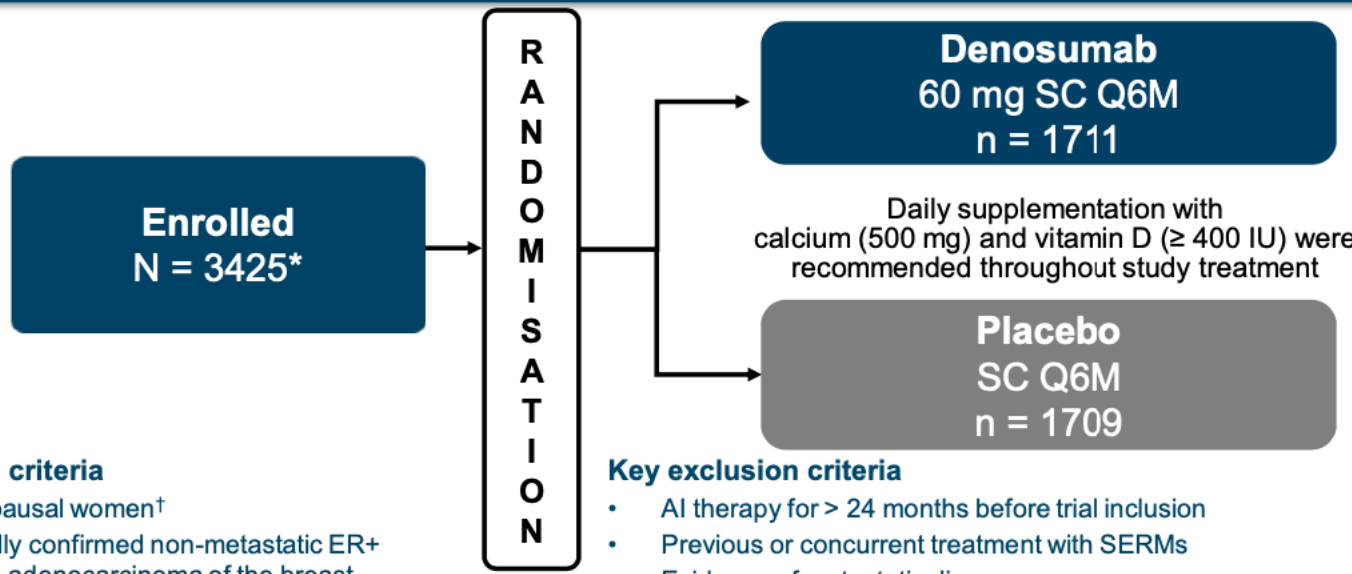
è il **denosumab**

60 mg/sc/ogni 6 mesi
per 24 mesi



Smith MR, Egerdie B, Toriz NH et al Denosumab in men receiving androgen deprivation therapy for prostate cancer. N Eng J Med 2010; 361: 745-755

ABCSG-18: study design



Key inclusion criteria

- Postmenopausal women†
- Histologically confirmed non-metastatic ER+ and/or PR+ adenocarcinoma of the breast
- Receiving or due to receive adjuvant non-steroidal AI therapy
- ECOG performance score: 0 or 1

Key exclusion criteria

- AI therapy for > 24 months before trial inclusion
- Previous or concurrent treatment with SERMs
- Evidence of metastatic disease
- Ongoing or previous IV BPs; oral BPs‡
- Previous denosumab therapy
- Known history of: Paget's disease, Cushing's disease, hyperprolactinaemia, hypercalcaemia, hypocalcaemia or other active metabolic bone disease
- Major surgery or traumatic injury < 4 weeks before randomisation

*5 patients withdrew consent to use their data;
†Defined as having undergone a bilateral oophorectomy, ≥ 60 years of age, or < 60 years of age but with follicle-stimulating hormone and oestradiol levels in the postmenopausal range;
‡Oral BP treatment if taken for 3 years or longer continuously or if taken for between 3 months and 3 years unless the patient had a washout period of at least 1 year before randomisation, or any use during the 3 months before randomisation.
IV, intravenous; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; Q6M, every 6 months; PR, progesterone receptor; SC, subcutaneous; SERM, selective oestrogen receptor modulator.

