Castrate-resistant prostate cancer: Bone-targeted agents

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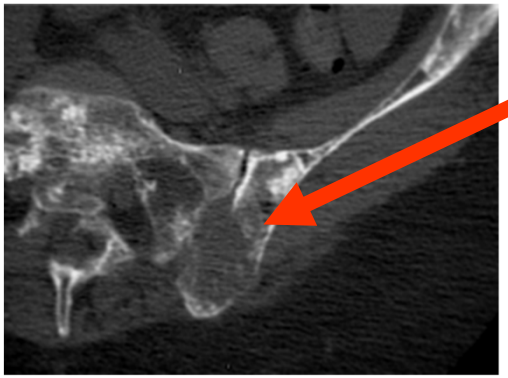
Disclosure

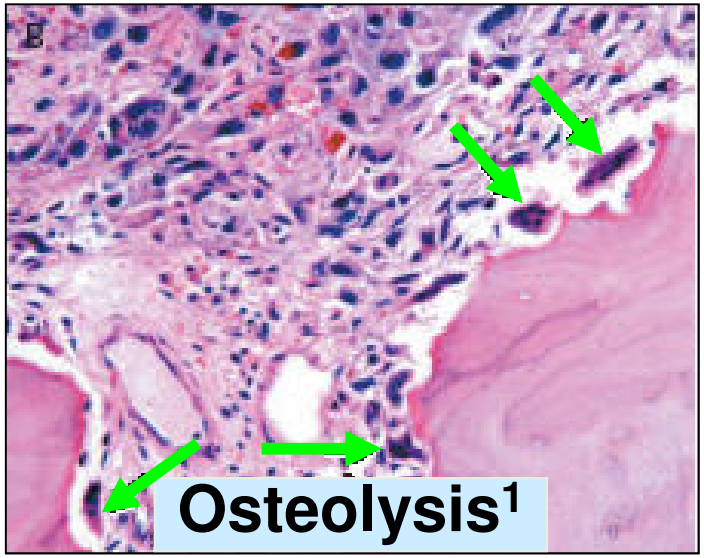
Participation in advisory boards or as a speaker for: Amgen, Astellas, Astrazeneca, Bayer, Curevac, Janssen, Orion, Roche, Sanofi-Aventis

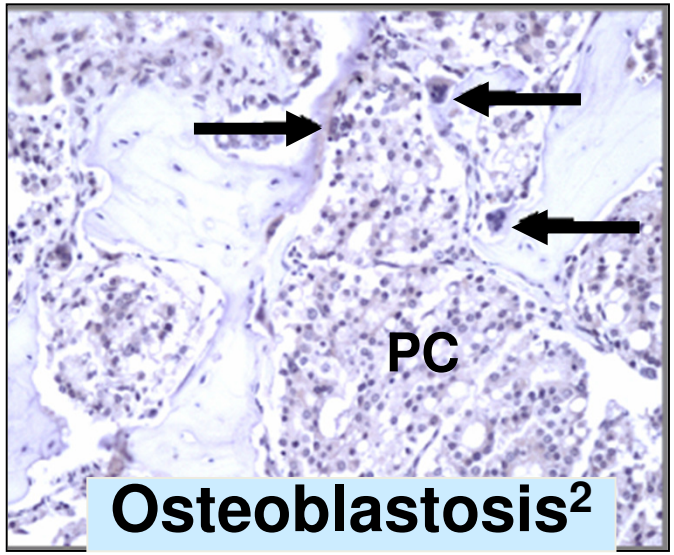
Osteolytic and osteoblastic bone metastases: presence of osteoclasts irrespective of radiology



Osteolysis

Osteoblastosis



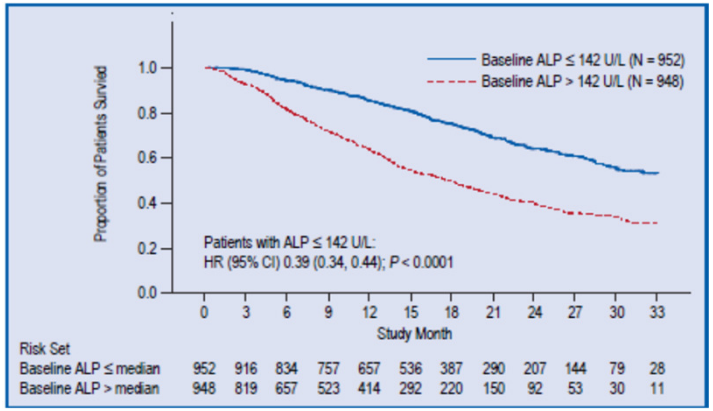


Black arrows = osteoclasts

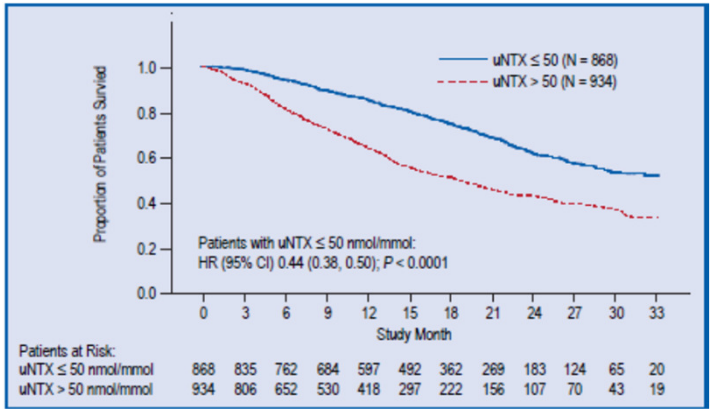
1. Roodman GD. *N Engl J Med* 2004;350:1655–1664
2. Amgen, data on file

