Prevention of Bone Fragility in Cancer Survivors

Azeez Farooki, MD
Attending Physician

Endocrinology Service

Memorial Sloan Kettering Cancer Center

Fred Hutchinson Cancer Center Survivorship Program

5th CME course

Outline: bone health in cancer survivors

1) Appreciate risk factors for osteoporotic fracture relevant to cancer survivors and when to screen
2) Discuss adjuvant data on reduction of bone recurrence in postmenopausal breast cancer with antiresorptives
3) Outline current indications, dosing and administration of currently available bone protective agents used in patients with cancer
4) Describe the adverse effects and safety considerations of approved bone protective agents

- Osteoporosis is characterized by:
  - low bone mass
  - structural deterioration of bone tissue
  - susceptibility to fragility fractures
    - commonly: spine, hip & wrist
- Silent until a fracture occurs hence screening bone density rec for:
  - Women ≥ 65, men ≥ 70
    - Younger if risk factors

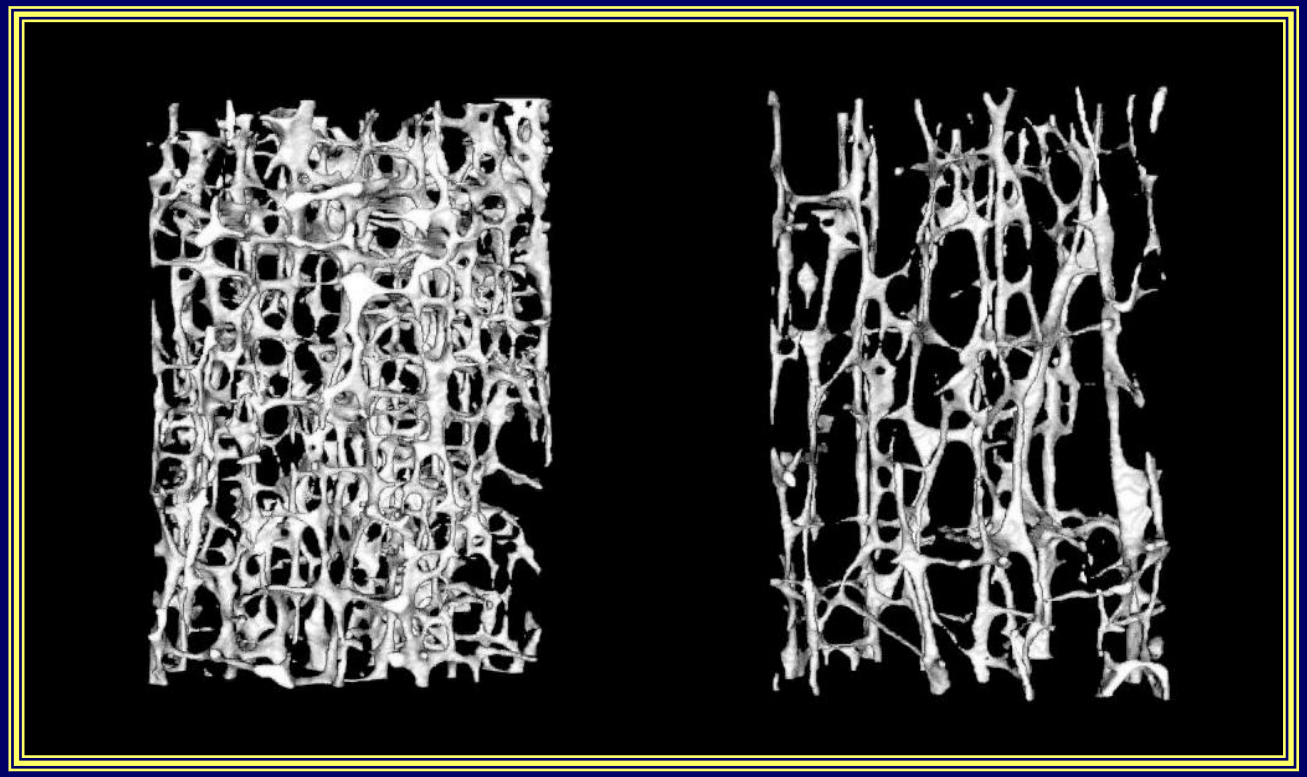
Previous fracture, glucocorticoid therapy, parental history of hip fracture, low body weight, current smoking, ↑ EtOH, rheumatoid arthritis, "secondary osteoporosis" =

- hypogonadism or premature menopause (<45 years), DM-1, chronic malnutrition or malabsorption, chronic liver disease

3-D Micro CT: loss of horizontal trabeculae in osteoporosis

52 year old Female

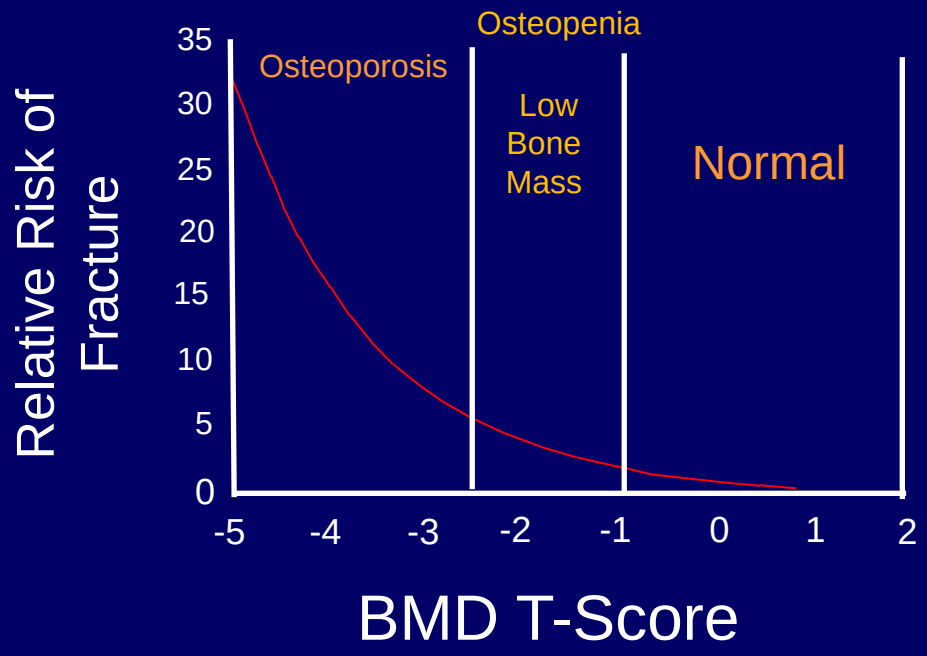
84 year old Female
(with vertebral fracture)



Borah et al, The *Anatomical Record, 265:101-110,* 2001.

Bone density is a major determinant of fracture risk

The more negative the T score, the higher the risk



A fragility fracture of the hip or spine makes the clinical diagnosis of osteoporosis and warrants treatment

Fragility fracture = a fracture after fall from standing height or without trauma

Meunier P. et al. Clin Ther 1999: 21:1025

Mechanisms of bone loss / fragility in cancer

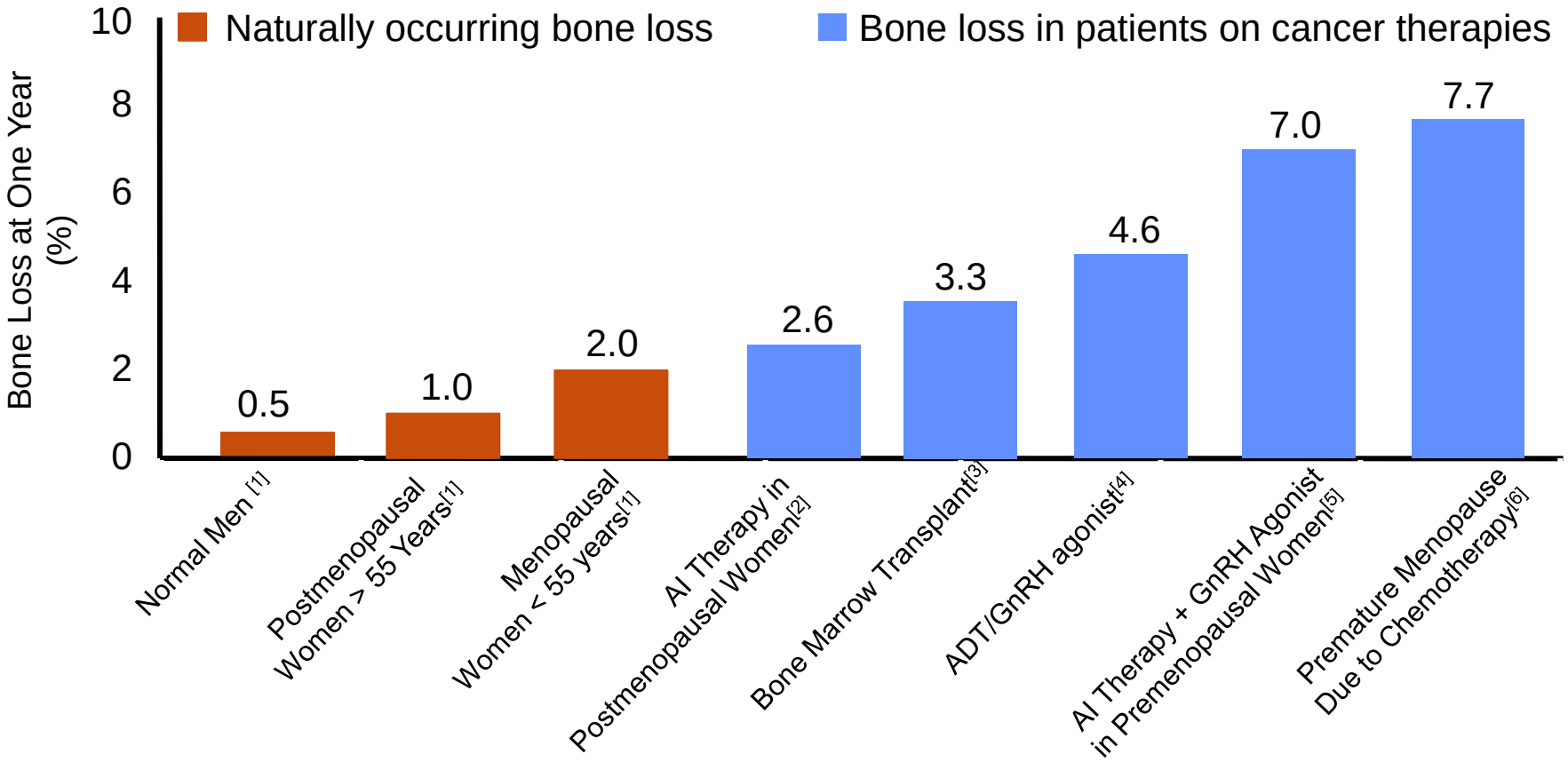
	Mechanisms
Drugs: opiates, steroids, alkylating agents	hypogonadism
Solid tumors: Breast, Endometrial, Ovarian Prostate	Hypogonadism “ “ +/- secondary hyperparathyroid
Various	Weight loss, cachexia
Myeloma spectrum disorders	OB inhibition, rarely osteomalacia
Leukemia (ALL, CML)	Steroids, ? TKIs
Lymphoma	steroids
Stem cell transplant	Steroids / GVHD, malabsorption, immunosuppressives, chemo
Neuroendocrine cancer (ANY)	Ectopic ACTH, Cushing’s

