Bifosfonatos y MAb antirresortivos en Oncología

Controversias

Escenarios

- Metástasis óseas
- Reducción de riesgo de metástasis óseas (adyuvancia)
- Prevención y tratamiento de osteopenia secundaria a tratamientos oncológicos
- Hipercalcemia
- Tratamiento del Tumor de Células Gigantes

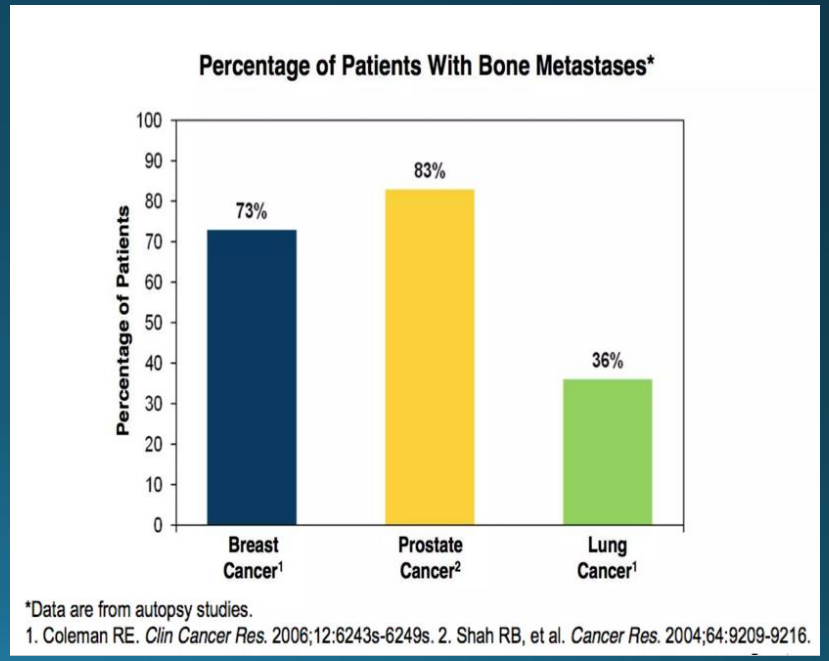
Metástasis Óseas

- Es uno de los sitios más frecuentes de metástasis
- Vía hematógena
- Diferentes modos de diseminación, de presentación y pronóstico dependiendo del origen
- Condicionan la calidad de vida
- Merecen un abordaje específico independientemente del origen

Metástasis Óseas

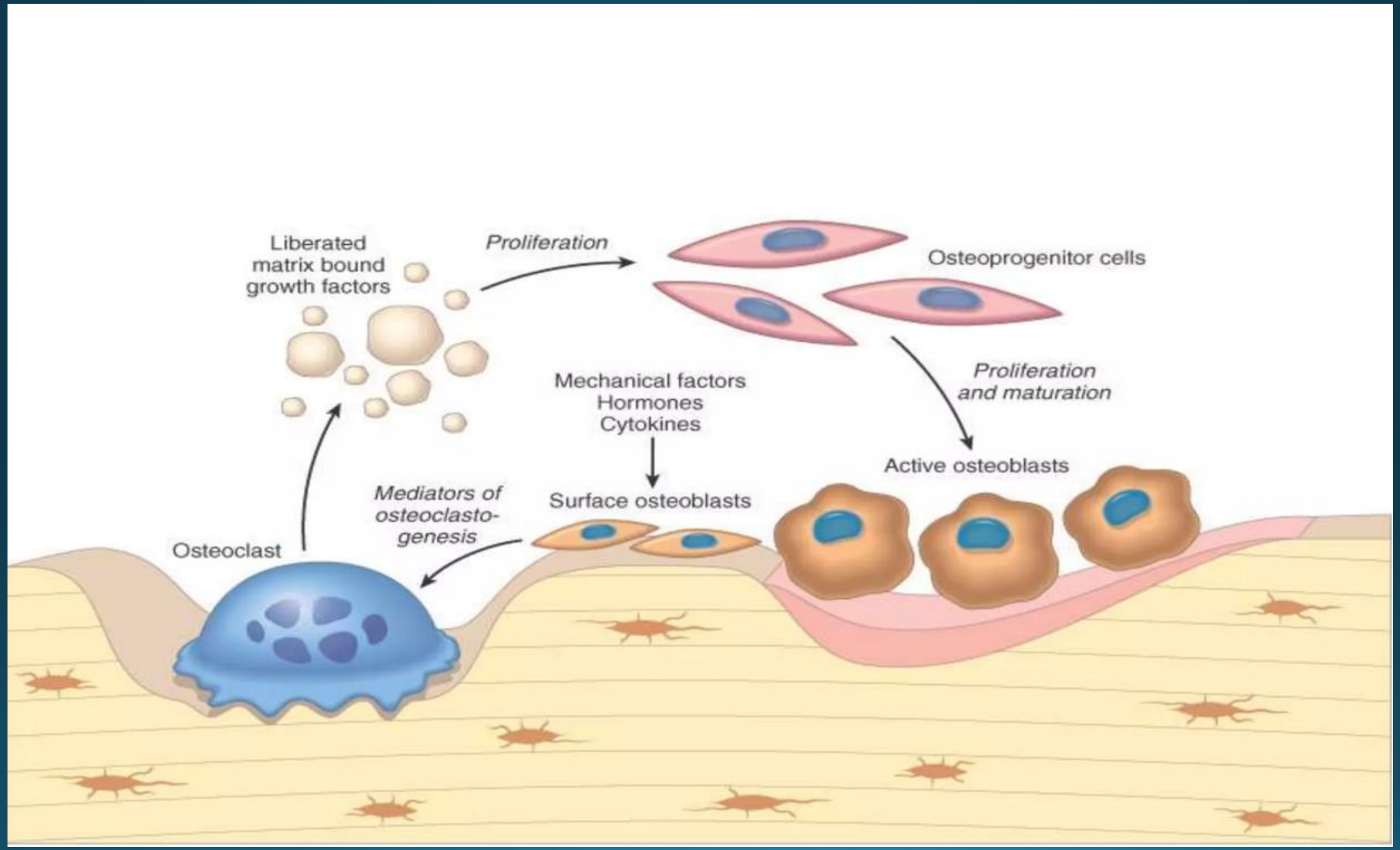
- Los sitios más comunes de afección son:
  - Vértebras
  - Costillas
  - Pelvis ósea

- Los tumores que afectan con más frecuencia el hueso son:
  - Mama
  - Pulmón
  - Próstata
  - Riñón
  - Tiroides



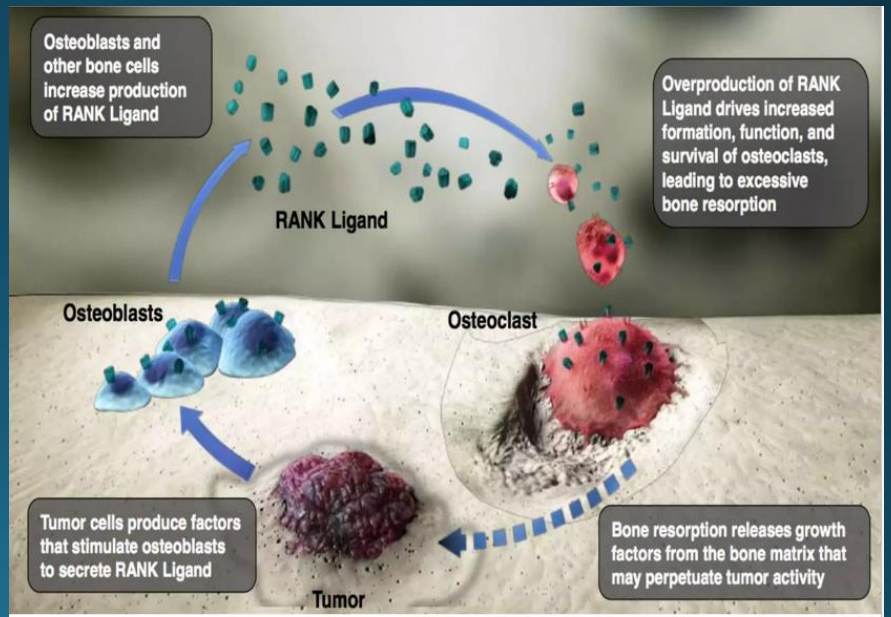
Metástasis Óseas

- Entre el 8 y el 30% de los pacientes pueden experimentar fracturas patológicas
- El sitio más frecuente es el fémur proximal
- El síntoma de presentación más común es el dolor progresivo
- Otros: mieloptisis, hipercalcemia, compresión medular o radicular


Liberated
matrix bound
growth factors
Proliferation
Osteoprogenitor cells
Proliferation
and maturation
Mechanical factors
Hormones
Cytokines
Active osteoblasts
Mediators of
osteoclasto-
genesis
Surface osteoblasts
Osteoclast

Metástasis Óseas

- 1. Intravasación de células tumorales
- 2. Migración facilitada por PDGF
- 3. Atracción por quimiocina CKCL12 de las células estromales del hueso
- 4. Invasión por medio de metaloproteinasas
- 5- Inducción de angiogénesis
- 6. Liberación de factores activadores de osteoblastos
- 7. Secreción de RANKLs que se unen a RANK (receptor activador del factor nuclear Kappa-b) de los osteoclastos activándolos



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

Evaluación de Metástasis Óseas

- Imágenes
  - Radiología
  - TAC
  - RMN
  - COT – PET/TC
- LAB
  - Hemograma/Plaquetas
  - FAL
  - Calcemia
- AP
  - Primario desconocido
  - Confirmación histológica
  - Tumor primario

Tratamiento de las Metástasis Óseas

Objetivos

- Control del dolor
- Preservación o recuperación de la función
- Prevención de complicaciones (fractura, compresión, etc.)
- Prolongación de la supervivencia
- Curación?

Table 1. Management of skeletal related events.

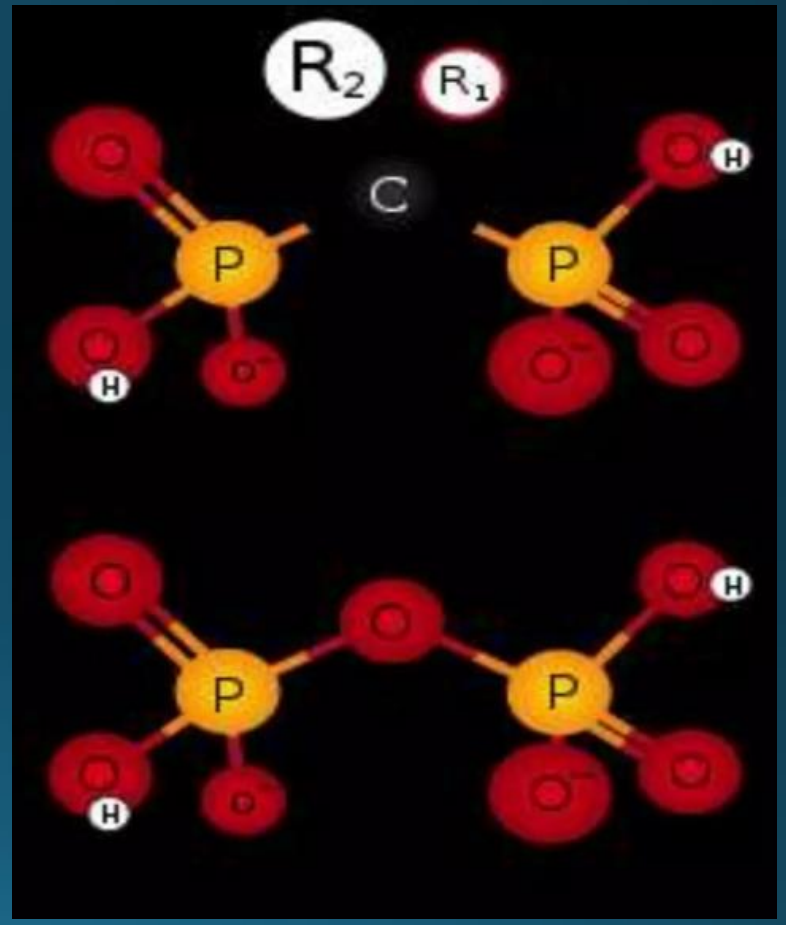
Skeletal Related Event	Management	Effects
Bone pain	NSAIDs, Opioids	Analgesic effects
	Bisphosphonates	Inhibition of pathological bone resorption Analgesic effects
	Denosumab	Inhibition of pathological bone resorption Analgesic effects
	Radiation	Analgesic effects Tumor shrinkage
Pathological bone fracture	Surgery	Stabilization of fracture
	Radiation	Supportive therapy to prevent local recurrence
	Bisphosphonates	Prophylaxis
	Denosumab	Prophylaxis
Spinal cord compression	Steroids	Stabilization of vascular membranes Reduction of inflammation and edema
	Radiation	Tumor shrinkage effects
	Surgery	Relief for the compression
	Bisphosphonates	Prophylaxis
	Denosumab	Prophylaxis
Hypercalcemia	Hydration	Promotion of renal calciuresis
	Loop diuretics	Promotion of renal calciuresis
	Bisphosphonates	Inhibition of pathological bone resorption
	Denosumab	Inhibition of pathological bone resorption

NSAID: nonsteroidal anti-inflammatory drug.