The prognostic importance of bone-related factors in mCRPC

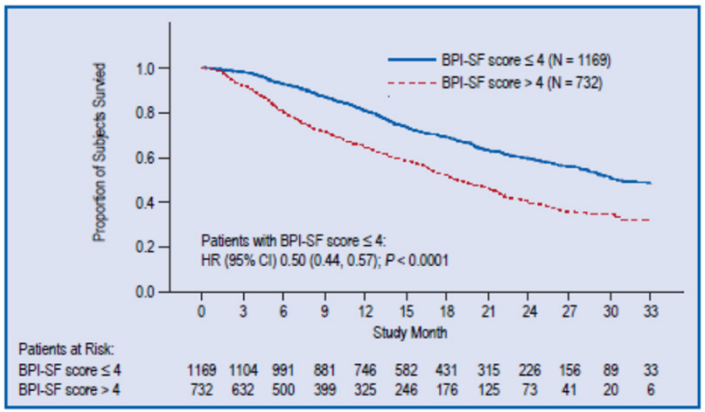
Alkaline Phosphatase



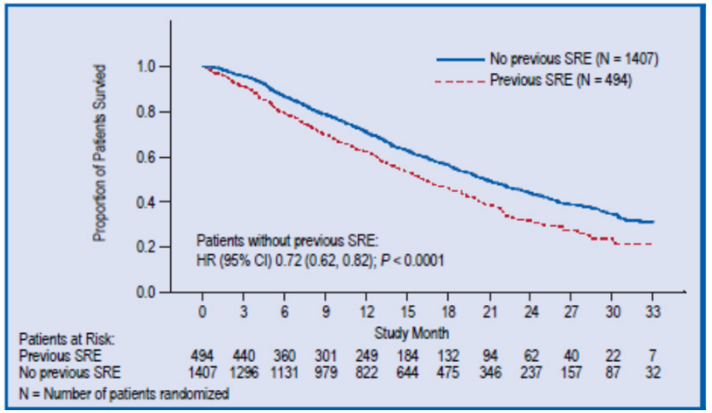
Urinary N-telopeptide



Bone pain

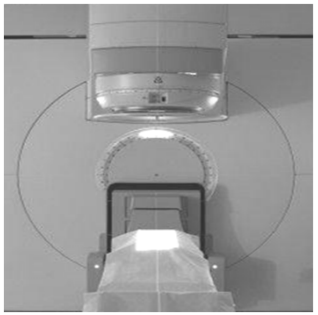


Previous SRE



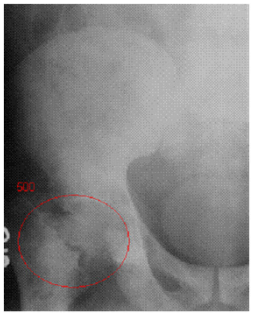
Fizazi K, Eur Urol 2015; 68: 42-50

Skeletal-Related Events (SRE) in men with bone metastases from prostate cancer



Pain requiring Radiation to Bone

33%

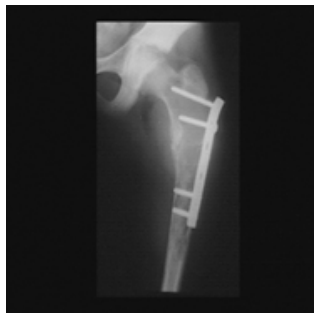


Pathologic Fracture

25%

Spinal Cord Compression

8%

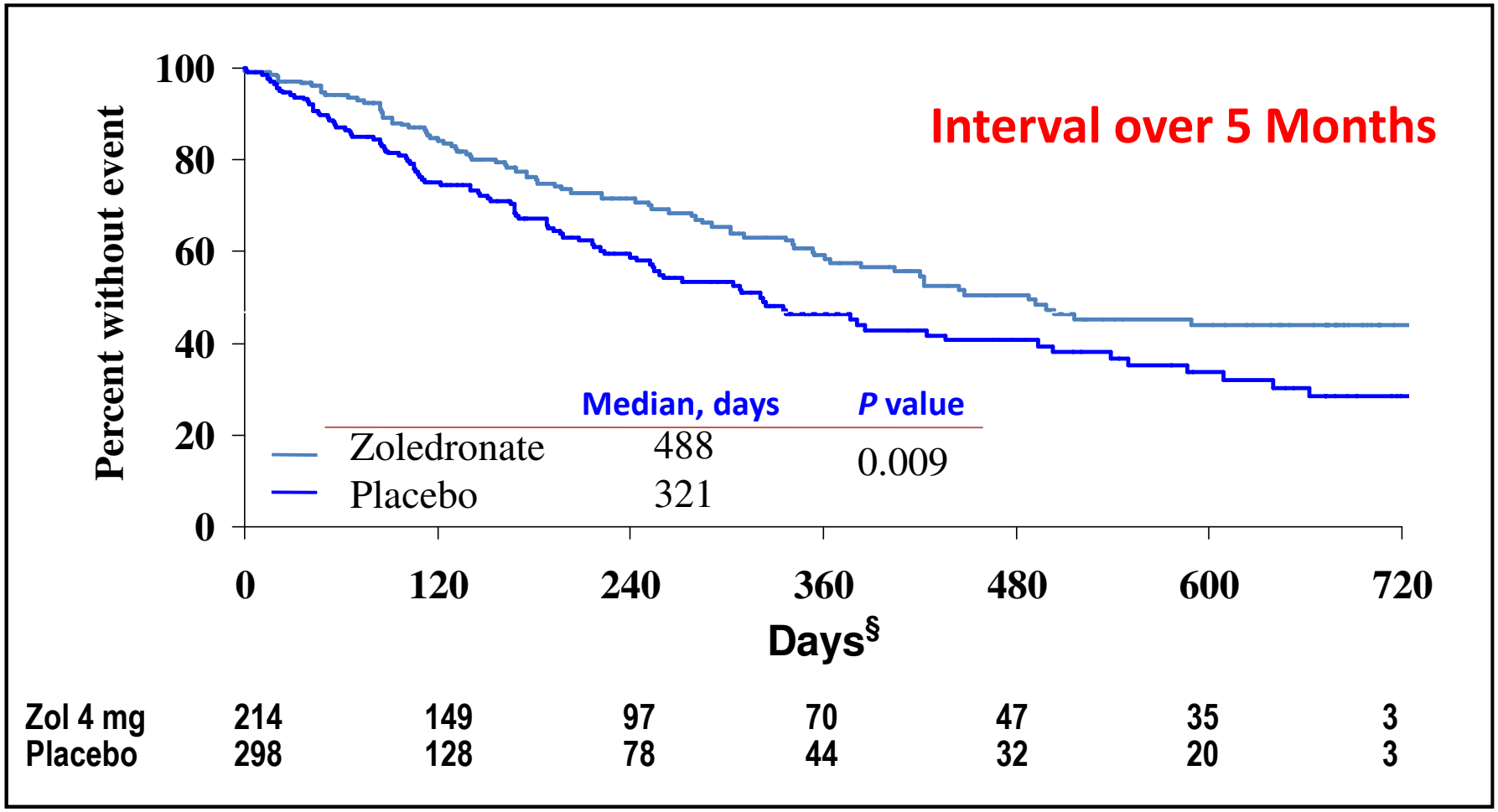


Surgery to Bone

4%

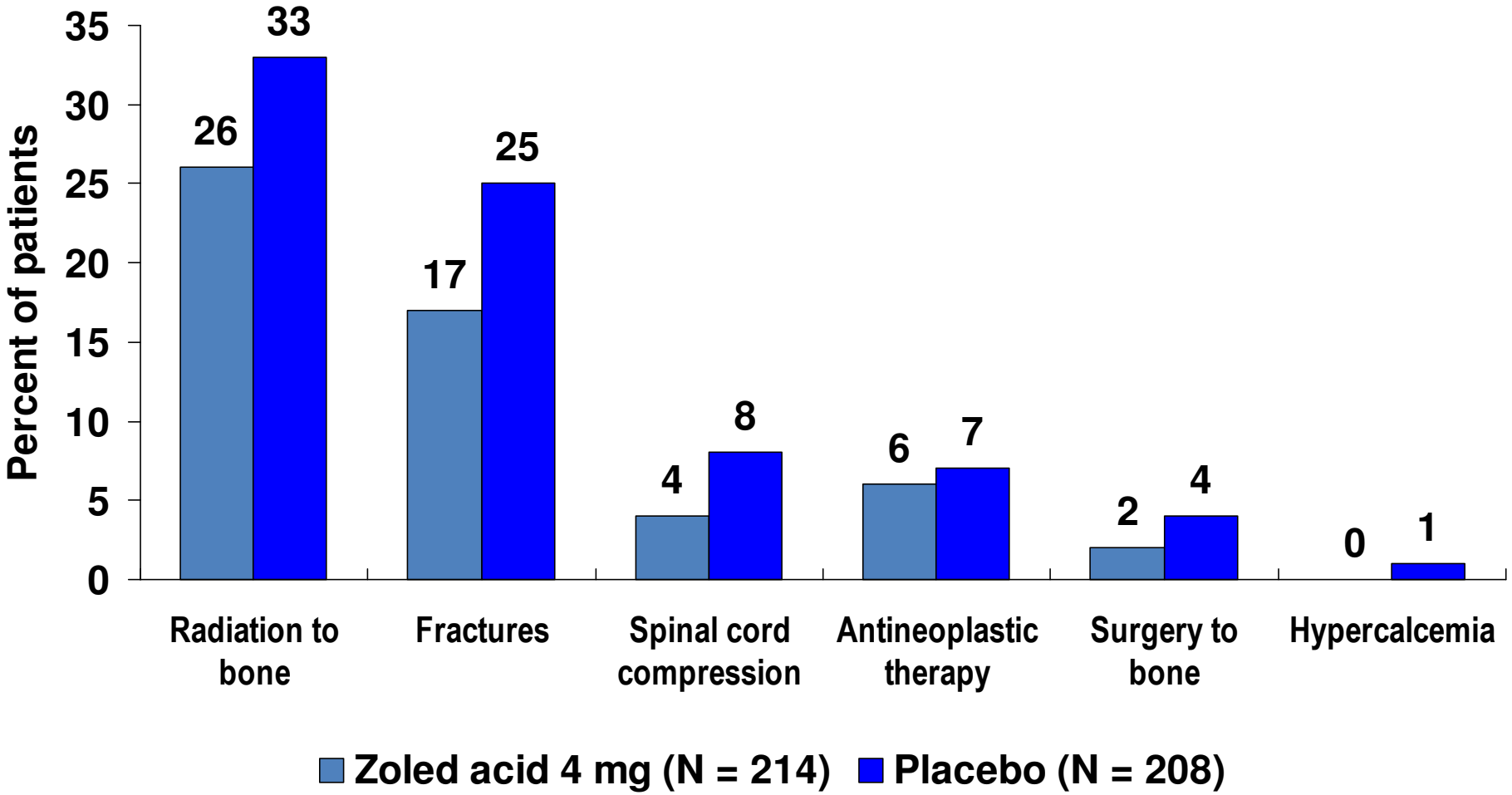
Saad, et al. J Urol 2003;169(Suppl).

