How should we use bone treatments:

Bisphosphonates, denosumab and radium-223?

(A personal view)

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Disclosures
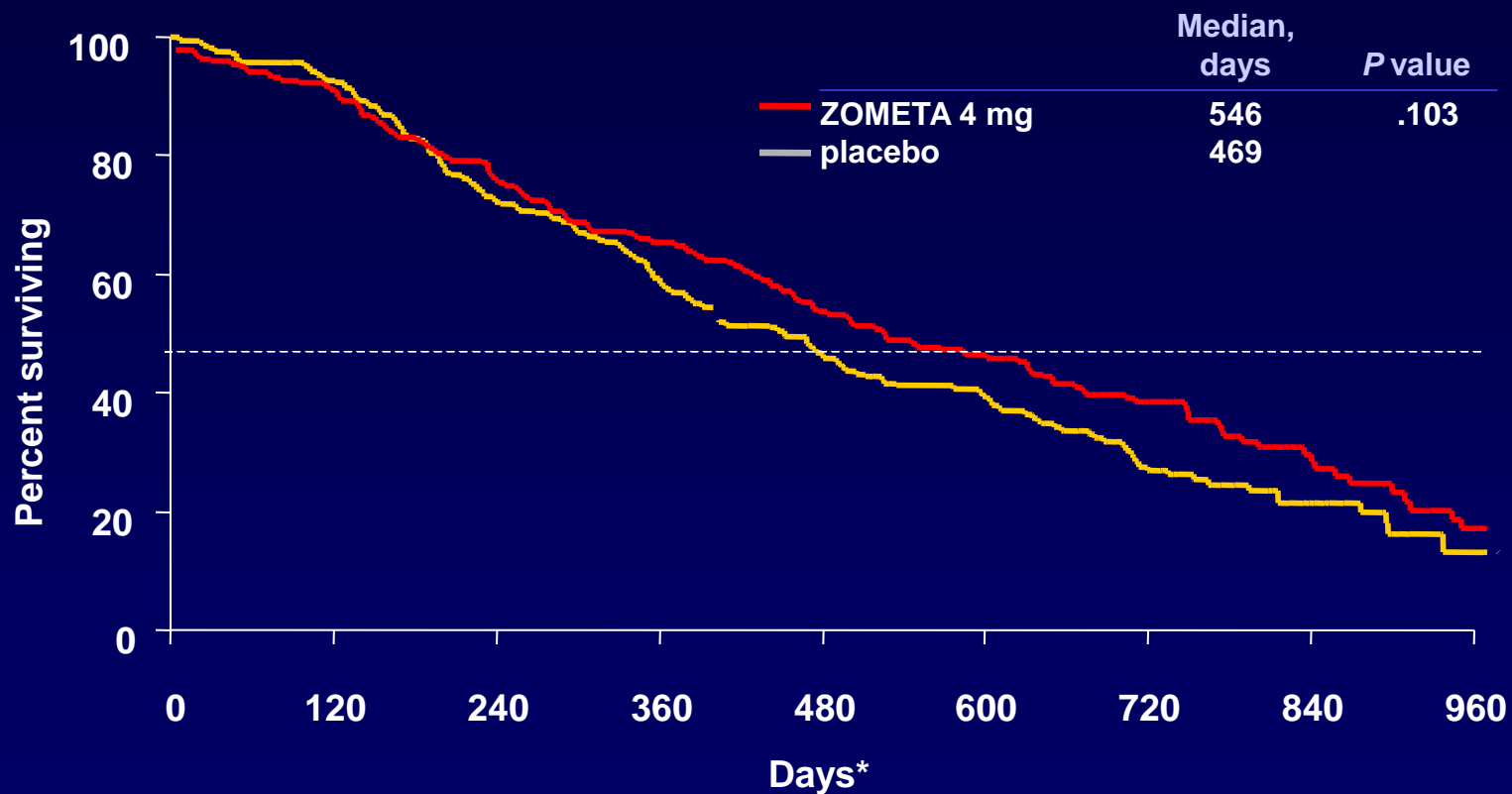
Amgen, Astellas, BNIT, Bayer, Janssen, Takeda

Why should we use bone treatments?

- **To improve overall survival**

- **To improve quality of life**

- **To delay symptomatic SREs**

- **To delay bone metastases**

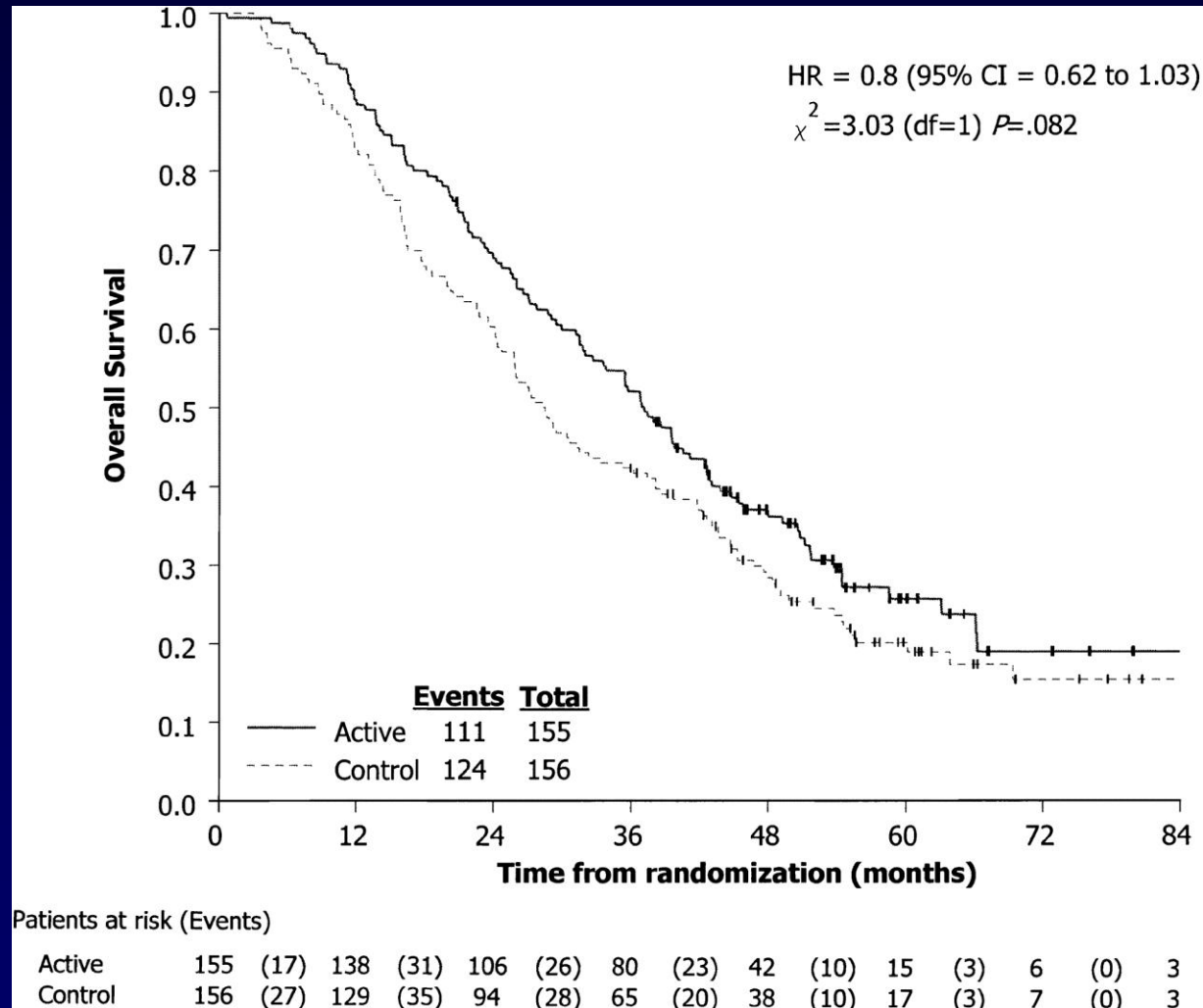# Effect of bone treatments on overall survival
Zoledronate