Bifosfonatos

- Análogos del pirofosfato donde el oxígeno en p-o-p es reemplazado por un carbono (p-c-p)

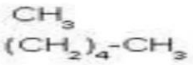
- Estructura metabólicamente más estable y resistente a la degradación enzimática



Bifosfonatos

- Tienen dos cadenas:
  - R1: sitio de unión y afinidad con el hueso
  - R2: capacidad antirresortiva y efectos secundarios

- Varían en potencia según la estructura de estas cadenas

Agent	R_1 side chain	R_2 side chain
Etidronate	-OH	$-CH_3$
Clodronate	-Cl	-Cl
Tiludronate	-H	-S-  -Cl
Pamidronate	-OH	$-CH_2-CH_2-NH_2$
Neridronate	-OH	$-(CH_2)_5-NH_2$
Olpadronate	-OH	$-(CH_2)_2N(CH_3)_2$
Alendronate	-OH	$-(CH_2)_3-NH_2$
Ibandronate	-OH	$-CH_2-CH_2N$ 
Risedronate	-OH	
Zoledronate	-OH	

Bifosfonatos

Mecanismo de acción

- Intervienen en el metabolismo óseo inhibiendo la vía del mevalonato
- Afectan la osteoclastogénesis y producen apoptosis celular
- El más utilizado es el Zoledronato, que demostró actividad tanto en lesiones líticas como blásticas

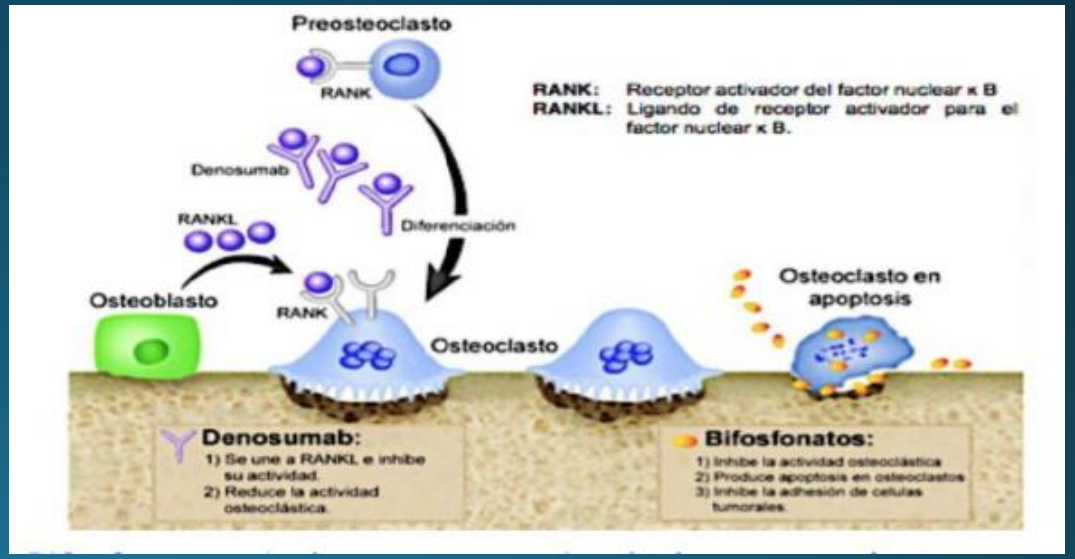
Bifosfonatos

Efectos adversos

- Gastrointestinales: esofagitis, gastritis, N/V, estreñimiento
- Deterioro de la Función Renal
- Hipocalcemia
- Osteonecrosis del hueso mandibular

Denosumab

- Es un Mab humano que se une al ligando del receptor activador del factor nuclear kappa (RANKL) evitando la activación de RANK
- Inhibición de la proliferación y diferenciación de osteoclastos
- Reduce la formación de osteoclastos y la resorción ósea, aumentando la densidad ósea



ZOLEDRONATO

Review > Clin Breast Cancer. 2005 Jun;6(2):125-31. doi: 10.3816/CBC.2005.n.014.

Efficacy and safety of intravenous bisphosphonates for patients with breast cancer metastatic to bone: a review of randomized, double-blind, phase III trials

David H Gordon [1]

Original

The New B... Decreases Skeletal Complications in Both Osteolytic and Osteoblastic Lesions: A Comparison to Pamidronate

Allan Lipton, E. Small, Fred Saad, D. Gleason, David Gordon, M. Smith, ...show all

Pages 45-54 | Published online: 24 Sep 2002

...onate in the treatment ...nts with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial

L S Rosen [1], D Gordon, M Kaminski, A Howell, A Belch, J Mackey, J Apffelstaedt, M Hussein, R E Coleman, D J Reitsma, J J Seaman, B L Chen, Y Ambros

Denosumab

Randomized Controlled Trial > Clin Cancer Res. 2006 Feb 15;12(4):1221-8.
doi: 10.1158/1078-0432.CCR-05-1933.

**A study of the biological recept
factor-kappaB ligand inhibitor,
patients with multiple myelom
from brea**

Jean-Jacques Boc
Donna Holloway,

Clinical Trial > J Clin Oncol. 2007 O
Epub 2007 Sep 4.

**Randomized active-c
denosumab efficacy
breast cancer-relate**

Allan Lipton [1], Guenther G Steger, Jazmin Figueroa, Cristina Alvarado, Philippe Solal-Celigny, Jean-Jacques Body, Richard de Boer, Rossana Berardi, Pere Gascon, Katia S Tonkin, Robert Coleman, Alexander H G Paterson, Mark C Peterson, Michelle Fan, Amy Kinsey, Susie Jun

Clinical Trial > J Clin Oncol. 2009 Apr 1;27(10):1564-71. doi: 10.1200/JCO.2008.19.2146.
Epub 2009 Feb 23.

Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates

Karim Fizazi [1], Allan Lipton, Xavier Mariette, Jean-Jacques Body, Yasmin Rahim, Julie R Gralow, Guozhi Gao, Ling Wu, Winnie Sohn, Susie Jun

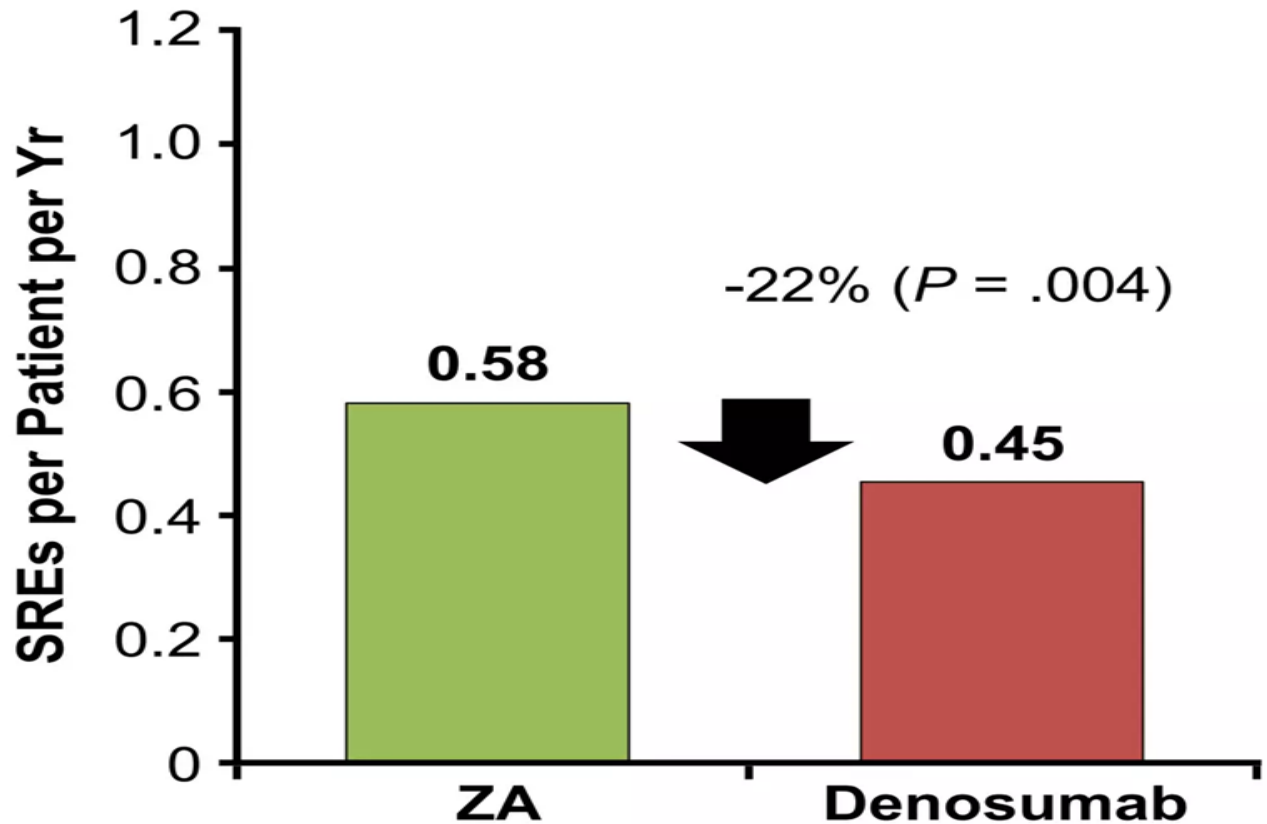
Cáncer de Mama

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

Alison T. Stopeck, Allan Lipton, Jean-Jacques Body, Guenther G. Steger, Katia Tonkin, Richard H. de Boer, Mikhail Lichinitser, Yasuhiro Fujiwara, Denise A. Yardley, María Viniegra, Michelle Fan, Qi Jiang, Roger Dansey, Susie Jun, and Ada Braun

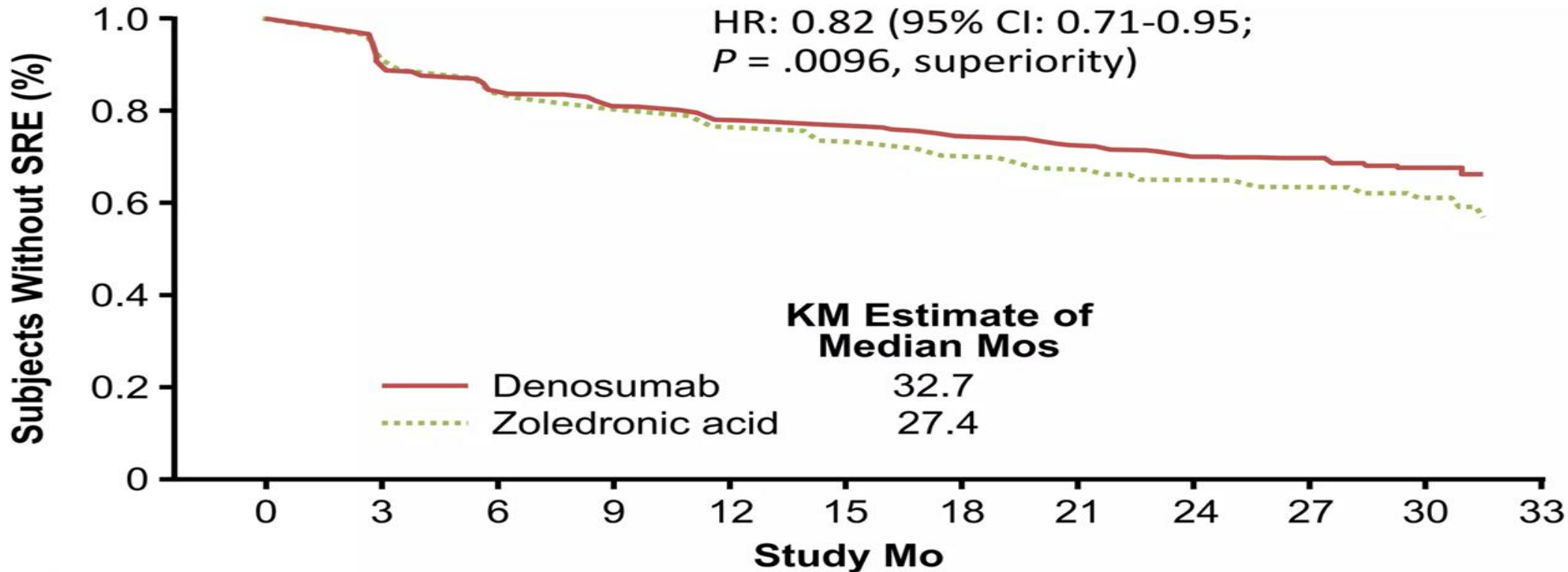
J Clin Oncol 28:5132-5139. © 2010

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



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

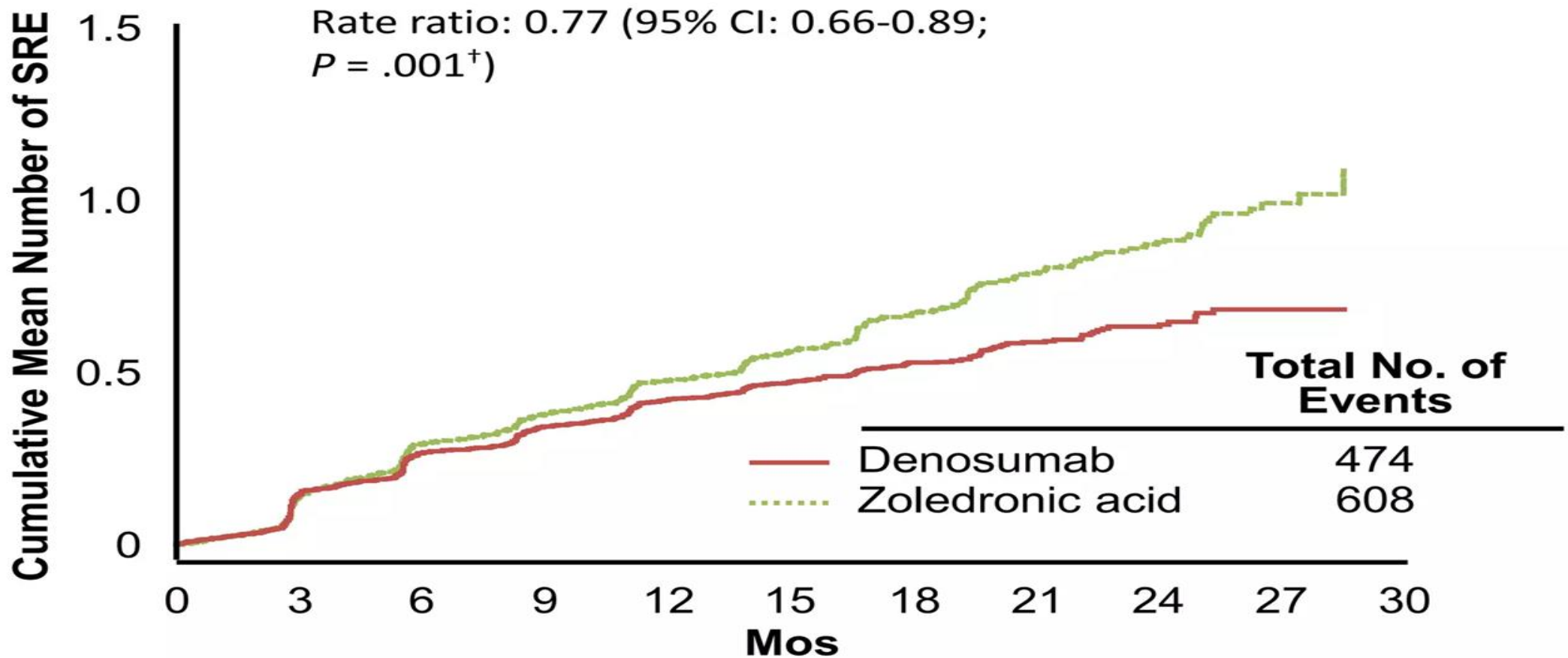
Time to First On-Study SRE: Extended Analysis



