

Anti-resorptive therapy to reduce SRE risk in men with bone-metastatic CRPC: Only for very select men with CRPC and bone metastases

Chris Parker

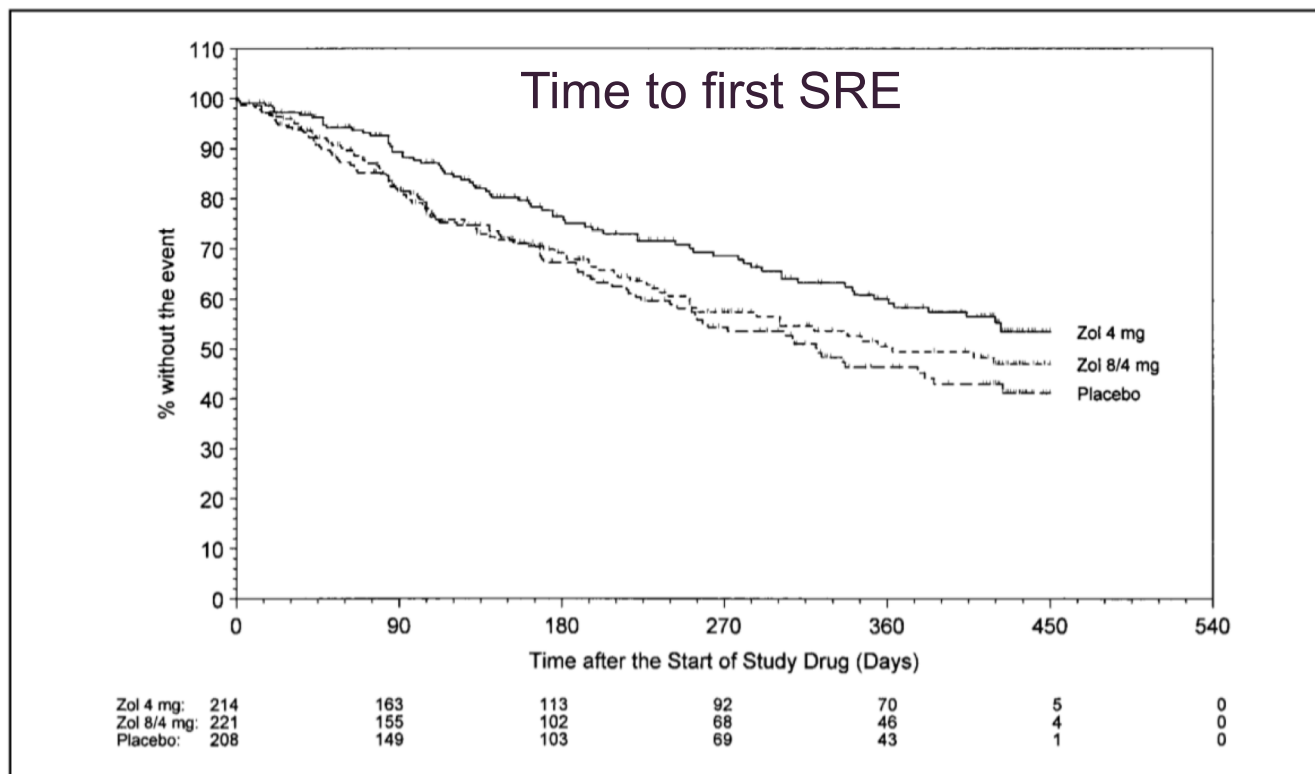
The Royal Marsden

Disclosures

AAA, Bayer, Janssen



Anti-resorptive therapy to reduce SRE risk in men with bone-metastatic CRPC: evidence base in 2002



Saad et al. JNCI (2002) Vol 94: 1458-1468



Anti-resorptive therapy to reduce SRE risk in men with bone-metastatic CRPC: evidence base in 2002

