Current Management to Maintain Bone Health in Cancer Patients

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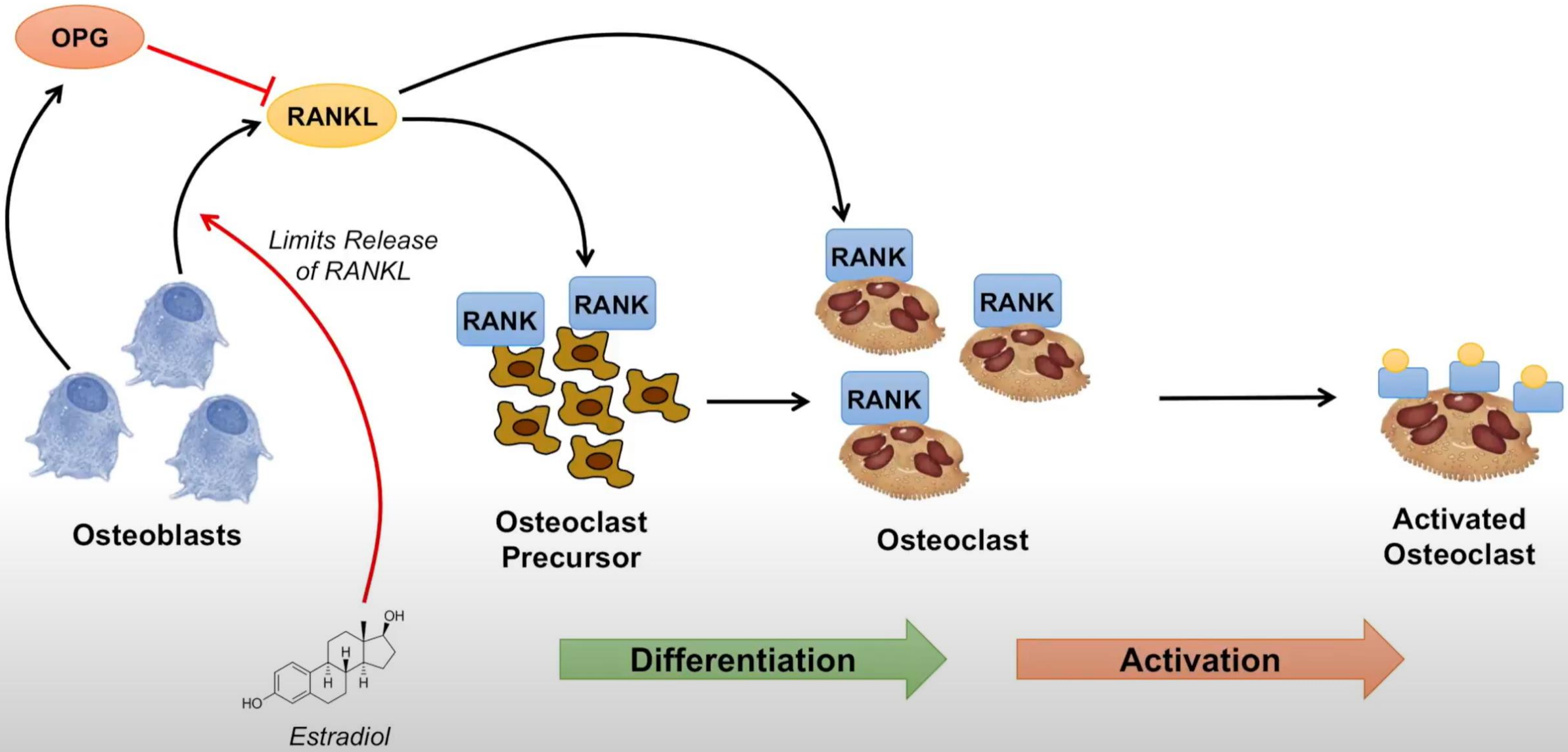
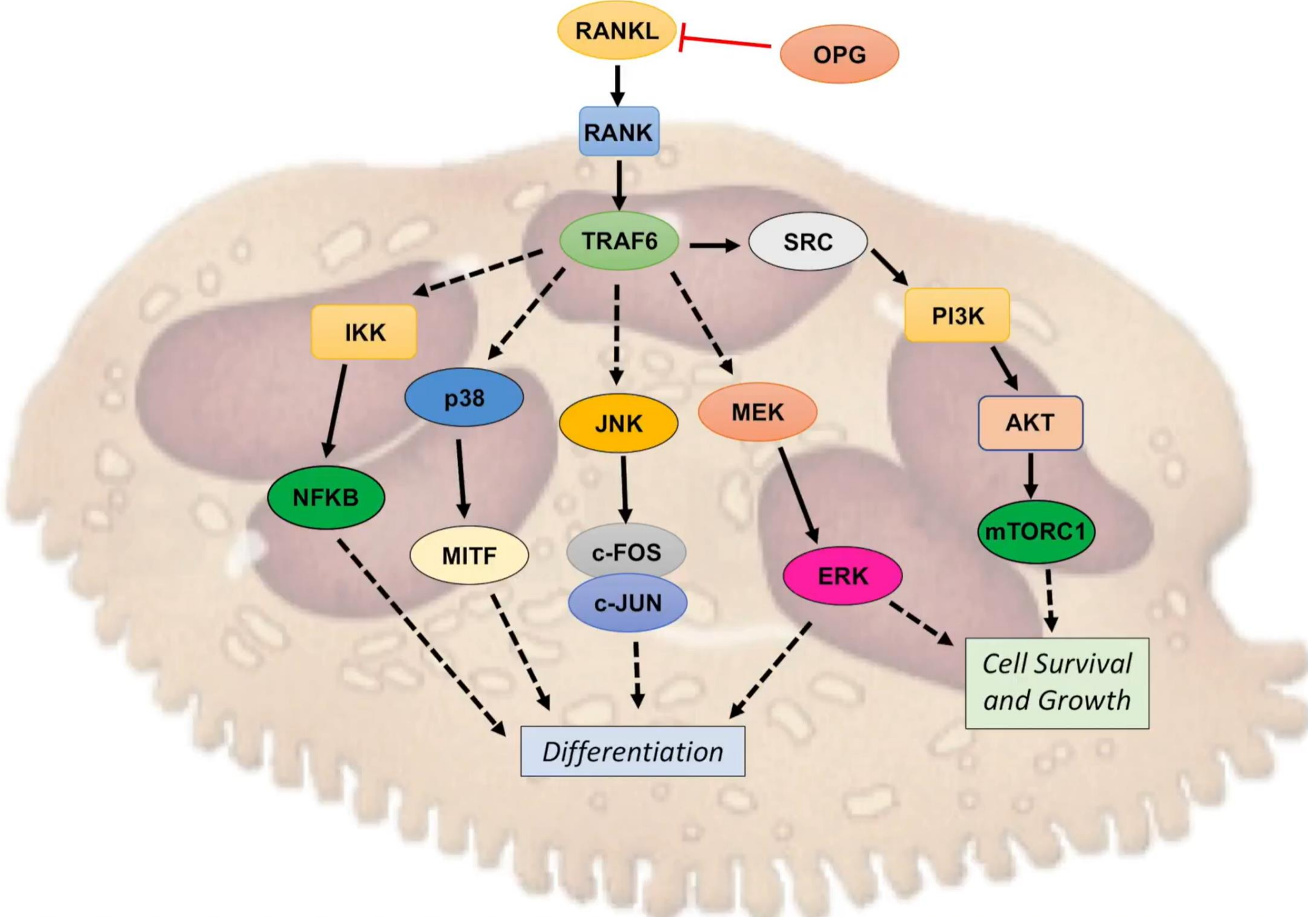
RANKL-RANK-OPG Signaling Pathway

- **RANKL**
  - Receptor activator of nuclear factor kappa-B ligand
  - Expressed by *osteoblasts*
  - Plays an important osteoclast formation, function and survival
- **RANK**
  - Receptor activator of nuclear factor kappa-B
  - Located on *osteoclast precursors* and *mature osteoclasts*
- **OPG**
  - Osteoprotegerin
  - Binds to and *inhibits* RANKL
  - Expressed by *osteoblasts* and other tissues including spleen, bone marrow, heart, liver and kidneys
  - Protective against bone loss


OPG
RANKL
Limits Release of RANKL
RANK
RANK
RANK
RANK
RANK
Osteoblasts
Osteoclast Precursor
Osteoclast
Activated Osteoclast
OH
H
H
H
HO
Estradiol
Differentiation
Activation


RANKL
OPG
RANK
TRAF6
SRC
IKK
p38
JNK
MEK
PI3K
AKT
NFKB
MITF
c-FOS
c-JUN
ERK
mTORC1
Cell Survival and Growth
Differentiation

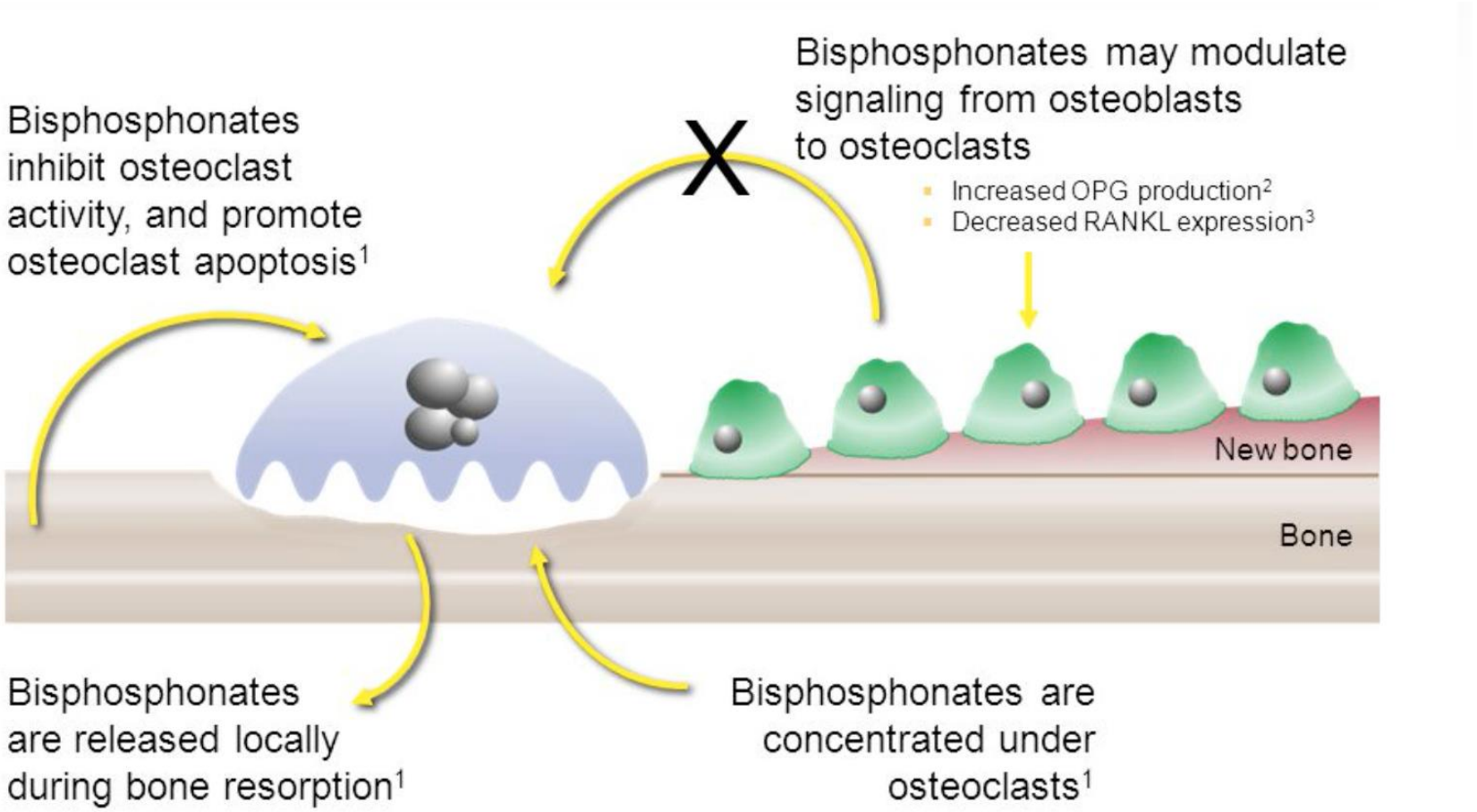
Bone Events Defined

- **Skeletal Related Event (SRE)**
  - Radiation to bone
  - Pathologic fracture
  - Surgery to bone
  - Spinal cord compression
  - Hypercalcemia of malignancy
- **Symptomatic Skeletal Event (SSE)**
  - EBRT to relieve skeletal symptoms
  - **New symptomatic pathologic bone fracture**
  - Occurrence of spinal cord compression
  - Tumor-related orthopedic surgical intervention

Bone Targeting Agents (BTA)