Patients at Risk, n

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

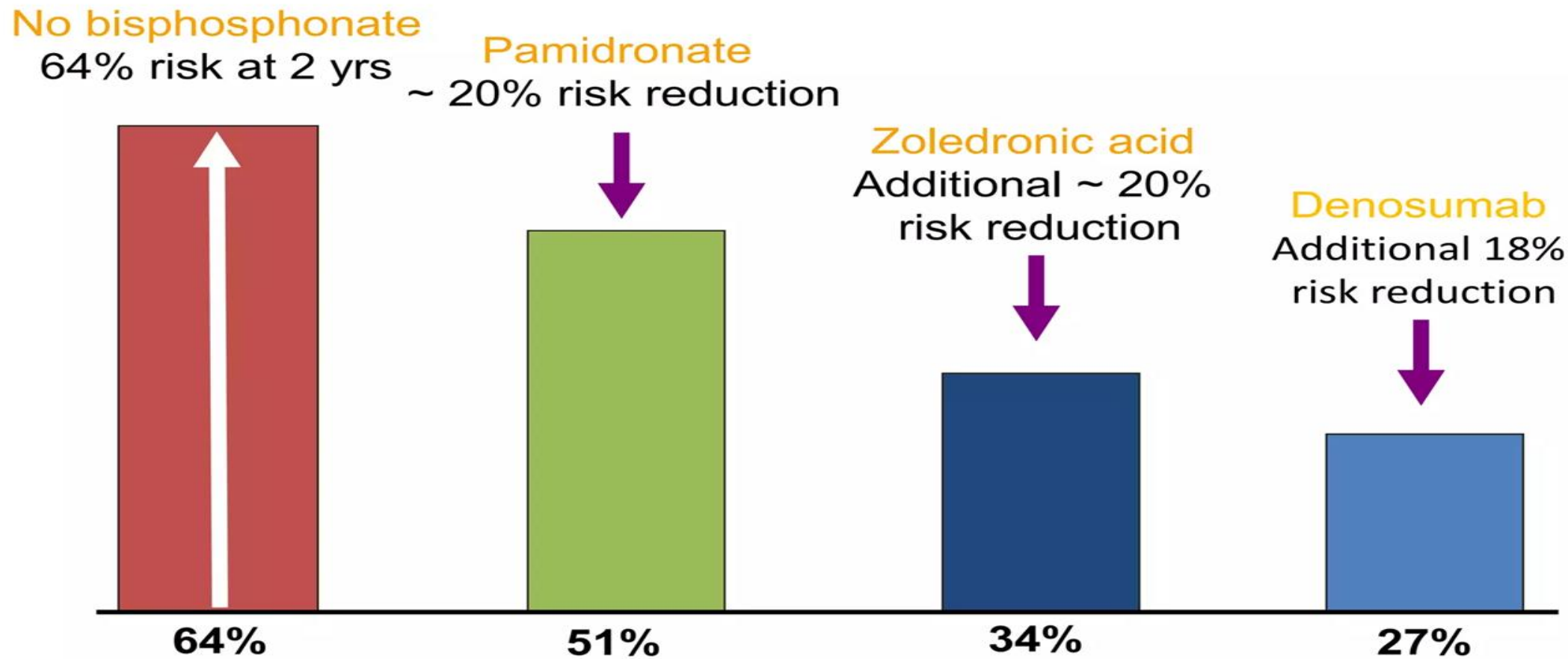
Time to First and Subsequent On-Study SRE* (Multiple Event Analysis)



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

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

Skeletal Complication Risk: Incremental Benefits in Breast Cancer



Lipton A, et al. Cancer. 2000;88:3033-3037. Rosen LS, et al. Cancer. 2003;100:36-43. Stopeck A, et al. ECCO/ESMO 2009. Abstract 2LBA. Stopeck AT, et al. J Clin Oncol. 2010;28:5132-5139.

Cáncer de Próstata

Open access Review

ESMO Open
Cancer Horizons

Check for updates

Bone health management in the continuum of prostate cancer disease: a review of the evidence with an expert panel opinion

Daniele Santini [1], Alfredo Berruti,[2] Massimo Di Maio [3], Giuseppe Procopio,[4] Sergio Bracarda,[5] Toni Ibrahim,[6] Francesco Bertoldo[7]

Cáncer de Próstata

- El riesgo de fracturas en pacientes con enfermedad hormono sensible y resistentes a castración varía entre 5% y 48%
- El riesgo de muerte es 2,4 veces mayor en un paciente con fractura de cadera
- ADT tienen un efecto negativo en la salud ósea

Cáncer de Próstata

- Enfermedad M0 HS
  - Densoumab demostró una reducción en la incidencia de fracturas óseas (1.5% vs 3.9% RR 0.38, 95% CI 0.19 to 0.78; p=0.006), en un estudio randomizado contra placebo

- Enfermedad M1 HS
  - Zoledronato no demostró beneficio en pacientes con metástasis óseas (CALGB 90202)
  - Las guías actuales no recomiendan el uso de BMAs

Cáncer de Próstata

- Enfermedad M1 CR
  - BMAs demostraron beneficio clínico en términos de OS, ECOG y demora en la necesidad de opioides
  - En pacientes con enfermedad ósea, Denosumab demostró ser superior a Zoledronato

Cáncer de Pulmón

Clin Orthop Relat Res (2021) 479:2047-2057
DOI 10.1097/CORR.0000000000001749

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

Clinical Research

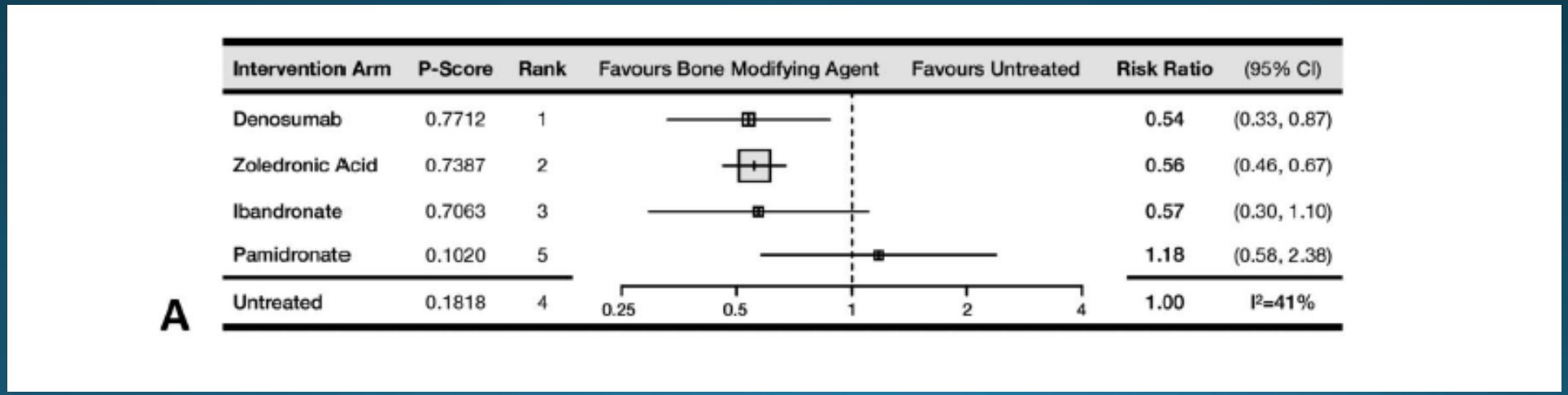
Which Bone-Modifying Agent is Associated with Better Outcomes in Patients with Skeletal Metastases from Lung Cancer? A Systematic Review and Network Meta-analysis

Anthony Bozzo MD, MSc[1], Jiawen Deng BSc[2], Umaima Abbas BSc[2], Richa Bhasin BSc[2], Marisa Deodat BSc[2], Sajid Wariach BSc[2], Stephanie Sanger BSc[2], Daniel Axelrod MD, MSc[1], Karim Masrouha MD[1,3], Robert Turcotte MD, FRCSC[4], David Wilson MD, FRCSC[1,3], Michelle Ghert MD, FRCSC[1,2,3]

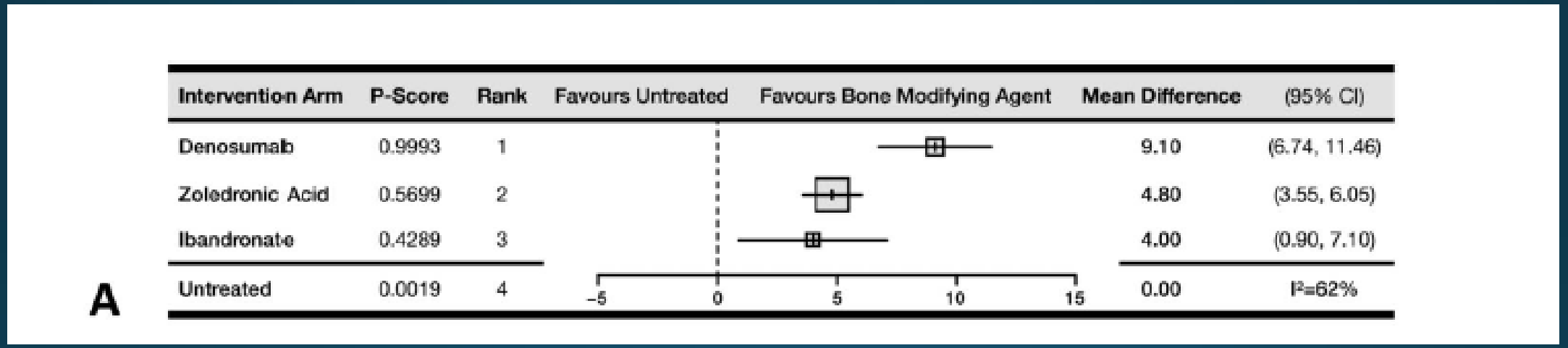
Received: 23 February 2021 / Accepted: 5 March 2021 / Published online: 7 April 2021

Incidencia de SRE:

- Denosumab y Zoledronato fueron igualmente efectivos
- El HR fue de 0.54 (95% CI 0.33-0.87) para Denosumab y 0,56 (95% CI 0.46-0.67) para Zoledronato
- No hubo beneficio para los pacientes tratados con Ibandronato o Pamidronato



Cáncer de Pulmón



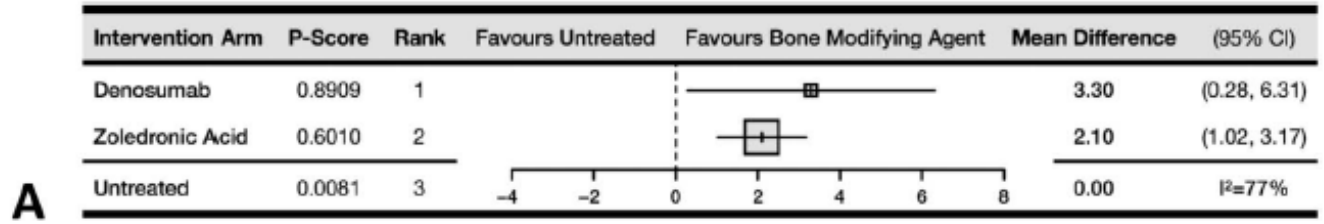
Intervention Arm	P-Score	Rank	Mean Difference	(95% CI)
Denosumab	0.9993	1	9.10	(6.74, 11.46)
Zoledronic Acid	0.5699	2	4.80	(3.55, 6.05)
Ibandronate	0.4289	3	4.00	(0.90, 7.10)
Untreated	0.0019	4	0.00	I^2=62%

A

Tiempo al primer SRE:

- Denosumab fue la terapia más efectiva, con una prolongación del tiempo a SRE de 9,1 meses
- Zoledronato e Ibandronato prolongaron el tiempo a SRE en 4,8 y 4 meses respectivamente

Cáncer de Pulmón



Intervention Arm	P-Score	Rank	Favours Untreated	Favours Bone Modifying Agent	Mean Difference	(95% CI)
Denosumab	0.8909	1			3.30	(0.28, 6.31)
Zoledronic Acid	0.6010	2			2.10	(1.02, 3.17)
Untreated	0.0081	3			0.00	I^2=77%

OS:

Denosumab y Zoledronato prolongan la supervivencia en 3,3y 2,1 meses respectivamente comparados con pacientes no tratados

Otros Tumores Sólidos

Análisis integrado pre-especificado de 3 estudios de igual diseño

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

Alison T. Stopeck, Allan Lipton, Jean-Jacques Body, Guenther G. Steger, Katia Tonkin, Richard H. de Boer, Mikhail Lichinitser, Yasuhiro Fujiwara, Denise A. Yardley, María Viniegra, Michelle Fan, Qi Jiang, Roger Dansey, Susie Jun, and Ada Braun

J Clin Oncol 28:5132-5139. © 2010

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

Karim Fizazi, Michael Carducci, Matthew Smith, Ronaldo Damião, Janet Brown, Lawrence Karsh, Piotr Milecki, Neal Shore, Michael Rader, Huei Wang, Qi Jiang, Sylvia Tadros, Roger Dansey, Carsten Goessl

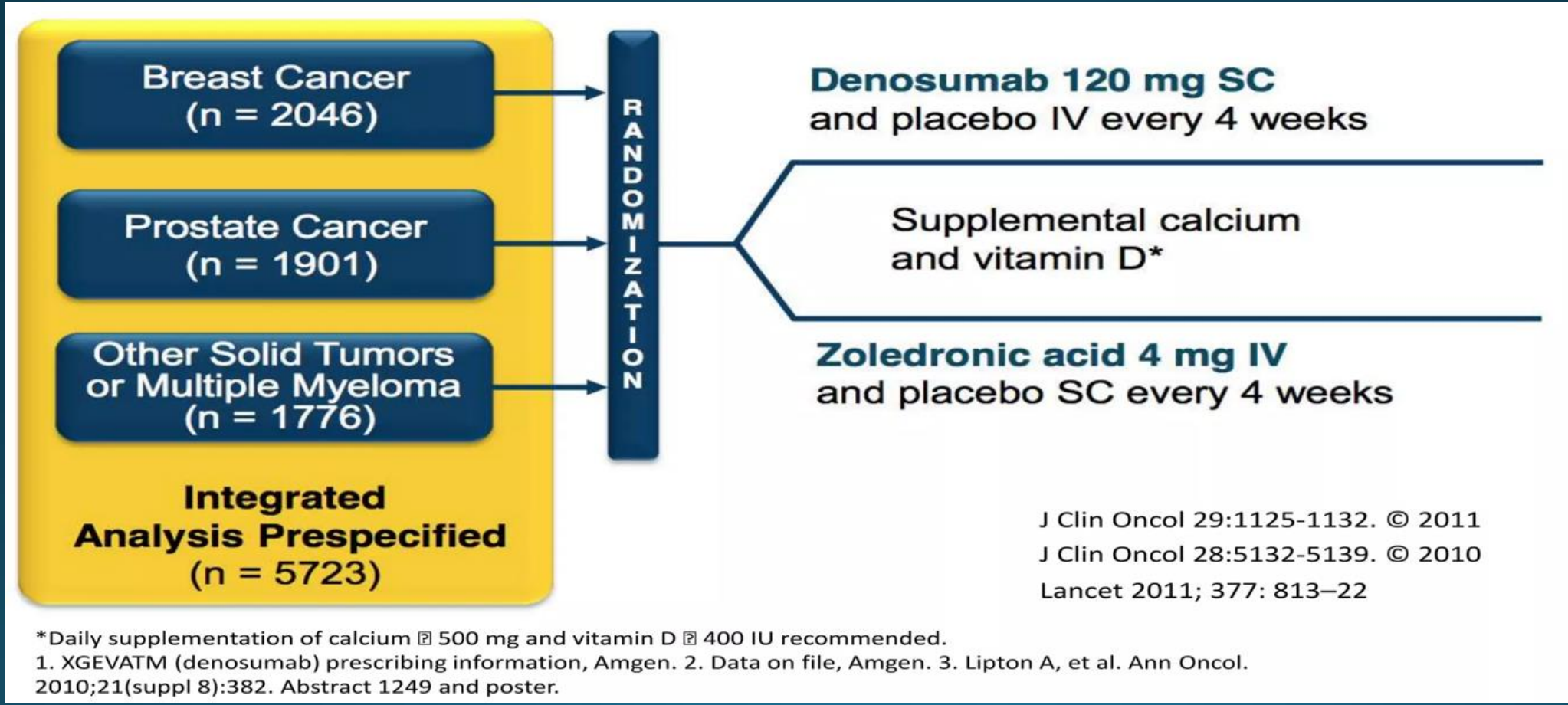
Lancet 2011; 377: 813–22

Randomized, Double-Blind Study of Denosumab Versus Zoledronic Acid in the Treatment of Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma

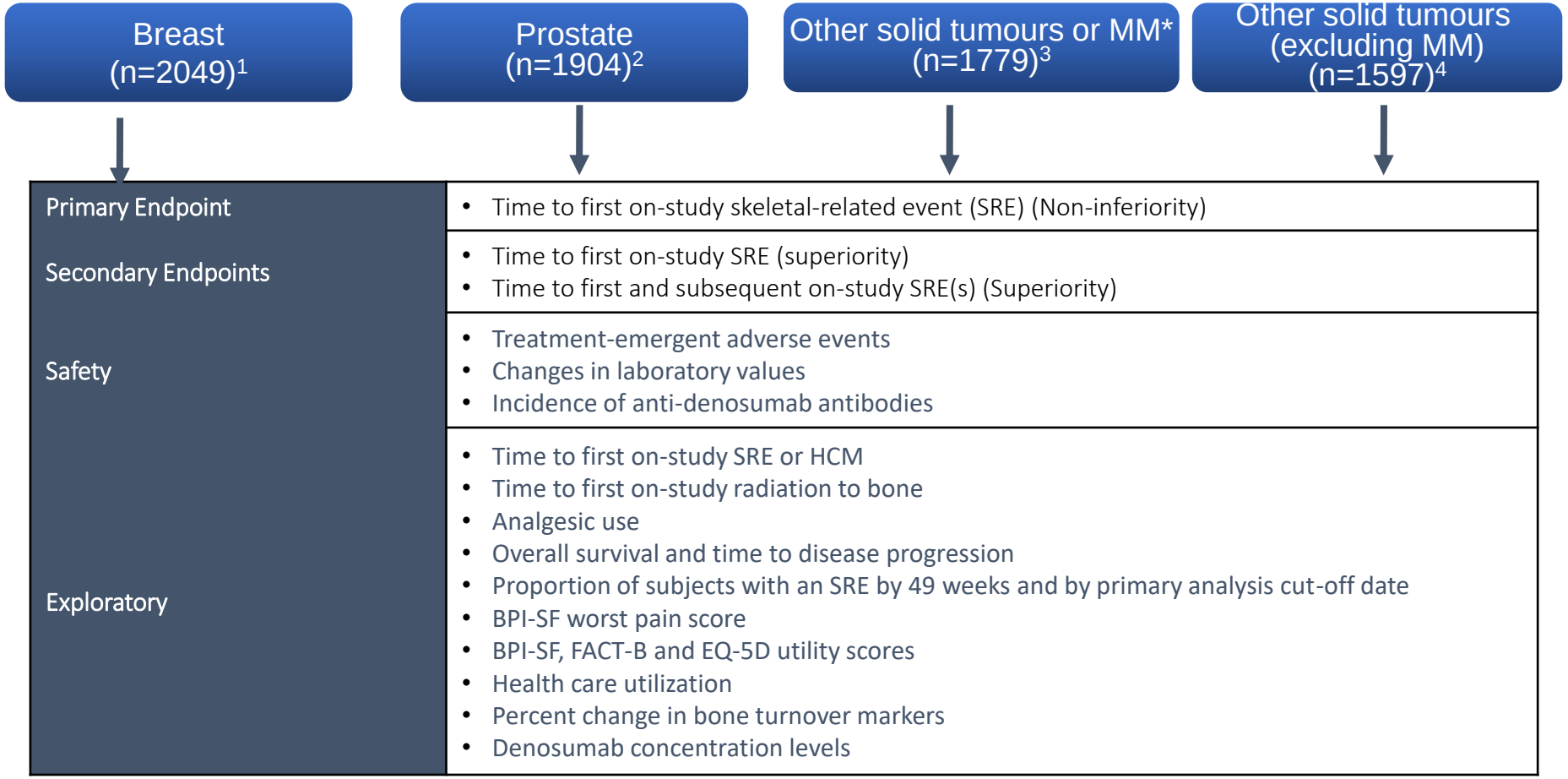
David H. Henry, Luis Costa, Francois Goldwasser, Vera Hirsh, Vania Hungria, Jana Prausova, Giorgio Vittorio Scagliotti, Harm Sleeboom, Andrew Spencer, Saroj Vadhan-Raj, Roger von Moos, Wolfgang Willenbacher, Penella J. Woll, Jianming Wang, Qi Jiang, Susie Jun, Roger Dansey, and Howard Yeh

J Clin Oncol 29:1125-1132. © 2011

Análisis integrado pre-especificado de 3 estudios de igual diseño



Pre-planned Integrated Analysis



1. Stopeck AT, et al. J Clin Oncol 2010;28:5132-9; 2. Fizazi K, et al. Lancet 2011;377:813-22;
3. Henry DH, et al. J Clin Oncol 2011;29:1125-32; 4. Henry D, et al. Support Care Cancer 2014;22:679–87

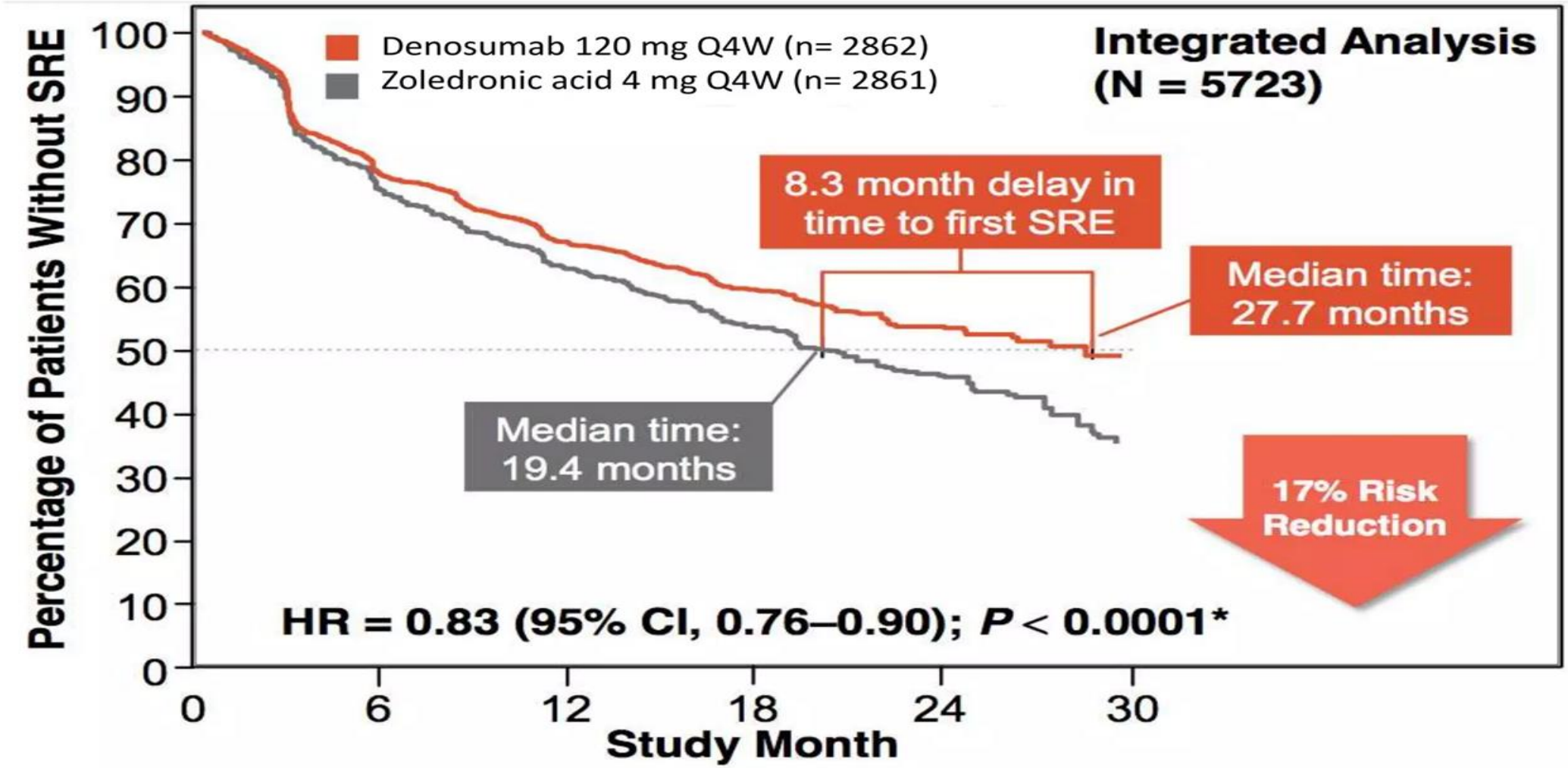
SRE=skeletal-related event, ST=solid tumor;
MM=multiple myeloma
.

Characteristics	Denosumab (n=2862)	Zoledronic Acid (n=2861)
Tumor type*, n (%)		
Breast	1026 (36)	1020 (36)
Prostate	950 (33)	951 (33)
Non-small cell lung	350 (12)	352 (12)
Multiple myeloma	87 (3)	93 (3)
Renal	70 (2)	85 (3)
Small cell lung	61 (2)	48 (2)
Bladder	28 (1)	35 (1)
Rectal	25 (1)	35 (1)
Colon	30 (1)	29 (1)
Other[#]	235 (8)	213 (7)

*Based on randomization; total number may not equal 100% due to rounding; [#]Includes >50 other tumor types each representing 1% or less of total sample

Lipton A, et al. *Eur J Cancer* 2012;48:3082-92

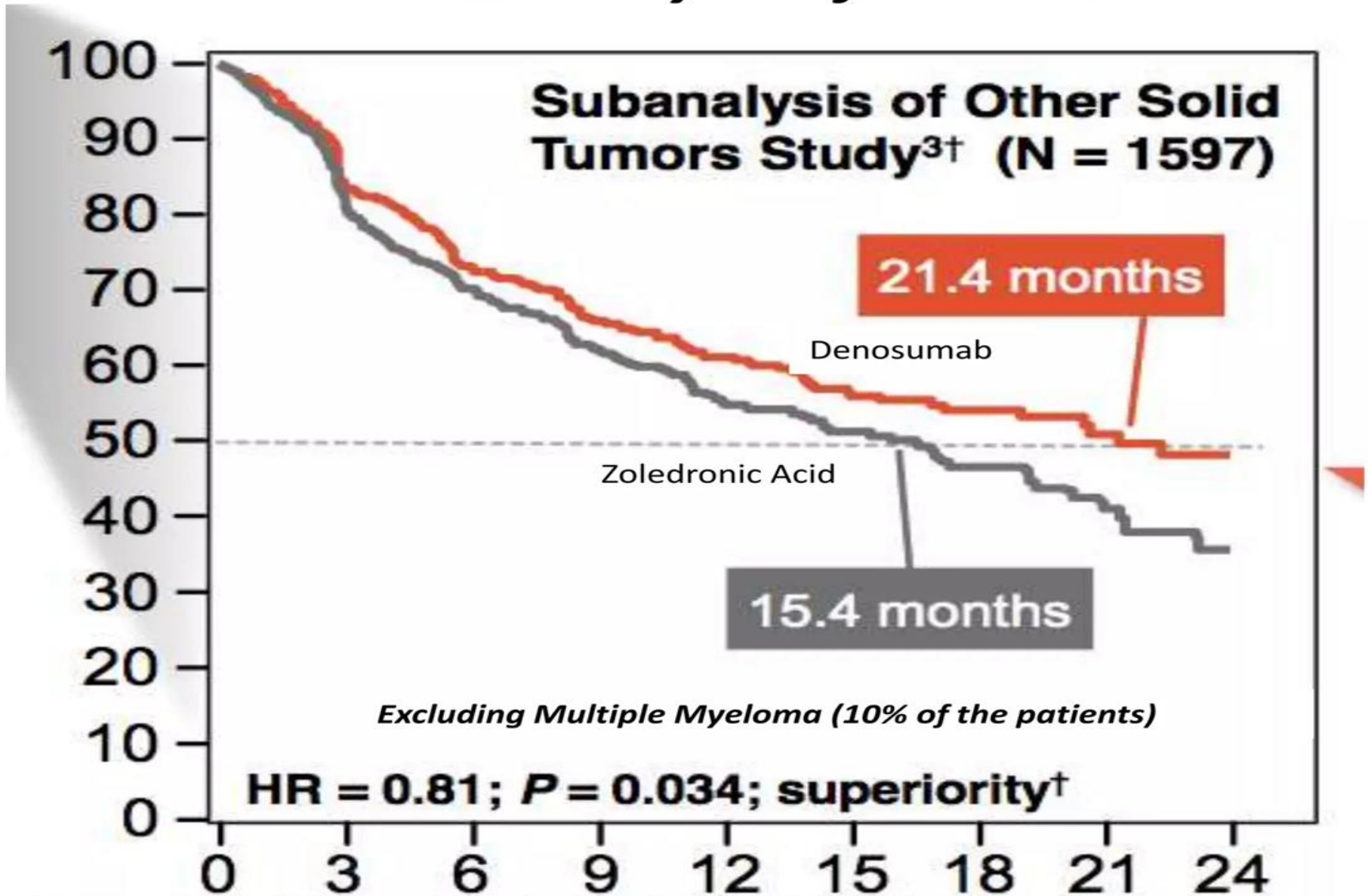
Denosumab Was Superior to Zoledronic Acid: 17% Risk Reduction in First SRE



P value for superiority.