1. De Maddalena C et al, Pain Physician 2012
2. Drake MT JBMR 2014
3. Ruchlemer et al, Support Care Cancer (2018) 26:3013–3020
4. Westin JR et al Clin Lymphoma Myeloma Leuk 2013;13(2):99-105.
5. Pundole X et al, Bone Marrow Transplant. 2017

Drugs that may ↑ fracture risk

- Glucocorticoids (PO + high dose inhaled)
- Excessive thyroid replacement
- Proton pump inhibitors
- Anticonvulsants
- Long-term heparin use
- GnRH agonists (Lupron): prostate cancer
- aromatase inhibitors
- Thiazolidinediones
- Sedative hypnotics (FALL risk)
- Furosemide: falls ± calciuresis
- Opiates (cause hypogonadism)

DXA at the 1 year mark can be justified based on potential large amounts of bone loss with cancer therapies



1. Kanis JA. Osteoporosis.1997:22-55.
2. Eastell R, et al. J Bone Mineral Res. 2002.
3. Lee WY, et al. J Clin Endocrinol Metab. 2002;87:3329-3353.
4. Maillefert JF, et al. J Urol. 1999;161:1219-1222.
5. Gnant M. SABCS 2002. Abstract.
6. Shapiro CL, et al. J Clin Oncol. 2001;19:3306-3311.

Abbreviations: ADT: androgen deprivation therapy; AI: aromatase inhibitor; GnRH: gonadotropin-releasing hormone

5 years on aromatase inhibitor versus tamoxifen: ↑ bone loss & fractures

- Mean baseline age = 64 n= 108

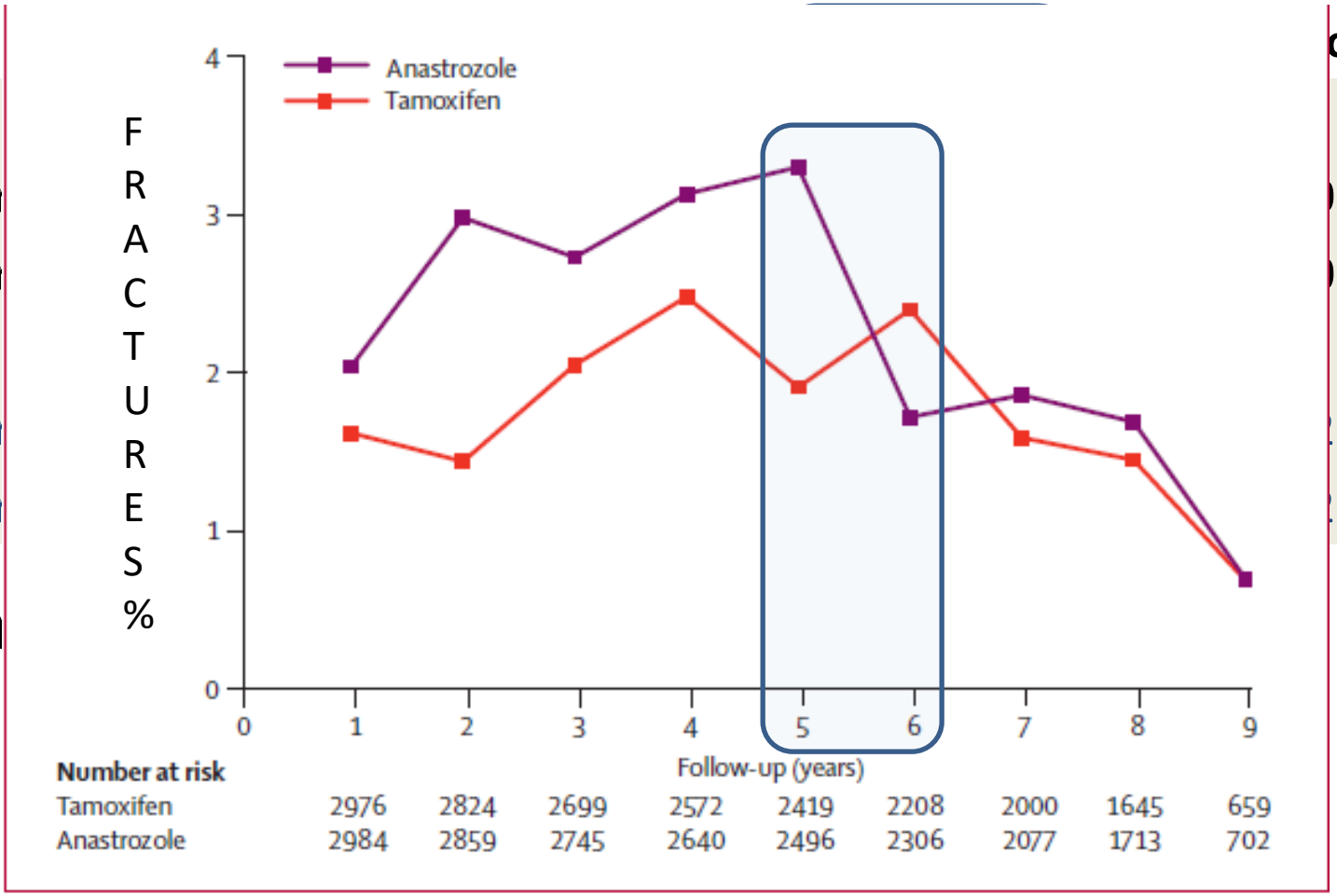
median Δ BMD

	anastrozole	tamoxifen
Lumbar Spine	**6.1% loss**	**2.8% gain**
Hip	**7.2% loss**	**0.7% gain**
Fracture incidence (P < .0001)	**11%**	**7.7%**

Eastell et al. Effect of Anastrozole on Bone Mineral Density: 5-Year Results From the Anastrozole, Tamoxifen, Alone or in Combination Trial. **J Clin Oncol 2008**

After AI stopped at 5 yr mark:

1) BMD recovery year 6-7 2) ↓ fractures

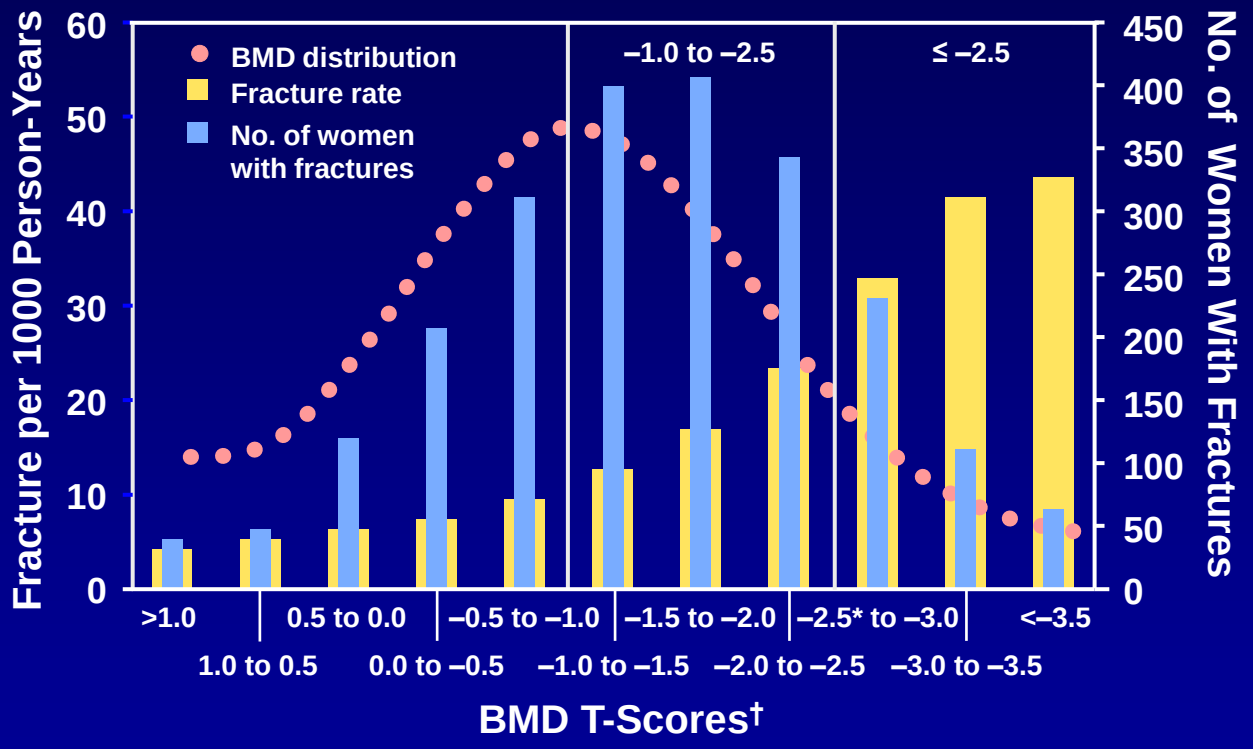


1. Eastell R, et al. Ann Oncol. 2011

2. Forbes JF et al. Lancet Oncol. 2008

Risk factors for osteoporotic fracture and the FRAX calculator

A higher **number** of fractures occur in women with osteopenia than with osteoporosis



*The World Health Organization defines osteoporosis as a T-score ≤ –2.5
†Peripheral devices used to measure T-score
Adapted with permission from Siris ES et al. *Arch Intern Med*. 2004;164:1108-1112.

Prior fracture at any site increases risk of future fracture at all other sites

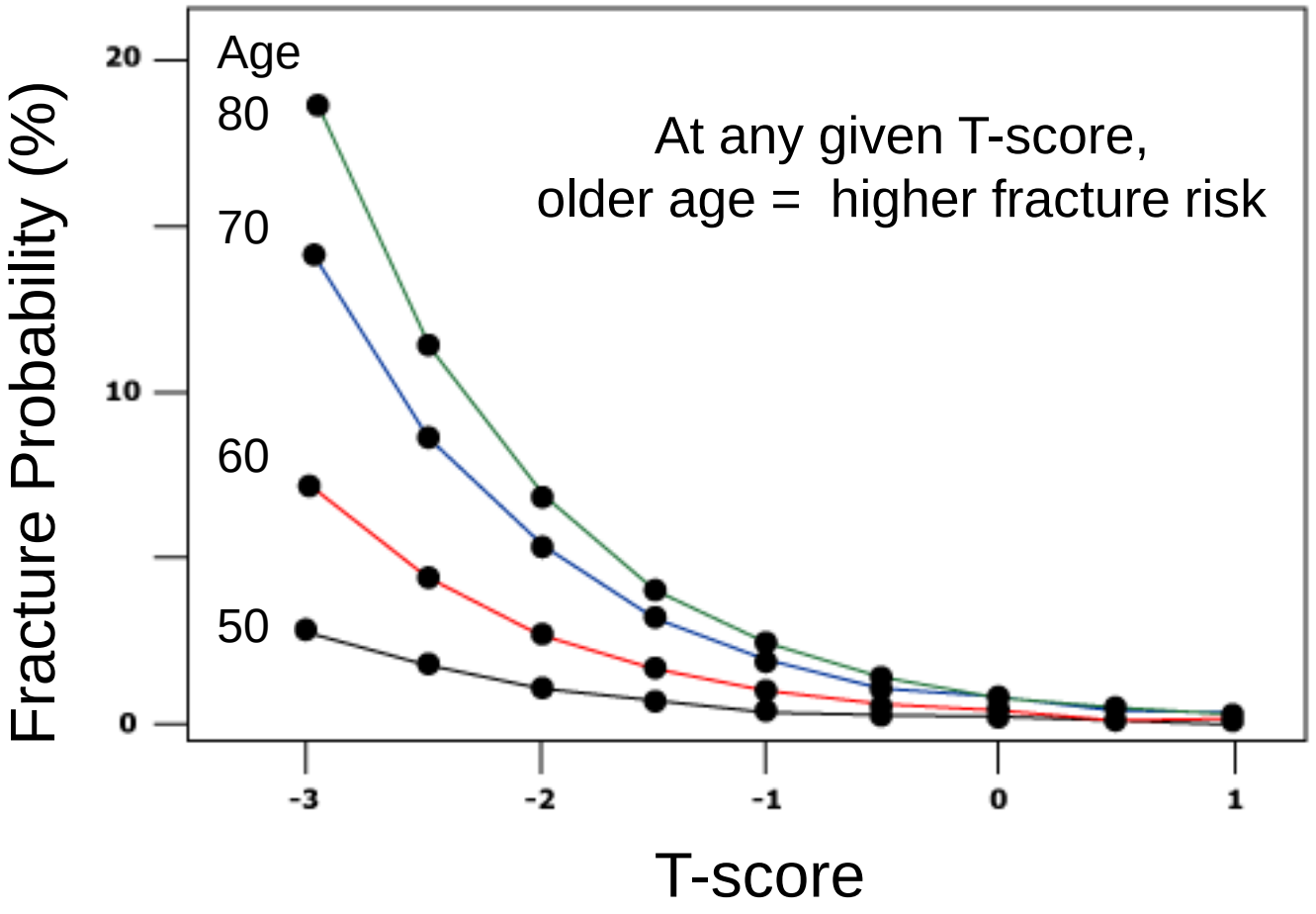
Prior Fracture	Relative Risk of Future Fractures		
	Wrist	Vertebral	Hip
Wrist	3.3	1.7	1.9
Vertebral	1.4	4.4	2.3
Hip	NA	2.5	2.3

Fragility fracture = without trauma or after fall from standing height

NA = not available.

Klotzbuecher CM et al. *J Bone Miner Res.* 2000;15:721-739.

Age Independently Predicts Hip Fracture Risk



T-score= standard deviations below healthy young normal bone density

Adapted from Kanis et al, Osteoporos Int 2001;12(5):417-27.

FRAX Online WHO Fracture Risk Calculator: For Use in Osteopenia (T score -1.1 to -2.4)

Calculation Tool

Weight Conversion:
pound: 105
convert
105 pound = 47.63 kg

Height Conversion:
inch : 60
convert
60 inch = 152.4 cm

Steroids: ≥ 5 mg prednisone per day for ≥ 3 months

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

Country : US(Caucasian) Name / ID : About the risk fact

Questionnaire:

1. Age (between 40-90 years) or Date of birth
   Age: 75 Date of birth: Y: M: D:
2. Sex ○ Male ◉ Female
3. Weight (kg) 47
4. Height (cm) 152
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 more units per day ◉ No ○ Yes
12. Femoral neck BMD
    T-score -2.5

Clear Calculate

BMI 20.3
The ten year probability of fracture (%)
with BMD

Major osteoporotic	40
Hip fracture	8.5

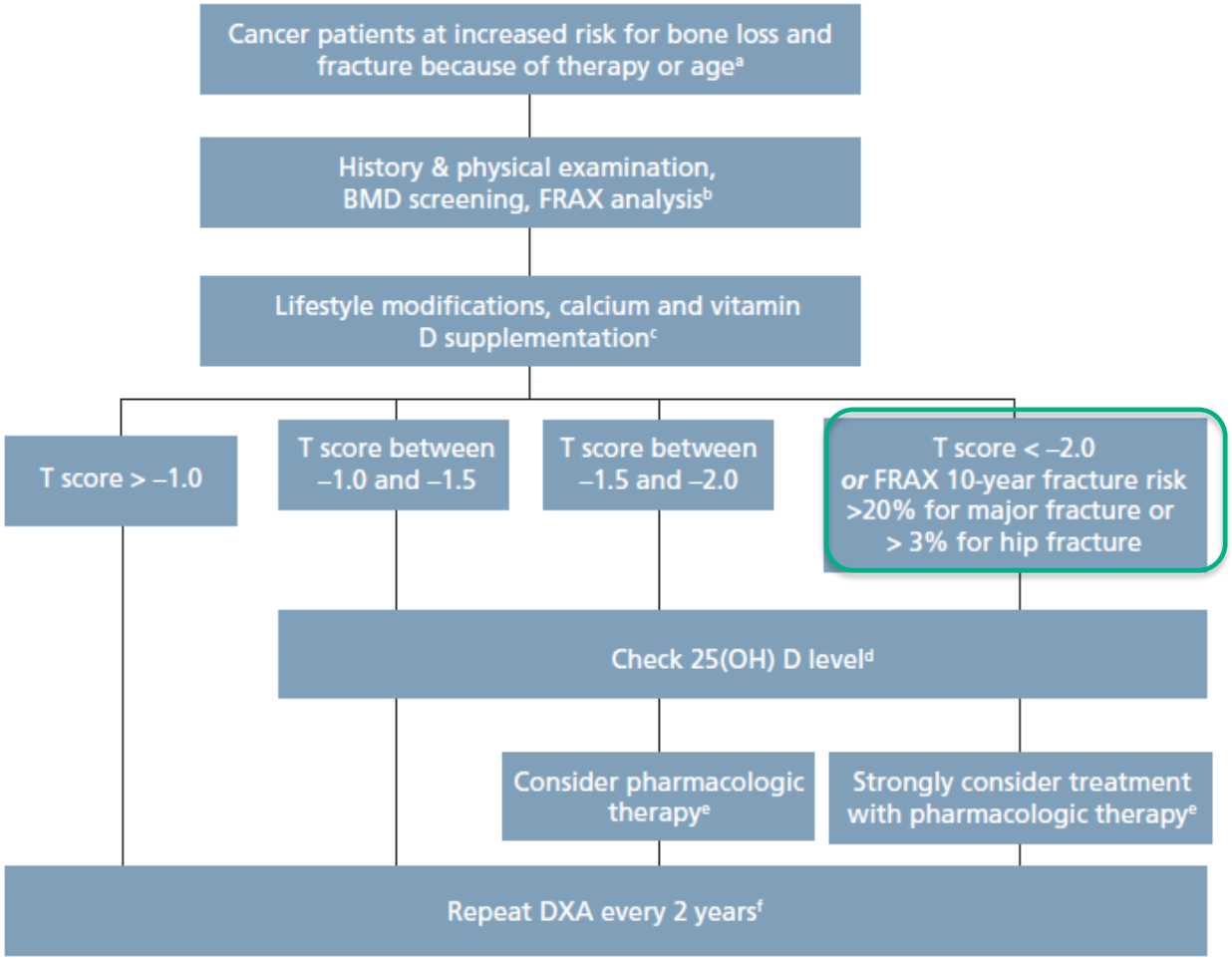
If BMD is known, this is a “dummy button”