Zoledronate: Time to Skeletal-Related Event in mCRPC

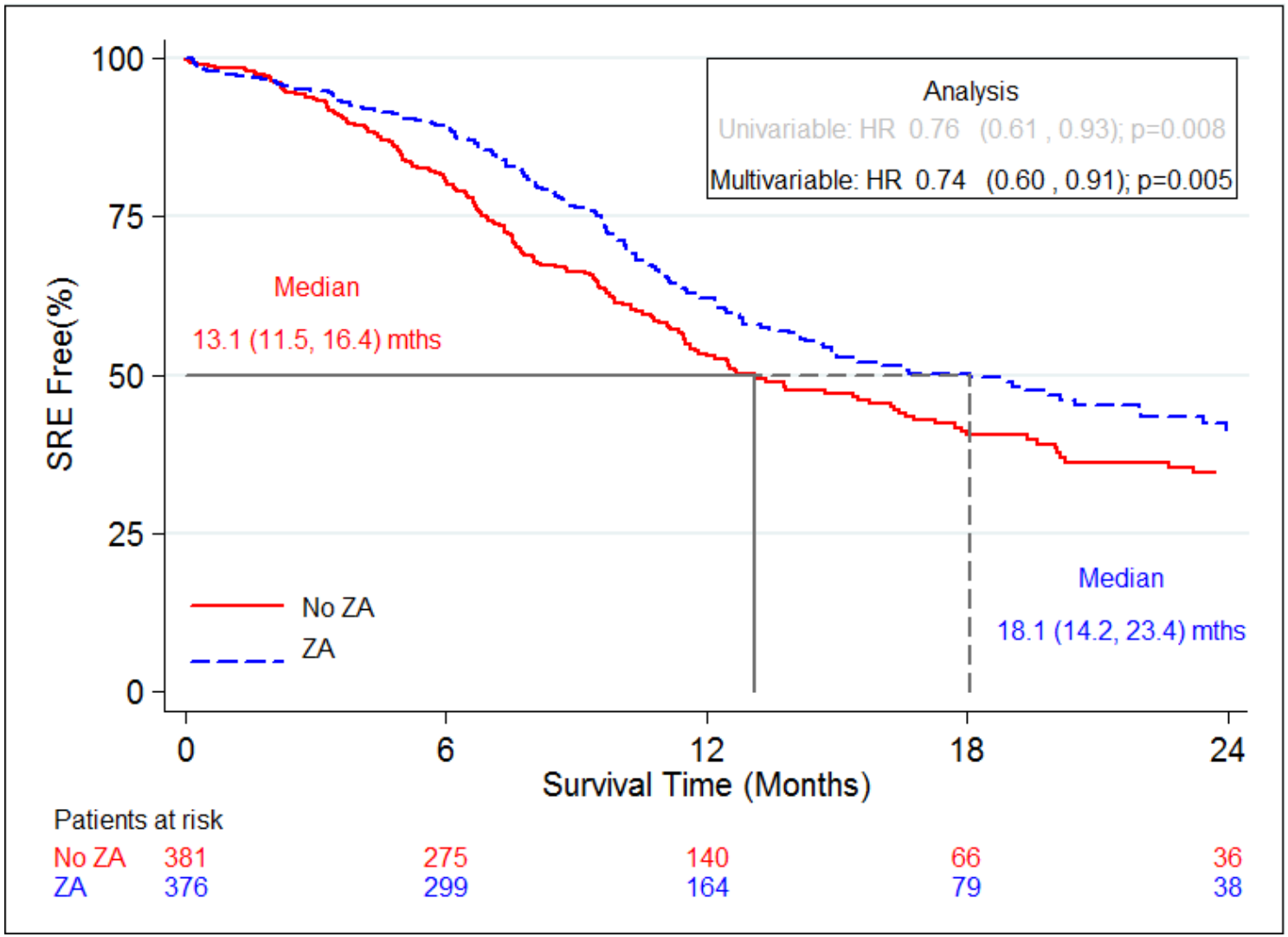


Saad et al. *JNCI 2004; 96:879*

Proportion (%) of Patients With Each SRE

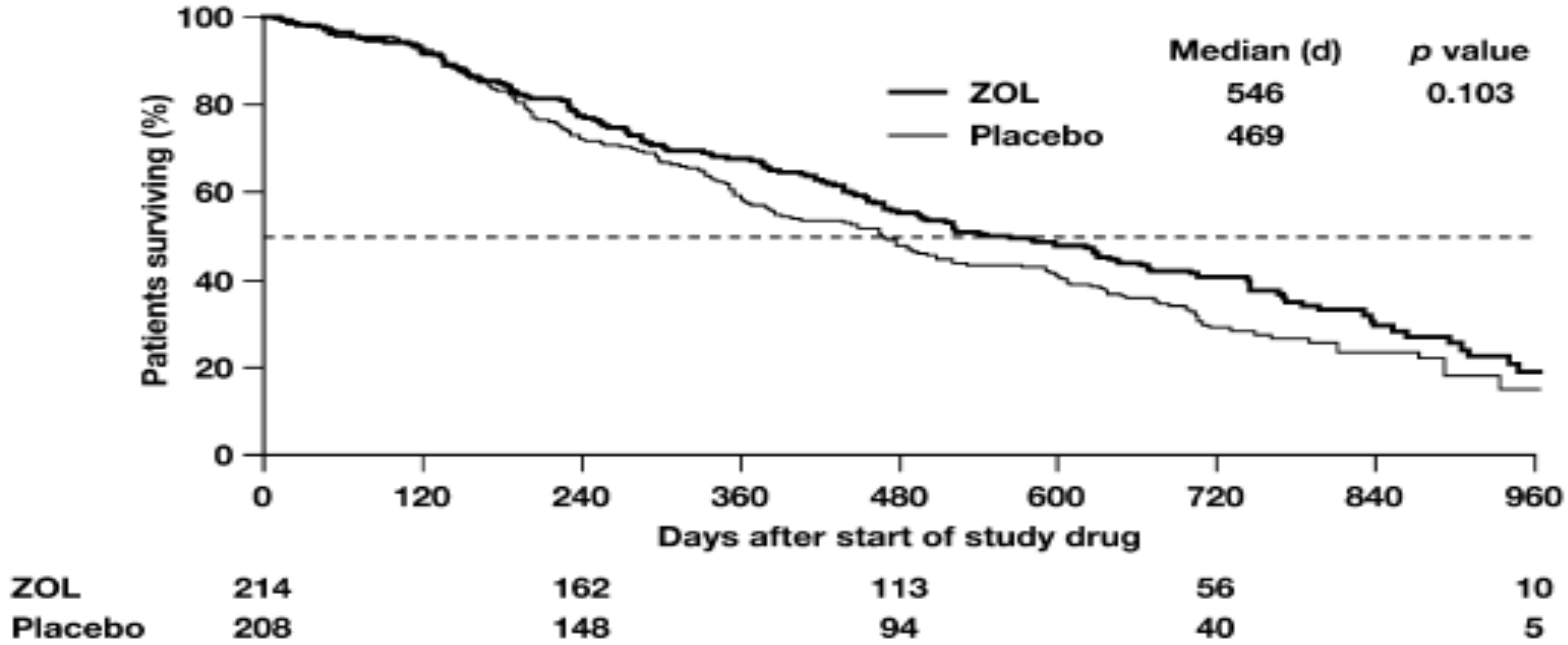


Trapeze Phase III trial in mCRPC: Symptomatic Skeletal Events (SSE)



James N, JAMA Oncol 2016; 2: 493-99

Zoledronic Acid for CRPC: Overall survival



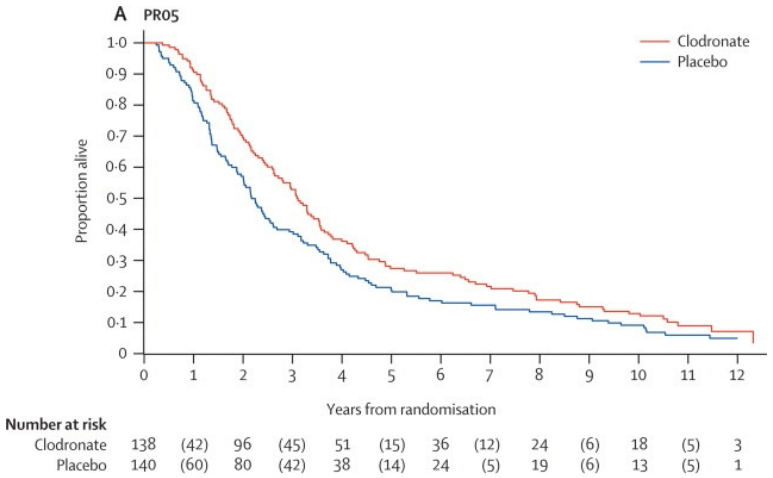
- Median OS: 18.2 vs 15.6 months
- 1-year survival 85.2% vs. 78.3% (P = 0.21)[2]

[1]Saad F: Cancer Treatment Reviews (2008) 34, 183– 192

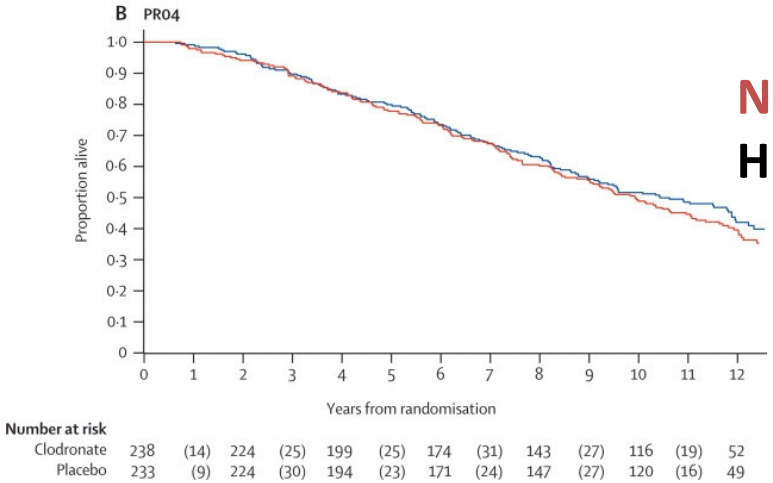
2Weinfurt KP, et al. *Annals of Oncology*. 2006;17: 986-989.

Clodronate in Hormone-Sensitive Prostate Cancer

Overall survival



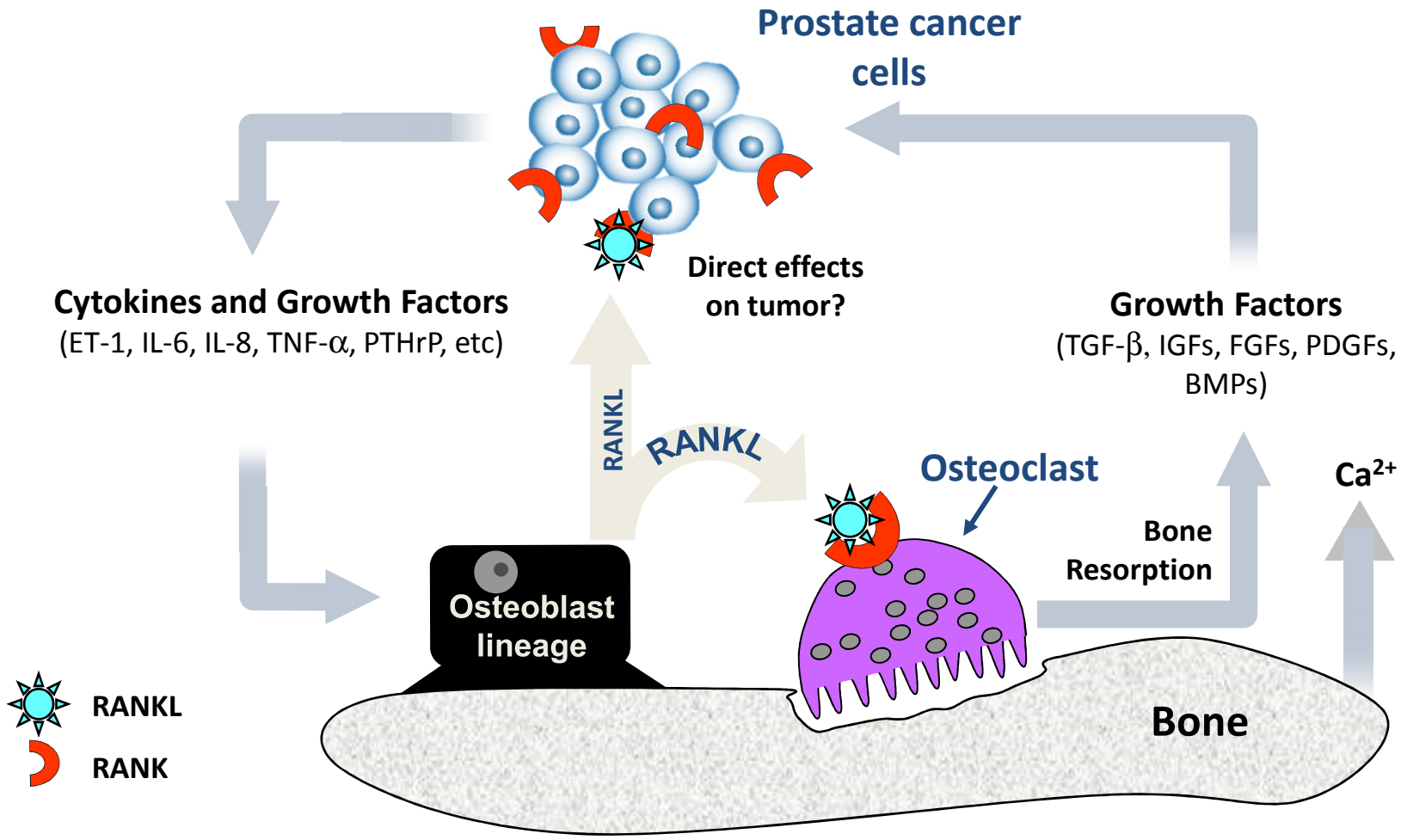
Metastatic disease (PR05 trial, n = 278)
HR: 0.77 (0.60-0.98), *P* = .032



Nonmetastatic disease (PR04 trial, n = 471)
HR: 1.12 (0.89-1.42), *P* = .94

Dearnaley DP, et al. *Lancet Oncol* 2009;10: 872-876.

