NOVEDADES EN EL MANEJO SISTÉMICO DE METÁSTASIS ÓSEAS

II SIMPOSIO INTERNACIONAL DE RADIOCIRUGÍA ESTEREOTÁCTICA

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MANEJO SISTÉMICO DE METÁSTASIS ÓSEAS

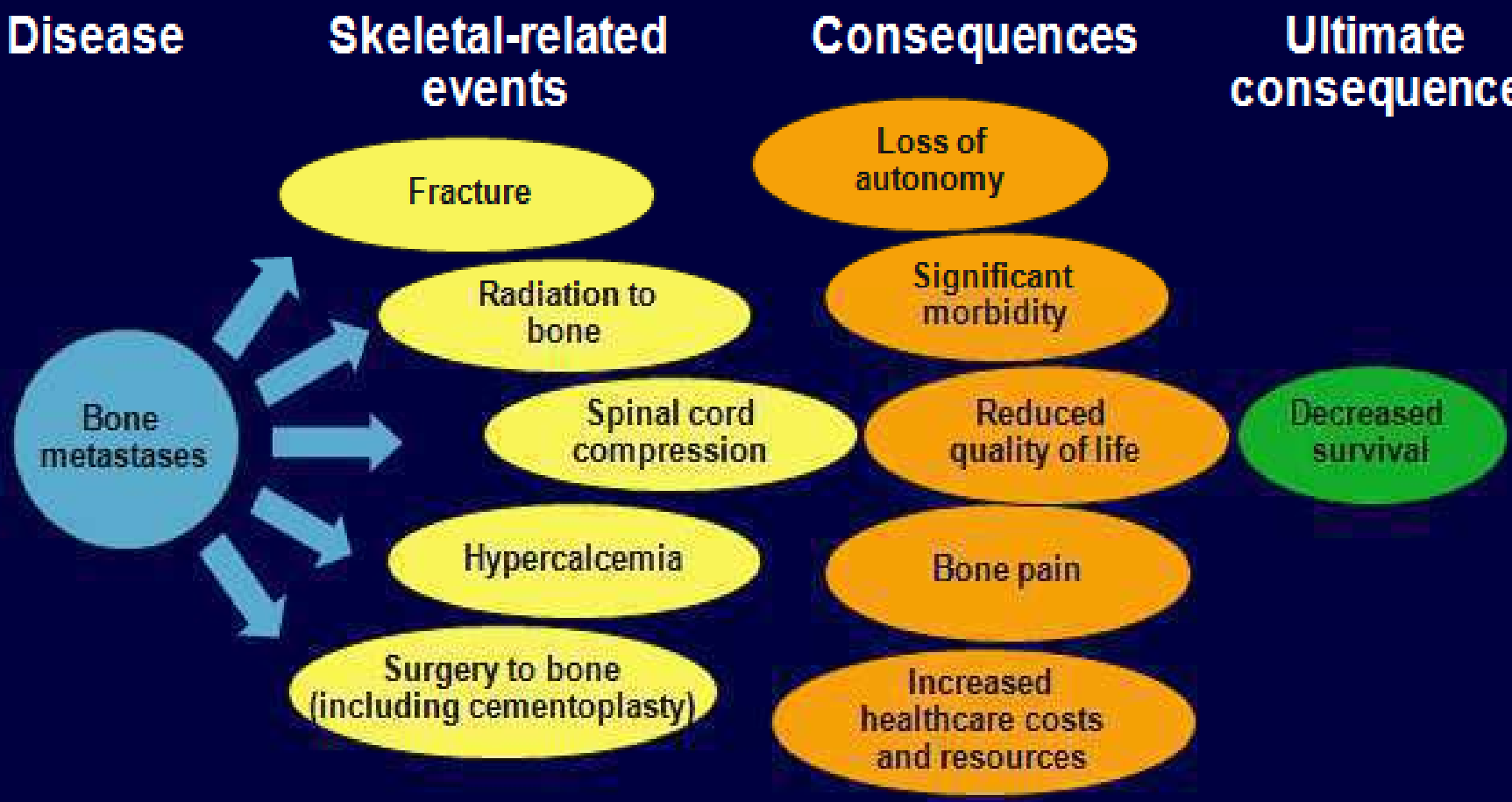
- Generalidades
- Carcinoma de Mama:
  - Prevención
  - Adyuvancia
  - Tratamiento
- Carcinoma de Pulmón
- Carcinoma de Próstata
- Mieloma Múltiple
- Conclusiones

Bone Metastases Epidemiology: Scope of the Problem

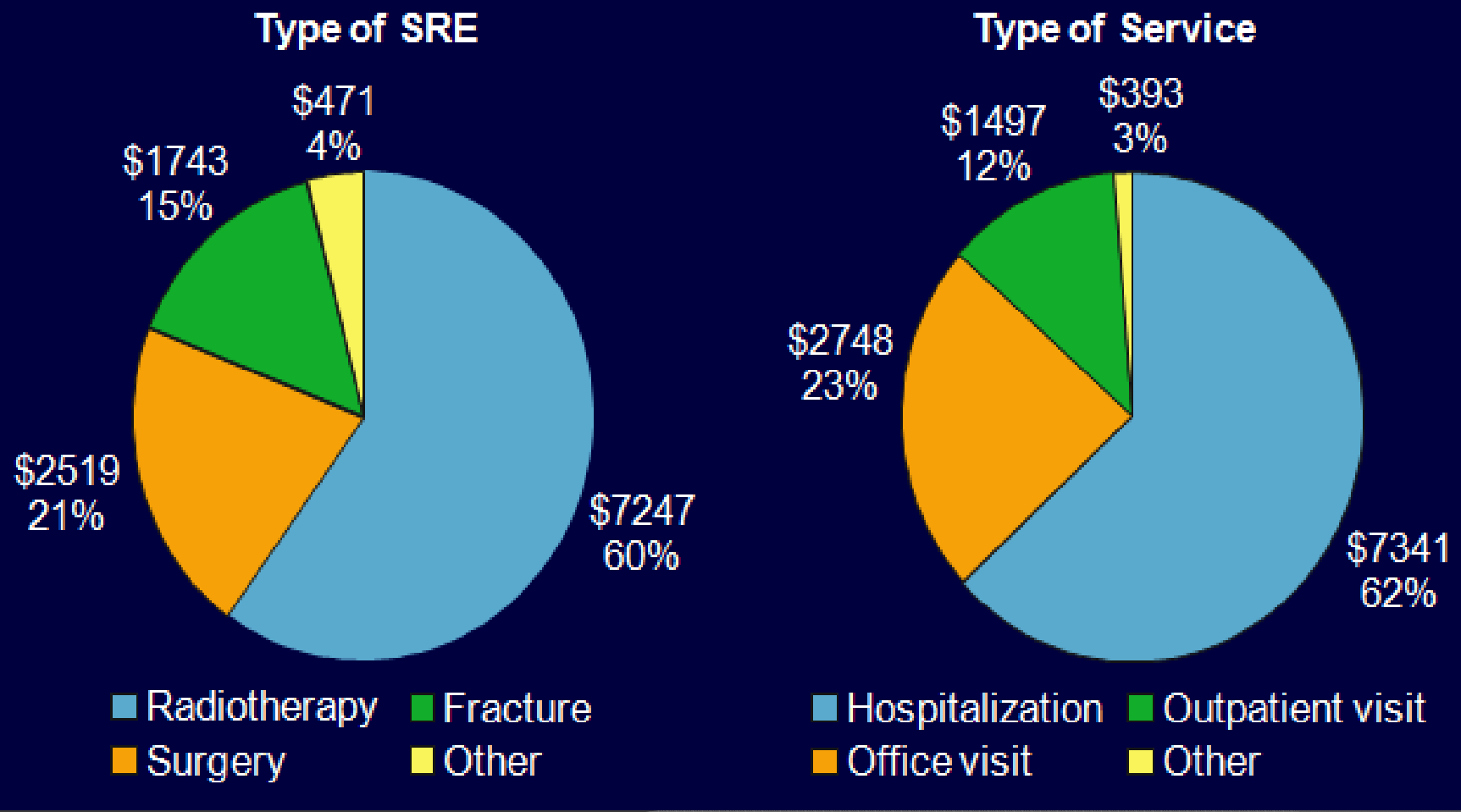
- Affects > 400,000 individuals in the US each yr[1]
  - Greater than any other site of tumor metastasis

	Incidence of Bone Metastases in Patients With Advanced Disease, %	Median Survival of Patients With Bone Metastases, Mos
Myeloma	70-95[2]	37-58[3]
Lung	30-40[2]	8-10[4]
Breast	65-75[2]	19-25[5]
Prostate	65-75[2]	30-35[6]

Bone Metastases Have Debilitating Consequences



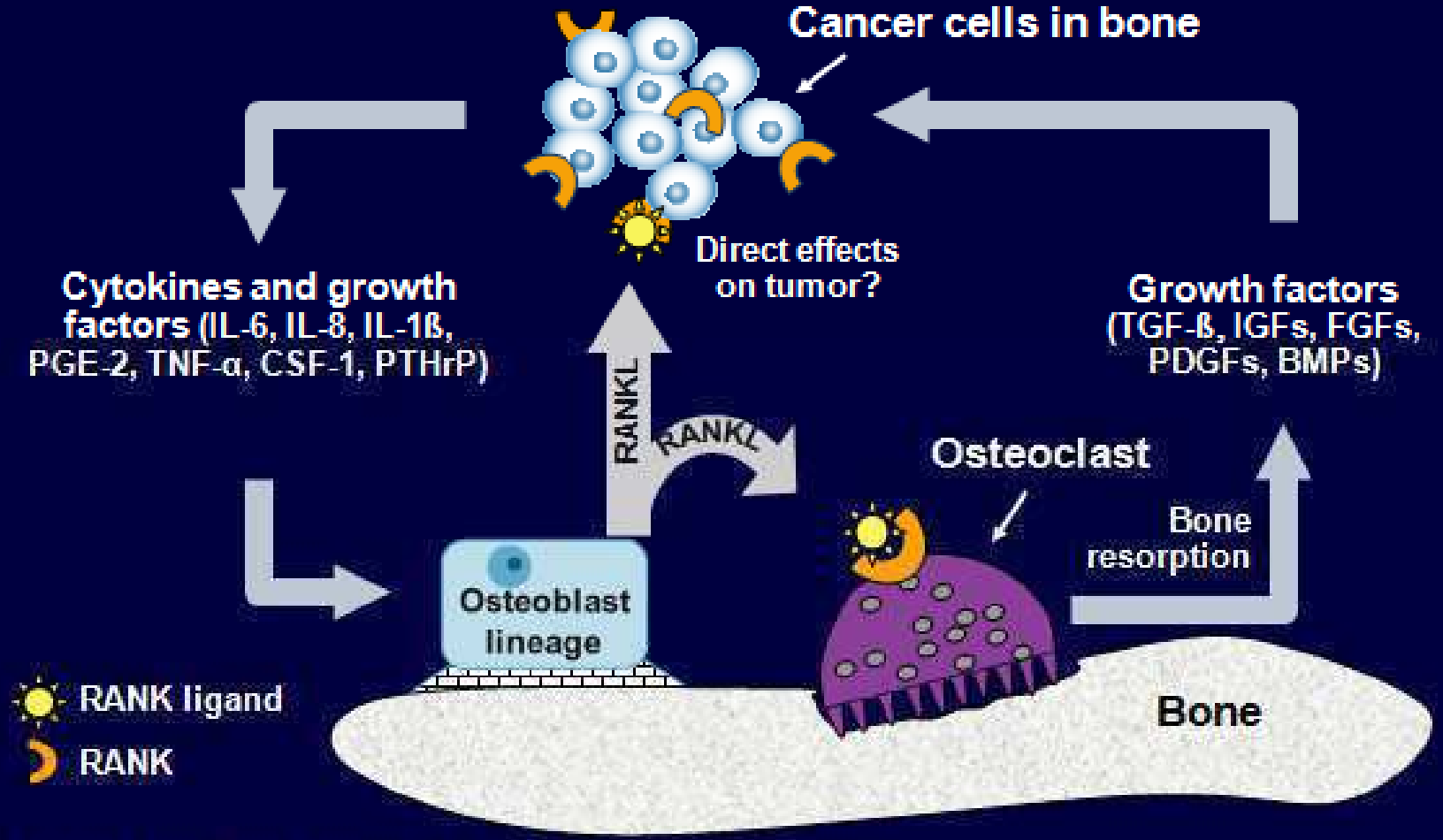
Estimated Costs of Skeletal Complications in Patients With Lung Cancer



Primary Treatment Options for Bone Metastases

- Bone-modifying agents
  - Bisphosphonates
  - RANK ligand–blocking monoclonal antibody
- Radiation therapy
  - External beam
  - Radiopharmaceuticals
- Surgery
  - Prevent /repair structural damage, spinal cord compression

RANK Ligand Is a Key Mediator in the "Vicious Cycle" of Bone Destruction



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

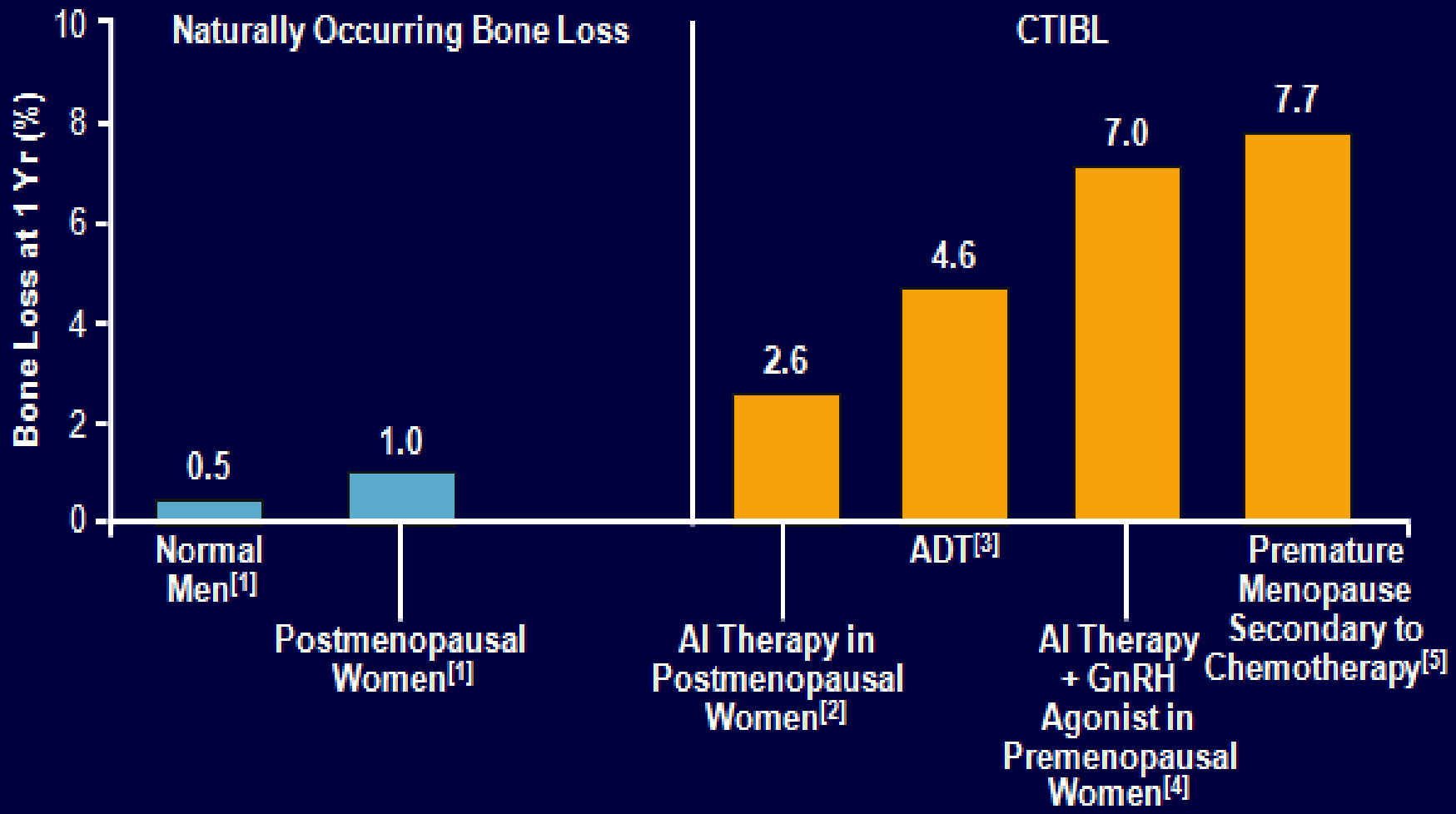
Carcinoma de Mama

Prevención de Osteoporosis

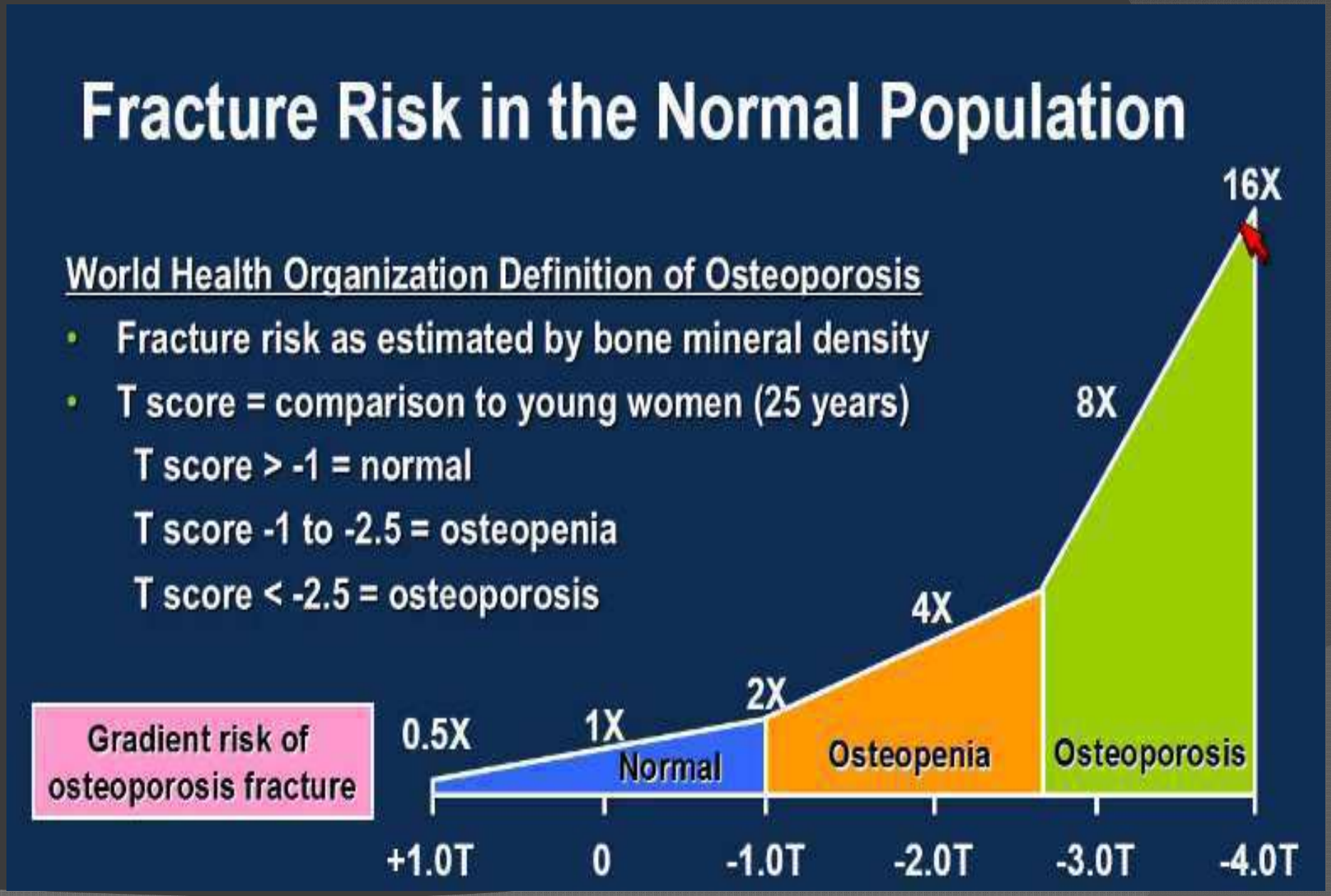
The Natural History of Bone Metastases in Breast Cancer