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

Effect of bone treatments on overall survival
Zoledronate

	4mg	8mg	placebo
Deaths	25	40	32
Median OS	546 days	407 days	464 days

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

A Double-Blind, Placebo-Controlled, Randomized Trial of Oral Sodium Clodronate for Metastatic Prostate Cancer (MRC PR05 Trial)

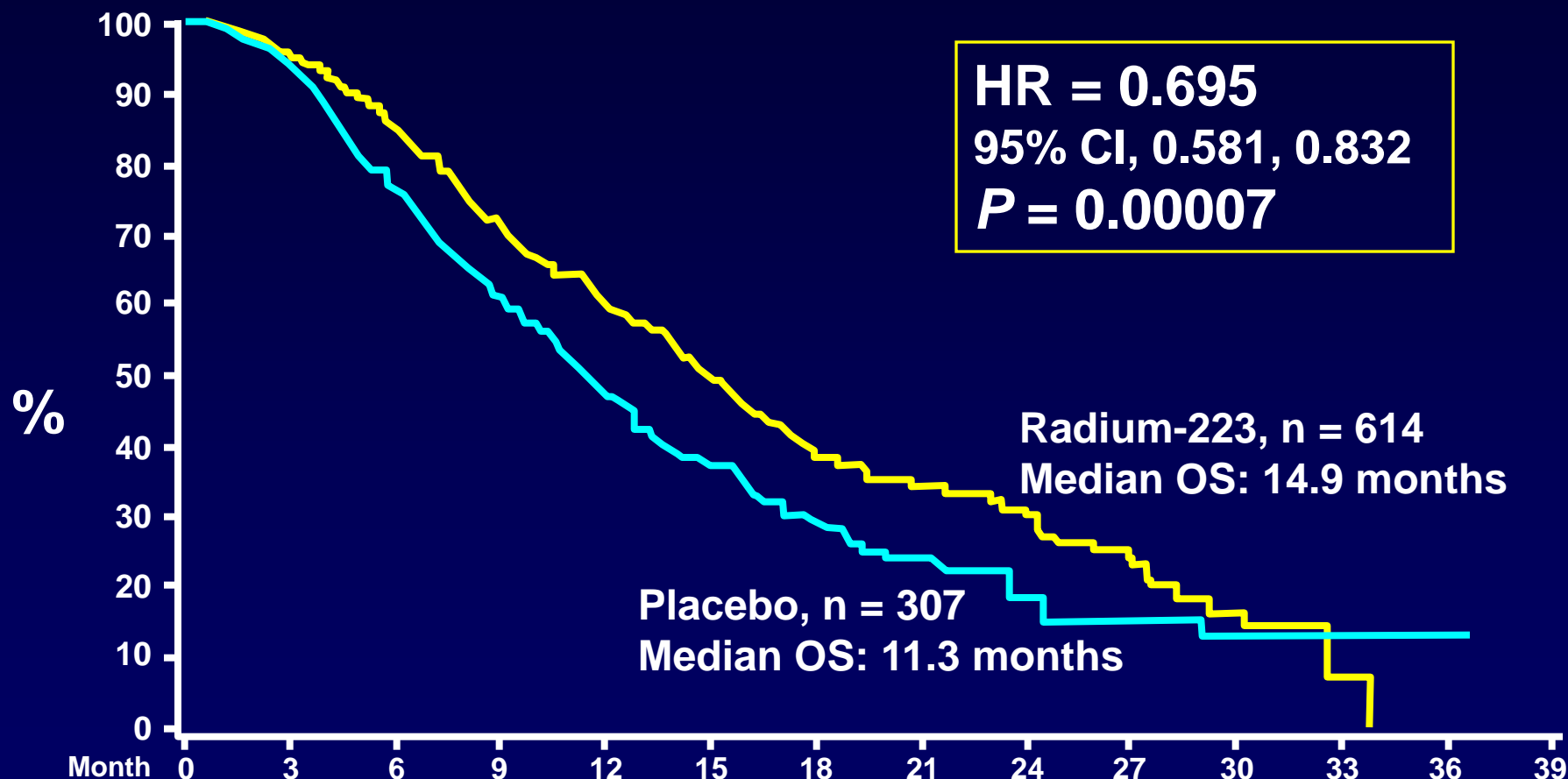# Effect of bone treatments on overall survival
Denosumab vs zoledronate

Fizazi et al. Lancet (2011) 377:813
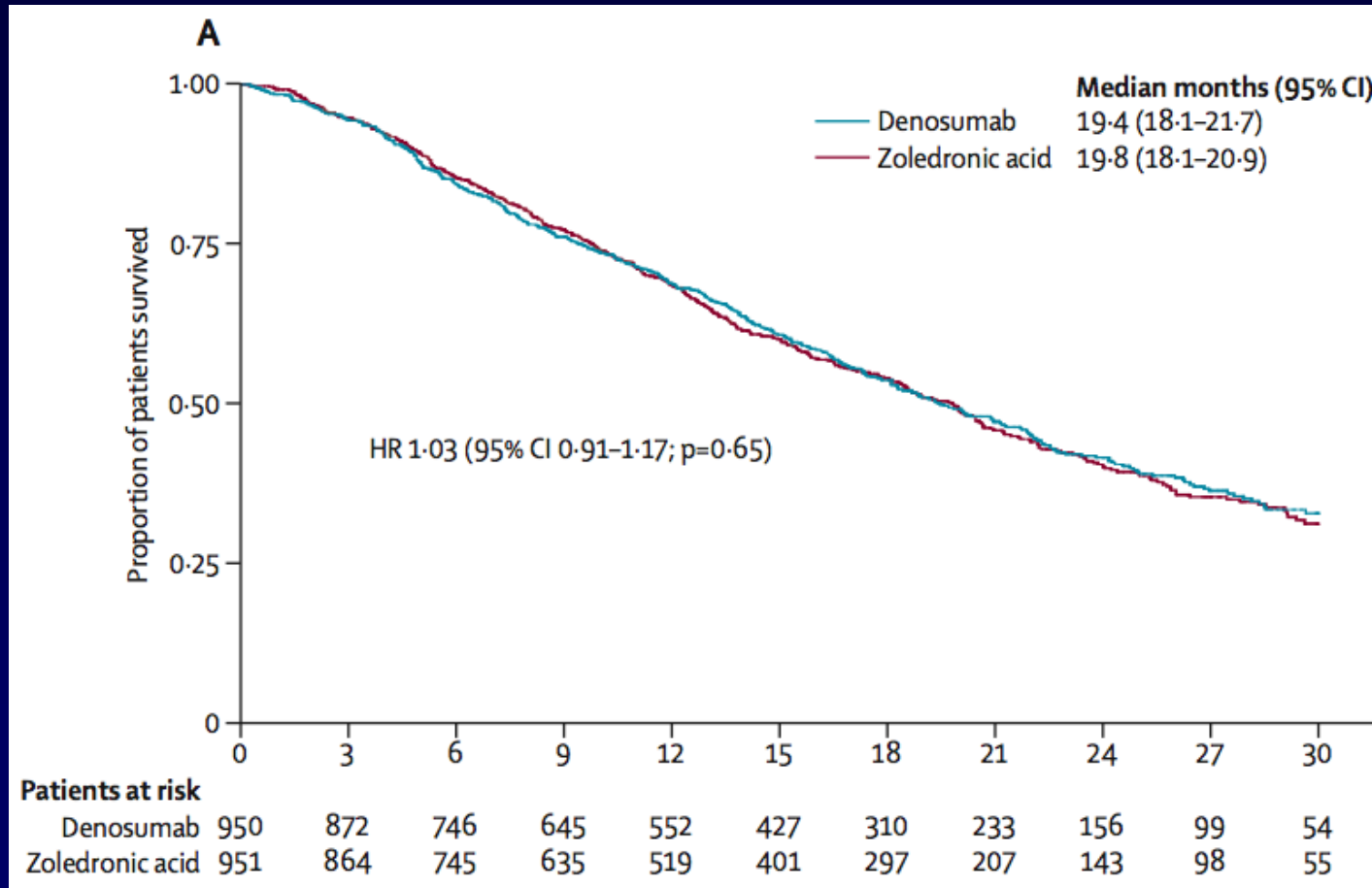
Effect of bone treatments on overall survival
Radium-223

HR = 0.695
95% CI, 0.581, 0.832
P = 0.00007

Radium-223, n = 614
Median OS: 14.9 months

Placebo, n = 307
Median OS: 11.3 months

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

Parker et al. ASCO 2012

Why should we use bone treatments?

