



# Best Use of Osteoclast-Targeted Therapy



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# Disclosures

## Personal financial interests

Consultant: Amgen, Astellas, Bayer, Clovis, Gilead, Janssen, Lilly, Novartis, Pfizer

## Institutional financial interests

Contracted clinical research: Amgen, Bayer, Clovis, Gilead, Janssen, Lilly

## Skeletal-Related Events vs Fragility Fractures/Osteoporosis

	Fragility Fractures/ Osteoporosis	Skeletal-Related Events
Population at Risk	All men	mCRPC, bone metastases
Anatomic site	normal bone	bone metastases
Effects of cancer treatment:		
• ADT	↑	↓
• Abiraterone acetate	↑	↓
• Enzalutamide	↑	↓
Osteoclast activation	+	+++

## FDA Approved Uses of Osteoclast-Targeted Therapy

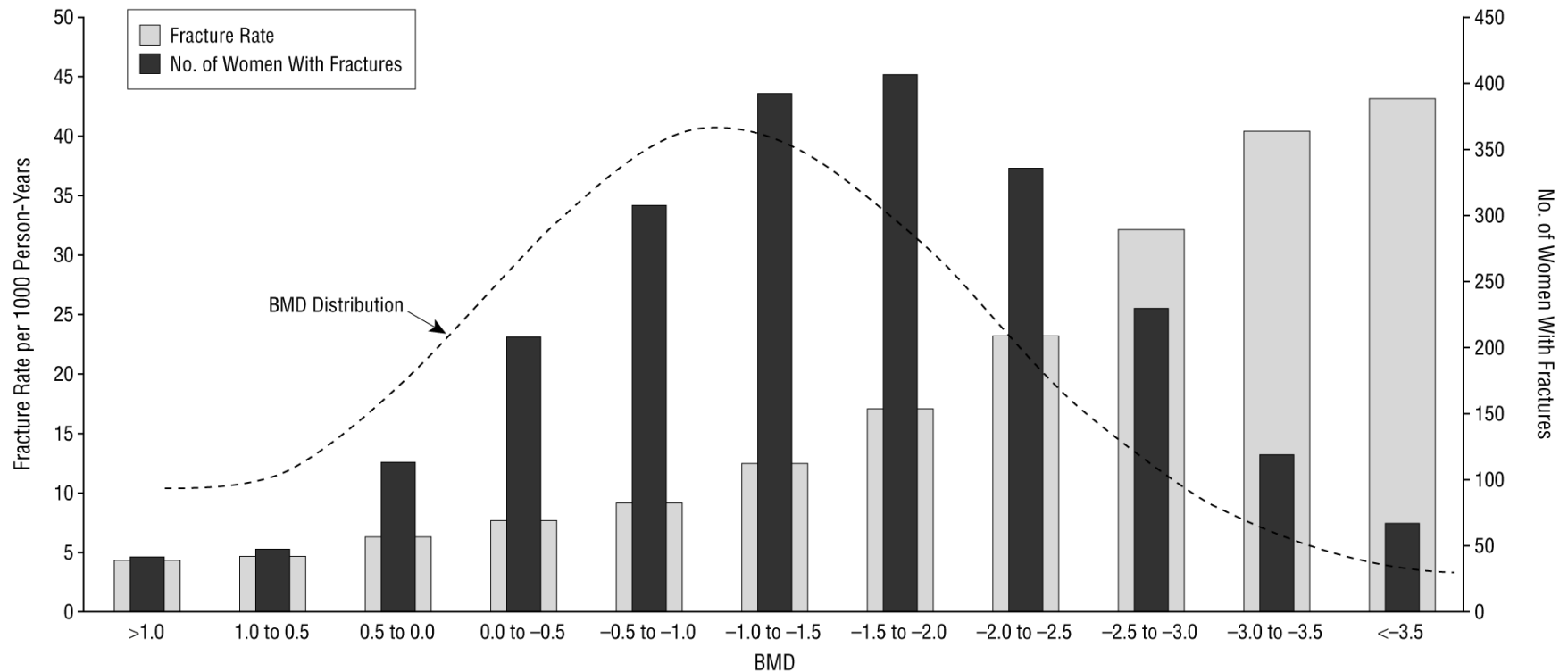
	Fragility Fractures/ Osteoporosis	Skeletal-Related Events
Oral bisphosphonates (alendronate, risedronate, ibandronate)	✓	
Zoledronic acid		
• 5 mg q12 months (Reclast)	✓	
• 4 mg q3-4 weeks (Zometa)		✓
Denosumab		
• 60 mg every 6 months (Prolia)	✓	
• 120 mg q4 weeks (Xgeva)		✓