- 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

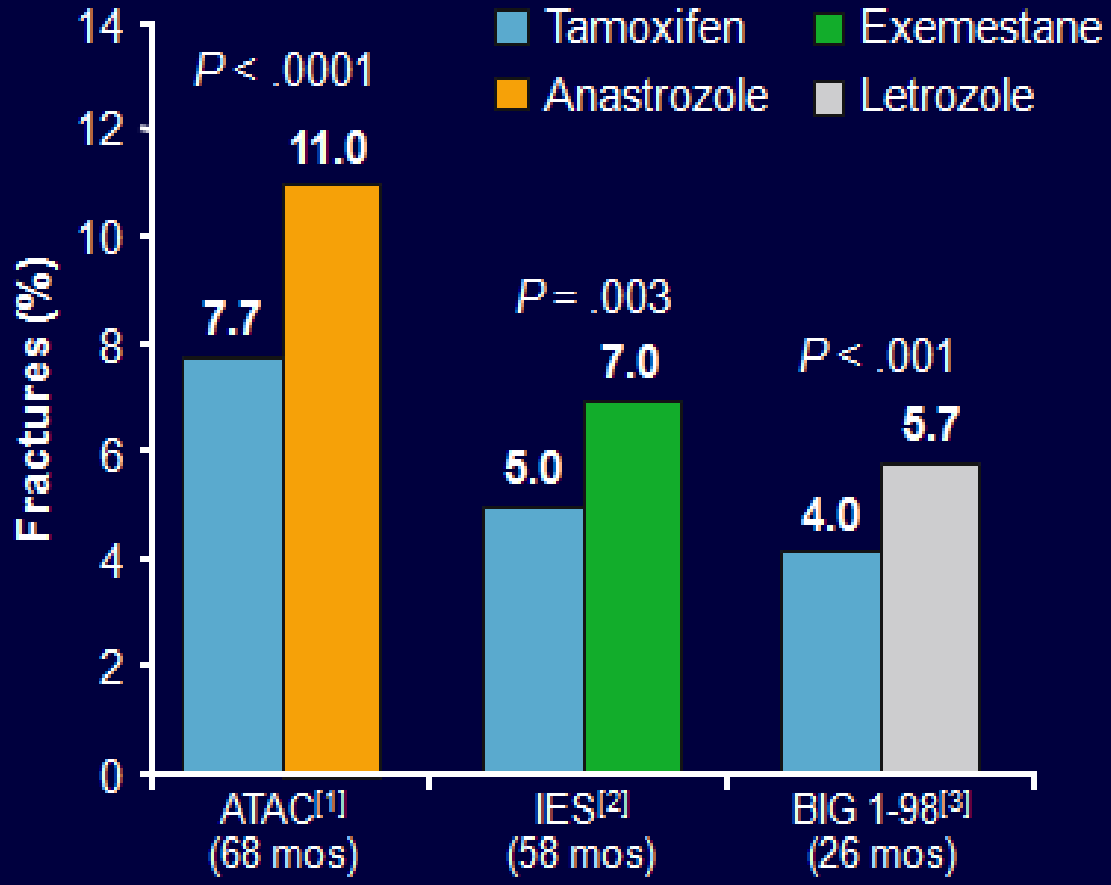
Rates of Bone Loss



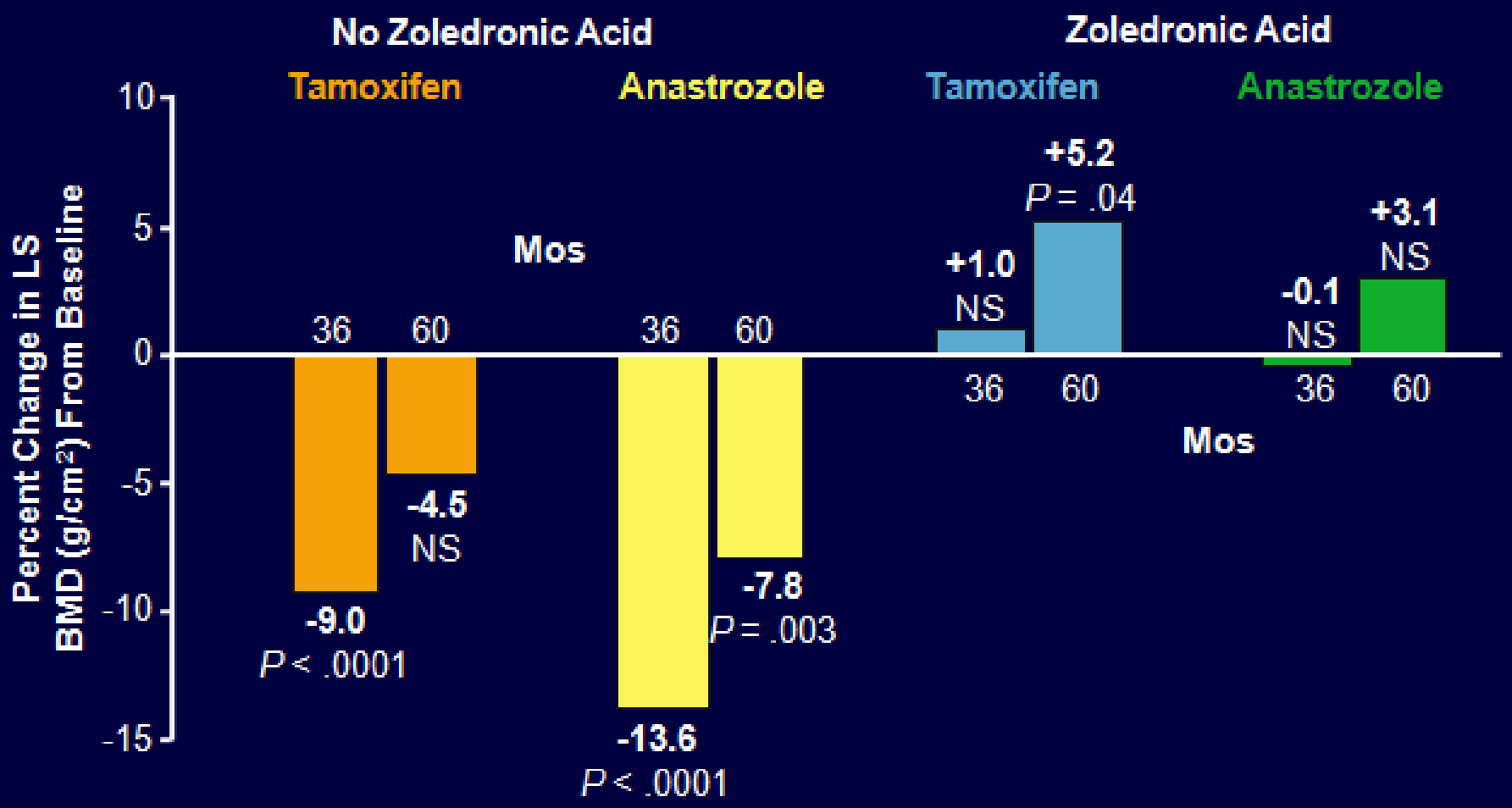
Fracture Risk in the Normal Population



Steroidal and Nonsteroidal AIs Increase Fracture Risk Compared With Tamoxifen

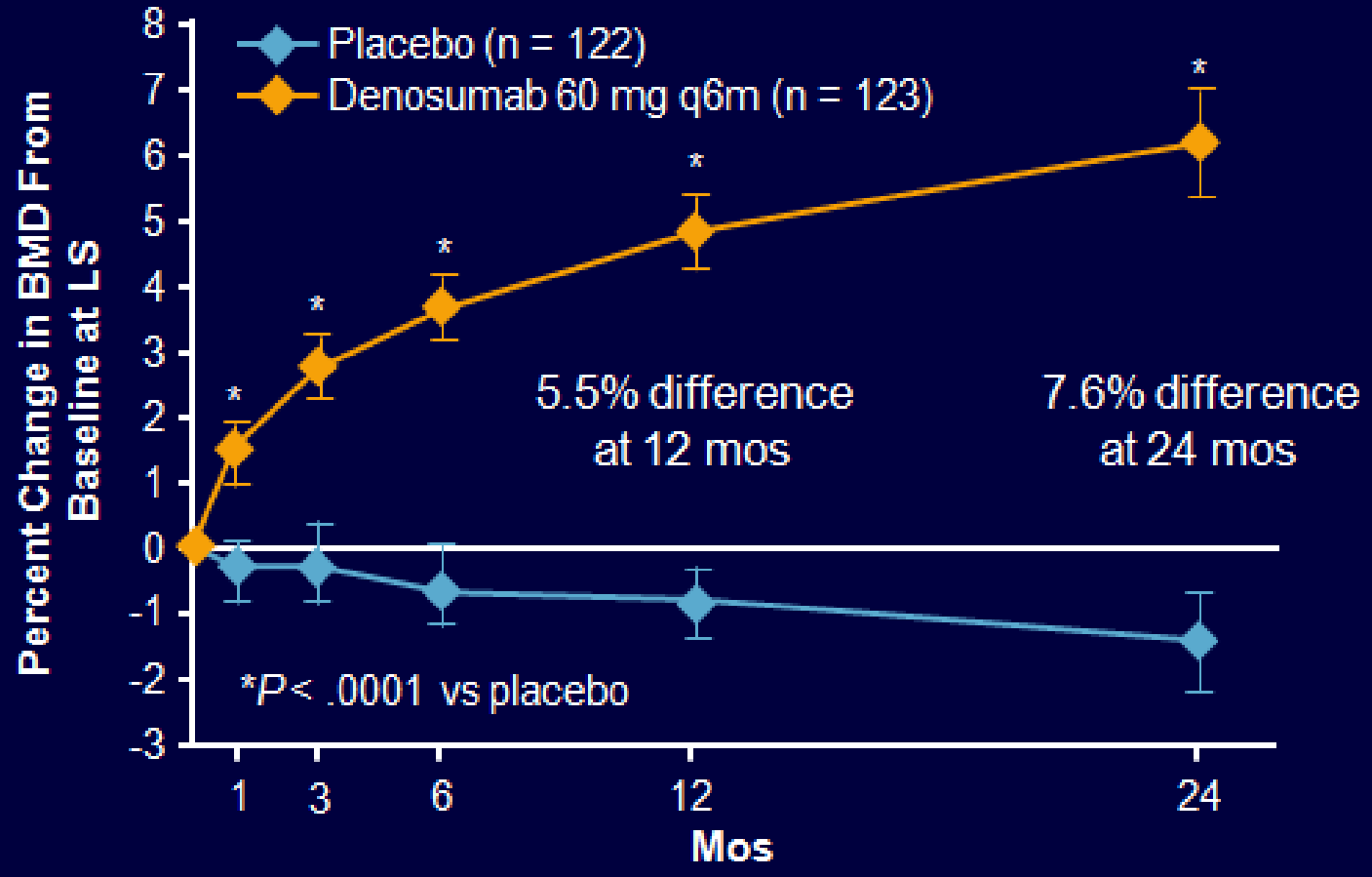


ABCSG-12 Bone Substudy: Change in BMD at Yrs 3 and 5



Gnant M, et al. Lancet Oncol. 2008;9:840-849.

Denosumab in Patients With Breast Cancer Receiving Adjuvant AIs



Toxicity: no significant difference in AEs between denosumab and placebo arm

Ellis GK, et al. J Clin Oncol. 2008;26:4875-4882.

Bisphosphonates: Indications for the Prevention and Treatment of Osteoporosis

Agent	Dose	PM Women	Men	GIO
Zoledronic acid[1]	**P:** 5 mg IV every 2 yrs **T:** 5 mg/yr IV	P, T	T	P, T (annually for both)
Alendronate[2]	**P:** 5 mg/day PO or 35 mg/wk PO **T:** 10 mg/day PO or 70 mg/wk PO	P, T	T	T (5-10 mg/day)
Ibandronate[3]	**P, T:** 2.5 mg/day PO or 150 mg/mo PO **T:** 3 mg IV every 3 mos	P, T	Not approved	Not approved
Risedronate[4]	**P, T:** 5 mg/day PO, 35 mg/wk PO, 75 mg PO on 2 days/mo (consecutive), or 150 mg/mo PO	P, T	T (35 mg/wk)	P, T (5 mg/day)

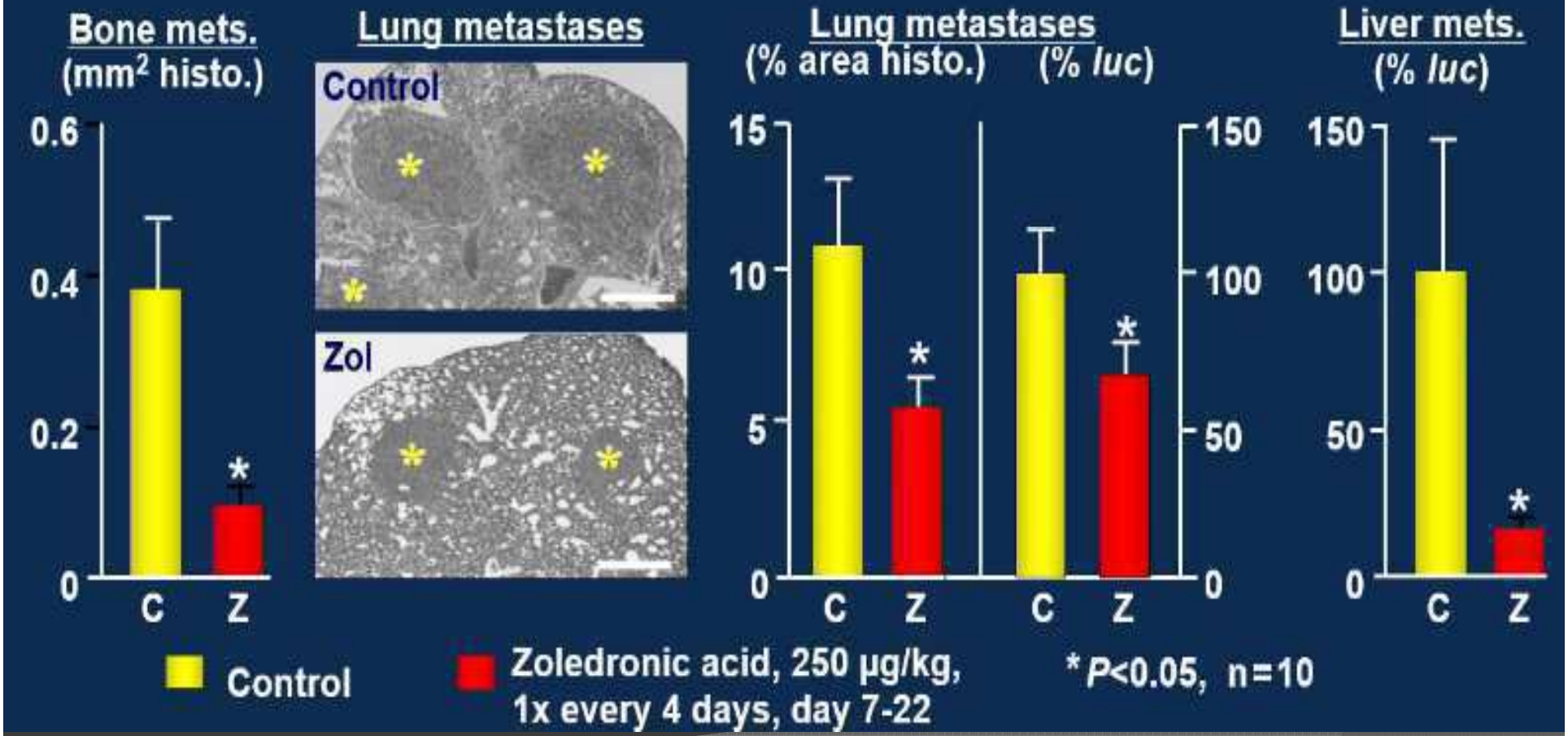
Denosumab Indications for Osteoporosis Treatment

- High-affinity human monoclonal antibody that binds RANK ligand
  - RANK ligand promotes maturation, activation, and survival of osteoclasts
- Inhibits formation and activation of osteoclasts
- SC administration (60 mg every 6 mos)
- Current FDA-approved osteoporosis-related indications
  - Treatment of osteoporosis in postmenopausal women[1,2]
  - Treatment to ↑ bone mass in men with osteoporosis[3]
  - Treatment to ↑ bone mass in women who are receiving adjuvant aromatase inhibitor treatment for breast cancer and who are at high risk for fracture[4]
  - Treatment to ↑ bone mass in men who are receiving ADT for nonmetastatic prostate cancer and who are at high risk for fracture[5]

Carcinoma de Mama

Tratamiento Adyuvante

Zoledronic Acid Reduces Bone, Liver and Lung Metastases in the Murine 4T1/luc Orthotopic Breast Cancer Model

