

A Review of Bone Health Issues in Oncology

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Disclosures

- David Kendler has received research grants, speaking honoraria, and/or consultancies from Amgen, Merck, AstraZenica, Astellis, and Eli Lilly

Objectives:

- Challenging real-life cases in oncology (focus on breast cancer and aromatase inhibitor therapy)
 - Risk assessment
 - Required testing
 - Diet and lifestyle
 - Treatment options
 - Risks and benefits of therapy

Case History: Jean Smith 3 months after Colles fracture

- 67 year old woman
 - She has just returned to you after having Colles fracture from a fall from standing height
 - ER(+) breast cancer age 60 with surgery, radiation, tamoxifen 5 years and now letrozole 2 years
 - Concerned more about breast cancer than osteoporosis and fracture

Lifetime risk at the age of 50

	Women	Men
Osteoporotic fracture ^{1,2}	46-53%	21-22%
Hip fracture ^{2,3}	15-23%	5-11%
Radiographic vertebral fracture ⁴	27%	11%
Clinical vertebral fracture ²	15%	8%
Breast cancer	10-13%	
Prostate cancer		9-11%

NB: variable between countries

¹Van Staa TP et al (2001) Bone 29: 517

²Kanis JA et al (2000) Osteoporos Int 11: 669

³Samelson EL et al (2007) J Bone Miner Res 22: 1449

⁴Samelson EL et al (2006) J Bone Miner Res 21: 1207

“Approximately

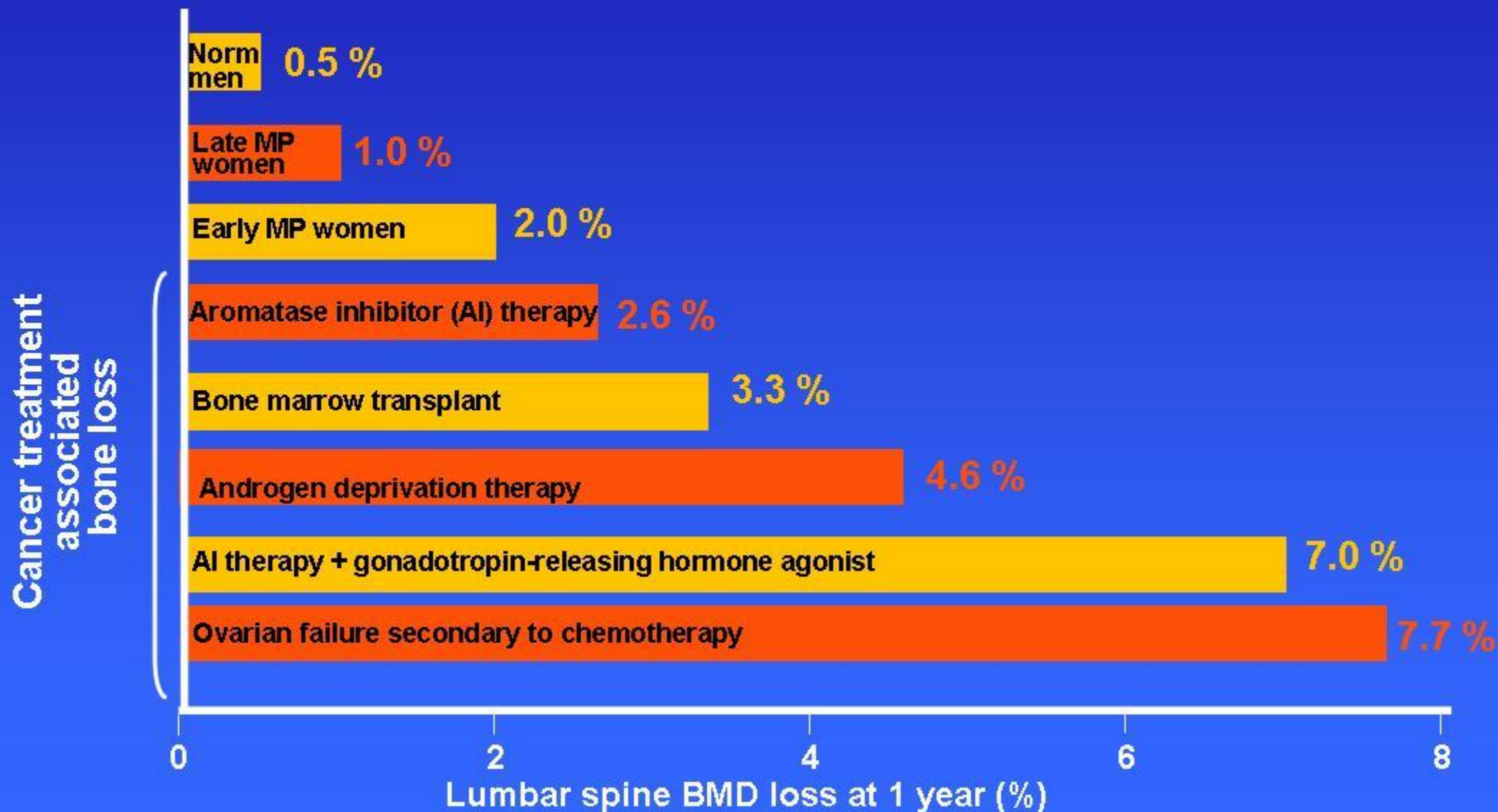
50%

*of people with 1 osteoporotic fracture
will have another, with the risk
of new fractures rising exponentially
with each fracture.”*

– International Osteoporosis Foundation

Bone loss and fracture risk associated with cancer therapy

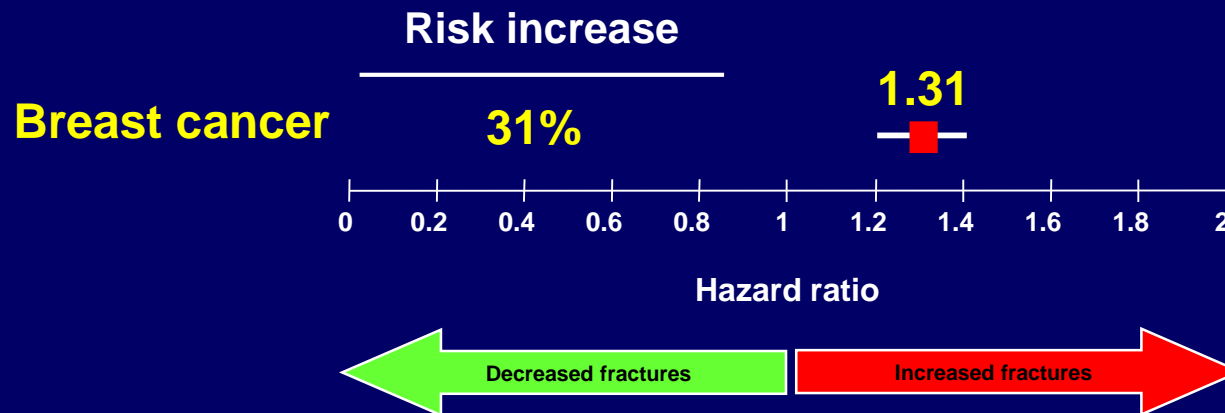
T.A. Guise, The Oncologist 2006



Breast Cancer Increases Fracture Risk

Results of the WHI observational study

- Prospective cohort study with 5.1 years of follow-up¹
 - 5,298 breast cancer survivors in WHI study
 - 80,848 reference population with no history of cancer
 - Adjustment for age, weight, and ethnicity
- **Women with history of BC had a 31% increased risk of fracture**



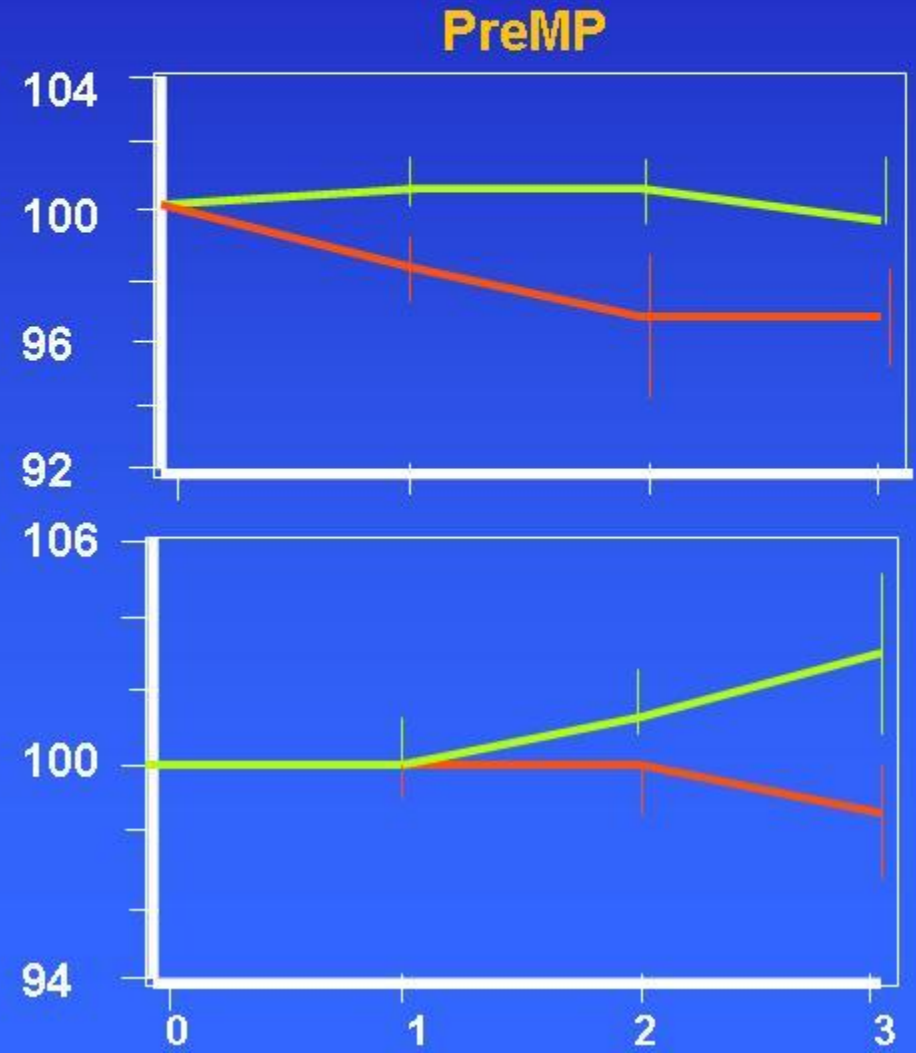
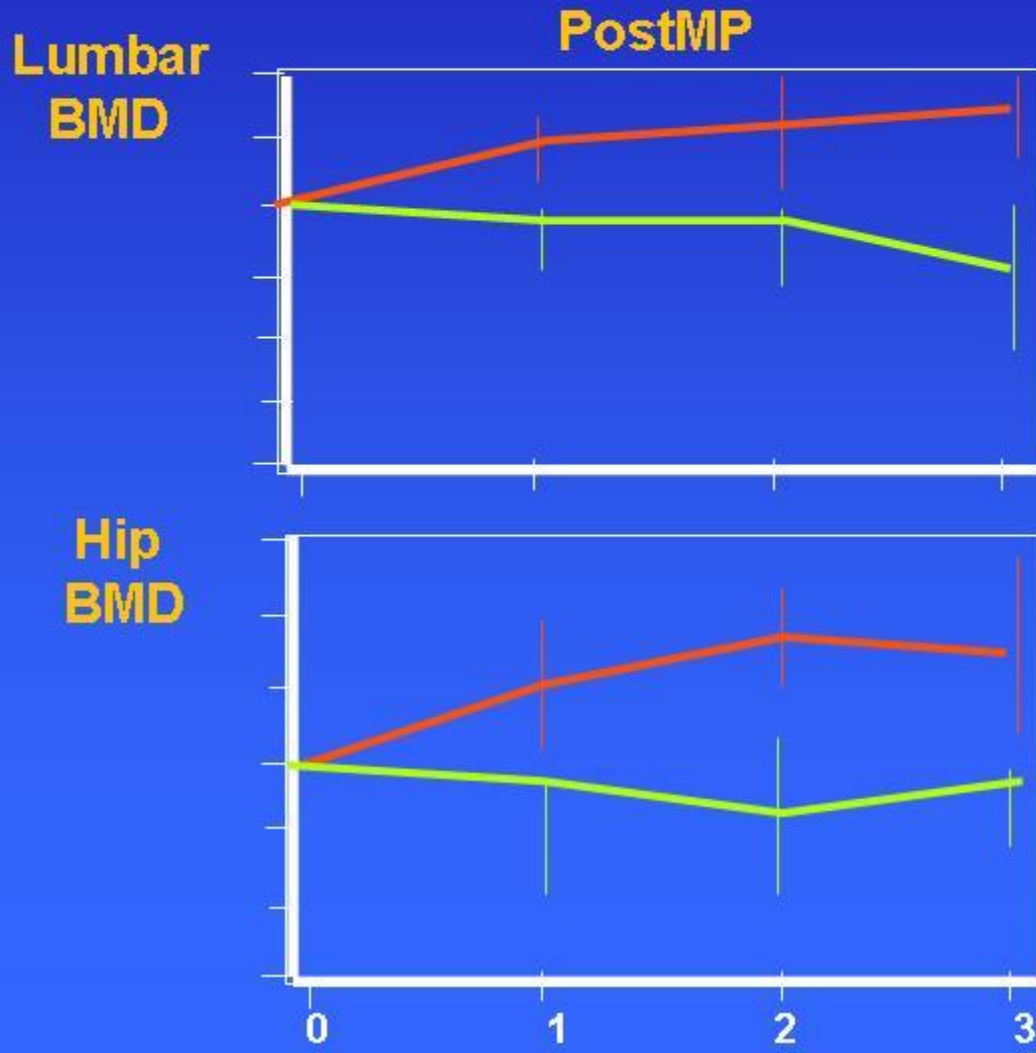
WHI = Women's Health Initiative.