## National Osteoporosis Foundation (NOF) Fracture Prevention Guidelines for Men

Consider FDA-approved medical therapies based on the following:

- A vertebral or hip fracture
- Femoral neck or spine T-score  $\leq -2.5$
- FRAX 10-year probability of a hip fracture  $\geq 3\%$  or  
10-year probability of any major fracture  $\geq 20\%$

# Most Fractures Occur in Patients *without* Osteoporosis



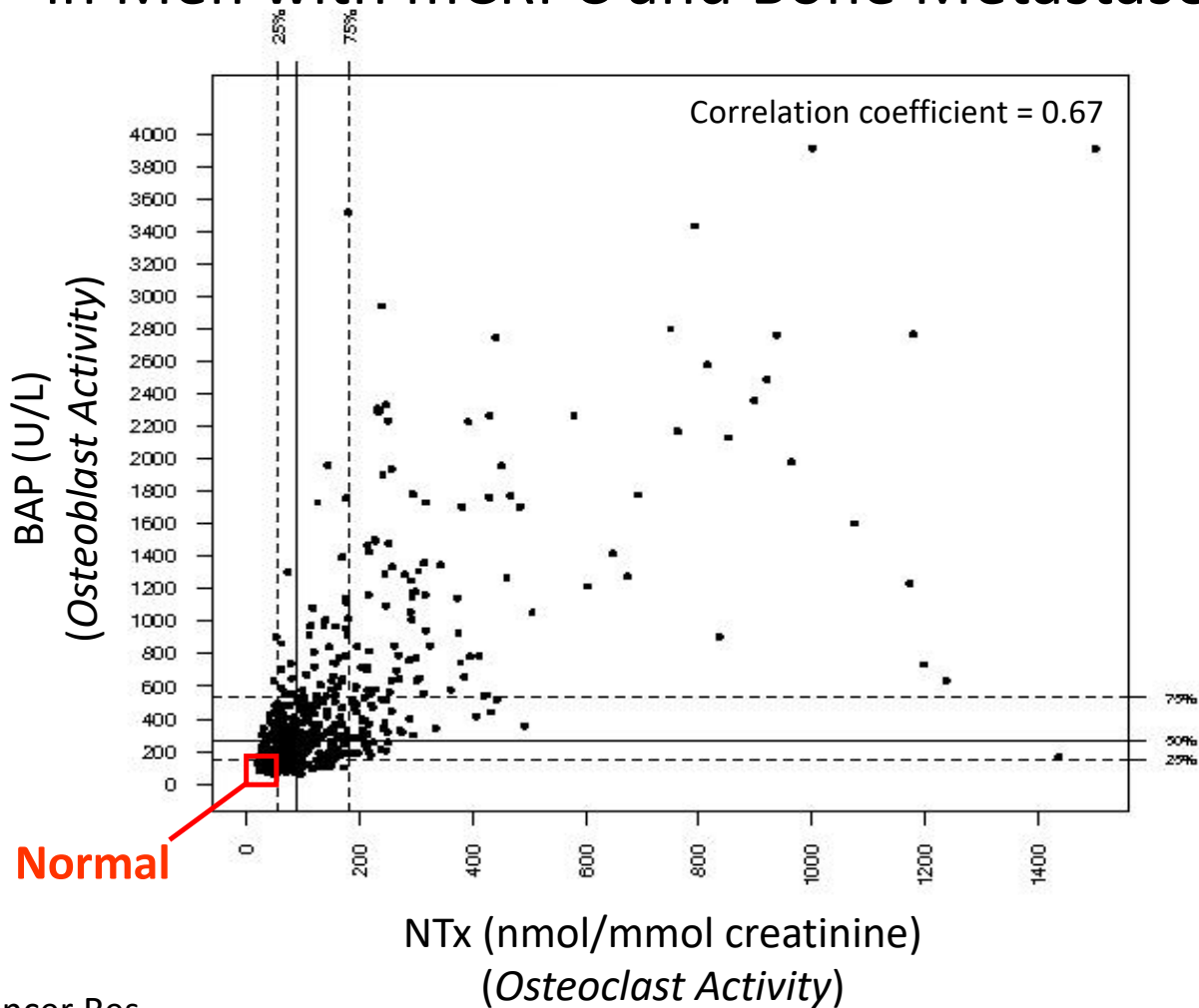
## *National Osteoporosis Risk Assessment (NORA):*

- 149,524 post-menopausal women, mean age of 65 years
- 82% of 2,259 women with fragility fractures had baseline T-score > -2.5

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## Markers of Osteoblast (BAP) and Osteoclast (NTx) Activity in Men with mCRPC and Bone Metastases