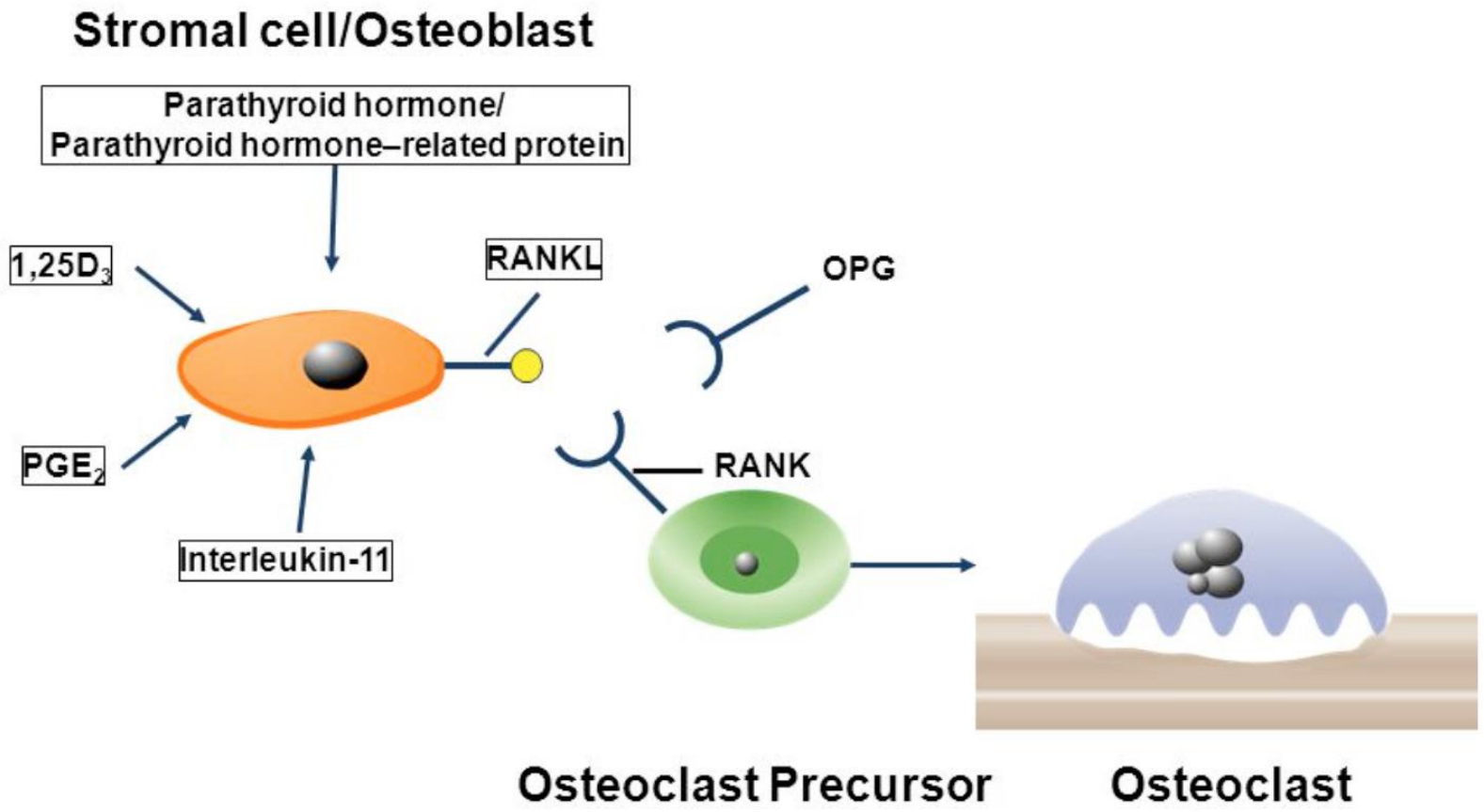
- Bisphosphonates
  - Stimulate osteoclast apoptosis
  - For treatment of HCM and patients with MM and patients with documented bone metastasis from solid tumors, in conjunction with standard antineoplastic therapy
- Denosumab
  - monoclonal antibody that binds avidly to RANK
  - For prevention of SREs in patients with bone metastasis from solid tumors

Mechanism of Bisphosphonate Inhibition of Osteoclast Activity



1. Reszka AA, Rodan GA. *Curr Rheumatol Rep*. 2003;5:65-74. **2.** Viereck V et al. *Biochem Biophys Res Commun*. 2002;291:680-686. **3.** Pan B et al. *J Bone Miner Res*. 2004;19:147-154.

Receptor Activator of Nuclear Factor κB Ligand (RANKL) and osteoprotegerin (OPG)



Derived from Roodman GD. *N Engl J Med*. 2004;350:1655-1664.

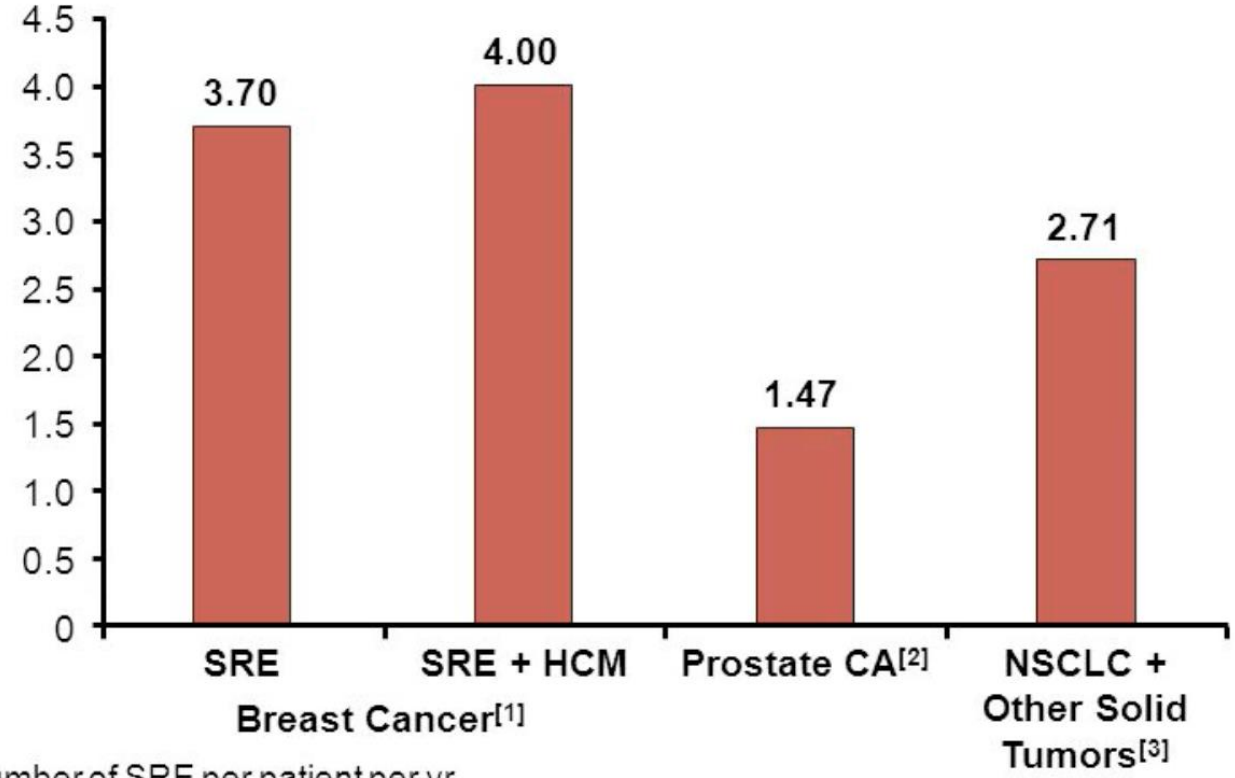
Breast Cancer

The Natural History of Bone Metastasis 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.

Untreated Patients Experience Multiple SREs



*Mean number of SRE per patient per yr.

1. Lipton A, et al. Cancer. 2000;88:1082-1090. 2. Saad F. Clin Prostate Cancer. 2005;4:31-37.
3. Rosen LS, et al. Cancer. 2004;100:2613-2621.

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

Agent	Drug Class	Recommended Dose and Schedule
Zoledronic acid	Bisphosphonate	4 mg IV q3-4w
Pamidronate	Bisphosphonate	90 mg IV q3-4w
Denosumab	RANKL-targeted MAb	120 mg SQ q4w

- Both ASCO and NCCN recommend all 3 agents[1,2]
  - No agent recommended over another

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

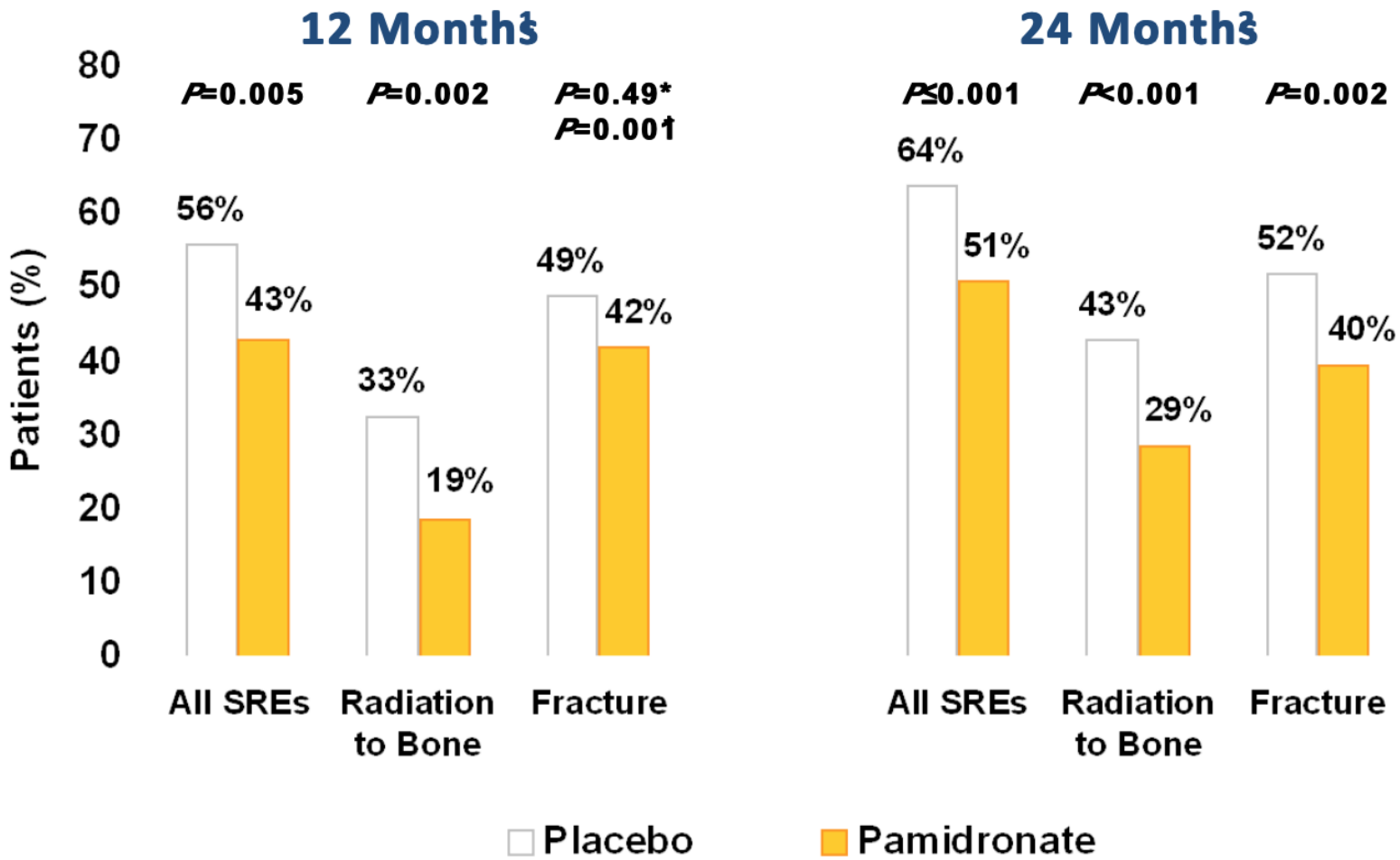
Bisphosphonates Reduce SREs in Breast cancer

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		49	NS
▪ Zoledronic acid		46	
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. 2003;98:1735-1744.
3. Kohno N, et al. J Clin Oncol. 2005;23:3314-3321.

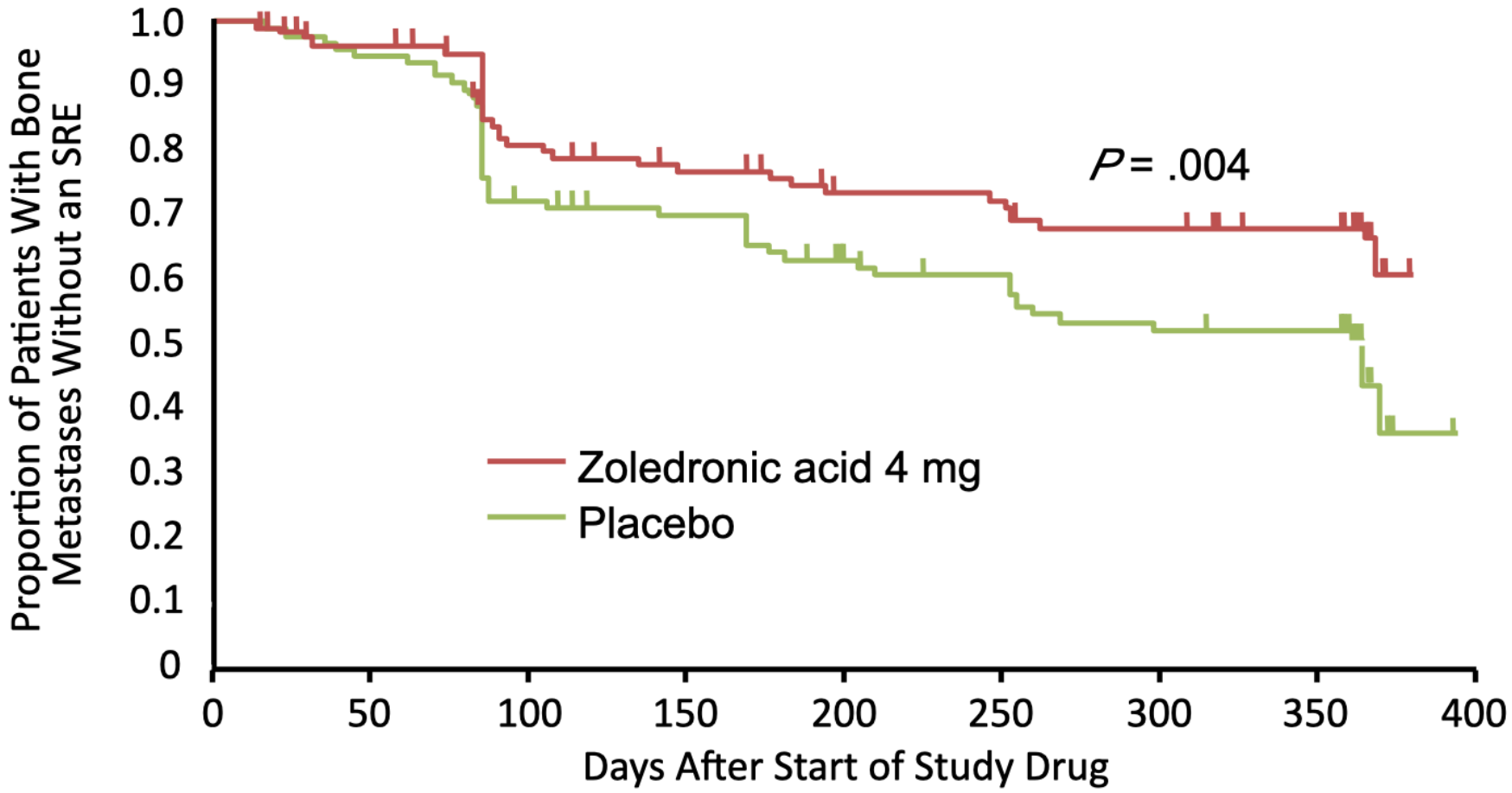
Proportion of Breast Cancer Patients Having Skeletal-Related Events (SREs) With Pamidronate



*P=0.49 for nonvertebral fracture; †P=0.001 for vertebral fracture.