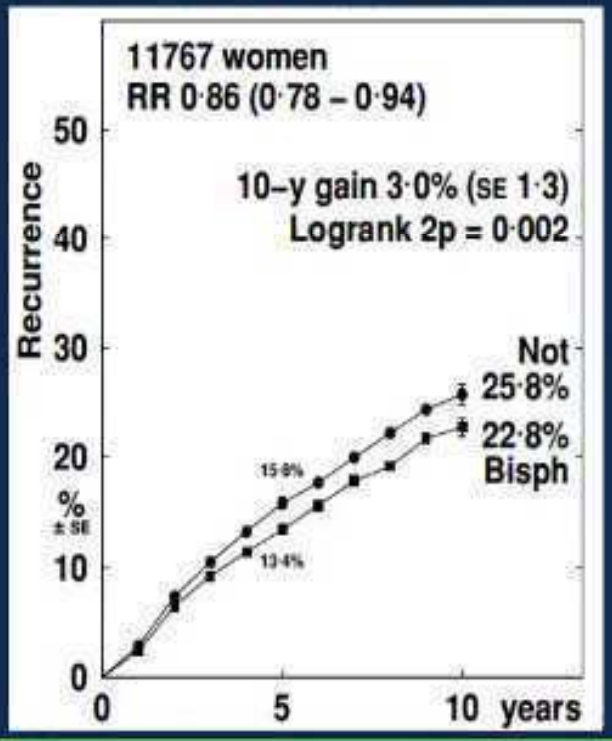


EBCTCG Meta-Analysis

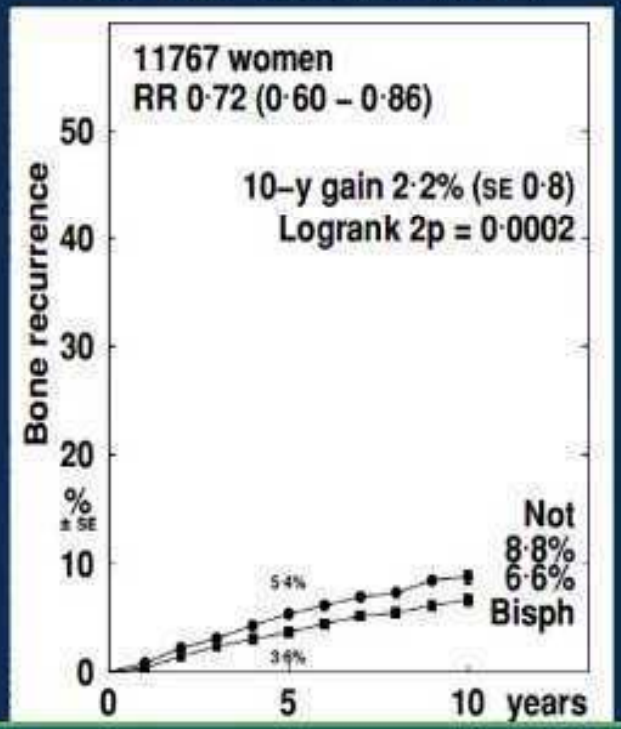
- 18,766 women treated with 2-5 years bisphosphonates
  - Median FU 5.6 woman years
  - Impact on breast cancer recurrence
    - Reduction in recurrence: HR 0.94 (2p=0.08), δ1.1%
    - Reduction in distant recurrence: HR 0.92 (·85–·99; 2p=0·03)
    - Breast cancer mortality: HR 0.91 (.83-.94, 2p=0.004), δ1.7%
  - Reduction in bone recurrence
    - HR 0.83 (0.73-0.94; 2p=0.004), δ1.1%
- Impact related to menopausal status
  - Improved outcome seen only in postmenopausal women

Adjuvant Bisphosphonates in Postmenopausal Women

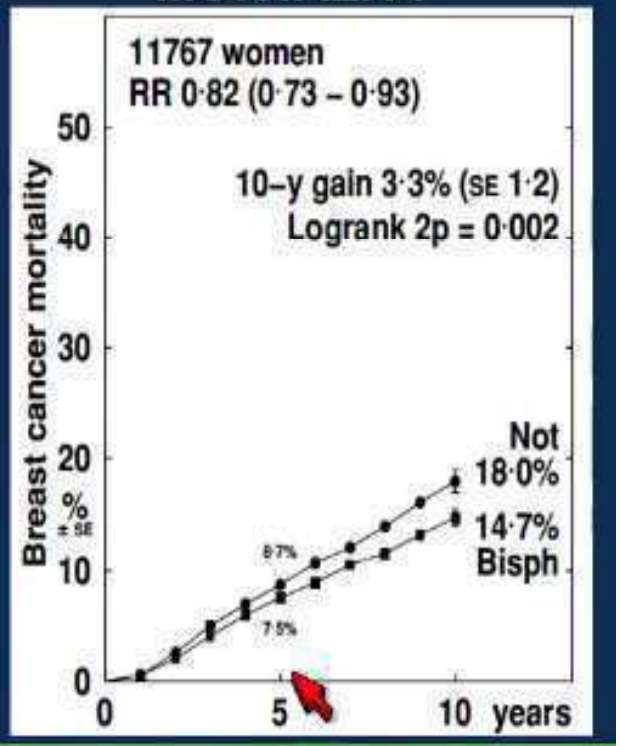
ALL RECURRENCE



BONE RECURRENCE

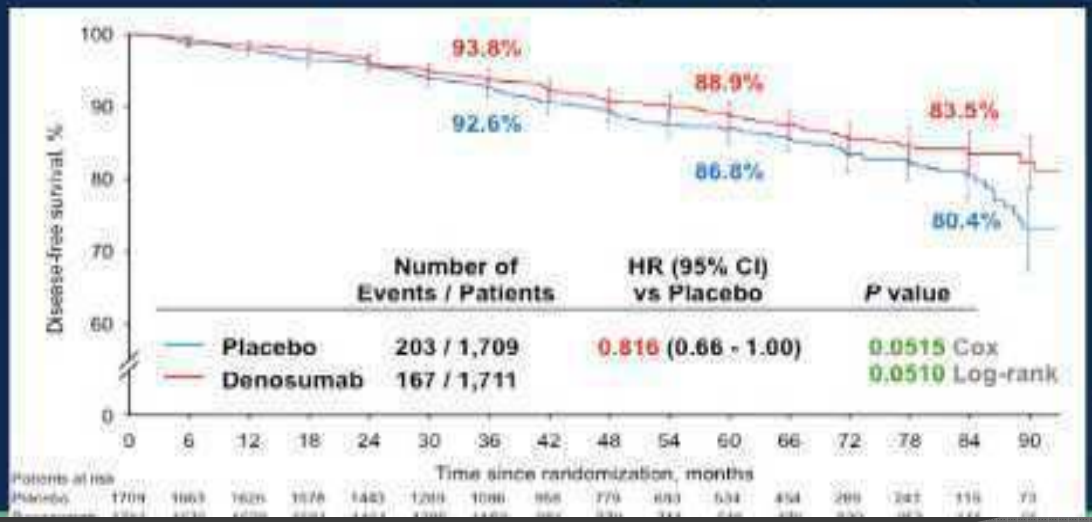


BREAST CANCER MORTALITY



ABCSG-18: Impact of Denosumab on DFS

- Secondary objective of ABCSG-18
  - 3425 PM women on AIs
  - Denosumab 60 mg q 6 mos vs placebo
  - After fracture results, DSMB recommended unblinding
    - 71% node negative, 19% G3, 72% T2, med age 64 (38-91)



- Final results expected in 2018
- D-CARE: denosumab vs placebo monthly x 6 doses then q 3 mo x 5 yrs
- Primary endpt: BMFS
- N=4500

Cancer Care Ontario and ASCO Clinical Practice Guideline: Use of Adjuvant Bone Modifying Agents in Breast Cancer (Dhesy-Thind et al. JCO 2017)

- Expert panel to develop evidence based recommendations
- Adjuvant bisphosphonates reduce bone recurrence and improve survival in postmenopausal patients with ESBC.
- Absolute benefit > in patients at higher risk of recurrence
  - Most studies evaluated zoledronic acid or clodronate; data extremely limited for other bisphosphonates.
  - Denosumab reduces fractures, long-term survival data is still required

Recommendation

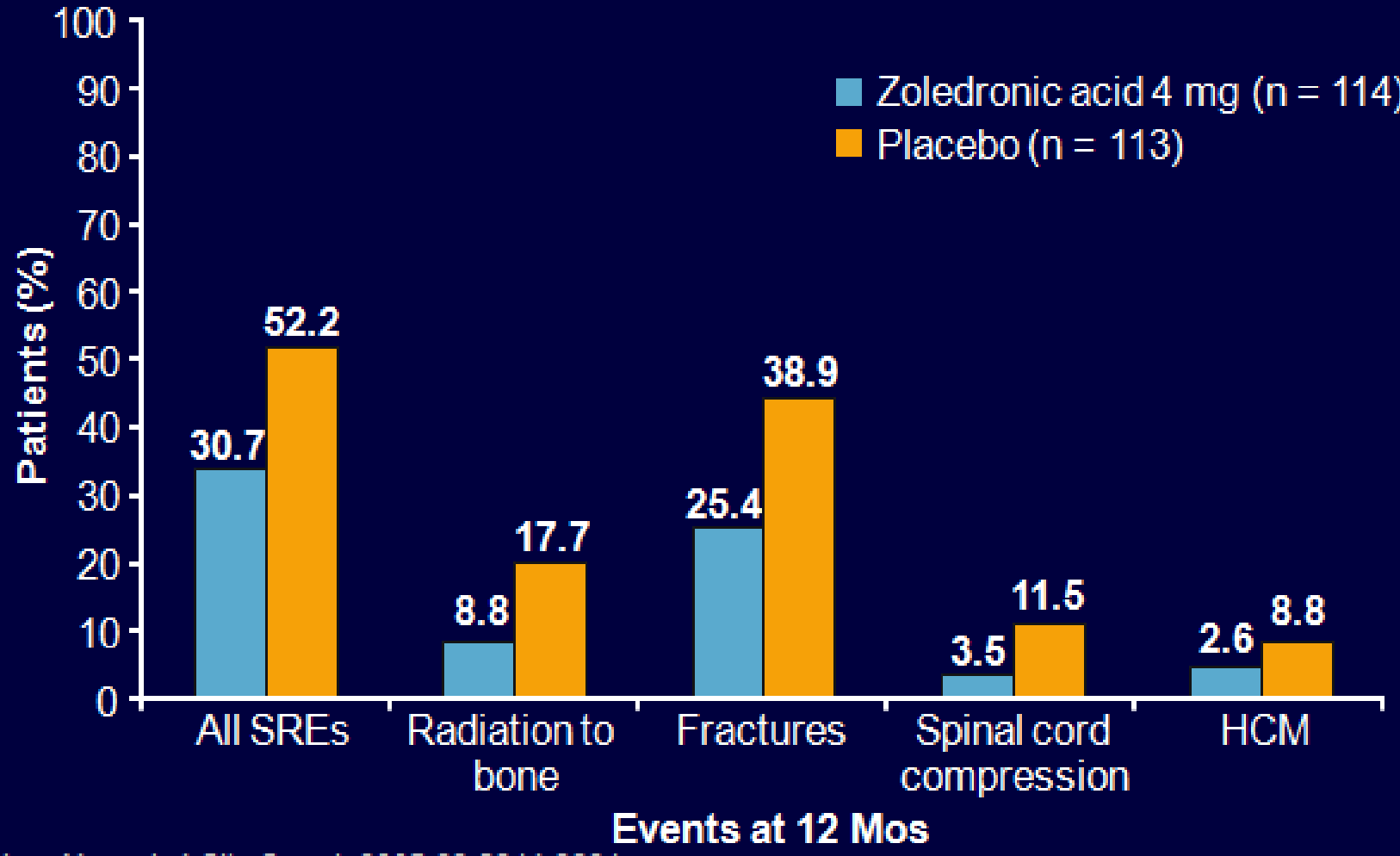
- It is recommended that bisphosphonates as adjuvant therapy be considered for postmenopausal patients with ESBC
  - The absolute benefit is small (consider in high risk)
- Zoledronate (4 mg q 6mo x 3-5yrs) and clodronate 1600 mg q d x 2-3yrs) are the recommended bisphosphonates
- Results for adjuvant denosumab look promising; data are insufficient at this time

Dhesy-Thind et al. JCO 2017

Carcinoma de Mama

Enfermedad Metastásica

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



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

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. ESMO 2010. Abstract 1249P.

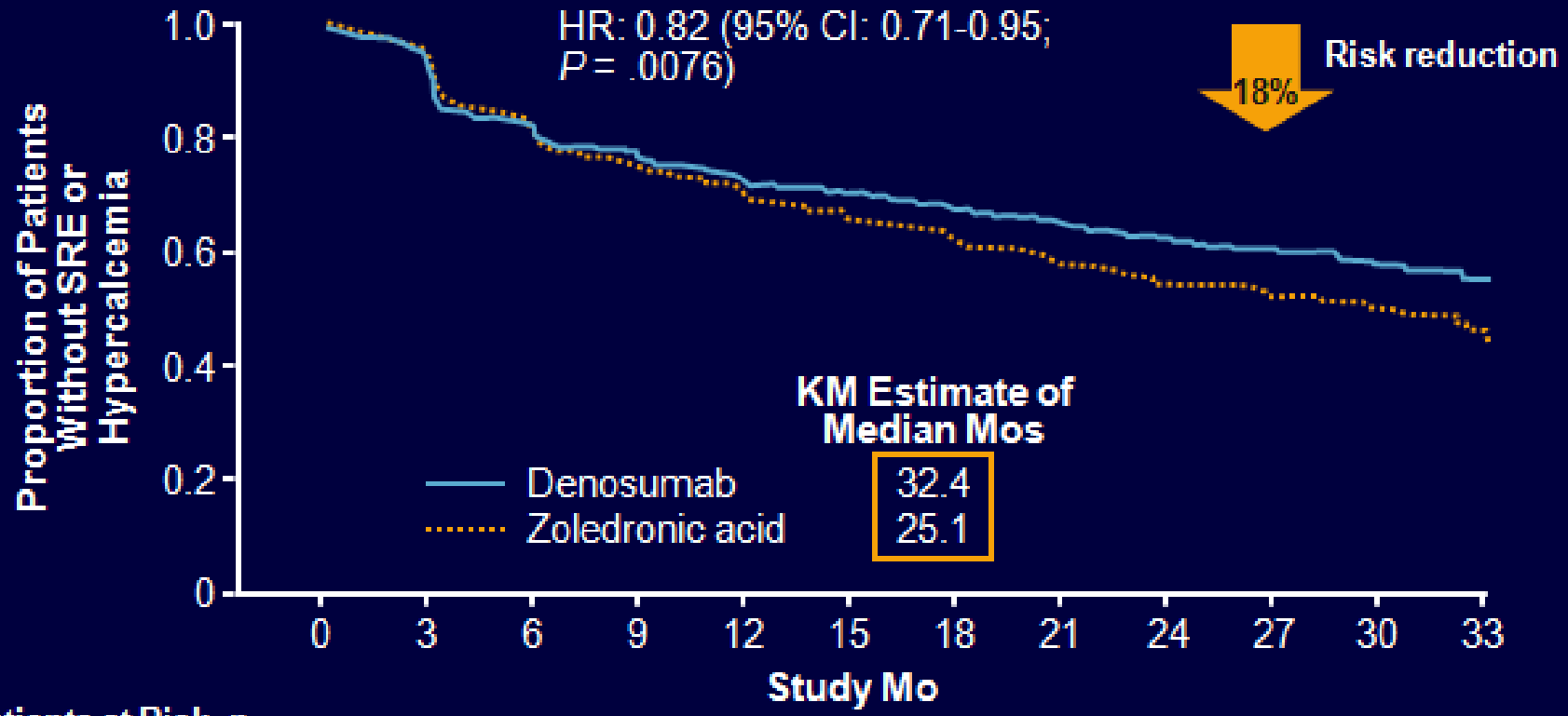
Zoledronic Acid vs Denosumab in Breast Cancer: Baseline Characteristics

Characteristic	Zoledronic Acid (n = 1020)	Denosumab (n = 1026)
Women, n (%)	1011 (99)	1018 (99)
Median age, yrs	56	57
ECOG score of 0 or 1, n (%)	932 (91)	955 (93)
Hormone receptor positive, n (%)	726 (71)	740 (72)
Median time from initial diagnosis of bone metastasis to randomization, mos	2.0	2.1
Previous SRE,* n (%)	373 (37)	378 (37)
Previous oral bisphosphonate use,* n (%)	38 (4)	42 (4)
Presence of visceral metastases, n (%)	525 (51)	552 (54)

*Based on randomization stratification.