1. Chen Z, et al. *Arch Intern Med.* 2005;165:552-558.

Effect of tamoxifen on BMD measured by DXA in pre- versus post-MP women

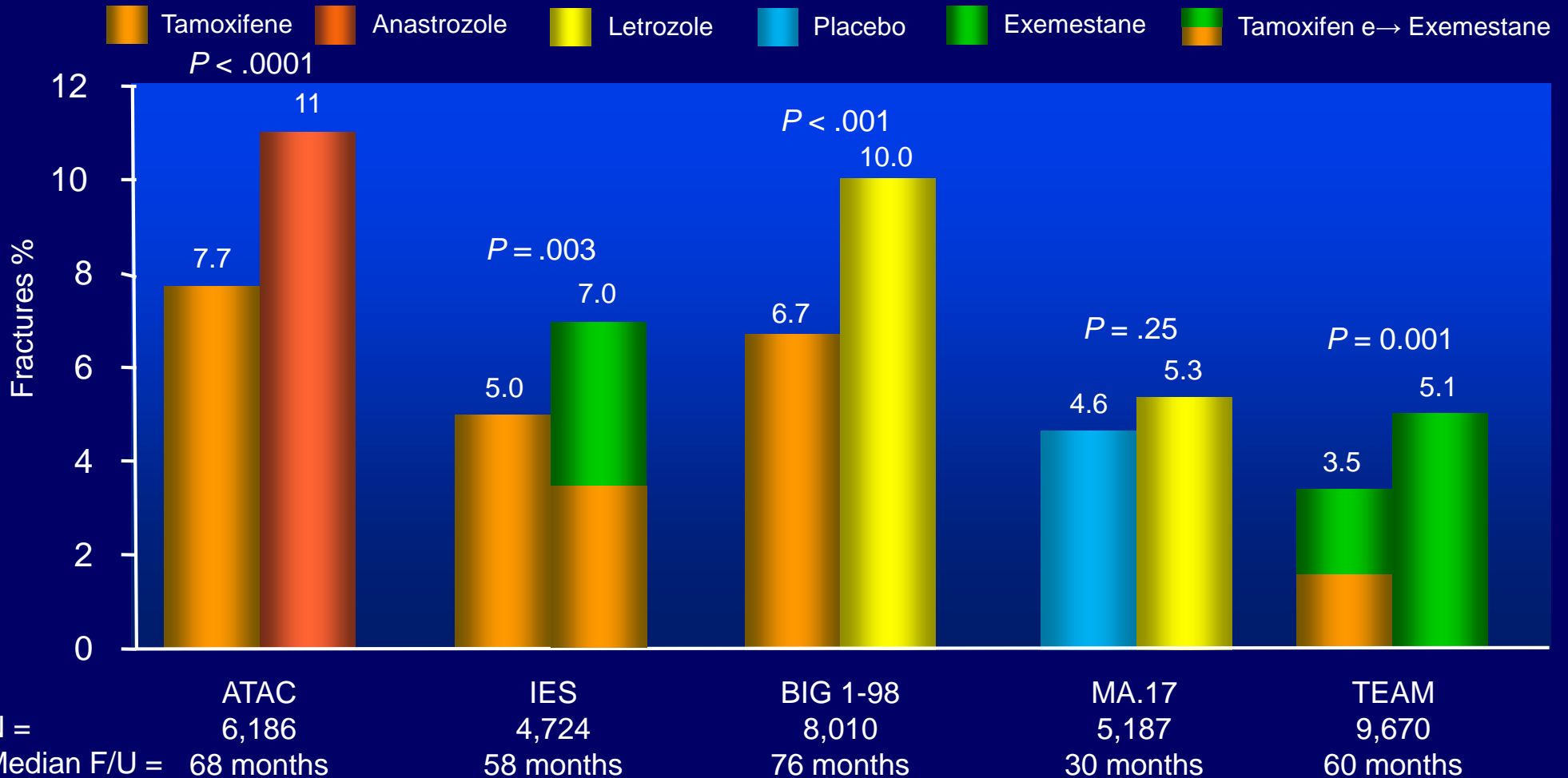
n = 179 (Tam 20 mg/d vs placebo 3 yrs;
clemoprevention trial of breast cancer)

Powles et al., JCO 1995



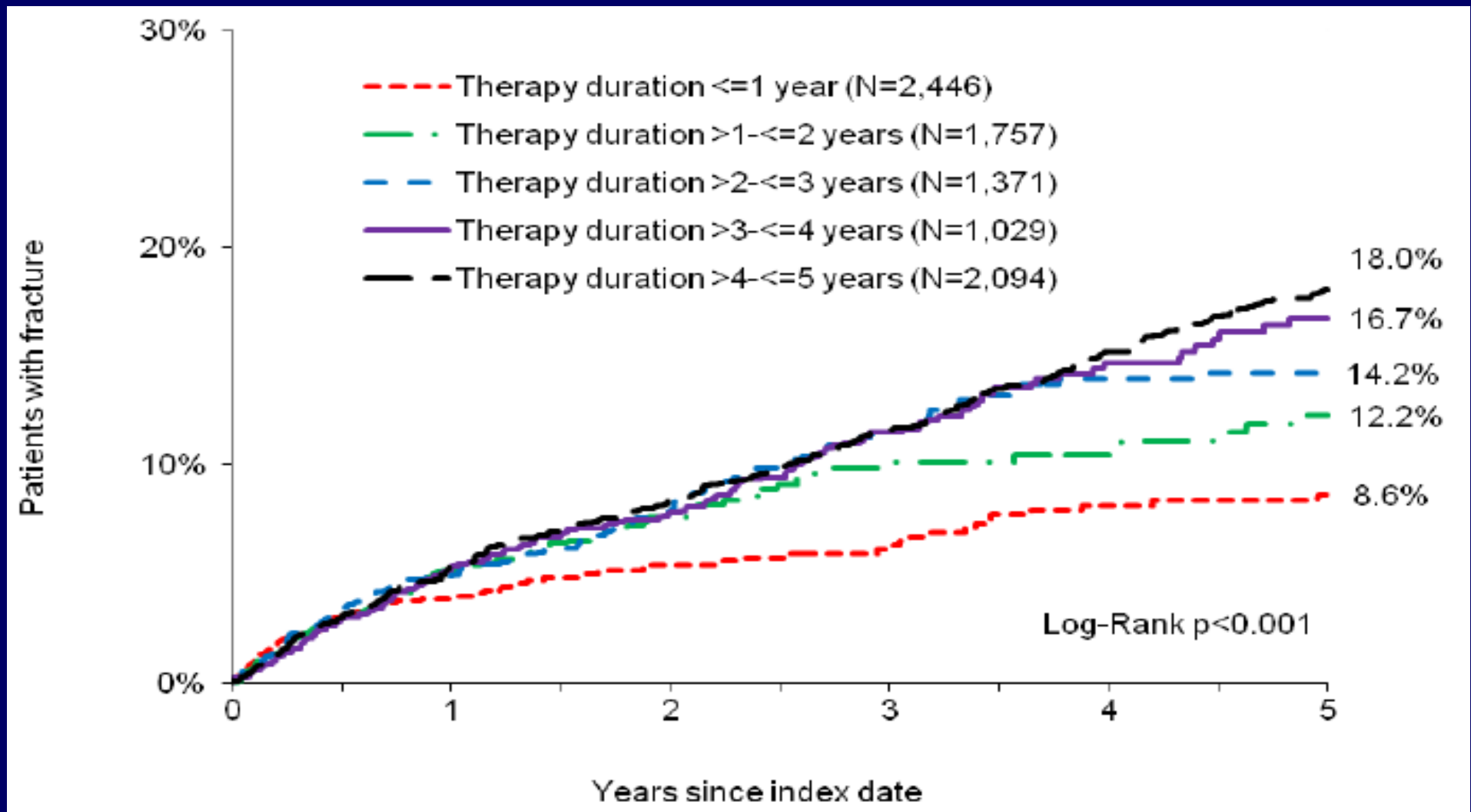
Influence of AI on fracture and osteoporosis risk

No head to head studies



F/U, follow-up; NS, not significant; ATAC, Arimidex tamoxifen alone or in combination; IES, intergroup exemestane study; BIG 1-98, breast international group 1-98 collaborative group; TEAM, tamoxifen exemestane adjuvant multinational.

Fracture incidence of postmenopausal healthy and BC women on TAM and AI



Case History: Jean Smith and BMD results

- 67 year old woman with Colles fracture on AI for breast cancer

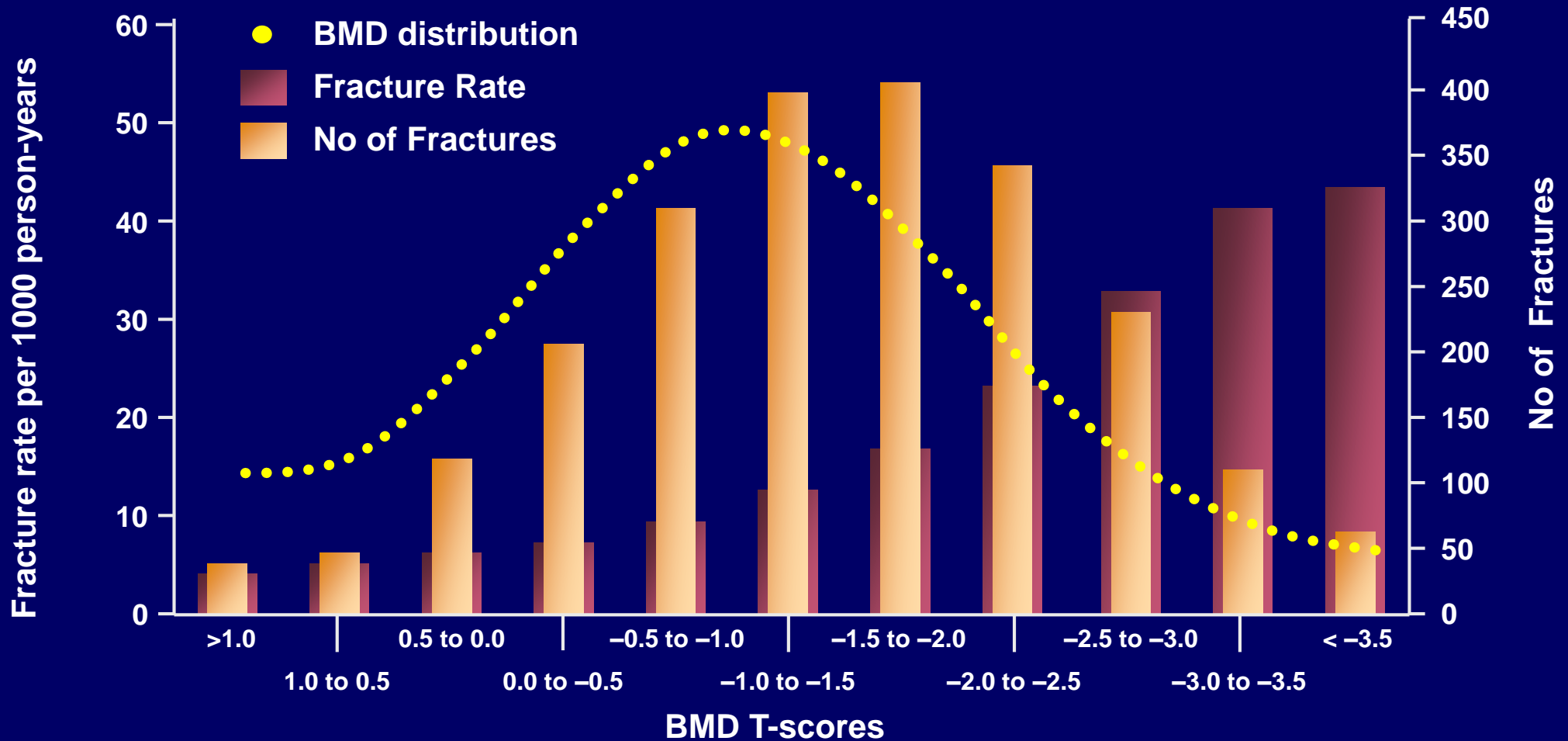
New information:

- DXA femoral neck T-score = -2.3

Definitions of osteoporosis

- » Osteoporosis can be defined clinically and by DXA
 - **Clinical definition:** Fragility fracture especially hip or spine
 - **Densitometric definition:** T-score \leq -2.5 at spine, total hip or femoral neck (or 1/3 radius) in a postmenopausal woman or man over age 50

Fracture Rates, Population BMD Distribution and Number of Fractures



FRAX Risk Factors

Age (40-90), sex and clinical risk factors

- BMI/DXA
- Prior fragility fracture
- Parental history of hip fracture
- Current tobacco smoking
- Ever long-term use of glucocorticoids (> 3mo and > 5mg/d)
- Rheumatoid arthritis or other secondary causes
- Alcohol intake 3 or more units daily

Case History: Jean Smith and 10 year Absolute Fracture Risk

- 67 year old woman with low bone density (osteopenia), AI for breast cancer
 - Femoral neck T-score = -2.3

New information:

- Risk factors
 - History of Colles fracture, on AI for breast cancer
 - Maternal hip fracture
 - Used Prednisone for 1 year in the past for Polymyalgia Rheumatica

FRAX[®] WHO Fracture Risk Assessment Tool

Home

Calculation Tool

Paper Charts

FAQ

References

English

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.



Country: **Canada**

Name/ID:

[About the risk factors](#)

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth

Age:

Date of Birth:

Y: M: D:

2. Sex

Male Female

3. Weight (kg)

4. Height (cm)

5. Previous Fracture

No Yes

6. Parent Fractured Hip

No Yes

7. Current Smoking

No Yes

8. Glucocorticoids

No Yes

9. Rheumatoid arthritis

No Yes

10. Secondary osteoporosis

No Yes

11. Alcohol 3 or more units/day

No Yes

12. Femoral neck BMD (g/cm²)

T-Score

BMI: 23.4
The ten year probability of fracture (%)



with BMD

Major osteoporotic	43
Hip Fracture	9.2

If you have a TBS value, click here:

Weight Conversion

Pounds kg

Height Conversion

Inches cm

00472278

Individuals with fracture risk assessed since 1st June 2011

FRAX: Jean Smith's Risk Calculation

BMI 26.6

The ten year probability of fracture (%)



with BMD

■ Major osteoporotic	43
■ Hip fracture	9.2

High risk = 10-year osteoporosis fracture risk over 20% or hip fracture risk over 3%

Case history: Jean Smith Treatment Guidelines

- 67 year old woman with low bone density (osteopenia)
 - Femoral neck T-score = -2.3
 - History of Colles fracture, on AI for breast cancer
 - Maternal hip fracture
 - Used Prednisone for 1 year in the past for Polymyalgia Rheumatica
 - FRAX MOF 43%, HF 9.2%

- Does she meet guidelines criteria for treatment?

