The Optimal Treatment of Bone Metastases

Philip Saylor, M.D.

NASPCC Annual Meeting

October 2019

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Bone metastases: Ground to cover

- The basics of PCa bone metastases
  - Prevalence, imaging, and morbidity
- Classes of relevant medicines
  - Zoledronic acid & denosumab
  - Cancer treatments themselves
  - Radium-223 blurs the line
- Recent data / open questions
- Take home points

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Bone metastases: Very common

Abiraterone phase III

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Abiraterone Acetate (N=797)	Placebo (N=398)
Age		
Median (range) — yr	69 (42–95)	69 (39–90)
≥75 yr — no. of patients/total no. (%)	220/797 (28)	111/397 (28)
Disease location — no. of patients/total no. (%)		
Bone	709/797 (89)	357/397 (90)
Node	361/797 (45)	164/397 (41)
Liver	90/797 (11)	30/397 (8)

Cabazitaxel phase III

Extent of disease		
Metastatic	356 (94%)	364 (96%)
Bone metastases	328 (87%)	303 (80%)
Visceral metastases	94 (25%)	94 (25%)

Docetaxel phase III

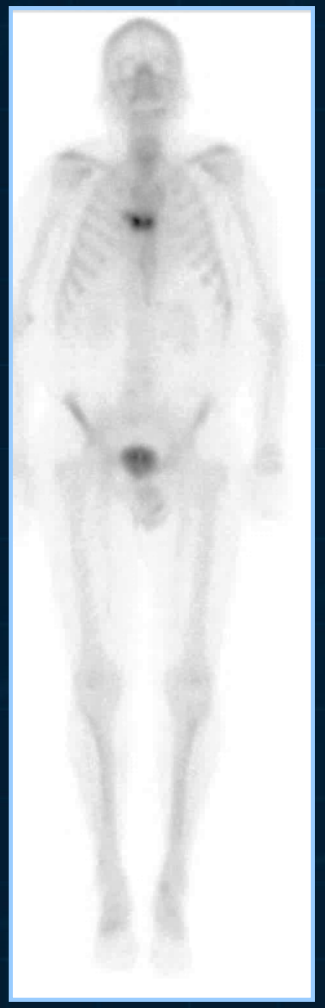
Sites of disease (%) *		
Bone	84	88
Soft tissue		
Lymph node	24	26
Liver	8	9
Lung	10	10

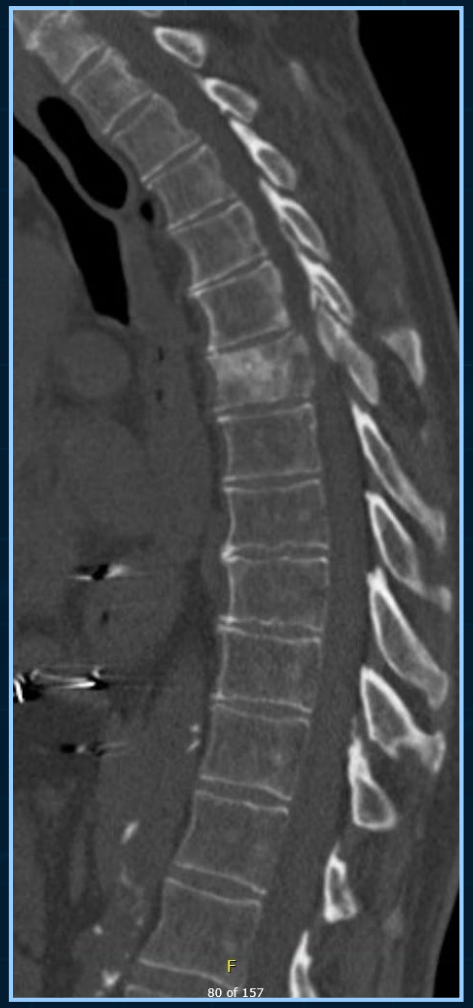
- Often the main (or only) thing going on
- Symptoms and mortality
  - Pain & immobility
  - Worsened QOL
  - Cancer-related fractures
  - Spinal cord compression
  - Often seems to determine how long a person can live with advanced prostate cancer