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

ABCSG-18: outcomes

Primary endpoint

Time to first clinical fracture*

Secondary endpoints

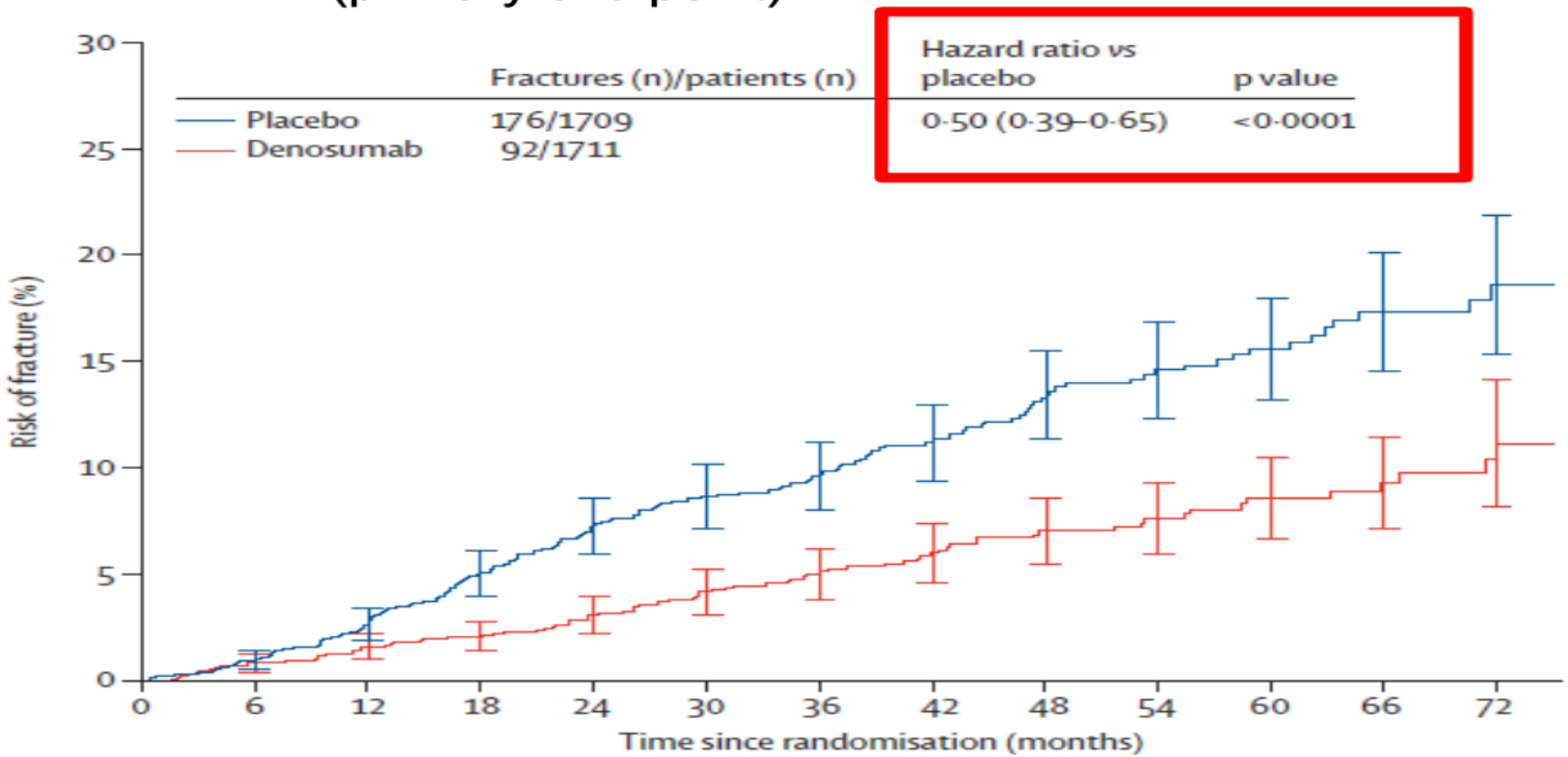
- Percentage change in total lumbar spine, total hip and femoral neck BMD from baseline to Month 36
- Incidence of new vertebral fractures† at Month 36
- Incidence of new or worsening of pre-existing vertebral fractures† at Month 36
- Disease-free survival (DFS)
- Bone metastasis-free survival (BMFS)
- Overall survival (OS)

- Exploratory endpoints were: the percentage change in total lumbar spine, total hip and femoral neck BMD from baseline to Months 12 and 24 (at preselected sites); the percentage change in total lumbar spine, total hip and femoral neck BMD from baseline to Months 12, 24 and 36 (at all participating clinical sites); new† and new or worsening vertebral fractures† at Months 12 and 24
- Safety endpoints were: incidence of treatment-emergent adverse events (TEAEs); clinically significant changes in laboratory values; anti-denosumab antibody formation

*Defined as clinically evident fractures with associated symptoms, except for those of the skull, face, fingers, and toes, which are typically not associated with osteoporosis;
†Morphometric fractures identified from study radiographs and clinical vertebral fractures confirmed by radiographs.