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

Time to First On-Study SRE or Hypercalcemia: Extended Analysis

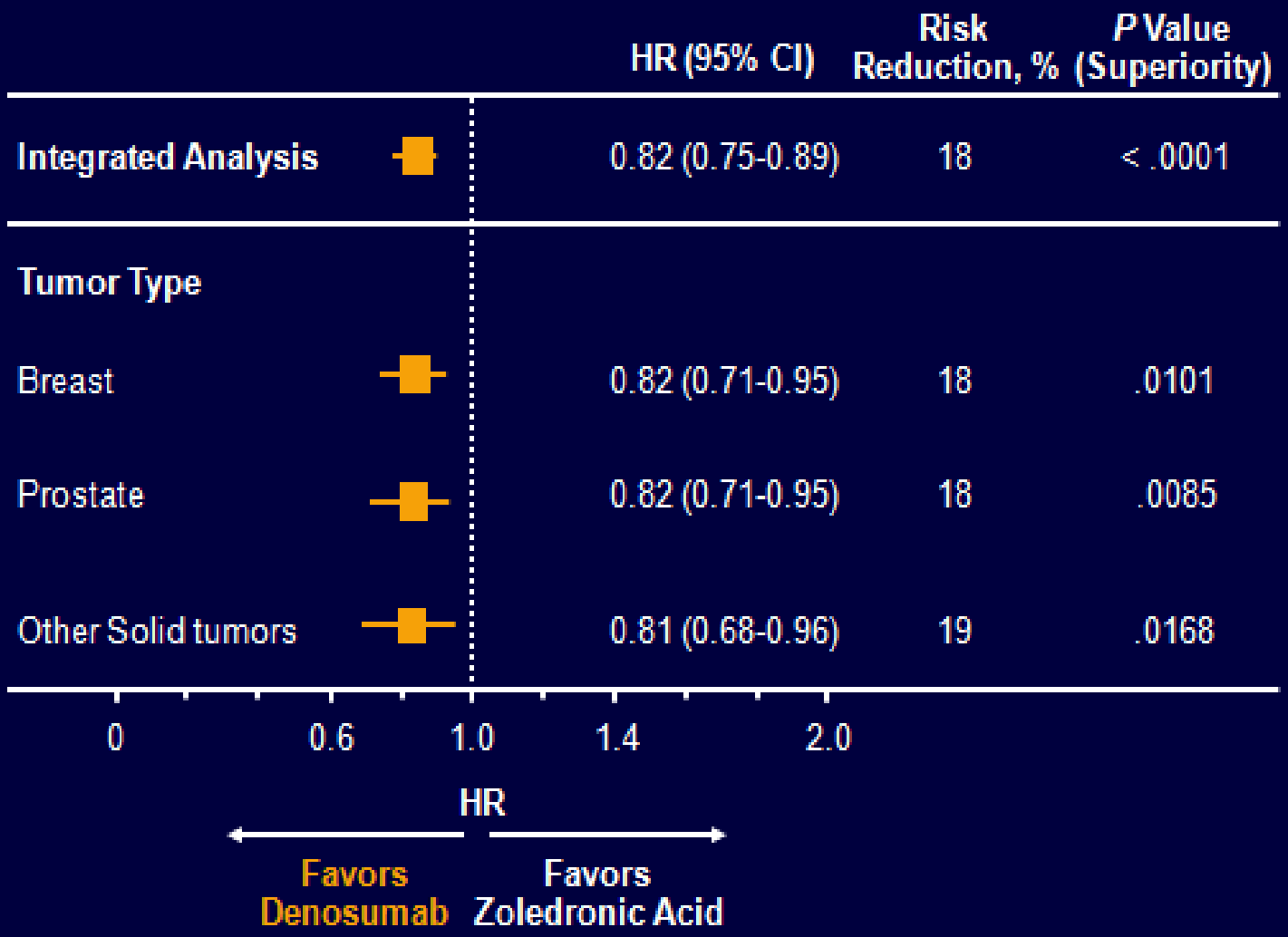


Patients at Risk, n

Zoledronic acid	1020	831	673	581	492	424	355	263	185	109	38	4
Denosumab	1026	834	688	594	506	441	381	276	191	100	37	8

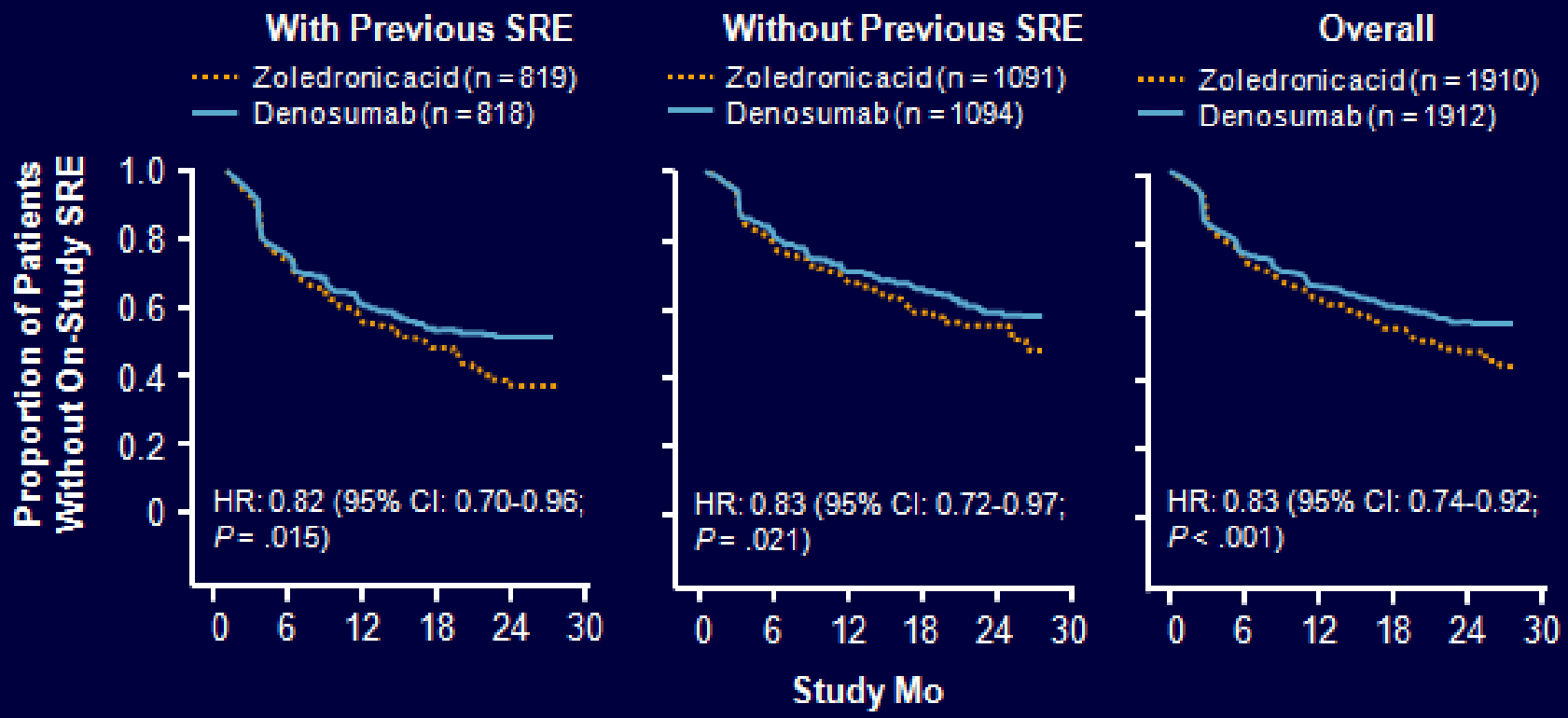
StopeckA, et al. SABCS 2010. Abstract P6-14-01.

Risk of First On-study SRE by Solid Tumor Type



Richardson G, et al. Clinical Oncological Society of Australia Annual Meeting 2011. Abstract 296.

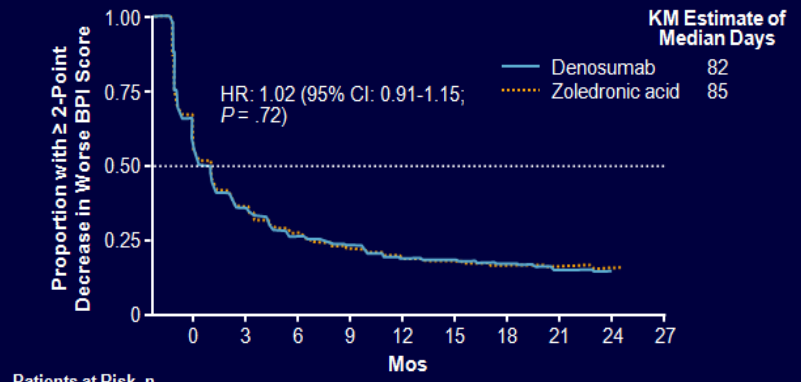
Pooled Analysis: Time to First On-Study SRE by Previous SRE History



Pts at Risk, n																		
Zoledronicacid	819	425	266	145	36	0	1091	627	426	237	78	4	1910	1052	692	382	114	4
Denosumab	818	411	266	144	48	1	1094	673	450	258	79	3	1912	1084	716	402	127	4

Lipton A, et al. ASCO 2010. Abstract 9015.

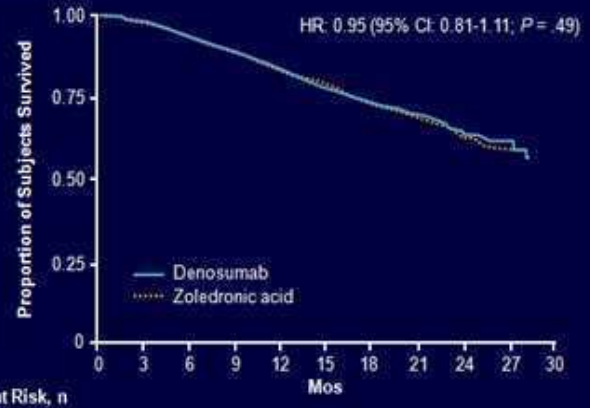
Pain Improvement With Denosumab vs Zoledronic Acid



Patients at Risk, n									
Denosumab	745	351	196	138	108	88	68	51	33
Zoledronic acid	747	344	208	148	106	88	71	52	25

StopeckA, et al. ASCO 2010. Abstract 1024.

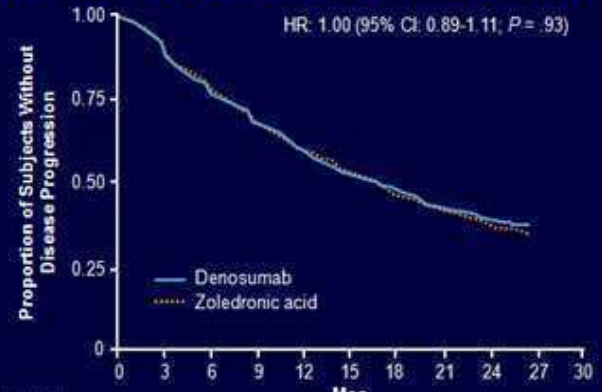
Zoledronic Acid vs Denosumab in Breast Cancer: OS



Pts at Risk, n										
Zoledronic acid	1020	962	897	834	757	699	515	352	184	54
Denosumab	1026	984	916	849	771	690	511	336	177	57

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

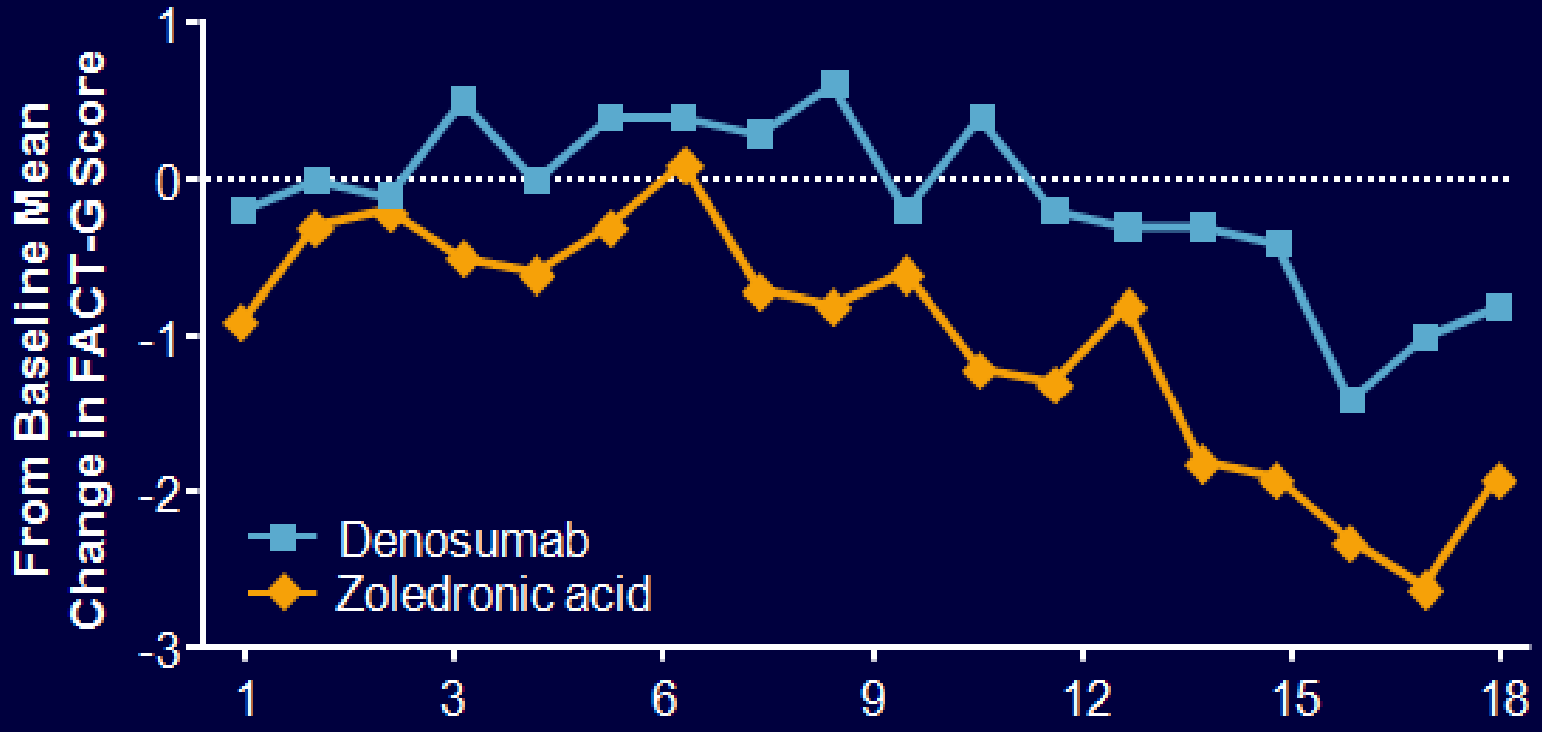
Zoledronic Acid vs Denosumab in Breast Cancer: Time to Disease Progression



Pts at Risk, n										
Zoledronic acid	1020	842	686	563	462	370	240	148	65	17
Denosumab	1026	858	693	567	453	351	241	128	65	20

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

QoL: FACT-G Mean Change From Baseline



Pts at risk, n							
Denosumab	913	878	787	709	640	575	460
Zoledronic acid	890	845	768	700	640	592	467

Health-related QoL higher with denosumab than zoledronic acid throughout study

Fallowfield L, et al. ASCO 2010. Abstract 1025.

FDA-Approved Agents for Prevention 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 is recommended over another
  - Bone-modifying agent therapy is only recommended for patients with evidence of bone metastases
  - Patients should receive a dental exam and preventive dentistry before initiating bone-modifying agent therapy

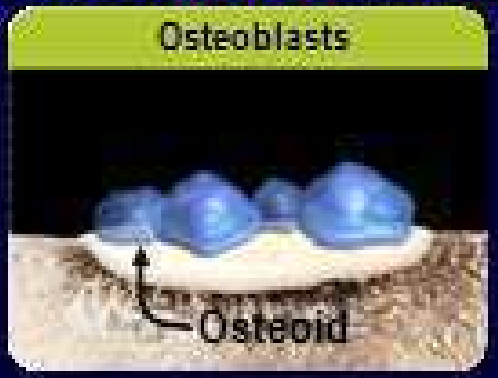
- # Carcinoma de Pulmón

Biochemical Markers of Bone Formation and Resorption

Resorption

- Collagen degradation
  - NTx (urine/serum)*
  - CTx
- Collagen crosslinks: PYD and DPD crosslinks of type I collagen
- Osteoclasts
  - TRAcP-5b
  - BSP

Initiation of bone formation

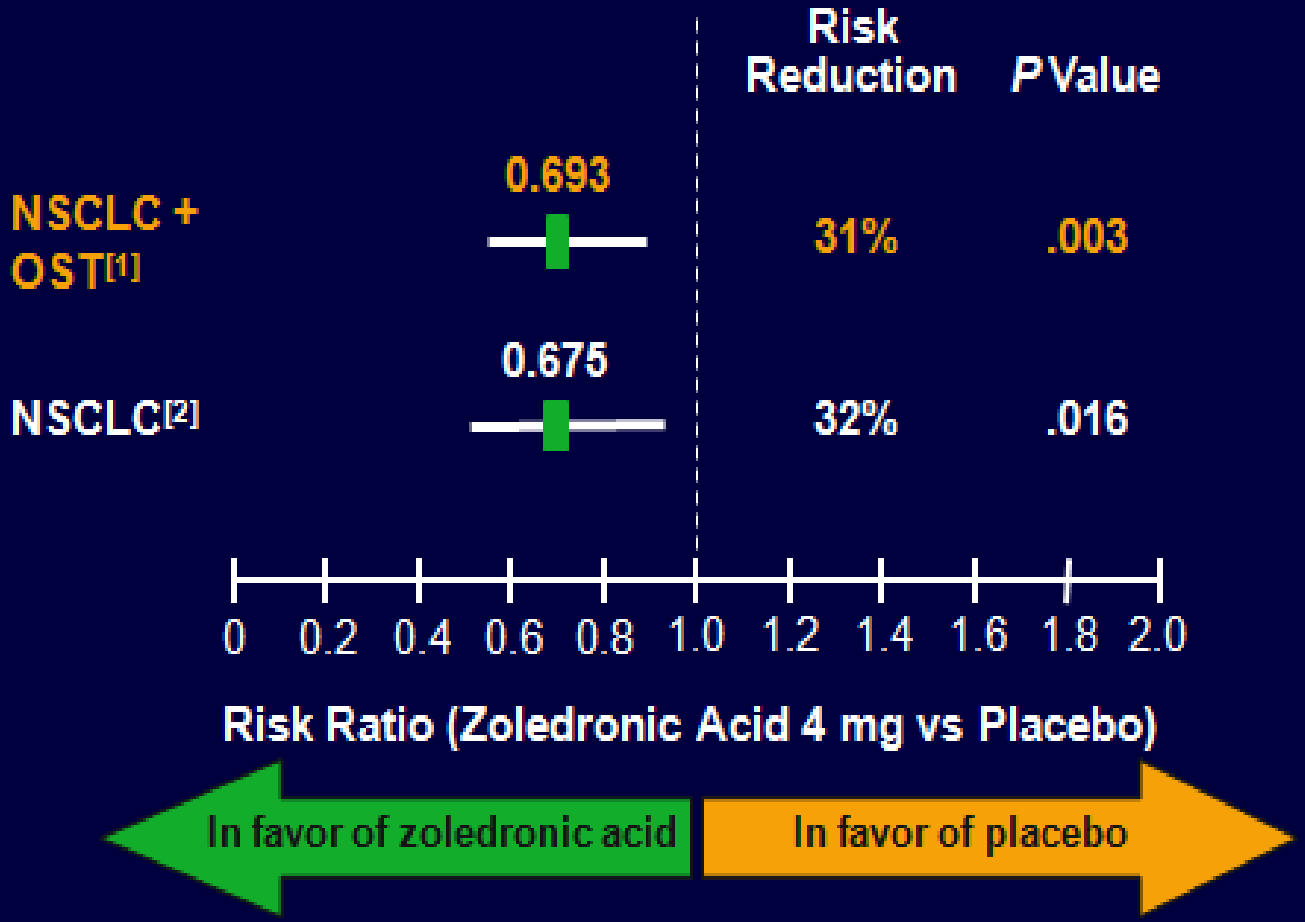


- Liver/bone/gut: serum ALP
- Osteoblasts
  - Maturation: serum bone-specific alkaline phosphatase
  - Mineralization: osteocalcin
- Initiation of collagen production: serum P1NP

*Most commonly used for marker of resorption in clinical practice.

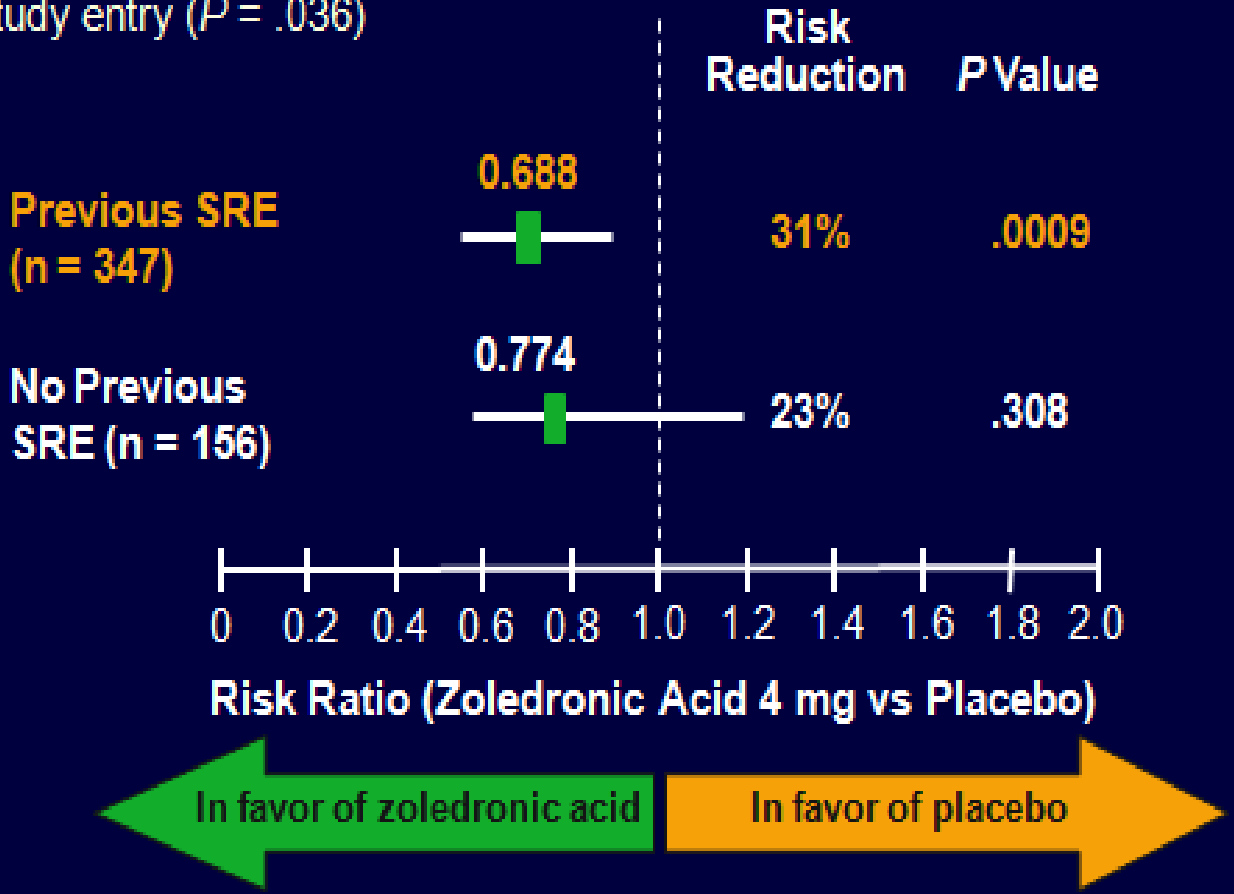
Coleman R, et al. Cancer Treat Rev. 2008;34:629-639.

Zoledronic Acid Reduced the Risk of Developing an SRE

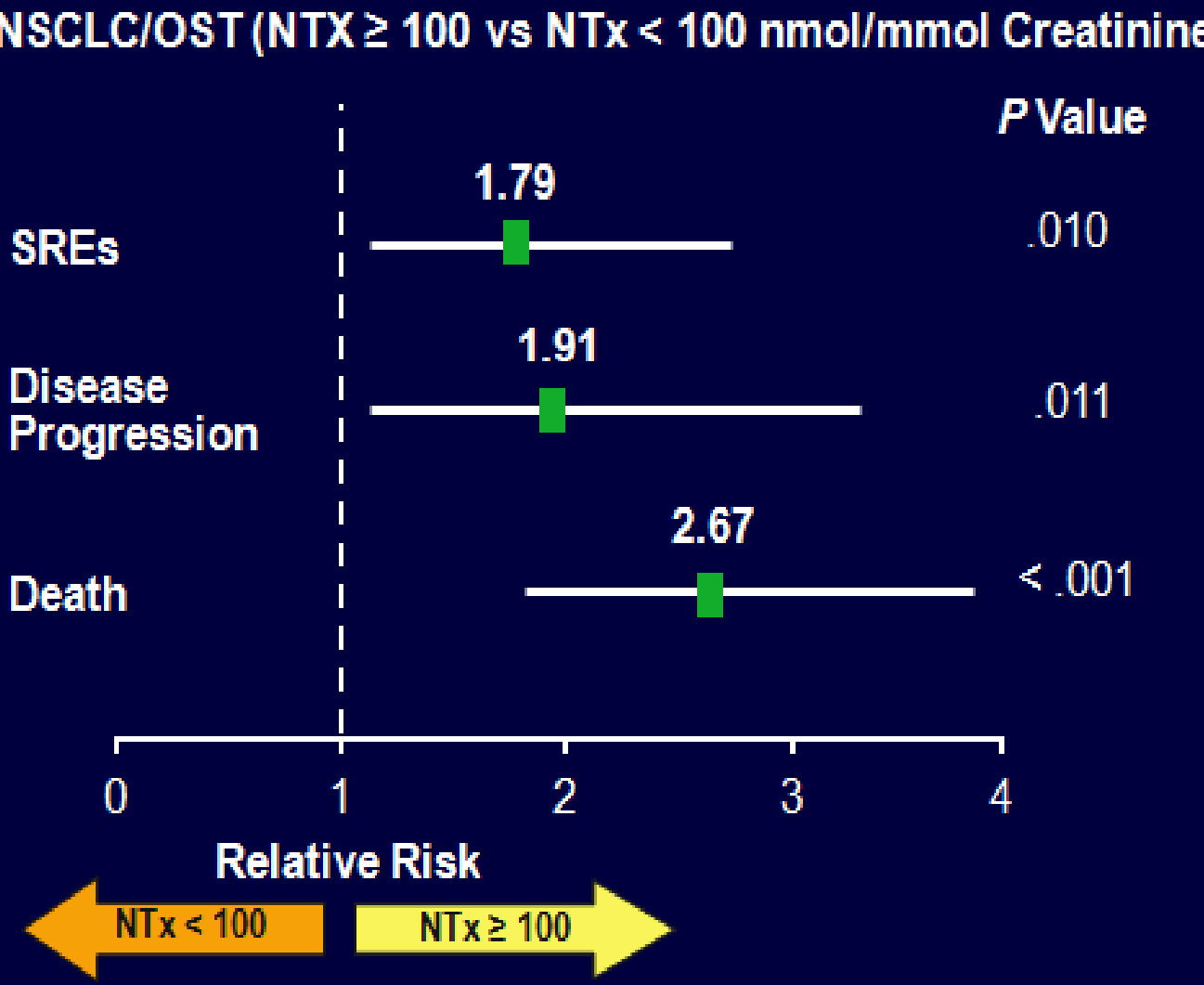


Zoledronic Acid Reduced the Risk of SREs in Patients With a History of SREs

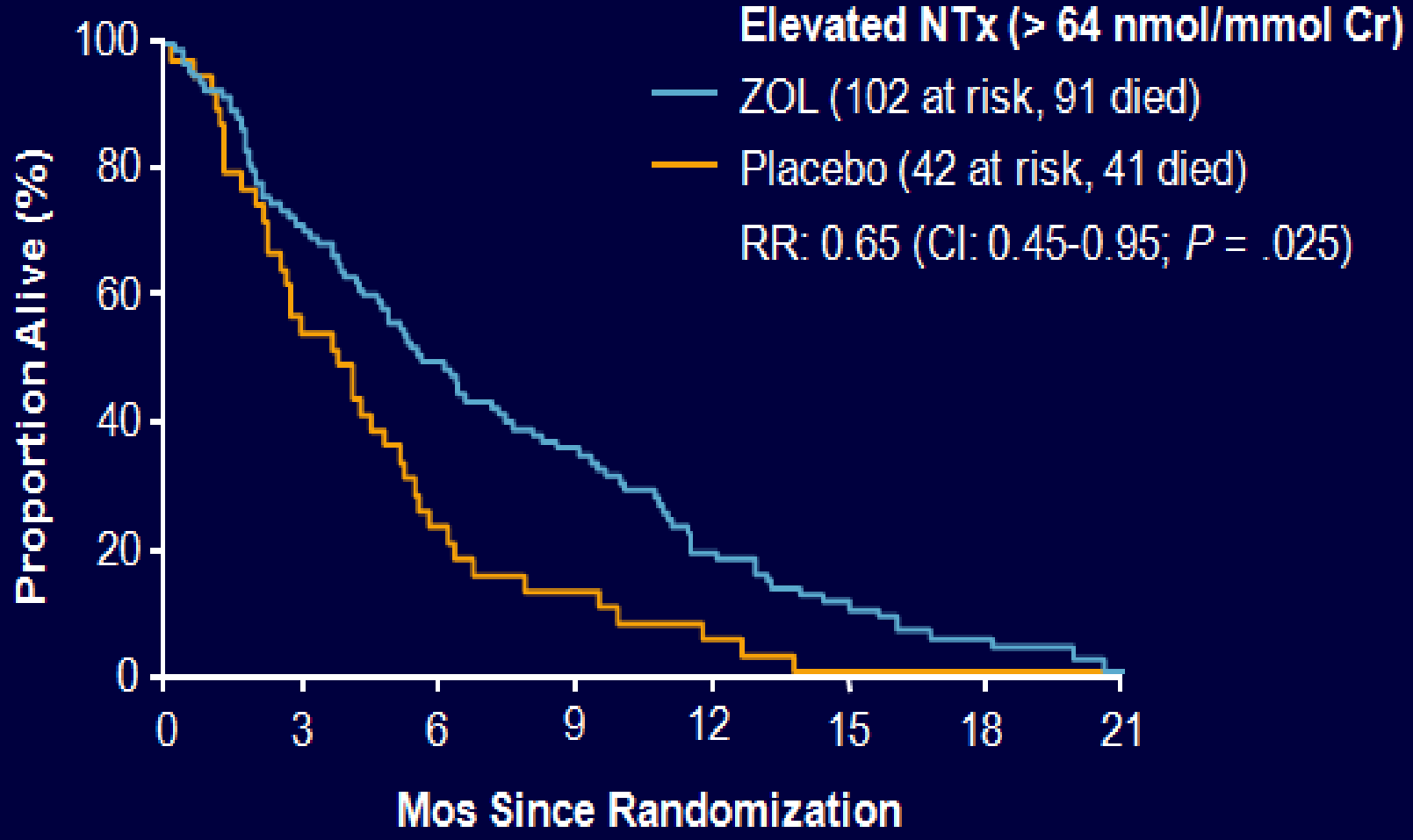
- In patients with a history of ≥ 1 SRE before the study
  - Risk of on-study SREs was increased by 41% vs patients with no previous SRE at study entry (*P* = .036)



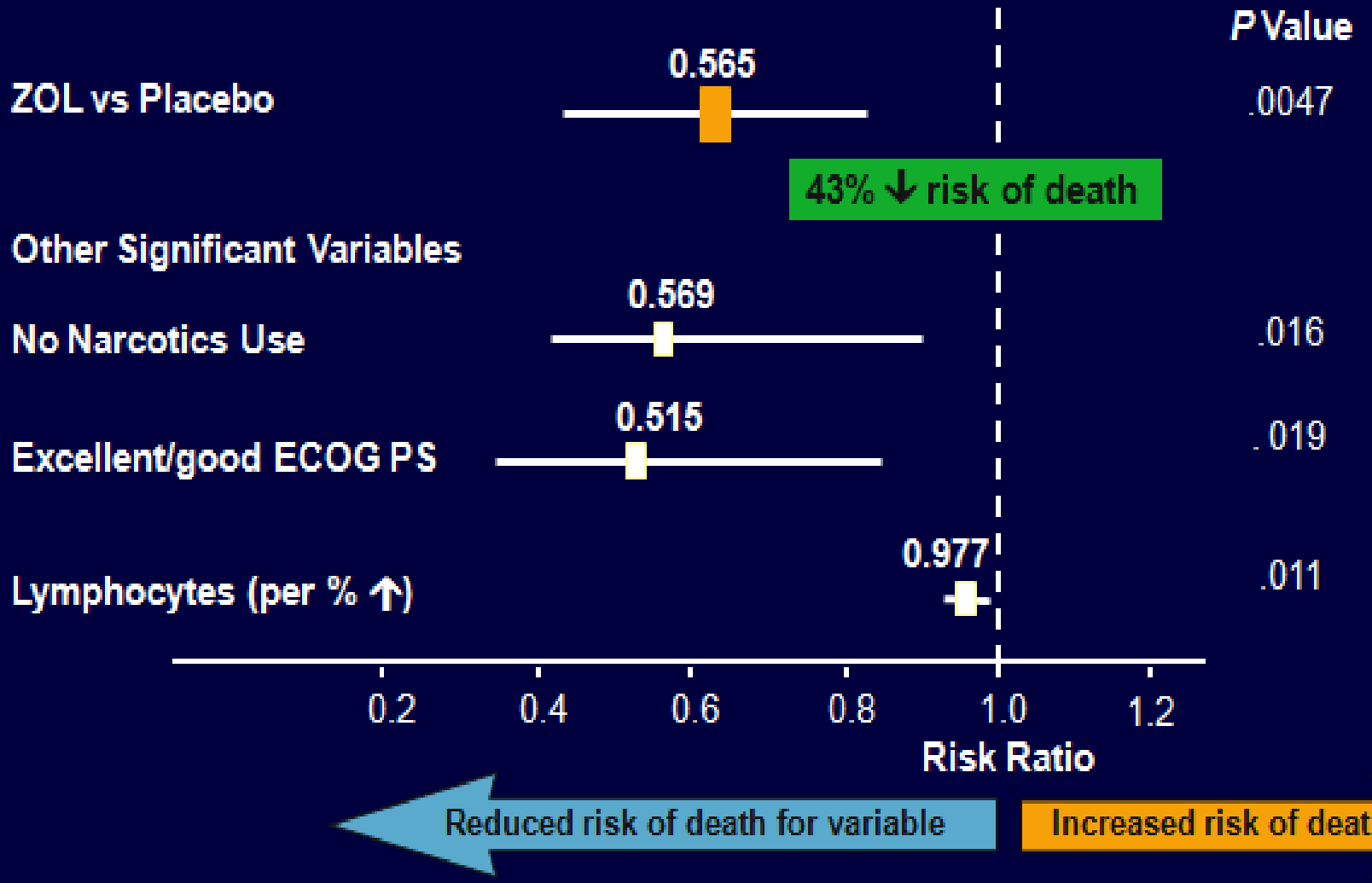
Elevated NTx Levels Associated With Incr. Risk of Negative Clinical Outcomes



Survival in Pts With NSCLC and High BL NTx Who Received ZOL or Placebo



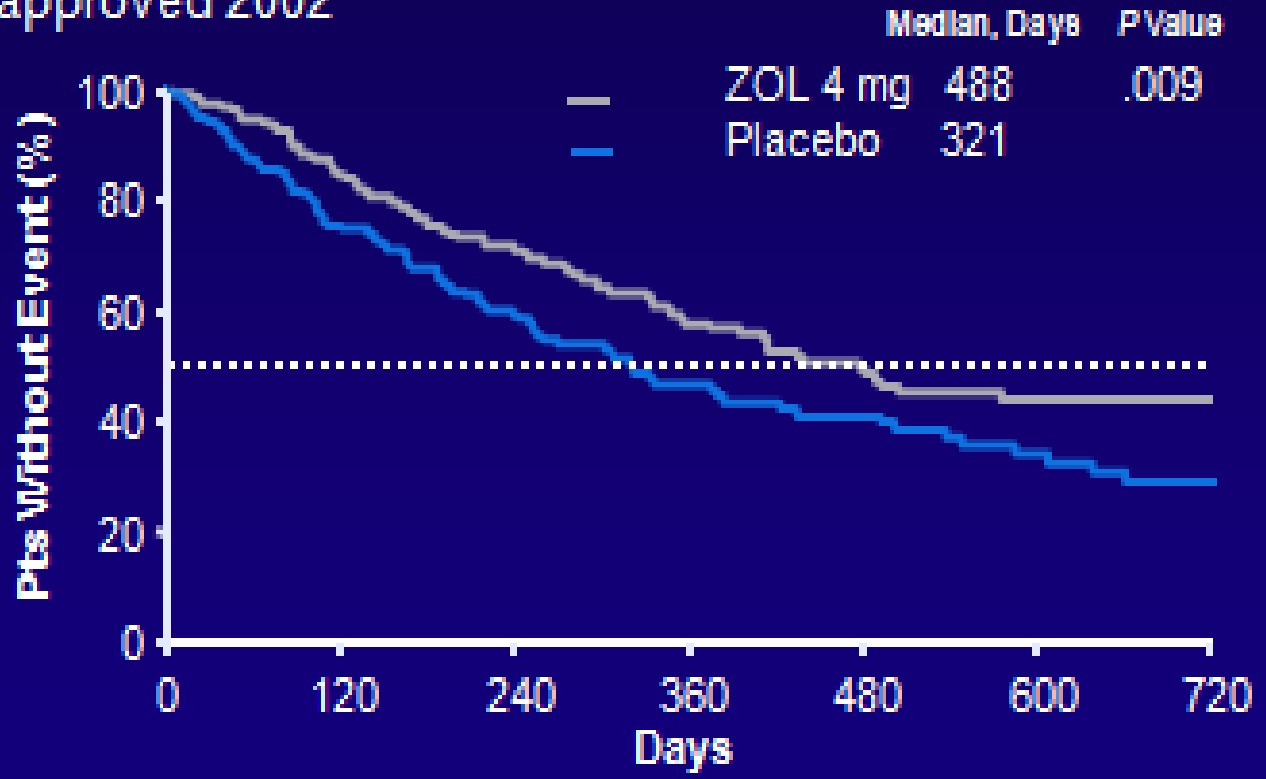
ZOL ↑ Survival in Pts With NSCLC and High Baseline NTx: Multivariate Analysis



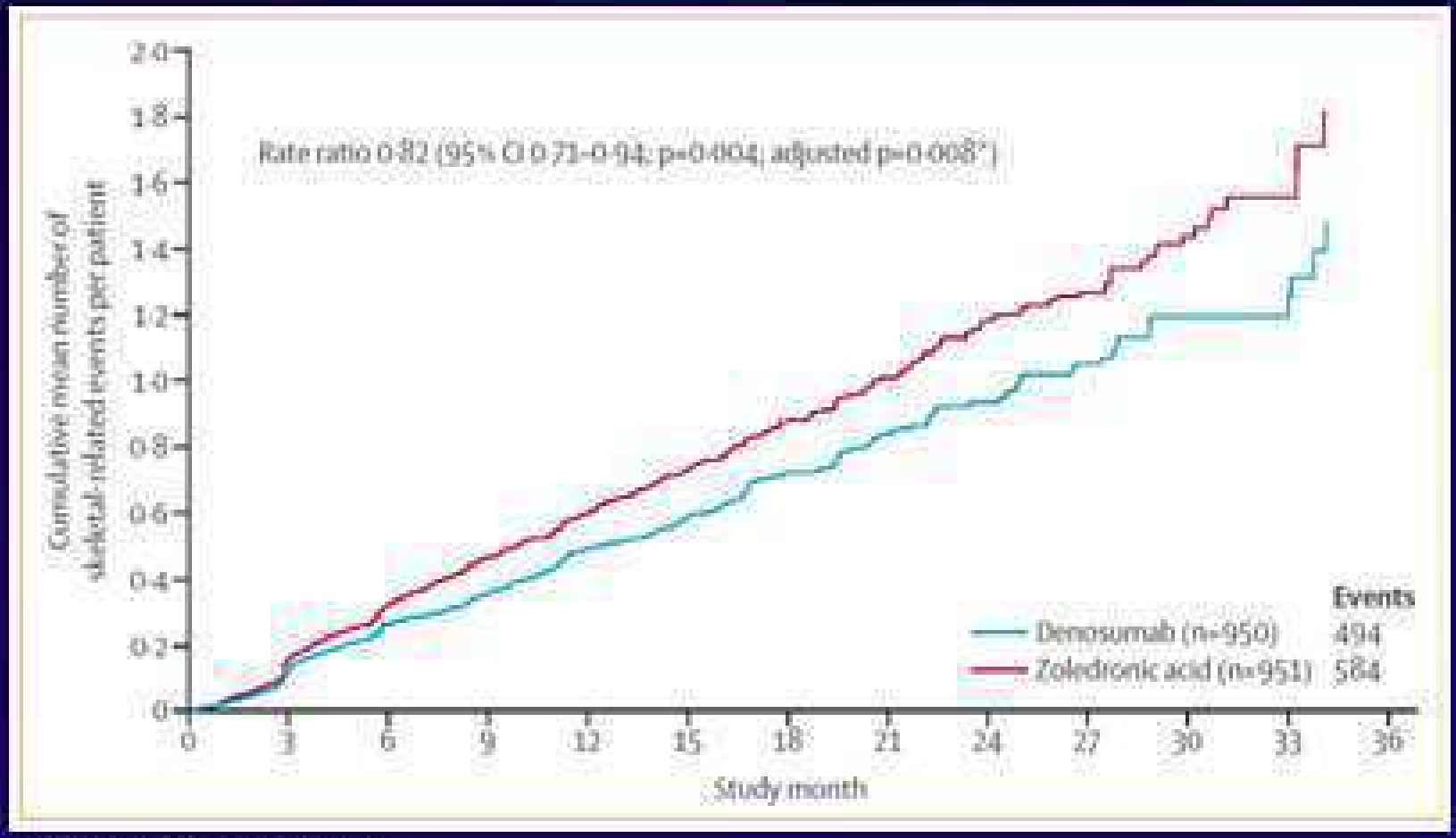
- **Carcinoma de Próstata**

Zoledronic Acid and Skeletal Morbidity

- Zoledronic acid superior to placebo
  - Prevention or delay of SREs: 11% absolute risk reduction in ≥ 1 SRE
  - Pain/analgesia scores increased less with ZOL
- FDA approved 2002



Denosumab vs Zoledronic Acid



*Adjusted for multiplicity.

Fizazi K, et al. Lancet. 2011;377:813-822.

Denosumab vs Zoledronic Acid in mCRPC

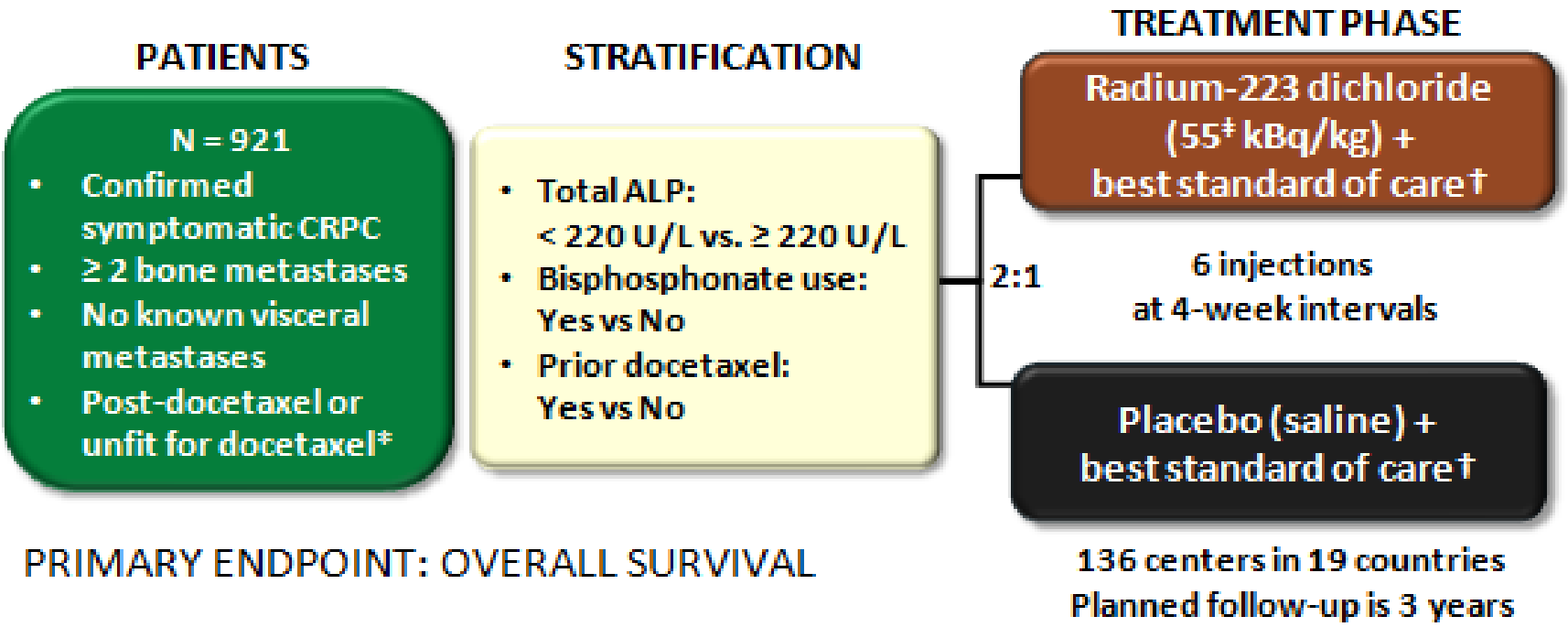
Outcome	Denosumab, Mos	Zoledronic Acid, Mos	HR (95% CI)	*P* Value
OS	19.4	19.8	1.03 (0.91-1.17)	.65
TTP	8.4	8.4	1.06 (0.95-1.18)	.30
Median time to first on-study SRE	20.7	17.1	0.82 (0.71-0.95)	.008

Fizazi K, et al. Lancet. 2011;377:813-822.

NCCN Guidance: Bone Antiresorptive Therapies

- Both zoledronic acid and denosumab are effective at delaying the time to SRE in men with mCRPC
- Neither agent improves OS or delays PFS
- ONJ risk increases over time and with more frequent dosing
- Not recommended in metastatic hormone-sensitive disease

ALSYMPCA: Phase III Study Design



PRIMARY ENDPOINT: OVERALL SURVIVAL

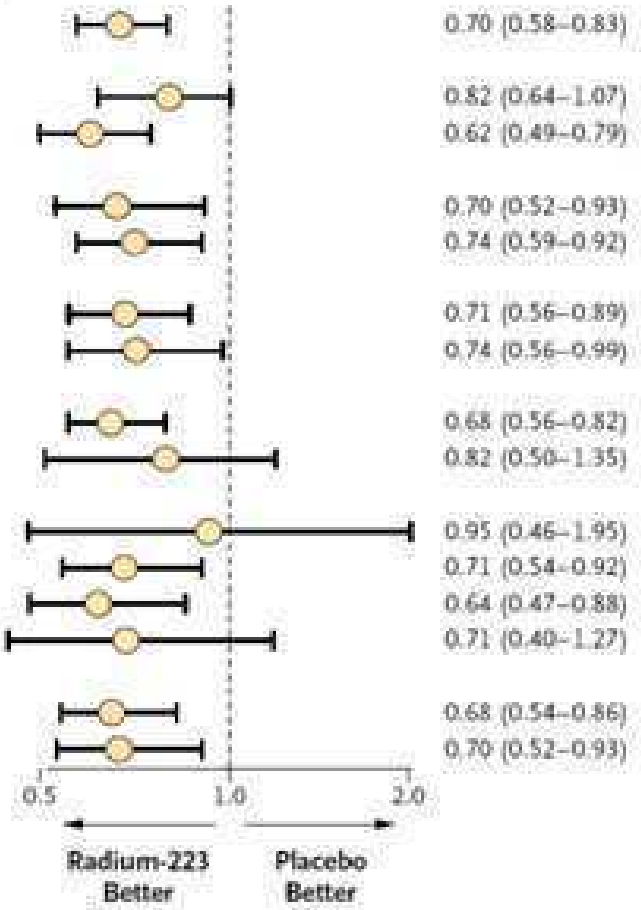
136 centers in 19 countries
Planned follow-up is 3 years

*Unfit for docetaxel includes pts who were ineligible for docetaxel, refused docetaxel, or lived where docetaxel was unavailable.
†Best standard of care defined as a routine standard of care at each center, eg, local external-beam radiotherapy, corticosteroids, antiandrogens, estrogens (e.g., diethylstilbestrol or estramustine), or ketoconazole.
‡NIST update 2016.

Parker C, et al. New Engl J Med. 2013;369:213-223.

ALSYMPCA: Predictors of Radium-223 Benefit?

Subgroup	Radium-223	Placebo	Radium-223	Placebo	Hazard Ratio (95% CI)
	no. of patients		*median overall survival (mo)*		
All patients	614	307	14.9	11.3	0.70 (0.58–0.83)
Total ALP level at baseline					
<220 U/liter	348	169	17.0	15.8	0.82 (0.64–1.07)
≥220 U/liter	266	138	11.4	8.1	0.62 (0.49–0.79)
Current bisphosphonate use					
Yes	250	124	15.3	11.5	0.70 (0.52–0.93)
No	364	183	14.5	11.0	0.74 (0.59–0.92)
Previous docetaxel use					
Yes	352	174	14.4	11.3	0.71 (0.56–0.89)
No	262	133	16.1	11.5	0.74 (0.56–0.99)
Baseline ECOG performance-status score					
0 or 1	536	265	15.4	11.9	0.68 (0.56–0.82)
≥2	77	41	10.0	8.4	0.82 (0.50–1.35)
Extent of disease					
<6 metastases	100	38	27.0	NE	0.95 (0.46–1.95)
6–20 metastases	262	147	13.7	11.6	0.71 (0.54–0.92)
>20 metastases	195	91	12.5	9.1	0.64 (0.47–0.88)
Superscan	54	30	11.3	7.1	0.71 (0.40–1.27)
Opioid use					
Yes	345	168	13.9	10.4	0.68 (0.54–0.86)
No	269	139	16.4	12.8	0.70 (0.52–0.93)



Parker C, et al. New Engl J Med. 2013;369:213-223.

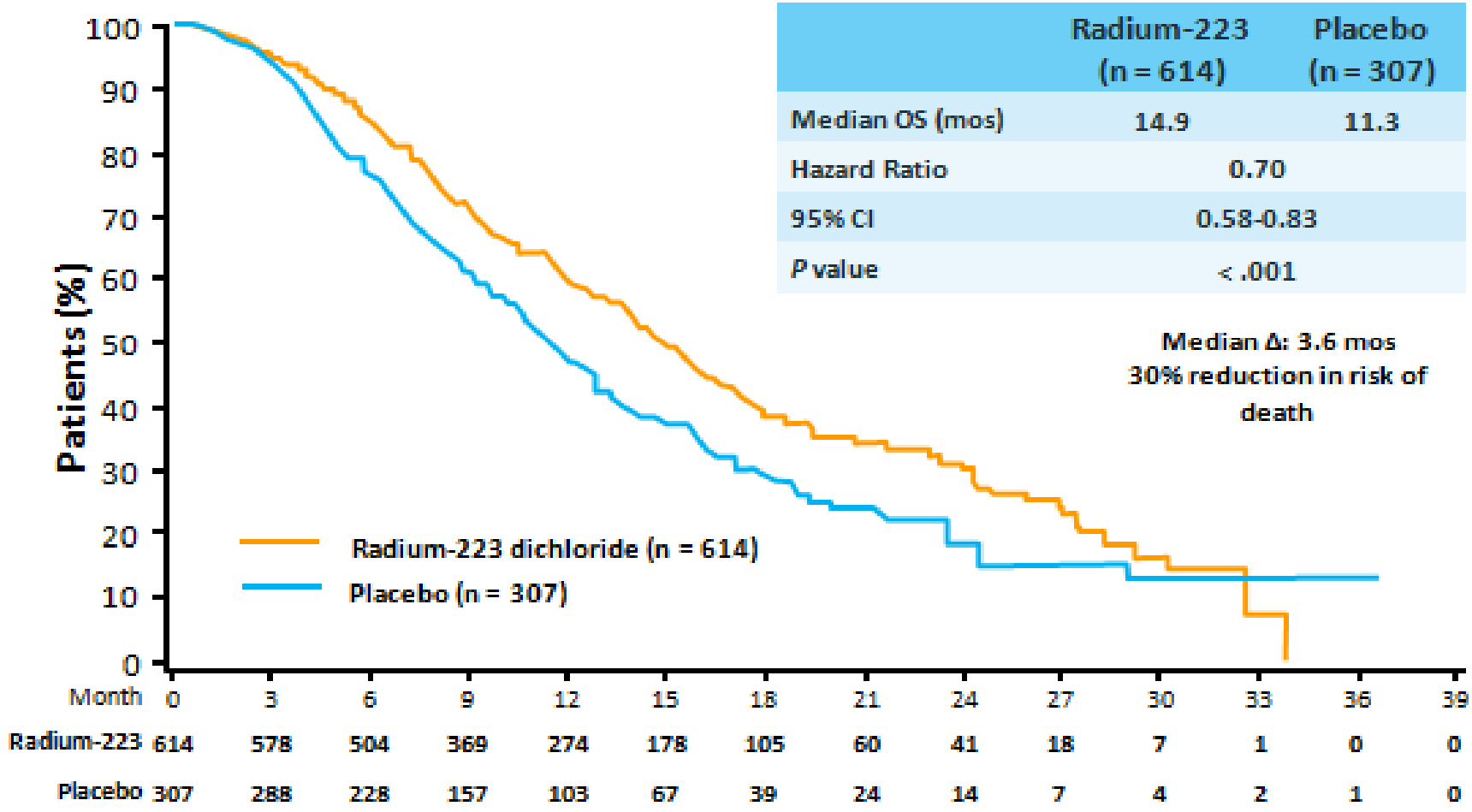
ALSYMPCA Updated Analysis: Select Adverse Events

	All Grades		Grades 3 or 4	
Patients with AEs n, (%)	Radium-223 n = 600	Placebo n = 301	Radium-223 n = 600	Placebo n= 301
Hematologic				
Anemia	187 (31)	92 (31)	77 (13)	39 (13)
Neutropenia	30 (5)	3 (1)	13 (2)	2 (1)
Thrombocytopenia	69 (12)	17 (6)	38 (6)	6 (2)
Non-Hematologic				
Bone pain	300 (50)	187 (62)	125 (21)	77 (26)
Diarrhea	151 (25)	45 (15)	9 (2)	5 (2)
Nausea	213 (36)	104 (35)	10 (2)	5 (2)
Vomiting	111 (18)	41 (14)	10 (2)	7 (2)
Constipation	108 (18)	64 (21)	6 (1)	4 (1)

Safety of taxane chemotherapy following radium-223 not well characterized

Parker C, et al. New Engl J Med. 2013;369:213-223.

ALSYMPCA Updated Analysis: OS



	Radium-223 (n = 614)	Placebo (n = 307)
Median OS (mos)	14.9	11.3
Hazard Ratio	0.70	
95% CI	0.58-0.83	
P value	< .001	

Median Δ: 3.6 mos
30% reduction in risk of death

Parker C, et al. New Engl J Med. 2013;369:213-223.

Radium-223 Retreatment in CRPC: Study Background

- Radium-223: alpha-emitting radiopharmaceutical that exerts potent cytotoxic effects on bone metastases
  - In phase III ALSYMPCA trial, improved OS by 3.6 mos ($P < .001$), delayed time to first symptomatic skeletal event by 5.8 mos ($P < .001$), and had favorable safety profile for CRPC pts with bone metastases[1,2]
  - Outcomes based on one 50-kBq/kg injection Q4W for 6 injections[1,2]
- Data suggest radium-223 retreatment may provide added benefit to pts who received initial 6-injection course[3]
- Current international, prospective, open-label phase I/II study evaluated efficacy and safety of radium-223 retreatment in pts with CRPC and bone metastases[4]

Radium-223 Retreatment in CRPC: Baseline Characteristics

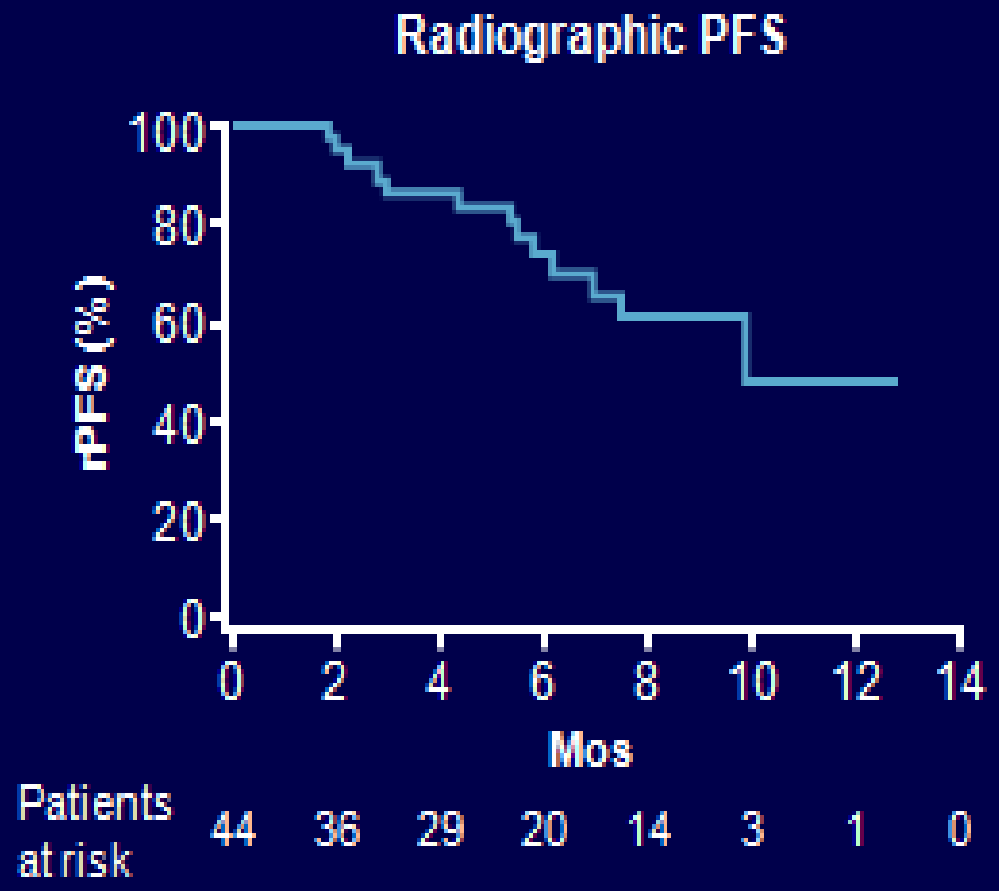
Characteristics	Retreatment Study (N = 44)	ALSYMPCA (N = 614)
Median age, yrs (range)	71 (52-91)	71 (49-90)
ECOG PS 0/1/≥ 2, %	32/61/7	27/60/13
< 6/6-20/> 20 bone metastases, %	41/34/25	16/43/41
Prior treatment, %		
▪Docetaxel	45	57
▪Abiraterone	61	NA
▪Enzalutamide	30	NA
▪Bisphosphonates	11	20
▪Denosumab	48	NA
Concurrent treatment, %		
▪Abiraterone	27	NA
▪Enzalutamide	9	NA
▪Denosumab	16	NA
Median PSA, µg/L	68	146

Radium-223 Retreatment in CRPC: Safety

TEAEs, %	Retreatment Study (N = 44)			ALSYMPCA (N = 600)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Pts with ≥ 1 TEAE	93	41	7	93	35	9
Hematologic						
▪Anemia	14	5	0	31	11	2
▪Thrombocytopenia	2	2	0	12	3	3
▪Leukopenia	2	0	0	4	1	< 1
▪Neutropenia	0	0	0	5	2	1
Nonhematologic (in > 10% of retreatment pts)						
▪Fatigue	27	0	0	26	4	1
▪Nausea	25	2	0	36	2	0
▪Diarrhea	21	0	0	25	2	0
▪Decreased appetite	18	0	0	6	< 1	0
▪Arthralgia	14	0	0	5	1	0
▪Hypertension	14	11	0	2	1	0
▪Back pain	11	0	0	2	1	0
▪Fall	11	0	0	1	< 1	0
▪Vomiting	11	0	0	19	2	0

Radium-223 Retreatment in CRPC: rPFS

- Median rPFS: 9.9 mos
  - 13 pts had rPFS events, largely consisting of soft tissue tumor progression (n = 8)
  - Only 1 pt with confirmed radiographic bone progression
  - 12.8-mos max follow-up time for rPFS and radiographic bone progression



Radium-223 Retreatment CRCP: Conclusions

- Second round of radium-223 treatment following initial course safe and feasible[1]
  - Well tolerated, with minimal hematologic toxicity
  - Low rate of radiographic bone progression
  - Encouraging early effects on OS, time to SSE, pain
- Investigators conclude positive data warrant analysis of radium-223 retreatment in larger prospective trials[1]
- Ongoing study to address expanded radium-223 dosing and duration of treatment[2]

- **GAMMAPATIAS MONOCLONALES**

Denosumab vs ZA in Newly Diagnosed MM: Study Design

- International, randomized, double-blind phase III trial (primary analysis cutoff: July 19, 2016; enrollment ended: March 29, 2016)

Stratified by antimyeloma tx (IMiD/PI vs other), planned autologous PBSC transplantation (yes vs no), disease stage (ISS 1 vs 2 vs 3), prior SRE (yes vs no), region (Japan vs other)

Pts with assessed MM, ≥ 1 lytic bone lesion or ≥ 1 focal lesion per MRI, first-line antimyeloma tx (duration ≤ 30 d pre-screening), ECOG PS 0-2, adequate organ function, no BL CrCl < 30 mL/min, no nonsecretory MM (unless BL SFLC elevated), no POEMS syndrome, no plasma cell leukemia, no prior denosumab, no prior bisphosphonates (oral: cumulative exposure > 1 yr; IV: ≥ 1 dose), no history of jaw osteonecrosis/osteomyelitis (N = 1718)

Denosumab 120 mg SC + **Placebo** IV over 15 min Q4W (n = 859)*

Zoledronic acid 4 mg† IV over 15 min Q4W + **Placebo** SC (n = 859)*

Until accrual of 676 on-study SREs; if benefit:risk determined to be positive, pts offered open-label denosumab up to 2 yrs; if negative, pts followed for 2 yrs

*Both arms received daily calcium and vitamin D supplements.
†ZA dose adjusted per BL CrCl, with subsequent dose intervals dictated by serum CrCl.

- Primary endpoint: time to first on-study SRE (noninferiority)

Denosumab vs ZA in Newly Diagnosed MM: Time to SRE

- Primary endpoint met: denosumab noninferior to ZA for time to first on-study SRE
  - Denosumab not superior to ZA for time to first on-study SRE or time to first-and-subsequent on-study SRE

On-study Endpoint	Denosumab (n = 859)	ZA (n = 859)	Difference (95% CI)	*P* Value		
				Noninferior	Superior	Superior (Adj.*)
Time to first SRE						
▪ Crude incidence, n (%)	376 (43.8)	383 (44.6)	HR: 0.98 (0.85-1.14)	.01	.82	.84
▪ KM median, mos (95% CI)	22.83 (14.72-NE)	23.98 (16.56-33.31)				
Time to first-and-subsequent SRE†			RR: 1.01 (0.89-1.15)	--	.84	.84
▪ Events, n	565	565				
▪ Mean events per pt, n	0.66	0.66				

Denosumab vs ZA in Newly Diagnosed MM: OS, PFS

Endpoint	Denosumab (n = 859)	ZA (n = 859)	HR (95% CI)
OS ▪ Deaths, n (%)	121 (14.1)	129 (15.0)	0.90 (0.70-1.16) *P* = .41
mPFS, mos (95% CI)	46.09 (34.30-NE)	35.38 (30.19-NE)	0.82 (0.68-0.99) *P* = .036*

*Descriptive *P* value for PFS exploratory endpoint.

Denosumab vs ZA in Newly Diagnosed MM: Investigator Conclusions

- Study met primary endpoint: denosumab noninferior to ZA for time to first SRE (HR: 0.98; *P* = .01)
  - Denosumab not superior to ZA (*P* = .82)
- No significant difference in OS between arms (HR: 0.90; *P* = .41)
- PFS prolonged by 10.7 mos with denosumab vs ZA (HR: 0.82; descriptive *P* = .036)
- Investigators reported that SRE profiles comparable to previous reports and generally similar between treatment arms
  - Significantly lower rates of renal TEAEs with denosumab (10.0% vs 17.1% with ZA; *P* < .001)
  - Significantly higher rate of hypocalcemia with denosumab (16.9% vs 12.4% with ZA; *P* < .05)
- Investigators concluded that denosumab a promising option due its potential PFS benefit and significantly lower rates of renal AEs

Adverse Effects of Bone-Modifying Agents Used for Bone Metastases/Lesions

- Common toxicities
  - ONJ (generally low incidence)
  - Hypocalcemia
  - Hypophosphatemia
  - Nausea
  - Fatigue/asthenia
- Selective for IV bisphosphonates
  - Acute phase reactions (10% to 20% incidence of influenzalike symptoms usually resolve in 24-48 hrs)
  - Renal toxicity (zoledronic acid or pamidronate; cumulative dosing)

Comparison of IV Bisphosphonates and Denosumab Toxicities

Toxicity	Denosumab[1]	Bisphosphonates[2-3]
Administration	Subcutaneous	Intravenous
ONJ	✓	✓
Hypocalcemia	✓	✓
Renal toxicity/renal elimination	--	✓
Dose adjustments (for renal function)	--	✓
Flulike symptoms	--	✓
Bone, joint, muscle pains	--	✓

Conclusiones

- Prevención de osteoporosis es importante.
- Zoledrónico produce beneficio en SV en pacientes con postmenospáusicas como Adyuvancia. (Mama).
- D y Z disminuyen los eventos óseos en Carcinoma de Mama, Pulmón, Próstata y Mieloma.
- Denozumab es equivalente o superior a Zoledrónico.
- En Estadios Avanzados, No aumentan la sobrevida.
- Radium 223 aumenta la SV en Carcinoma de Próstata avanzado.

Futuro

- 236 Trials Bifosfonatos
- 48 Trials Denosumab
  - Sobrevida
  - Neoadyuvancia
  - Tiempo administración
- 67 Trials Radium 223
  - Combinación otros tratamientos
  - Otras patologías

- Gracias por su atención !

Comparison of Antiresorptive Therapies

	Zoledronic Acid[1]	Denosumab[2]
Route	Intravenous	Subcutaneous
MOA	Bisphosphonate	Monoclonal antibody to RANK ligand
Dose and schedule	4 mg q3-4w*	120 mg q4w
Renal toxicity	Yes	No
Acute phase reactions	Yes, 18%	Some, 8%
Osteonecrosis of the jaw	Yes,1%	Yes, 2%
Hypocalcemia	Some, 6%	Yes, 13%
Calcium and vitamin D	Yes	Yes
Survival benefit	No	No
FDA approved indication	CRPC bone mets	Bone mets

*Dose adjust for renal insufficiency.

Hypercalcemia of Malignancy

- Symptoms
  - Nausea/vomiting
  - Increasing lethargy
  - Increased thirst
  - Polyuria
  - Constipation
  - Somnolence
  - Mental status changes
- Nursing assessment
  - Rule out narcotic oversedation and other etiologies
  - Assess calcium levels immediately
  - Know common malignancies associated with: breast cancer, lung cancer, and multiple myeloma

Treatment of Hypercalcemia

- IV hydration
- IV bisphosphonate therapy

Severity (Corrected Serum Calcium)	Dosing Recommendations	
	Pamidronate	**Zoledronic Acid**
Mild (< 12 mg/dL)	As appropriate with adequate hydration	As appropriate with adequate hydration
Moderate (12.0-13.5 mg/dL)	60-90 mg, single dose, IV infusion over 2-24 hrs	4 mg IV infusion over ≥ 15 mins
Severe (> 13.5 mg/dL)	90 mg, single dose, IV infusion over 2-24 hrs	4 mg IV infusion over ≥ 15 mins

- Admission may be necessary in severe cases

Bone-Modifying Agents Approved for Treating Bone Metastases

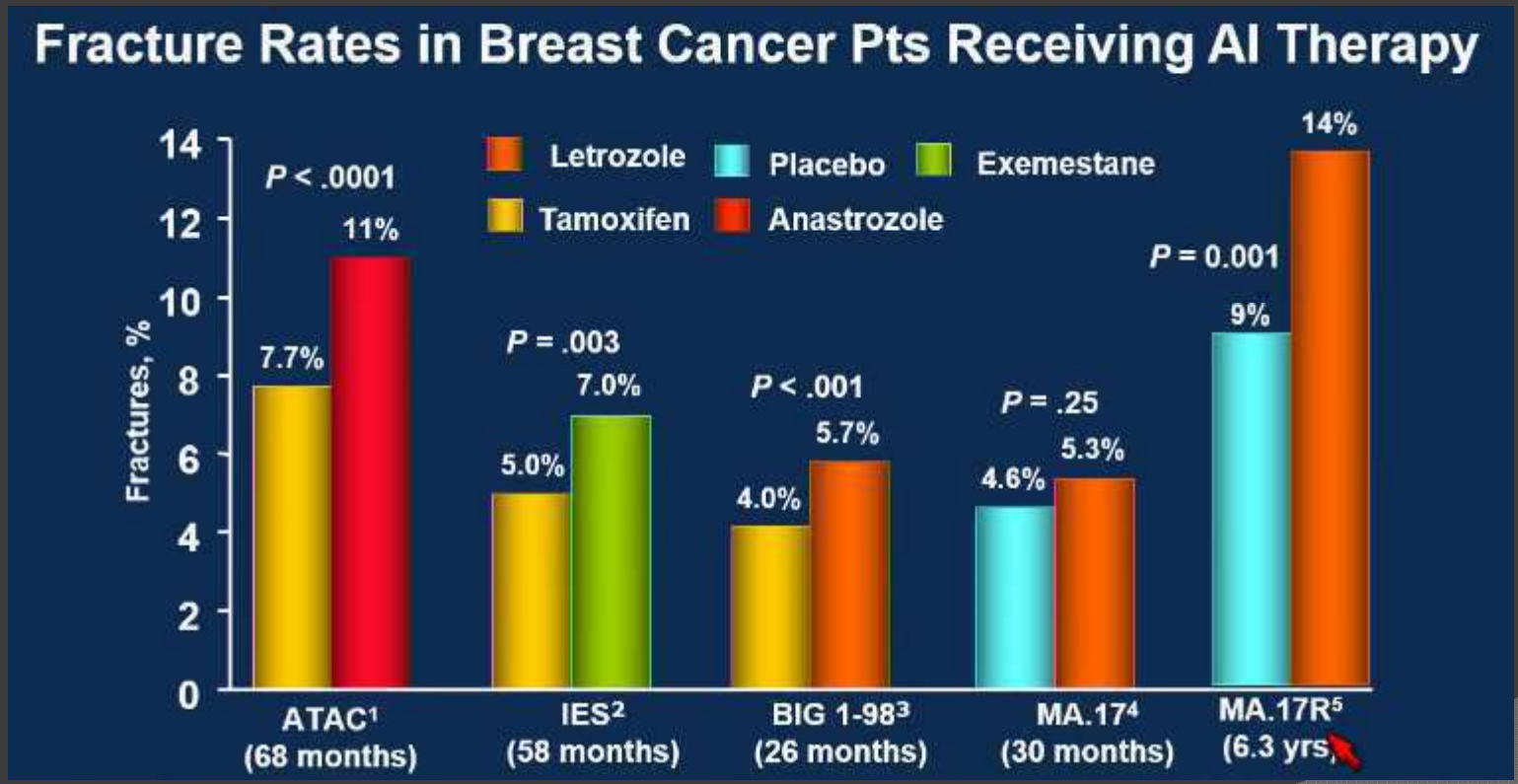
Agent	Indications (Bone Lesions/Metastases)
Denosumab (RANKL inhibitor) 120 mg SC every 4 wks	Prevention of SREs from bone metastases of solid tumors ***Not indicated for patients with multiple myeloma***
Pamidronate (IV bisphosphonate) 90 mg over 2-4 hrs every 3-4 wks	Osteolytic bone metastases of breast cancer Osteolytic lesions of multiple myeloma
Zoledronic acid (IV bisphosphonate) 4 mg over at least 15 mins every 3-4 wks	Bone metastases from solid tumors and multiple myeloma Prostate cancer with progression after ≥ 1 previous hormonal therapy

IV Bisphosphonate Dosing for Renal Impairment

Reduced Doses of Zoledronic Acid for Patients With Baseline CrCl < 60 mL/min

Baseline CrCl, mL/min	Dose
> 60	4.0 mg
50-60	3.5 mg
40-49	3.3 mg
30-39	3.0 mg
< 30	Not recommended

- Withhold therapy if
  - CrCl < 30 mL/min or
  - ≥ 0.5 mg/dL rise from normal baseline creatinine or
  - ≥ 1.0 mg/dL rise from abnormal baseline creatinine
  - Further doses withheld until creatinine returns to within 10% of baseline
- Pamidronate: consider dose reduction or longer infusion time


Fracture Rates in Breast Cancer Pts Receiving AI Therapy
Fractures, %
14
12
10
8
6
4
2
0
Letrozole
Placebo
Exemestane
Tamoxifen
Anastrozole
P < .0001
11%
7.7%
P = .003
7.0%
5.0%
P < .001
5.7%
4.0%
P = .25
5.3%
4.6%
P = 0.001
14%
9%
ATAC[1] (68 months)
IES[2] (58 months)
BIG 1-98[3] (26 months)
MA.17[4] (30 months)
MA.17R[5] (6.3 yrs)

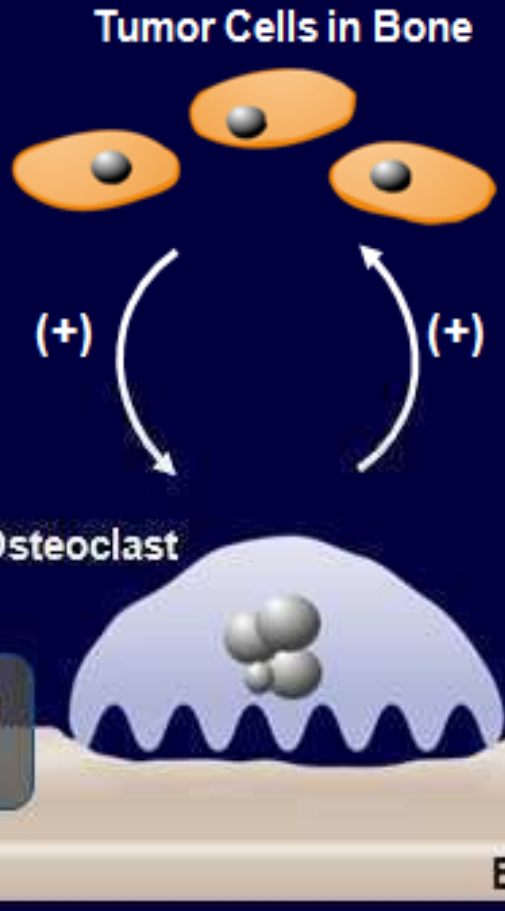
Pivotal Studies With Denosumab in Patients With Bone Metastases

- Fully human monoclonal antibody with high affinity and specificity for human RANK ligand

Tumor Type	Comparator	Result
Breast cancer[1]	Zoledronic acid	Denosumab superior for preventing/delaying SREs
Castration-resistant prostate cancer[2]	Zoledronic acid	Denosumab superior for preventing/delaying SREs
Solid tumors and multiple myeloma[3]	Zoledronic acid	Denosumab noninferior (trend to superior) for preventing/delaying SREs

The Vicious Cycle of Bone Metastasis

Tumor cells produce factors that stimulate osteoblasts to secrete RANKL



Bone resorption releases growth factors from the bone matrix that may perpetuate tumor activity

Tumor-derived osteoclast activating factors

- Parathyroid hormone–related protein
- Interleukin-6, -8, -11
- Tumor necrosis factor
- Macrophage colony–stimulating factor

Bone-derived tumor growth factors

- Transforming growth factor-β
- Insulin-like growth factors
- Fibroblast growth factors
- Platelet-derived growth factor
- Bone morphogenic proteins

Osteoblasts and other bone cells increase expression of RANKL

Overexpression of RANKL drives increased formation, function and survival of osteoclasts, leading to excessive bone resorption

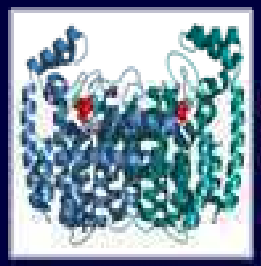
Adapted from Roodman GD. N Engl J Med. 2004;350:1655-1664.

Molecular Mechanisms of Action of Nitrogen-Containing Bisphosphonates

HMG-CoA

Mevalonate

Geranylpyrophosphate + IPP



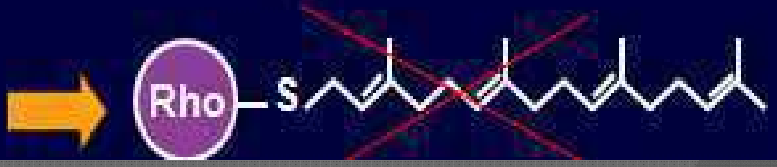
FPP synthase

NBPs inhibits FPP synthase, thus blocking the prenylation of small signaling proteins required for cell function and survival

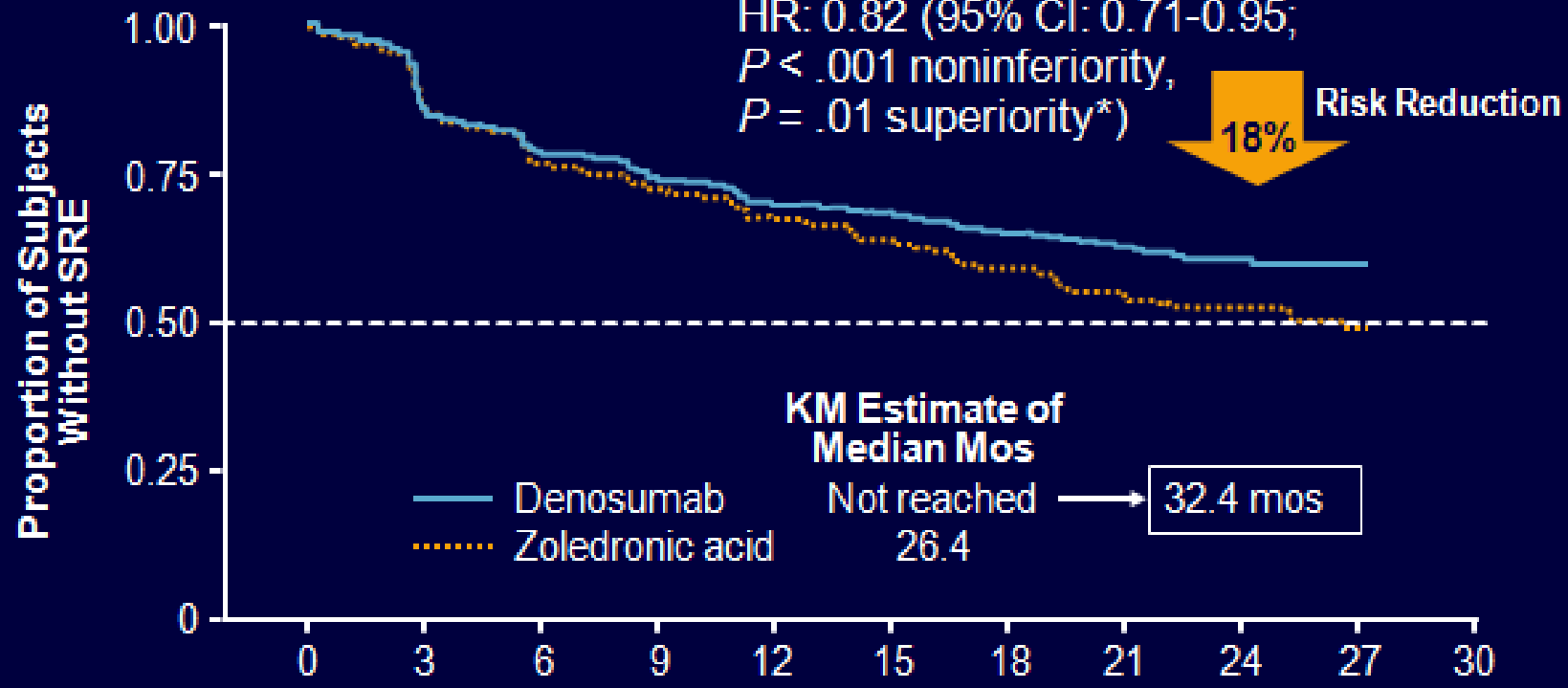
FPP

GGPP synthase

Geranylgeranyl diphosphate



Zoledronic Acid vs Denosumab in Breast Cancer Time to First On-Study SRE

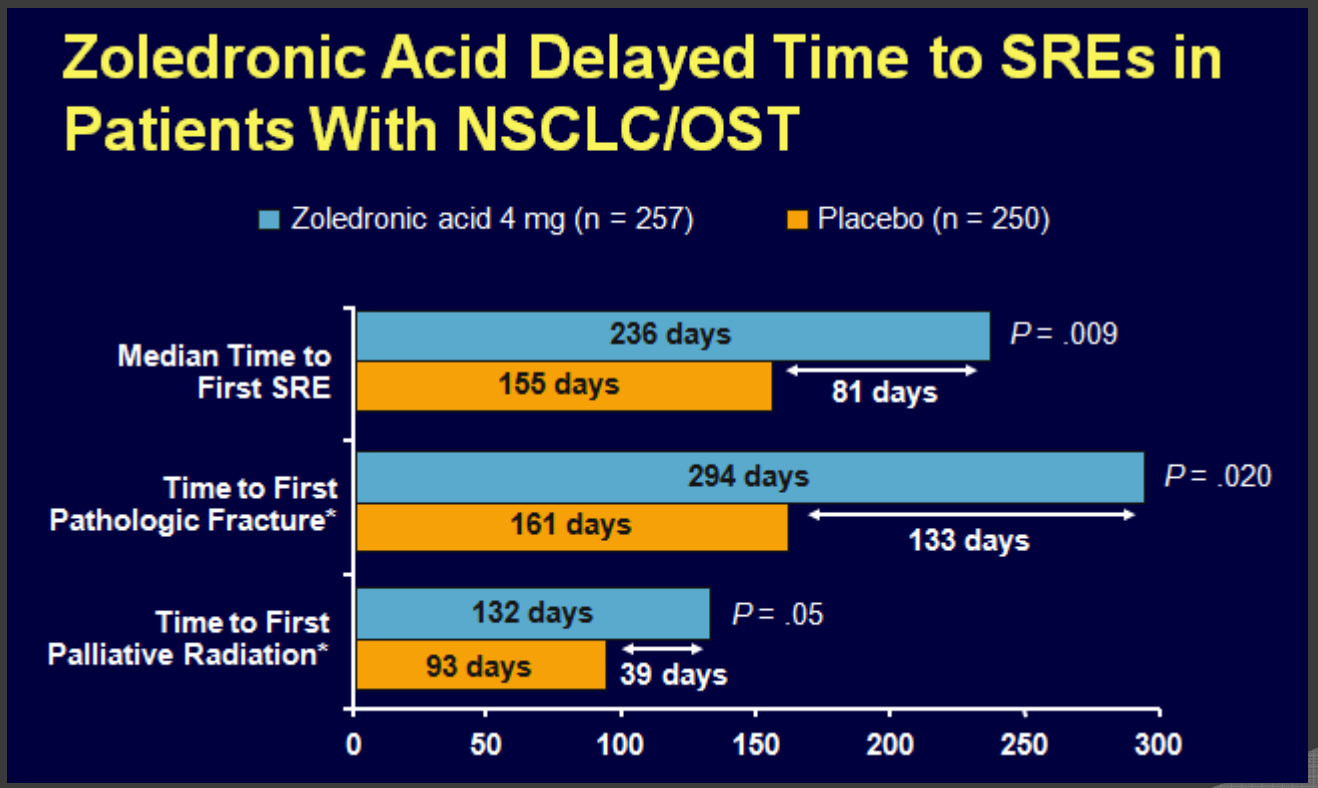


Patients at Risk, n										
Zoledronic acid	1020	829	676	584	498	427	296	191	94	29
Denosumab	1026	839	697	602	514	437	306	189	99	26

*Adjusted for multiplicity.

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

Zoledronic Acid Delayed Time to SREs in Patients With NSCLC/OST



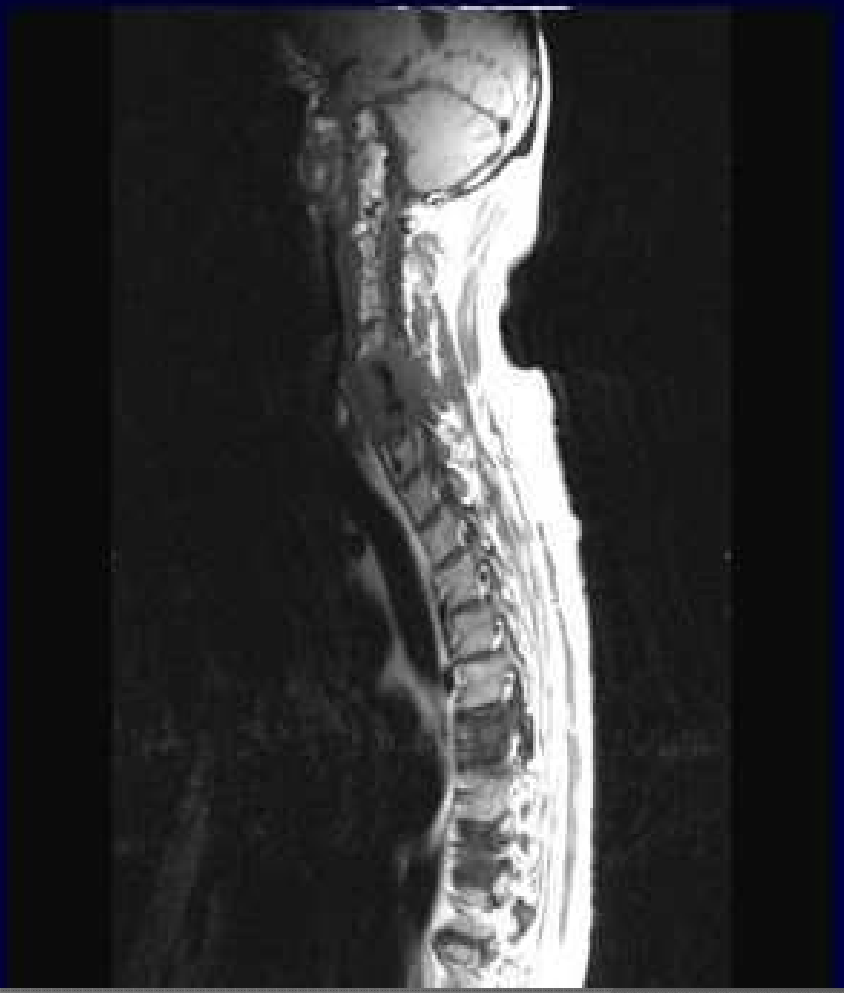
NCCN Guidelines

- Radium-223 is an NCCN category 1 recommendation for men with symptomatic bone-predominant CRPC
- Can be used before or after docetaxel given similar survival benefit
- Pts should be followed carefully for bone marrow toxicity prior to dosing and over time
- Concurrent use of hormonal therapies, external beam palliative radiation, steroids are reasonable given the lack of drug interactions and safety issues

NCCN Guidelines for Prostate Cancer, v.3.2016.

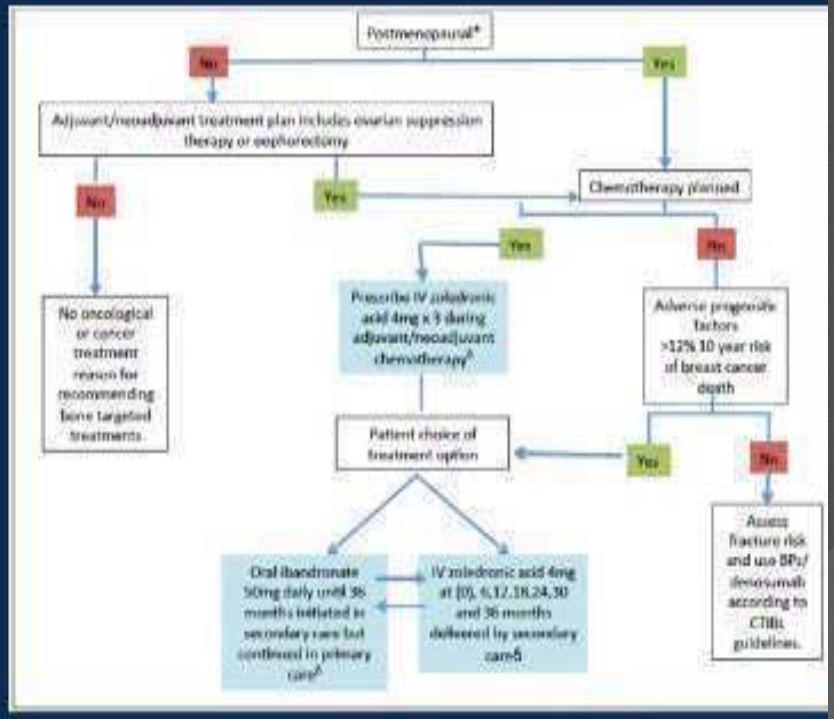
Complications of Bone Metastases

- Pain
- Fracture
- Spinal cord compression
- Hypercalcemia
- Skeletal complications account for 63% of hospital costs in patients with advanced breast cancer



Clinical Implications

- Consider potent bisphosphonates in patients with high risk early stage breast cancer
  - Post-menopausal or with OS/oophorectomy
  - Node positive, use of chemotherapy, other high risk features
  - Bone loss not required
- Denosumab: fracture prevention



Radium-223: Summary

Administration:

- Once every 4 wks for 6 infusions
- 60-second IV infusion
- Given by radiation oncologist or nuclear medicine radiologist
- Enteric excretion
- No pre-medication, no post-medication
- CBC check before each treatment

Clinical Benefit:

- Primary endpoint of improvement in symptomatic SRE
- 3.6-mo benefit in OS
- Should be considered in symptomatic men with bone-predominant mCRPC
- Consider spinal imaging for epidural disease in men with high burden of disease and rapid progression; palliative EBRT should be used if high risk for spinal cord compression

Cochrane Database of Systematic Reviews

Bisphosphonates in multiple myeloma: a network meta-analysis

New search | Conclusions changed | Review | Intervention

Rahul Mhaskar, Jasmina Redzepovic, Keith Wheatley, Otavio Augusto Camara Clark, Branko Miladinovic, Axel Glasmacher, Ambuj Kumar ✉, Benjamin Djulbegovic

Bisphosphonates for prevention of skeletal-related events in multiple myeloma

Patient or population: patients with prevention of skeletal-related events in multiple myeloma
Intervention: Bisphosphonates

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Bisphosphonates				
Overall mortality 2292 patients	Medium risk population		HR 0.96 (0.82 to 1.13)	2292 (12 studies)	⊕⊕⊖⊖ low [1,2,3]	
	530 per 1000	504 per 1000 (449 to 561)				
Progression-free survival 364 Patients	Medium risk population		HR 0.70 (0.41 to 1.19)	364 (4 studies)	⊕⊖⊖⊖ very low [1,4]	
	350 per 1000	260 per 1000 (162 to 401)				

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Vertebral fractures 1116 Patients	Low risk population[5]	RR 0.74 (0.62 to 0.89)	1116 (7 studies)	⊖⊖⊖⊖ moderate [1,6]
	100 per 1000 — 74 per 1000 (62 to 89)			
	Medium risk population[5]			
	350 per 1000 — 259 per 1000 (217 to 311)			
	High risk population[5]			
	690 per 1000 — 511 per 1000 (428 to 614)			
Nonvertebral fractures 1389 patients	Medium risk population	RR 1.03 (0.68 to 1.56)	1389 (6 studies)	⊖⊖⊖⊖ moderate [1,7]
	140 per 1000 — 144 per 1000 (95 to 218)			
Skeletal-related events 1497 patients	Low risk population[5]	RR 0.80 (0.72 to 0.89)	1497 (7 studies)	⊖⊖⊖⊖ moderate [1,8]
	240 per 1000 — 194 per 1000 (173 to 221)			
	Medium risk population[5]			

Cochrane Database of Systematic Reviews

Bisphosphonates in multiple myeloma: a network meta-analysis

New search | Conclusions changed | Review | Intervention

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Pain 1281 patients	Low risk population[5]		RR 0.75 (0.6 to 0.95)	1281 (8 studies)	⊖⊖⊖⊖ very low [9,10]
	60 per 1000	45 per 1000 (36 to 57)			
	Medium risk population[5]				
	500 per 1000	375 per 1000 (300 to 475)			
	High risk population[5]				
	1000 per 1000	750 per 1000 (600 to 950)			
Hypercalcemia 1934 patients	Medium risk population		RR 0.79 (0.56 to 1.11)	1934 (8 studies)	⊖⊖⊖⊖ moderate [1]
	100 per 1000	87 per 1000 (61 to 124)			