North American Menopause Society 2010 Treatment Recommendations

- Postmenopausal women and men over age 50:
 - A hip or vertebral (clinical or morphometric) fracture
 - T-score ≤ -2.5 after excluding secondary causes
 - Low bone mass (-1 to -2.5)
 - 10 year probability of hip fracture $\geq 3\%$
 - Or of any osteoporosis fracture $\geq 20\%$
- based on the Canadian-adapted WHO algorithm

Case History: Jean Smith and Calcium/Vit D

- 67 year old woman with low bone density (osteopenia)
 - Femoral neck T-score = -2.3, Colles fracture, on AI for breast cancer, maternal hip fracture, past prednisone for Polymyalgia Rheumatica; FRAX 43/9.2

New information:

- She is taking 1500mg of supplement elemental Ca, 4 dairy servings, and 400IU of Vitamin D daily

Calcium and Vitamin D: OC Guidelines for Women and Men over age 50

Calcium (from diet and supplement)

- » 1200 mg/day

Vitamin D

- » 800 - 2000 IU/day

- » Can use dosing weekly or monthly

- » Vitamin D3 better than D2

Jean Smith

- » 67 year old woman with low bone density (osteopenia), Femoral neck T-score = -2.3, Colles fracture, on AI for breast cancer, maternal hip fracture, past prednisone for Polymyalgia Rheumatica; FRAX 43/9.2 taking appropriate Ca and Vitamin D

Does she need any laboratory testing?

Screen for Secondary Etiologies of Osteoporosis

- » CBC diff (thalassemia, anemia)
- » Ca, PO₄ (hyperparathyroidism, malabsorption)
- » ALP (Paget's, liver disease, osteomalacia, fracture)
- » eGFR (renal osteodystrophy, renal clearance for BP)
- » TSH (hyperthyroidism)
- » Maybe SPEP (myeloma)
- » Maybe 25 OH Vitamin D after > 3 months on 2000IU/d (Vit D deficiency or insufficiency)

Case History: Jean Smith's Treatment Options

- » 67 year old woman with low bone density (osteopenia), Femoral neck T-score = -2.3, Colles fracture, on AI for breast cancer, maternal hip fracture, past prednisone for Polymyalgia Rheumatica; FRAX 43/9.2 on Ca and Vitamin D

New information:

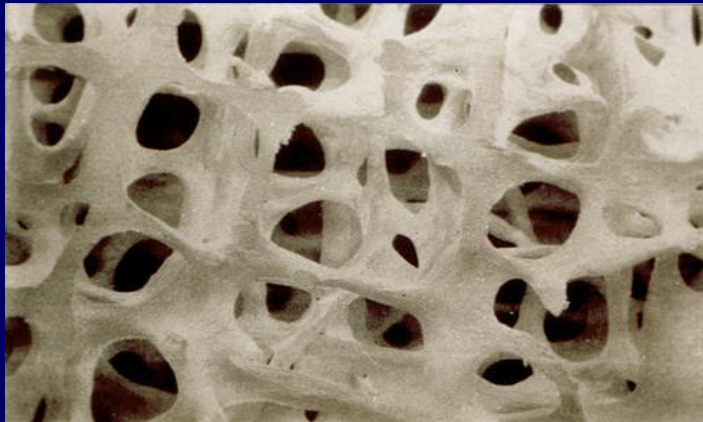
- » No secondary cause of osteoporosis

What medications will reduce her fracture risk?

Treatment Strategies for Osteoporosis

Mild Osteoporosis

**Antiresorptive Therapy
(Bisphosphonate,
estrogen, calcitonin,
denosumab or SERM)**

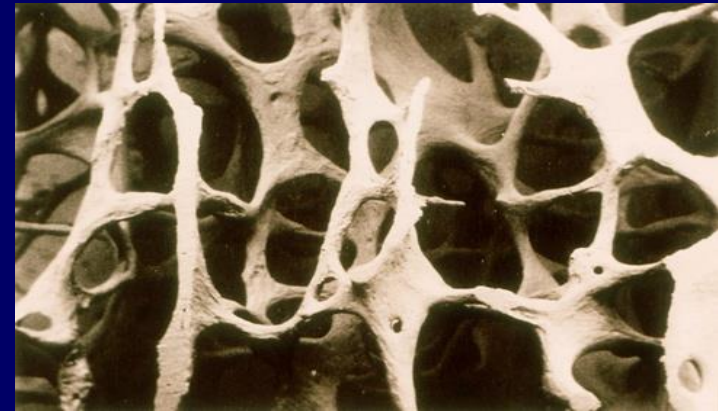


Normal bone

Severe Osteoporosis

**Bone Anabolic therapy
(teriparatide)**

Antiresorptive Therapy



Osteoporosis

Osteoporosis Canada Guidelines: Therapy

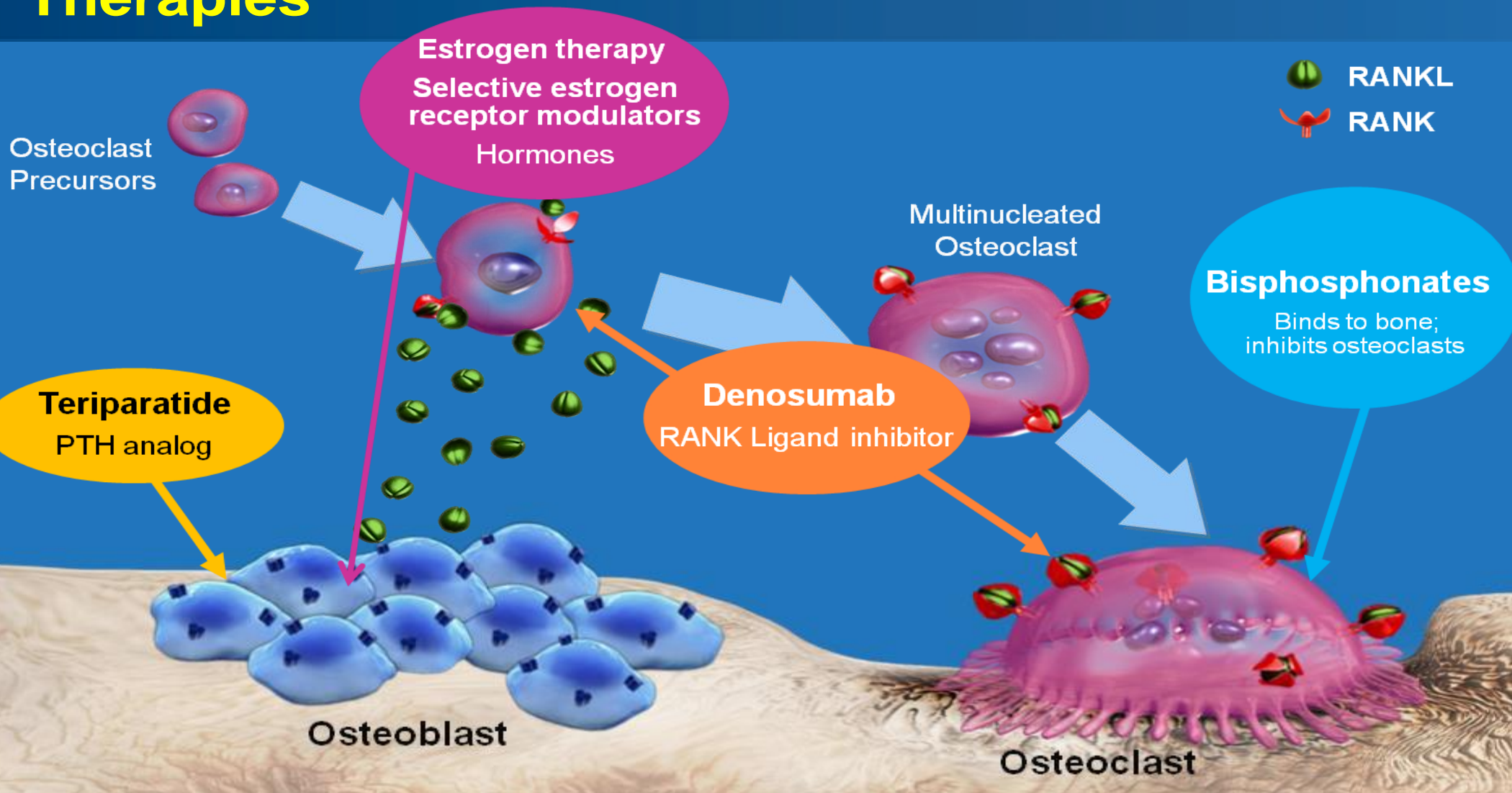
» First line therapies

- Alendronate, Risedronate, Zoledronic acid, Estrogen, Raloxifene, Denosumab and Teriparatide

First Line Therapies with Evidence for Fracture Prevention in Postmenopausal Women*

Type of Fracture	Antiresorptive Therapy						Bone Formation Therapy
	Bisphosphonates			Denosumab	Raloxifene	Estrogen** (Hormone Therapy)	Teriparatide
	Alendronate	Risedronate	Zoledronic Acid				
Vertebral	✓	✓	✓	✓	✓	✓	✓
Hip	✓	✓	✓	✓	-	✓	-
Non-vertebral†	✓	✓	✓	✓	-	✓	✓

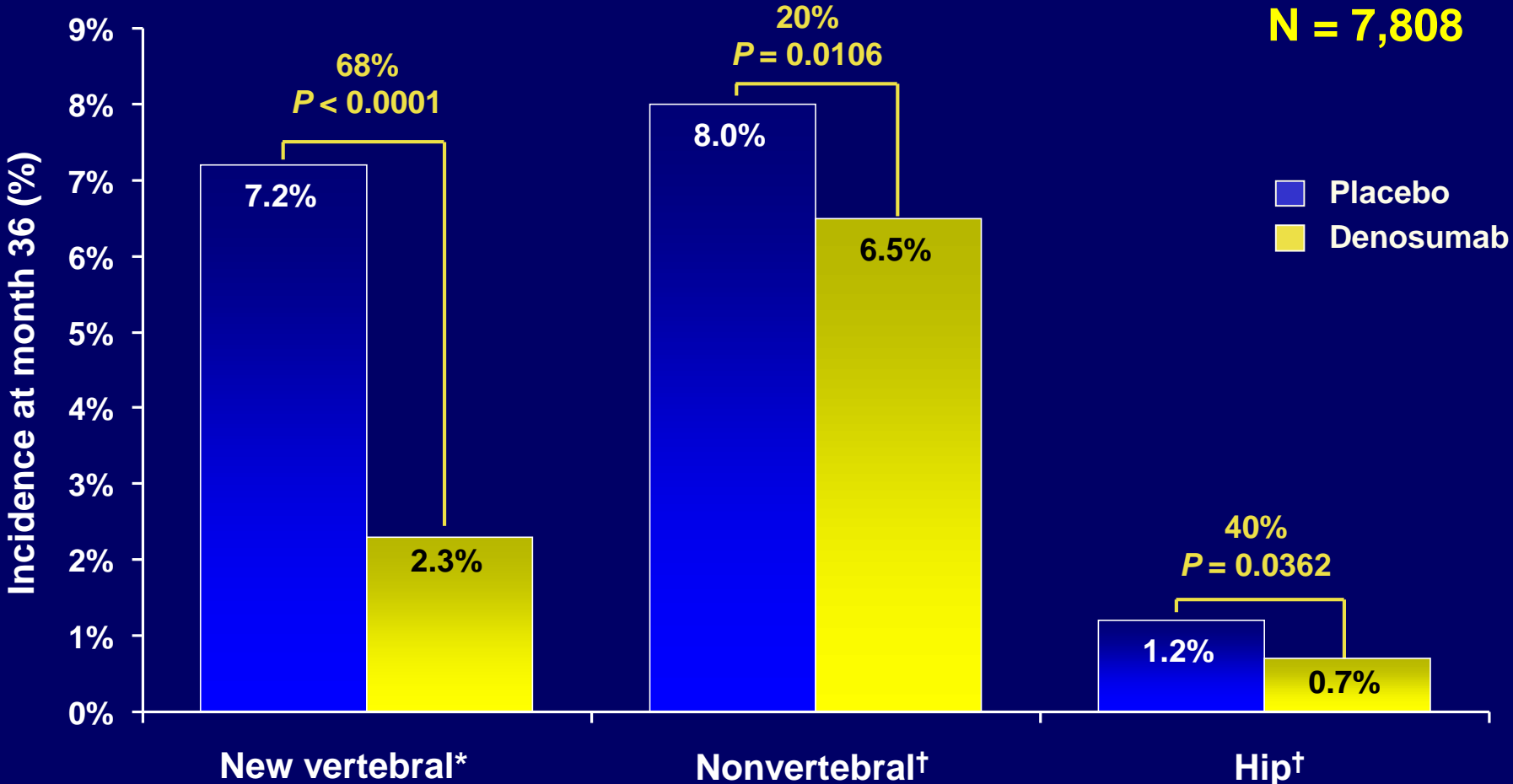
Mechanism of Action of Available Osteoporosis Therapies



What are the Key Considerations in Choosing a Therapy?