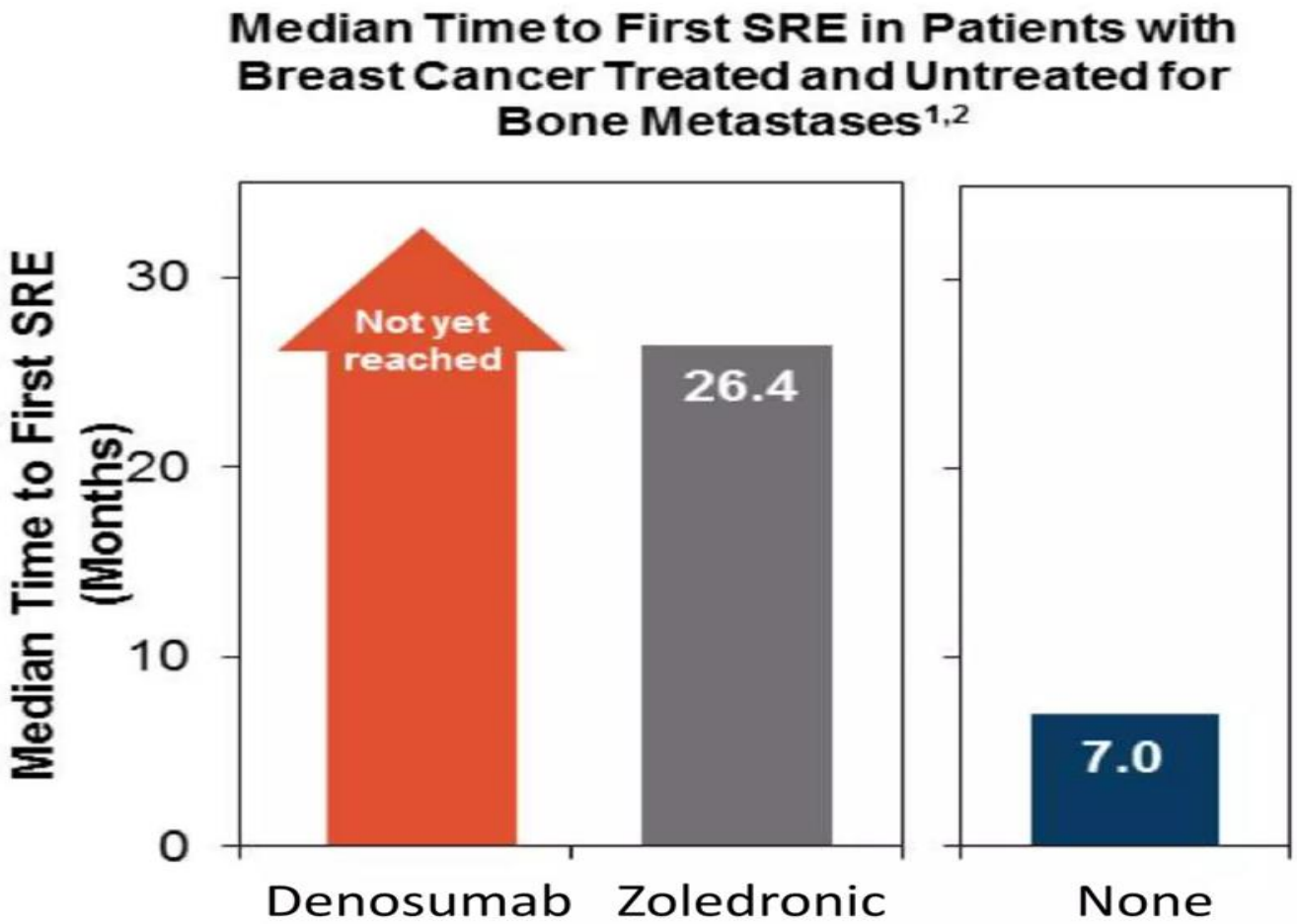
1. Data on file, Amgen. 2. Lipton A, et al. Ann Oncol. 2010;21(suppl 8):382. Abstract 1249 and poster.

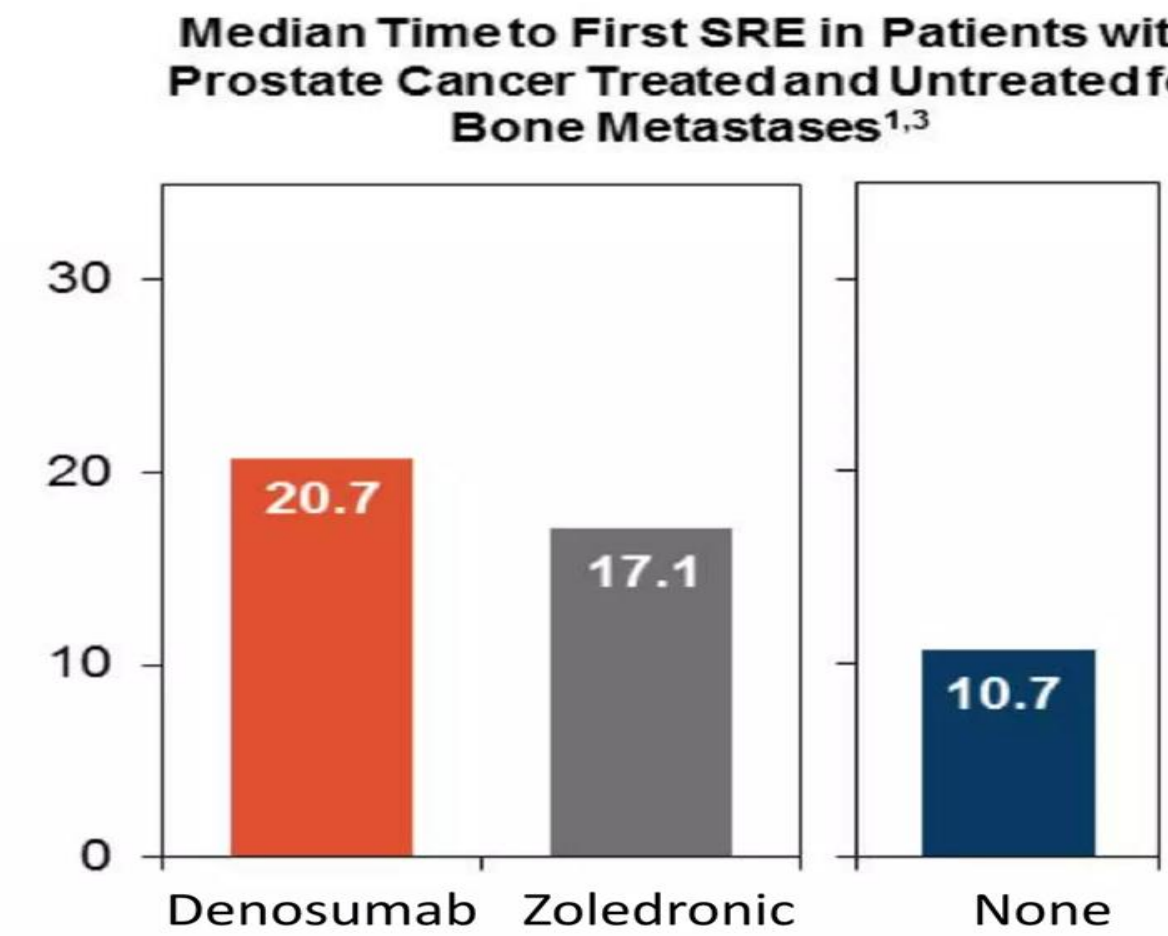
Proven Efficacy in Multiple Solid Tumor Types: Reduction in Risk in the Subanalysis of Other Solid Tumors



Henry D, et al. Presentation at: ASCO Annual Meeting. June 4-8, 2010; Chicago, IL

Increased Time to First SRE

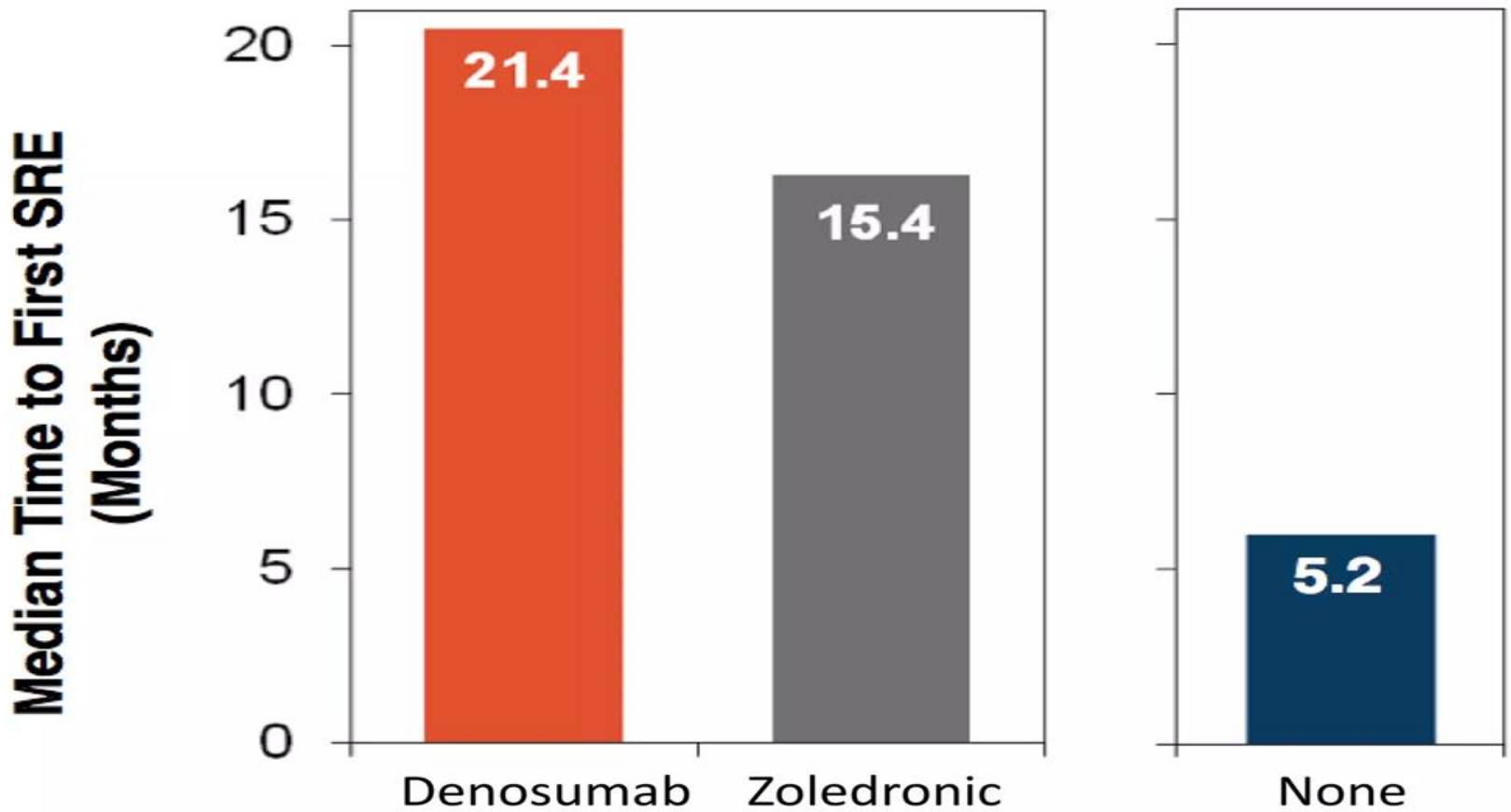




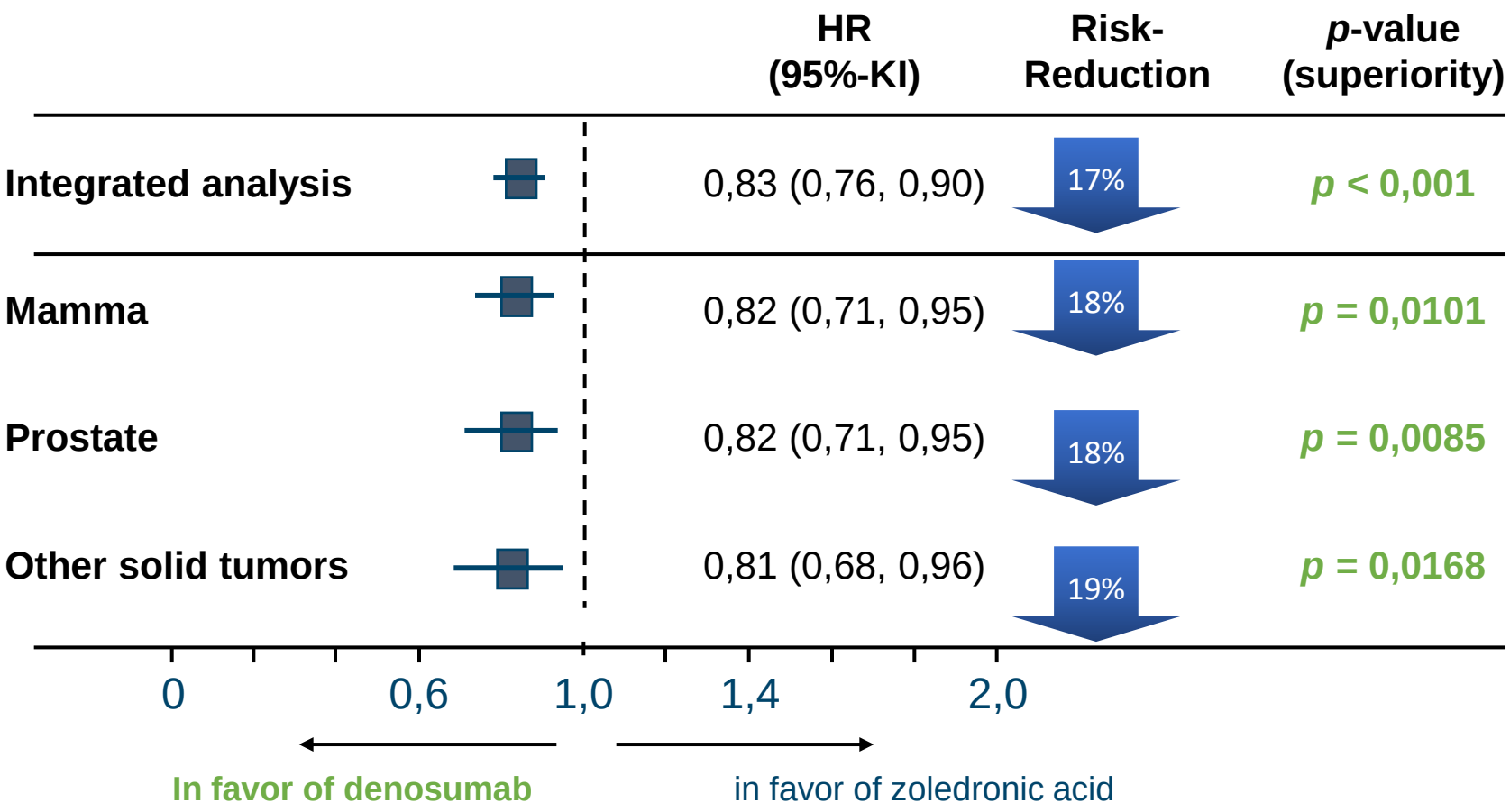
1. Denosumab prescribing information, Amgen. 2. Lipton A, et al. Cancer 2000;88:1082-1090. 3. Saad F, et al. J Natl Cancer Inst. 2002;94:1458-1468.