	No. of patients in treatment group (%)				
	Zoledronic acid				
	4 mg (N = 214)*	8/4 mg (N = 221)	Placebo (N = 208)	Difference (95% CI) between 4-mg and placebo groups†	P
Skeletal-related events					
All skeletal-related events	71 (33.2)	85 (38.5)	92 (44.2)	-11.1 (-20.3 to -1.8)	.021
All pathologic fractures	28 (13.1)	33 (14.9)	46 (22.1)	-8.8 (-14.8 to -2.8)	.015
Vertebral fractures	8 (3.7)	17 (7.7)	22 (10.6)	-6.9 (-11.1 to -2.7)	.053
Nonvertebral fractures	20 (9.4)	26 (11.8)	34 (16.3)	-6.4 (-14.8 to 1.9)	.092
Radiation therapy to bone	11 (5.1)	14 (6.3)	17 (8.2)	-6.4 (-14.8 to 1.9)	.136
Surgery to bone	9 (4.2)	6 (2.7)	7 (3.4)	-1.0 (-4.2 to 2.1)	.514
Spinal cord compression	9 (4.2)	11 (5.0)	14 (6.7)	-2.5 (-6.9 to 1.8)	.256
Change in antineoplastic treatment	10 (4.7)	18 (8.1)	14 (6.7)	-2.1 (-6.5 to 2.4)	.362

39% reduction in fracture risk



Anti-resorptive therapy to reduce SRE risk in men with bone-metastatic CRPC: evidence base in 2002

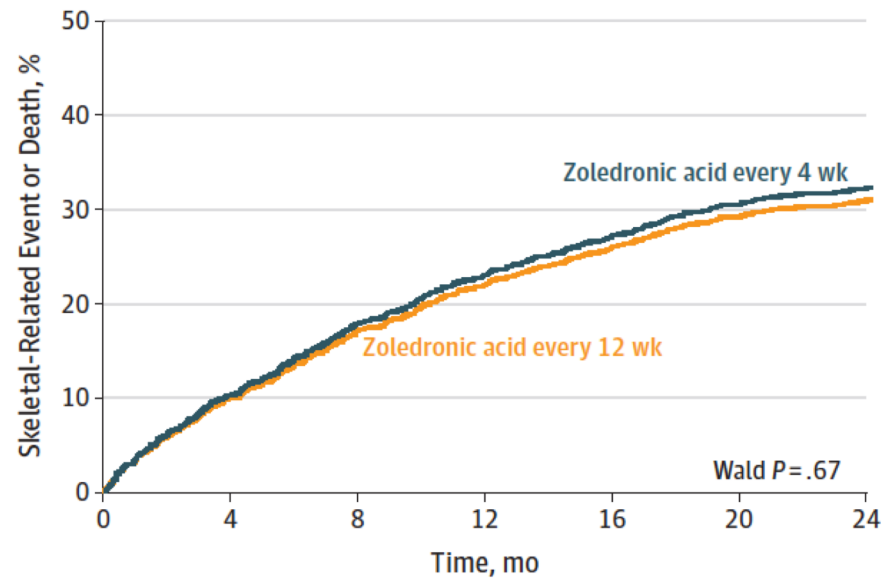
- Median duration of treatment **only 9m**
- Skeletal survey q3m detected **asymptomatic** fractures
- Lower dose **better** than higher dose
- **No** overall survival benefit
- **No** quality of life benefit



Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases

A Randomized Clinical Trial

Figure 2. Cause-Specific Cumulative Incidence of Skeletal-Related Events



No. at risk							
Every 4 wk	911	882	703	586	467	367	245
Every 12 wk	911	884	726	576	484	392	244