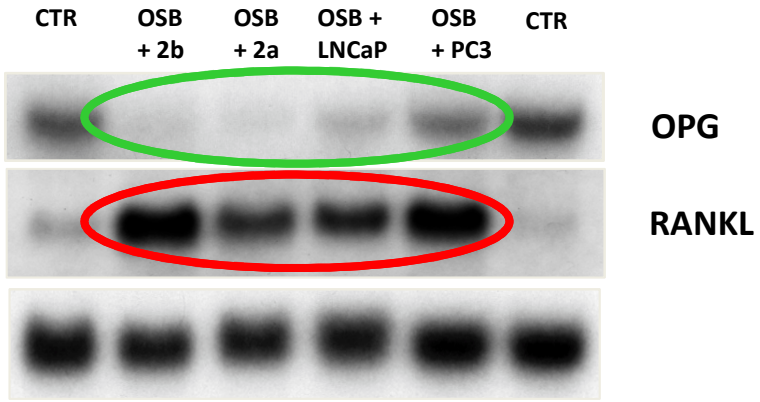
The “vicious cycle” of bone metastases



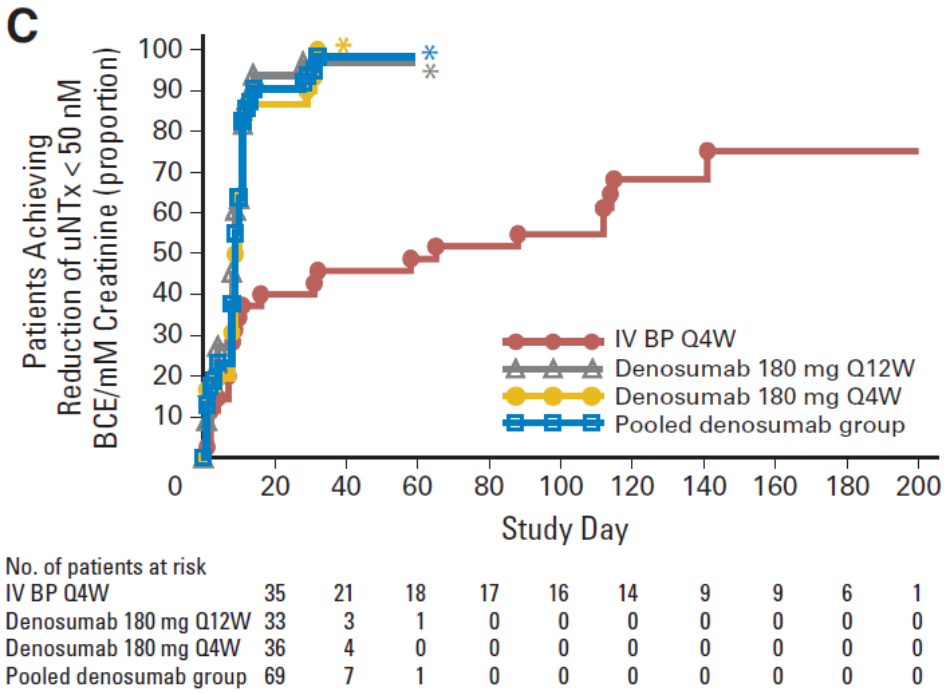
Adapted from Roodman GD. *N Engl J Med.* 2004;350:1655-64.

Targeting RANK-L: Proof of concept

RANK-L overexpressed by osteoblasts in bone metastases



Positive randomized Phase II: Denosumab decreases uNTx (biomarker for osteolysis)

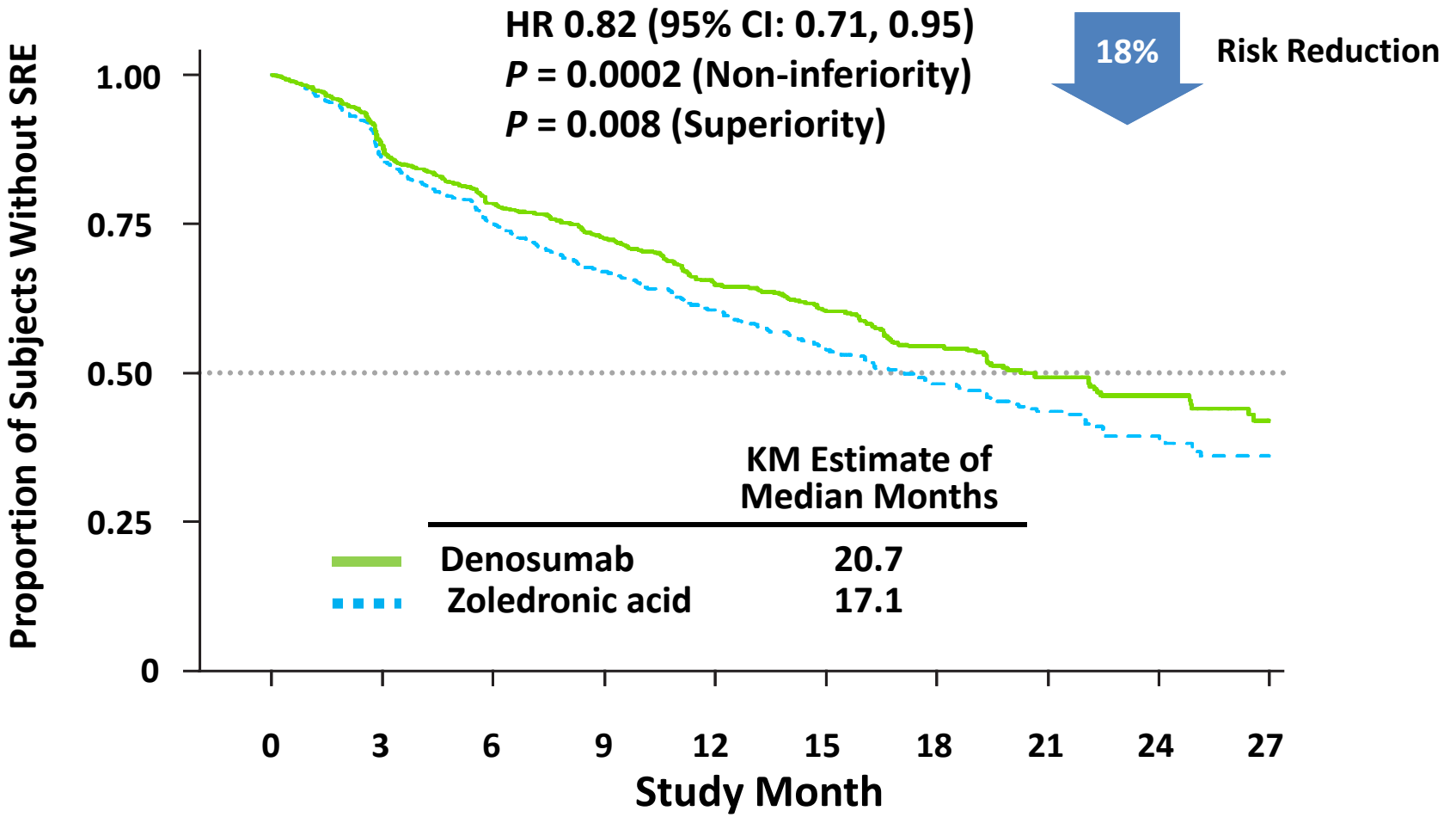


No. of patients at risk

IV BP Q4W	35	21	18	17	16	14	9	9	6	1
Denosumab 180 mg Q12W	33	3	1	0	0	0	0	0	0	0
Denosumab 180 mg Q4W	36	4	0	0	0	0	0	0	0	0
Pooled denosumab group	69	7	1	0	0	0	0	0	0	0