Increased Time to First SRE

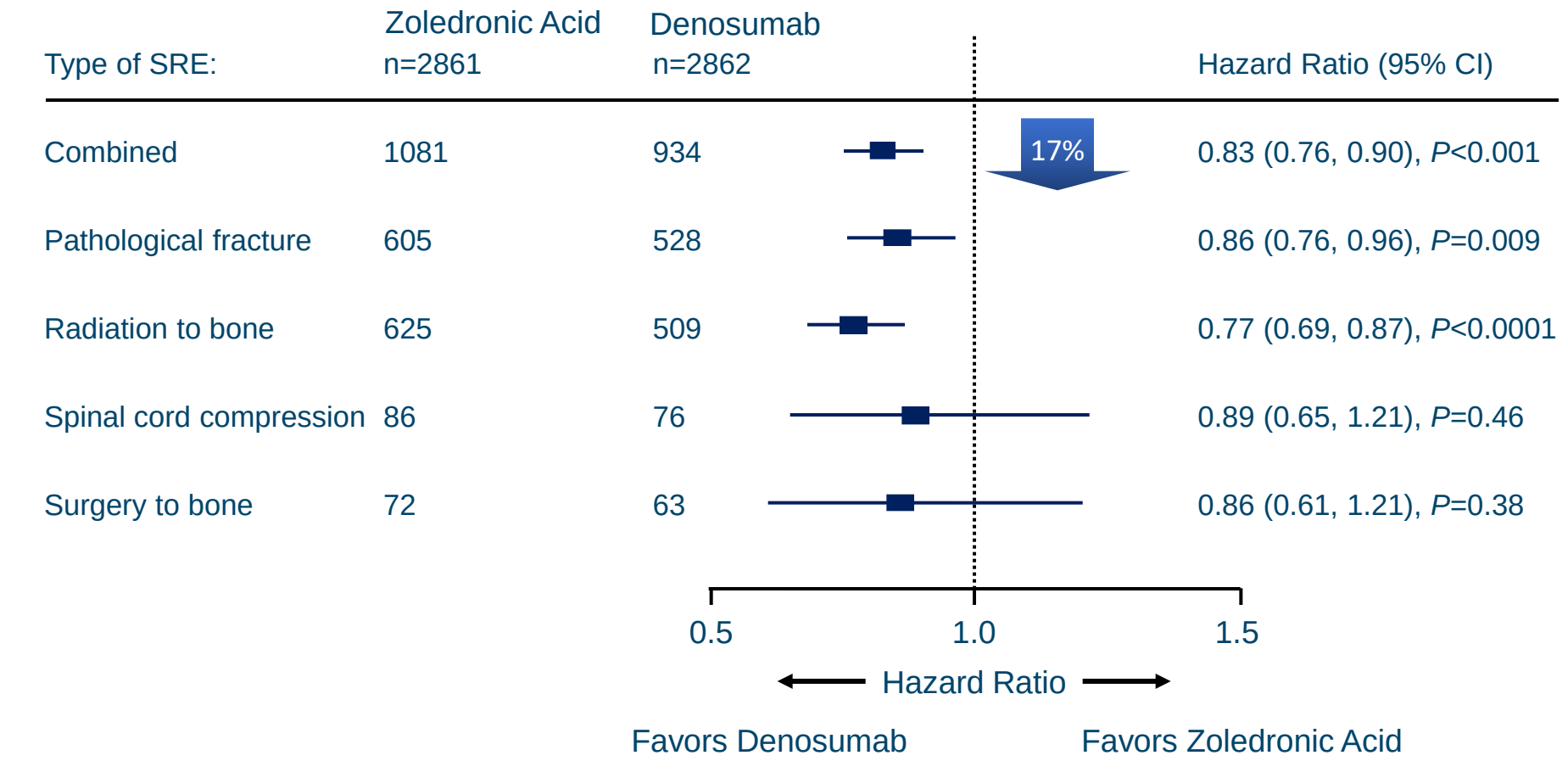
Median Time to First SRE in Patients with Other Solid Tumors Treated and Untreated for Bone Metastases[1,2]



1. Henry D, et al. Presentation at: ASCO Annual Meeting. June 4-8, 2010; Chicago, ILL. 2 Rosen LS, et al. Cancer. 2004;100:2613-2621.



Richardson G, Siena S, Lipton A, et al. *COSA 2011*: Abstract und Vortrag

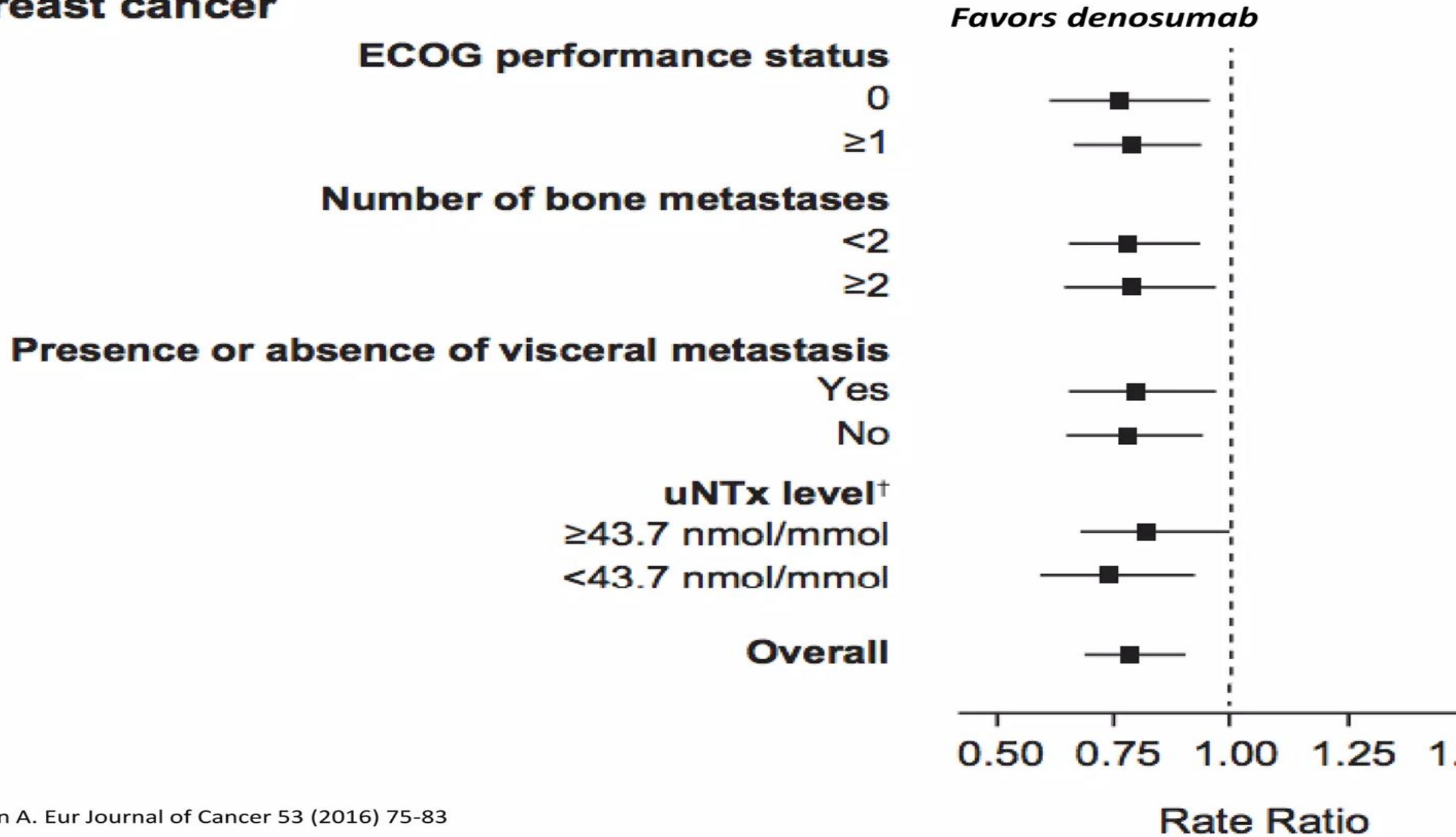


Test for heterogeneity, *P*=0.5377

Lipton A, et al. *Eur J Cancer* 2012;48:3082-92.

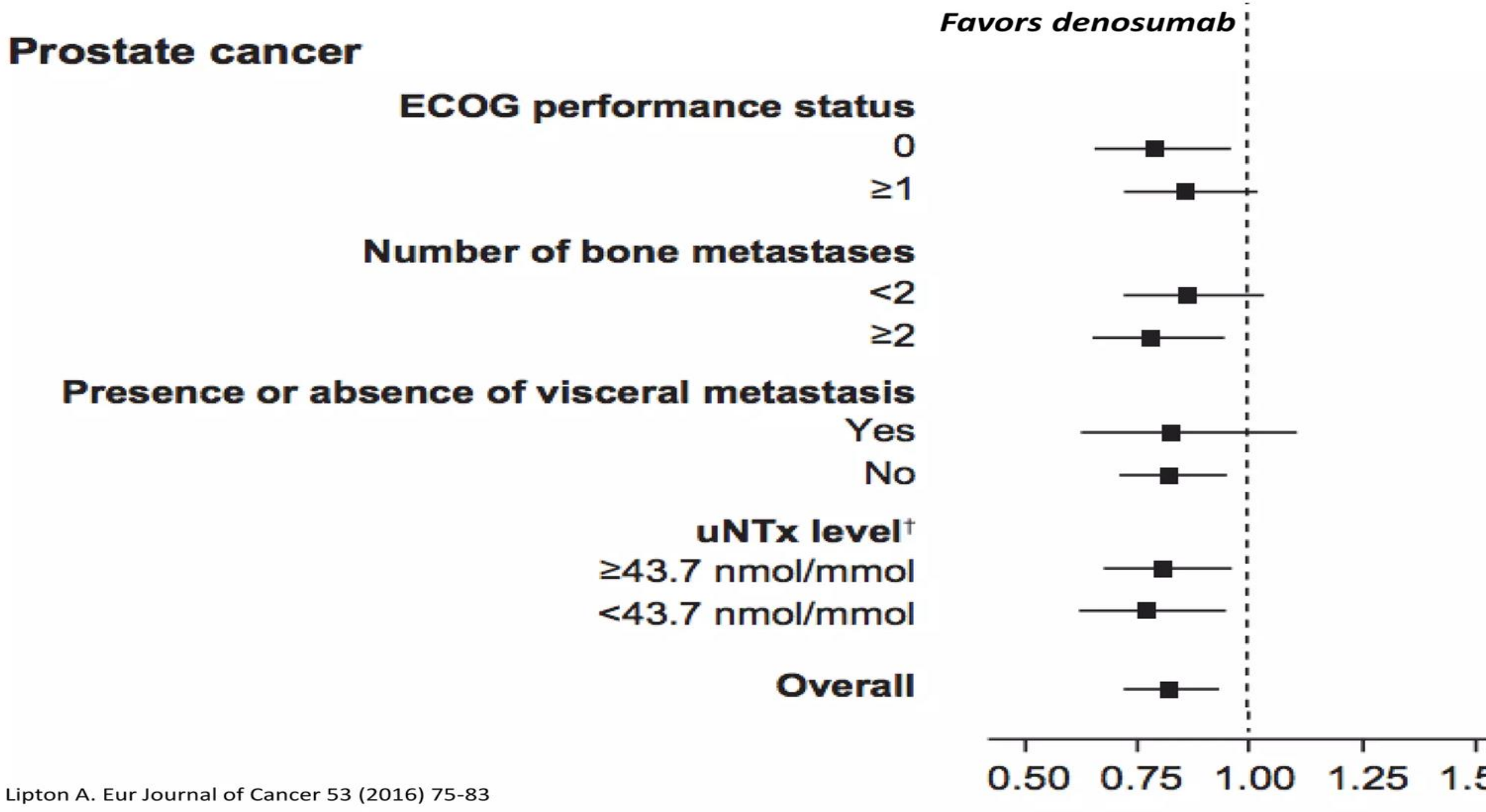
Podría haber algún subgrupo en el que podamos utilizar AZ en lugar de Denosumab?

Breast cancer



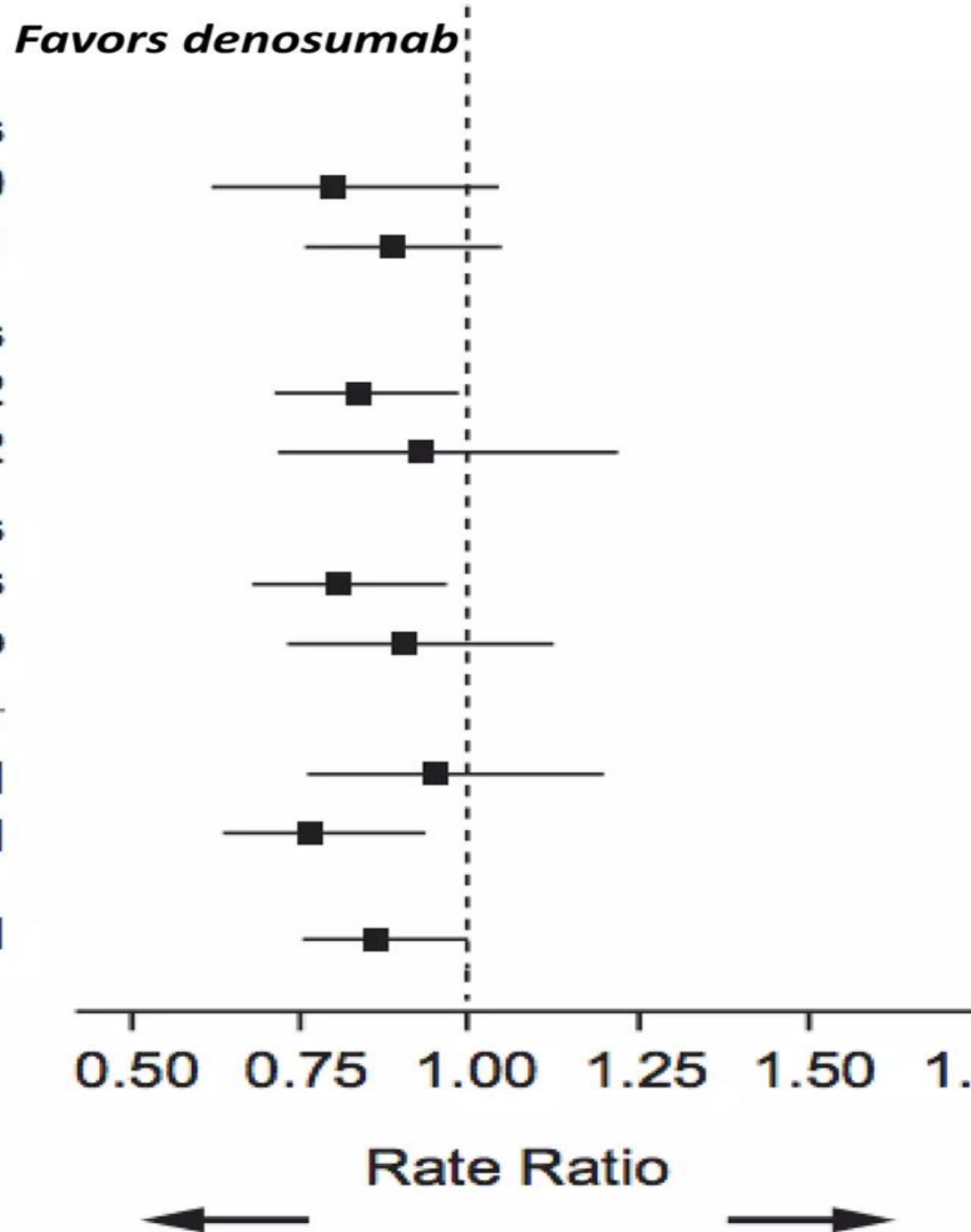
Lipton A. Eur Journal of Cancer 53 (2016) 75-83