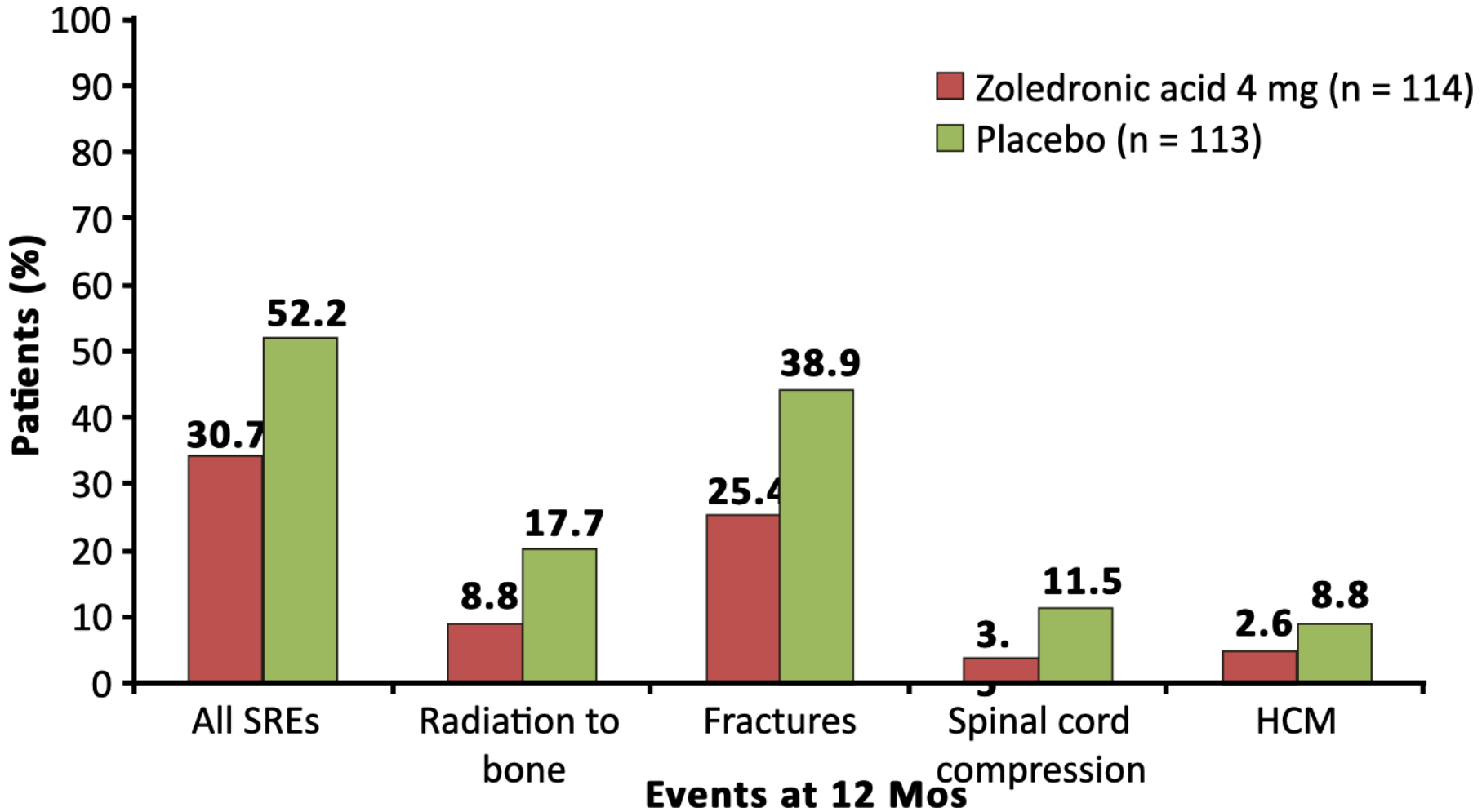
1. Hortobagyi GN et al. *N Engl J Med*. 1996;335:1785-1791. **2.** Lipton A et al. *Cancer*. 2000;88:1082-1090.

Zoledronic Acid Significantly Delays Time to First SRE Compared With Placebo



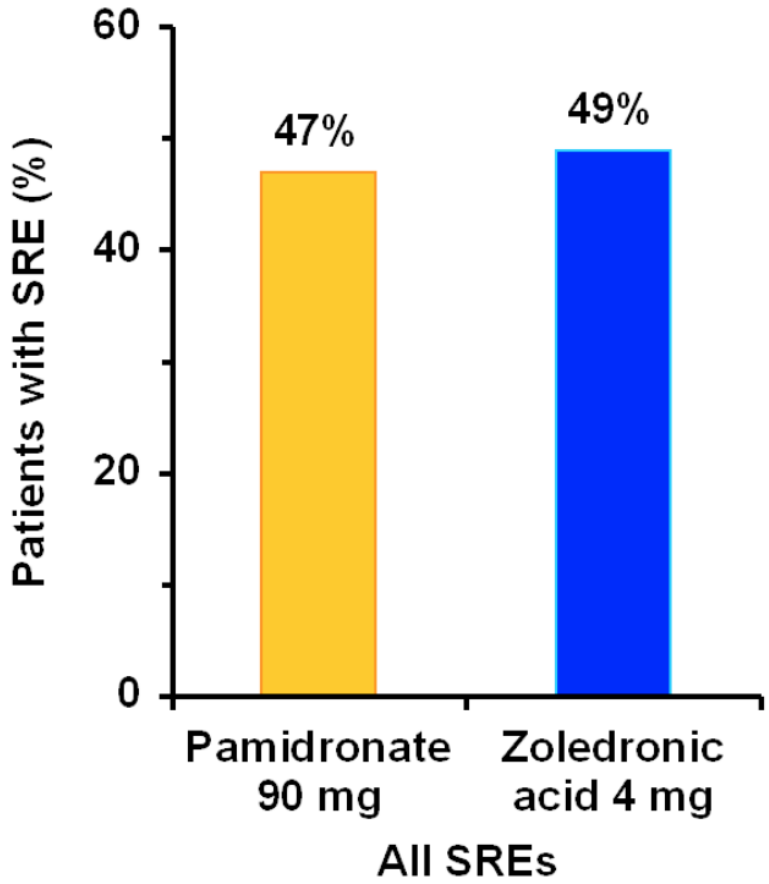
Kohno N, et al. SABCS 2004. Abstract 3060. Kohno N, et al. J Clin Oncol. 2005;23:3314-3321. Reprinted with permission.

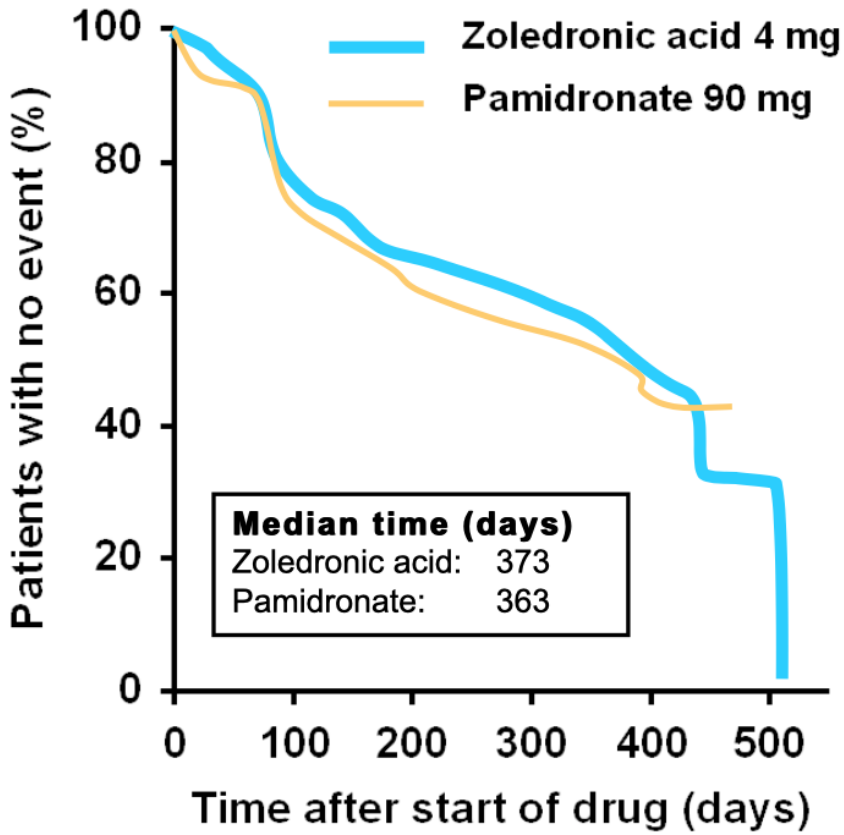
Zoledronic Acid vs Placebo in Stage IV Breast Cancer With Bone Metastases



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

Zoledronic Acid and Pamidronate in Breast Cancer and Multiple Myeloma Patients With Bone Metastases: 13-Month Data

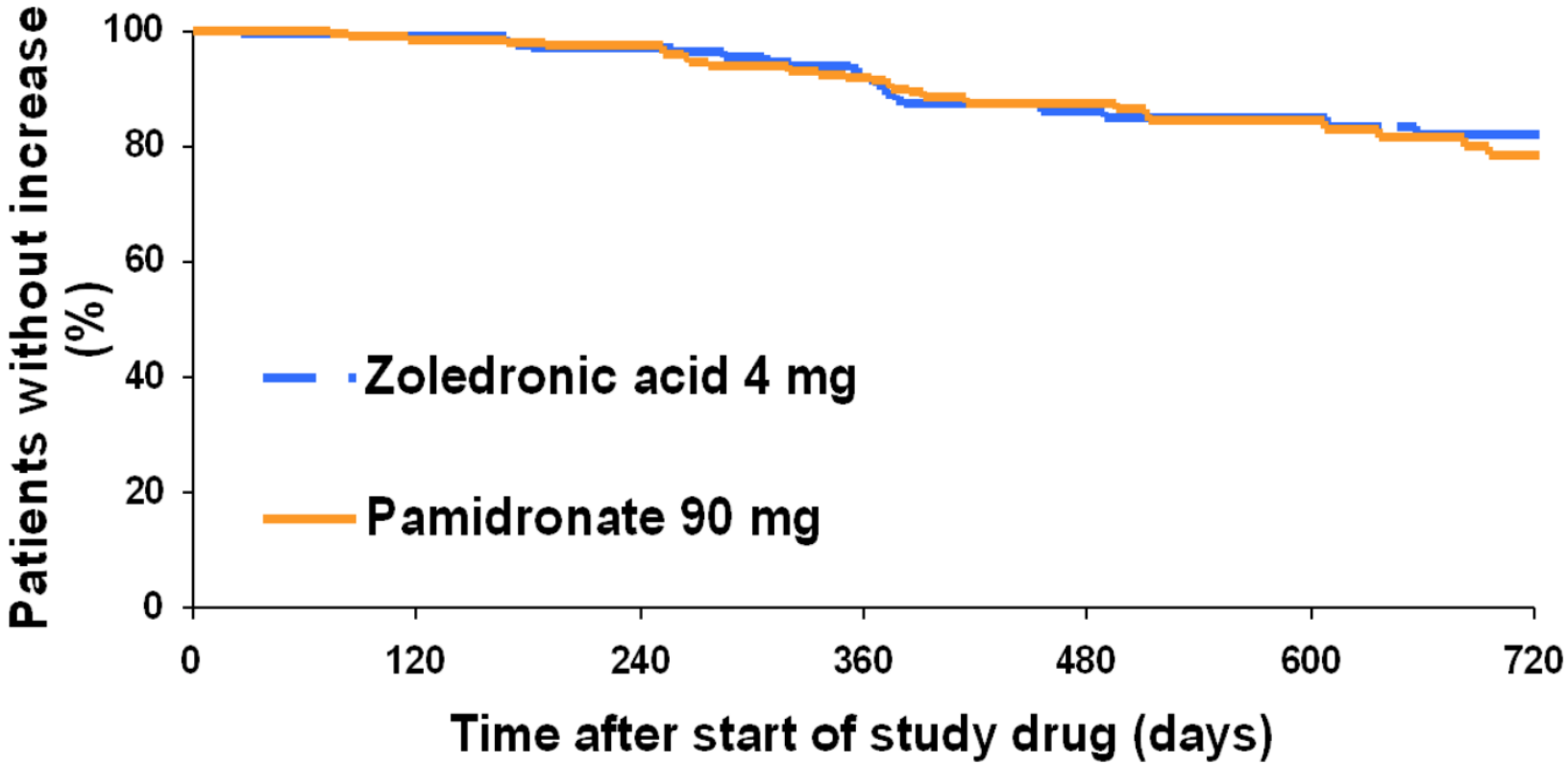




SREs=skeletal-related events.

Adapted with permission from Rosen LS et al. *Cancer J.* 2001;7:377-387.

Renal Profile of Pamidronate and Zoledronic Acid in Patients With Metastatic Breast Cancer or Multiple Myeloma



Zoledronic acid	4 mg	272	226	197	152	81	68	30
Pamidronate	90 mg	268	213	182	138	73	59	27

***Post–15-minute infusion amendment.**

Adapted with permission from Berenson JR. *The Oncologist*. 2005;10:52-62.