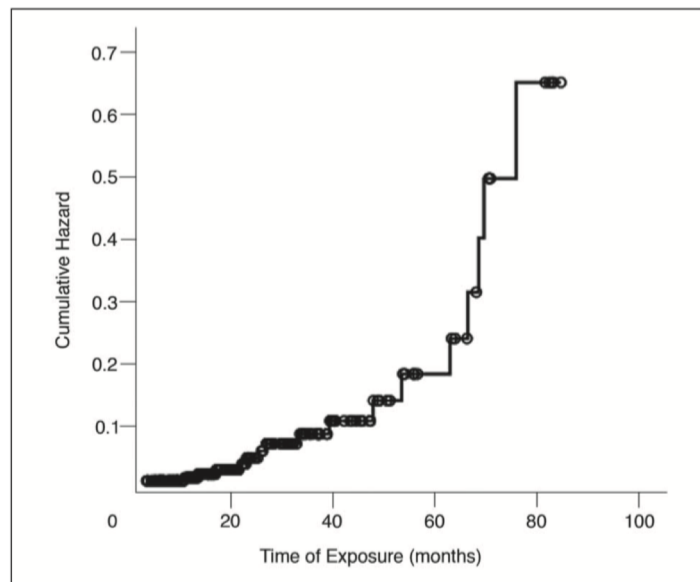
Himmelstein et al
JAMA (2017) 317: 48-58

What has changed in the last 20 years?

- **Overall survival**
 - Median OS increased from 15m to 32m
- **Risk of SRE**
 - Median time to SRE increased from 12m to 31m
- **Type of SRE**
- **Bone health management**



Osteonecrosis of the Jaw in Cancer After Treatment With Bisphosphonates: Incidence and Risk Factors



Bamias et al. JCO (2005) 23:8580-87

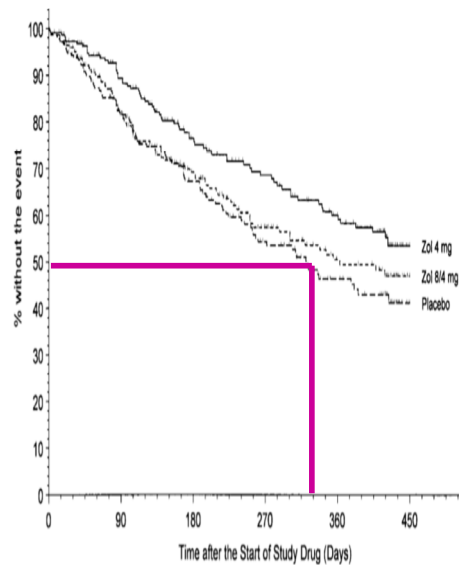
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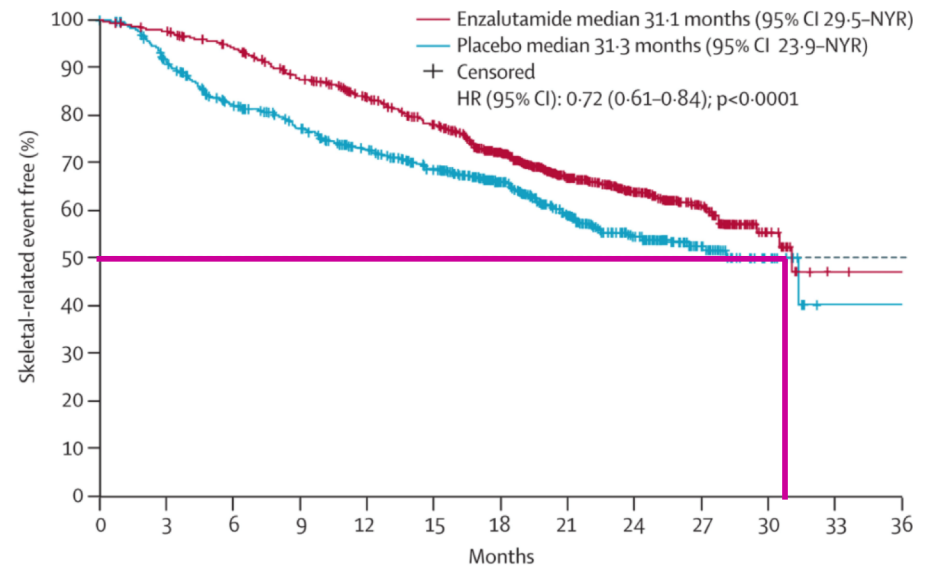
SREs are not as common as they used to be