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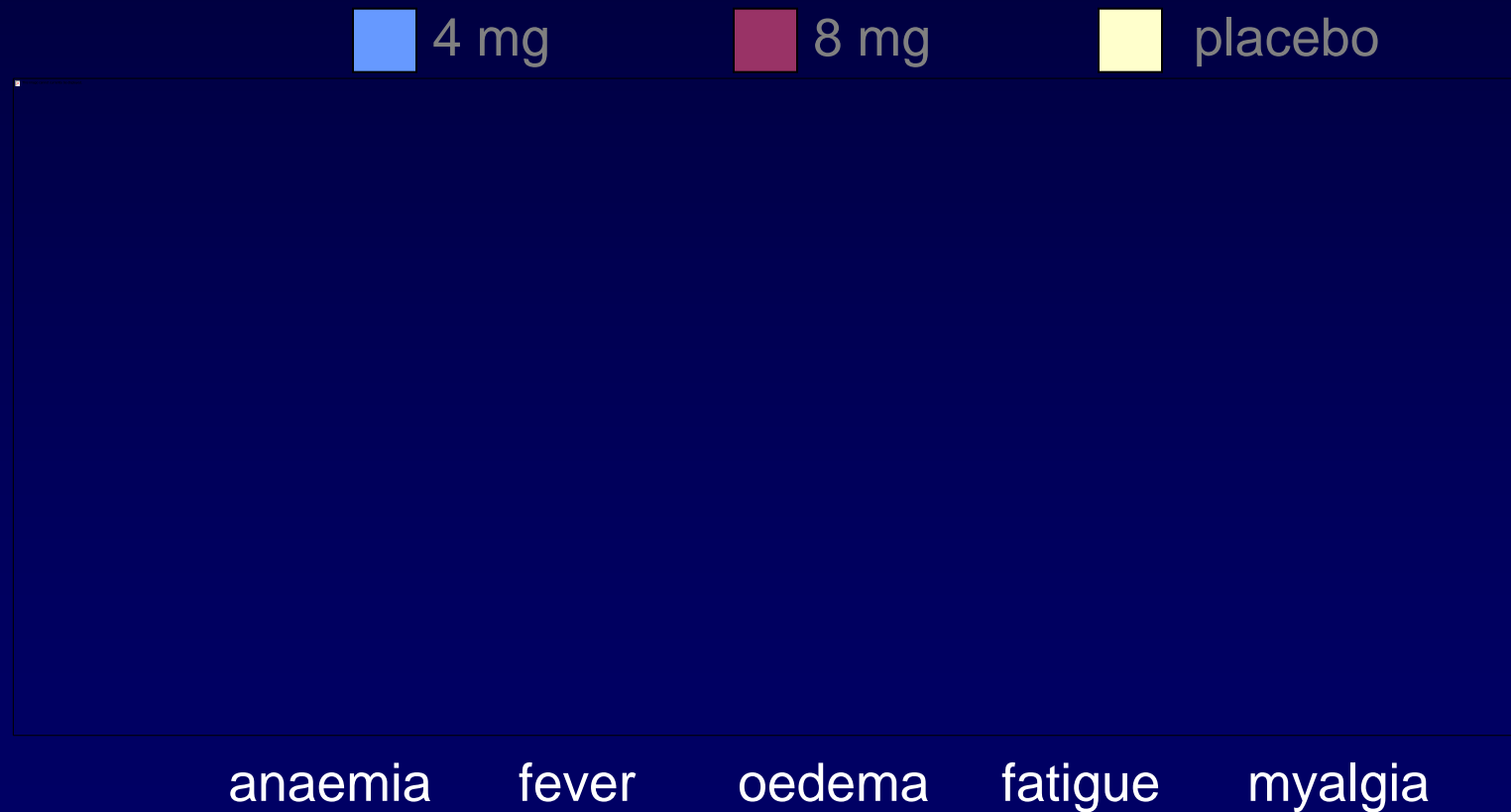
Effect of bone treatments on quality of life
Zoledronate

- **ECOG PS**

- **FACT-G**

"No statistically significant differences"

- **EURO-QOL**

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

Effect of bone treatments on quality of life
Zoledronate

■ 4 mg   ■ 8 mg   ■ placebo

anaemia   fever   oedema   fatigue   myalgia
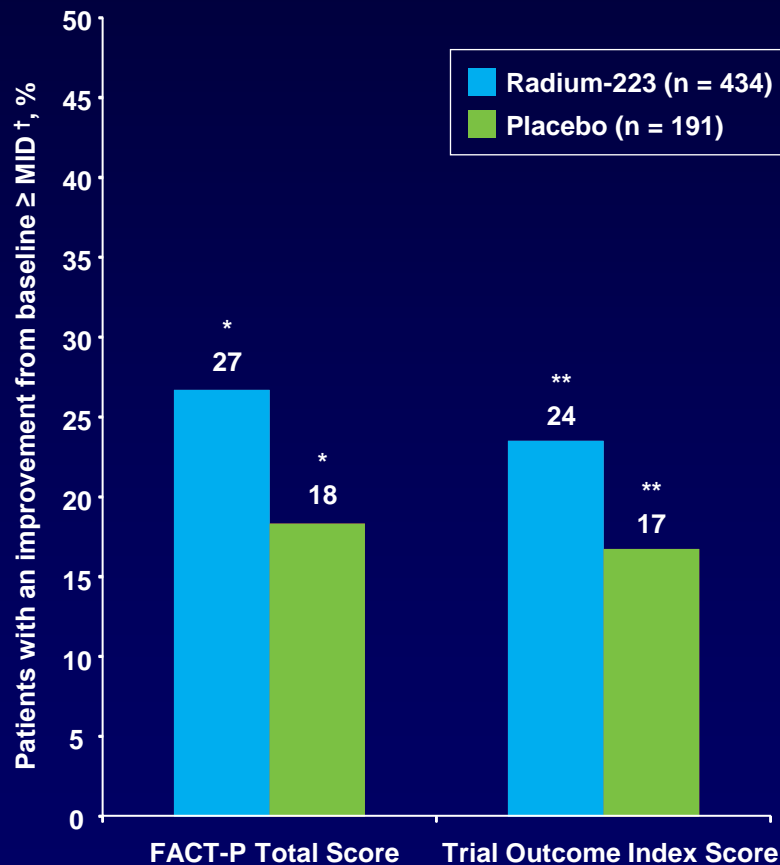
Saad et al. JNCI (2002) Vol 94: 1458-1468

Effect of bone treatments on quality of life
Denosumab vs Zoledronate

Effect of bone treatments on quality of life
Radium-223

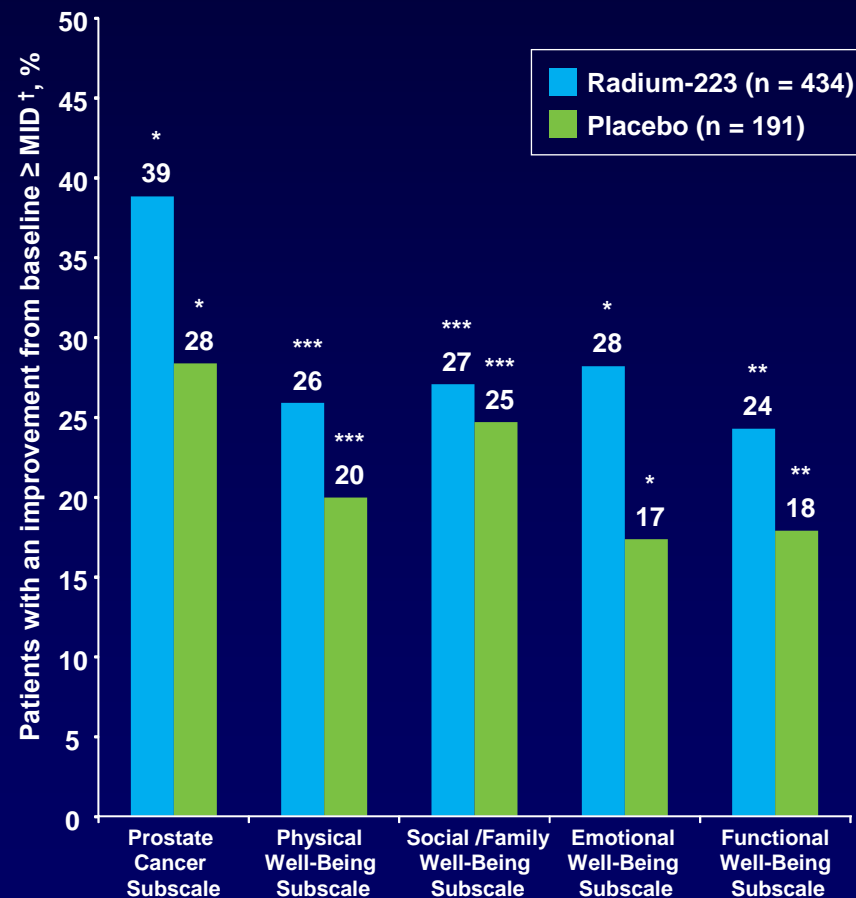**(A) Responder Analysis Based on Changes in FACT-P Summary Scores**

(B) Responder Analysis Based on Changes in FACT-P Subscale Scores

Patients with an improvement from baseline ≥ MID[†], %

Radium-223 (n = 434)
Placebo (n = 191)

(A) Values: FACT-P Total Score — 27*, 18*; Trial Outcome Index Score — 24**, 17**

(B) Values: Prostate Cancer Subscale — 39*, 28*; Physical Well-Being Subscale — 26***, 20***; Social /Family Well-Being Subscale — 27***, 25***; Emotional Well-Being Subscale — 28*, 17*; Functional Well-Being Subscale — 24**, 18**

*P < 0.05
** P < 0.1
†FACT-P MID = 10 points; TOI MID = 9 points
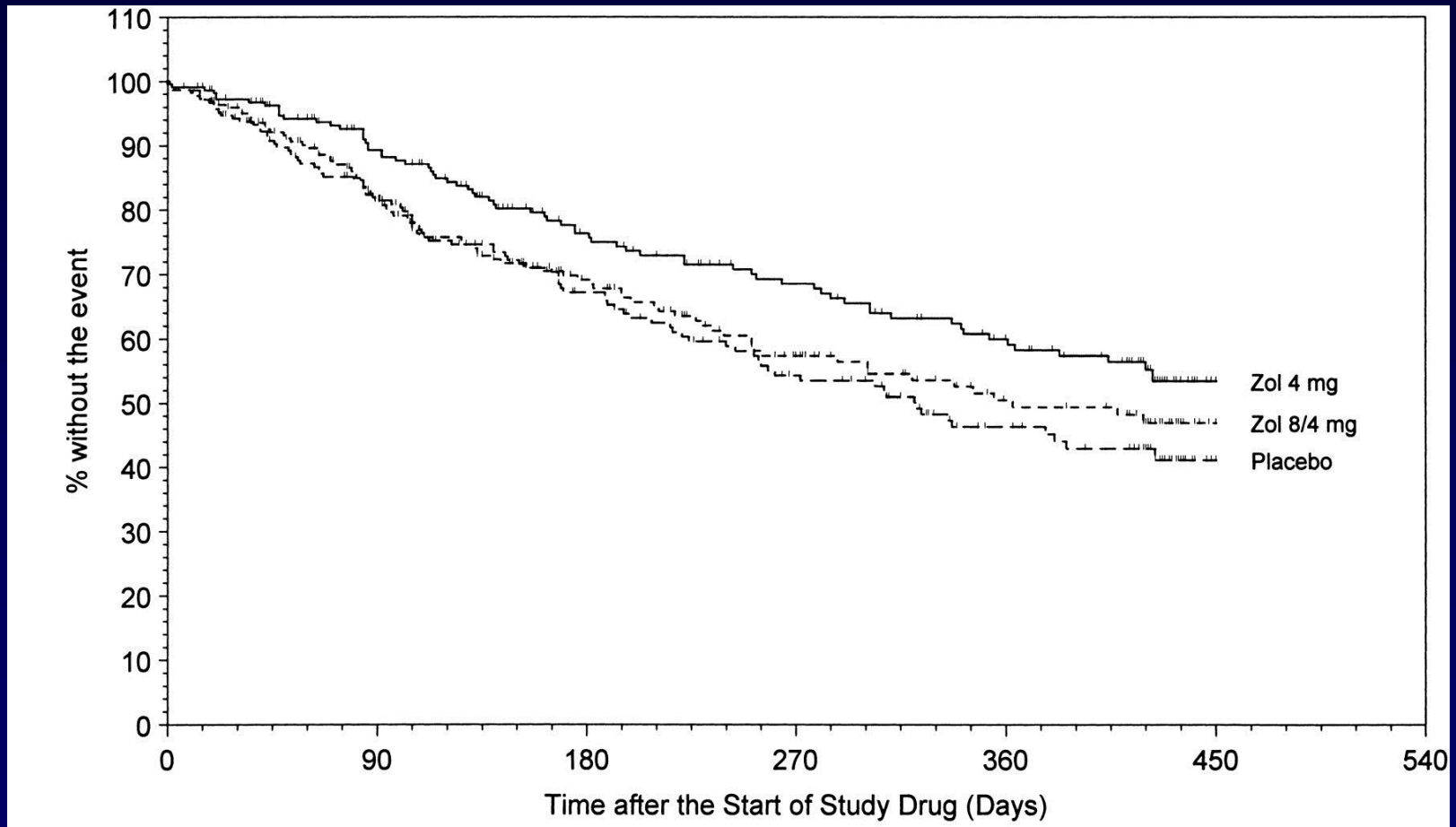
*P < 0.05
** P < 0.1
***Not significant
†For each subscale, MID = 3

Why should we use bone treatments?

- **To improve overall survival**

- **To improve quality of life**
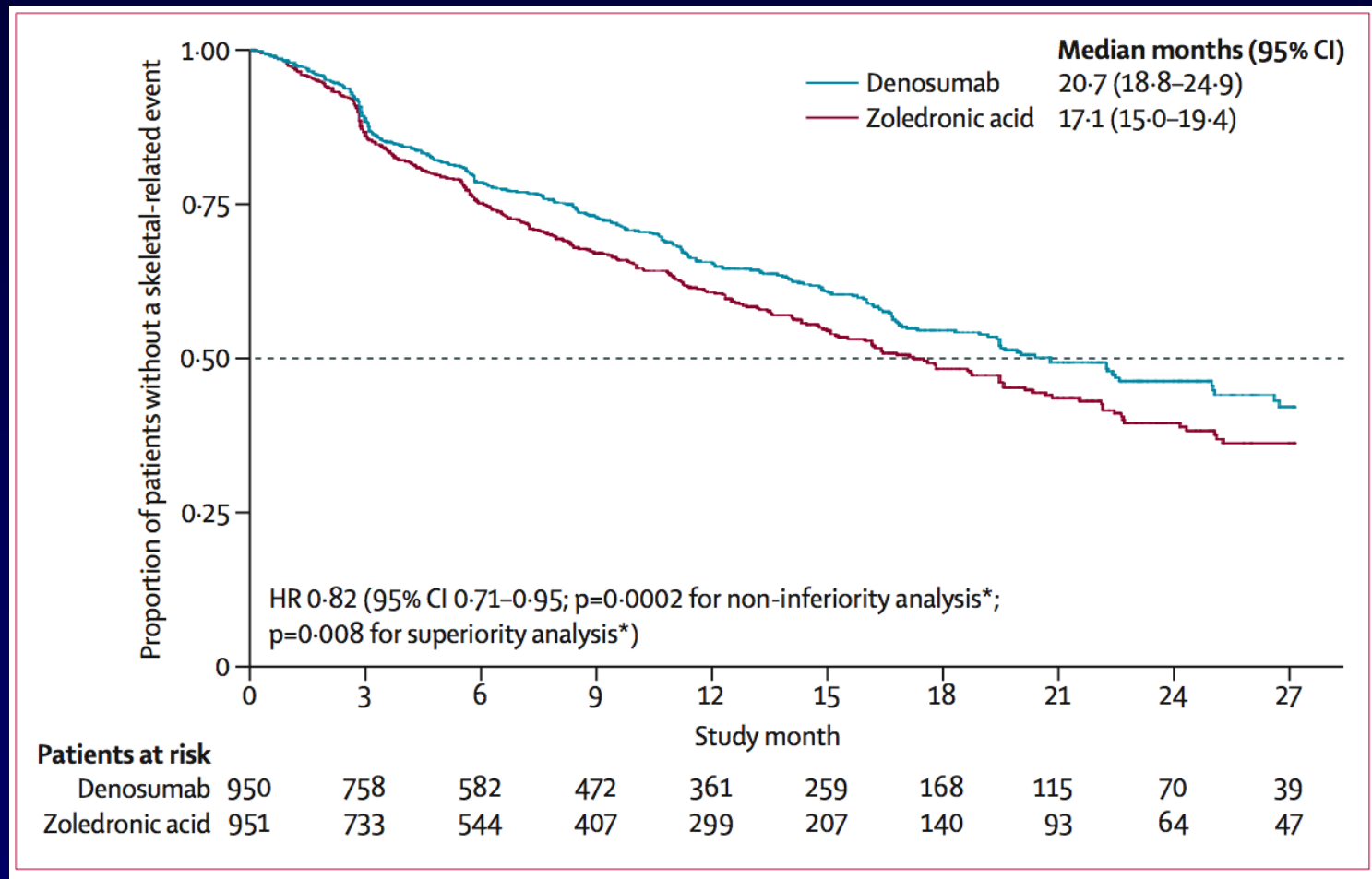
- **To delay symptomatic SREs**

- **To delay bone metastases**

Effect of bone treatments on time to SREs
Zoledronate

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

Effect of bone treatments on time to SREs
Denosumab vs Zoledronate
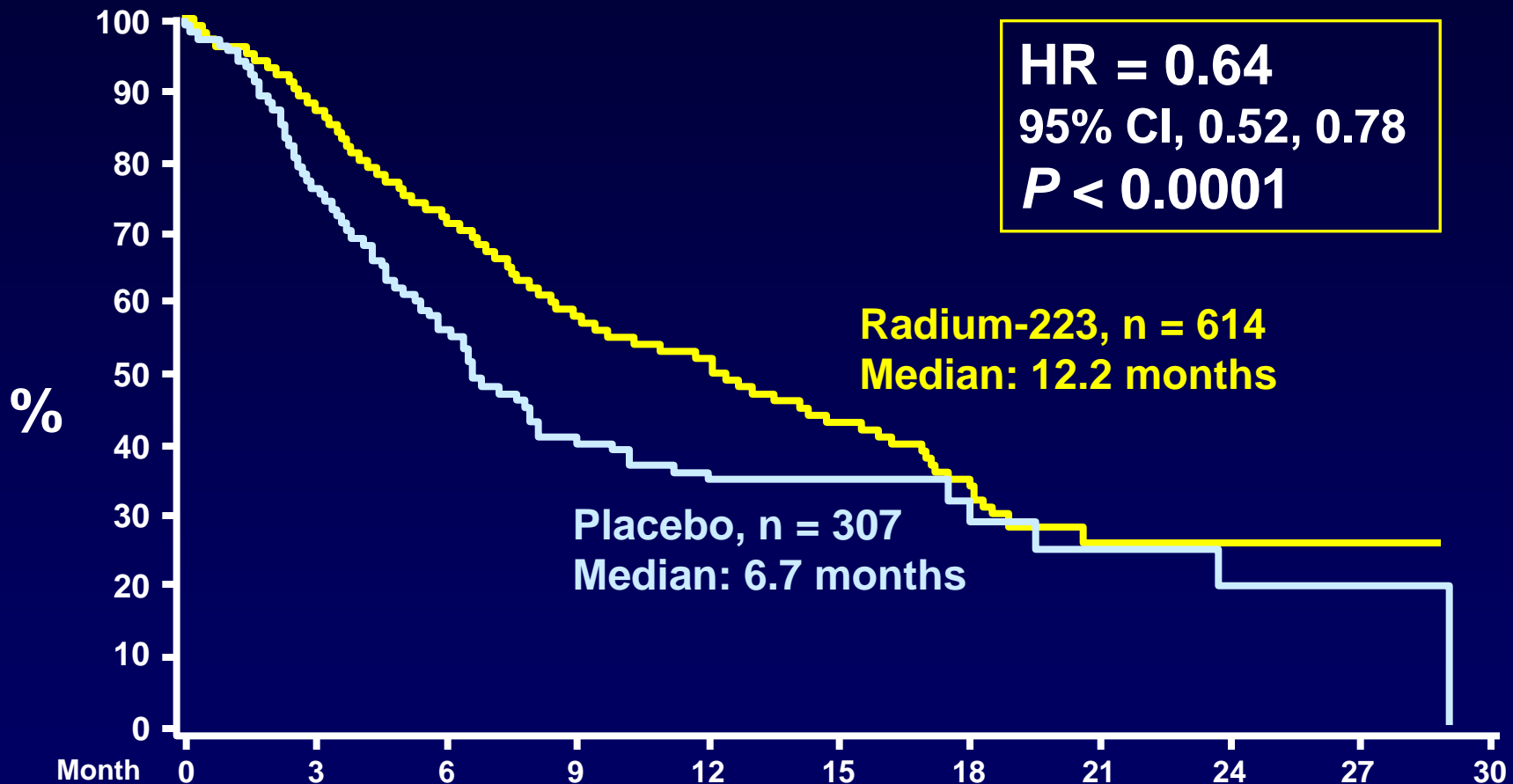
Proportion of patients without a skeletal-related event vs Study month.

Median months (95% CI)
- Denosumab: 20·7 (18·8–24·9)
- Zoledronic acid: 17·1 (15·0–19·4)

HR 0·82 (95% CI 0·71–0·95; p=0·0002 for non-inferiority analysis*; p=0·008 for superiority analysis*)

Patients at risk									
Denosumab	950	758	582	472	361	259	168	115	70	39
Zoledronic acid	951	733	544	407	299	207	140	93	64	47

Effect of bone treatments on time to SREs
Radium-223

Variable	Subgroup	N	Hazard Ratio	HR	95% CI
All Patients		809		0.610	0.461–0.807
Total ALP	< 220 U/L	452		0.513	0.358–0.735
	≥ 220 U/L	357		0.828	0.534–1.284
Current Use of Bisphosphonates	Yes	331		0.464	0.288–0.748
	No	478		0.715	0.507–1.009
Prior Use of Docetaxel	Yes	470		0.561	0.400–0.788
	No	339		0.730	0.450–1.186