3 Identical International, Randomized, Double-Blind, Active-Controlled Trials

Enrollment Criteria

- 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

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

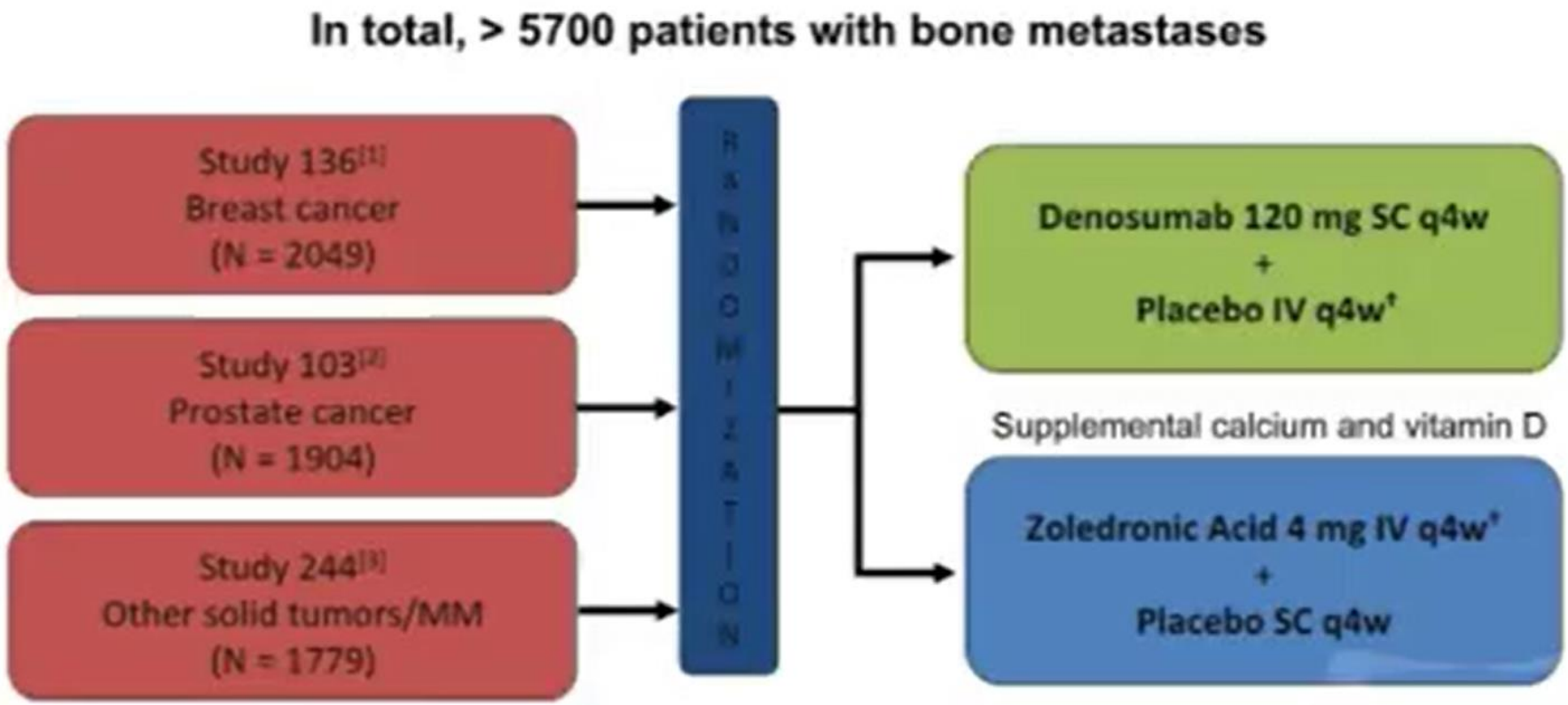
Supplemental Calcium and Vitamin D Recommended

Zoledronic Acid 4 mg IV* and **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)

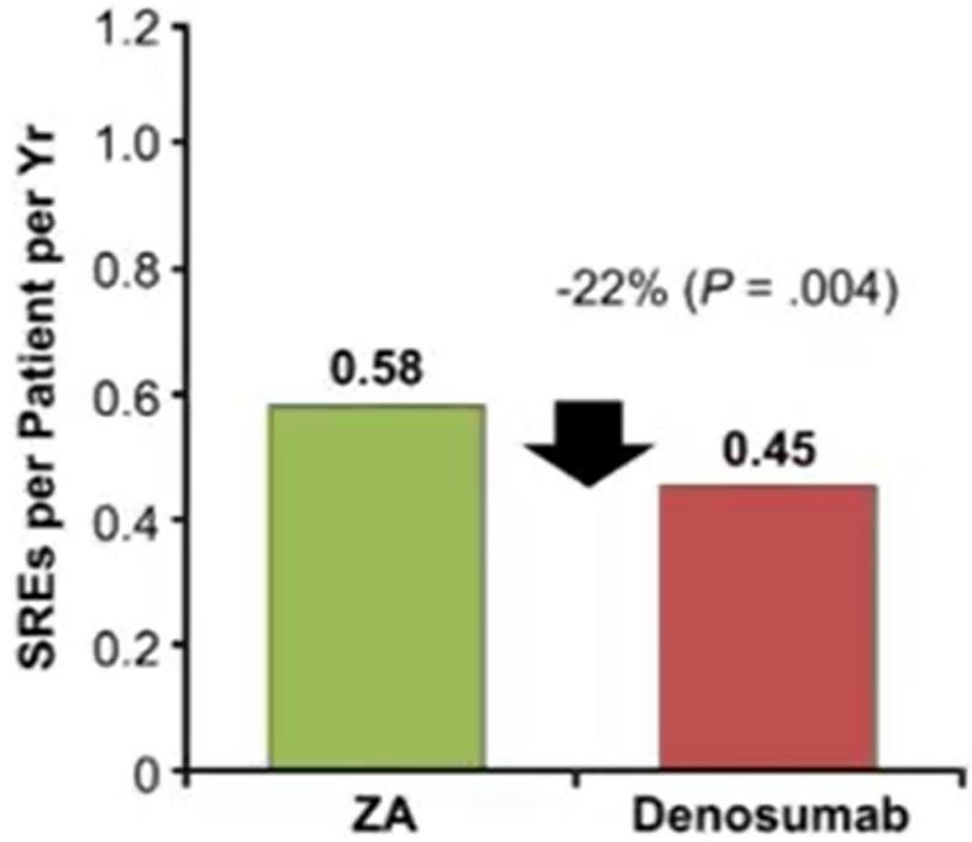
*Per protocol and zoledronic acid label, IV product dose adjusted for baseline creatinine.

Denosumab vs Zoledronic Acid Pivotal Phase III SRE Prevention Trials



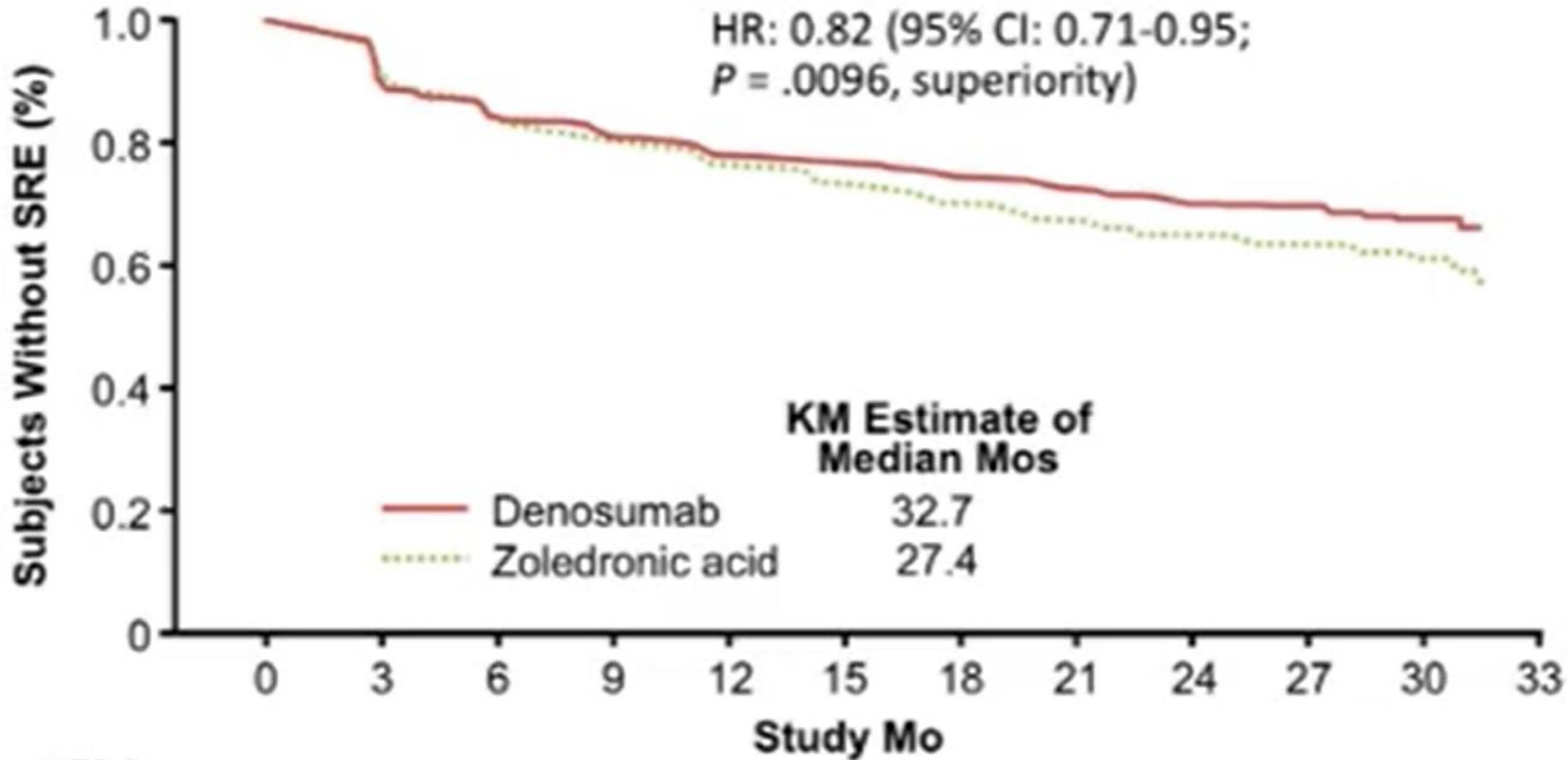
1. Stopeck AT, et al. J Clin Oncol. 2010;28:5132-5139. 2. Fizazi K, et al. Lancet. 2011;377:813-822.
3. Henry DH, et al. J Clin Oncol. 2011;29:1125-1132.

SRE Rate: Denosumab vs ZA in Breast Cancer Patients With Bone Metastases



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

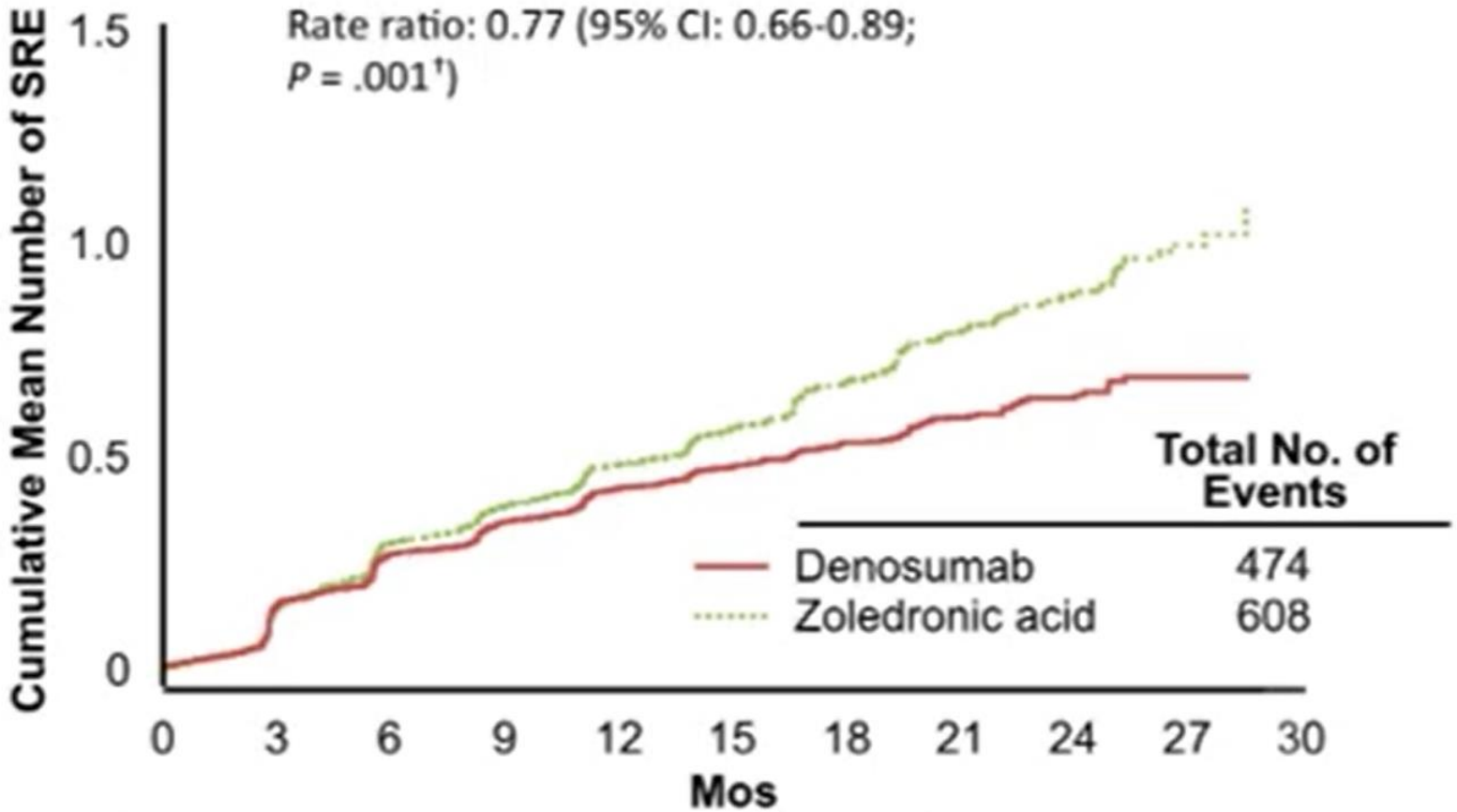
Time to First On-Study SRE: Extended Analysis



Patients at Risk, n

Stopeck A, et al. SABCS 2010. Abstract P6-14-01.

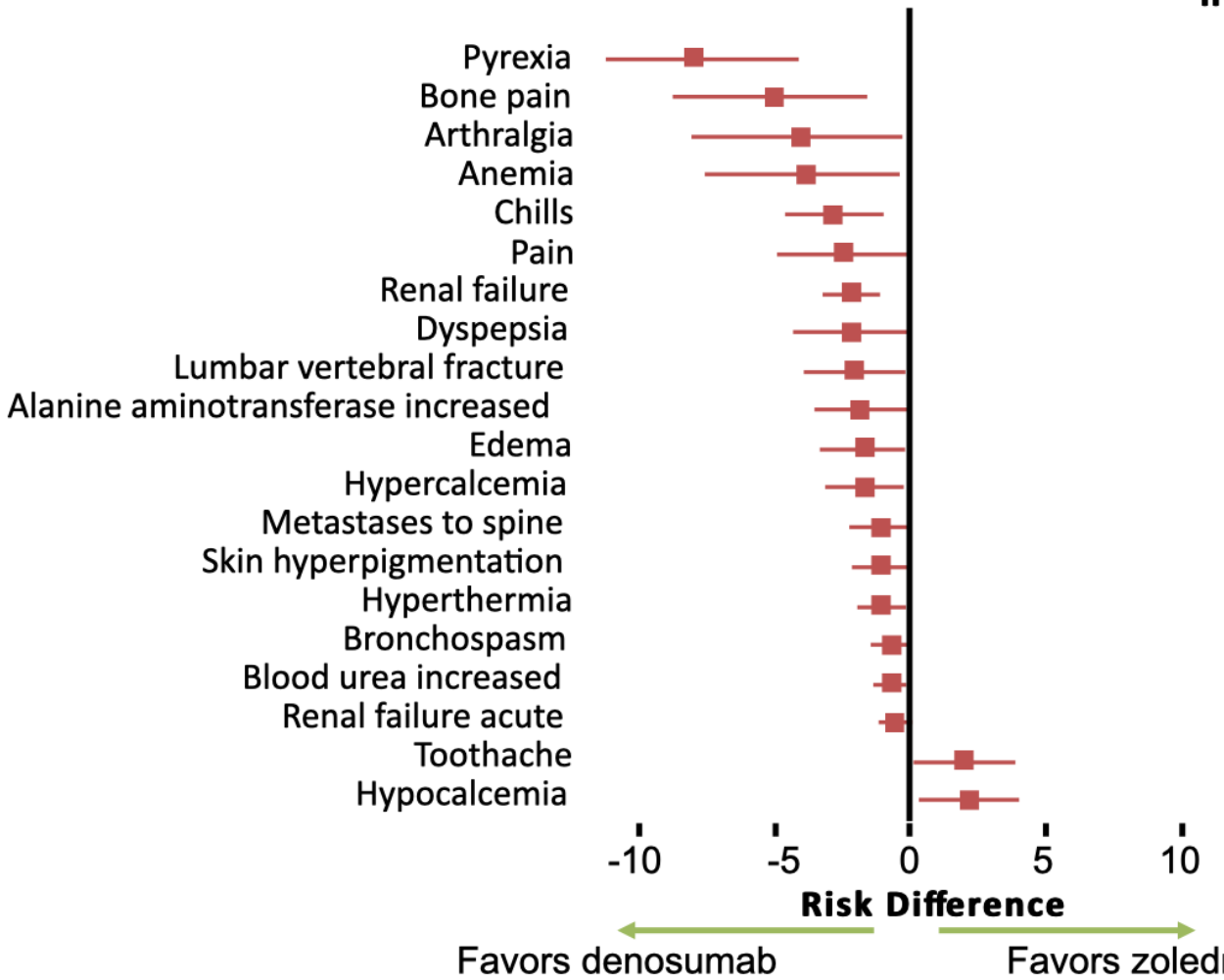
Time to First and Subsequent On-Study SRE* (Multiple Event Analysis)



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

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

Between-Group Differences in AEs With Unadjusted $P < .05$



	Denosumab, n (%) (n = 1020)		Zoledronic Acid, n (%) (n = 1013)	
Pyrexia	170	(16.7)	247	(24.4)
Bone pain	186	(18.2)	238	(23.5)
Arthralgia	250	(24.5)	291	(28.7)
Anemia	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)
Alanine aminotransferase increased	28	(2.7)	47	(4.6)
Edema	22	(2.2)	40	(3.9)
Hypercalcemia	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)
Blood urea increased	0	(0.0)	8	(0.8)
Renal failure acute	1	(0.1)	7	(0.7)
Toothache	57	(5.6)	37	(3.7)
Hypocalcemia	56	(5.5)	34	(3.4)

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

Adverse Events: From Extended Analysis

Event, n (%)	Zoledronic Acid (n = 1013)	Denosumab (n = 1020)
All adverse events	987 (97.4)	961 (96.2)
Serious adverse events	509 (50.2)	489 (47.9)
Adverse events related to renal toxicity	95 (9.4)	55 (5.4)
Osteonecrosis of the jaw*	18 (1.8)	26 (2.5)
Hypocalcemia (any)	37 (3.7)	62 (6.1)
▪ Hypocalcemia of grade 3 or 4†	12 (1.2)	18 (1.8)
Acute-phase reactions‡	286 (28.2)	109 (10.7)

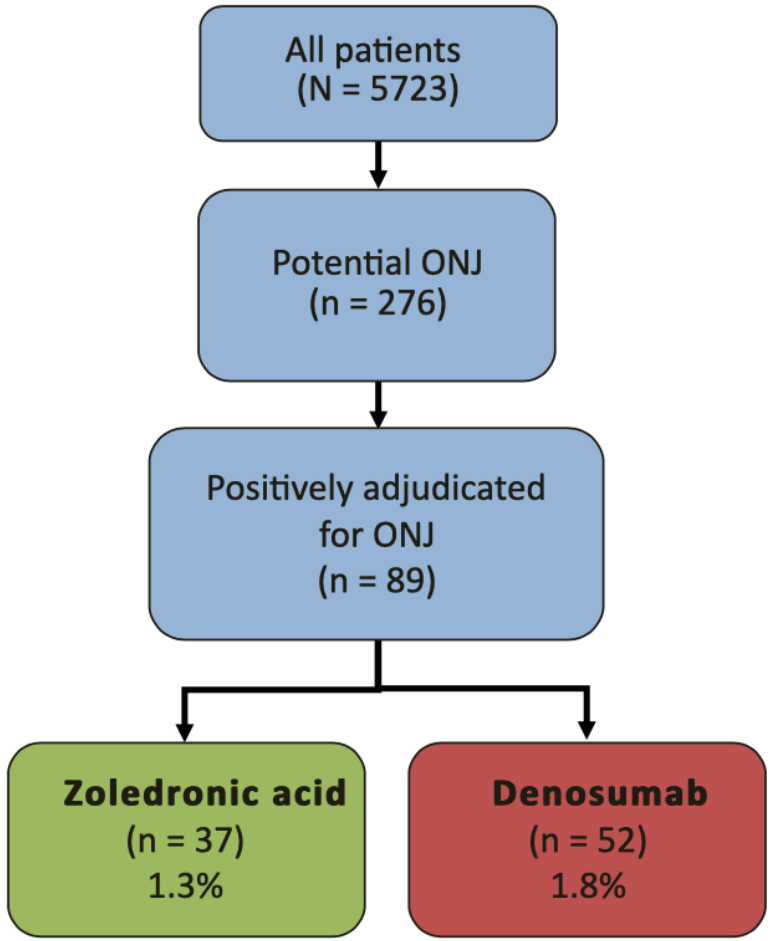
*P = .2861

†No cases of hypocalcemia were grade 5 (fatal).

‡In the first 3 days after initial treatment.

Stopeck A, et al. SABCS 2010. Abstract P6-14-01.

ONJ Associated With Bone-Targeted Therapy in Patients With Bone Metastases



Integrated analysis of pivotal denosumab SRE prevention trials

No significant difference between groups (P = .13)

Saad F, et al. Ann Oncol. 2012;23:1341-1347.

Associated Oral Events

n (%)	Zoledronic Acid (n = 37)	Denosumab (n = 52)	All (N = 89)
Tooth extraction	24 (65)	30 (58)	**54 (61)**
Jaw pain	25 (68)	46 (88)	**71 (80)**
Local infection	17 (46)	26 (50)	**43 (48)**

Location of ONJ

n (%)	Zoledronic Acid (n = 37)	Denosumab (n = 52)	All (N = 89)
Mandible	31 (84)	34 (65)	**65 (73)**
Maxilla	5 (14)	15 (29)	**20 (22)**
Both	1 (3)	3 (6)	**4 (4)**

Saad F, et al. Ann Oncol. 2012;23:1341-1347.

Systemic Risk Factors

n (%)	Subjects With ONJ			Subjects Without ONJ		
	ZA (n = 37)	Denosumab (n = 52)	All (N = 89)	ZA (n = 2824)	Denosumab (n = 2810)	All (N = 5634)
Diabetes	11 (30)	9 (17)	**20 (22)**	431 (15)	443 (16)	**874 (16)**
Anemia (Hb <10)	17 (46)	23 (44)	**40 (45)**	1185 (42)	1119 (40)	**2304 (41)**
Chemotherapy agents	27 (73)	36 (69)	**63 (71)**	1950 (69)	1921 (68)	**3871 (69)**
Antiangiogenics	8 (22)	6 (12)	**14 (16)**	236 (8)	214 (8)	**450 (8)**
Corticosteroids	28 (76)	39 (75)	**67 (75)**	1786 (63)	1762 (63)	**3548 (63)**

Saad F, et al. Ann Oncol. 2012;23:1341-1347.

Preventing and Managing ONJ

Risk factors	▪ Invasive dental procedures ▪ Poor oral hygiene or pre-existing dental disease ▪ Advanced malignancies, infections, concomitant therapies
Before bone-targeted treatment	▪ Consider dental examination and preventive dentistry in patients with active dental/jaw conditions
During treatment	▪ Avoid invasive dental procedures ▪ Maintain good oral hygiene
Suspected cases	▪ Refer to dentist or oral surgeon ▪ Extensive dental surgery may exacerbate

Denosumab. EPAR and summary of product characteristics; Amgen.
Zoledronic acid. Summary of product characteristics; Novartis.

Incidence of Hypocalcemia in the 3 Pivotal Phase III Trials

Hypocalcemia Events, n (%)	Denosumab (n =2841)	Zoledronic Acid (n =2836)
Hypocalcemia	273 (9.6)	141 (5.0)
IV calcium Rx	104 (3.7)	47 (1.7)
SAE of hypocalcemia	41 (1.4)	18 (0.6)
▪ Grade 3*	72 (2.5)	33 (1.2)
▪ Grade 4*	16 (0.6)	5 (0.2)

*CTCAE grading, grade 3 < 7 mg/dL, grade 4 < 6 mg/dL;

No fatal events of hypocalcemia were reported

Body JJ, et al. Presentation from the 12th International Conference on Cancer-Induced Bone Disease, November 15-17, 2012, Lyon, France.

Hypocalcemia in Relation to Calcium/Vit D Supplementation With Denosumab

	Patients, n	Incidence of Hypocalcemia,* n (%)
Reported supplements	2461	213 (8.7)
Did not report supplements	380	60 (15.8)

*All AEs of hypocalcemia.

- Median time to hypocalcemia was 2.8 mos
- Most common in the first 6 mos of initiation of denosumab therapy

Body JJ, et al. Presentation from the 12th International Conference on Cancer-Induced Bone Disease, November 15-17, 2012, Lyon, France.

Hypocalcemia in Relation to Tumor Type With Denosumab Treatment

Primary Tumor Type, n (%)	PatientsWith Hypocalcemia
Multiple myeloma (N = 86)	12 (14.0)
Prostate (N = 943)	121 (12.8)
Other solid tumors (N = 386)	48 (12.4)
Lung (N = 406)	35 (8.6)
Breast (N = 1020)	57 (5.6)

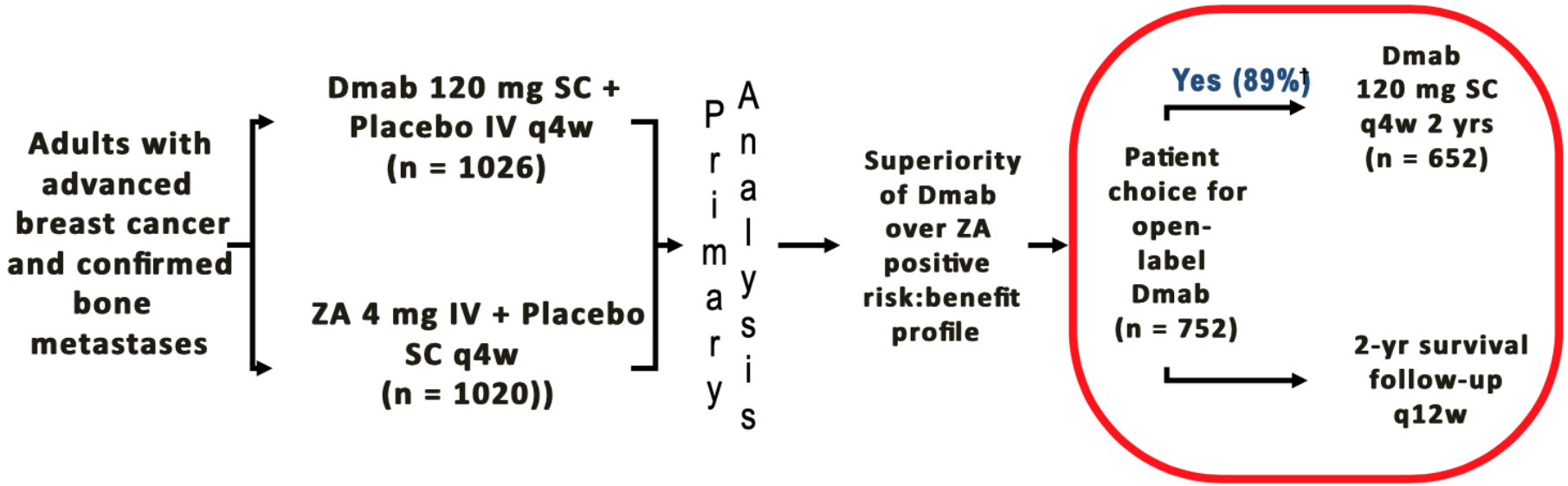
Body JJ, et al. Presentation from the 12th International Conference on Cancer-Induced Bone Disease, November 15-17, 2012, Lyon, France.

Question: What is the Maximum Time You Provide Bone-Modifying Therapy

Guidelines and Duration of Bone-Targeted Therapy

ESMO[1]	"The timing and optimal duration of bisphosphonate treatment are unknown; benefit of duration beyond 2 yrs has not been demonstrated . . . Long-term treatment seems wise due to ongoing risk of skeletal events"
NCCN[2]	"Optimal schedule and duration are unknown . . . Limited long-term safety data indicating bisphosphonate treatment can continue beyond 2 yrs"
ASCO[3]	"Until evidence of substantial decline (clinical judgment) in general performance status"

2-Yr Open-Label Extension Phase



Among patients previously receiving denosumab or zoledronic acid, 89% in each treatment group chose to receive open-label denosumab

Cumulative median exposure to denosumab for the entire study (including blinded and open-label treatment phases) was 19.1 mos (range: 0.1-59.8 mos, ie, ~ 5 yrs)

- 216 patients received denosumab for ≥ 3 yrs
- 76 patients received denosumab for ≥ 4 yrs

Stopeck AT, et al. SABCS 2011. Abstract P3-16-07.

AEs During Open-Label Treatment Phase

Event,n (%)	Dmab/Dmab (n = 318)	ZA/Dmab (n = 334)
All AEs	283 (89)	303 (91)
Serious AEs	126 (40)	133 (40)
ONJ	20 (6)	18 (5)
Hypocalcemia	12 (4)	9 (3)
Hypocalcemia, grade 3 or 4	4 (1)	3 (1)

- No new safety signals were observed with up to ~ 5 yrs of monthly denosumab therapy
- Incidence and pattern of AEs in patients who switched from zoledronic acid to denosumab were similar to those observed in pts who continued with denosumab
- Cumulative incidence of positively adjudicated ONJ was 4.7% for denosumab/ denosumab pts when administered for up to ~ 5 yrs and 3.5% for pts who switched from zoledronic acid to denosumab
- No neutralizing anti-denosumab antibodies were detected in either group

Stopeck AT, et al. SABCS 2011. Abstract P3-16-07.

BTA Optimal Interval

ZOOM: A Prospective, Randomized Trial of Zoledronic Acid for Long-term Treatment in Patients With Bone-Metastatic Breast Cancer After 1 Year of Standard Zoledronic Acid Treatment

D. Amadori, M. Aglietta, B. Alessi, L. Gianni,
T. Ibrahim, G. Farina, F. Gaion, F. Bertoldo,
D. Santini, R. Rondena, P. Bogani, C. Ripamonti

On behalf of ZOOM Investigators

Ripamonti C, et al. ASCO 2012 (Abstract 9005)

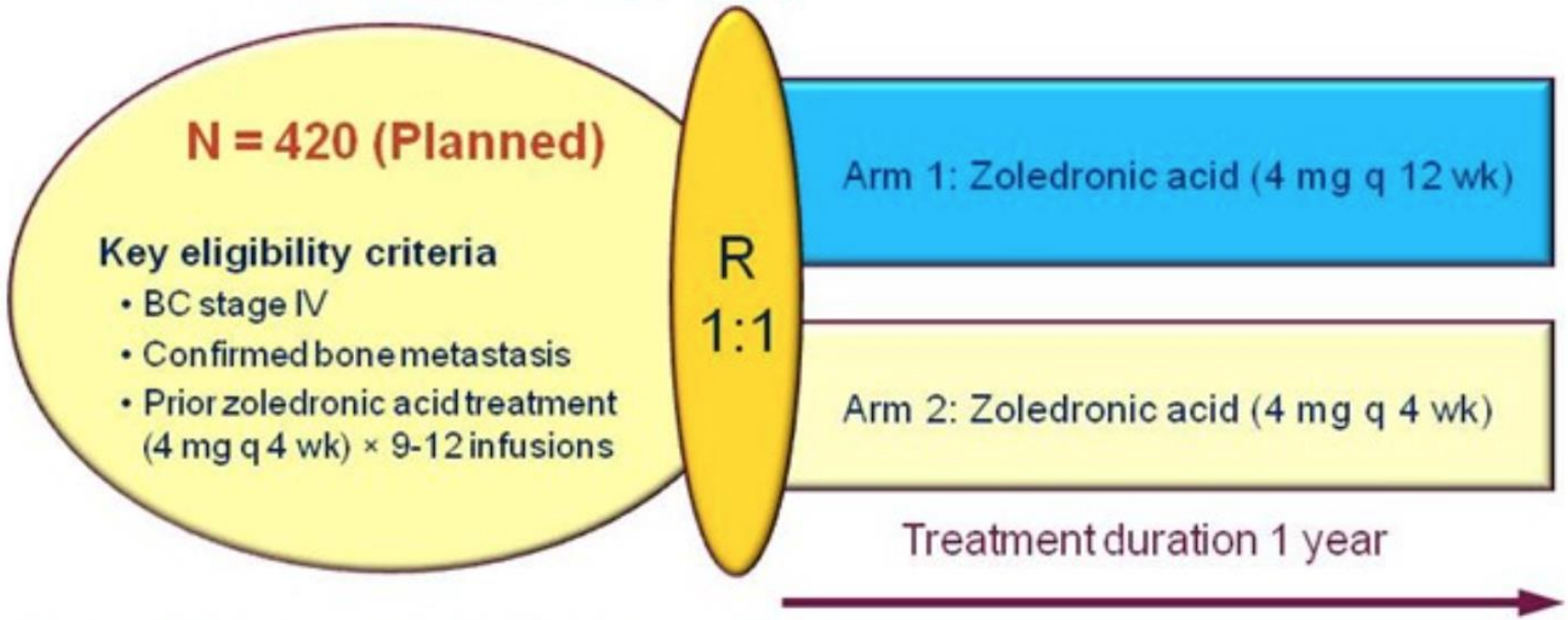
ASCO Annual '12 Meeting

ZOOM Study Design

Endpoints:

Primary: Skeletal morbidity rate (SMR)

Secondary: Proportion of patients experiencing SREs (overall and by event), time to first SRE, SMR by event, bone pain, use of analgesics, bone marker levels, safety



Accrual: February 2006 - February 2010

Abbreviations: q, every; R, randomization; SRE, skeletal-related event.

http://www.clinicaltrials.gov. Identifier NCT00375427.

Primary Efficacy Analysis—SMR

	ZOL q 12 wk (Arm 1)	ZOL q 4 wk (Arm 2)
N (ITT population)	209	216
Mean SMR (95% CI)	0.26 (0.15, 0.37)	0.22 (0.14, 0.29)
95% CI	-0.09 to 0.17	

The upper limit of the CI (0.17) was less than the recalculated non-inferiority margin of 0.19. This result indicates that the efficacy of the q 12 wk arm was not inferior to the q 4 wk arm.

*95% CI of LS mean difference was –0.09, +0.17.

Abbreviations: CI, confidence interval; ITT, intent to treat; LS, least squares; q, every; SMR, skeletal morbidity rate; ZOL, zoledronic acid.

ZOOM: Summary

- ZOOM is the first trial to compare quarterly vs monthly ZOL in BC patients after ~1 y of standard ZOL therapy
- Primary endpoint of SMR was met: q 12 wk ZOL was non-inferior to q 4 wk ZOL
- Safety profiles of the 2 treatment schedules were similar
  - No meaningful differences in renal AEs or ONJ event rates
- Exploratory analyses of median NTX levels showed an increase from baseline in the q 12 wk arm, but almost no change in the q 4 wk arm

Abbreviations: AE, adverse event; BC, breast cancer; NTX, N-telopeptide of type I collagen; ONJ, osteonecrosis of the jaw; q, every; SMR, skeletal morbidity rate; ZOL, zoledronic acid

Management Summary

- Patients with bone metastases from breast cancer should be offered therapy with a bone modifying agent in the absence of contraindications
- BMA should be used as an adjunct to systemic therapy for the underlying malignancy
- Appropriate bone modifying agents include subcutaneous denosumab, IV pamidronate, and IV zoledronic acid
- For patients receiving a bisphosphonate, creatinine clearance must be monitored and dose adjustments should be made as necessary
- The use of calcium and vitamin D supplements should be explored in patients receiving bone modifying agents particularly with denosumab use
- Routine dental care should be performed prior to initiation of a bone modifying agent
- Continuation of the bone modifying agent for up to 2 years is certainly acceptable though the optimal duration of therapy remains unclear

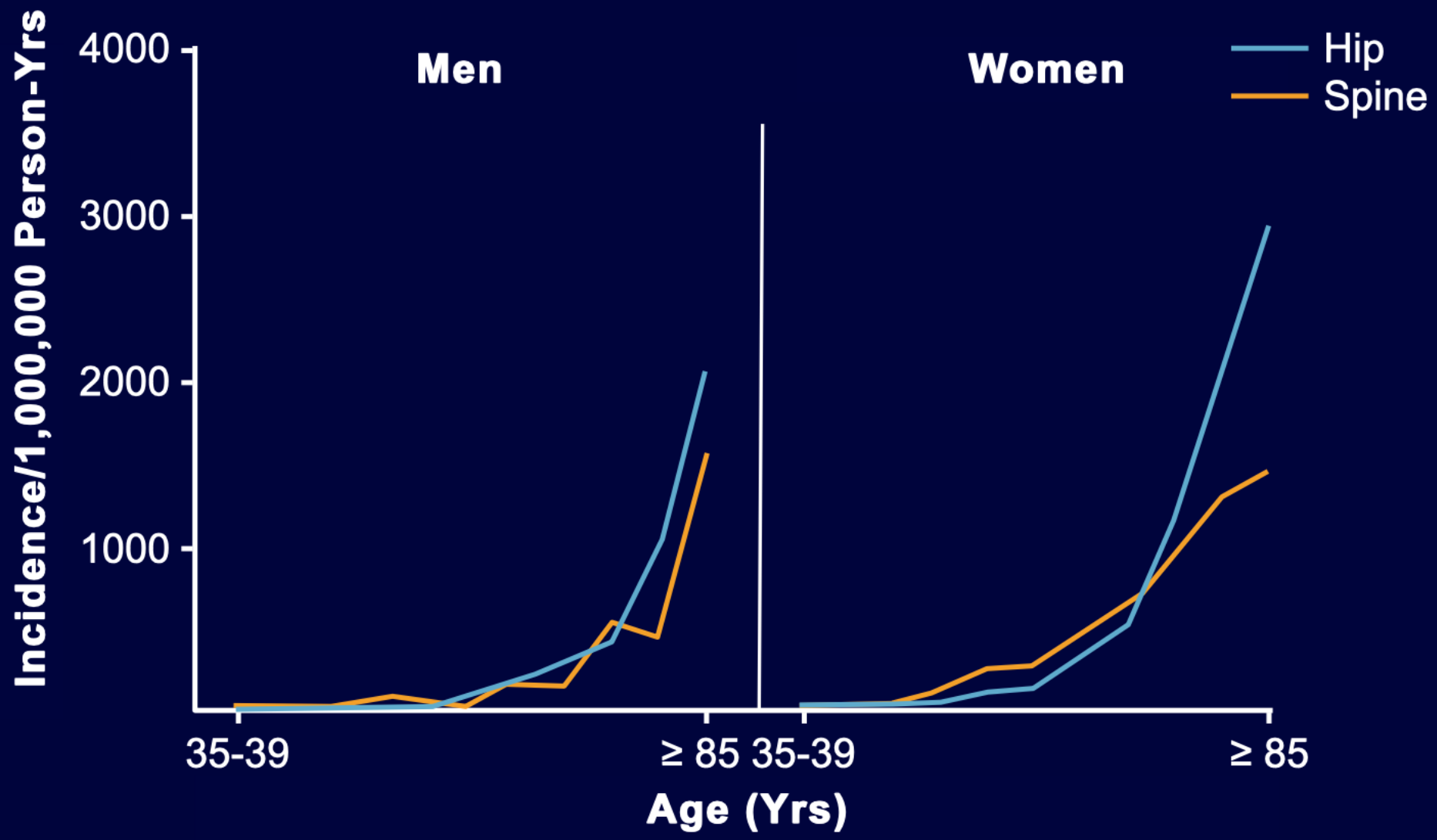
Conclusions

- Bisphosphonates and denosumab are both effective at
  - Preventing SREs and HCM
  - Palliating pain from bone mets
  - Preventing the development of pain
- 2 distinct choices
  - Different toxicity profiles
    - Zoledronic acid: flulike symptoms, fevers, bone pains, renal toxicity
    - Denosumab: hypocalcemia
  - Subcutaneous vs intravenous administration

Prostate cancer

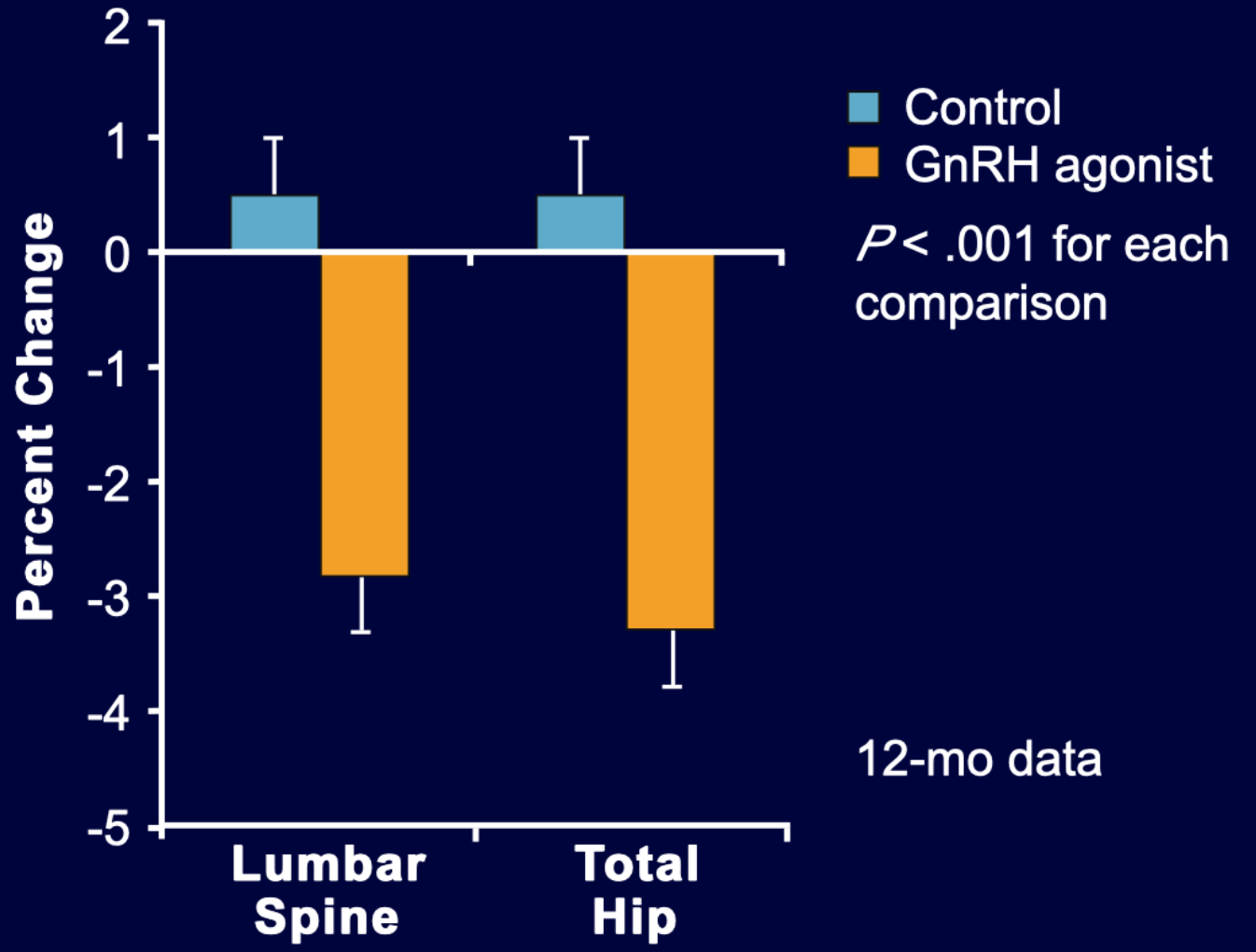
- Fracture Prevention in Early-stage Prostate Cancer
- Treatment of Bone Metastasis Secondary to Castration-Resistant Prostate Cancer
- Treatment of Bone Metastasis Secondary to Hormone-Sensitive Prostate Cancer

Fracture Risk by Sex and Age



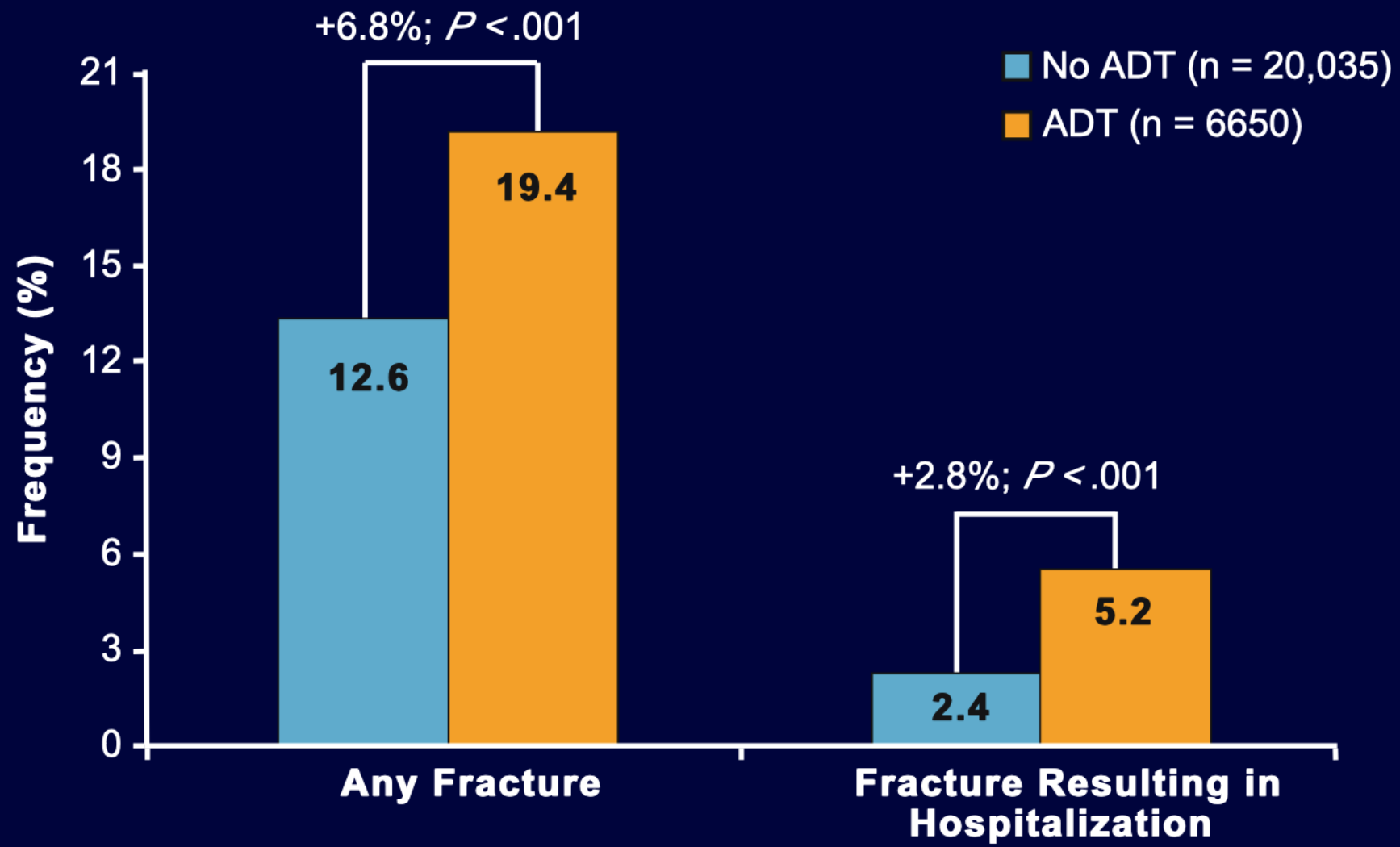
Melton LJ 3rd, et al. J Bone Miner Res. 1992;7:1005-1010.

GnRH Agonists Decrease BMD in Men With Prostate Cancer



Mittan D, et al. J Clin Endocrinol Metab. 2002;87:3656-3661.

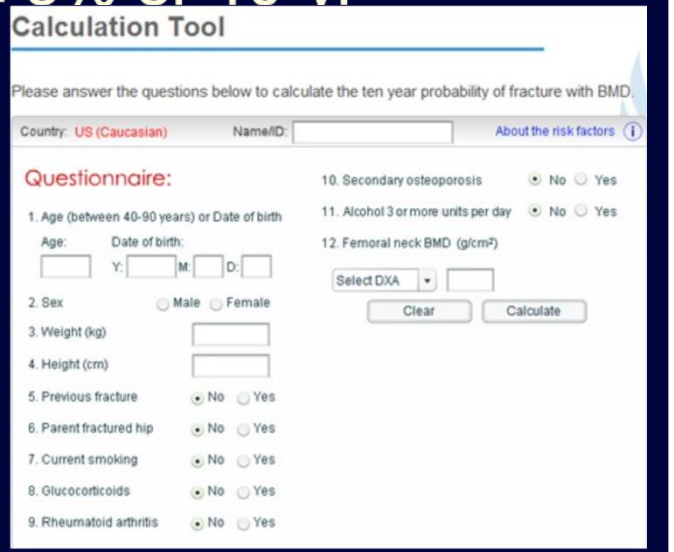
Proportion of Patients With Fractures 1-5 Yrs After Cancer Diagnosis



Shahinian VB, et al. N Engl J Med. 2005;352:154-164.

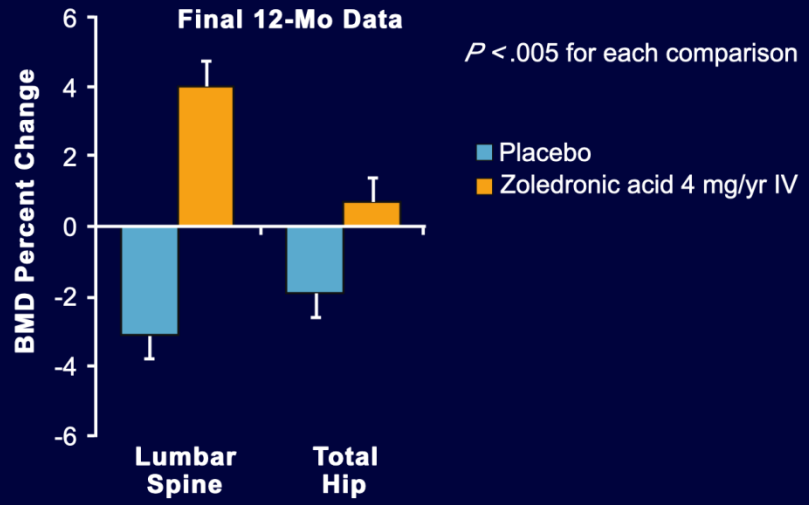
National Osteoporosis Foundation Fracture Prevention Guidelines for Men

- Consider FDA-approved medical therapies based on the following
  - A vertebral or hip fracture
  - Femoral neck or spine T-score ≤ -2.5
  - FRAX 10-yr probability of a hip fracture ≥ 3% or 10-yr probability of any major fracture ≥ 20%



National Osteoporosis Foundation Clinician's Guide to Prevention and Treatment of Osteoporosis. 2010.

Annual Zoledronic Acid Increases BMD During GnRH Agonist Therapy



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

Denosumab Fracture Prevention Study

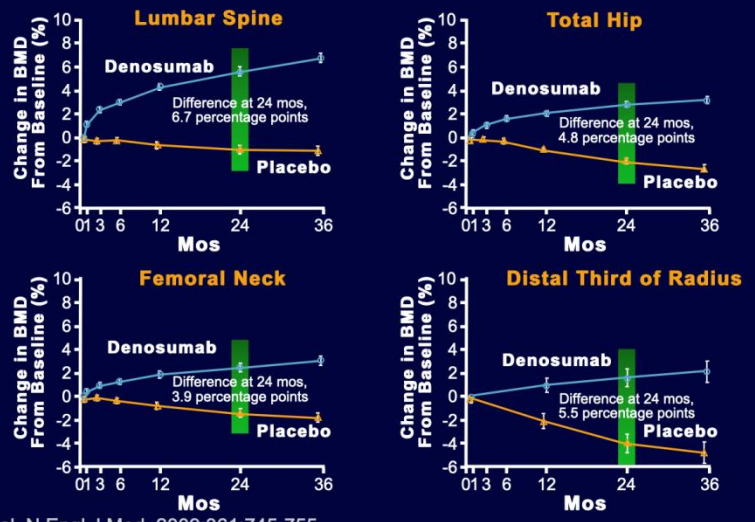
Current androgen deprivation therapy for prostate cancer patients older than 70 yrs of age or with T score < -1.0 (N = 1468)

- **Denosumab** q6m for 3 yrs
- **Placebo** q6m for 3 yrs

- Primary endpoints: bone mineral density, new vertebral fractures

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

Denosumab Increased BMD at All Skeletal Sites



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

Zoledronic Acid in Castration-Resistant Prostate Cancer

Eligibility Criteria

- Patients with prostate cancer
- Castration resistant
- Bone metastases

(N = 643)

RANDOMIZED

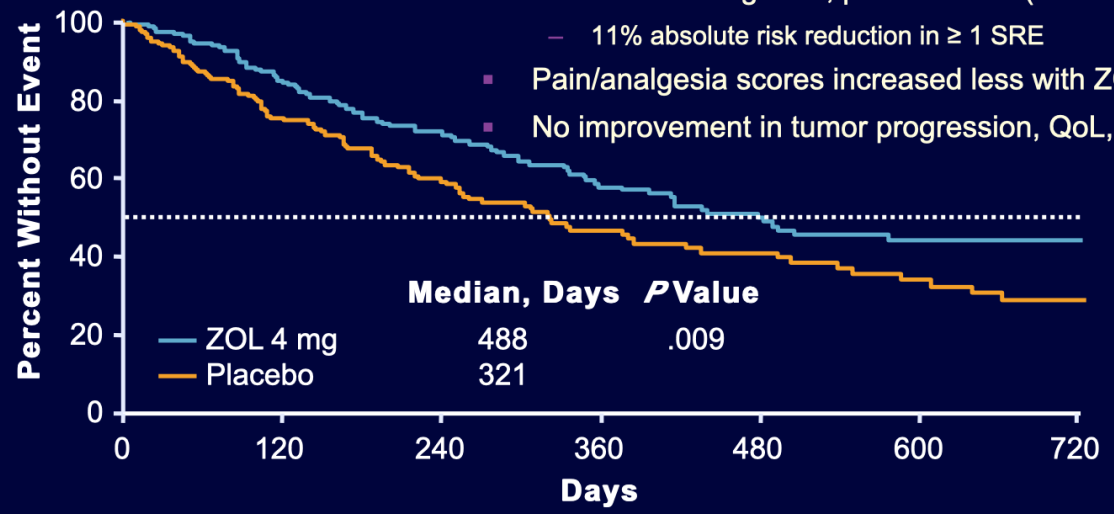
- **Zoledronic acid** 4 mg q3w (n = 214)
- **Zoledronic acid** 4 mg q3w (initially 8 mg) (n = 221)
- **Placebo** q3w (n = 208)

- Patients in 8-mg arm reduced to 4 mg because of renal toxicity
- Primary outcome: proportion of patients having ≥ 1 SRE
- Secondary outcomes: time to first on-study SRE, proportion of patients with SREs, and time to disease progression

Saad F, et al. J Natl Cancer Inst. 2002;94:1458-1468.

Time to First SRE: Zoledronic Acid vs Placebo

- SREs: ZOL 4 mg 38%; placebo 49% (*P* = .028)
  - 11% absolute risk reduction in ≥ 1 SRE
- Pain/analgesia scores increased less with ZOL
- No improvement in tumor progression, QoL, OS

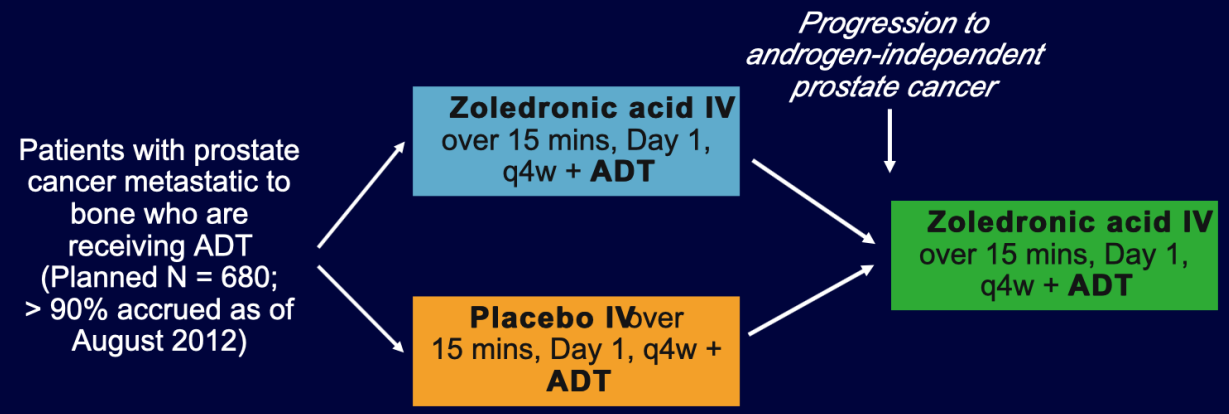


ZOL 4 mg	214	149	97	70	47	35	3
Placebo	208	128	78	44	32	20	3

Saad F, et al. J Natl Cancer Inst. 2002;94:1458-1468. Saad F, et al. ASCO 2003. Abstract 1523. Saad F, et al. J Natl Cancer Inst. 2004;96:879-882.

Biphosphonate in HSPC is not recommended

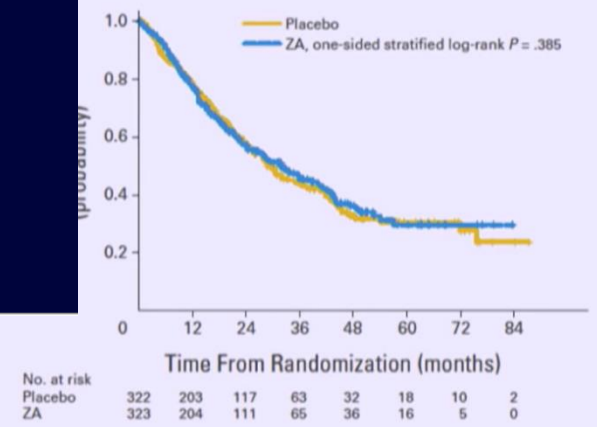
CALGB 90202: Zoledronic Acid in Hormone-Sensitive PC With Bone Mets



- Currently, there is no proven role for zoledronic acid in this setting
- Primary endpoint: time to first SRE
- Secondary endpoints: OS, PFS, toxicity

ClinicalTrials.gov. NCT00079001.

ALGB (Alliance) Cooperative Group Study 90202



- Routine use of bone modifying agent in hormone-sensitive setting not indicated (in absence of osteoporosis)
- Possible exceptions
  - Lytic predominant metastases
  - Impending fracture (cortical thinning)

Smith MR, et al J Clin Oncol 2014

Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study

- 1904 men with metastatic CRPC were randomized to receive denosumab (human monoclonal antibody against RANKL) or zolendronic acid
- The primary endpoint was time to first on-study SRE (pathological fracture, radiation therapy, surgery to bone, or spinal cord compression), and was assessed for non-inferiority
- The same outcome was further assessed for superiority as a secondary endpoint

Fizazi K, et al. Lancet. 2011
377:813-22

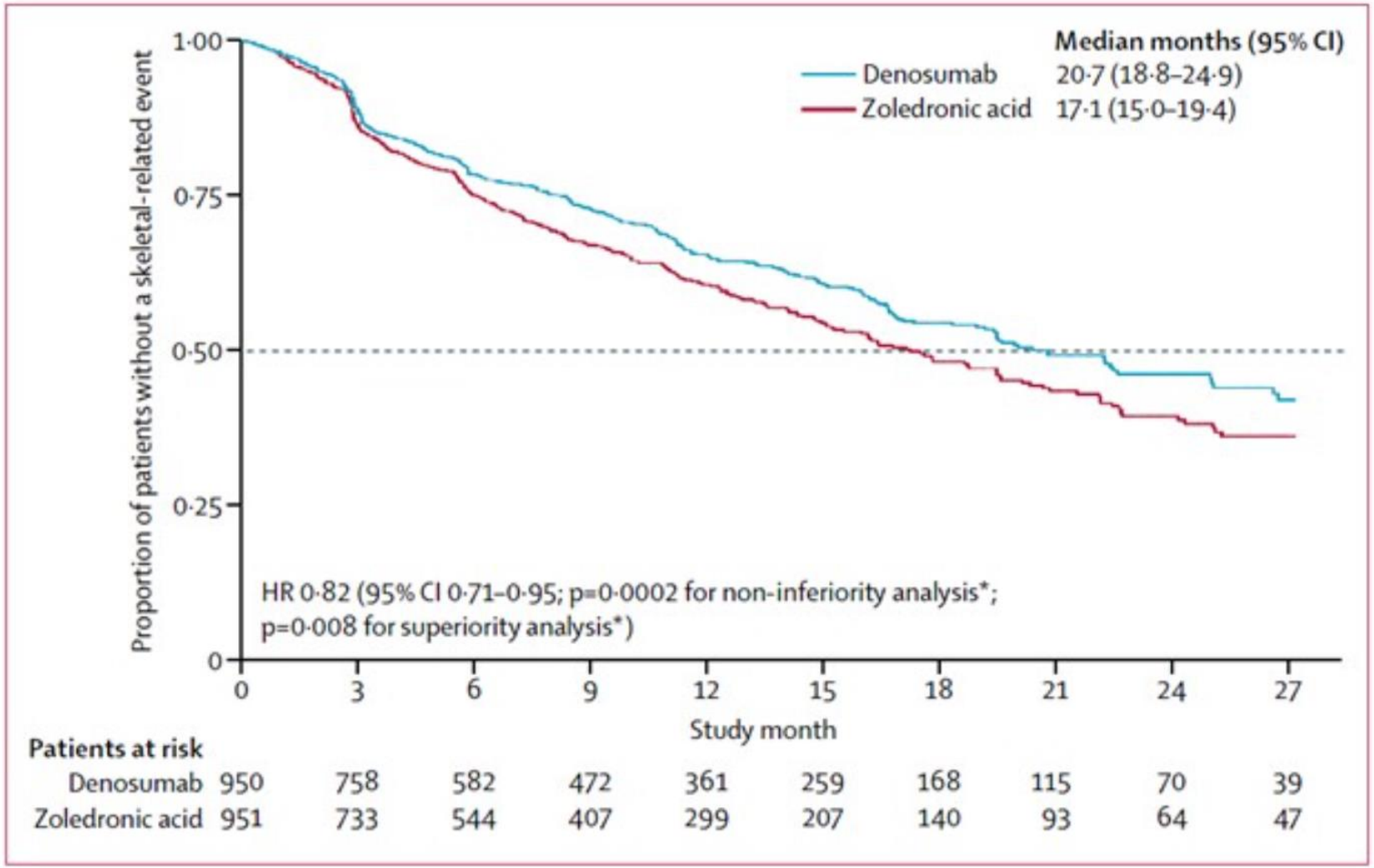
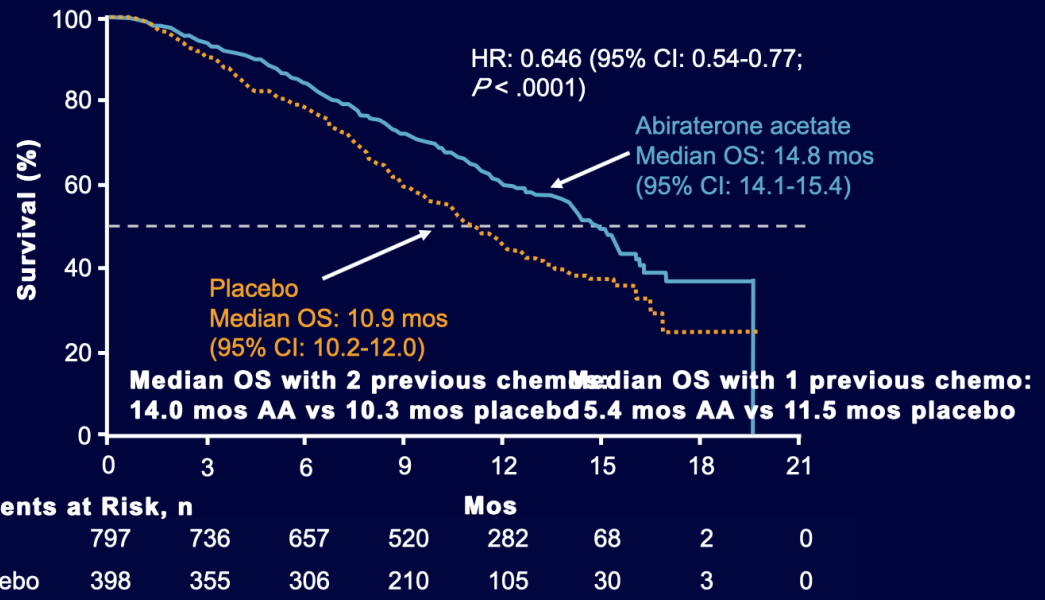


Figure 2: **Kaplan-Meier estimates of time to first on-study skeletal-related event**
Patients were assessed from baseline to the primary analysis cutoff date. HR=hazard ratio. *p values were adjusted for multiplicity.

Fizazi K, et al. Lancet.
2011 377:813-22

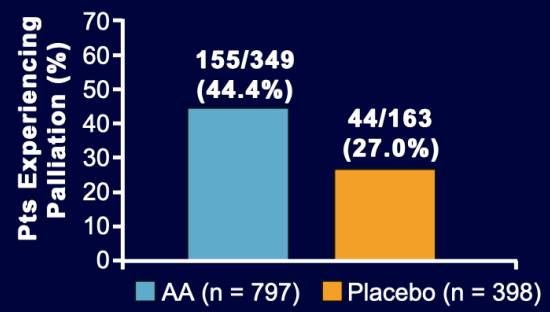
COU-AA-301: Abiraterone Acetate Improves OS in Metastatic CRPC

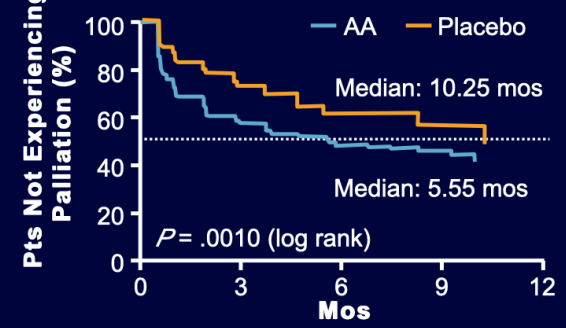


de Bono J, et al. N Engl J Med. 2011;364:1995-2005.

COU-AA-301: Effect of Abiraterone Acetate on Pain Palliation and SREs

- Nearly one half of COU-AA-301 patients report significant pain at baseline



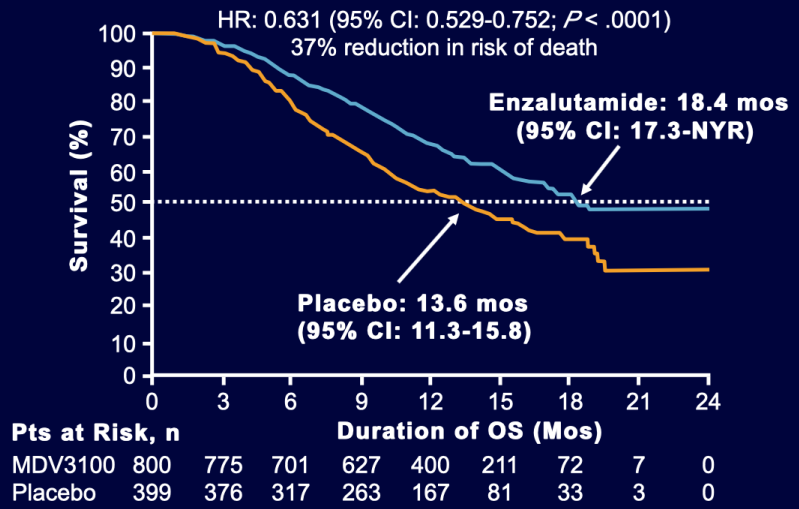


Efficacy Measure	Abiraterone (n = 797)	Placebo (n = 398)	*P* Value
Median OS, mos	14.8	10.9	< .0001
Median radiographic PFS, mos	5.6	3.6	< .0001
Time to first SRE* (25th percentile), days	301	150	< .0001

Logothetis C, et al. ASCO 2011. Abstract 4520.

Phase III AFFIRM Trial of Enzalutamide (MDV3100) in Post-Docetaxel CRPC: OS

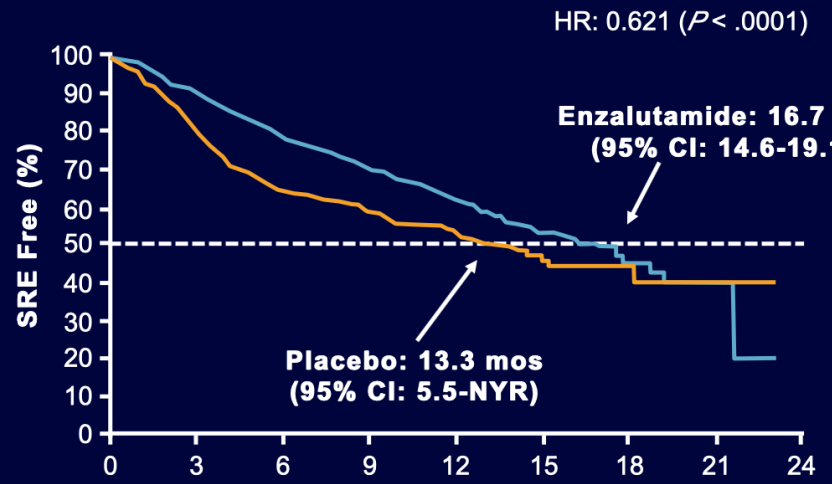
- OS improved with enzalutamide vs placebo
- Median follow-up: 14.4 mos



Pts at Risk, n									
MDV3100	800	775	701	627	400	211	72	7	0
Placebo	399	376	317	263	167	81	33	3	0

Scher HI, et al. ASCO GU 2012. Abstract LBA1.

AFFIRM Trial of Enzalutamide in Post-Docetaxel CRPC: Time to First SRE



Pts at Risk, n									
Enzalutamide	800	676	548	379	209	87	19	2	0
Placebo	399	278	196	128	68	33	11	0	0

De Bono JS, et al. ASCO 2012. Abstract 4519^.

Treatment	Indication	Typical administration
Treatment of bone metastases and myeloma bone disease		
Denosumab[a,b]	All solid tumours	120 mg s.c. every 4 weeks
Zoledronate[a,b]	All solid tumours and MM	4 mg i.v. every 3–4 weeks
Pamidronate[a,b]	Breast cancer and MM	90 mg i.v. every 3–4 weeks
Clodronate[a]	Osteolytic lesions	1600 mg p.o./day
Ibandronate[a]	Breast cancer	50 mg p.o./day 6 mg i.v./month

a EMA-approved.
b FDA-approved.
ESMO Clinical Practice Guidelines

Prevention of treatment induced bone loss		
Denosumab[a,b]	Prostate cancer on ADT	60 mg s.c. 6-monthly
Denosumab[b]	Breast cancer	60 mg s.c. 6-monthly
Zoledronate	Breast cancer[c] Prostate cancer on ADT[c]	4 mg i.v. 6-monthly 5 mg i.v. 12-monthly
Alendronate	Breast cancer[c] Prostate cancer on ADT[c]	70 mg p.o./week
Risedronate	Breast cancer[c] Prostate cancer on ADT[c]	35 mg p.o./week
Ibandronate	Breast cancer[c] Prostate cancer on ADT[c]	150 mg p.o./month

a EMA-approved.
b FDA-approved.
c Not approved by regulatory agencies but recommended by international guidelines
ESMO Clinical Practice Guidelines