Saad et al. (2002)



Median 11 months

PREVAIL(2015)

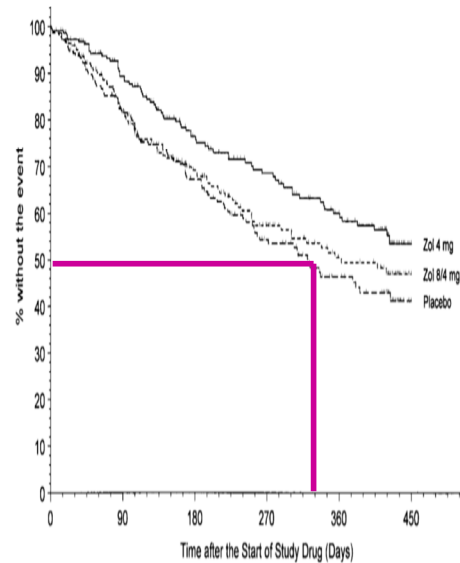


Median 31 months
(26% on bone health agent)
(84% with bone mets)



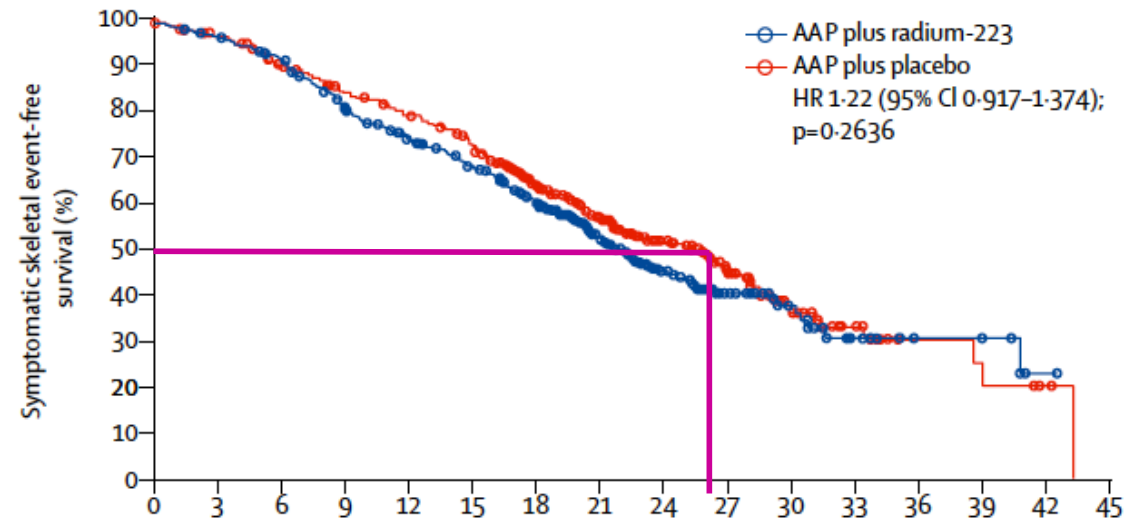
SREs are not as common as they used to be

Saad et al. (2002)



Median 11 months

ERA-223 (2019)



Median 26 months
(42% on bone health agent)