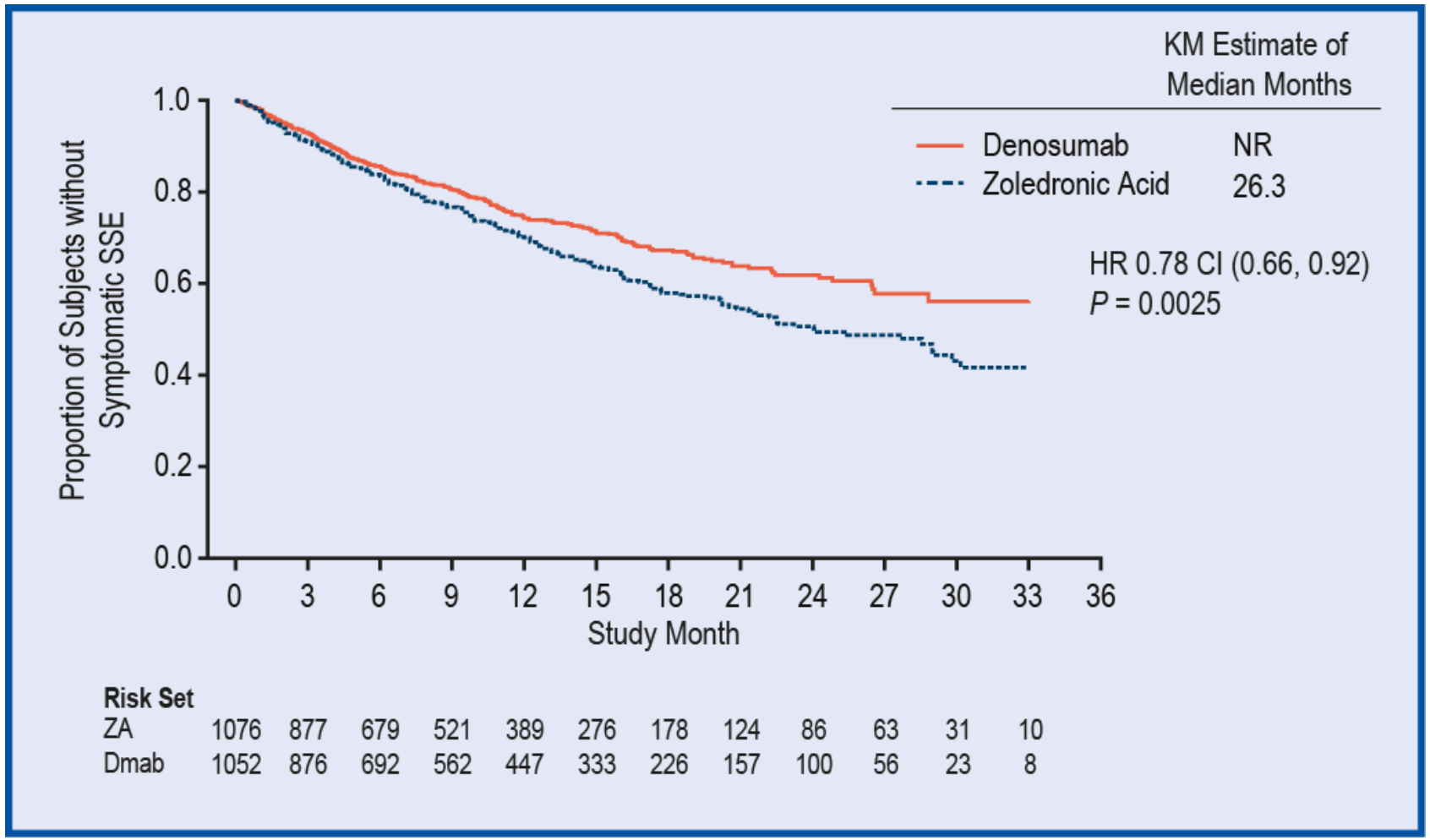
Fizazi et al., Clin Cancer Res 2003;9:2587–2597
Fizazi et al., J Clin Oncol 2009; 27: 1564-71

Denosumab: Time to First SRE in patients with established bone metastases



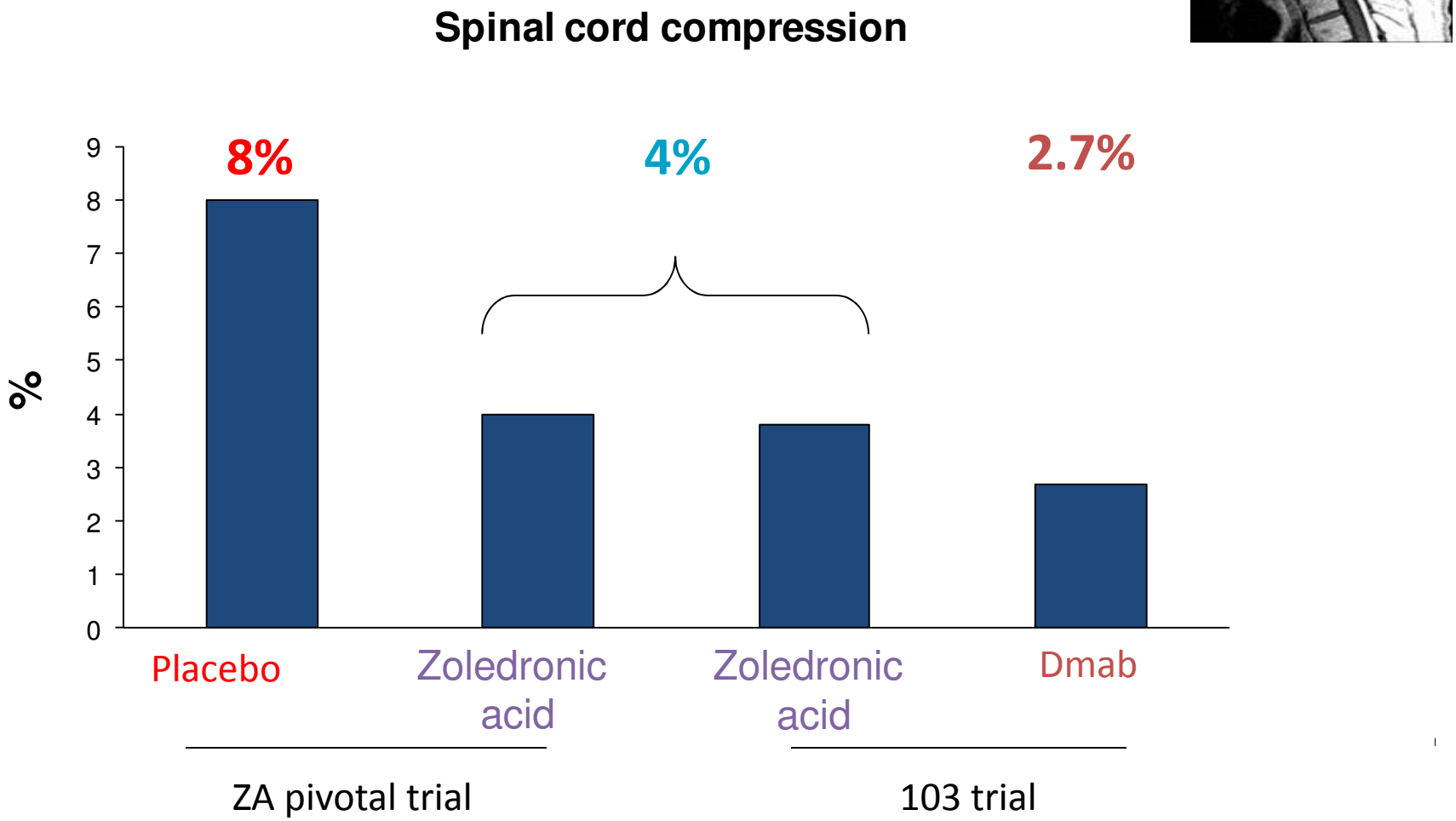
Fizazi et al. Lancet 2011; 377: 811-822

Denosumab:
time to first symptomatic event (SSE)



Smith M et al., Ann Oncol 2015; 26: 368-74

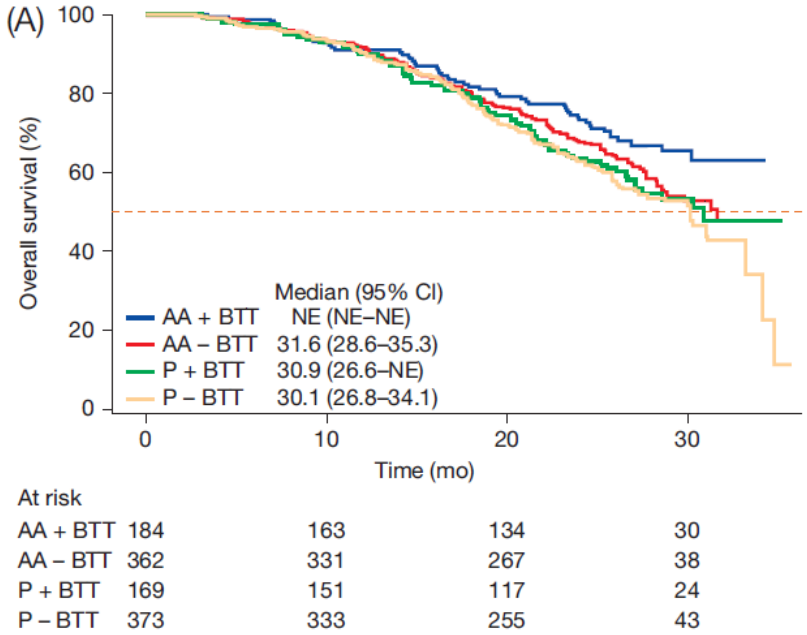
Preventing the onset of the worst enemy:



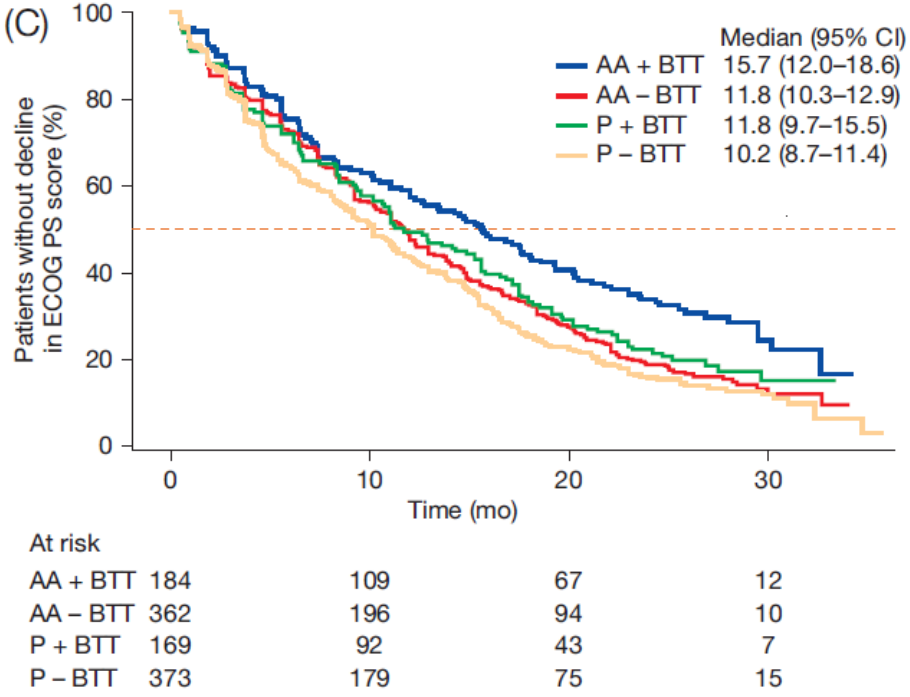
Saad, et al. J Natl Cancer Inst 2004;96:879–82;
Fizazi et al. Lancet 2011; 377: 811-822

Use of bone-targeted agents with abiraterone (COU-302)

OS



TT deterioration in PS



Saad F, Eur Urol 2016; 68: 570-7

Bone-targeted agents: Are they worth using?