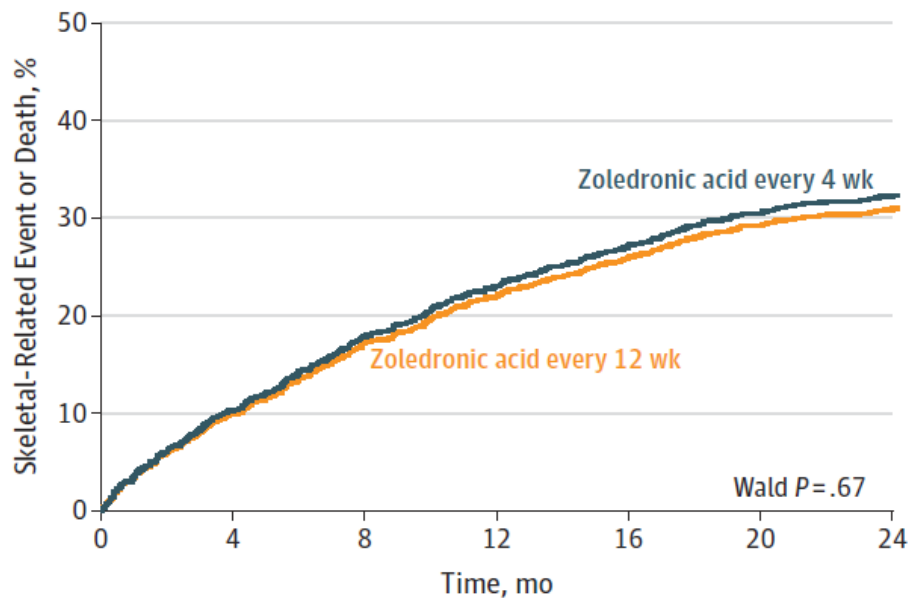




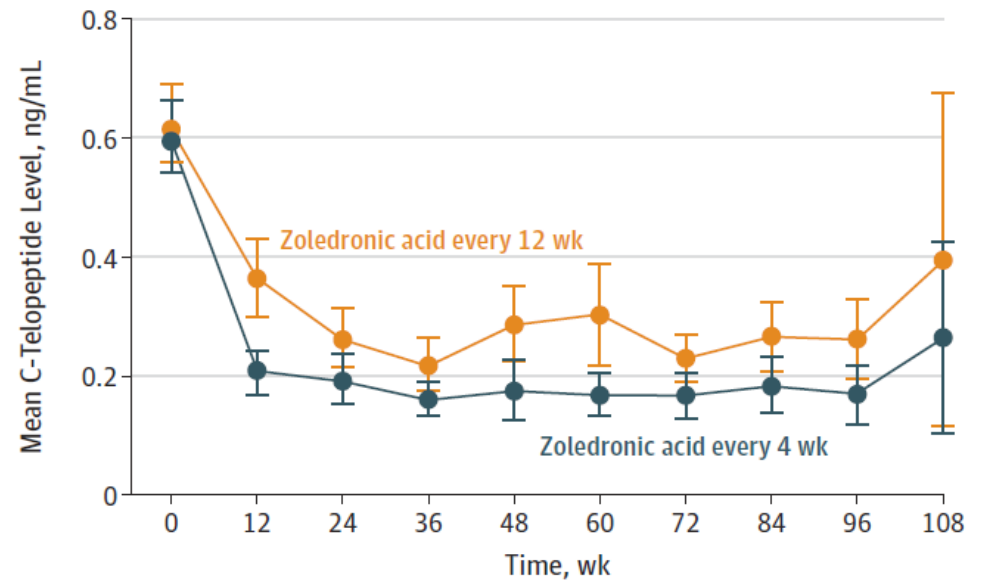
# CALGB 70604: Longer Interval vs Standard Dosing of Zoledronic Acid and SREs in Patients with Bone Metastases

Differences in osteoclast inhibition but *not* SRE incidence

Cumulative Incidence of Skeletal-Related Events or Death



Changes in C-Telopeptide Levels



## Limitations of CALGB 70604

- There can be no assumption of constancy, a requirement for valid inference for non-inferiority studies<sup>1</sup>
  - Substantial changes in standards of care, event rate, and survival
- Included some patients (men with HSPC) with no potential for benefit<sup>2,3</sup>
- SRE definition differed from prior studies
- Primary analysis was 24 month event rate, but only 43% completed the study at 2 years (median follow-up only 14 months)
- Non-inferiority margin included clinically important difference
- Longer dosing interval did *not* improve safety/tolerability