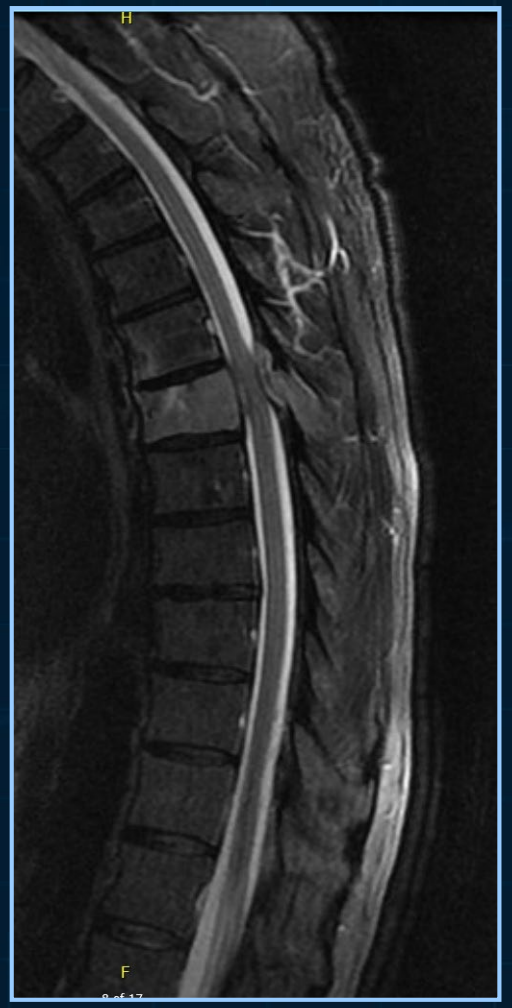
MGH 1811 MASS GEN CA

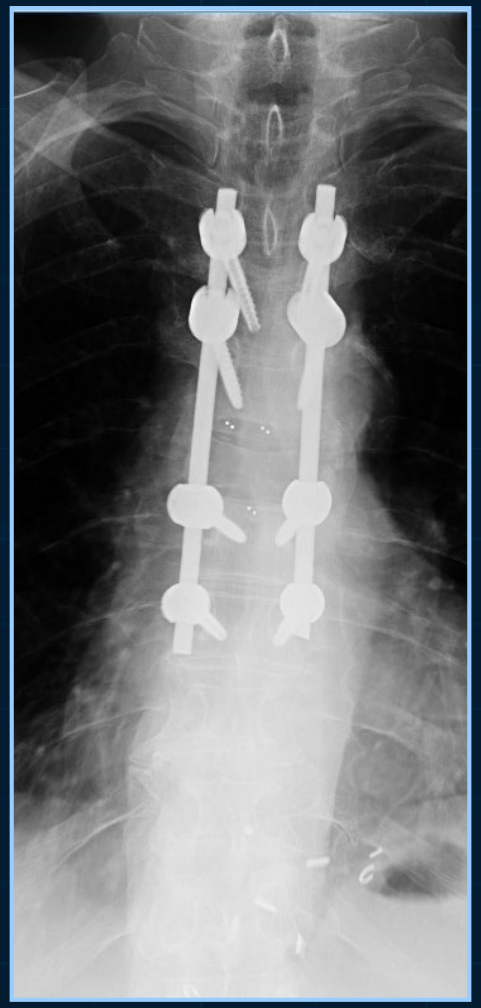
DeBono, NEJM, 2011. DeBono, Lancet, 2010. Petrylak, NEJM, 2004.