- Morbidity reduced
- Prevention vs treatment
- Overall good tolerance
- Cheaper than most new cancer drugs

- No demonstrated role in survival
- ONJ (1-2%), hypocalcemia

Osteonecrosis of the jaw

- Data from 3 randomized trials (n=5723)
- ONJ in 89 (1.6%) pts
  - 37 (1.3%) zoledronic acid
  - 52 (1.8%) denosumab (p = 0.13)
- **Tooth extraction in 62% of pts with ONJ**
  - **Disruption of denosumab recommended**
  - **Antibiotics recommended**
- ONJ conservative treatment in >95%
- ONJ resolution in 36%

Saad F, Ann Oncol 2012; 23: 1341-7

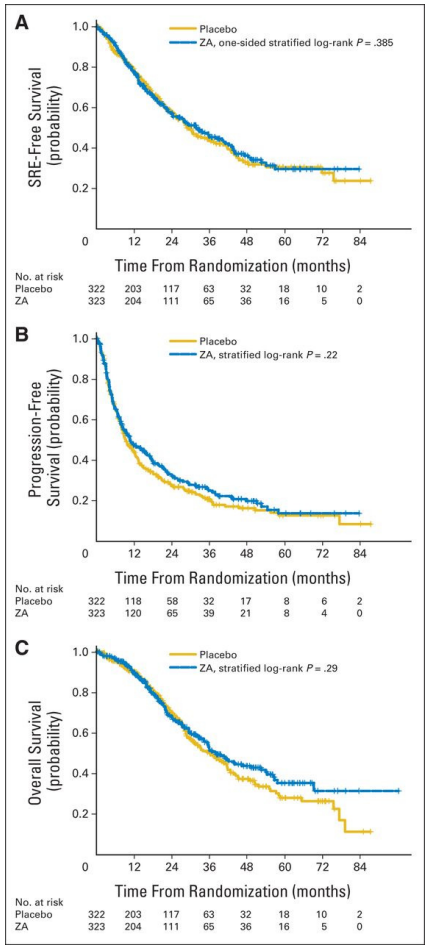
No benefit of zoledronic acid in pts with castrate-sensitive metastatic CaP

n= 645 pts with HSPC and bone mets

R → **Immediate Zoledronic Acid**

R → **Zoledronic Acid when CRPC**

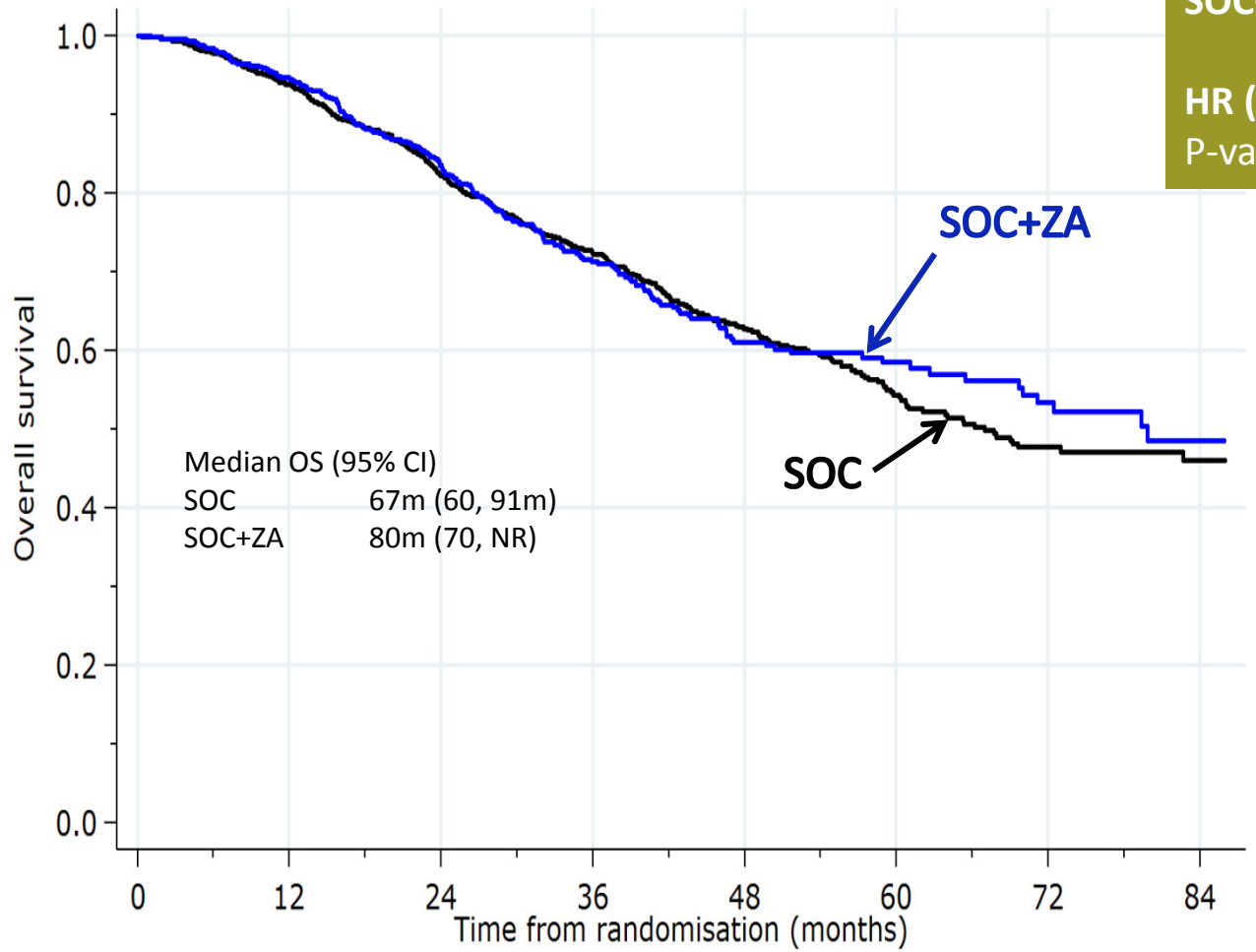
Median time to SRE:
32 mo vs 30 mo (HR=0.97)



Smith MR, J Clin Oncol 2014; 32: 1143-50

Zoledronic acid in hormone-sensitive CaP: Survival (Stampede)

SOC	**405 deaths**
SOC+ZA	**197 deaths**
HR (95%CI)	**0.93** (0.79, 1.11)
P-value	0.44



Non-PH p-value 0.83

Group
At risk (events)

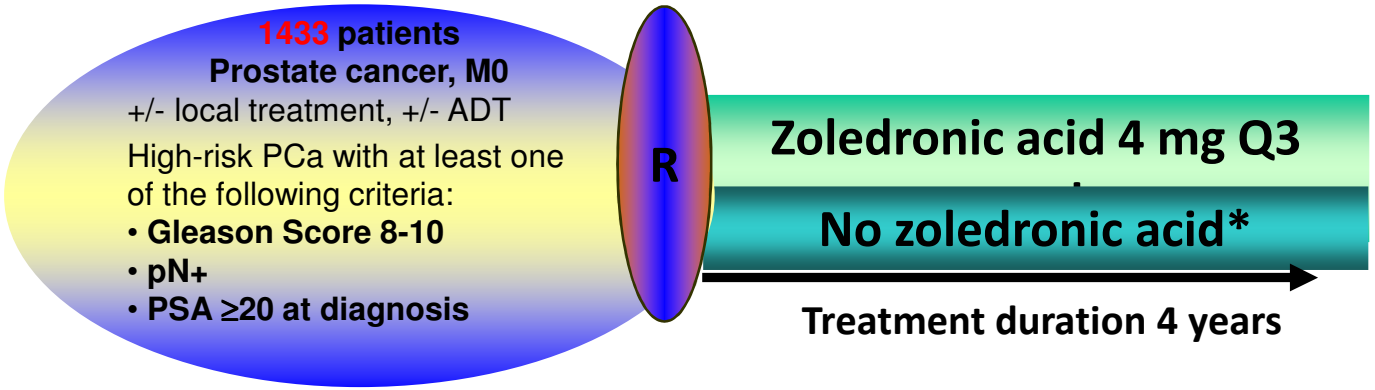
SOC	1184	(73)	1092	(130)	860	(89)	521	(59)	310	(33)	156	(17)	81	(2)	36
SOC+ZA	593	(32)	553	(63)	444	(56)	272	(32)	147	(5)	85	(6)	46	(3)	19

Restricted mean OS time

SOC	58.5m
SOC+Doc	59.5m
Diff (95%CI)	1.0m (-1.4, 3.4m)