10-year fracture probability

Treat if:
> 20% or
> 3%

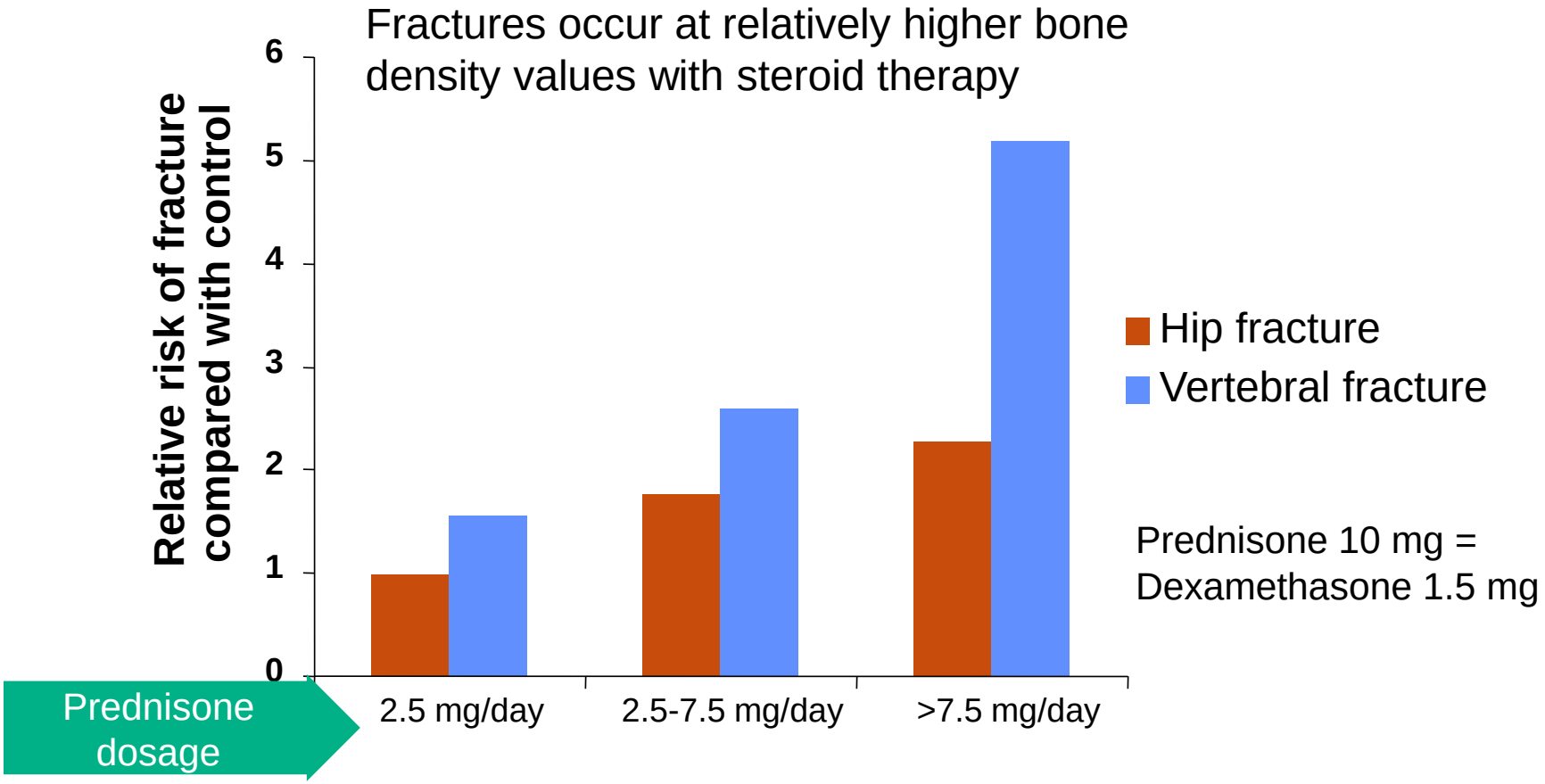
FRAX Online WHO Fracture Risk Calculator

NCCN bone health task force: lower treatment threshold in cancer patients, use clinical judgment



Gralow et al JNCCN 2013

Fracture Risk Increases at Low Doses of Daily Corticosteroids



For all patients on steroid ≥ 7.5 mg/day, anticipated duration ≥ three months: start calcium, vitamin D, and drug therapy

Relative risk of fracture by dosages of corticosteroids- prednisolone. van Staa TP, et al, 1998.

Multiple uses of antiresorptives (bisphosphonates and denosumab) in cancer

Non-metastatic:

Osteoporosis doses

- Prevent bone loss, fractures
  - ADT[1], aromatase inhibitor[2]
- 2015: adjuvant effect in breast cancer[3,4]

1. Smith MR et al, NEJM 2009 2. Gnant M et al, Lancet 2015 3. Gnant M, Lancet Oncol 2019
4. EBCTCG, Lancet 2015 5. Mancini I, et al. J Clin Oncol. 2004[5]

Meta analysis of 38 trials of adjuvant bisphosphonate vs placebo in breast CA

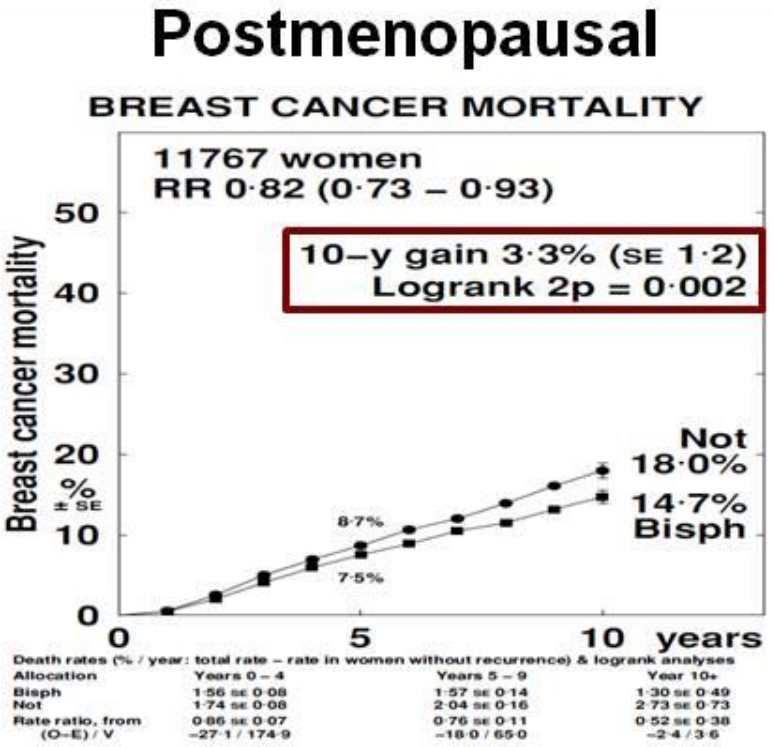
	# trials	# patients	Trials received	Patients received	% received
Any clodronate regimen	7	5167	5	5053	98%
Any amino-bisphosphonate	31	16860	21	13713	81%
Total, all regimens	**38**	22027	26	18766	85%

- treatment duration: 2–5 years (mean 3.4 years)
  - median follow up 5.6 woman-years

EBCTCG. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials, Lancet 2015

In postmenopausal: mortality benefit similar to adjuvant chemotherapy, regardless of ER status

	Absolute benefit	Follow up Duration
Bisphos-phonates	3.1%	10 years
Anthracyclin over CMF	3%	5 years
Taxanes + anthracyclin e	3.2%	8 years



Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	2·43 SE 0·14	2·26 SE 0·21	1·13 SE 0·28
Not	2·50 SE 0·15	2·03 SE 0·19	1·29 SE 0·30
Rate ratio, from (O–E) / V	0·97 SE 0·09 −3·3 / 130·6	1·10 SE 0·15 5·0 / 50·0	0·71 SE 0·32 −2·3 / 6·9

Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	1·56 SE 0·08	1·57 SE 0·14	1·30 SE 0·49
Not	1·74 SE 0·08	2·04 SE 0·16	2·73 SE 0·73
Rate ratio, from (O–E) / V	0·86 SE 0·07 −27·1 / 174·9	0·76 SE 0·11 −18·0 / 65·0	0·52 SE 0·38 −2·4 / 3·6

‡ includes women aged < 45 if unknown

PRESENTED AT: ASCO Annual '15 Meeting

"postmenopausal" definition: natural or induced by GnRH agonist

EBCTCG, Lancet 2015

3.3% mortality benefit (= to adjuvant chemo) in postmenopausal was driven by less bone recurrence over yrs 0-4

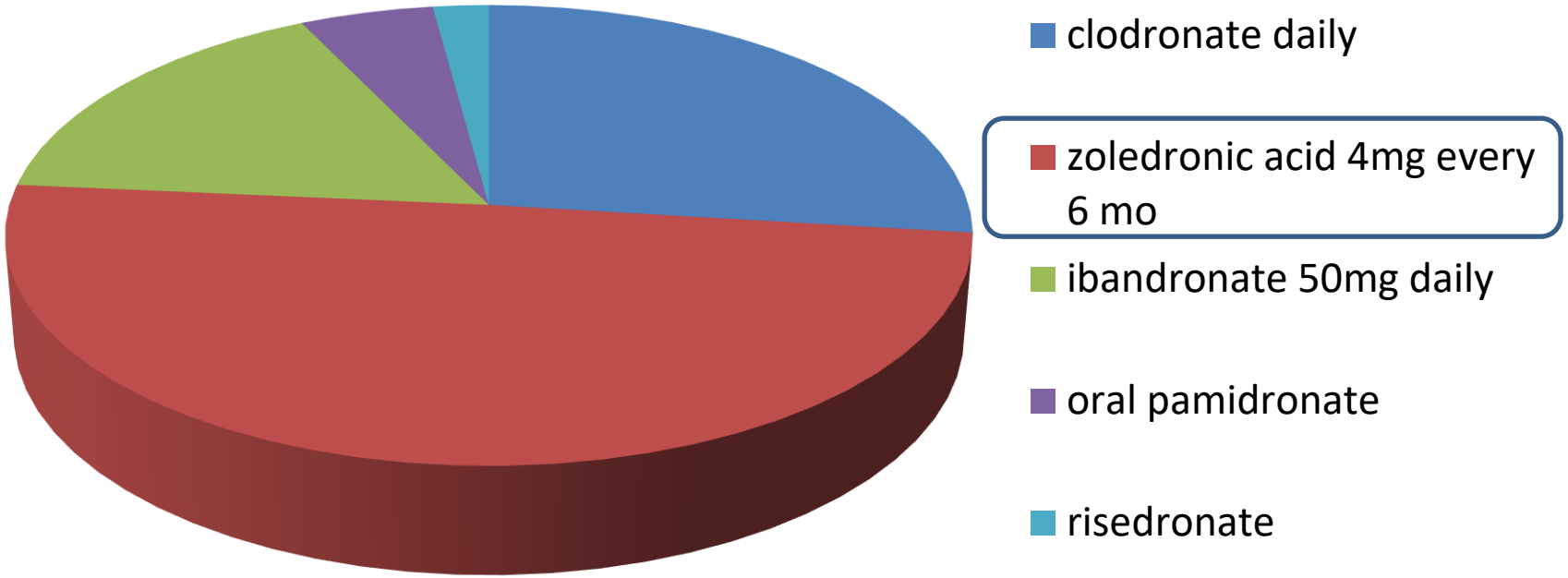
11,767 postmenopausal women	Bone recurrence %		Breast cancer mortality %	
	placebo	bisphos	Placebo	bisphos
5 years	5.4	3.6	8.7	7.5
10 years	8.8	6.6	18	14.7
	RR= 0.72 (0.6-0.86) 2p=0.0002		RR= 0.82 (.73-.93) 2p=0.002	

No difference in non-breast cancer mortality RR = 0.99 (0.82 – 1.19)