Bone: Need multi-modality imaging







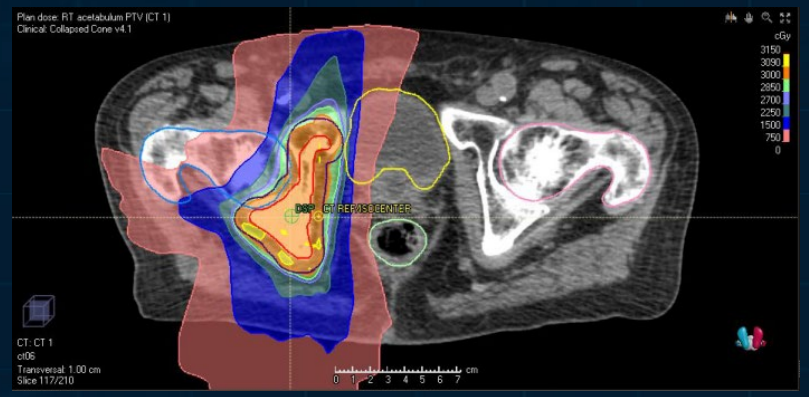


MGH 1811 MAS GEN CA

What, exactly, is an “SRE”?

- Artificial problem: Need an “endpoint” to measure in clinical trials of bone-targeted medicines

- SRE = Skeletal related event
  - Pathologic fracture
  - Radiation to bone
  - Surgery to bone
  - Spinal cord compression



- Original: Primary endpoint for bone targeted therapy
- Recent: Secondary endpoint for every therapy

SRE vs. osteoporotic fracture

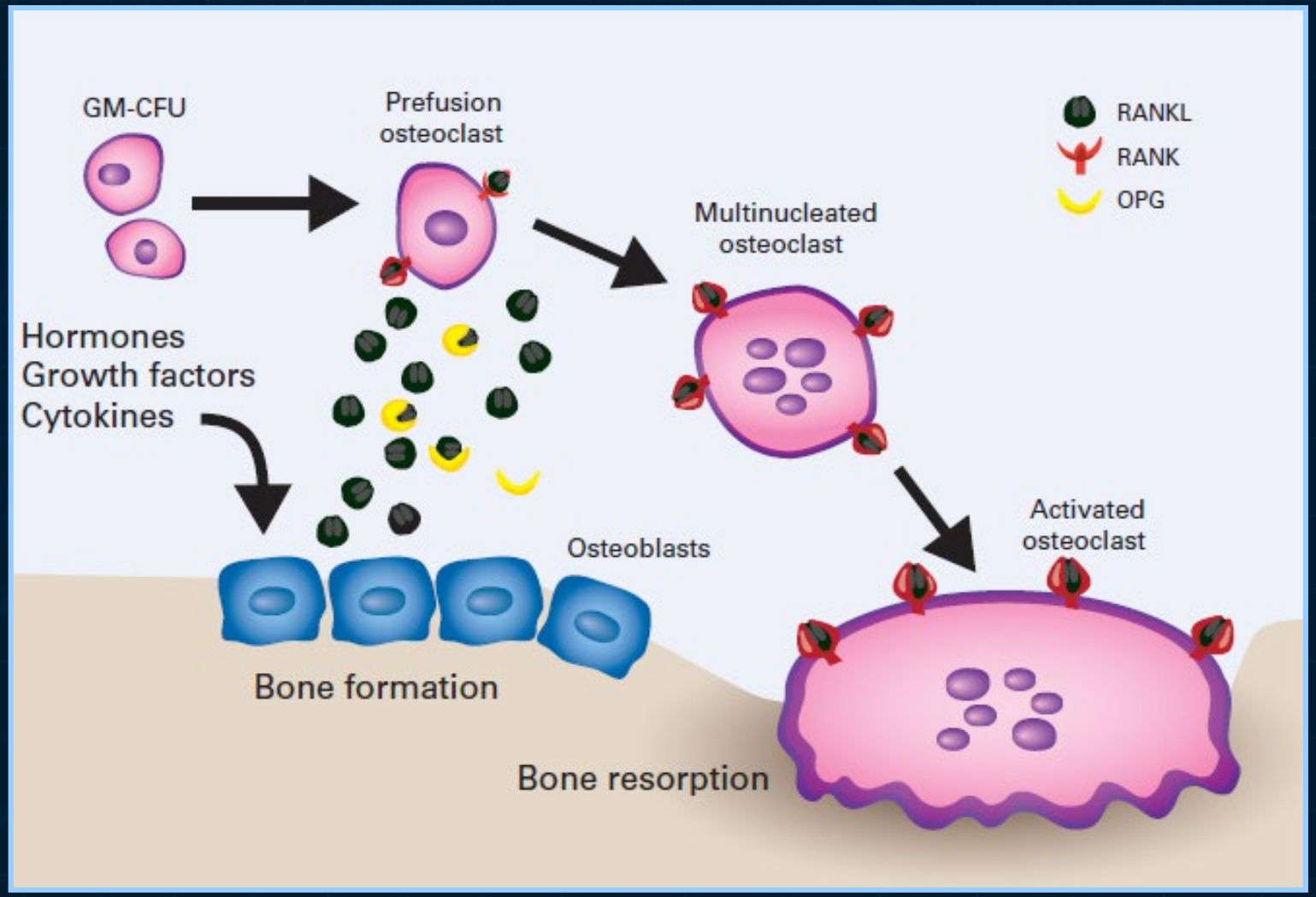
Skeletal related events:

- PCa with bone metastases & ADT resistance
- Just 2 options, either is monthly:
  - Denosumab
  - Zoledronic acid

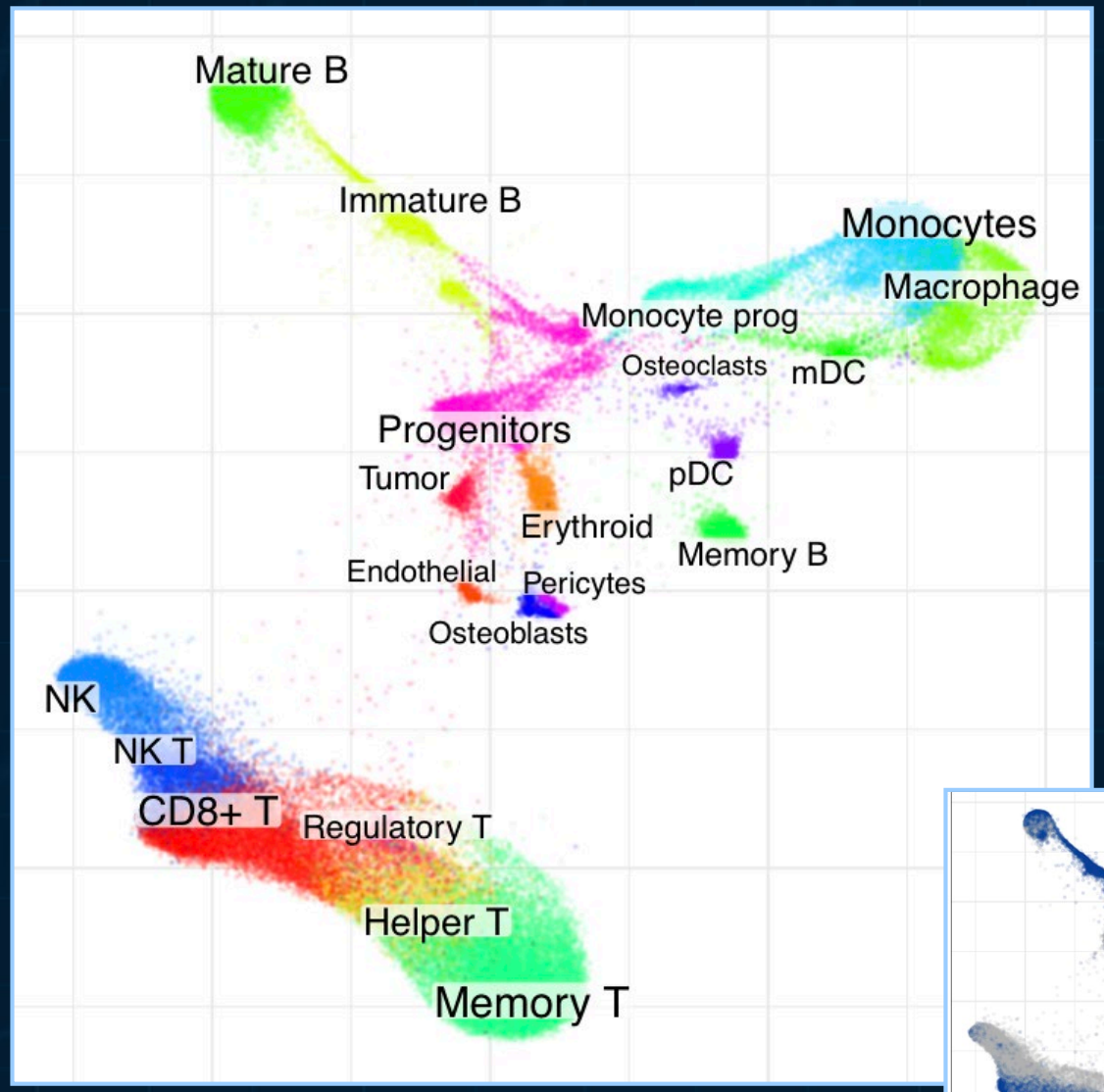
Fragility fractures:

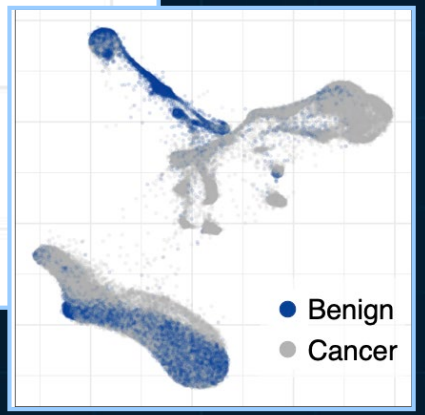
- All on ADT are at risk
- Must remember to screen them
- Many options:
  - Alendronate qwk
  - Denos q6mo
  - Z.A. yearly
  - (anything works)

Concept: The vicious cycle

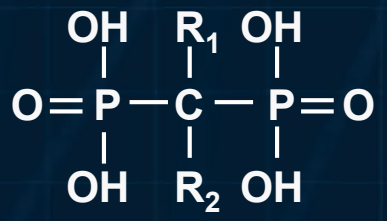


Saylor, J Clin Oncol, 2011.

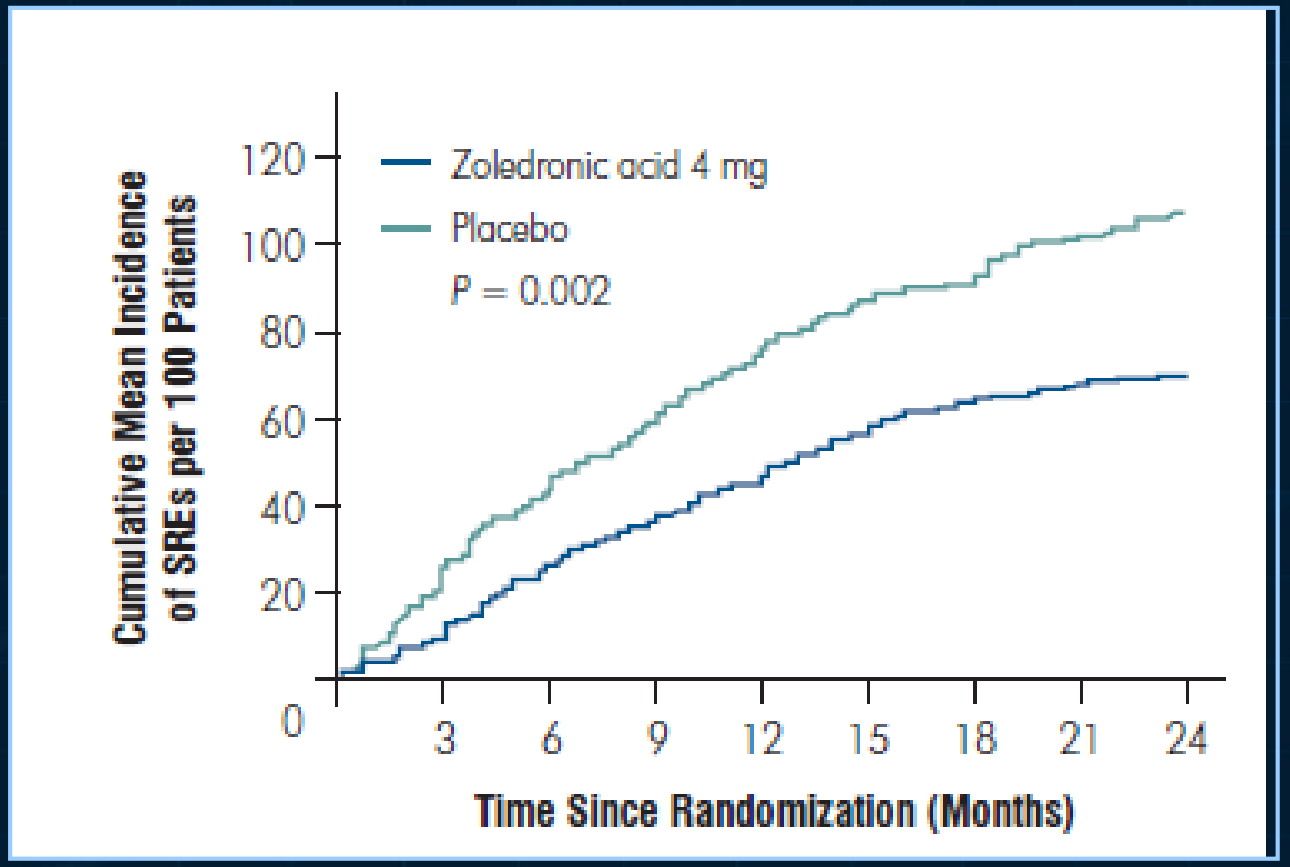




MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER



Zoledronic acid vs. placebo

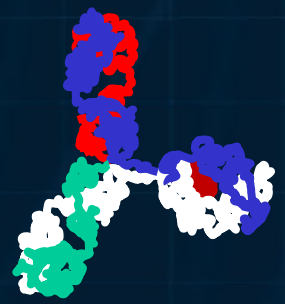


- CRPC with bone metastases
  - Z.A.: 33%
  - Control: 44%
- Beware kidneys!
  - Inf'n: 15 min
  - Dose reduce for stable mild renal insufficiency

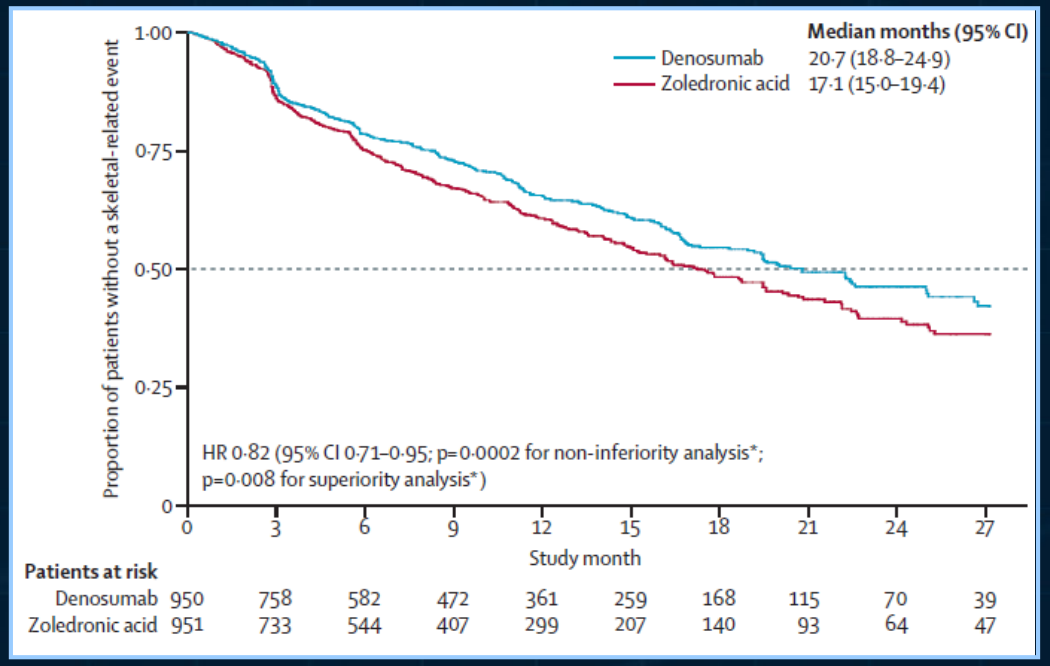
Failures in this setting: pamidronate, clodronate