James N, ASCO 2015

Does Zoledronic Acid prevent the onset of bone metastases? The *ZEUS* trial

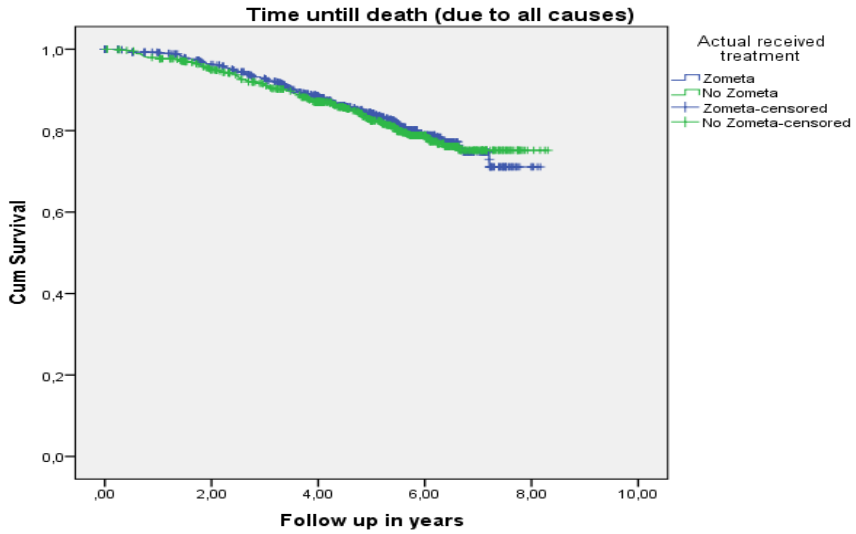


Median follow-up: 4.8 years

Primary endpoint: Bone metastases

Zoledronate	**13.7%**
Control	**13%**
	p=0.72

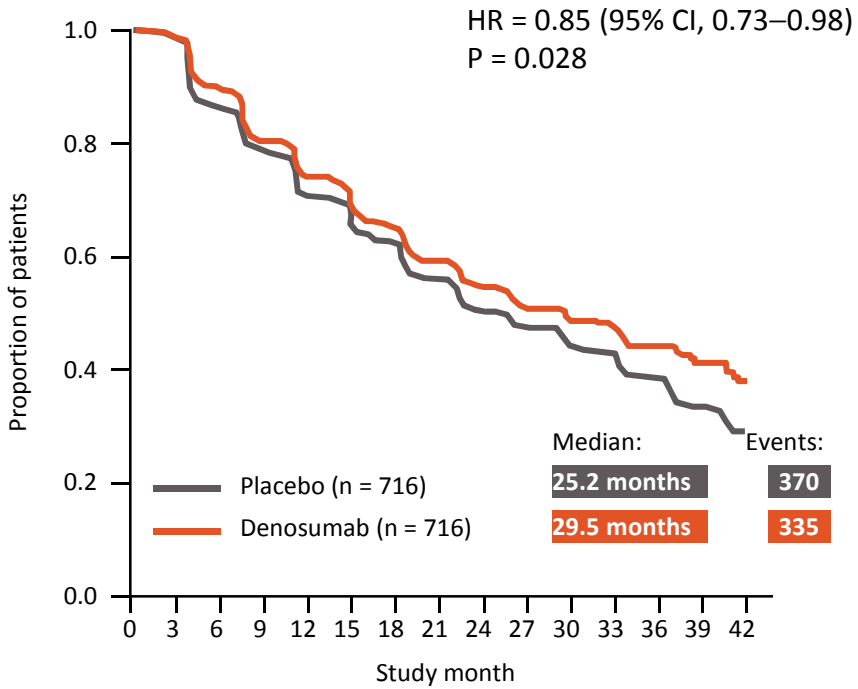
Overall survival



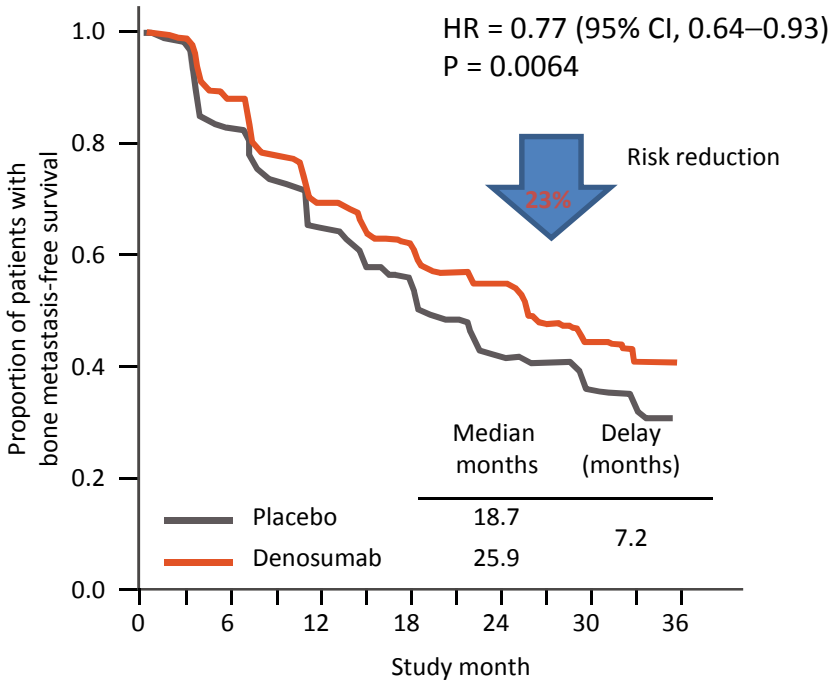
Wirth M, EAU 2013

Should Denosumab be used to prevent the onset of bone metastases in CRPC? The « 147 » trial

Overall population



Pts with PSA DT ≤ 6 months

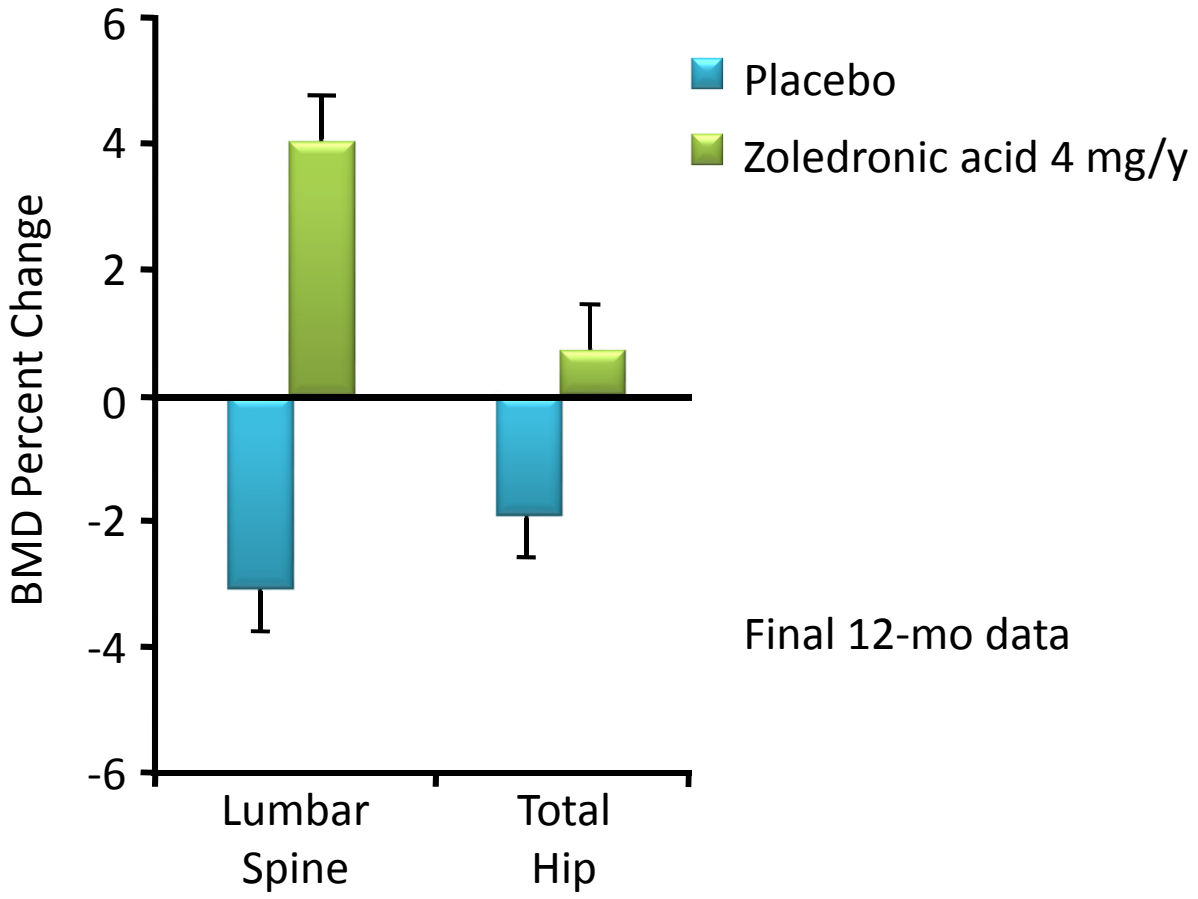


Smith MR, et al. Lancet 2012;379:39–46

Smith MR, et al. J Clin Oncol 2013

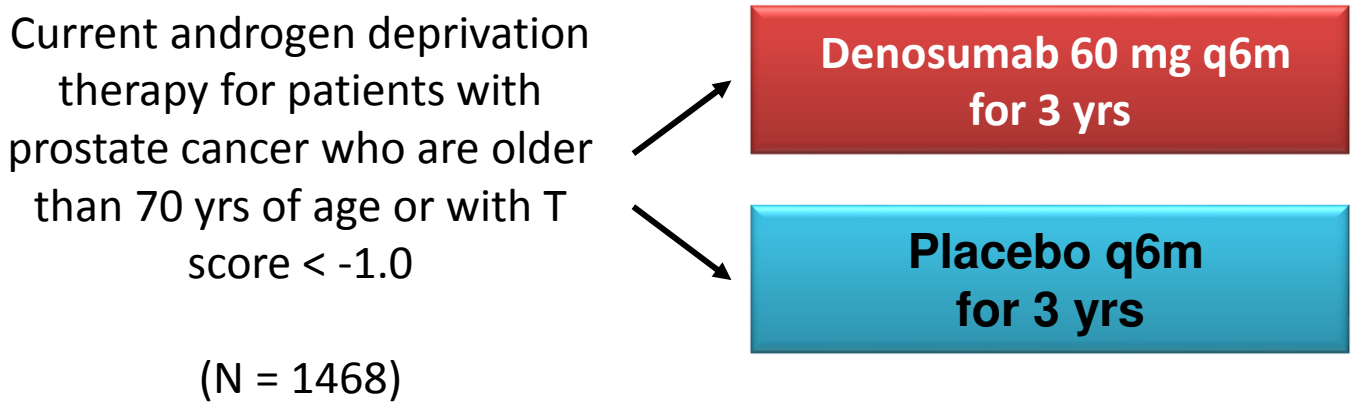
Should we use bone-targeted agents to prevent bone loss in men receiving ADT?

Annual Zoledronic Acid Increases BMD During GnRH Agonist Therapy



Michaelson MD, et al. J Clin Oncol. 2007;25:1038-1042.

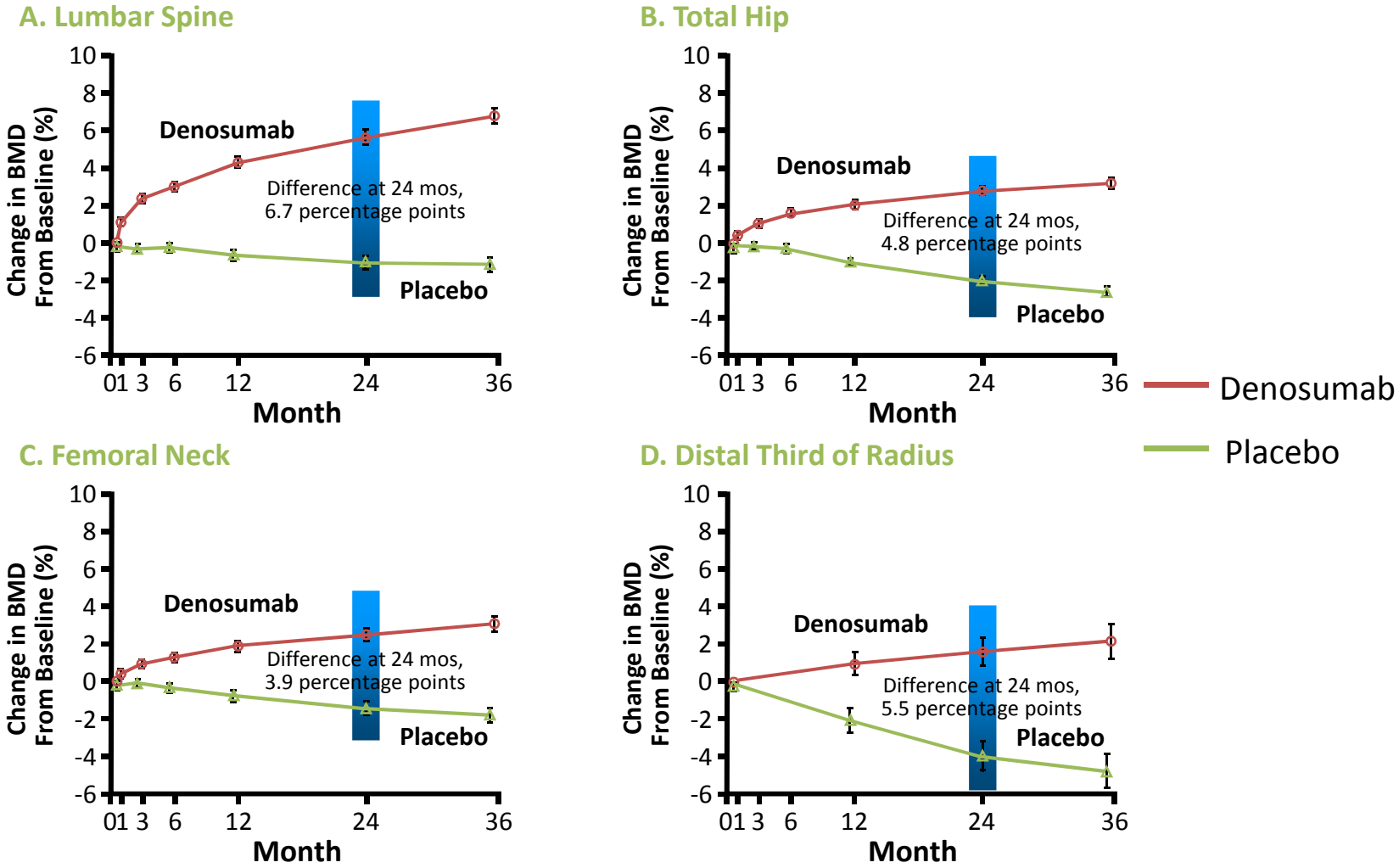
Denosumab Fracture Prevention Study



- Primary endpoint: BMD
- Secondary endpoint: new vertebral fractures

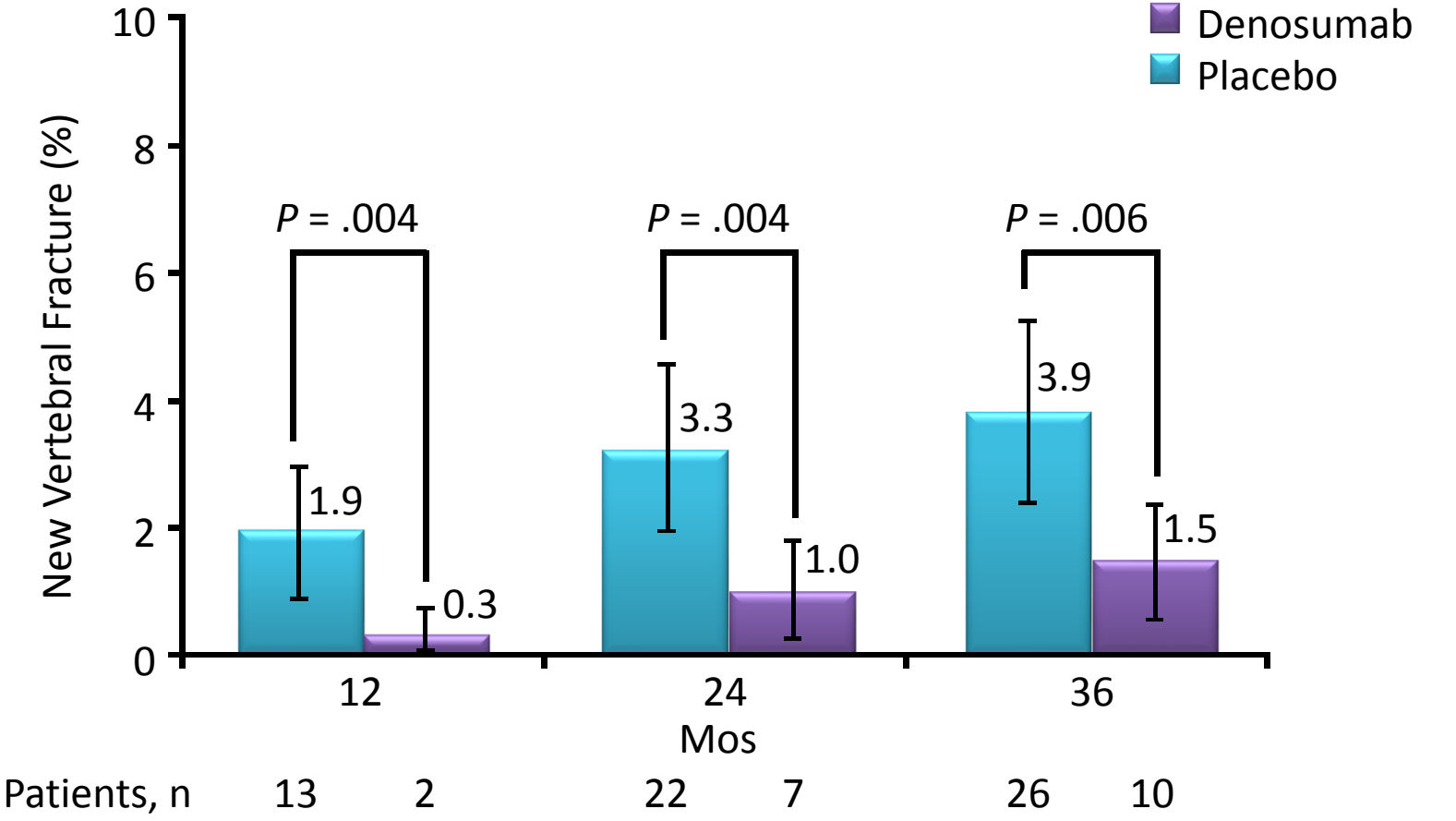
ClinicalTrials.gov. NCT00089674.

Denosumab Increased BMD at All Skeletal Sites



Smith MR, et al. N Engl J Med. 2009;361:745-755

Denosumab to Prevent Fractures



Smith MR. N Engl J Med. 2009;361:745-755

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GRAND PARIS

Conclusion: Bone-targeted agents in advanced prostate cancer

- In metastatic CRPC:
  - Zoledronic acid: SRE improved
  - Denosumab: SRE improved (>ZA)
  - SSE also improved
- No current role in hormone-sensitive metastatic prostate cancer (except for prevention of bone loss)
- Not approved in non-metastatic CRPC (unfavorable risk/benefit balance)

Toward team treatment for **Bone** metastases