Prostate cancer



Lipton A. Eur Journal of Cancer 53 (2016) 75-83

Other solid tumors

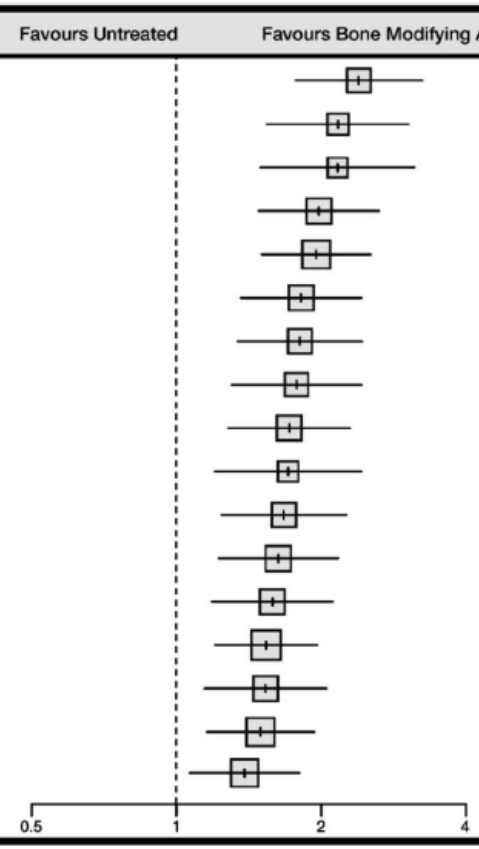


Lipton A. Eur Journal of Cancer 53 (2016) 75-83

Control del Dolor

Control del dolor

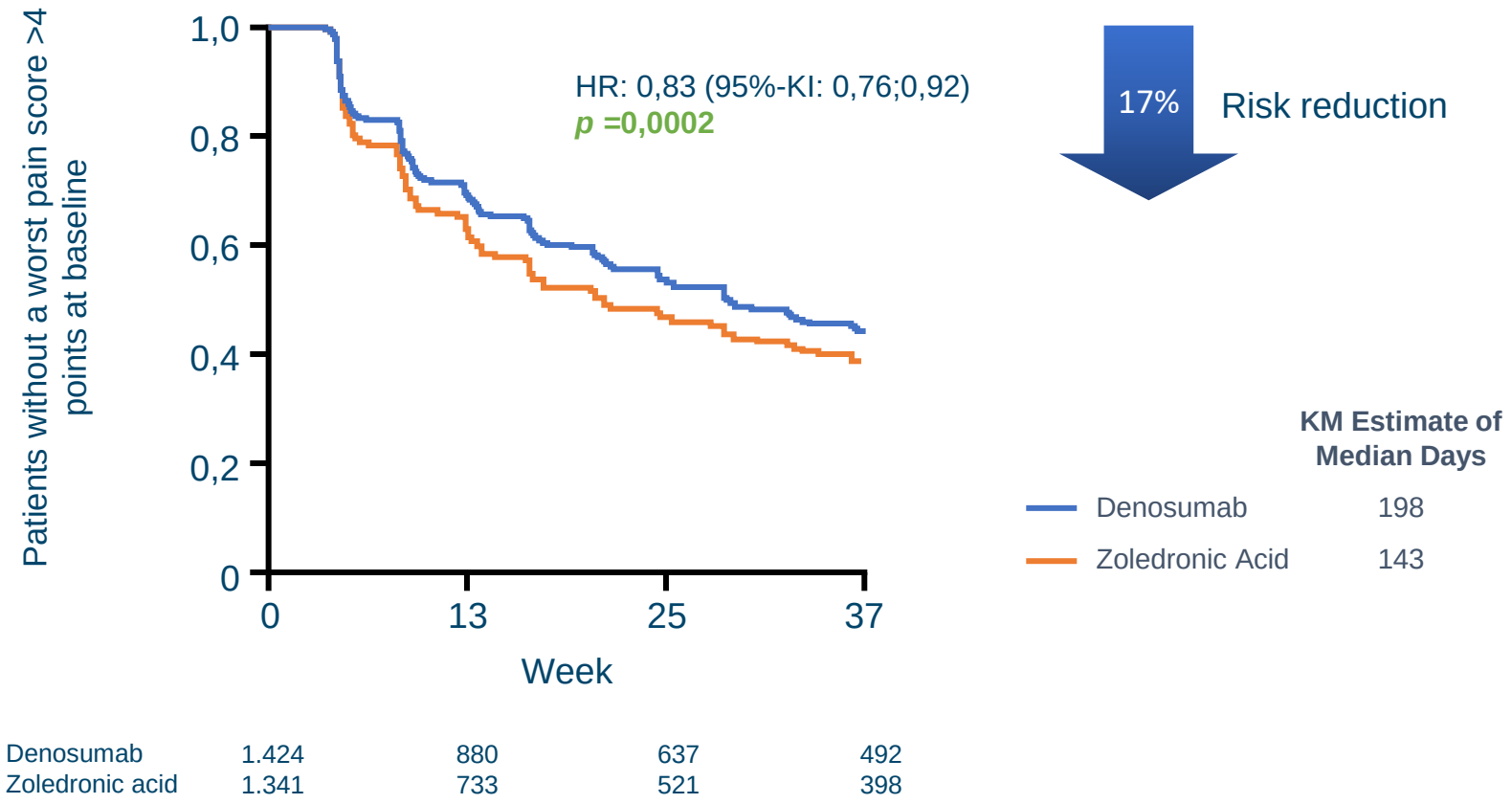
Intervention Arm	P-Score	Rank	Risk Ratio	(95% CI)
Ibandronate+Nuclide	0.9677	1	2.40	(1.77, 3.24)
Zoledronic Acid+Nuclide	0.8758	2	2.17	(1.54, 3.04)
Clodronate+Chemotherapy	0.8589	3	2.16	(1.50, 3.13)
Pamidronate+Nuclide	0.7824	4	1.98	(1.48, 2.64)
Zoledronic Acid+Chemotherapy	0.7677	5	1.95	(1.51, 2.53)
Zoledronic Acid+Radiotherapy	0.6273	6	1.82	(1.36, 2.43)
Ibandronate+Chemotherapy	0.6027	7	1.81	(1.34, 2.43)
Pamidronate+Radiotherapy	0.5761	8	1.78	(1.30, 2.43)
Pamidronate+Chemotherapy	0.5035	9	1.72	(1.28, 2.30)
Clodronate+Nuclide	0.4907	10	1.71	(1.20, 2.43)
Ibandronate	0.4534	11	1.67	(1.24, 2.26)
Nuclide	0.3889	12	1.63	(1.23, 2.17)
Radiotherapy	0.3194	13	1.58	(1.19, 2.12)
Zoledronic Acid	0.2583	14	1.54	(1.20, 1.96)
Clodronate	0.2526	15	1.53	(1.14, 2.05)
Pamidronate	0.1883	16	1.50	(1.16, 1.93)
Chemotherapy	0.0855	17	1.39	(1.07, 1.80)
Untreated	0.0009	18	1.00	I^2=12%



A

Menos pacientes con Denosumab tuvieron progresión del dolor

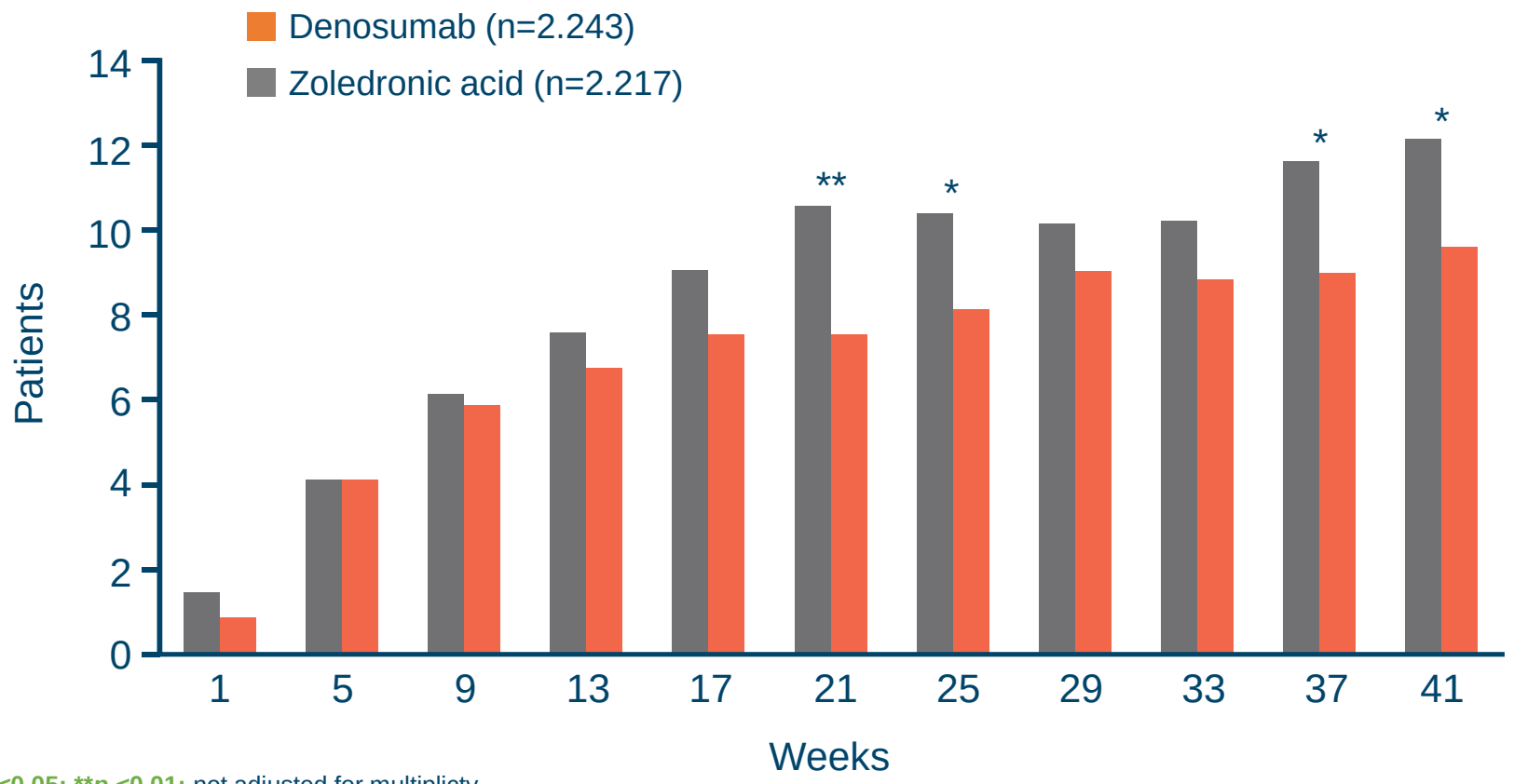
Progression to moderate or strong pain (> 4 points) in patients that had no oder light pain at baseline (0-4 points).



Cleeland CS, Patrick DL, Fallowfield L, et al. *ESMO 2010*: Abstract 1248P and poster.

Menos pacientes con Denosumab debieron cambiar a opioides mayores

Patients (%) that shift from no analgetic, not-opioid analgetic use or weak opioids to strong opioids use



***p* <0,05; ****p* <0,01;** not adjusted for multiplicty

Cleeland CS, Patrick DL, Fallowfield L, et al. *ESMO 2010*: Abstract 1248P and Poster.

Dosis e intervalo de administración

Dosis e Intervalo de BMAs

- Todavía es controversial cuál sería el mejor intervalo de administración
- El régimen recomendado fue desarrollado para hipercalcemia y para adecuarse a la administración de tratamientos oncológicos y no en base a estudios farmacodinámicos comparativos
- Debido a la prolongación de la espectativa de vida de los pacientes con tumores avanzados, sus efectos tóxicos podrían incrementarse progresivamente por acumulación de dosis
- No existe suficiente información en escenario del mundo real acerca de la seguridad y eficacia clínica de regímenes alternativos de administración

Dosis e Intervalo de BMAs

Cancer Management and Research

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Efficacy and safety of de-escalation bone-modifying agents for cancer patients with bone metastases: a systematic review and meta-analysis

- 2,878 participantes en 8 estudios
- Intervalo de 4 vs 12 semanas

Dosis e Intervalo de BMAs

- SREs: el de-escalamiento a cada 12 semanas no resultó inferior a cada 4 semanas para el primer SER (16,8 m vs 15,7 m respectivamente)
- Radioterapia: sin diferencias significativas (c/12 sem: 25 eventos; c/4 sem: 31 eventos)
- Sin diferencias significativas en control del dolor, efectos adversos, deterioro de la FR y osteonecrosis mandibular

Dosis e Intervalo de BMAs

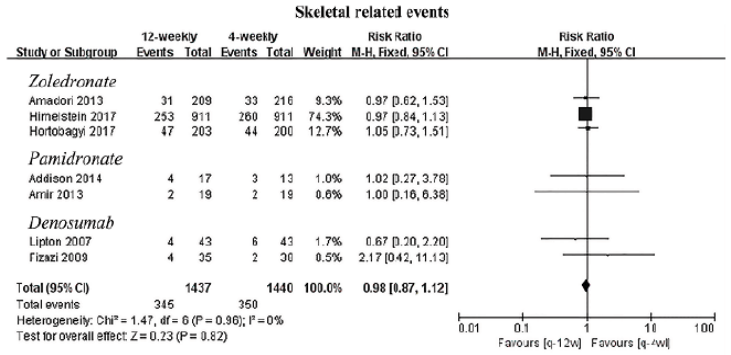


Figure 3 Meta-analysis results for skeletal-related events.

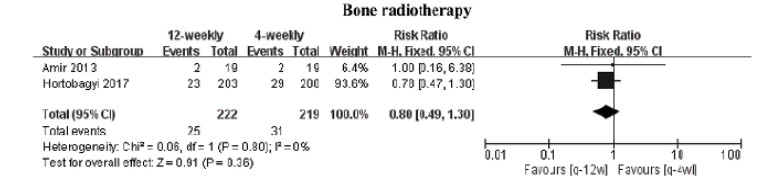


Figure 4 Meta-analysis results for bone radiotherapy.