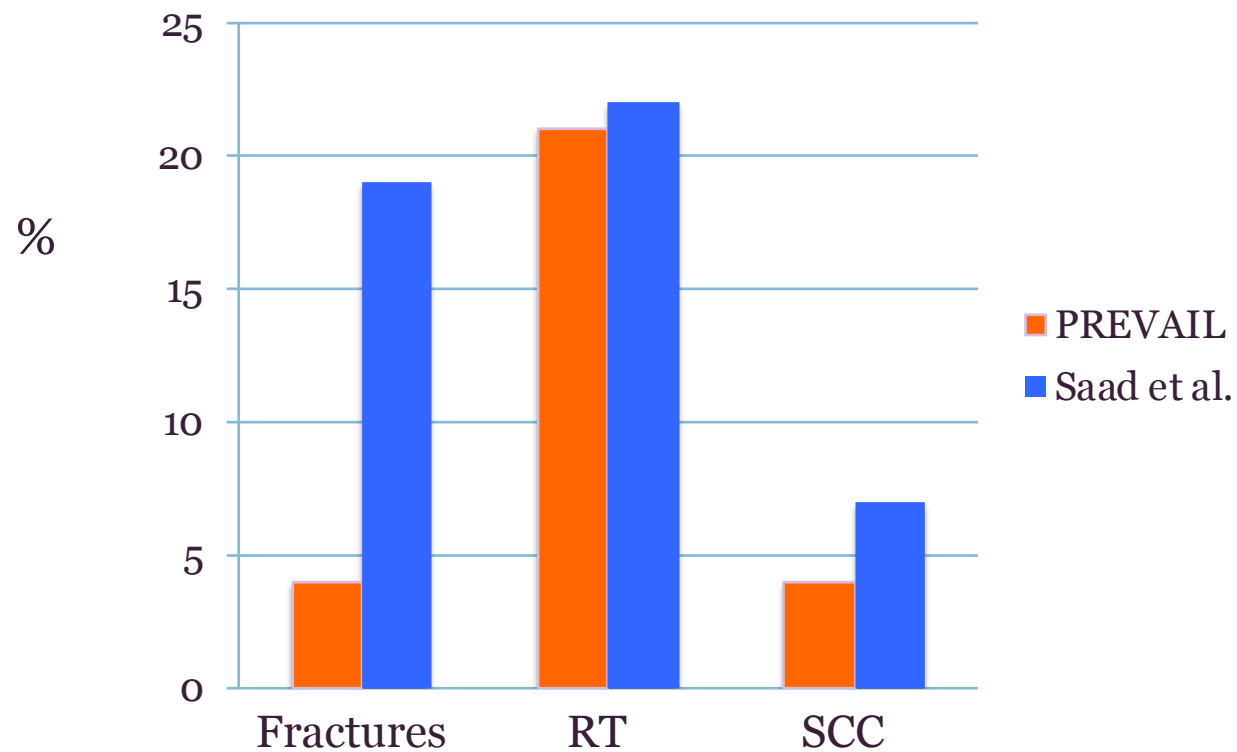


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- **Type of SRE**
- Bone health management



SREs are not what they used to be



Saad et al. JNCI (2002) 94:1458-1468; Loria et al Lancet Oncol (2015) 16(5) 509-21



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- Type of SRE
- **Bone health management**



What has changed? - Bone health management

- Men with prostate cancer are now on ADT for longer
- New drugs for prostate cancer both reduce SRE risk and have adverse effect on bone health
- **So, bone health is increasingly important, and “skeletal related events” are less important**



NICE guidance on bone health (2017)

- **Oral** bisphosphonates are recommended as options
if the 10-year probability of osteoporotic fragility
fracture is at least **1%**
- 10yr probability of major osteoporotic fracture for a
60yr old man with no risk factors: **3.8%** (FRAX)



UK Prostate Clinical Excellence Group guidance (2019)

- Lifestyle measures for men on ADT
 - weight bearing exercise, stop smoking, ≤ 2 units alcohol daily, adequate Ca intake and Vit D status
- Men starting ADT for over 1 year should be considered for oral bisphosphonates



EFFECT OF ORAL ALENDRONATE ON BONE MINERAL DENSITY AND THE INCIDENCE OF FRACTURES IN POSTMENOPAUSAL OSTEOPOROSIS

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THOMAS CAPIZZI, PH.D., ANTONIO LOMBARDI, M.D.,
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FOR THE PHASE III OSTEOPOROSIS TREATMENT STUDY GROUP*











48% reduction in fracture risk

Overall, treatment with alendronate was associated with a 48 percent reduction in the proportion of women with new vertebral fractures (3.2 percent, vs. 6.2 percent in the placebo group; $P=0.03$)



A systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures

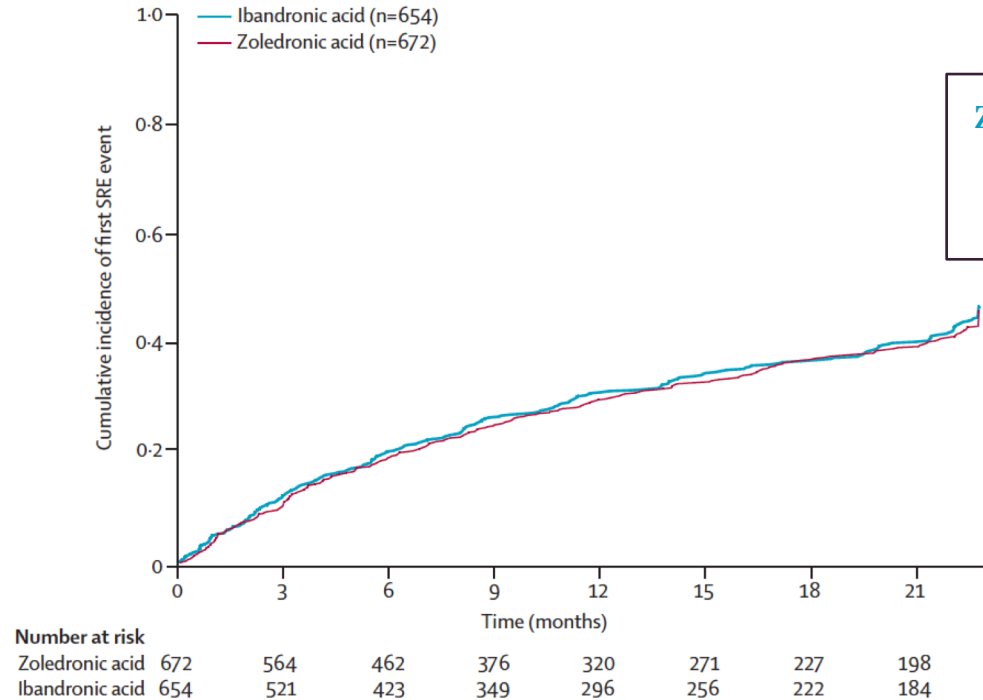
Effect on vertebral fractures

Treatment comparison		HR (95% CrI)
Versus placebo		
Risedronic acid		0.50 (0.38 to 0.66)
		0.51 (0.27 to 0.84)
Alendronic acid		0.45 (0.35 to 0.58)
		0.45 (0.25 to 0.79)
Zoledronic acid		0.41 (0.28 to 0.56)
		0.41 (0.23 to 0.76)
Ibandronic acid 150mg/month		0.45 (0.24 to 0.81)
		0.45 (0.21 to 0.96)
Ibandronic acid 2.5mg/day		0.46 (0.32 to 0.67)
		0.47 (0.25 to 0.86)



Oral ibandronic acid versus intravenous zoledronic acid in treatment of bone metastases from breast cancer: a randomised, open label, non-inferiority phase 3 trial

Cumulative incidence of SREs



zoledronate 4mg q3-4weeks
 vs
 ibandronate 50mg daily

Barrett-Lee et al. Lancet Oncol (2014) 15: 114-22



Anti-resorptive therapy to reduce SRE risk in men with bone-metastatic CRPC

2002	2020
Median duration of treatment only 9m	
Skeletal survey q3m detected <u>asymptomatic</u> fractures	
Lower dose better than higher dose	
No overall survival benefit	
No quality of life benefit	



Anti-resorptive therapy to reduce SRE risk in men with bone-metastatic CRPC

2002	2020
Median duration of treatment only 9m	Toxicity increased by prolonged use
Skeletal survey q3m detected <u>asymptomatic</u> fractures	Less potential for benefit because of lower fracture risk
Lower dose better than higher dose	No proven benefit over standard bone health management
No overall survival benefit	No overall survival benefit
No quality of life benefit	No quality of life benefit