<sup>1</sup>Koopmeiners and Hobbs (2018) Stat Methods Med Res 27: 1547-1558

<sup>2</sup> Smith et al (2014) J Clin Oncol 32:1143-50

<sup>3</sup> James et al (2016) Lancet 387:1163-77

## Conclusions: Fragility Fractures/Osteoporosis

- Fragility fractures are common in men
  - Age, prior fractures, and low BMD are strongest predictors of fracture
- In men with prostate cancer, fracture risk is increased by androgen deprivation therapy and androgen pathway inhibitors (abiraterone plus prednisone, apalutamide, enzalutamide)
- Assessment of fracture risk should include evaluation of BOTH clinical risk factors and BMD
- Treatment-related fractures are preventable

## Conclusions: Skeletal-Related Events (SREs)

- SREs are a distinct set of clinical problems related to cancer progression in bone
- Approved therapies for osteoporosis (drug/dose/schedule) are *not* sufficient to prevent SREs
- Zoledronic acid (4 mg every 3-4 weeks) and denosumab (120 mg every 4 weeks) significantly decrease SREs in mCRPC and bone metastases
- Zoledronic acid (4 mg every 12 weeks) might be sufficient for SRE prevention but evidence for efficacy is weak and no proven safety benefit
- Optimal treatment duration for SRE prevention is undefined



MASSACHUSETTS  
GENERAL HOSPITAL  
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Thank you!

## APCCC 2019

### Key Questions for Prevention of Skeletal Related Events (SREs)

90. Do you recommend osteoclast-targeted therapy (zoledronic acid or denosumab) at the higher dose and more frequent schedule used for reducing the risk of SREs in patients with CRPC and bone metastases?

**YES, there is no evidence that drug/dose/schedule approved for osteoporosis is adequate to prevent disease-related skeletal morbidity (SREs)**

93. When you use osteoclast-targeted therapy at the dose and schedule used for reducing the risk of SRE in patients with mCRPC and bone metastases, what treatment frequency do you recommend?

**Every 4 weeks *although* optimal schedule is undefined**

## APCCC 2019

### Key Questions about Fracture Prevention

85. Do you routinely screen for osteoporosis (fracture) risk factors in patients with prostate cancer starting on long-term ADT?

**YES, *most* fractures occur in patients with normal BMD**

86. Do you routinely recommend measurement of bone mineral density (BMD) in patients with prostate cancer starting on long-term ADT?

**YES, *but* BMD measurement alone is *not* sufficient to evaluate fracture risk**

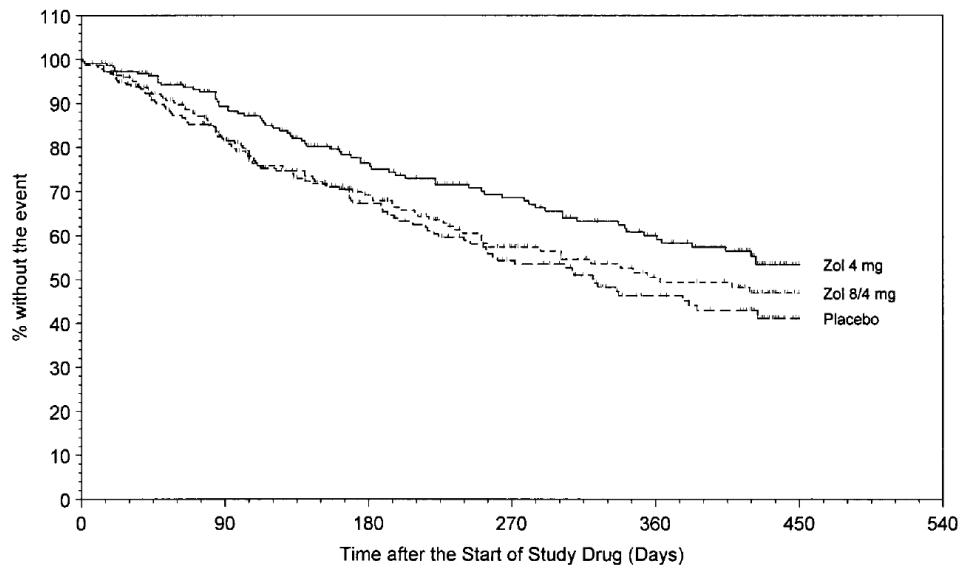
87. Is it appropriate to start an osteoclast-targeted therapy (osteoporosis dose/schedule) to prevent fractures *without* BMD measurement?

**YES, *particularly* in patients who are at high risk for fracture based on clinical assessment**

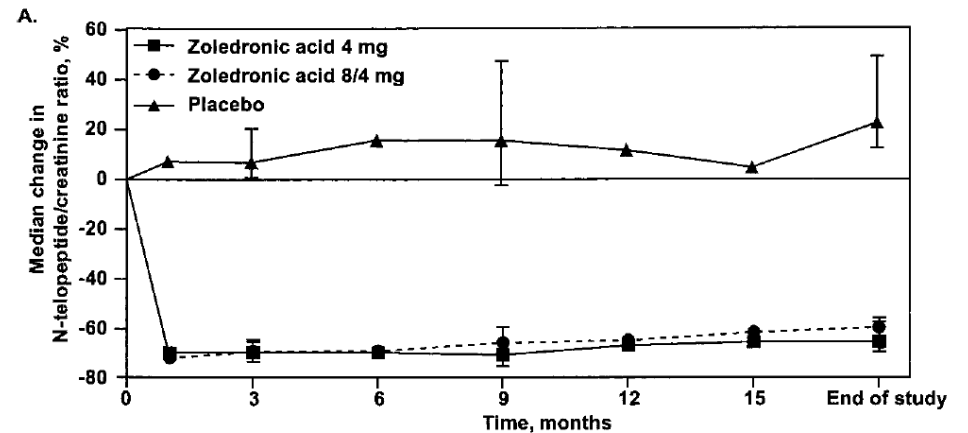
# Zoledronic Acid vs Placebo in Men with mCRPC and Bone Metastases

Potent osteoclast inhibition *significantly* decreased SREs

Time to First Skeletal-Related Events



Changes in Urinary NTx



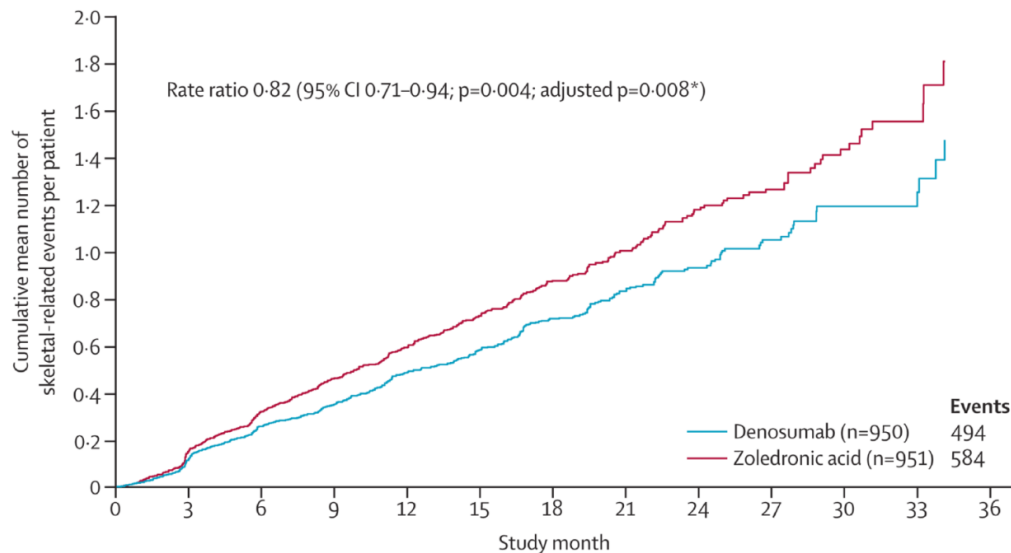
Zoledronic acid vs placebo q3 weeks for 24 months



# Denosumab versus Zoledronic Acid in Men with mCRPC and Bone Metastases

More potent osteoclast inhibition further decreased SREs

Cumulative Incidence of Skeletal-Related Events



Changes in Bone Turnover Markers

	Zoledronic acid		Denosumab		p value
	Patients	Median absolute change (% IQR)	Patients	Median absolute change (% IQR)	
uNTx/Cr (nmol/mmol)	719	-28.4 (-69%, -83 to -43)	738	-40.3 (-84%, -92 to -66)	p<0.0001
Bone-specific alkaline phosphatase (µg/L)	739	-4.8 (-27%, -47 to 16)	755	-7.9 (-35%, -54 to -3)	p<0.0001

Data are presented for patients who had assessments at both baseline and week 13. uNTx/Cr=urinary N-telopeptide adjusted for creatinine.

Denosumab vs Zoledronic acid q4 weeks indefinitely

## Assessment of Fracture Risk

- Age, prior fracture history, and low BMD are the strongest predictors of fracture risk in men
- Most fragility fractures occur in individuals with normal BMD
- BMD alone is insufficient to evaluate fracture risk