RR = 0.99, 95% CI 0.82–1.19; 2p=0.91

Memorial Sloan Kettering Cancer Center

Zoledronic acid: most commonly studied, dosing frequency available in US



EBCTCG. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials, Lancet 2015

Adjuvant denosumab in breast CA

primary endpoint = time to 1st clinical fracture

- Prospective, randomized, double-blind, placebo-controlled
- Mean age = 64 (38-91); 45% subjects with normal BMD

Postmenopausal early HR+ breast cancer receiving adjuvant AI*

→ Denosumab 60 mg SC Q6M (n = 1711)

→ Placebo SC Q6M (n = 1709)

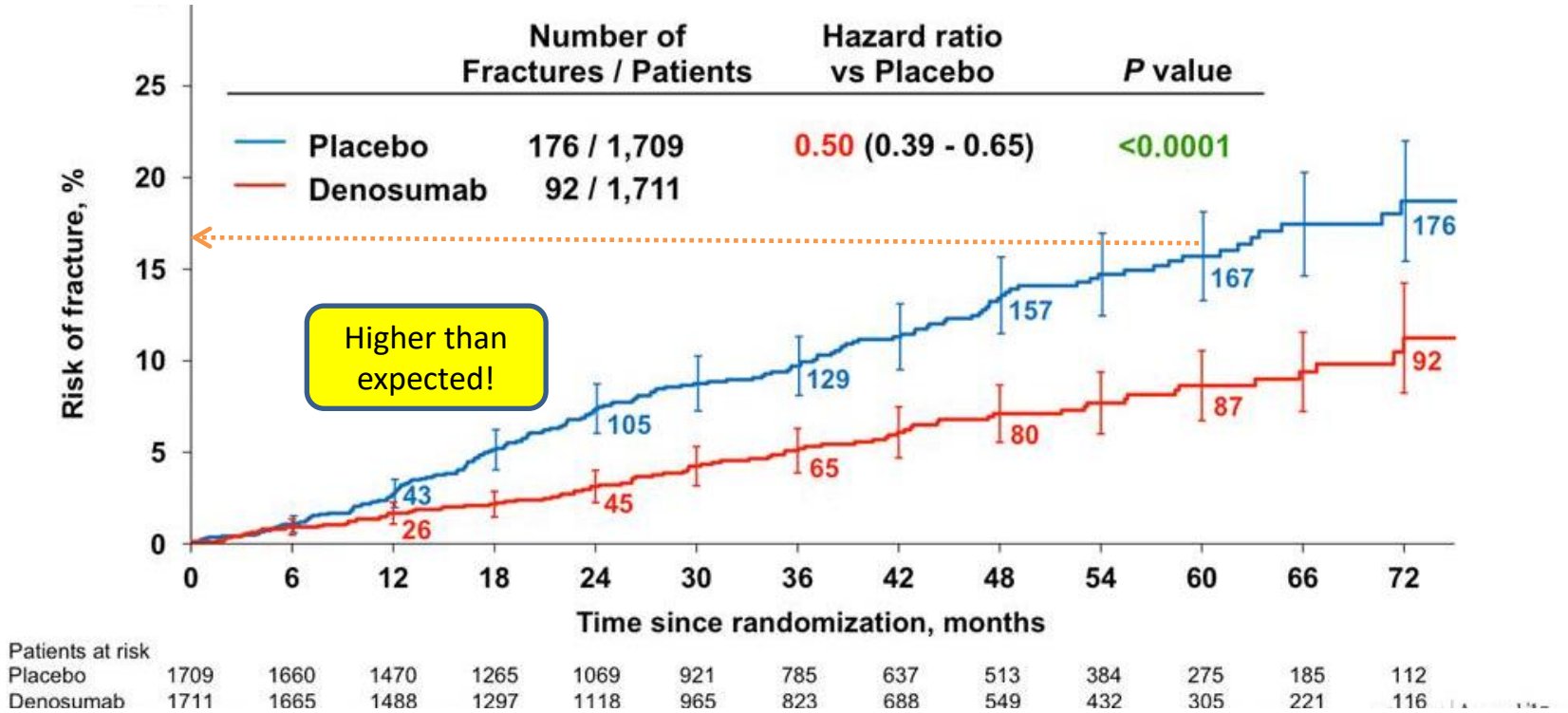
*EXCLUSIONS: history IV bisphosphonate, oral bisph x 3 years (or if less, off x 1 year), SERMS, Cushing's disease, Paget's disease, hyper / hypocalcemia, hyperprolactinemia, or other active metabolic bone disease.

- Secondary endpoints: Δ BMD, vertebral fractures, cancer free survival, bone met free survival, overall survival

Memorial Sloan Kettering Cancer Center

Gnant M, et al. ABCSG-18 Lancet. 2015.

1. Denosumab reduced fracture risk vs placebo
2. BMD may underestimate fracture risk in aromatase inhibitor treated patients



- Zero case of osteonecrosis of the jaw and atypical femur fracture
- Median doses / time on study: 7 doses / 38 months.
- Patients treated until the prespecified # of 247 first clinical fractures reached

Memorial Sloan Kettering Cancer Center

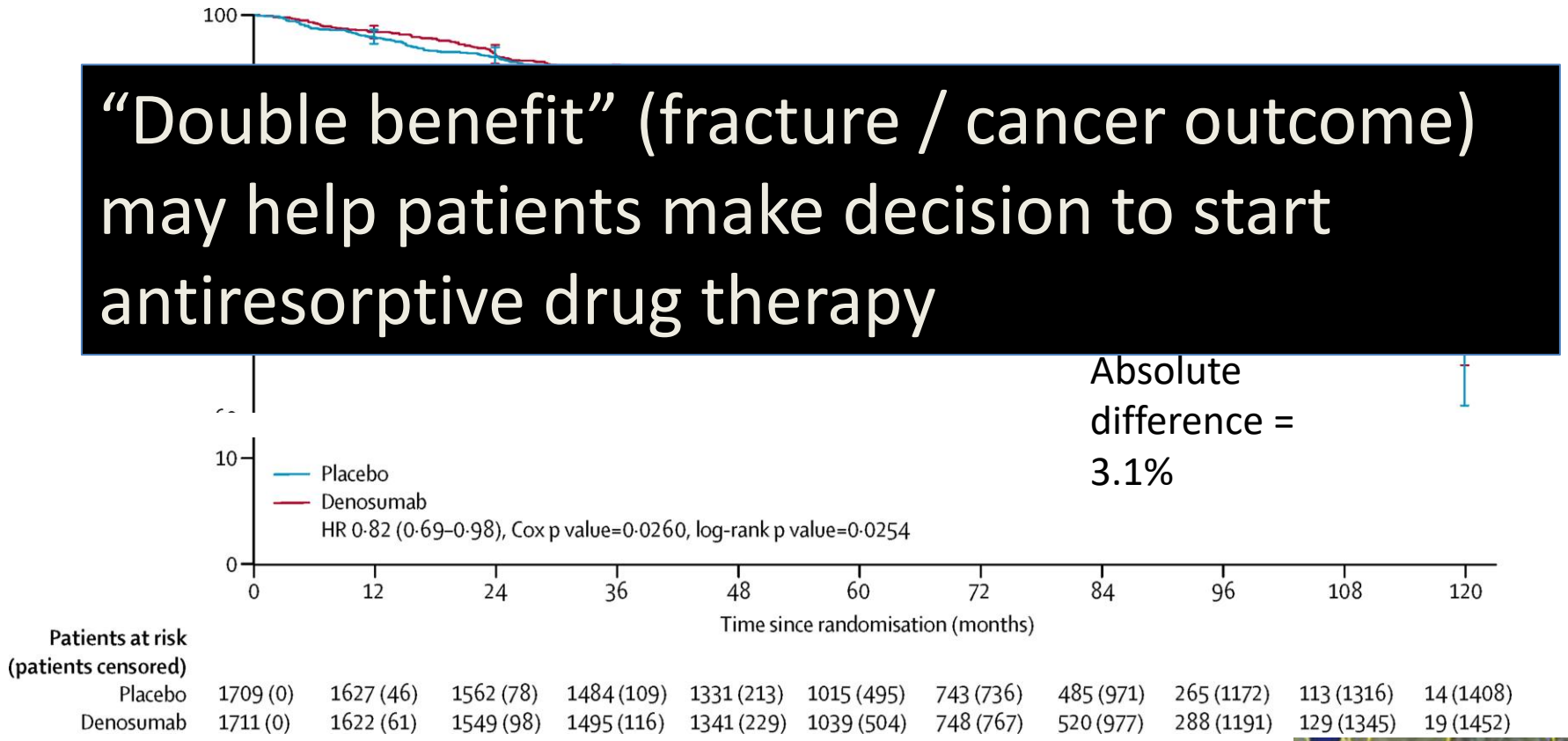
Gnant et al, Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2015

FRAX 10 yr risk for 64 yo Caucasian with osteopenia ~ double that of other ethnicities hence ABCSG-18 population was higher risk for fractures

	FRAX major osteoporotic fracture	FRAX hip fracture risk
US Caucasian	11%	1.6%
Austria	9.8%	2.3%
US Black	4.8%	0.7%
US Latino	6.0%	0.9%
US Asian	5.9%	0.9%

99% Austrian or Swedish patients in ABCSG-18

Denosumab 60mg q6 months improves Disease-Free Survival in breast CA



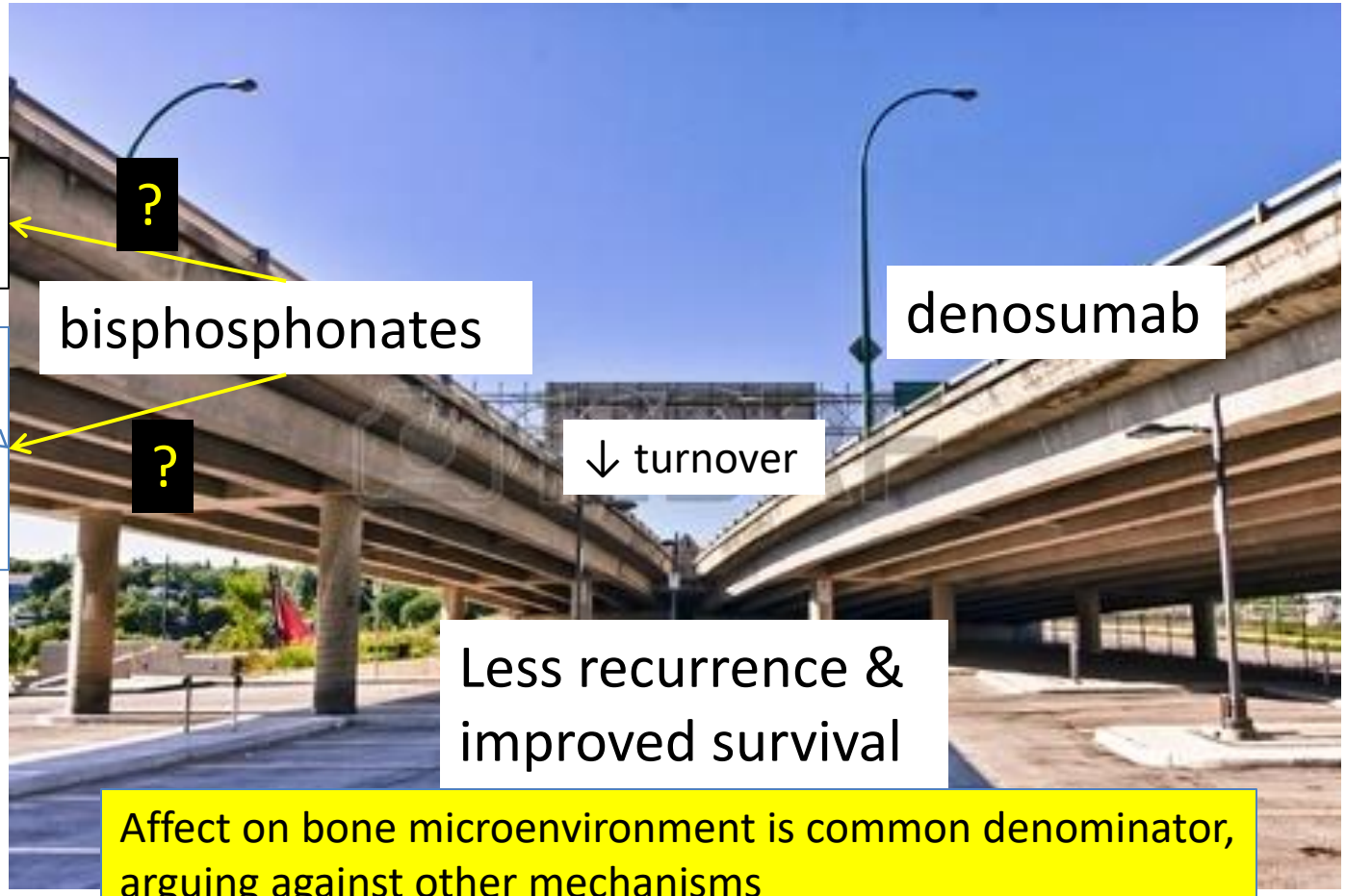
"Double benefit" (fracture / cancer outcome) may help patients make decision to start antiresorptive drug therapy

***All subjects had recently initiated adjuvant aromatase inhibitors**
- Median doses of DMAb = 7 [IQR 4-10]

Memorial Sloan Kettering Cancer Center

Not FDA approved adjuvant therapy. Gnant et al, Lancet Oncol. 2019

2015: Converging data for better survival (adjuvant) in postmenopausal breast CA



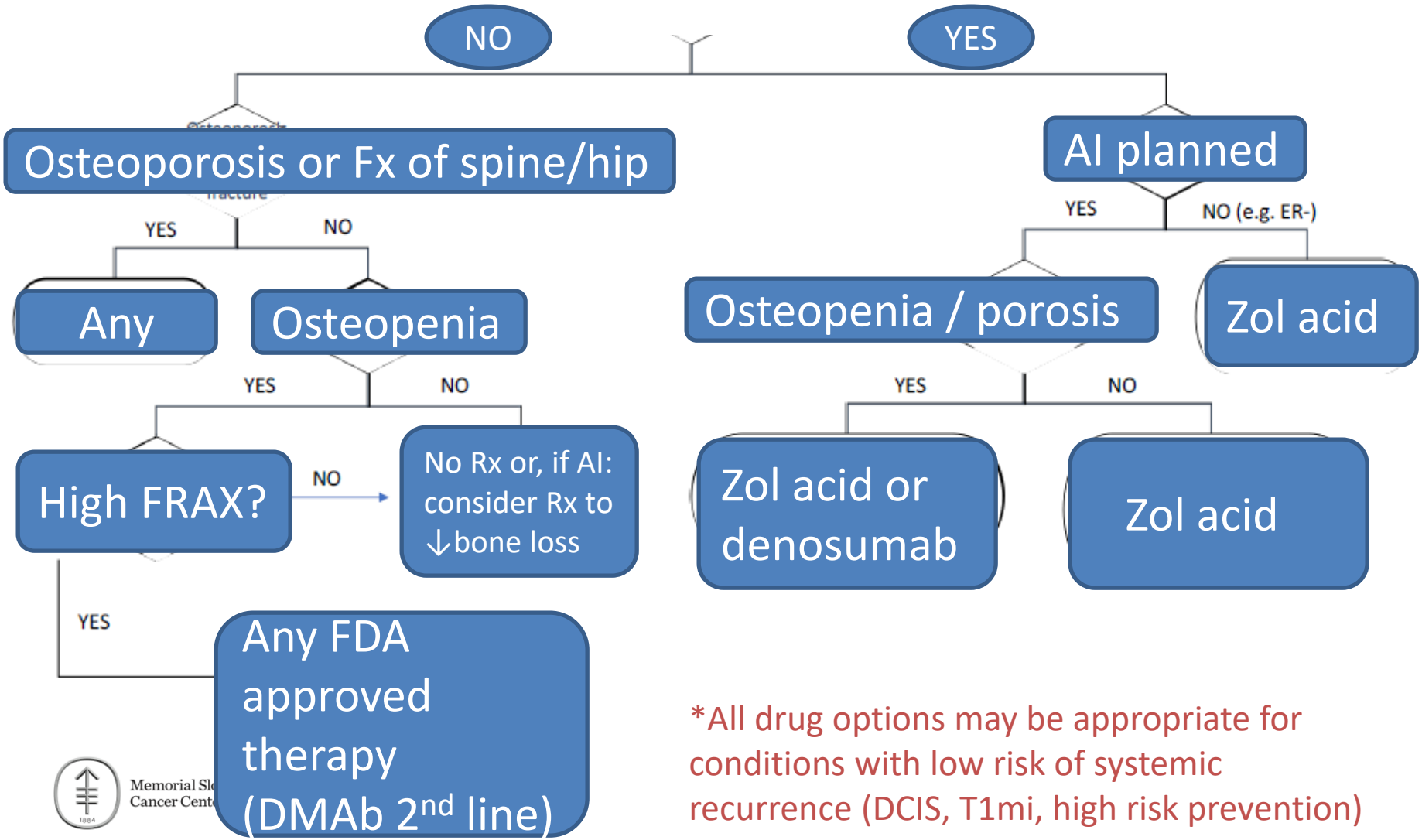
Affect on bone microenvironment is common denominator, arguing against other mechanisms

In contrast to ABCSG-18, the D-CARE study of DMAb 120mg fails to show adjuvant benefit

	ABCSG -18	D-CARE
Inclusion criteria	Postmenopausal ER/PR+ (100%) HER2+ or - All on adjuvant non-steroidal Aromatase inhibitors (AI)	Pre or postmenopausal (% not presented) HR+ or – (75%) HER2+ or – Not all on adjuvant AIs
Dose and Schedule	60mg SC q6m	120mg SC q3-4w for 1st 6 doses 120mg SC q3m for next 54m
Patients demography	**71% Node negative** 6% HER2+ **75% No chemo**	**95% Node positive** 20% HER2+ **4% No chemo**
Primary endpoint	Time to first clinical fracture	Bone metastasis-free survival
Secondary endpoint	DFS	DFS/OS
Results primary endpoint	Benefit for denosumab (HR 0.50)	No benefit for denosumab
Results secondary endpoint	Benefit for denosumab (HR 0.82)	No benefit for denosumab
Osteonecrosis of Jaw	None	5%

Coleman RE et al, Lancet Oncol 2020; 21: 60–72

POSTmenopausal breast cancer algorithm for use of bone modifying agents to protect bone mineral density and/or achieve adjuvant benefit



Treatments for osteoporosis: FDA approval requires ↓ spine fractures

ANTIRESORPTIVE = ANTI-CATABOLIC = inhibitor of osteoclast activity

Antiresorptives

- Bisphosphonates: IV & PO
- **SERMs:** raloxifene, tamox
- ~~Calcitonin~~
- Estrogen (HRT)
- Denosumab

ANABOLIC= stimulates OSTEOBLAST activity

Anabolics

In patients with cancer[2]

- Teriparatide, abaloparatide
- Romosozumab (sclerostin mAb)

Calcium and vitamin D are important in cancer patients with bone loss

- When using potent antiresorptives (zol acid and densoumab), essential to get enough calcium and vitamin D to prevent hypocalcemia
- Calcium goal: 1200mg from food plus pills
  - Caution if calcium nephrolithiasis
- Vitamin D : check 25-OHD level
  - Goal 25-OHD level = 30 ng/mL
  - 2022 NEJM randomized trial[1] found no effect of 2000 IU vitamin D in healthy subjects
    - Vast majority did not have osteoporosis
    - Vast majority had normal 25-OHD level to start with

1. LeBoff MS et al, NEJM 2022

Specific FDA approval for zoledronic acid and denosumab for “endocrine therapy” in cancer

	Zoledronic Acid	Denosumab 120mg monthly	Zoledronic Acid 5mg yearly	Denosumab 60mg every 6 months
CANCER RELATED				
Endocrine-therapy[1] induced osteoporosis / osteopenia	√ 4mg q6 months	-	-	√
OSTEOPOROSIS				
Postmenopausal osteoporosis (PMO)	-	-	√	√
Prevention of PMO (osteopenia)	-	-	√	-
Men	-	-	√	√
Glucocorticoid therapy	-	-	√	√

Memorial Sloan Kettering Cancer Center

1. aromatase inhibitors or androgen deprivation therapy

Concerns with use of PTH analogues in CA survivors of solid tumors that can go to bone

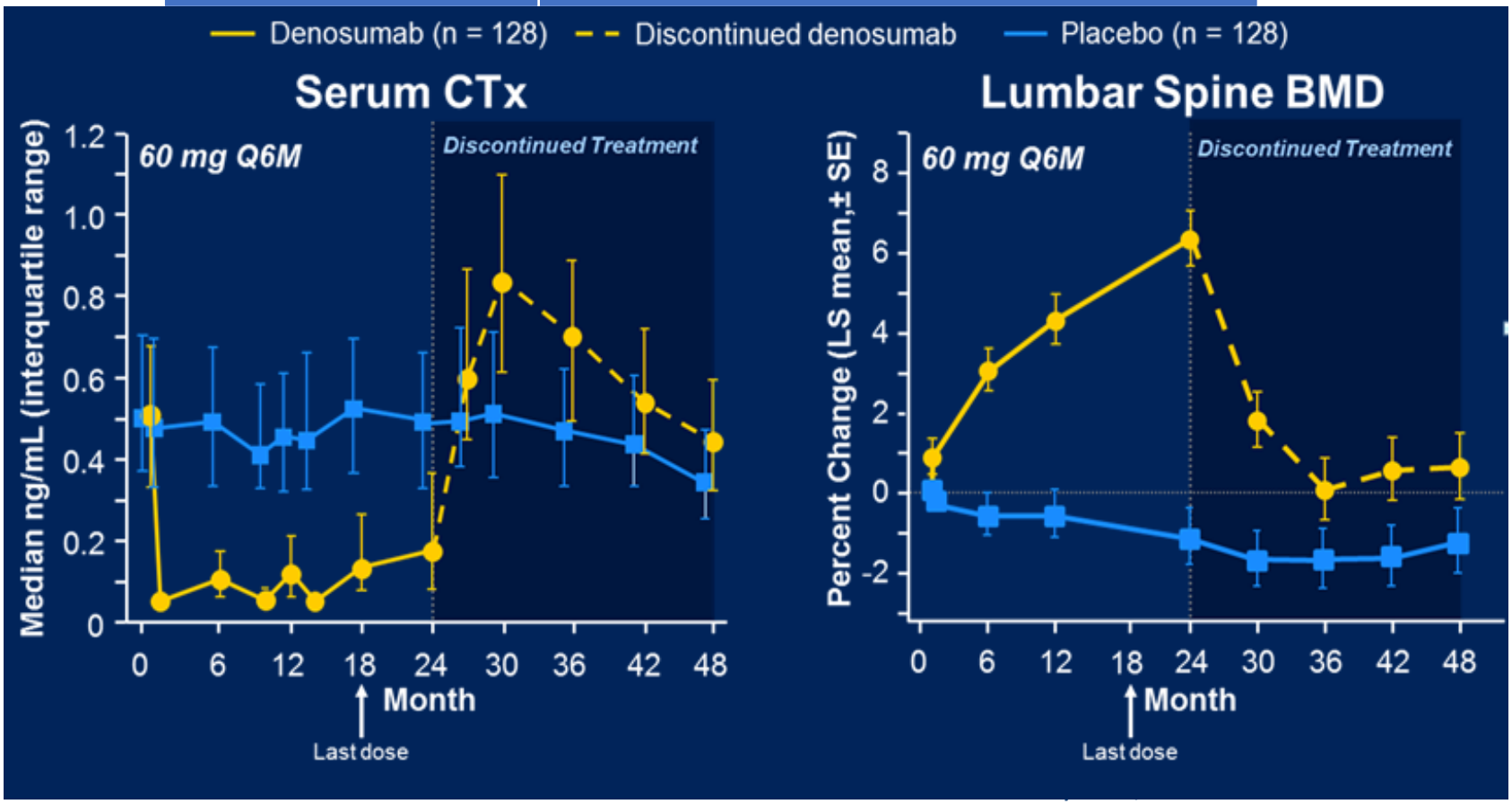
- For CA patients with severe osteoporosis, what about anabolic drugs like teriparatide (rPTH) and abaloparatide (rPTHrp)?
  - Contraindicated if history of XRT
  - Would avoid unless:

    1) in remission ~ 10 yrs

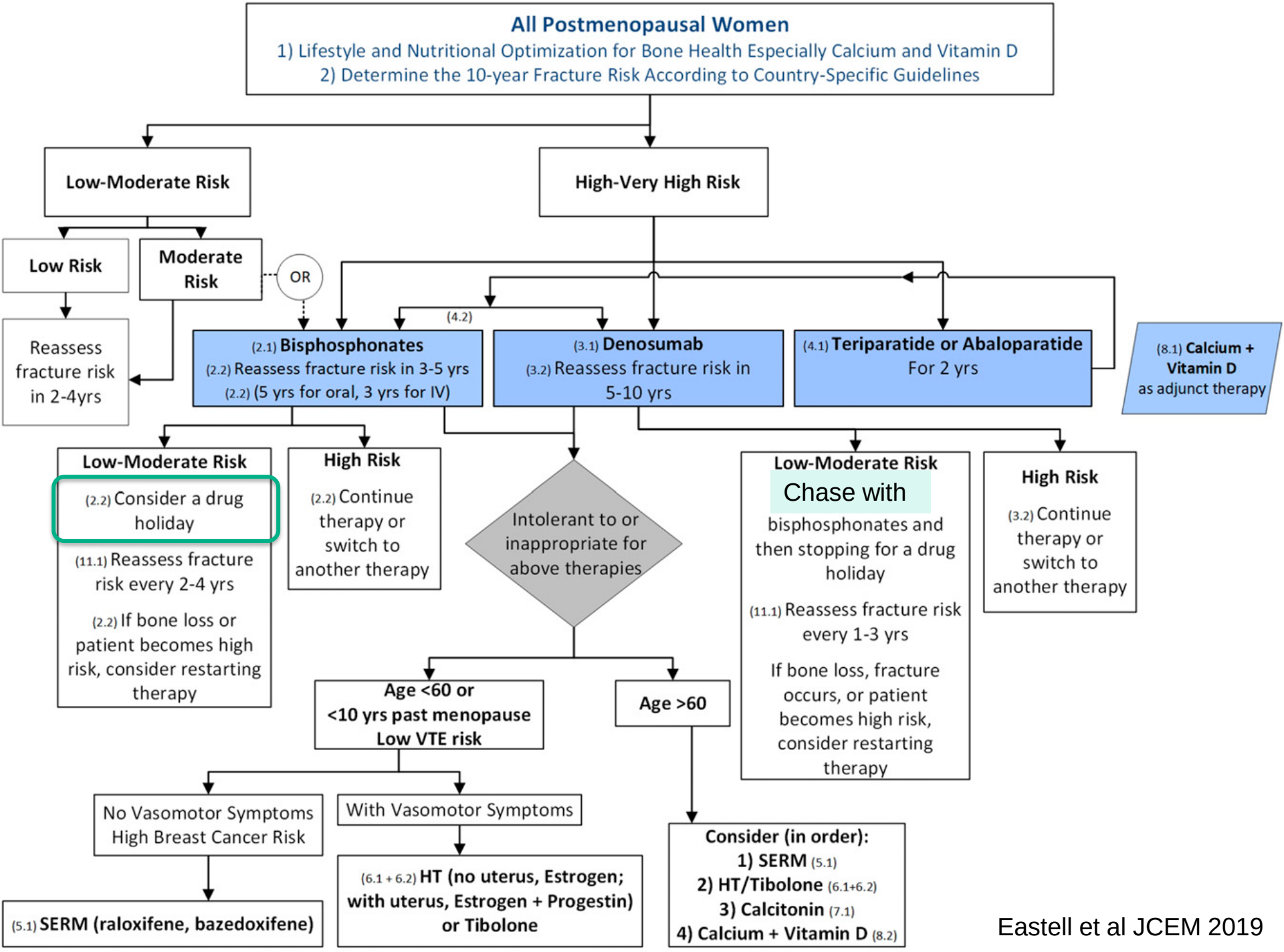
    2) benefit > theoretical risks (activating dormant cancer cells[1,2])
- 2019 romosozumab (mAb sclerostin) FDA approval
  - No data in cancer patients
  - Attractive since ↑bone formation & ↓bone resorption

1. Farooki et al [Letter], NEJM 2007
2. Ottewell et al, Clin Cancer Res 2014

RESIDUAL antiresorptive effect in BONE after stoppage?



- Denosumab 60mg or 120mg should not be held for > 6 months due to concerns about “rebound” ↑ in bone resorption
- “Chase” DMAb with bisphosphonate for 1-2 years to (mostly) block rebound bone loss



Eastell et al JCEM 2019

Case: 27-year-old female hematologic malignancy survivor, hx of XRT
- Complains of hot flashes

- Premature menopause due to chemotherapy
- Bone density scan shows osteopenia
  - No history of fractures
- Adequate calcium, vitamin D intake
- What is the most physiologic drug for bone health?

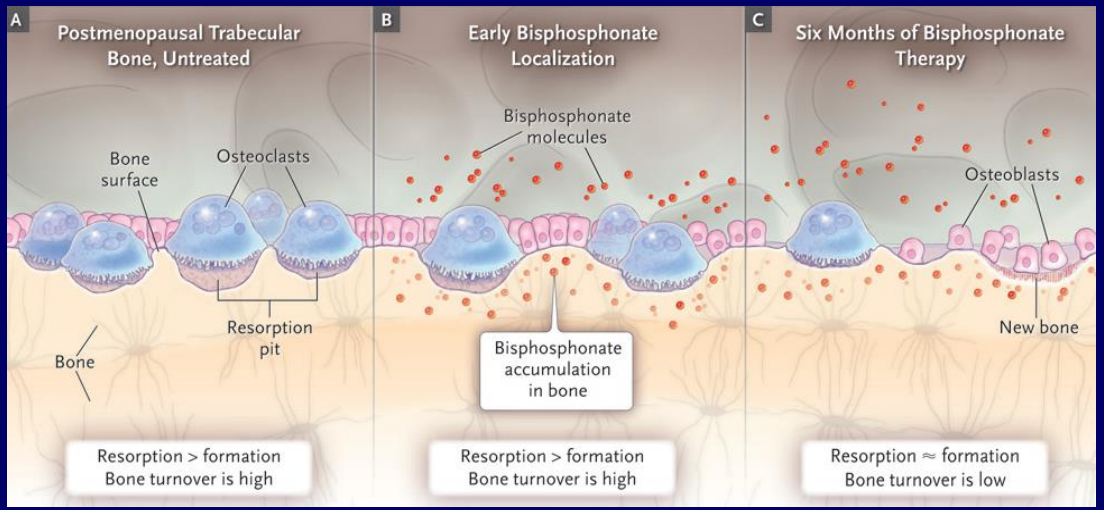
A) alendronate, a weekly oral bisphosphonate
B) Raloxifene
C) Hormone replacement therapy (estradiol + progesterone)
D) Denosumab (subcutaneous injection every 6 months)
E) Zoledronic acid (yearly intravenous infusion)
F) Teriparatide (SC daily x 2 years)

Case Summary: 27-year-old female hematologic malignancy survivor

- If possible given underlying malignancy, age and history: replace gonadal steroid
  - represents the most physiologic option for a patient with premature menopause
- Give hormone replacement therapy (HRT) or oral contraceptive pill (OCP) until ~ age 50
  - In patients with an intact uterus, unopposed estrogen should never be given
  - HRT or OCP not appropriate for patients at high risk for DVT
- Since the patient was having hot flashes, raloxifene (a Selective Estrogen Receptor Modulator not best choice
  - SERMs can cause hot flashes
  - If no hot flashes, could use this drug up until ~ age 65

Oral bisphosphonates: safe and effective method to decrease osteoclast activity

- Cannot give if esophageal stricture
- GERD is not a contraindication
- Do not cause abdominal pain, etc
- Must be taken on empty stomach, first thing in AM (do not lay down supine), with regular water
  - mineral water, coffee, vitamins will block absorption



Favus MJ, NEJM 2010

Bisphosphonate holiday results in signifcantly more clinical spine fractures

- 10 years of alendronate VS

  5 years on → 5 years off

  – lower risk of clinically recognized vertebral fractures with 10 years on drug

	Spine Fractures (%)
Stopped after 5 years	5.3%
Stayed on for 10 years	2.4%

RR, 0.45; 95% CI: 0.24-0.85

Black et al, JAMA. 2006;296(24):2927-38.

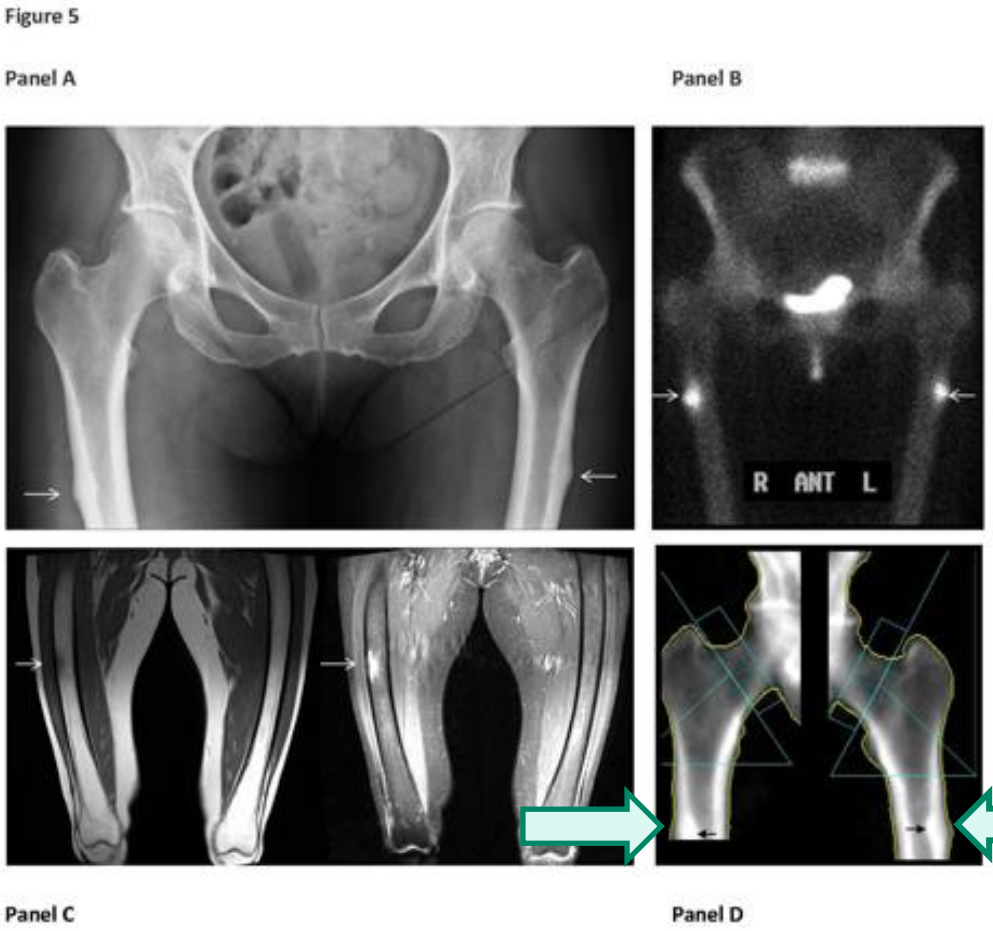
Selected Adverse Effects of Oral / IV Bisphosphonates and Denosumab

Adverse Effect	Oral bisphosphonates	Zoledronic acid	Denosumab
Esophagitis	possible	No	No
Acute phase reactions	Weekly – no Monthly - possible	Common after first dose	no
Hypocalcemia	no	↑ risk if: vitamin D deficient, if renal insufficiency, if blastic mets	
Acute renal insufficiency	No risk. "Not recommended" if GFR < 35	Can occur **Contraindicated** GFR < 35	No risk
Atypical (iatrogenic) femur fracture	Can occur – likely related to duration of use After 5 years of alendronate: 1 / 5,000		
"Rebound" spine fractures[1]	No		Yes- case reports
Osteonecrosis of the jaw	osteoporosis doses: 1/10,000 – 100,000 3 year RCT (n= 8000) of yearly zol acid 5mg: 1 case in placebo and 1 case in drug group 6 monthly DMAb 60mg: after 5 years (n=1457), 3 cases of ONJ		

1. Anastasilakis AD et al. JBMR 2017.

Atypical (iatrogenic) Femur Fracture: Often Bilateral

Plain X-rays



Bone Scan

MRI

Even DXA

Images courtesy of Fergus McKiernan, MD
McKiernan et al. J Clin Densitom. 2011;14:354-8.

Atypical Femur Fracture:
Underappreciated in Context of long term use of bisphosphonate or denosumab in cancer settings

- May present with a prodrome of dull or aching anterior thigh or groin pain
- Often bilateral
- Higher risk in Asian Americans

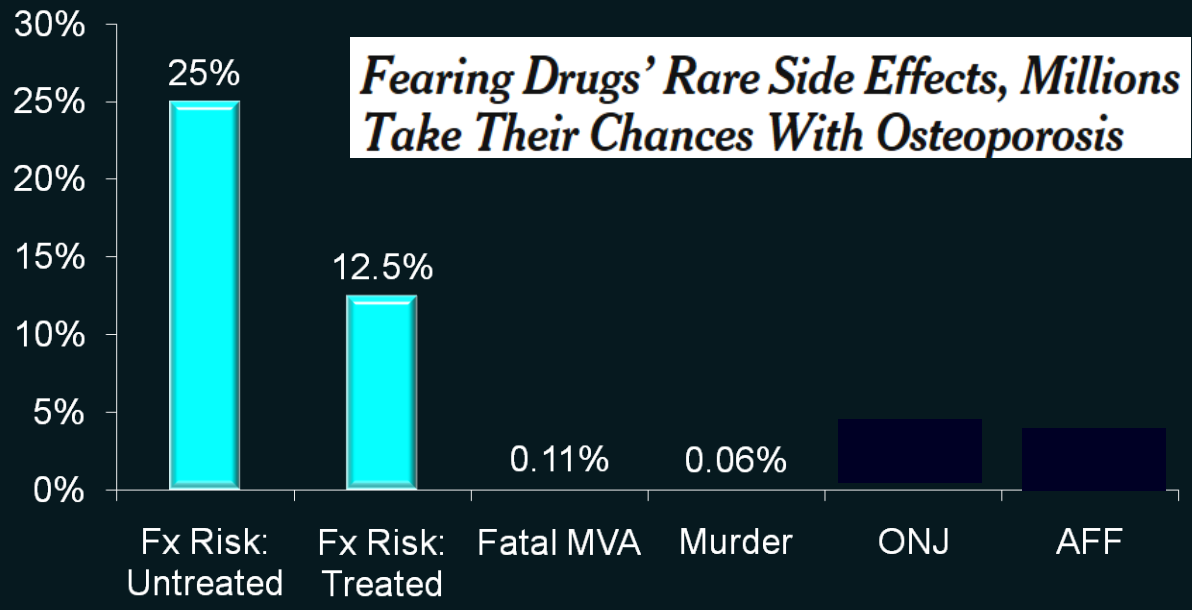
- Imaging early in clinical course consistent with “stress reaction” along lateral femur
  - May be confused with metastatic disease

- Stop drug and refer to orthopedist given potential for progression
  - Early imaging changes → complete fracture

Farooki et al, Ann Oncol 2015;26(4):819-20.

10-Year Probabilities

FRAX 10-year probability of major osteoporotic fracture for untreated 72 year-old woman with FN T-score = -3.0 is 25%



Fearing Drugs' Rare Side Effects, Millions Take Their Chances With Osteoporosis

Fracture risk typical of patient with osteoporosis; MVA and murder data from the CDC at http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_10.pdf ; ONJ estimate is 1/100,000 patient-treatment-years from the ADA at JADA. 2006;137:1144-1150. AFF estimate is 5/10,000 patient-treatment-years from Schilcher J et al. N Engl J Med. 2011;364:1728-1737.

“But doc, I am the one patient who gets every side effect”

- For such patients, I encourage them to take a “course” of bisphosphonate drug therapy for ~ 3 years
  - A “test dose” of zol acid 1-2mg can be offered
- Atypical femur fracture (AFF) and ONJ related to duration of use
    - drug holiday appears to cause reduction in risk of AFF
- Further discussions based on their bone density response and whether they are still taking cancer therapy with adverse bone effects
  - denosumab should usually be chased with bisphosphonate to block rebound bone loss

Summary

- Drug therapy to protect BMD & lower fracture risk if:
  - osteoporotic BMD, or if clinical osteoporosis (hip or vertebral fracture)[1]
  - FRAX risk calculation
    - > 3% for hip fracture, or, > 20% for any major fracture
  - chronic aromatase inhibitor or ADT
- Hormone replacement is most physiologic option for young survivors of non-estrogen dependent cancer with premature menopause
- Caution with PTH analogues in survivors of bone tropic cancers
- Consider bisphosphonate holiday depending on residual fracture risk
  - after IV bisphosphonate x 3 yrs or oral bisph 3-5 yrs
  - after aromatase inhibitor, GnRH analogue, or chronic steroid is stopped
- Stop denosumab with caution and bisphosphate “chaser”-- an evolving area

1. Cosman F et al, Clinician’s Guide to Prevention and Treatment of Osteoporosis. Osteoporosis International 2014

“Bone” appetite!

Comments and questions