- Efficacy
 - Fracture reduction: hip, vertebral, non vertebral
- Side effects / intolerance
- Adherence (compliance and persistence)
- Convenience and preference
- Cost and Access

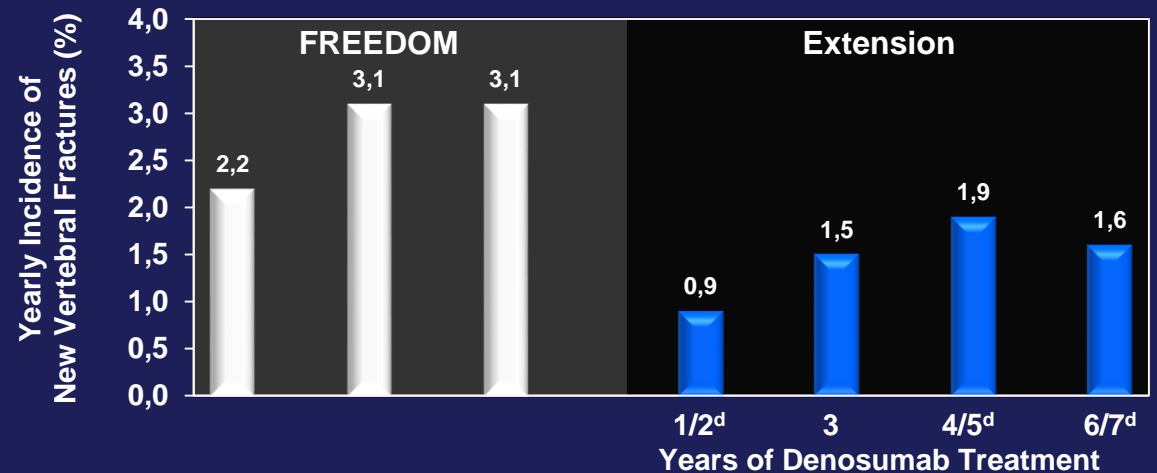
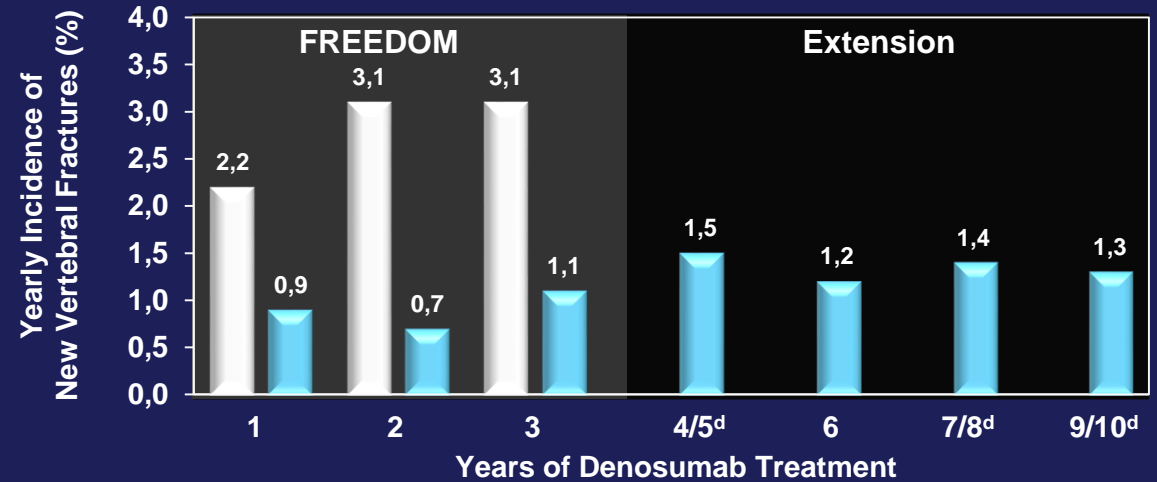
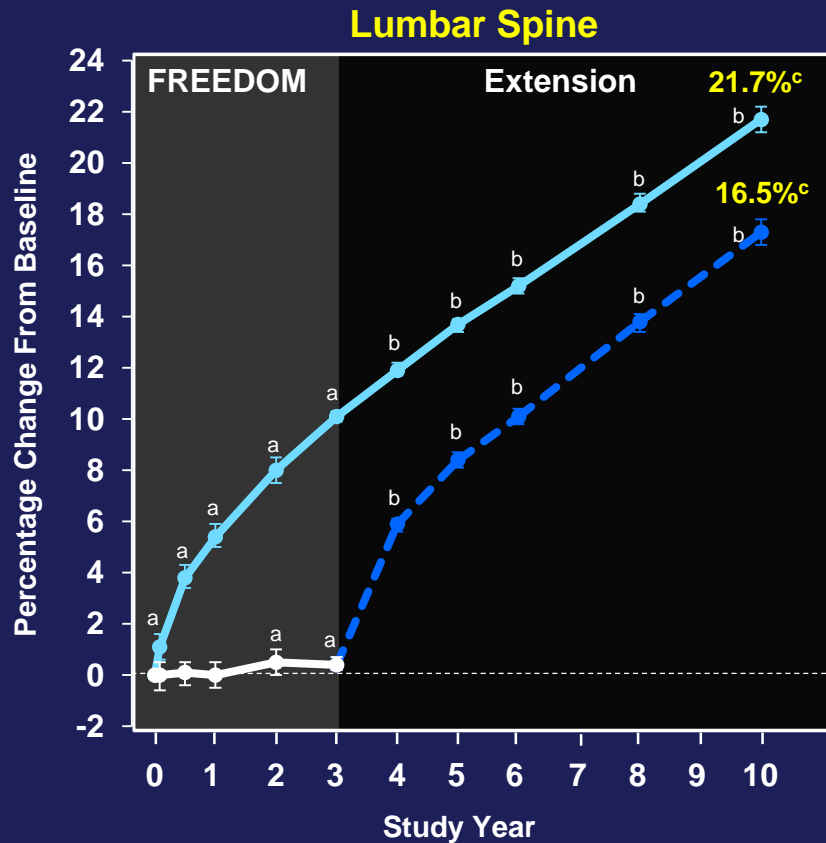
Effect of 3 Years of Treatment With Denosumab on Fractures in Women With PMO: FREEDOM



Cummings SR, et al. NEJM 2009;361:756-765.

Effects of Denosumab Treatment on Lumbar Spine BMD and New Vertebral Fractures Through 10 Years

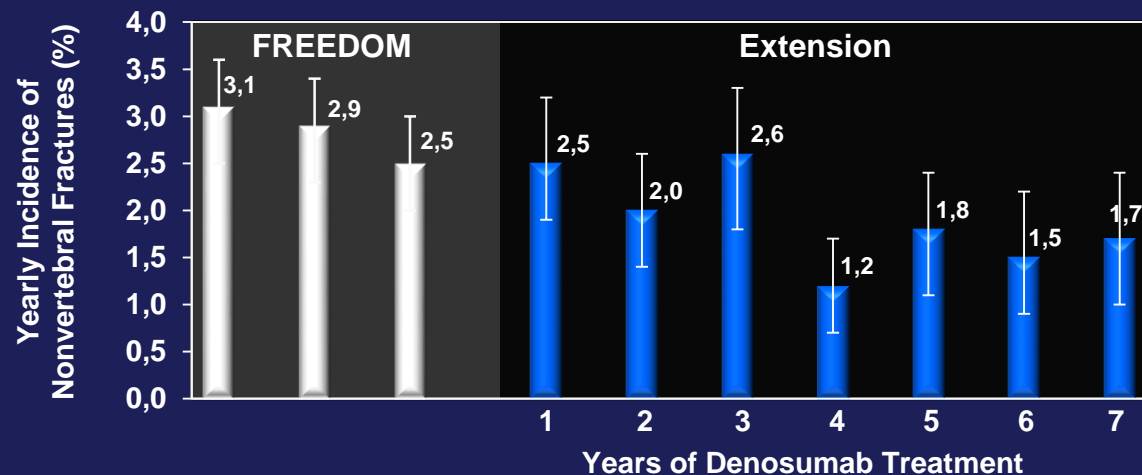
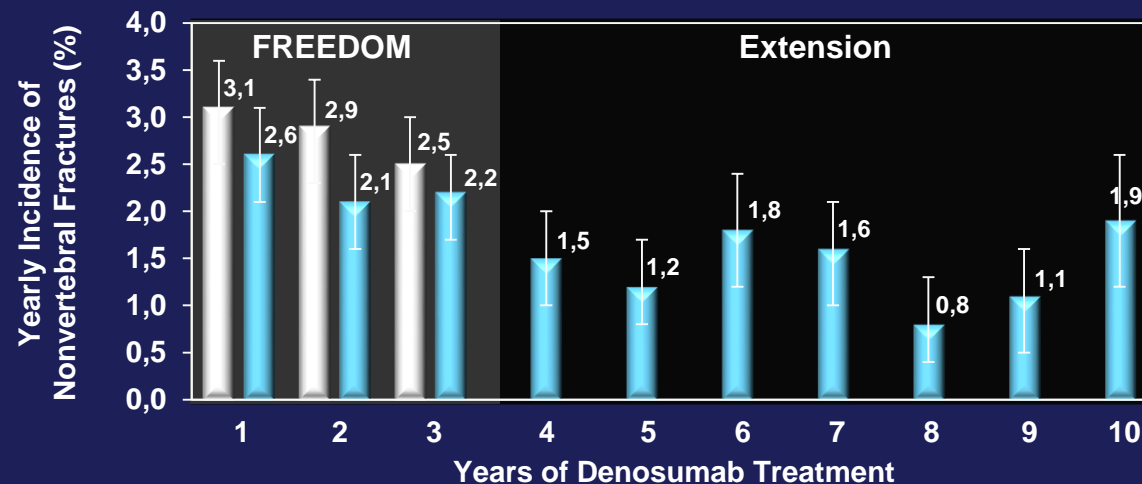
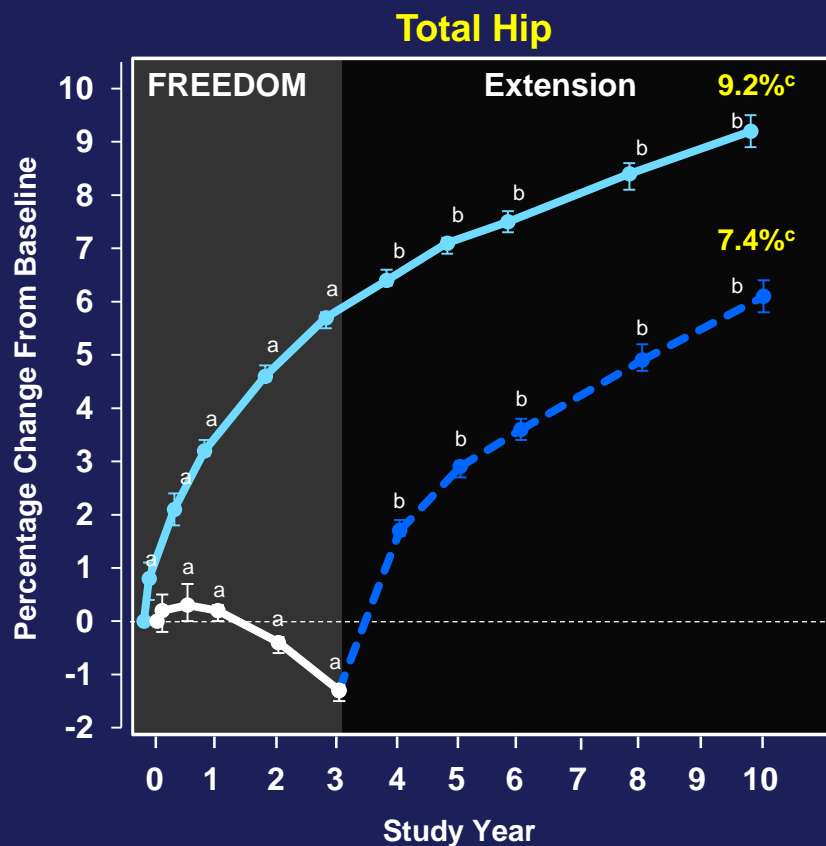
■ Placebo ■ Long-term Denosumab ■ Cross-over Denosumab



BMD data are LS means and 95% confidence intervals. ^a $P < 0.05$ vs FREEDOM baseline. ^b $P < 0.05$ vs FREEDOM and Extension baselines. ^cPercentage change while on denosumab treatment. ^dAnnualized incidence: (2-year incidence) / 2. Lateral radiographs (lumbar and thoracic) were not obtained at years 4, 7, and 9 (years 1, 4, and 6 of the Extension).

Effects of Denosumab Treatment on Total Hip BMD and Nonvertebral Fractures Through 10 Years

■ Placebo ■ Long-term Denosumab ■ Cross-over Denosumab



BMD data are LS means and 95% confidence intervals. ^a $P < 0.05$ vs FREEDOM baseline. ^b $P < 0.05$ vs FREEDOM and Extension baselines. ^cPercentage change while on denosumab treatment. Percentages for nonvertebral fractures are Kaplan-Meier estimates.