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

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

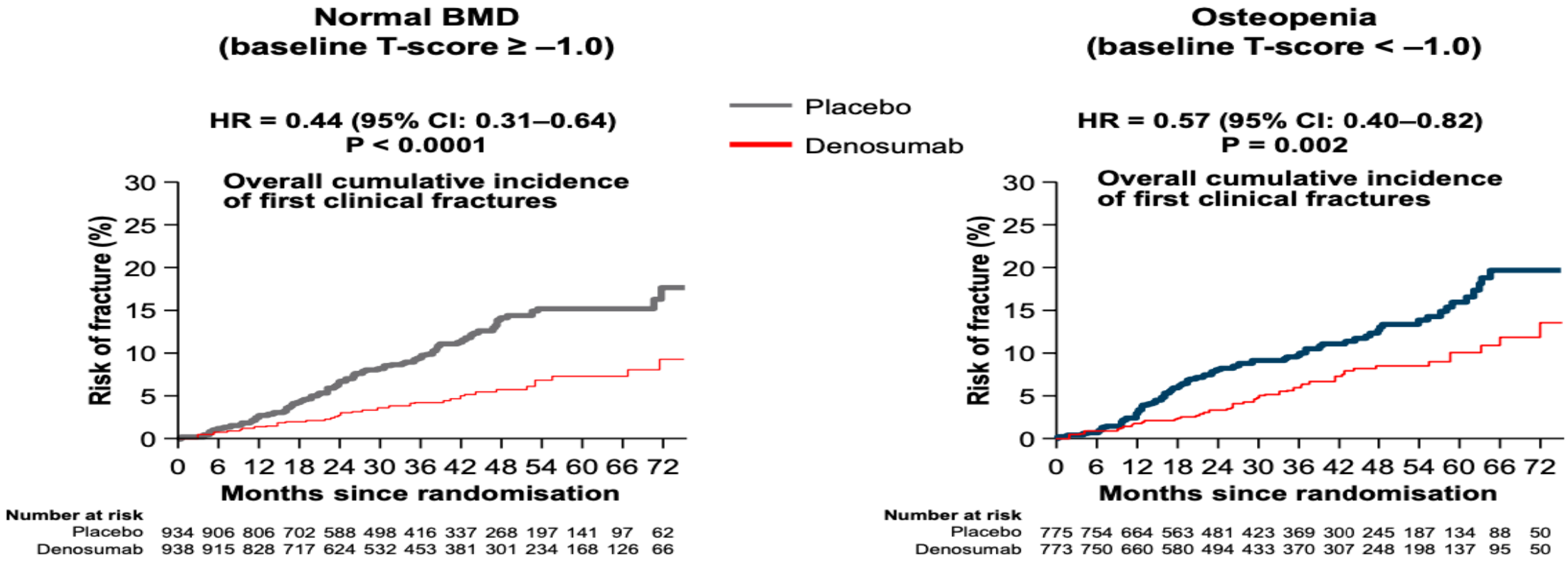


Number at risk

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

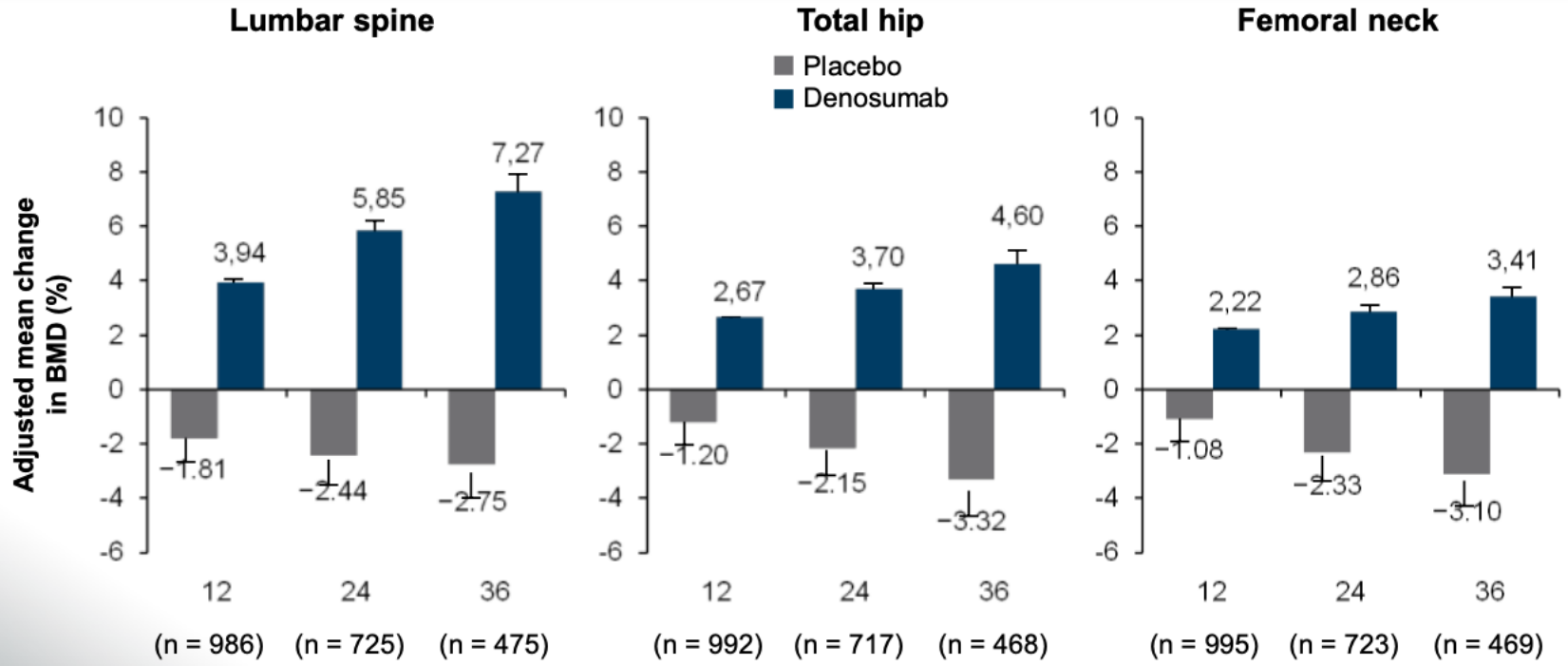
www.thelancet.com Published online June 1, 2015 http://dx.doi.org/10.1016/S0140-6736(15)60995-3