MGH 1811 MASS GEN CA

Major, Clin Ca Ther, 2005.



Denosumab vs. zoledronic acid



- Two distinct strategies to inhibit osteoclasts
- Monthly treatment
- N = 1,904
- Primary: Time to 1st SRE
- 20.7 vs. 17.1 mo
- Survival: No change
- Bottom lines:
  - Both agents help
  - Denosumab is better
  - Cost may be an issue

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

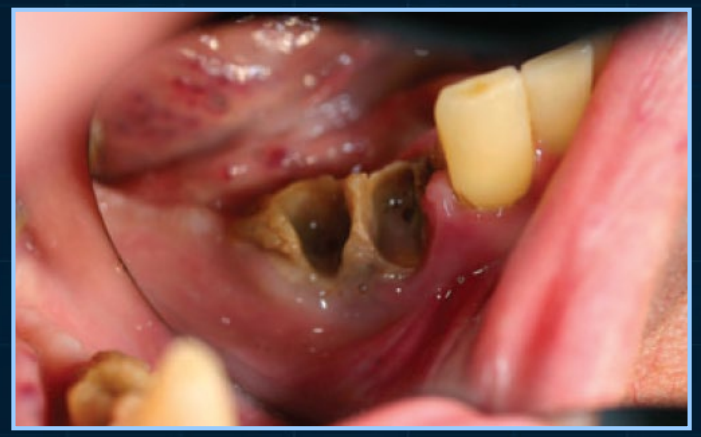
Fizazi, Lancet, 2011.

What has not worked?

- Failures:
  - Anything weaker than Z.A. or denosumab (for bone mets and resistance to ADT)
  - Treatment of bone metastases that are still responding to ADT
  - Preventing the first metastasis

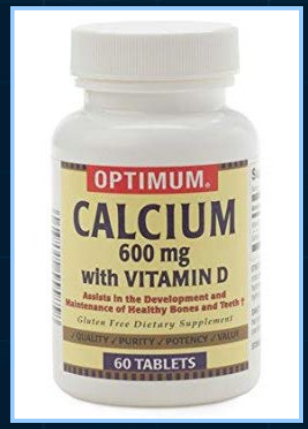
Safety reminders for either

- Beware of the jaw:



  - ONJ is a risk with either agent
  - Highest: Invasive dental work on therapy

- Beware of the calcium:
  - Hypocalcemia is a risk with either agent, sometimes is severe