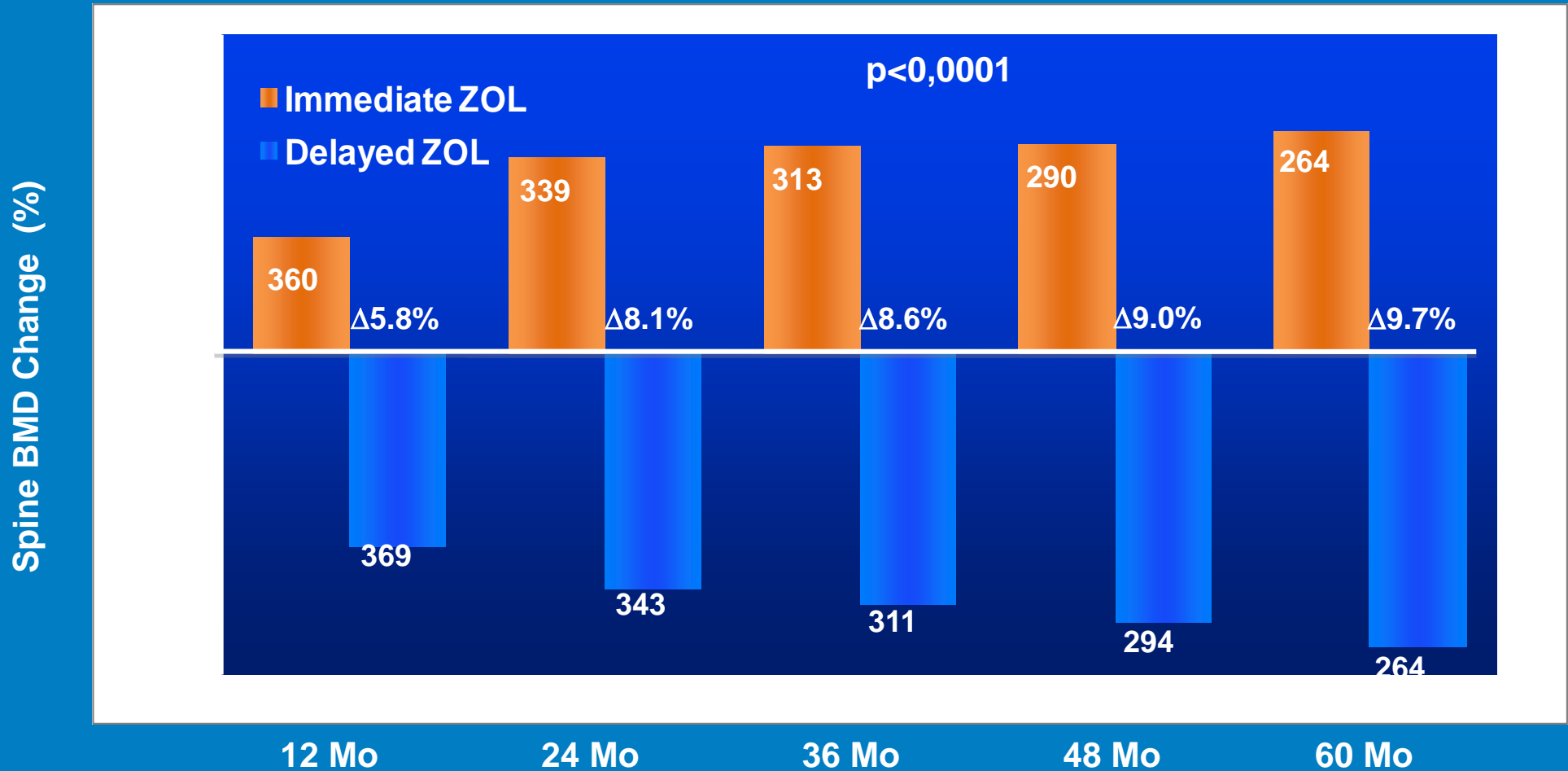
CTIBL Breast Cancer

- » Aromatase inhibitor (AI) therapy has greatly benefitted high risk ER+ breast cancer (BC) patients in reducing recurrence rates. Treatment is usually continued over many years.
- » AIs reduce circulating estradiol; even low levels of estradiol in postmenopausal women are important for bone health
 - All clinical trials of AI show decreases in bone density (BMD)
 - Clinical fractures in patients on AI are increased to a greater degree than one would expect from the modest declines in BMD
 - Different fracture locations are seen in patients on AI as compared with PMO (hip and ankle v. spine and wrist)
 - BC clinical trials collected fracture by adverse event reporting; dedicated fracture trials show 5-year clinical fracture incidence of 18%, double the rate reported in BC trials

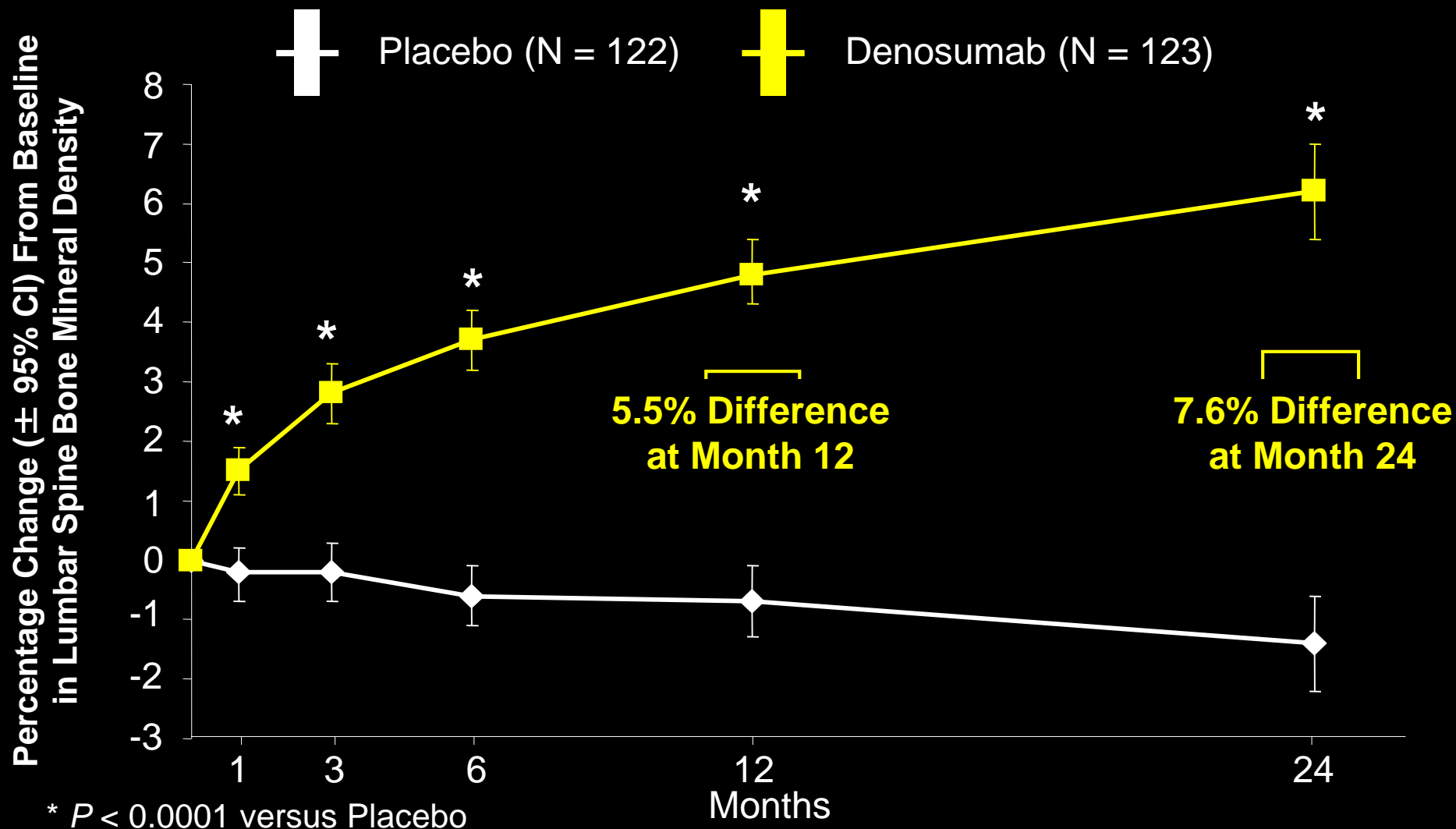
CTIBL Breast Cancer

- » Risk calculators (FRAX) do not capture the excess fracture risk from AIs
- » Many treatment algorithms for patients on AI recommend antiresorptive therapy if BMD T-score < -2 ; or < -1.5 if another risk factor is present
- » Potential therapies for CTIBL include oral and iv bisphosphonates, and denosumab
- » Clinical trials of ZOL suggest superior protection from bone loss when ZOL is given before AI initiation; no antifracture efficacy has been demonstrated. For CTIBL, ZOL 4mg iv 6-monthly was used.
- » Smaller clinical trials of oral bisphosphonates (ALN, IBN and RIS) have shown BMD effectiveness in preventing CTIBL but no fracture data

Upfront Zoledronic Acid Increases BMD in Spine/ and Hip: ZO-FAST Study (no fracture efficacy)

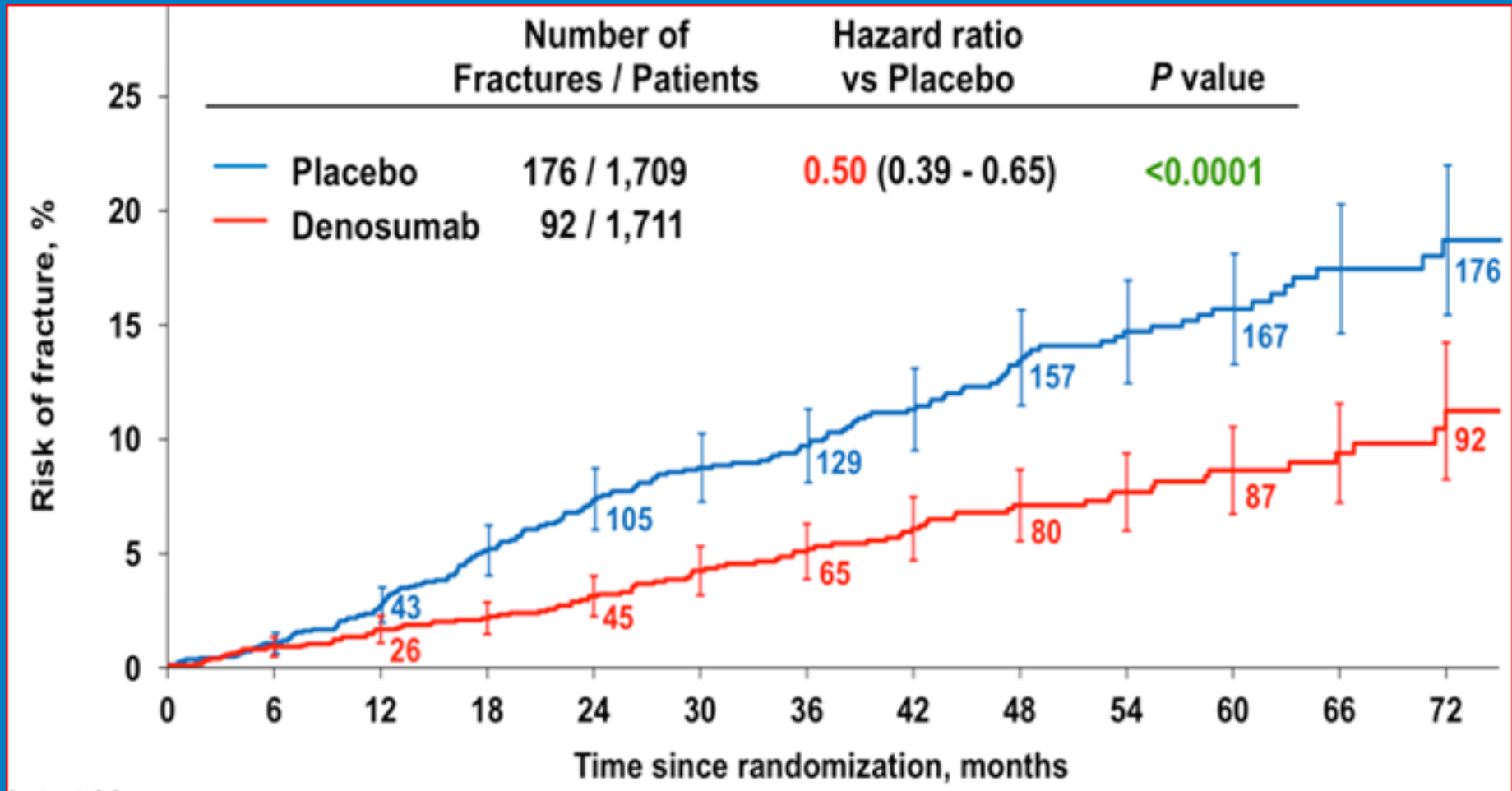


AI: Effect of Denosumab on Lumbar Spine Bone Mineral Density



ABCSG18 AI Fracture Risk with Dmab v. PBO

3425 breast cancer patients on aromatase inhibitor randomized to demand or placebo

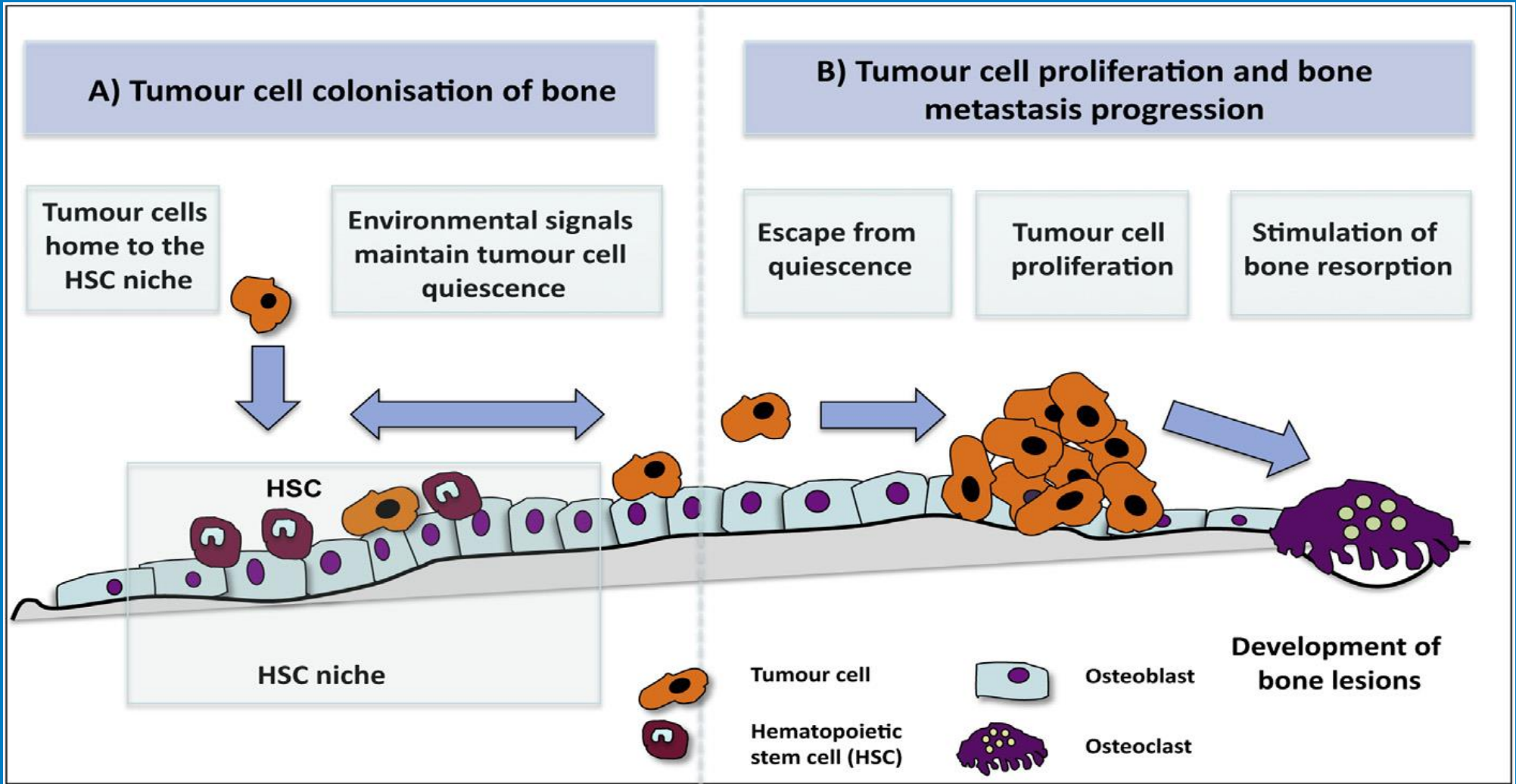


AI TIBL Disease Free Survival (DFS)

Breast cancer DFS and antiresorptive therapies

- » Metastatic BC has likely spread before surgical resection
- » Antiresorptive therapy benefits to BC DFS may be due to changes in the bone environment making it unfavourable to breast cancer cells
- » Meta-analysis of BP studies indicates likely BC DFS benefit of BP is restricted to PMP women

Stages of BC bone metastases

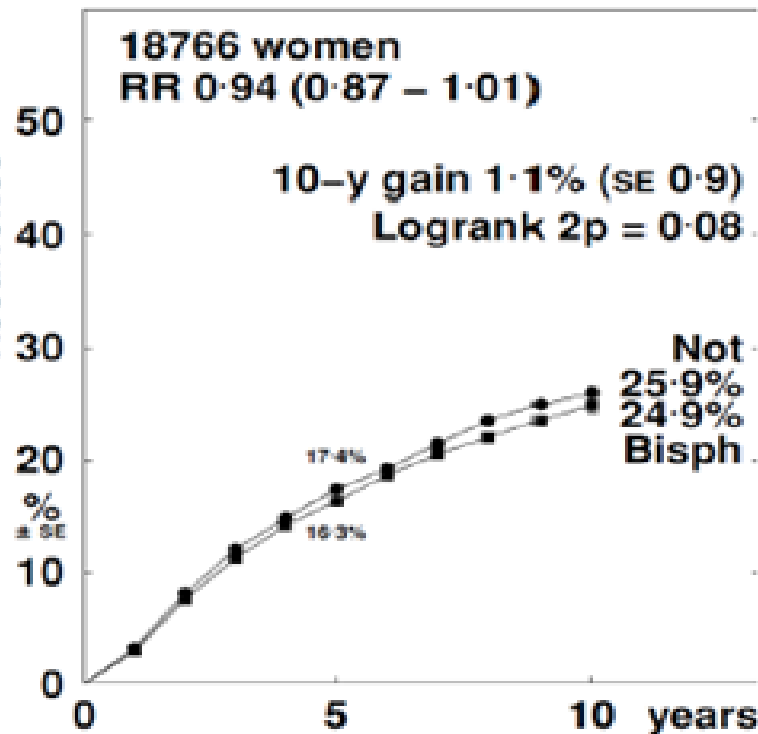


Breast cancer recurrence by menopausal status: Meta-analysis of BP studies

RECURRENCE

18766 women
RR 0.94 (0.87 – 1.01)

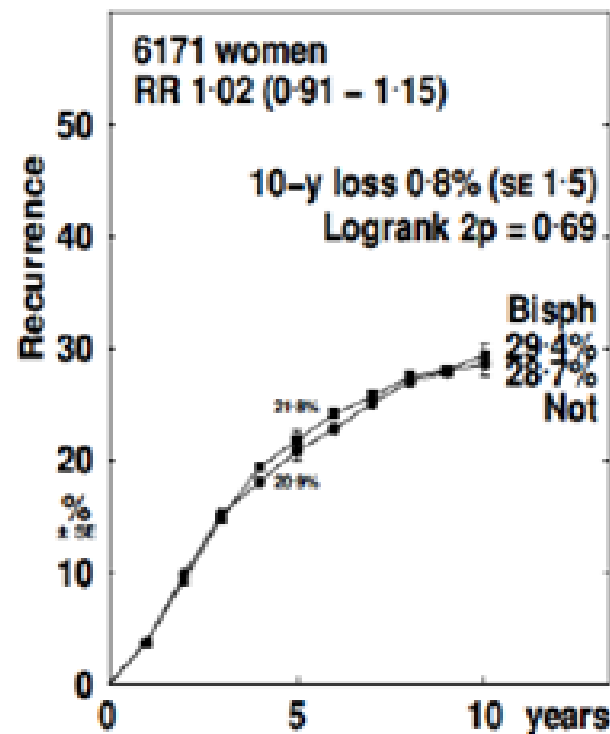
10-y gain 1.1% (SE 0.9)
Logrank 2p = 0.08



Premenopausal women RECURRENCE

6171 women
RR 1.02 (0.91 – 1.15)

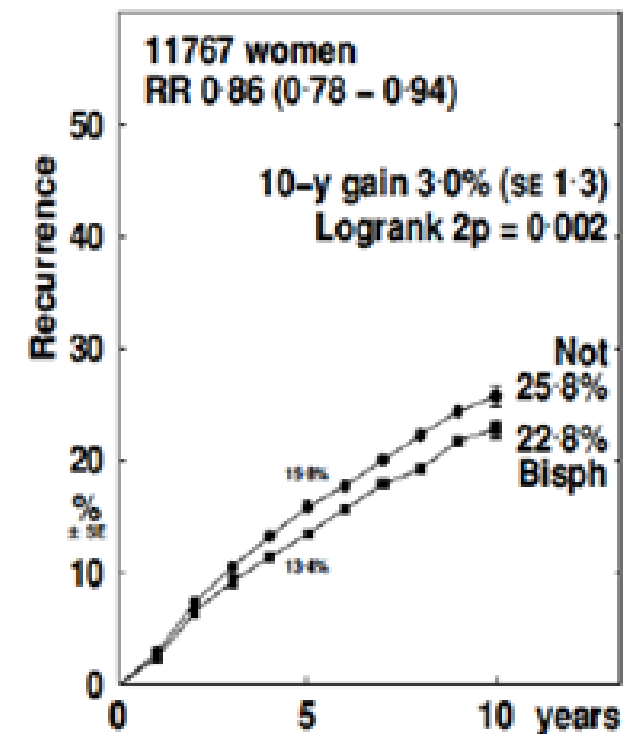
10-y loss 0.8% (SE 1.5)
Logrank 2p = 0.69



Postmenopausal women RECURRENCE

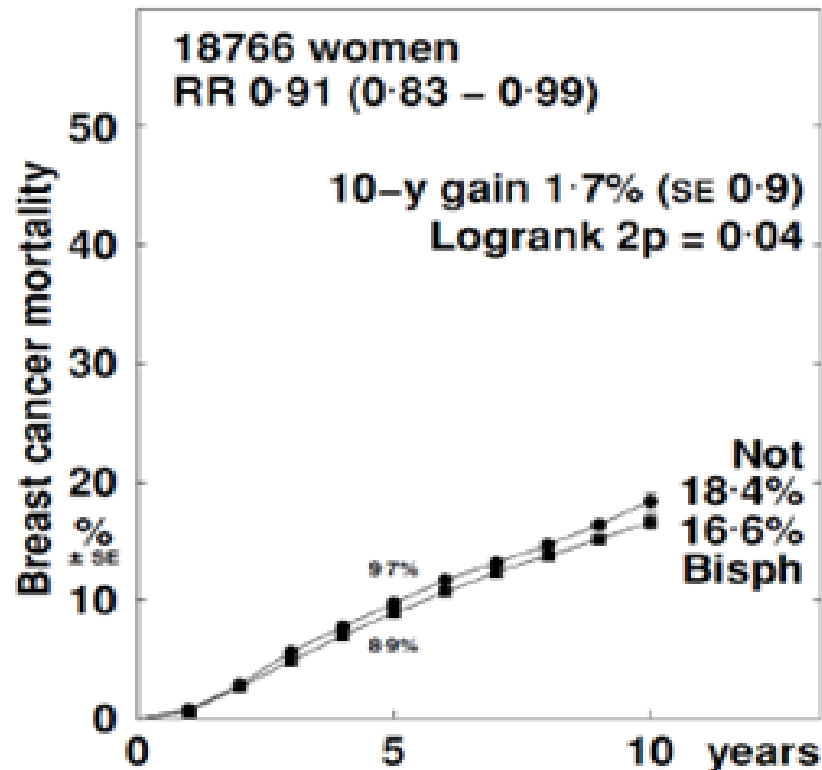
11767 women
RR 0.86 (0.78 – 0.94)

10-y gain 3.0% (SE 1.3)
Logrank 2p = 0.002

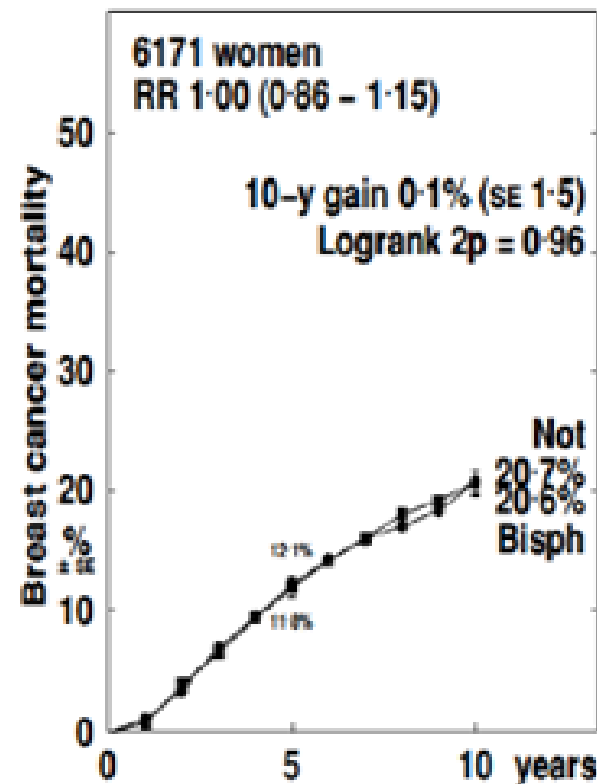


Breast cancer mortality by menopausal status: Meta-analysis of BP studies

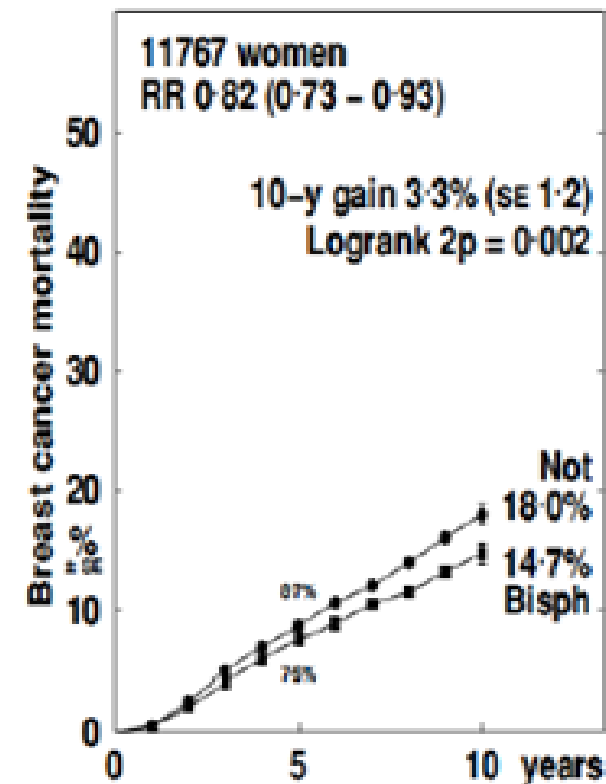
BREAST CANCER MORTALITY



Premenopausal women BREAST CANCER MORTALITY

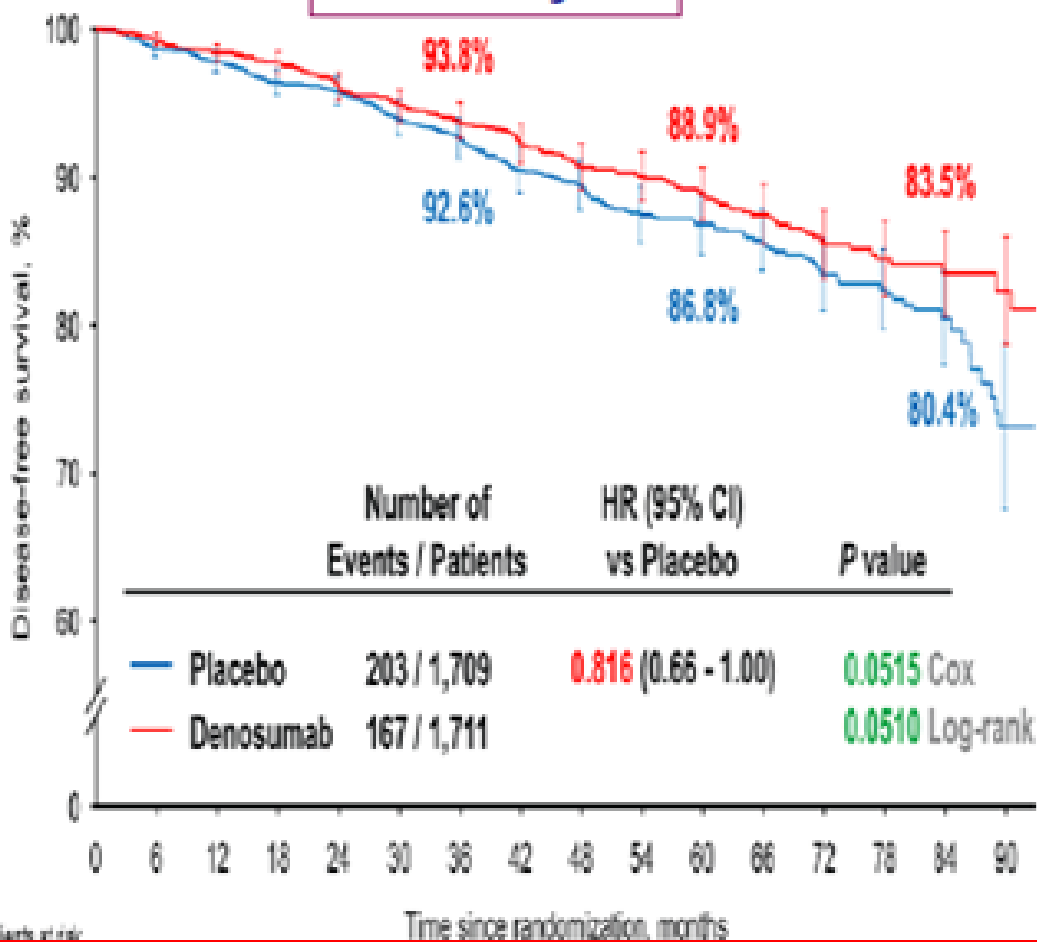


Postmenopausal women BREAST CANCER MORTALITY

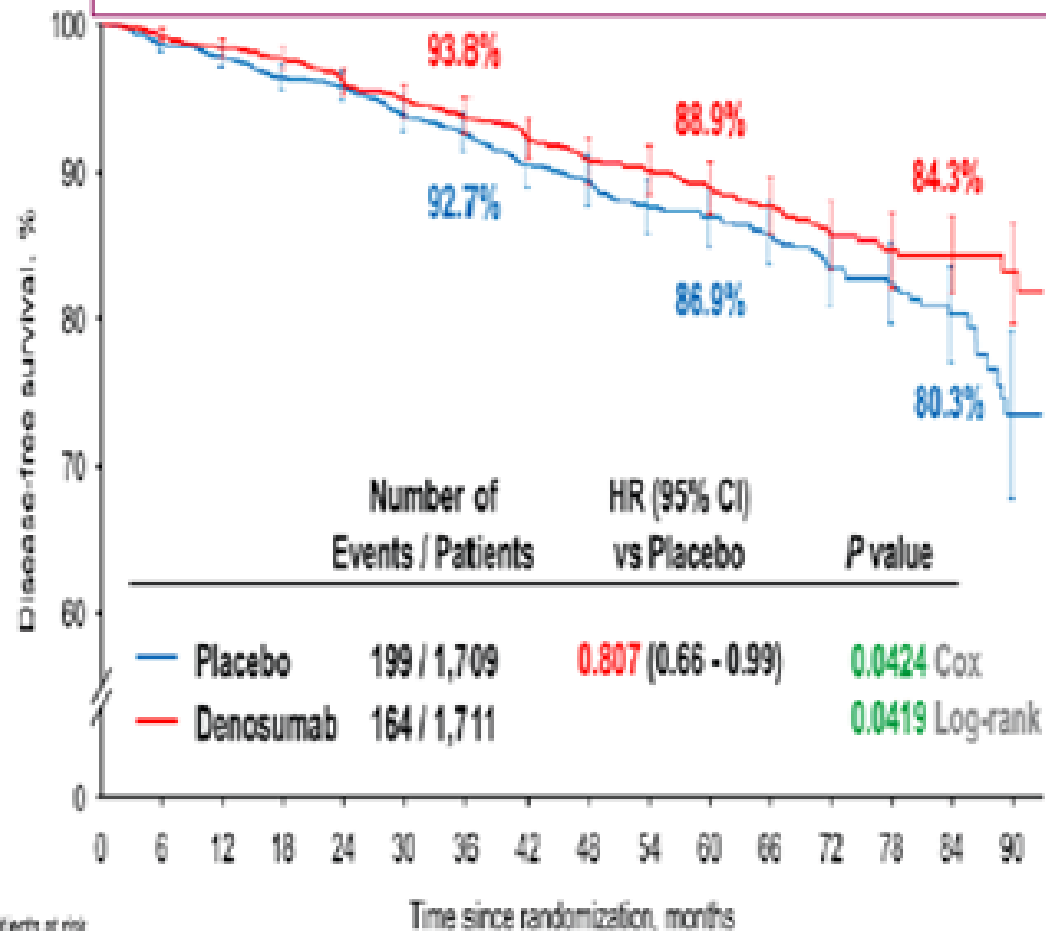


Breast cancer on AI Disease Free Survival: Dmab v. PBO. ABC SG18

ITT Analysis



With Cross-over Patients Censored



Case History: Jean Smith and Long Term Treatment Issues after 5 yr on ALN, now off AI

- » 67 year old woman with low bone density (osteopenia), FN T-score = -2.3, Colles fracture, on AI for breast cancer, maternal hip fracture, prednisone for Polymyalgia Rheumatica, FRAX 43/9.2, taking Ca and Vitamin D, no secondary cause of osteoporosis, on alendronate for 5 years.

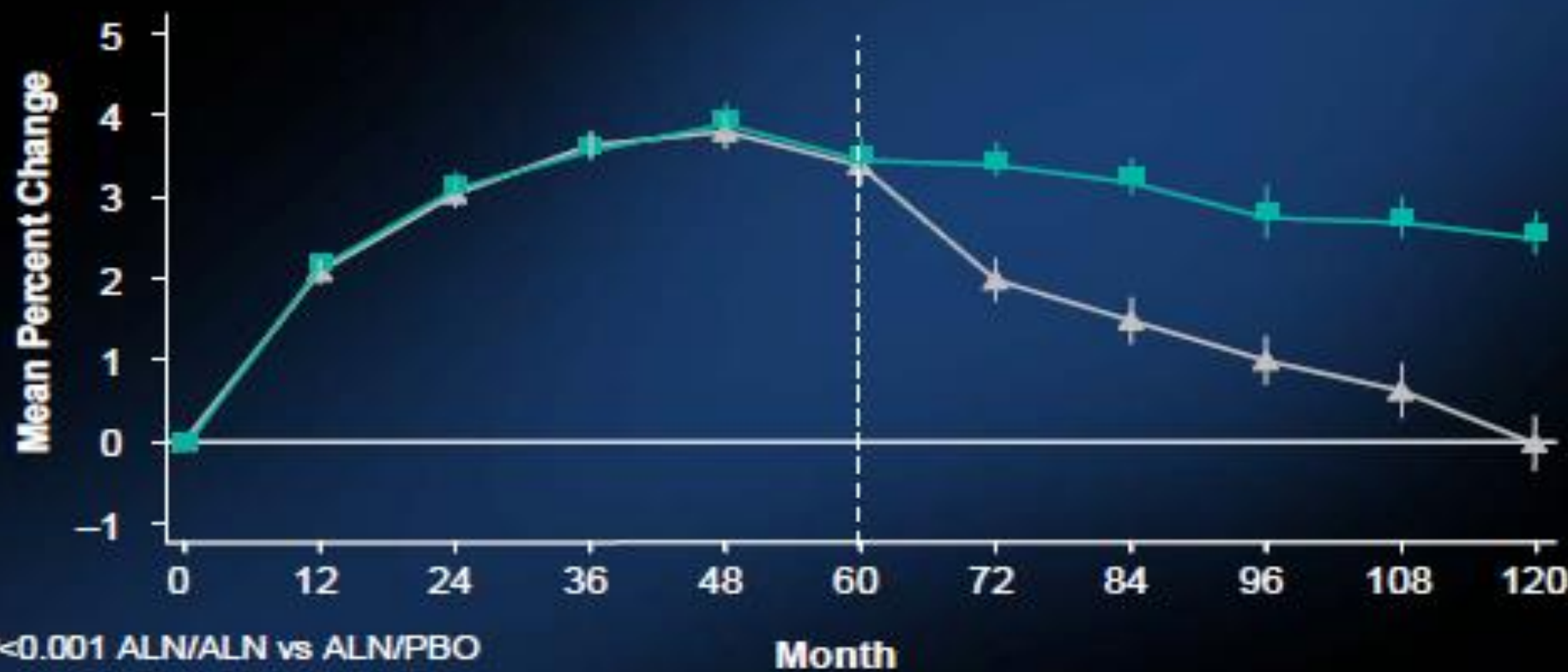
New information:

- Off AI
- Follow-up 5 years later shows FN DXA increased 5%.
Now, FN T-score = -1.9



FLEX — Total Hip BMD Changes From FIT Baseline (mITT)

Mean Percent Change (\pm SE) in Total Spine BMD
From Original FIT Baseline



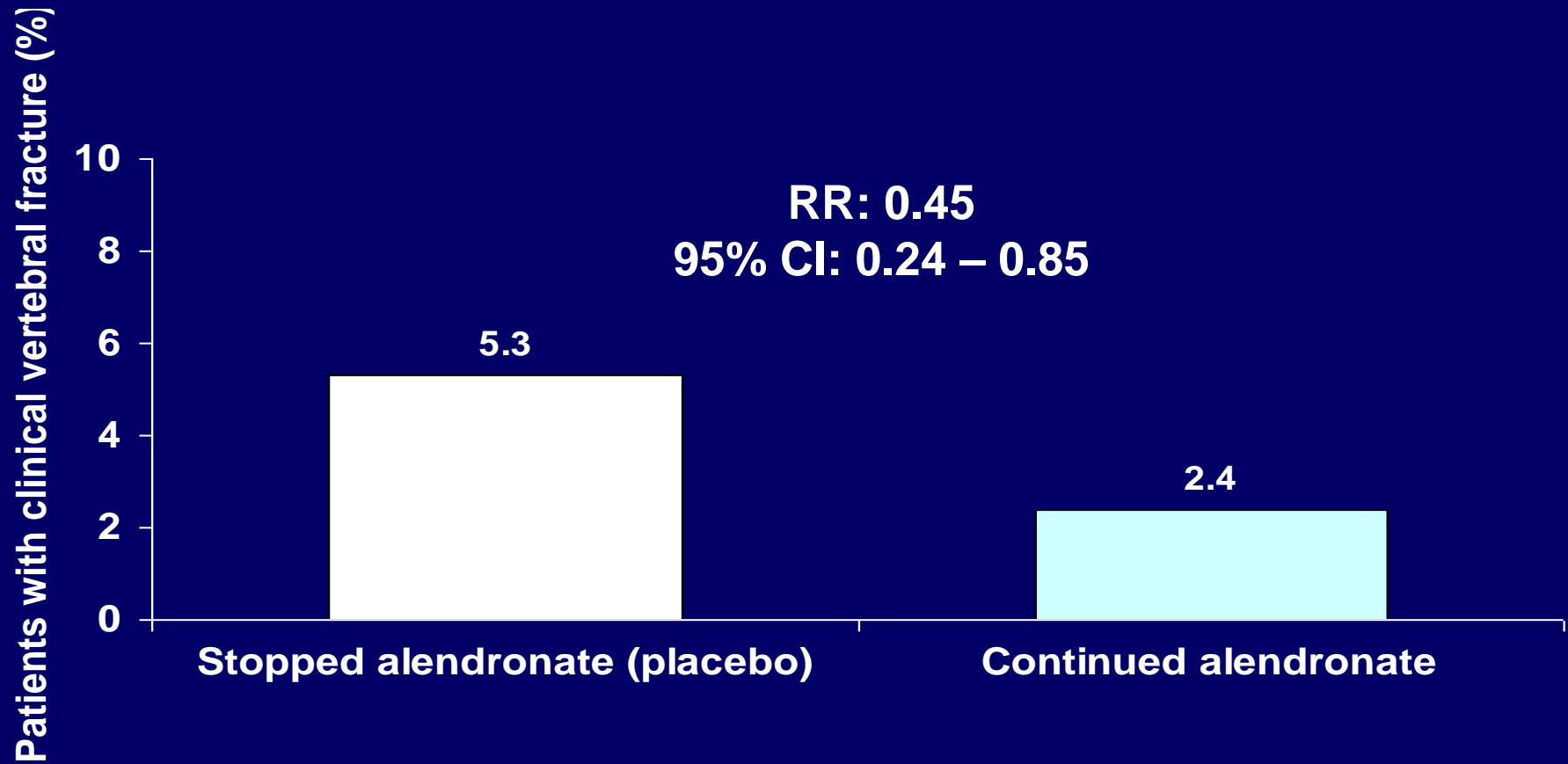
$P < 0.001$ ALN/ALN vs ALN/PBO

Month

▲ = ALN/Placebo

■ = ALN/ALN (Pooled 5 mg and 10 mg groups)

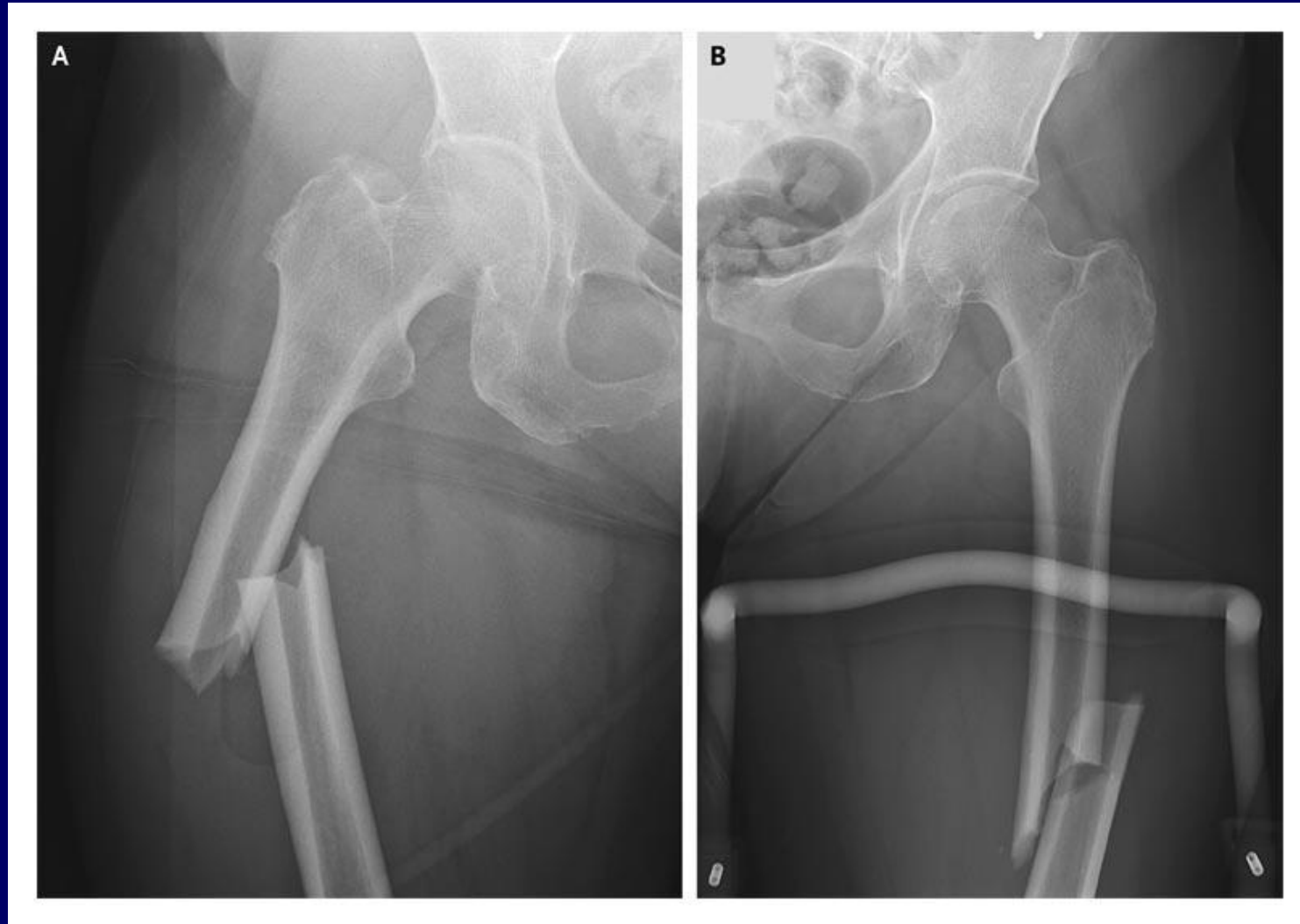
Continuing or Stopping Alendronate After 5 Years (FLEX): Clinical Vertebral Fractures



How long should antiresorptive therapy be continued?

- » Sustained efficacy
- » Sustained safety
- » Resolution of effect (ROE)
 - Incorporation of BP in bone long-term
 - With ALN and ZOL long resolution of effect
 - With all others, short ROE
- » Continue treatment as long as patient remains at risk
 - If, after 5 yr on ALN OR ZOL, BMD T-score < -2.5 or prevalent hip/spine fracture: NO DRUG HOLIDAY

Chalk Stick Fracture



Atypical (Subtrochanteric) Fractures With Antiresorptive Therapy

ASBMR Task Force Definition¹:

Major Features*

- » Subtrochanteric
- » Minimal trauma
- » Transverse configuration
- » Non-comminuted
- » Complete fractures through both cortices (may be associated with a medial spike)
- » Beaking



Image from: Lenart BA, et al. *N Engl J Med.* 2008;358:1304

*4/5 Major features required to define atypical femoral fracture.

Atypical (Subtrochanteric) Fractures With Antiresorptive Therapy

ASBMR Task Force Definition¹:

Minor Features*

- » Increase in cortical thickness
- » Prodromal symptoms
- » Bilateral fractures
- » Delayed healing
- » Comorbid conditions
- » Use of pharmaceutical agents (e.g., BPs, GCs, proton pump inhibitors)

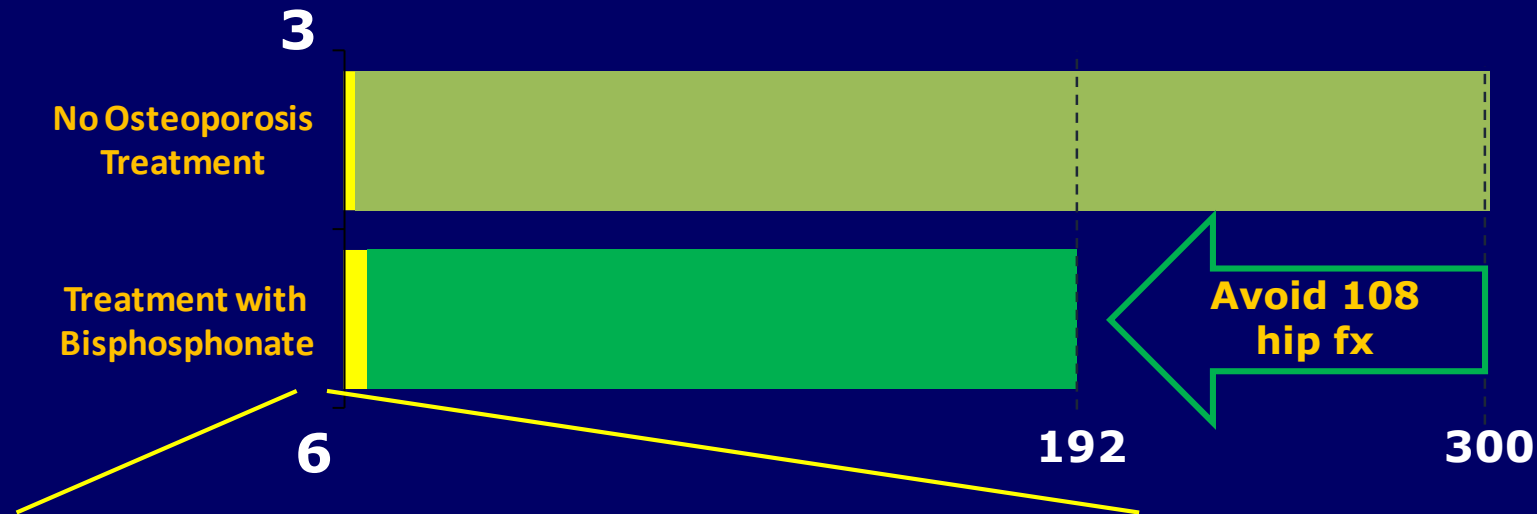


Image from: Lenart BA, et al. *N Engl J Med.* 2008;358:1304

*None of the Minor Features are required but have been sometimes associated with these fractures.

Bisphosphonates Prevent Hip Fractures

Expected Hip Fractures in 10,000 Patients at High Risk¹



Bisphosphonates potentially double subtrochanteric fractures (typical or atypical)¹

- ▶ Hip fractures cause a high rate of morbidity and mortality^{2,3}
- ▶ Incidence of subtrochanteric fracture very low

ONJ: Clinical Description



- » Exposed bone in maxillofacial area that occurs in association with dental surgery or occurs spontaneously, with no evidence of healing*

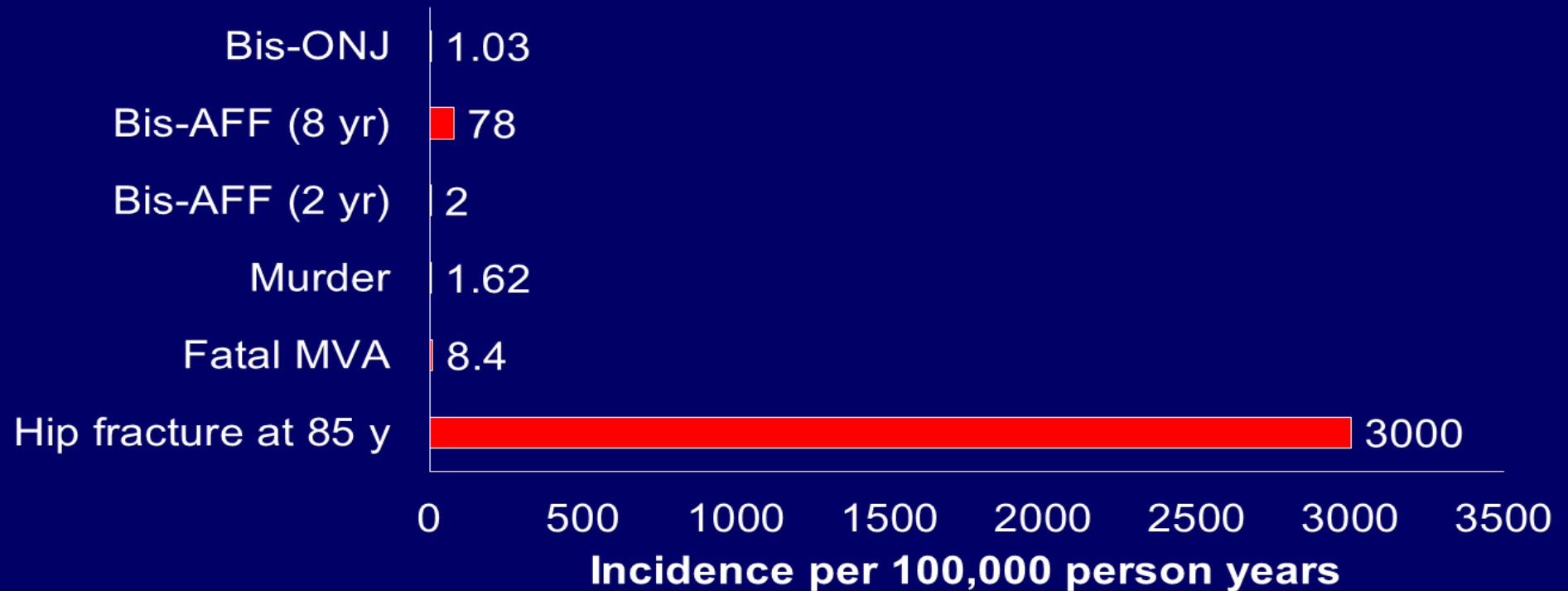


Working Diagnosis of ONJ

- » No evidence of healing after 8 weeks of appropriate evaluation and dental care
- » No evidence of metastatic disease in the jaw or osteoradionecrosis

Relative Risk/Benefit

Risk comparisons



1. Transportation Canada. 2007 Casualty Rates.

2. Statistics Canada. 2009 Homicide Rate.

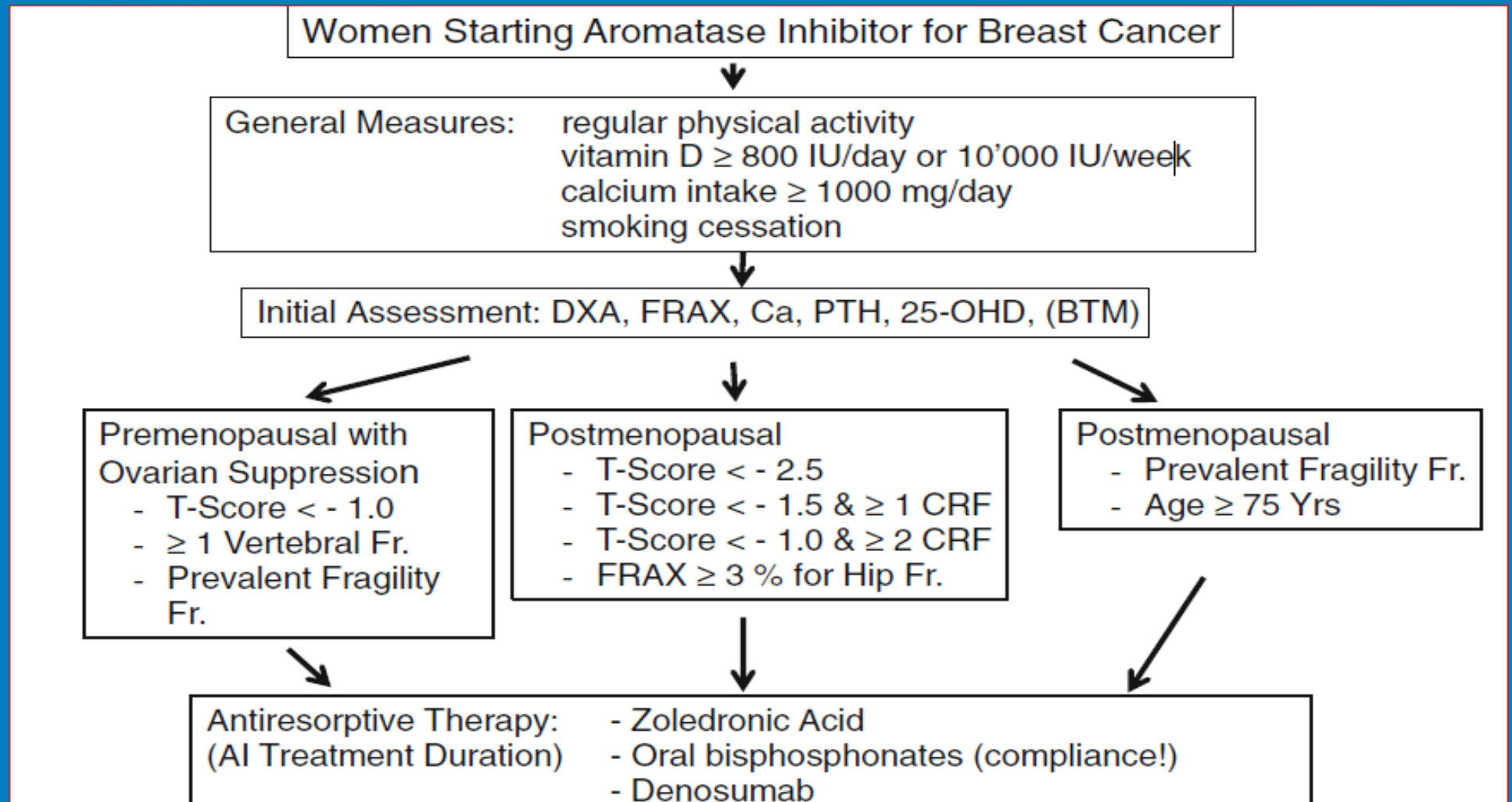
3. Khan A, et al. ASMBR, Toronto, 2010. Poster SA0384.

4. Dell R, et coll. JBMR 2010. 25(Suppl1):61. Abstract 1201

5. Johnell O, Oden A, Caulin F, Kanis JA. Osteoporos Int. 2001;12(3):207-14.

Guidelines for cancer treatment-induced bone loss

IOF 2013 algorithm for managing bone health on AI



ESMO 2014 algorithm for managing bone health during cancer treatment