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



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

ABCSG-18: denosumab significantly increased BMD in the lumbar spine, total hip and femoral neck vs placebo



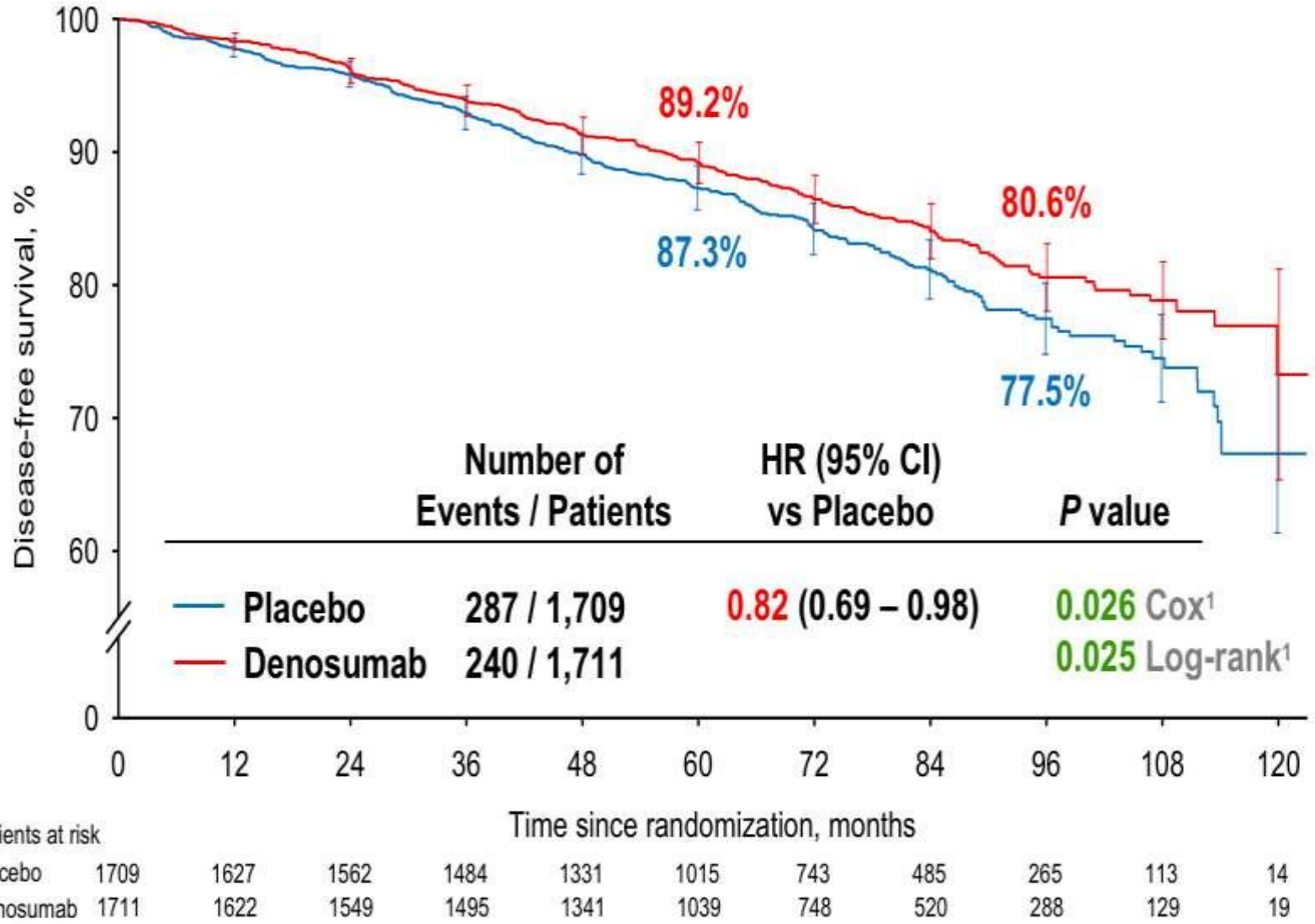
P < 0.0001 at all bone sites and time points

Lumbar spine	Total hip	Femoral neck
5.75% difference at Month 12*	3.86% difference at Month 12*	3.30% difference at Month 12*
8.28% difference at Month 24*	5.85% difference at Month 24*	5.19% difference at Month 24*
10.02% difference at Month 36†	7.92% difference at Month 36†	6.51% difference at Month 36†

*Note: these data represent an exploratory endpoint of the study;
†Note: these data represent a secondary endpoint of the study. Error bars are 95% CIs.

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

ABCSG-18 Results of the DFS ITT Analysis[1]



Patients at risk

Placebo	1709	1627	1562	1484	1331	1015	743	485	265	113	14
Denosumab	1711	1622	1549	1495	1341	1039	748	520	288	129	19

stratified by hospital type, use of prior aromatase inhibitor, and baseline lumbar spine bone mineral density [1] *Exploratory*

ASCO special articles

Management of Osteoporosis in Survivors of Adult Cancers With Nonmetastatic Disease: ASCO Clinical Practice Guideline

Charles L. Shapiro, MD[1]; Catherine Van Poznak, MD[2]; Christina Lacchetti, MHSc[3]; Jeffrey Kirshner, MD[4]; Richard Eastell, MD[5]; Robert Gagel, MD[6]; Sean Smith, MD[2]; Beatrice J. Edwards, MD, MPH[7]; Elizabeth Frank, EdM[8]; Gary H. Lyman, MD, MPH[9]; Matthew R. Smith, MD, PhD[10]; Rahul Mhaskar, PhD, MPH[11]; Tara Henderson, MD, MPH[12]; and Joan Neuner, MD, MPH[13]

CLINICAL QUESTION 1

Risk: Which patients with nonmetastatic cancer are at increased risk for developing osteoporotic fractures?

Recommendation 1.1. It is recommended that patients with nonmetastatic cancer who meet any of the following criteria be considered to be at increased risk for developing osteoporotic fractures:

- Advanced age
- Current cigarette smoking
- Excessive alcohol consumption
- History of prior nontraumatic fractures in adulthood
- Hypogonadism
- Impaired mobility
- Increased risks for falls
- Long-term exposure to glucocorticoids
- Low body weight
- Parental history of hip fracture
- Postmenopausal status

(Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Qualifying statement. Cutoffs used to define advanced age, excessive alcohol consumption, long-term glucocorticoid exposure, and low body weight vary across studies and populations. The specifics around these continuous predictors and the thresholds most often associated with increased risk are described further within the supporting text.

Recommendation 1.2. Clinicians should be aware that the patient's anticancer therapy (eg, aromatase inhibitors, antiandrogens, or GnRH agonists, or CIOF) may result in short- or long-term increased risk of osteoporotic fracture and should take anticancer therapy into account as potentially adding to baseline risk (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Management of Osteoporosis in Survivors of Adult Cancers With Nonmetastatic Disease: ASCO Clinical Practice Guideline

Charles L. Shapiro, MD[1]; Catherine Van Poznak, MD[2]; Christina Lacchetti, MHSc[3]; Jeffrey Kirshner, MD[4]; Richard Eastell, MD[5]; Robert Gagel, MD[6]; Sean Smith, MD[2]; Beatrice J. Edwards, MD, MPH[7]; Elizabeth Frank, EdM[8]; Gary H. Lyman, MD, MPH[9]; Matthew R. Smith, MD, PhD[10]; Rahul Mhaskar, PhD, MPH[11]; Tara Henderson, MD, MPH[12]; and Joan Neuner, MD, MPH[13]

CLINICAL QUESTION 3

Treatment: Which patients with nonmetastatic cancer should be treated and which interventions are effective in reducing the risk of osteoporotic fractures?

Nonpharmacologic Intervention

Recommendation 3.1. Clinicians should encourage patients to consume a diet with adequate calcium and vitamin D. If intake of calcium (1,000 to 1,200 mg/d) and vitamin D (at least 800 to 1,000 IU/d) is not being consumed, then supplements to reach those levels are recommended (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.2. Clinicians should actively encourage patients to engage in a combination of exercise types, including balance training, flexibility or stretching exercises, endurance exercise, and resistance and/or progressive strengthening exercises, to reduce the risk of fractures caused by falls. Whenever possible, exercise should be tailored according to the needs and abilities of the individual patient. Patients with an impairment hindering their gait or balance should be offered medical rehabilitation (Type: evidence based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.3. Clinicians should actively encourage patients to stop smoking and to limit alcohol consumption, as smoking and alcohol consumption are risk factors for osteoporosis (Type: evidence based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Pharmacologic Intervention

Recommendation 3.4. For patients with nonmetastatic cancer with osteoporosis (T scores of −2.5 or less in the femoral neck, total hip, or lumbar spine) or who are at increased risk of osteoporotic fractures based on clinical assessment or risk assessment tools (10-year probability of ≥ 20% for major osteoporotic fractures or ≥ 3% for hip fractures based on the US-adapted FRAX tool), bone-modifying agents, such as oral bisphosphonates, intravenous (IV) bisphosphonates or subcutaneous denosumab at the osteoporosis-indicated dosage, may be offered to reduce the risk of fracture. Hormonal therapies for osteoporosis management (eg, estrogens) are generally avoided in patients with hormonal-responsive cancers. For patients without hormonally responsive cancers, estrogens may be offered along with other bone-modifying agents when clinically appropriate (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statement. Current evidence suggests that oral bisphosphonates, IV bisphosphonates, and subcutaneous denosumab are each efficacious options. The choice of which bone-modifying agent to offer should be based on several important considerations, including patient preference, potential adverse effects, quality-of-life considerations, adherence, safety for that population, cost, and availability.

Recommendation 3.5. Provided that T score and/or risk assessment (eg, FRAX-estimated fracture risk) exceed threshold values for fractures (as described in Recommendation 3.4), the following specific populations may be considered appropriate candidate for bone-modifying agents:

- Premenopausal women receiving GnRH therapies causing ovarian suppression or with CIOF or who have undergone an oophorectomy
- Postmenopausal women who are receiving aromatase inhibitors
- Men who have received or are receiving androgen deprivation therapy
- Patients undergoing or with a history of bone marrow transplantation
- Patients with chronic (> 3 to 6 months) glucocorticoid use

(Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)

Qualifying statement. The short-term bone loss associated with these conditions can be rapid. Because of this, clinicians could consider treatment at higher bone density or T score than recommended using FRAX or similar tools, with decision making further guided by anticipated losses as reviewed in the text (ie, the bulleted conditions above should be included as having secondary osteoporosis in the FRAX assessment tool).

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Bone health in cancer: ESMO Clinical Practice Guidelines†

Tutti i pazienti devono svolgere

attività fisica

stop fumo

ridurre alcool

assumere con la dieta un quantitativo di Ca di 1000-2000 mg/d (supplementaz 500-1000 mg/d)

+ 1000-2000 UI vit. D3

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

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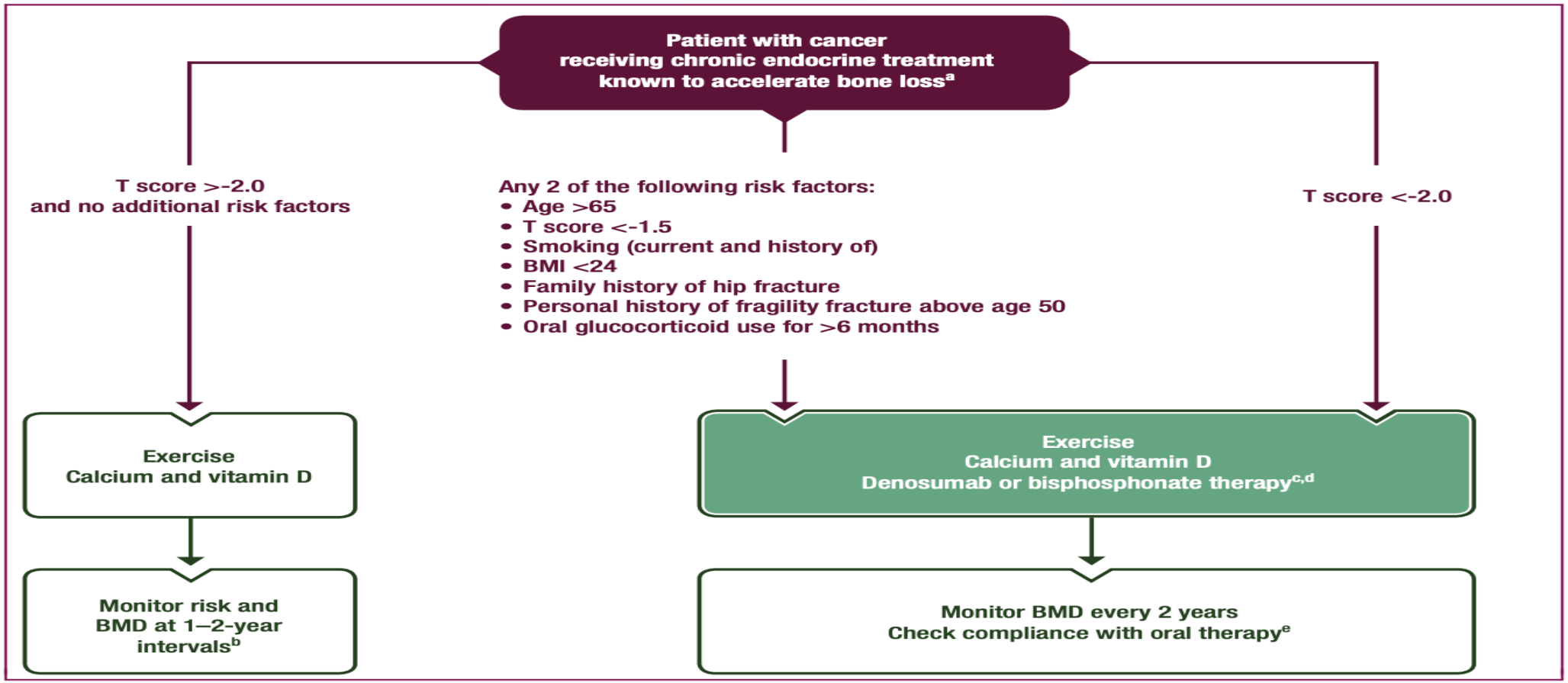

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
MODERATA	I bisfosfonati (in particolare l'ac zoledronico 4 mg/6 mesi) e il denosumab 60 mg/ogni 6 mesi prevengono la perdita di BMD nella donna con tumore della mammella in pre e post-menopausa in terapia ormonale adiuvante e nel maschio con cancro della prostata in blocco androgenico	**Positiva Forte**

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
MODERATA	Il denosumab 60 mg/ogni 6 mesi previene tutte le fratture da fragilità nella donna con tumore della mammella in postmenopausa in terapia con inibitori della aromatasi e le fratture vertebrali nel maschio con cr della prostata in blocco androgenico	**Positiva Forte**

DETERMINA 14 marzo 2017.

Aggiornamento della Nota 79 di cui alla determina 4 gennaio 2007: «Note AIFA 2006-2007 per l'uso appropriato dei farmaci». (Determina n. 446/2017).

ALLEGATO *1*

NOTA 79

La prescrizione a carico del SSN è limitata alle seguenti condizioni di rischio di frattura osteoporotica:

- **Prevenzione secondaria in soggetti con pregresse fratture osteoporotiche**
  - **vertebrali o di femore**

Condizione	Trattamento I scelta [a]	II scelta	III scelta
1-2 fratture [b]	Alendronato (± vit.D), Risedronato, Zoledronato [d],	Denosumab [e], Ibandronato, Raloxifene, Bazedoxifene	Stronzio ranelato [f]
≥ 3 fratture	Teriparatide [g]	Denosumab [e], Zoledronato [d]	Alendronato (± vit.D), Risedronato, Ibandronato Stronzio ranelato [f]
≥ 1 frattura + T-score colonna o femore [c] ≤ -4			
≥ 1 frattura + trattamento > 12 mesi con prednisone o equivalenti ≥ 5 mg/die			
Nuova frattura vertebrale o femorale nonostante trattamento in nota 79 da almeno 1 anno			

  - **non vertebrali e non femorali**

+ T-score colonna o femore ≤ -3	Alendronato (± vit.D), Risedronato, Zoledronato [d],	Denosumab [e], Ibandronato, Raloxifene, Bazedoxifene	Stronzio ranelato [f]

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			

d	Lo zoledronato è prescrivibile e somministrabile solo in strutture ospedaliere pubbliche o convenzionate.
e	Per il denosumab la nota si applica su diagnosi e piano terapeutico, rinnovabile, della durata di 12 mesi da parte di medici specialisti (internista, reumatologo, geriatra, endocrinologo, ginecologo, ortopedico, nefrologo, oncologo e specialista in medicina fisica e riabilitativa), Universitari o delle Aziende Sanitarie.

CTIBL da terapia ormonale adiuvante

1) **PERCHE' TRATTARE** — Perche' clinicamente utile (fratture/mortalità)

2) **CHI TRATTARE** — Sostanzialmente tutti (qualcuno di più)

3) **QUANDO TRATTARE** — SUBITO

4) **COME TRATTARE** — NOTA 79 (denosumab)

5) **PER QUANTO TEMPO TRATTARE** — Finchè Serve (fine CTIBL)

conclusioni

La normalizzazione del turn-over osseo permette:

- prevenzione della perdita di massa ossea
- prevenzione delle fratture
- (*DFS e probabilmente OS: effetto adiuvante*)

Si può realizzare con aminoBP e denosumab secondo la Nota 79 (con avvio precoce)

Il rischio fratturativo si riduce al termine del trattamento di blocco ormonale, ma occorre rivalutare tale rischio per eventuale proseguimento della terapia o per il «consolidamento» farmacologico

Esami ematici di I° livello

VES
Emocromo
Proteine totale + elettroforesi
Fosforo
Fosfatasi alcalina
Creatininemia
Calciuria nelle 24 h
Calcio (corretto se necessario)
Vitamina D

Anti-riassorbitivo nella ADT: evidenze

ALENDRONATO (Planas et al, 2009)
70 mg/settimana
End-point: BMD (raggiunto), fratture (non ci sono dati)
In nota 79

ZOLEDRONATO (Smith et al, 2003)
4 mg ev/anno oppure /3-6 mesi
End-point: BMD (raggiunto), fratture (non ci sono dati)
Off-label (dose e timing di somministrazione)

DENOSUMAB (Smith MR, 2009)
60 mg sc/6 mesi
End-point: BMD e fratture (raggiunto), DFS (non ci sono dati)
In nota 79

Durata della tp = controversa

Anti-riassorbitivo in post-M: evidenze

ZOLEDRONATO (ZO-FAST, Coleman et al, 2013)
Dose: 4 mg ev ogni 6 mesi (up-front)
End-point: **BMD** (raggiunto), **fratture** (non raggiunto), **DFS** (raggiunto)
Off-label (dose e timing di somministrazione)
DENOSUMAB (Ellis et al, 2008; *ABCSG-18*, Gnant et al, 2015)
Dose: 60 mg sc ogni 6 mesi
End-point: **BMD** (raggiunto), **fratture** (raggiunto), **DFS** (raggiunto)
Nota 79
BISFOSFONATI ORALI
Risedronato 35 mg/sett (Markopoulos et al, 2010)
Ibandronato 150 mg/mese (Lester et al, 2008)
Alendronato 5 mg/die (Rhee et al, 2013)
Minori evidenze
Nota 79 (risedronato)

Durata della tp = durata della terapia adiuvante