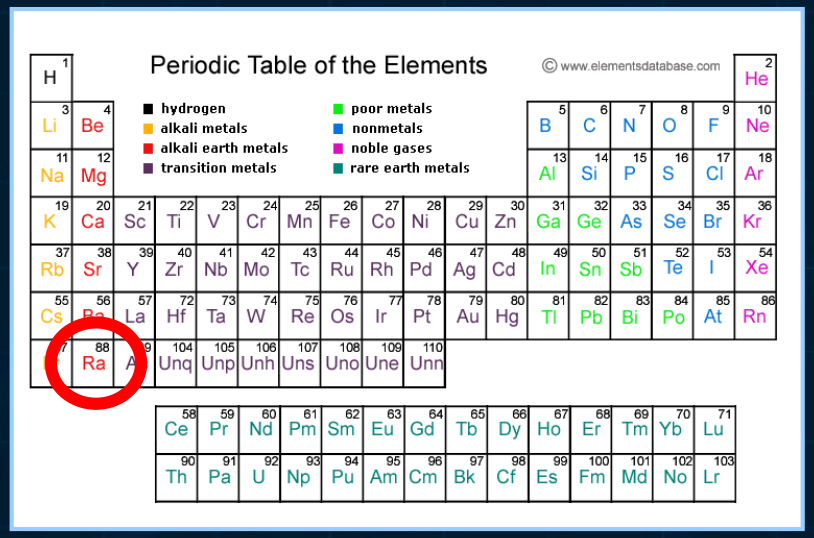
  - Always check 25-OH vit D level before starting
  - Supplement Ca/D during therapy with either agent

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Dickinson, Intern Med J, 2009.

Bridging categories: Radium

- Radium is an element!



- Alkaline earth metal!
- Alpha particle advantages
- Monthly IV x6
- Improves: Survival, SREs

- Questions:
  - Can it pair with other active agents?
  - If so, which ones?
  - What does it do to bone health longer term (in men who are likely to live longer)?
- Recent trials…

MGH 1811 MASS GEN CA

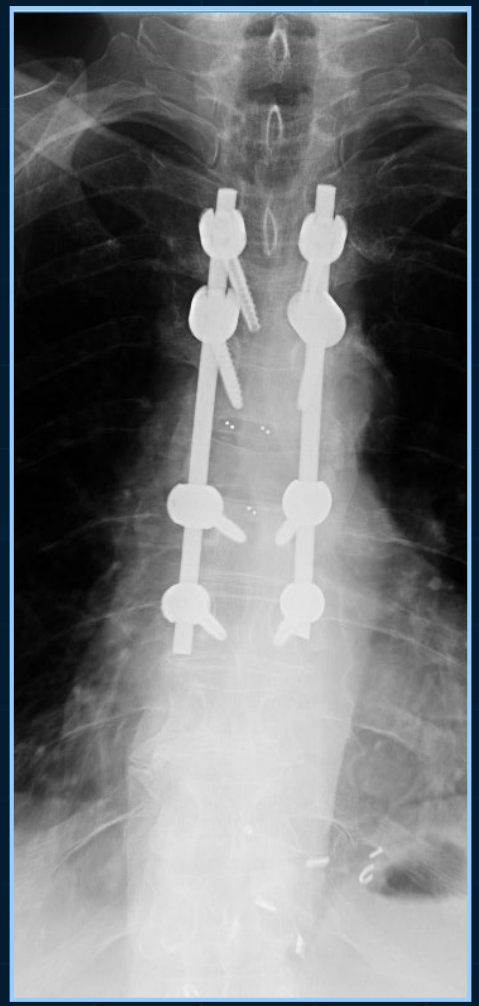
Recent developments

- ERA 223 trial:
  - Abiraterone + [radium or placebo]
  - N = 806
  - Fractures:
    - 29% with radium
    - 11% with placebo
  - Stopped early
  - Don’t do this combo
  - Mechanism of the harm is still uncertain

- PEACE III
  - Enzalutamide + [radium or placebo]
  - Bone protective agent mandated mid trial
  - Before rule fratures:
    - 18/77 (23.3%)
  - After rule fractures:
    - 1/69 (1.4%)
  - Bottom line: Free wheeling combination therapy is not wise

Bone mets: Take home points

- Bone mets are nearly universal if advanced
- Multiple imaging tools and multiple clinical disciplines are often needed
- SRE = invention for clinical trials
- Controlling cancer generally reduces SREs
- Also: Monthly zoledronic acid or denosumab* (*slightly better)
- Osteoporosis is a separate important issue
- Safety: Kidney function, dental, calcium
- Radium bridges categories, recent note of some hazard with drug combinations
- More therapeutic & biologic insights needed!



MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER