Metastasi Ossee

Il denosumab, quali vantaggi rispetto all'acido zoledronico

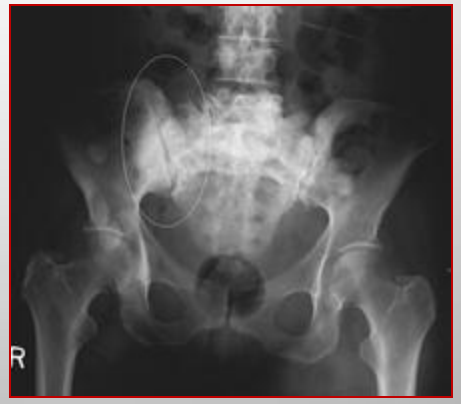
Elena Torrisi
CRO Aviano

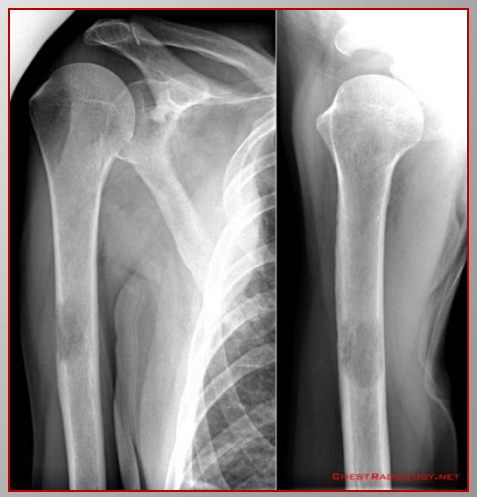
Bone metastases from Breast Cancer

- 70-80% of patients with MBC develop bone mets

- SREs occur in up 64% of MBC pts not with bisphoshonates

- ✓ Morbidity
- ✓ Reduced performance status
- ✓ Quality of life
- ✓ Reduced survival
- ✓ Hospital cost





Lipton A. Cancer. 2003;97:848-853

The Natural History of Bone Metastases in Breast Cancer

- Pathologic fracture is the most common SRE in patients with breast cancer
- Median onset is 11 mos from initial diagnosis of bone metastases
- ~ 20% develop hypercalcemia after a median of 14 mos
- ~ 10% develop cord compression after a median of 17 mos

Lipton A. Cancer. 2003;97:848-853

Bisphosphonates Reduce SREs in Breast Cancer

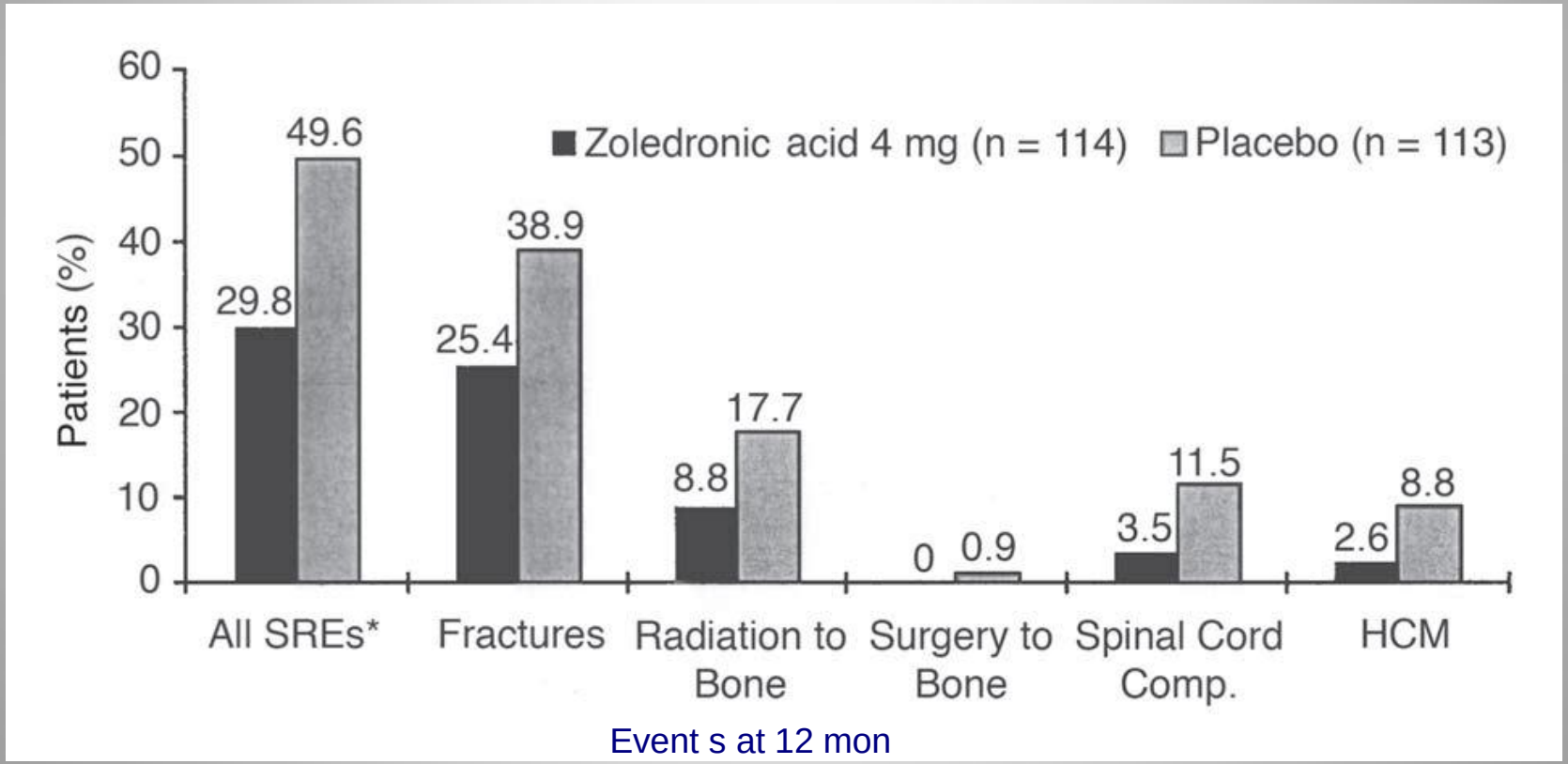
Study	Treatment Duration, Mos	Patients With SRE, %	*P* Value
Lipton et al*[1]	24		
▪ Placebo		64	< .001
▪ Pamidronate		51	
Rosen et al[2]	24		
▪ Pamidronate		43	NS
▪ Zoledronic acid		45	
Kohno et al[3]	12		
▪ Placebo		50	.003
▪ Zoledronic acid		30	

*Includes HCM.

1. Lipton A, et al. Cancer. 2000;88:1082-1090. 2. Rosen LS ,et al., Cancer. 2004 Jan 1;100(1):36-43..
3. Kohno N, et al. J Clin Oncol. 2005;23:3314-3321.

VOLUME 23 · NUMBER 15 · MAY 20 2005
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

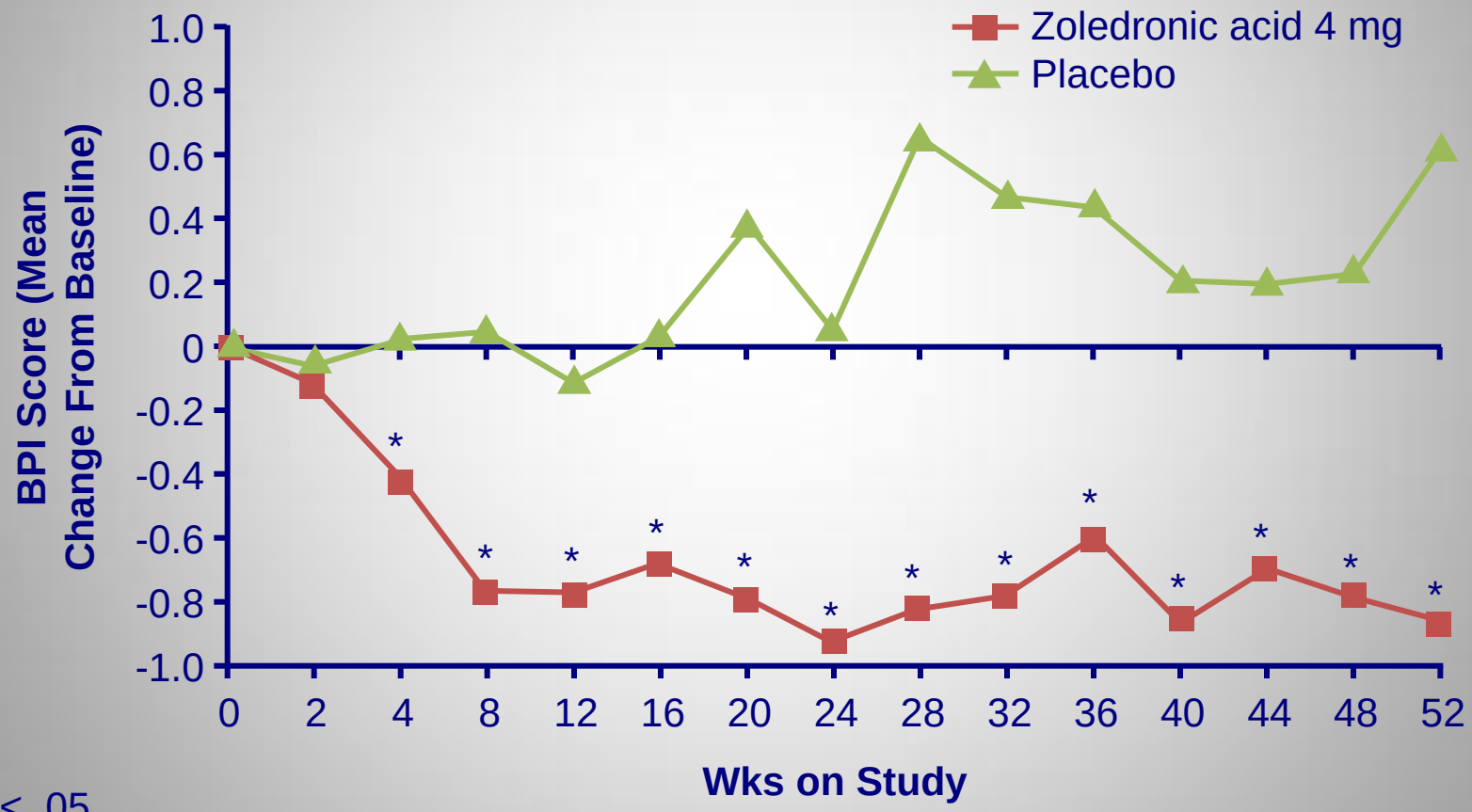
Zoledronic Acid Significantly Reduces Skeletal Complications Compared With Placebo in Japanese Women With Bone Metastases From Breast Cancer: A Randomized, Placebo-Controlled Trial



Event s at 12 mon

Kohno N, et al. J Clin Oncol. 2005;23:3314-3321

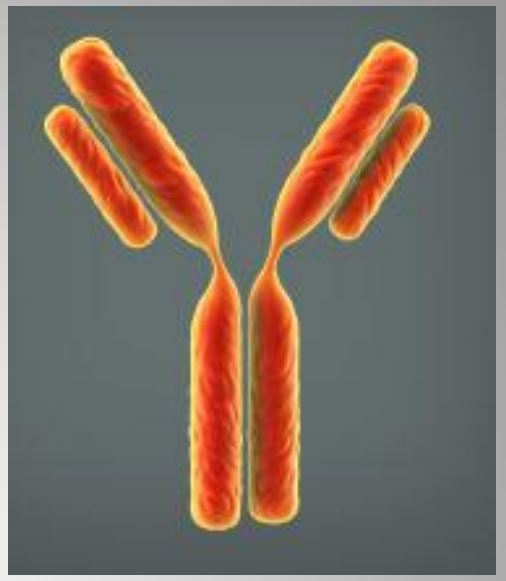
Zoledronic Acid vs Placebo Pain Scores (Brief Pain Inventory)



*$P < .05$

Kohno N, et al. J Clin Oncol. 2005;23:3314-3321.

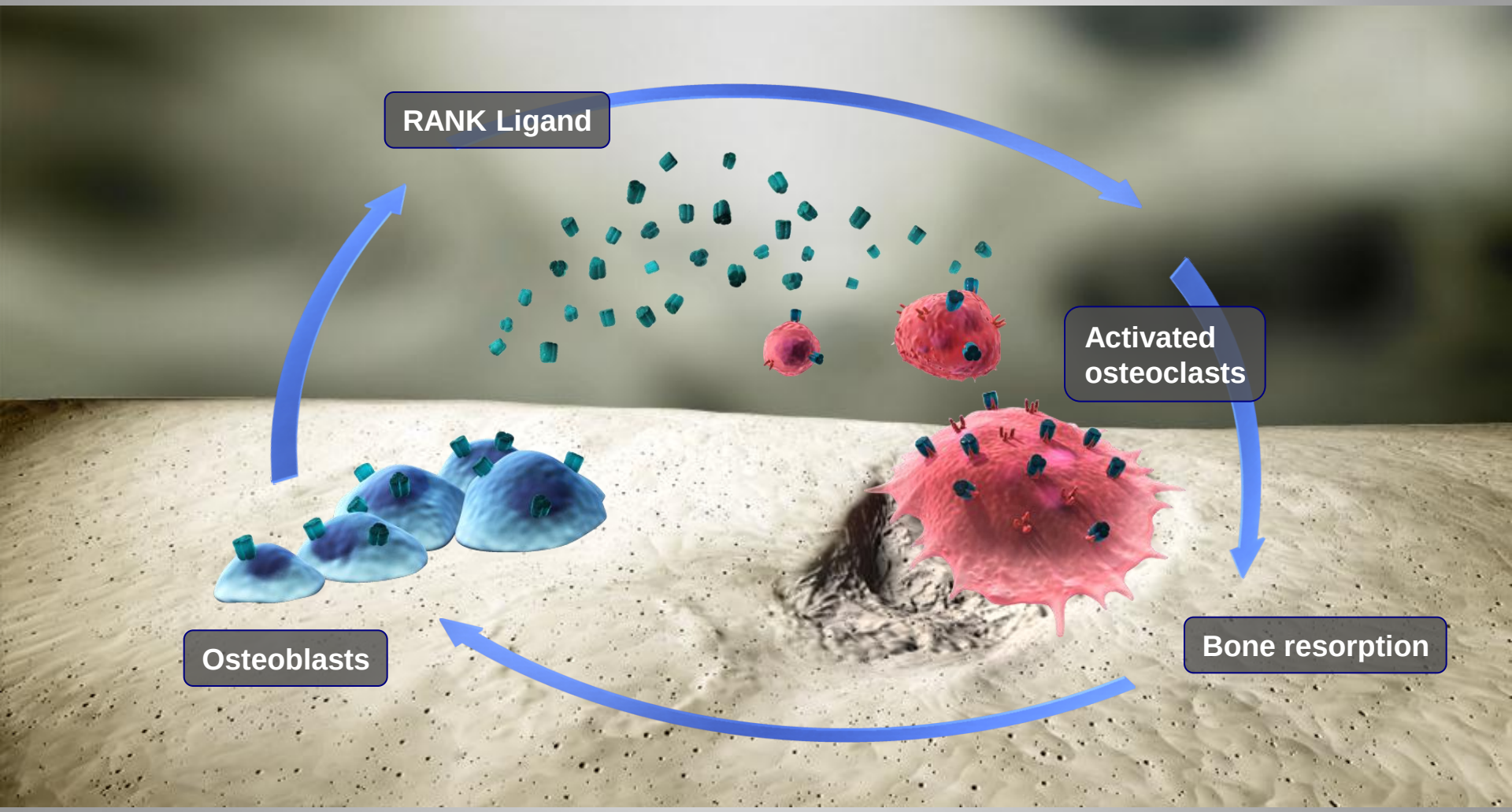
Denosumab



- Denosumab is a fully human monoclonal antibody that binds human RANK Ligand with high affinity and specificity[1]
- By binding to RANK Ligand, denosumab prevents activation of its receptor on the surface of osteoclasts and their precursors
- In clinical trials, no neutralising antibodies were detected[2–4]

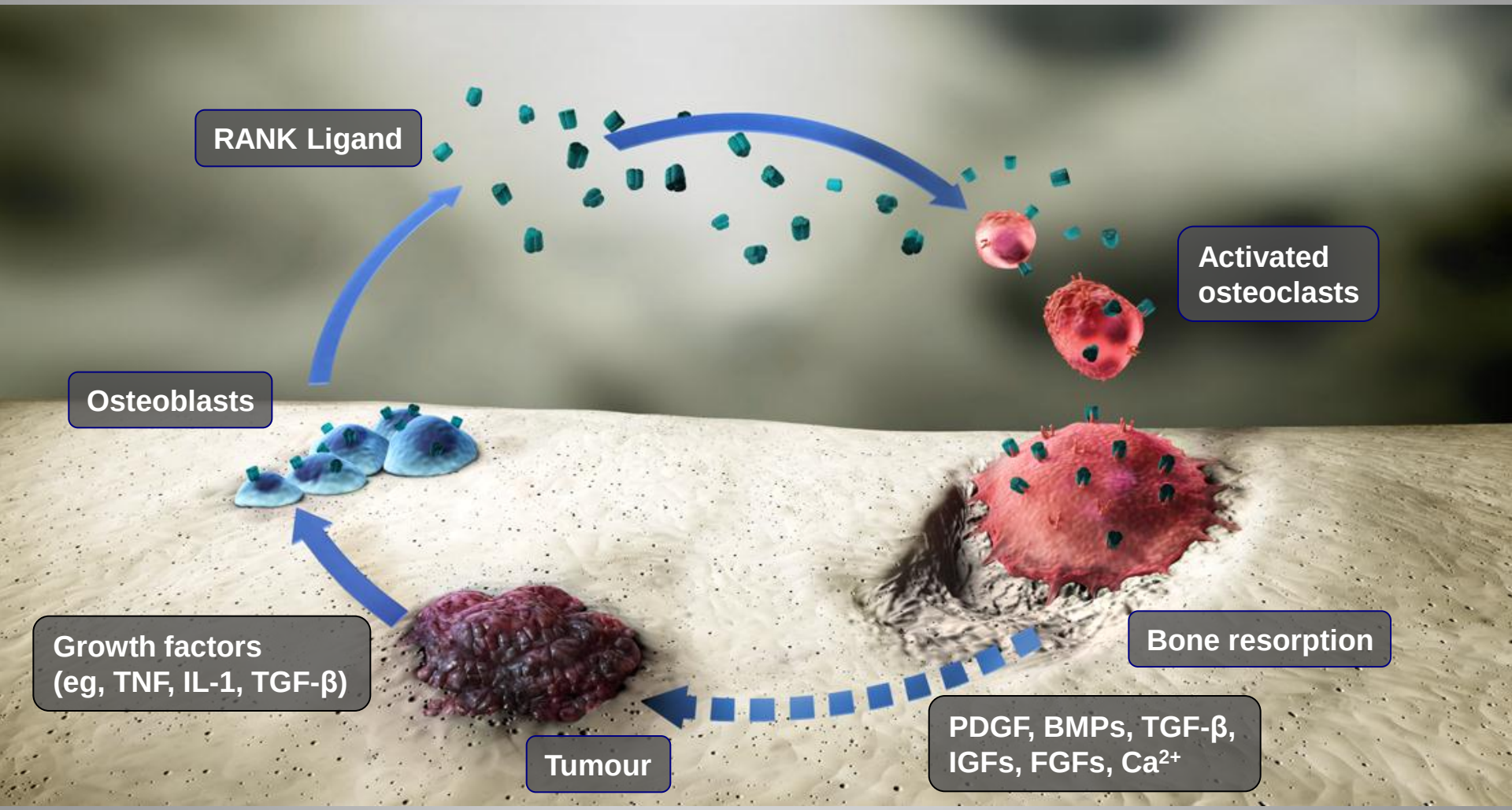
1. McClung MR et al. New Engl J Med 2006;354:821–31;
2. Stopeck AT et al. J Clin Oncol 2010;28:5132–9;
3. Fizazi K et al. Lancet 2011; Lancet 2011;377:813–22;
4. Henry DH et al. J Clin Oncol 2011;29:1125–32.

Bone turnover



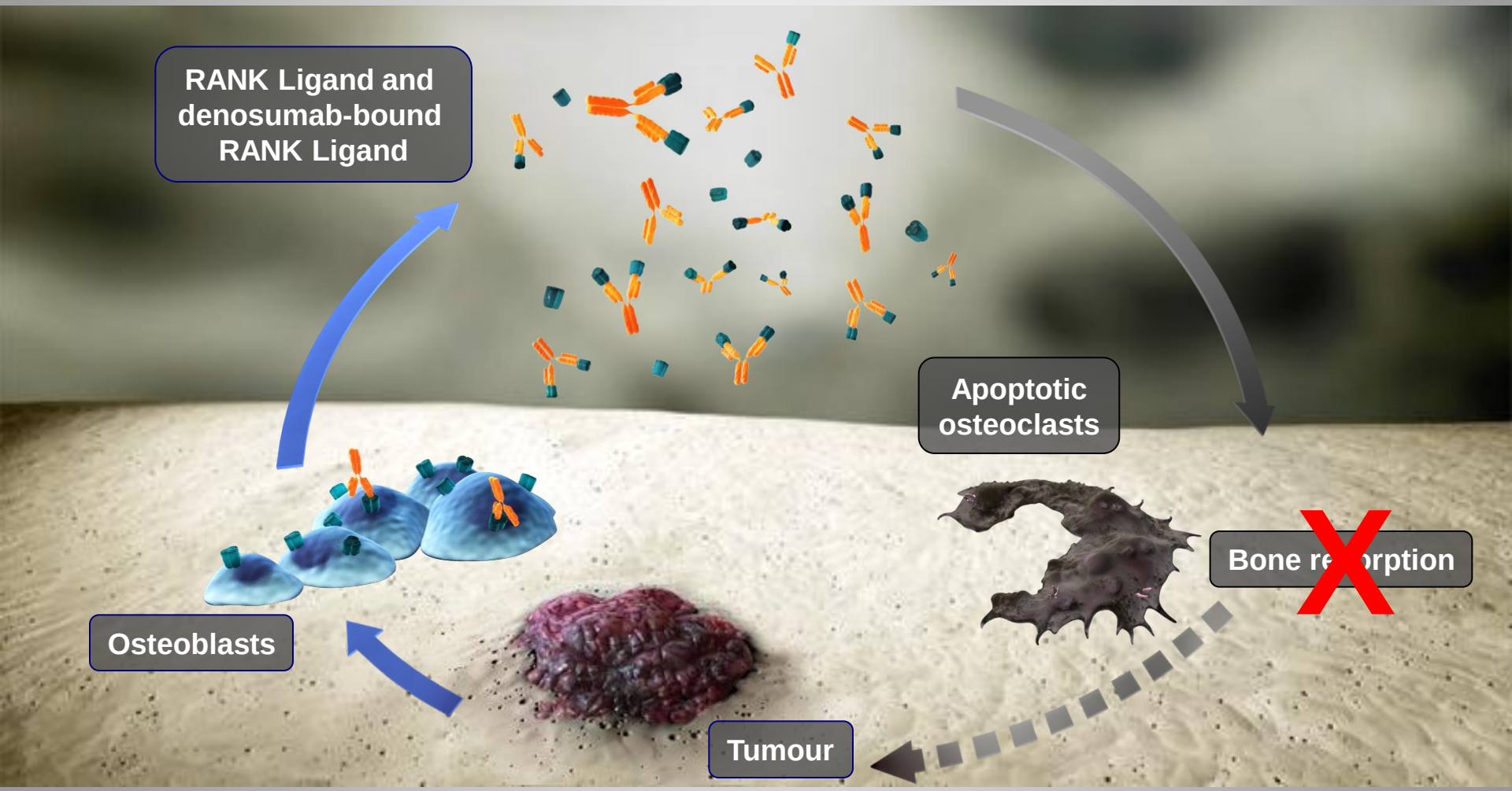
1. Adapted from: Boyle WJ, et al. Nature 2003;423:337–42;
2. Roodman GD. N Engl J Med 2004;350:1655–64.

The Vicious Cycle Of Bone Destruction



1. Adapted from: Boyle WJ, et al. Nature 2003;423:337–42;
2. Roodman GD. N Engl J Med 2004;350:1655–64.

Denosumab inhibits RANK Ligand to interrupt the vicious cycle of bone destruction



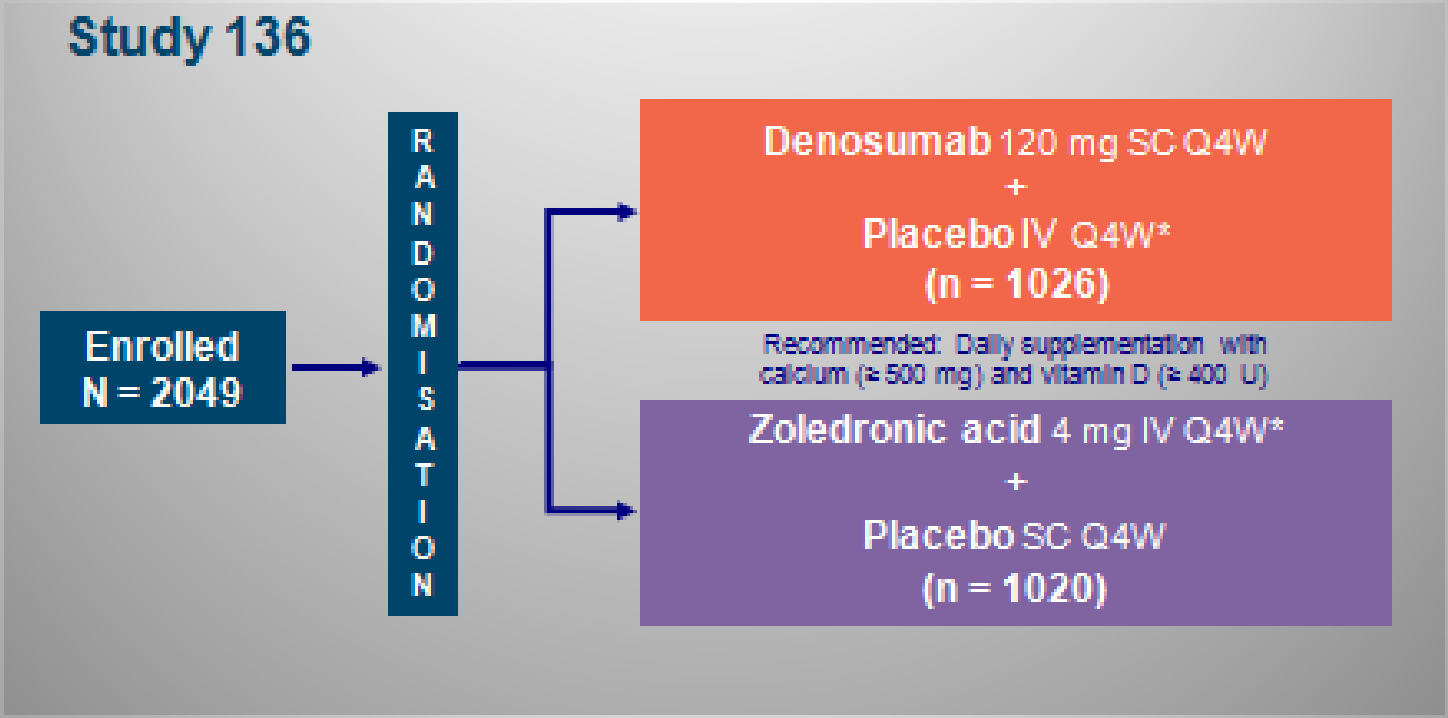
1. Adapted from: Boyle WJ, et al. Nature 2003;423:337–42;
2. McClung MR, et al. New Engl J Med 2006;354:821–31.

VOLUME 28 · NUMBER 35 · DECEMBER 10 2010

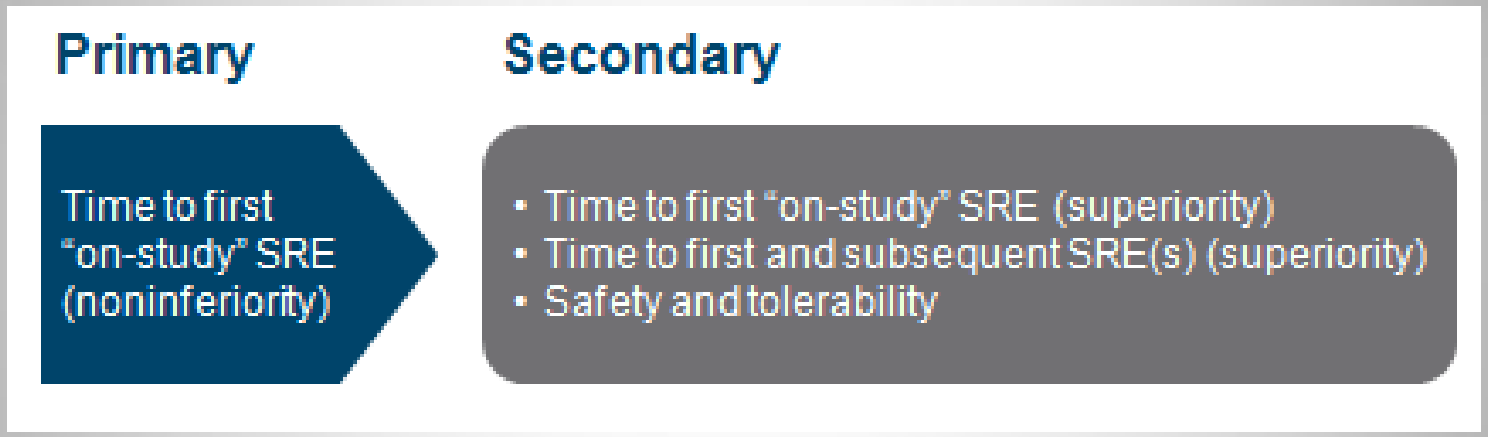
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

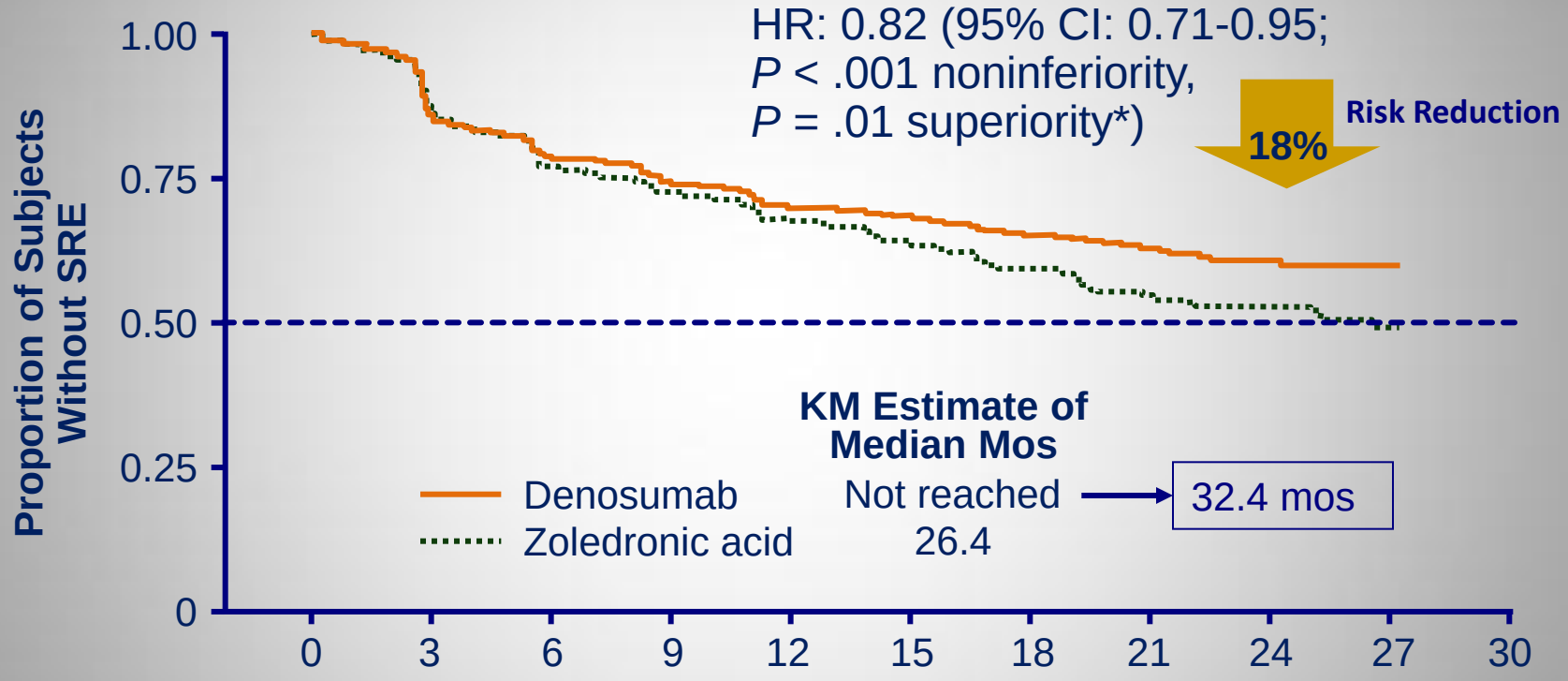
Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study



Stopeck AT et al., 2010


Primary
Secondary
Time to first "on-study" SRE (noninferiority)
• Time to first "on-study" SRE (superiority)
• Time to first and subsequent SRE(s) (superiority)
• Safety and tolerability

Primary end point: Time to First On-Study SRE



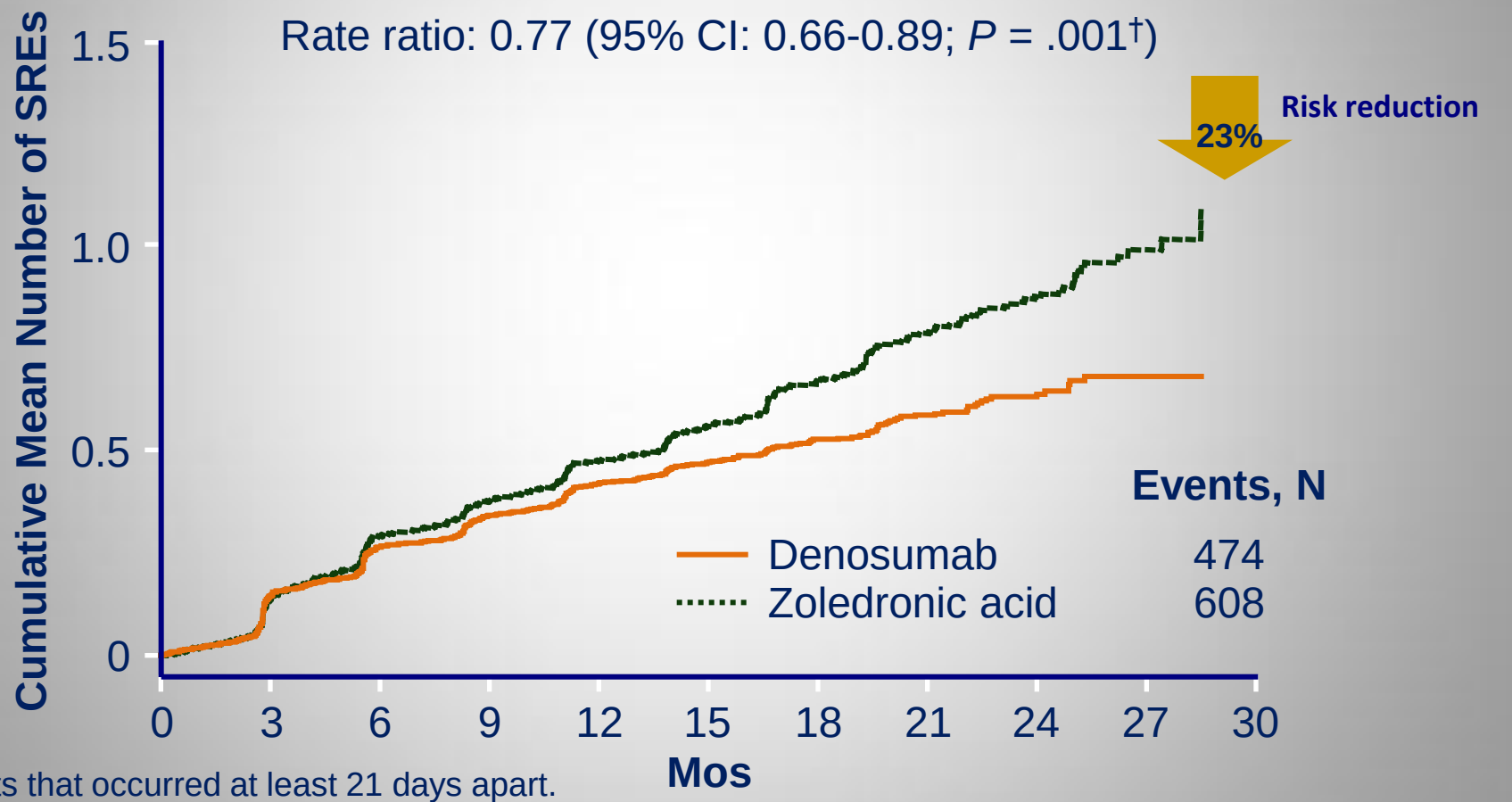
Patients at Risk, n

Zoledronic acid	1020	829	676	584	498	427	296	191	94	29
Denosumab	1026	839	697	602	514	437	306	189	99	26

*Adjusted for multiplicity.

Stopeck AT, et al. J Clin Oncol. 2010;28:5132-5139.

Secondary end point:Time to First and Subsequent On-Study SRE* (Multiple Event Analysis)

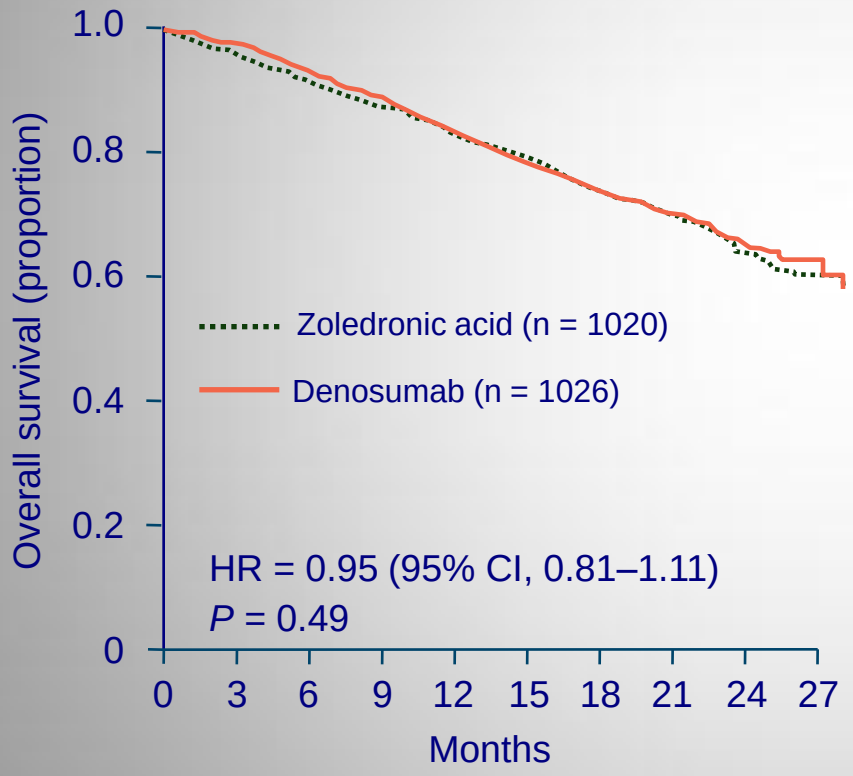


*Events that occurred at least 21 days apart.
†Adjusted for multiplicity.

Stopeck AT, et al. J Clin Oncol. 2010;28:5132-5139.

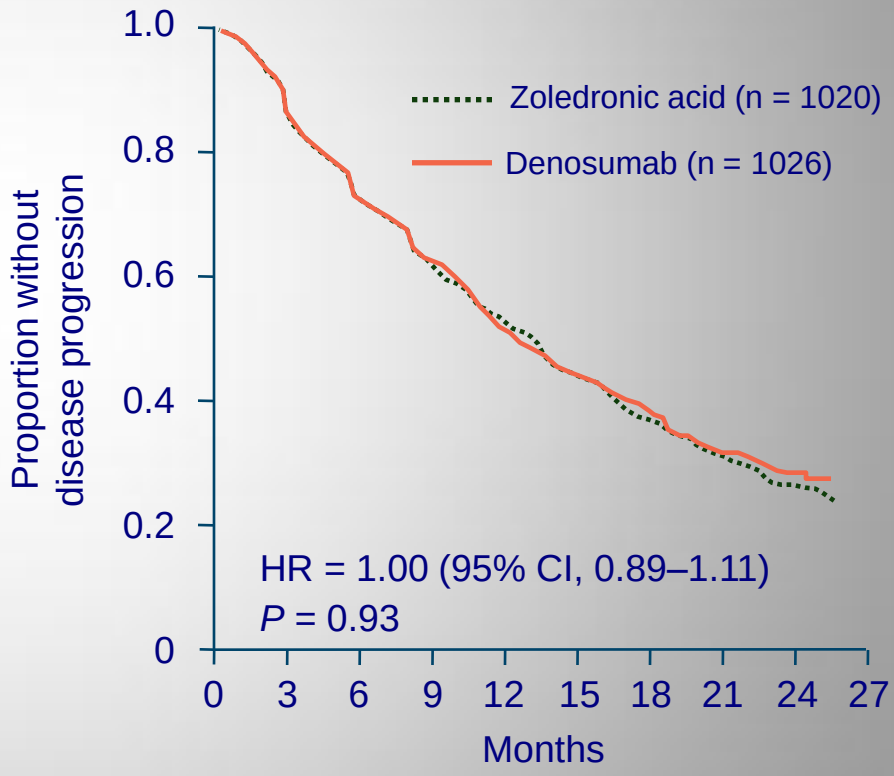
Exploratory endpoints: overall survival and disease progression

Overall survival



No. at risk										
IV zoledronic acid	1020	962	897	834	757	699	515	352	184	54
SC denosumab	1026	984	916	849	771	690	511	336	177	57

Disease progression



No. at risk										
IV zoledronic acid	1020	842	686	563	462	370	240	148	65	17
SC denosumab	1026	858	693	567	453	351	241	128	65	20

Stopeck AT, et al. J Clin Oncol 2010;28:5132–9.

Summary of Adverse Events

Event, n (%)	Zoledronic Acid (n = 1013)	Denosumab (n = 1020)
Adverse events	985 (97)	977 (96)
Most common adverse events in either arm		
▪ Nausea	384 (38)	356 (35)
▪ Fatigue	324 (32)	301 (30)
▪ Arthralgia	291 (29)	250 (25)
▪ Back pain	264 (26)	241 (24)
▪ Pyrexia	247 (24)	170 (17)
▪ Bone pain	238 (24)	186 (18)
CTC grade 3, 4, or 5 adverse events	635 (63)	609 (60)
Serious adverse events	471 (47)	453 (44)
Adverse events leading to treatment discontinuation	125 (12)	98 (10)

Stopeck AT, et al. J Clin Oncol. 2010;28:5132-5139.

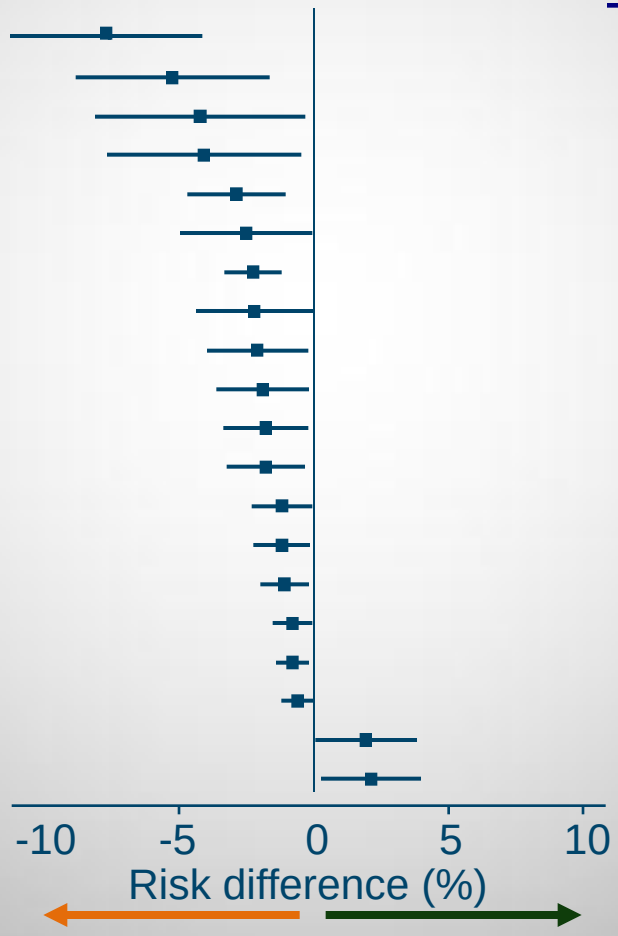
Adverse Events of Interest

Event, n (%)	Zoledronic Acid (n = 1013)	Denosumab (n = 1020)
Adverse events potentially associated with renal toxicity*	86 (8.5)	50 (4.9)
Occurring ≥ 1% frequency		
▪ Blood creatinine increased	41 (4.0)	31 (3.0)
▪ Renal failure	25 (2.5)	2 (0.2)
Serious adverse events potentially associated with renal toxicity	15 (1.5)	2 (0.2)
Decrease in CrCl < 60mL/min†	16.1	12.7
Osteonecrosis of the Jaw	14 (1.4)	20 (2.0)

*Includes blood creatinine increased, hypercreatininemia, oliguria, renal impairment, proteinuria, renal failure, urine output decreased, creatinine renal clearance decreased, renal failure acute, renal function test abnormal, anuria, blood urea increased, and chronic renal failure.
†In patients with baseline CrCl ≥ 60 mL/min.

Stopeck AT, et al. J Clin Oncol. 2010;28:5132-5139.

Forest plot of AD with between-group differences with an unadjusted $P < 0.05$



	Denosumab (n = 1020) No.	%	Zoledronic acid (n = 1013) No.	%
Pyrexia	170	(16.7)	247	(24.4)
Bone pain	186	(18.2)	238	(23.5)
Arthralgia	250	(24.5)	291	(28.7)
Anaemia	192	(18.8)	232	(22.9)
Chills	29	(2.8)	58	(5.7)
Pain	72	(7.1)	97	(9.6)
Renal failure	2	(0.2)	25	(2.5)
Dyspepsia	52	(5.1)	74	(7.3)
Lumbar vertebral fracture	35	(3.4)	56	(5.5)
Increased aminotransferase	28	(2.7)	47	(4.6)
Oedema	22	(2.2)	40	(3.9)
Hypercalcaemia	17	(1.7)	35	(3.5)
Metastases to spine	9	(0.9)	21	(2.1)
Skin hyperpigmentation	7	(0.7)	19	(1.9)
Hyperthermia	4	(0.4)	15	(1.5)
Bronchospasm	2	(0.2)	10	(1.0)
Increase blood urea	0	(0.0)	8	(0.8)
Acute renal failure	1	(0.1)	7	(0.7)
Toothache	57	(5.6)	37	(3.7)
Hypocalcaemia	56	(5.5)	34	(3.4)

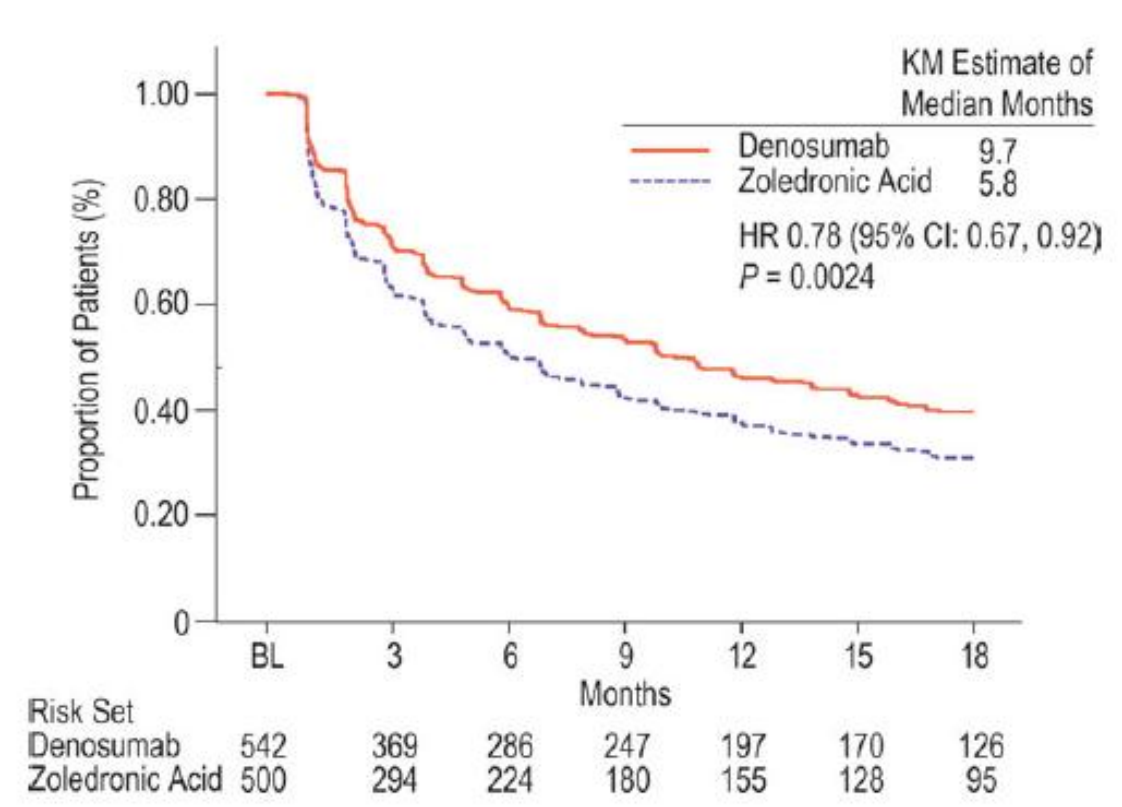
Stopeck AT, et al. J Clin Oncol 2010;28:5132–9.

Adverse events of interest

- Osteonecrosis of the jaw (ONJ) was infrequent and not significantly different between treatment groups
  - Zoledronic acid, 1.4% vs. Denosumab, 2.0% at 3 years
- Acute phase reactions were more common with zoledronic acid than denosumab
  - Zoledronic acid, 8.5% vs. Denosumab, 4.9% ($P = 0.001$)
- Decreases in serum calcium were generally mild, transient, and not associated with clinical sequelae

Stopeck AT, et al. J Clin Oncol 2010;28:5132–9.

Denosumab and Pain Scores (Brief Pain Inventory)



Pain prevenction is illustrated according to the time to moderate pain or severe worst pain (score > 4) among patients who had no pain or mild pain at baseline

Cleeland CS et al., Cancer 2013

3 Identical Randomized Trials of Zoledronic Acid vs Denosumab

- Adults with **breast, prostate**, or **other solid tumors** and bone metastases or **multiple myeloma**
- No current or previous IV bisphosphonate administration for treatment of bone metastases

(N = 5723)

Denosumab 120 mg SC + Placebo IV* q4w
(n = 2862)

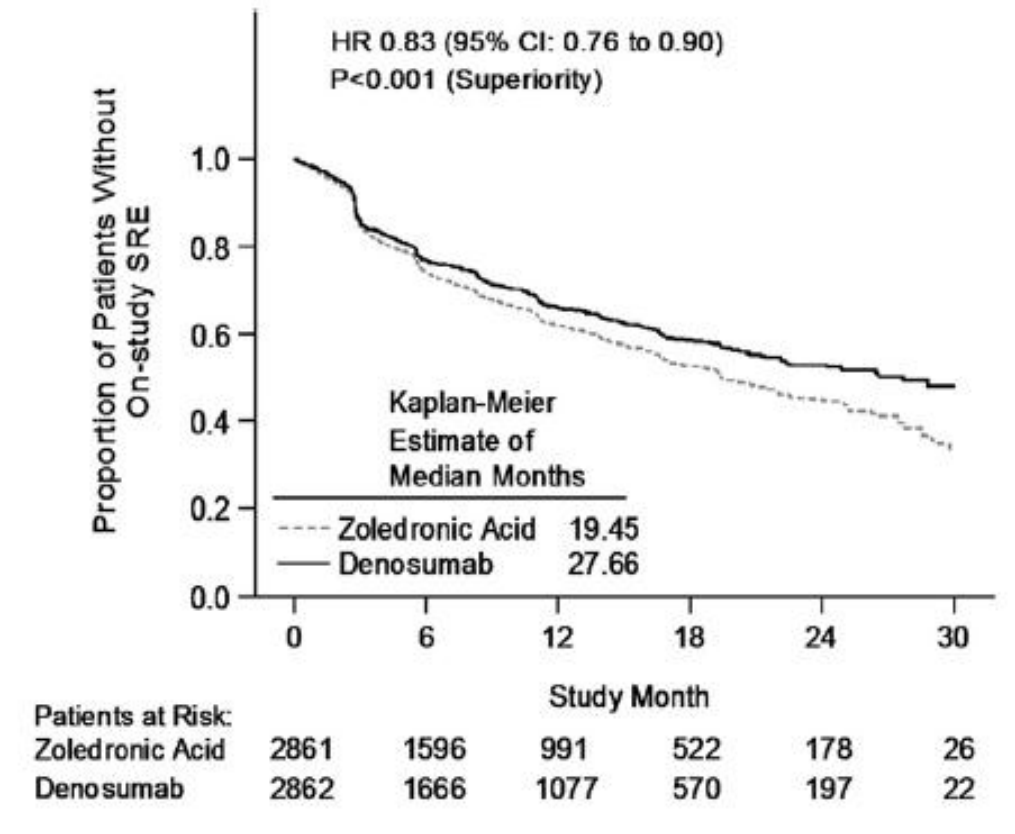
Supplemental calcium and vitamin D recommended

Zoledronic Acid 4 mg IV* + Placebo SC q4w
(n = 2861)

1° Endpoint	▪ Time to first on-study SRE (noninferiority)
2° Endpoints	▪ Time to first on-study SRE (superiority) ▪ Time to first and subsequent on-study SRE (superiority)

Lipton A, et al., Eur J Cancer. 2012 Nov;48(16)

Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomised, phase 3 trials ☆

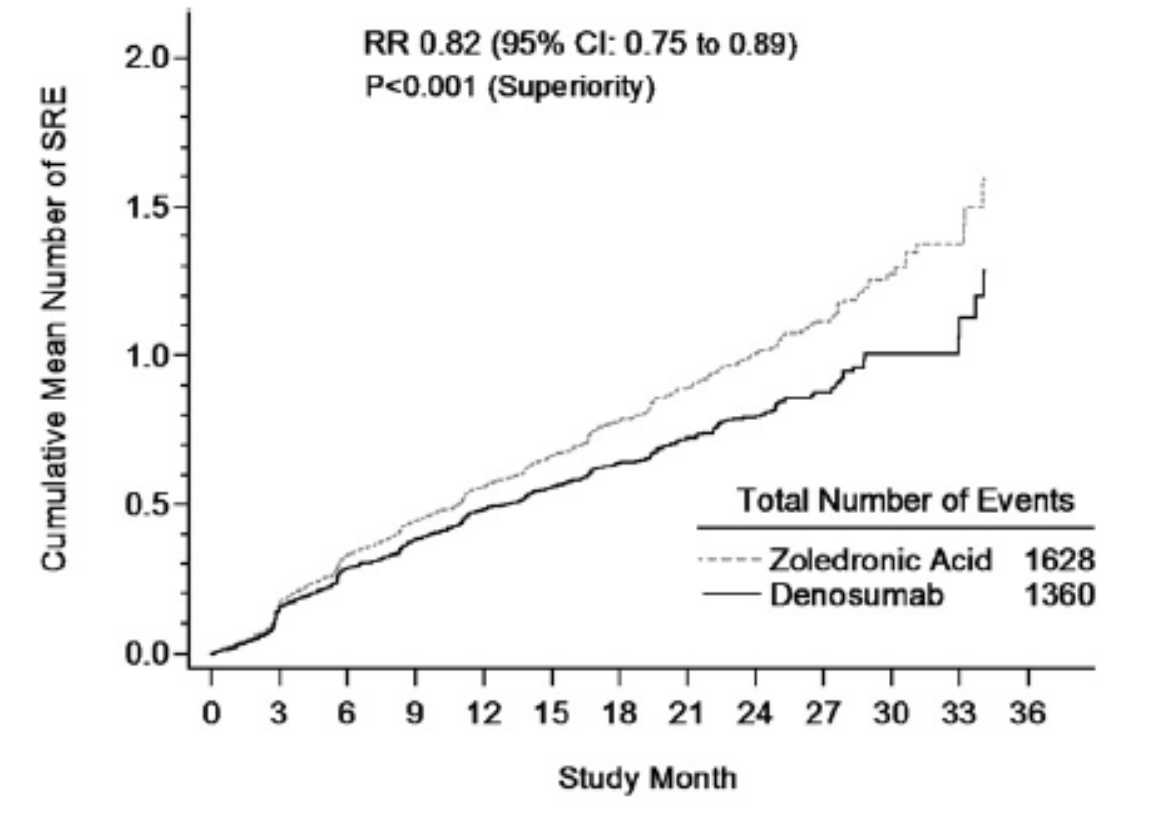


17%

Difference of 8.21 months

Time to the first on-study skeletal-related event

Lipton A, et al., Eur J Cancer. 2012 Nov;48(16)



Time to first and subsequent on-study skeletal-related event (multiple event analysis)

No significant difference in PFS and OS

Lipton A, et al., Eur J Cancer. 2012 Nov;48(16)

Denosumab in patients with cancer and skeletal metastases: A systematic review and meta-analysis

Efficacy outcome

Outcome	Tumor type	Denosumab (n/N)	Bisphosphonates (n/N)	RR	95% CI	I^2
Incidence of SRE						
Denosumab vs. pamidronate						
Body (2006)[32]	Breast Myeloma	1/44	0/10	0.73	0.03, 16.8	
Denosumab vs. zoledronic acid/pamidronate/ibandronate[a]						
Lipton (2007)[28]	Breast	25/212	7/43	0.72	0.33, 1.5	
Fizazi (2009)[33]	Prostate Breast Solid tumors[b]	6/73	6/37	0.51	0.18, 1.4	
Denosumab vs. zoledronic acid						
Stopeck (2010)[34]	Breast	471/1,026	595/1,020	0.79		
Fizazi (2011)[35]	Prostate	494/950	584/951			
Henry (2011)[36]	All tumors,[c] Myeloma	392/886				
						53%
Overall pooled estimate						7%
Time to first on-study						I^2
D					0.71, 0.95	
				0.84	0.71, 0.98	
Pool				**0.83**	**0.75, 0.90**	**0%**
Overa						
Den						
St	Breast	Not reached	Not reached	0.95	0.81, 1.1	
Fizazi (2011)[35]	Prostate	19.4	19.8	1.0	0.91, 1.1	
Henry (2011)[36]	All tumors,[c] Myeloma	13	13	0.95	0.83, 1.0	
Pooled				**0.98**	**0.90, 1.0**	**0%**
Time to worsening of pain[d,e]				HR	95%CI	I^2
Denosumab vs. zoledronic acid						
Stopeck (2010)[38]	Breast(1,042)	9.7	5.7	0.78	0.67, 0.92	
Brown (2011)[40]	Prostate (1,901)	5.8	4.8	0.89	0.77, 1.0	
Von Moos (2010)[39]	All tumors,[c] Myeloma (1,776)	5.5	4.7	0.85	0.73, 0.98	
Pooled				**0.84**	**0.77, 0.91**	**0%**

Incidence of SREs
SRE 1389 (44%) vs 1628 (55%) absolute risk reduction of 11% (95%CI 8.6 – 13.5%)
Overall pooled Rate risk 0.84 (95% CI 0.80 – 0.88)

Peddi p et al., Cancer Treat Rev 2013 n=6142 denosumab= 3191; biphosphonate= 2951

Adverse events

Outcome	Denosumab n/N	Bisphosphonates n/N	Pooled relative risk (RR)	95% CI	P value	I^2
CTCAE grade 3 AE[28,32–36,42]	2,041/3,170	2,003/2,926	0.97	0.89,1.0	0.51	74%
AE-associated hospitalization[28,32–36,42]	1,575/3,176	1,646/2,930	0.95	0.91,1.0	0.04	0%
AE leading to Rx discontinuation[28,32–36,42]	336/3,176	402/2,942	0.82	0.72, 0.94	**0.005**	0%
Acute phase reactions[28,32–36,42]	264/3,170	586/2,939	0.42	0.37, 0.49	**<0.00001**	37.9%
Renal toxicity[33–36]	262/2,841	335/2,836	0.76	0.59, 0.98	**0.03**	61%
Hypocalcemia[28,32–36,42]	295/3,170	143/2,926	1.9	1.6, 2.3	**<0.00001**	0%
New cancers[34–36]	28/2,841	18/2,836	1.6	0.86, 2.8	0.14	0%
Infections[28,33–36]	1,474/3,125	1,646/2,930	1.0	0.93, 1.1	0.76	48%
ONJ[32,34–36]	52/2,885	37/2,846	1.4	0.92, 2.1	0.11	0%

AE, adverse events; Rx, treatment; ONJ, osteonecrosis of jaw. Bold values represents statistically significant

- All patients with several risck factor for ONJ
- Resolution in 27 % denosumab and 8% zoledronic acid (p=0.48)
- Unable to evaluable Denosumab in patients with a baseline creatinine clearance < 30 mil/min
- Patient with several renal impairment are at greater risck of Hypocalcemia

Peddi p et al., Cancer Treat Rev 2013

Bone tumor markers

Percent reduction in BTM at 13 weeks. Denosumab vs. bisphosphonates.

BTM	Denosumab (*N*)	Bisphosphonates (*N*)	Pooled mean difference	95% CI	I^2	*P*-value
Denosumab vs. Zoledronic Acid/Pamidronate/Ibandronate[a]						
uNTX[b,28,32–36]	2980	2719	−14.9	−19.2,−10.7	78%	<0.0001
BSAP[34–36]	2771	2609	−6.5	−8.9,-4.2	13%	<0.0001
Denosumab vs. Zoledronic Acid						
uNTX	2650	2629	−12.5	−14.8,−10.3	53%	0.001
BSAP	2554	2552	−7.6	−9.9,−5.2	0%	<0.0001

uNTX, urine N-telopeptide; BSAP, serum bone-specific alkaline phosphatase.

[a] Insufficient information to analyze data separately for each bisphosphonates.

[b] Body et al.[32] reported percent reductions in uNTX for different doses of denosumab (0.1,0.3,1.0,3.0 mg/kg).

- Alkaline phosphatase and N telopeptide surrogate biomarkers for predicting SRE

Peddi p et al., Cancer Treat Rev 2013

Summary

- Denosumab was superior to zoledronic acid in reducing and delaying SREs
  - Palliating pain from bone metastasis
  - Preventing the development of pain
- Different toxicity profiles
  - Zoledronic acid: flulike symptoms, renal toxicity, osteonecrosis
  - Denosumab: hypocalcemia, osteonecrosis
- SC vs IV administration

Stopeck AT, et al. J Clin Oncol 2010;28:5132–9.

FDA-Approved Agents for Prevention of SREs in Metastatic Breast Cancer

AGENT	DRUG CLASS	DOSE AND SCHEDULE
Zoledronic Acid	Bisphosphonate	4 mg IV q3-4w
Pamidronate	Bisphosphonate	90 mg IV q3-4w
Denosumab	RANK-L targeted Mab	120 mg SQ q4w

Both ASCO and NCCN recommend all 3 agents[1,2]

- No agent is recommended over another
- Bone-modifying agent therapy is only recommended for patients with evidence of bone metastases

1.Van Poznak CH, et al. J Clin Oncol. 2011;29:1221-1227. 2. NCCN. Clinical practice guidelines in oncology: breast cancer. v.2.2013.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2013 Breast Cancer

- Patients should receive a dental exam and preventive dentistry before initiating bone-modifying agent therapy
- Frequent measurement of Ca, P, Mg
- Should be accompanied by calcium and Vit D supplementation.
- Duration of treatment: Biphosponate for up to 2 years. Denosumab unknown

NHS
National Institute for
Health and Clinical Excellence

NICE guidance

Denosumab is recommended as an option for preventing skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from breast cancer and from solid tumours other than prostate if:

- bisphosphonates would otherwise be prescribed and
- the manufacturer provides denosumab with the discount agreed in the patient access scheme.

Denosumab in Italia

Xgena: 120 mg sc q 4 settimane

Prevenzione di eventi correlati all'apparato scheletrico (fratture patologiche, radioterapia all'osso, compressione del midollo spinale o interventi chirurgici all'osso) negli adulti con metastasi ossee da tumori solidi.