0   0.5   1   1.5   2

Favours Radium-223 — Favours Placebo

Comparison of SREs across phase III trials

Effect of bone treatments on time to SREs
Zoledronate

Saad et al. JNCI (2002) Vol 94: 1458-1468
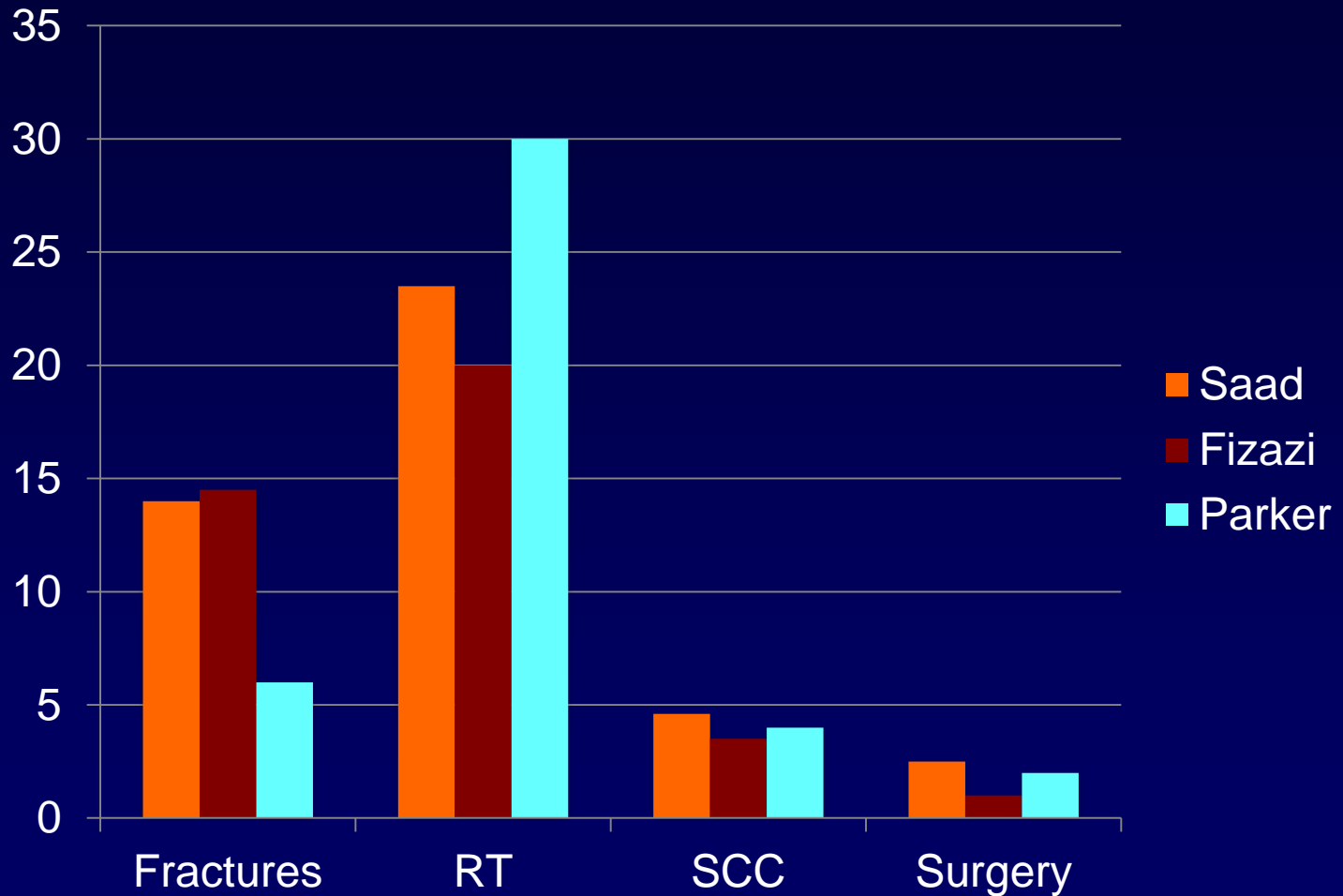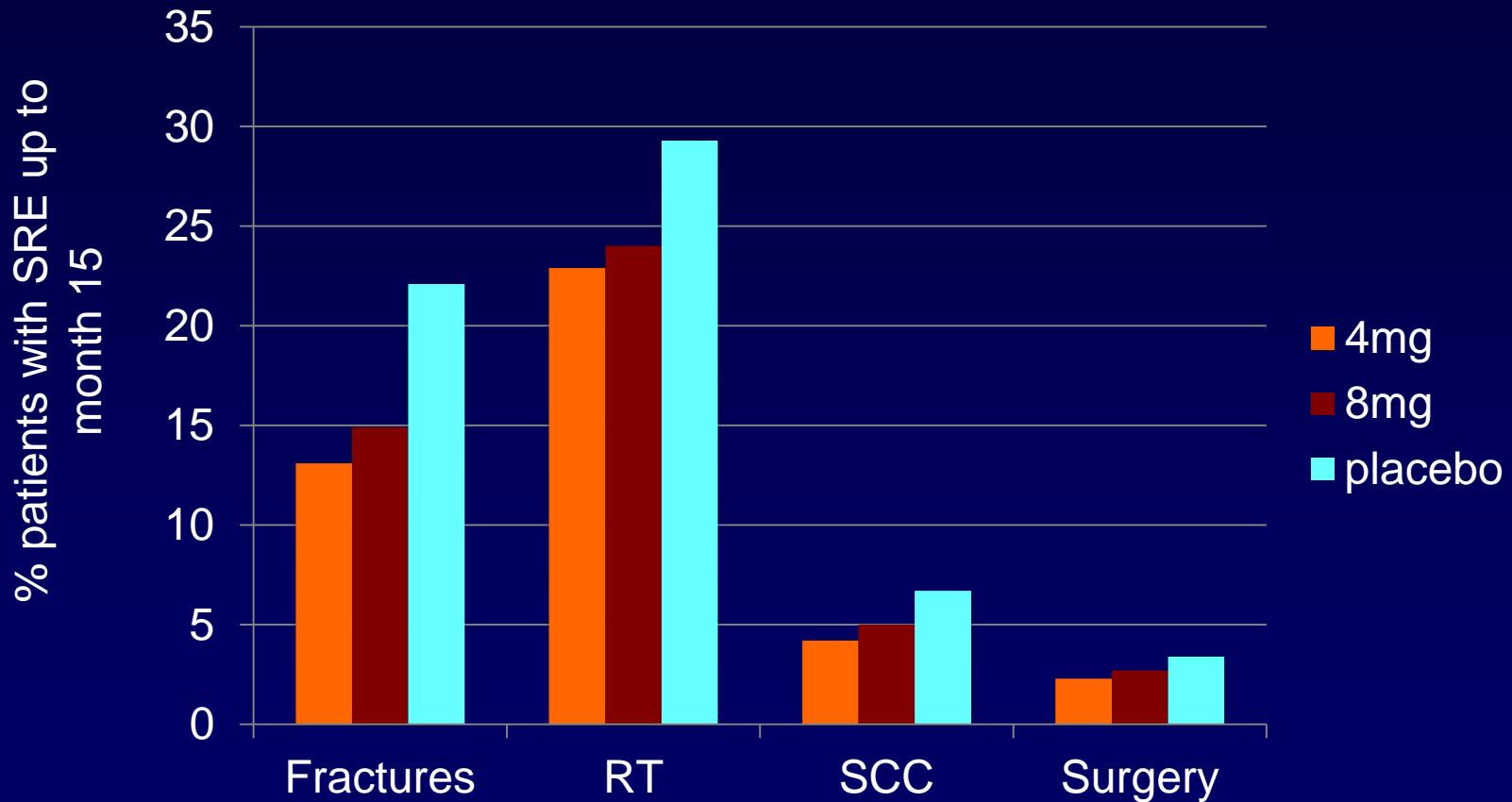
Effect of bone treatments on SREs
Denosumab vs Zoledronate
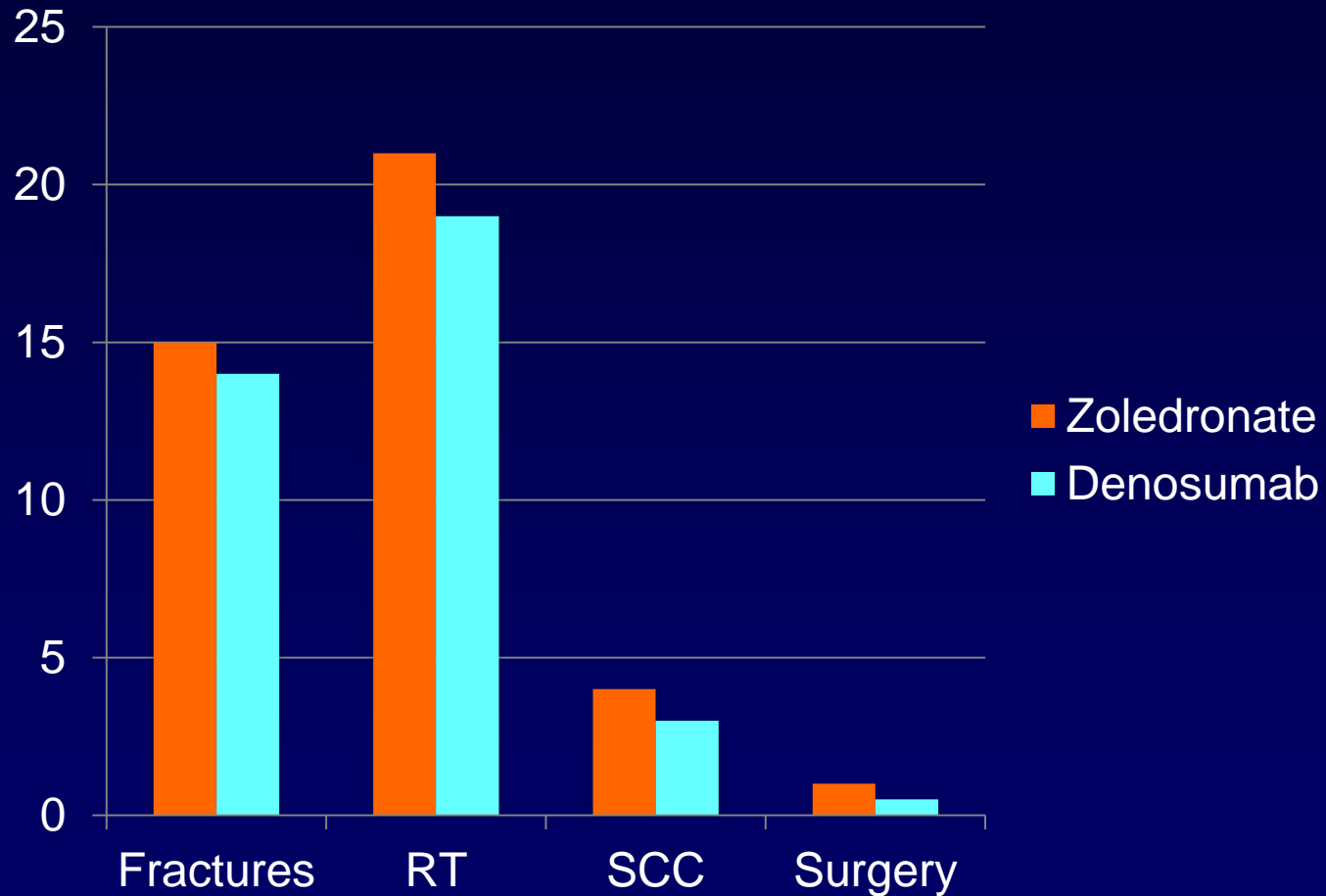
Effect of bone treatments on time to SREs
Radium-223

| SRE component*	Number (%) of events		Time to event (radium-223 vs. placebo)	
	Radium-223 (n = 614)	Placebo (n = 307)	P†	HR (95% CI)
External beam radiotherapy (EBRT)	186 (30.3)	105 (34.2)	0.00117	0.67 (0.52–0.85)
Spinal cord compression	25 (4.1)	21 (6.8)	0.025	0.51 (0.28–0.93)
Pathologic bone fracture	32 (5.2)	20 (6.5)	0.09	0.62 (0.35–1.09)
Surgical intervention	12 (2)	7 (2.3)	0.479	0.71 (0.28–1.80)

†Not adjusted for multiplicity

Parker et al. J Clin Oncol 2012;30(suppl.): abstr LBA4512.

Are SREs what they used to be?

- Skeletal morbidity rate = n of SREs per patient-year

- Skeletal morbidity rate in Saad trial (2002)
  - 1.49 for placebo
  - 1.06 for 8mg zoledronate
  - 0.8 for 4mg zoledronate

- Skeletal morbidity rate in Fizazi trial (2011)
  - 0.6 for zoledronate
  - 0.5 for denosumab

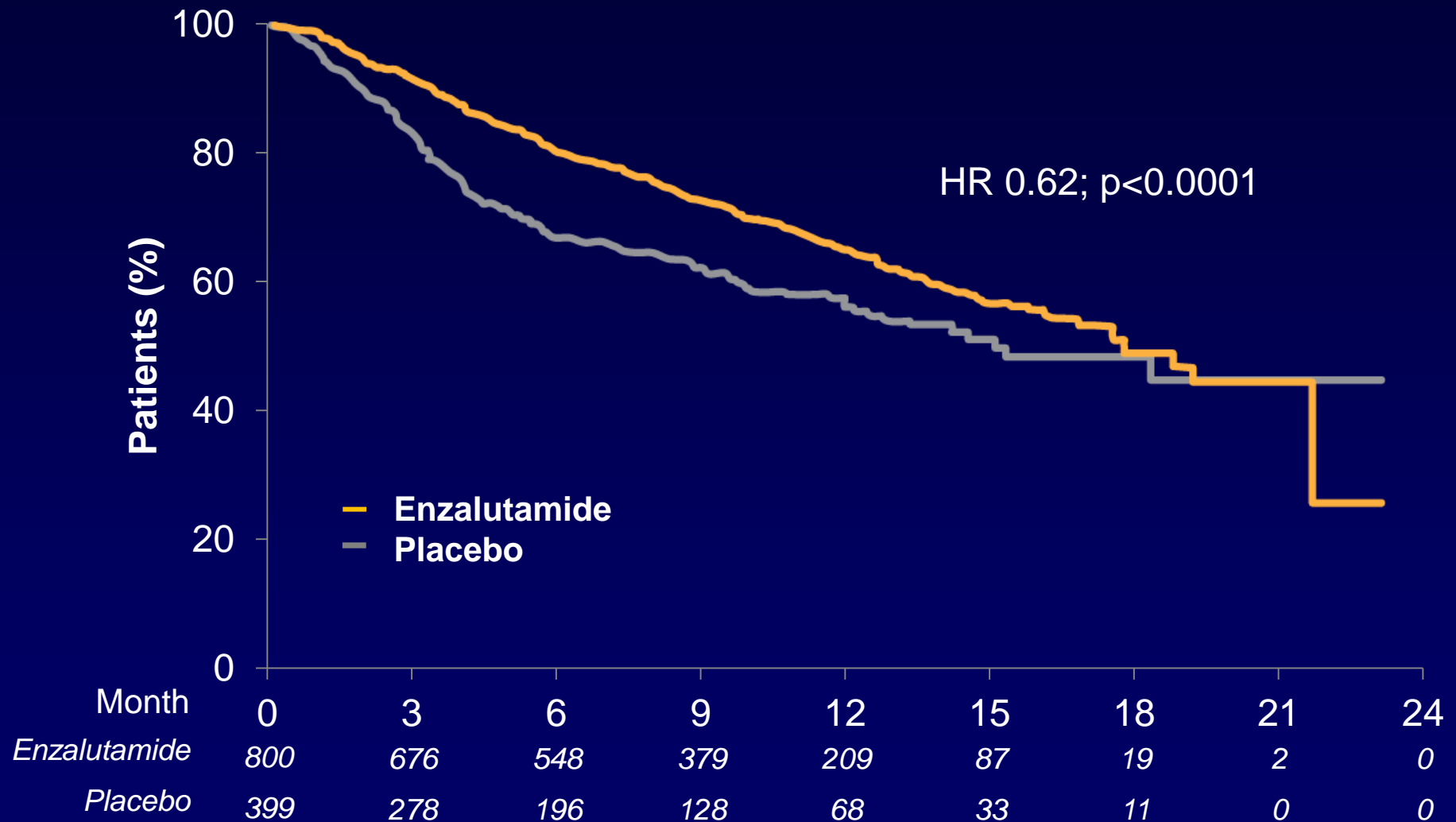# Effect of bone treatments on time to SRE
Denosumab vs Zoledronate
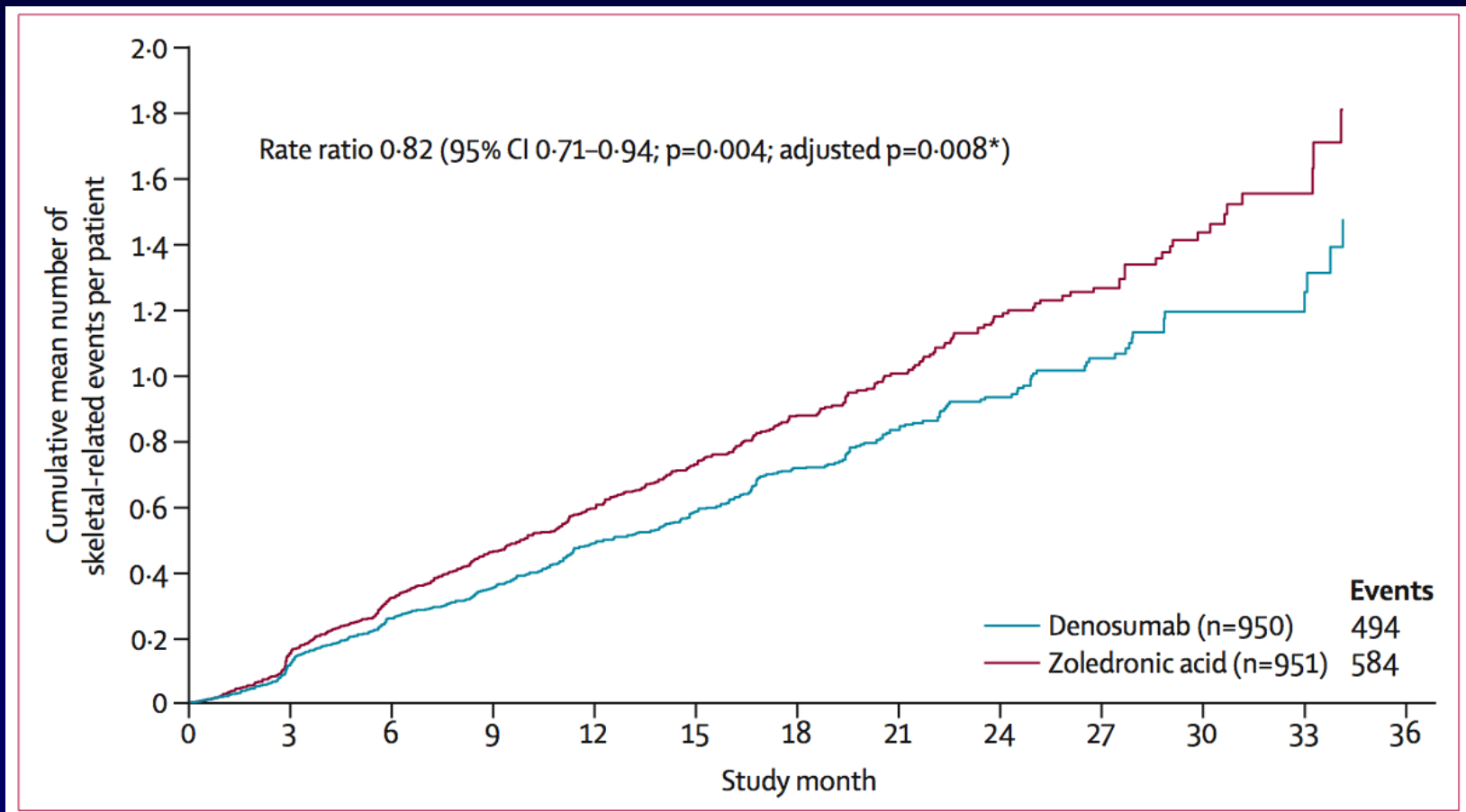
Abiraterone delays time to SRE

	AA (n = 797)	Placebo (n = 398)	*P* Value
Time to first SRE (pathologic fracture/spinal cord compression/ palliative radiation/bone surgery)			
25th percentile, days	301.0	150.0	< 0.0001

Logothetis et al. J Clin Oncol 2011; 29 (Suppl): Abstract 4520 (oral presentation)

Enzalutamide delays time to SRE

HR 0.62; p<0.0001

Legend: Enzalutamide, Placebo

Month	0	3	6	9	12	15	18	21	24
Enzalutamide	800	676	548	379	209	87	19	2	0
Placebo	399	278	196	128	68	33	11	0	0

De Bono et al. J Clin Oncol 2012;30(suppl.): abstr 4519 and accompanying presentation

Are SREs as common as they used to be?

- Abiraterone, enzalutamide and radium-223 delay SREs

- Do zoledronate and denosumab provide additional benefit in terms of SRE delay?

- If so, which SREs do they delay, and by how much?

Why should we use bone treatments?

- **To improve overall survival**

- **To improve quality of life**

- **To delay symptomatic SREs**

- **To delay bone metastases**

Effect of bone treatment on time to metastasis
Denosumab

Smith et al. Lancet (2011)
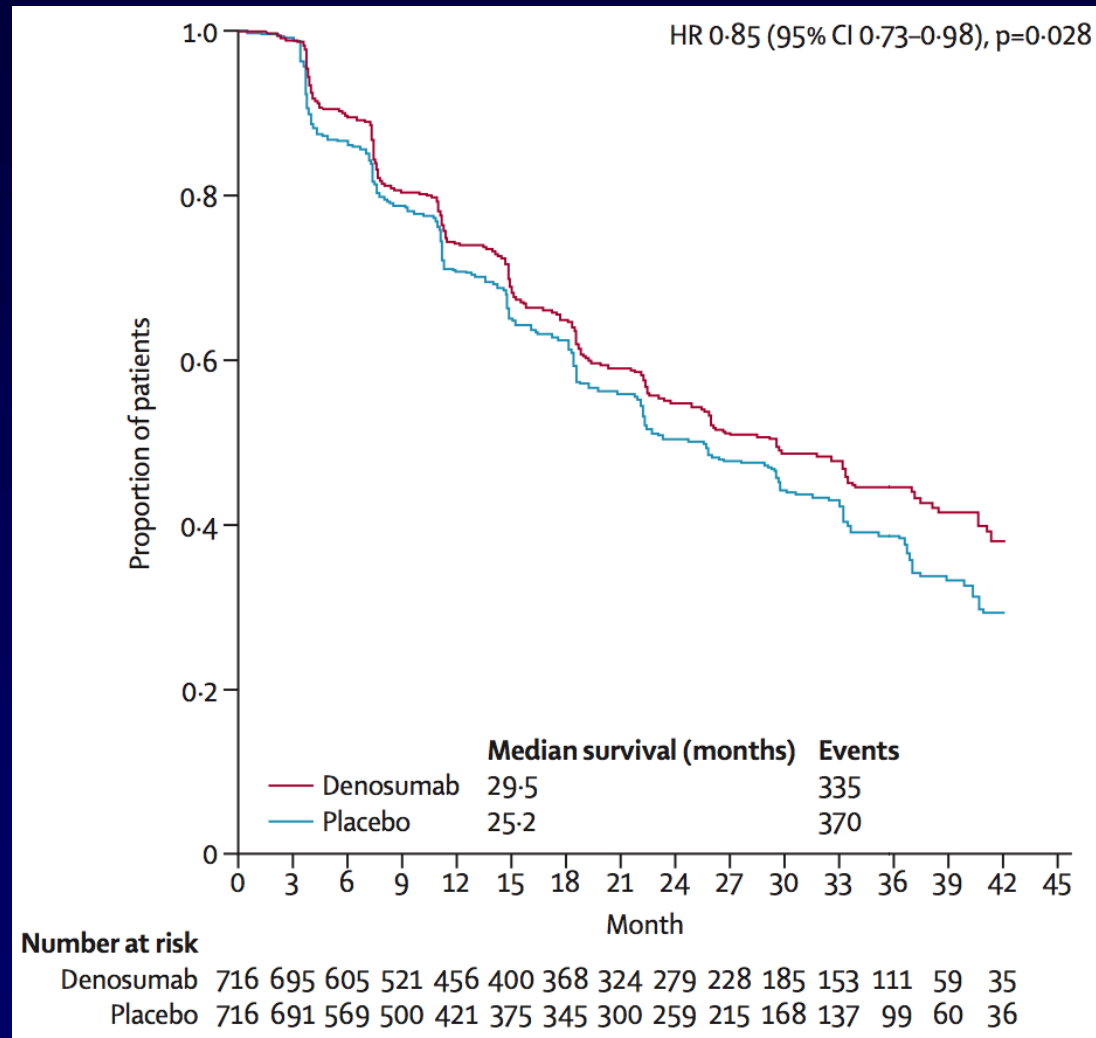
.... but were these men metastatic at baseline?

Technetium bone scan

NaF PET scan

Why should we use bone treatments?

	Zoledronate	Denosumab	Radium-223
Overall survival	✗	✗	✔
Quality of life	✗	?	✔
Symptomatic SRE prevention	?	?	✔

How should we use bone treatments?

- **Radium-223 in men with bony metastatic CRPC**
  - **in non-chemotherapy patients**
  - **and post-chemotherapy**

- **Zoledronate in clinical trials**
  - **eg. STAMPEDE, TRAPEZE**

- **Denosumab for treatment of osteoporosis**