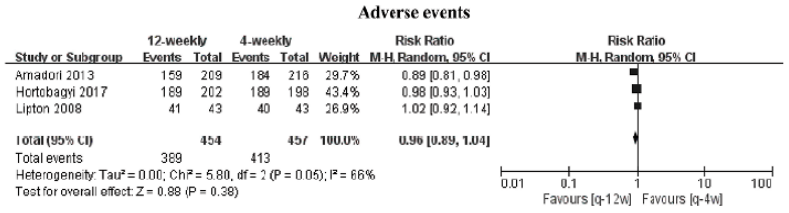


Figure 5 Meta-analysis results for adverse events.

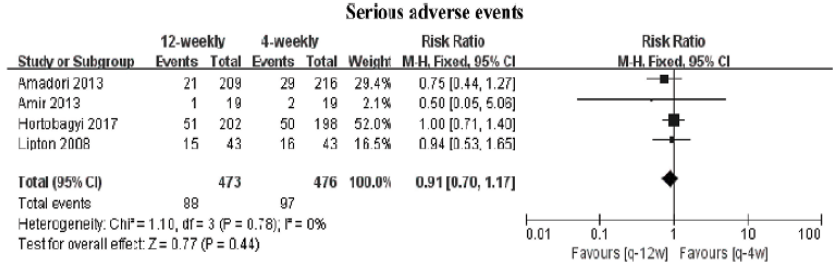


Figure 6 Meta-analysis results for serious adverse events.

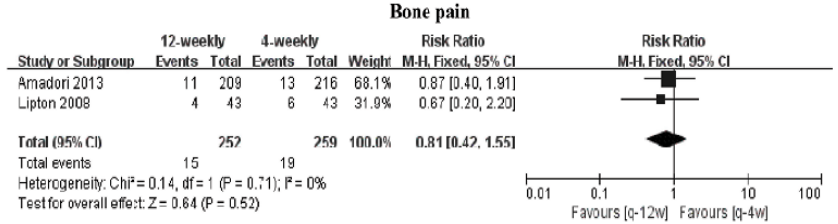


Figure 7 Meta-analysis results for bone pain.

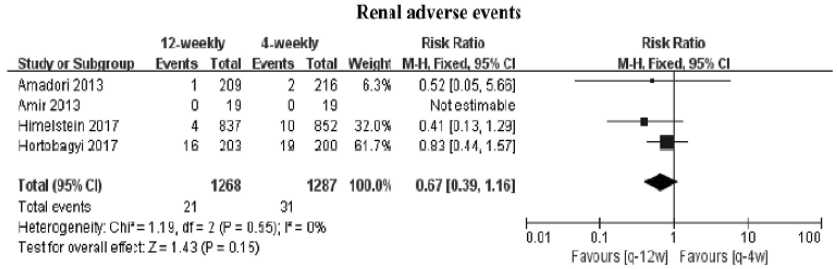
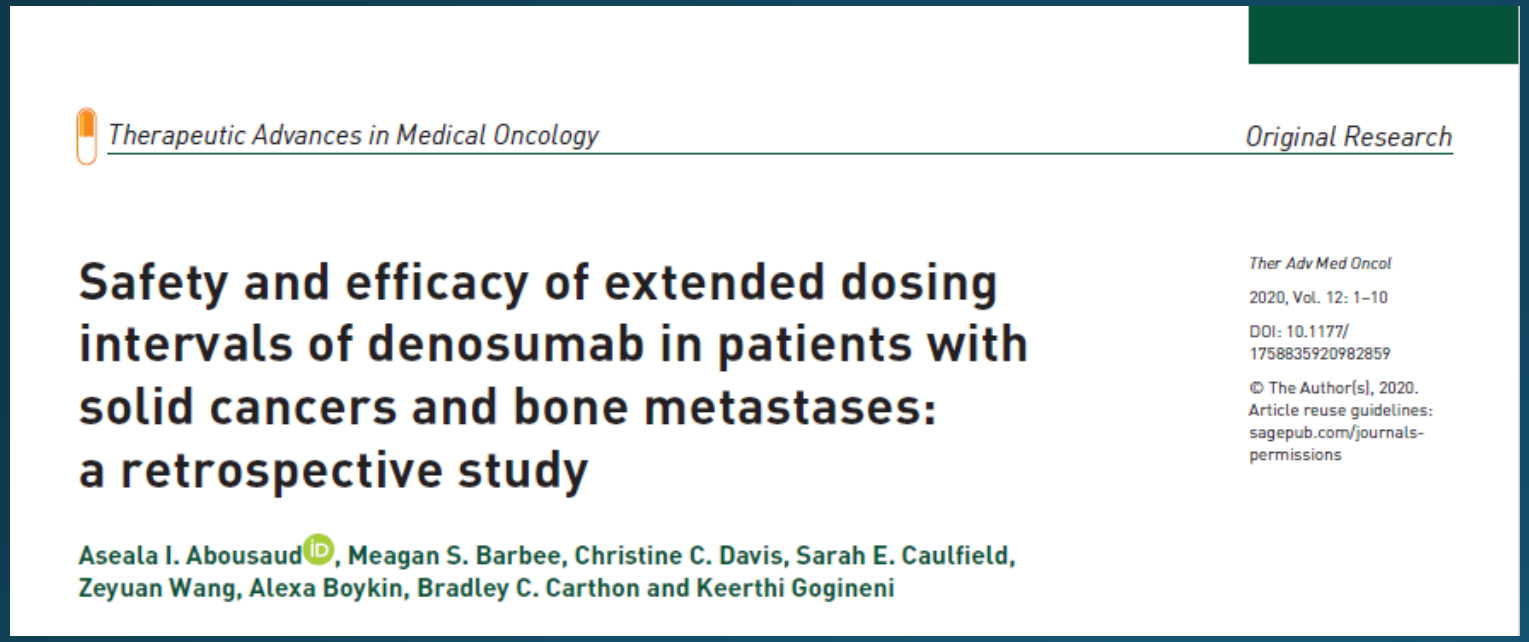


Figure 8 Meta-analysis results for renal adverse events.

Dosis e Intervalo de BMAs



Therapeutic Advances in Medical Oncology *Original Research*

Safety and efficacy of extended dosing intervals of denosumab in patients with solid cancers and bone metastases: a retrospective study

Aseala I. Abousaud, Meagan S. Barbee, Christine C. Davis, Sarah E. Caulfield, Zeyuan Wang, Alexa Boykin, Bradley C. Carthon and Keerthi Gogineni

Ther Adv Med Oncol
2020, Vol. 12: 1–10
DOI: 10.1177/1758835920982859

- Estudio retrospectivo de una cohorte del mundo real de 432 pacientes con metástasis óseas (9 años)
- Intervalo <5 semanas (interval corto) vs 5–11 semanas (intervalo medio) vs 12 semanas o más (intervalo largo)

Dosis e Intervalo de BMAs

- Sin diferencias significativas entre grupos para primer SRE

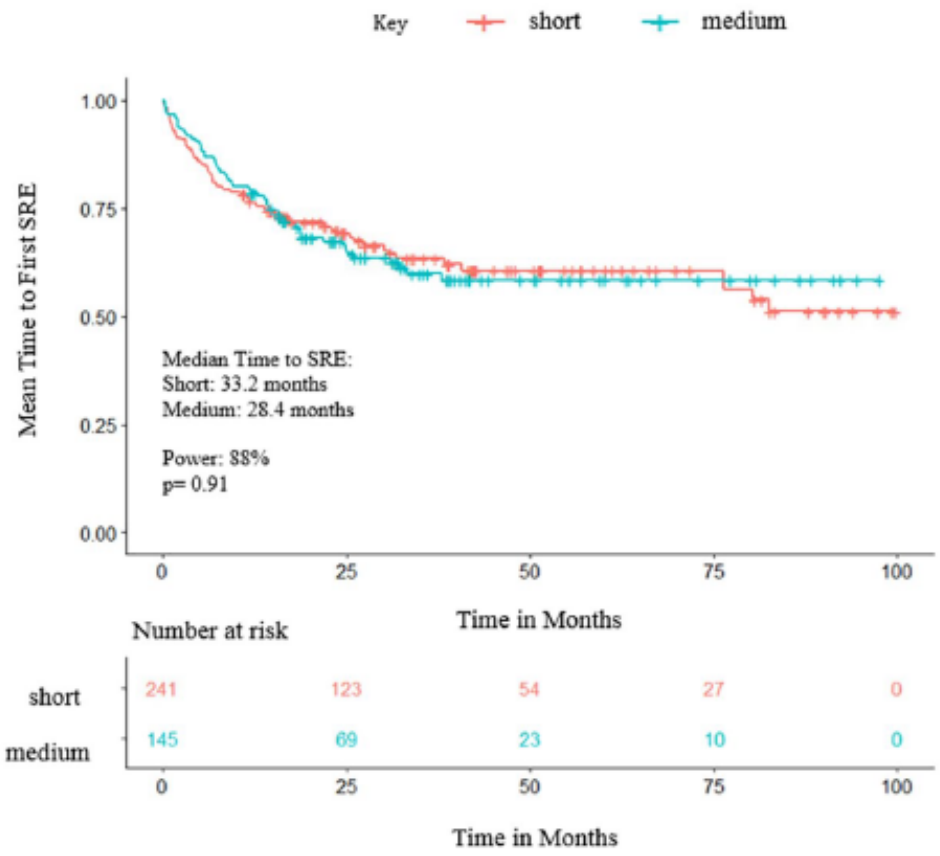


Figure 2. Kaplan–Meier-estimate time to first SRE short interval *versus* medium interval.
SRE, skeletal-related event.

Dosis e Intervalo de BMAs

- Sin diferencias significativas entre grupos para OS (mOS)

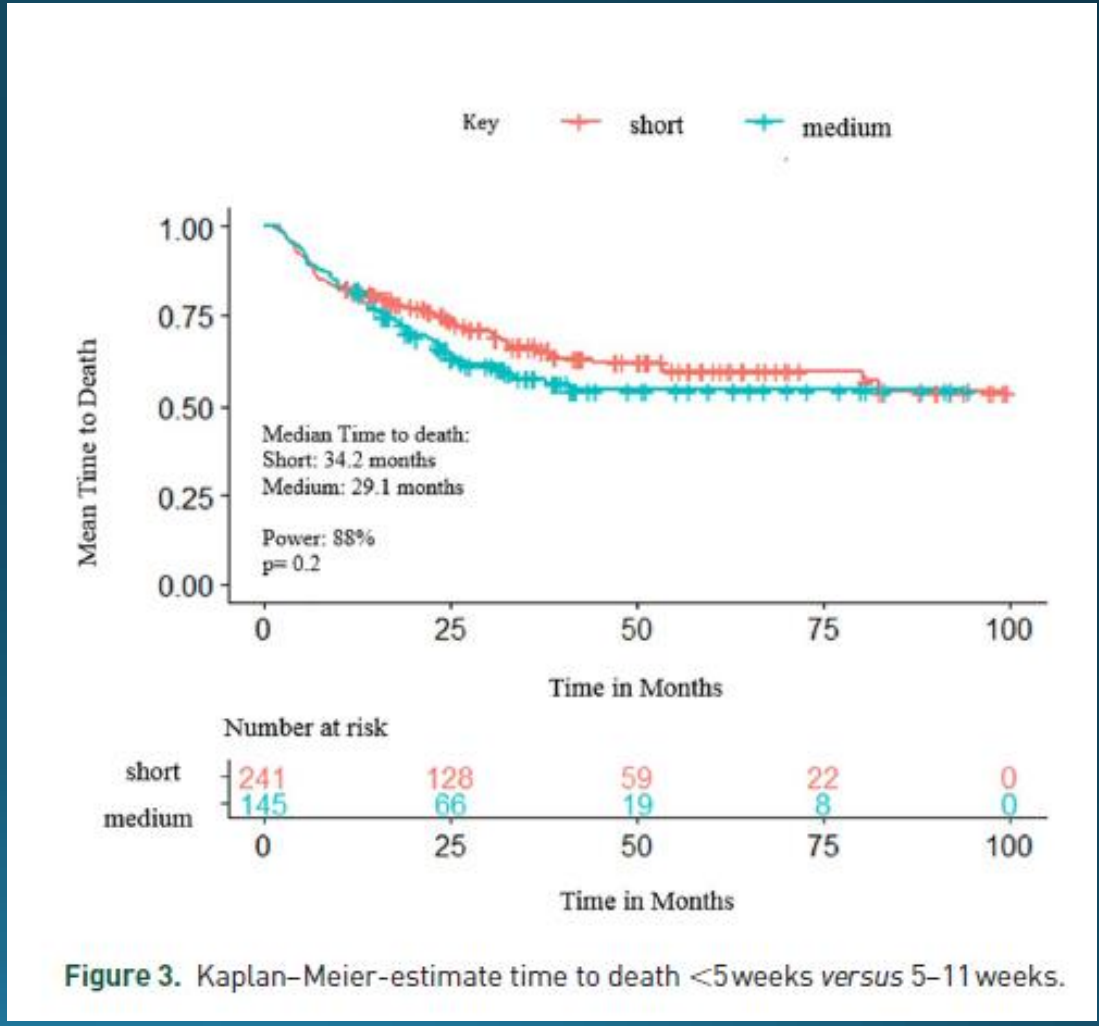


Figure 3. Kaplan–Meier-estimate time to death <5 weeks *versus* 5–11 weeks.

Dosis e Intervalo de BMAs

Table 2. Efficacy outcomes.

	Overall population ($n=432$)	Short-interval <5 weeks ($n=241$)	Medium-interval 5–11 weeks ($n=145$)	Long-interval ⩾12 weeks ($n=46$)
Median time to first SRE (months)	–	33.2	29.1	32.2
HR (95% CI), *p* value	–	1.13 (0.66–1.92) $p=0.91$[a]	1.15 (0.66–2.01) $p=0.62$[b]	$p=0.66$[c]
mOS (months)		34.2	28.4	32.9
HR (95% CI), *p* value	–	1.05 (0.60–1.82) $p=0.2$[a]	1.33 (0.75–2.34) $p=0.28$[b]	$p=0.86$[c]

[a]For the comparison between the short- and medium-interval groups, power = 88%.
[b]For the comparison between the medium- and long-interval groups, power = 84%.
[c]For the comparison between the short- and long-interval groups, power = 45%.
CI, confidence interval; mOS, median overall survival.

Dosis e Intervalo de BMAs

- Más hopitalizaciones para el período corto
- Las principales razones fueron dolor abdominal,hematuria y fiebre
- No hubo diferencias significativas en hypocalcemia y MRONJ

Table 3. Incidence of safety events while on Denosumab.

Covariates	Overall population ($n = 432$)	Denosumab dosing interval			
		Short interval <5 weeks ($n = 241$)	Medium interval 5–11 weeks ($n = 145$)	Long interval $\geqslant 12$ weeks ($n = 46$)	p value
Hospitalization, n (%)	196	133 (55.2)	49 (33.8)	14 (30.4)	**<0.001**
Hypocalcemia, n (%)[a]	118	76 (31.5)	34 (23.4)	8 (17.4)	0.063
ONJ, n (%)	7	6 (2.49)	1 (0.69)	0 (0.00)	0.36

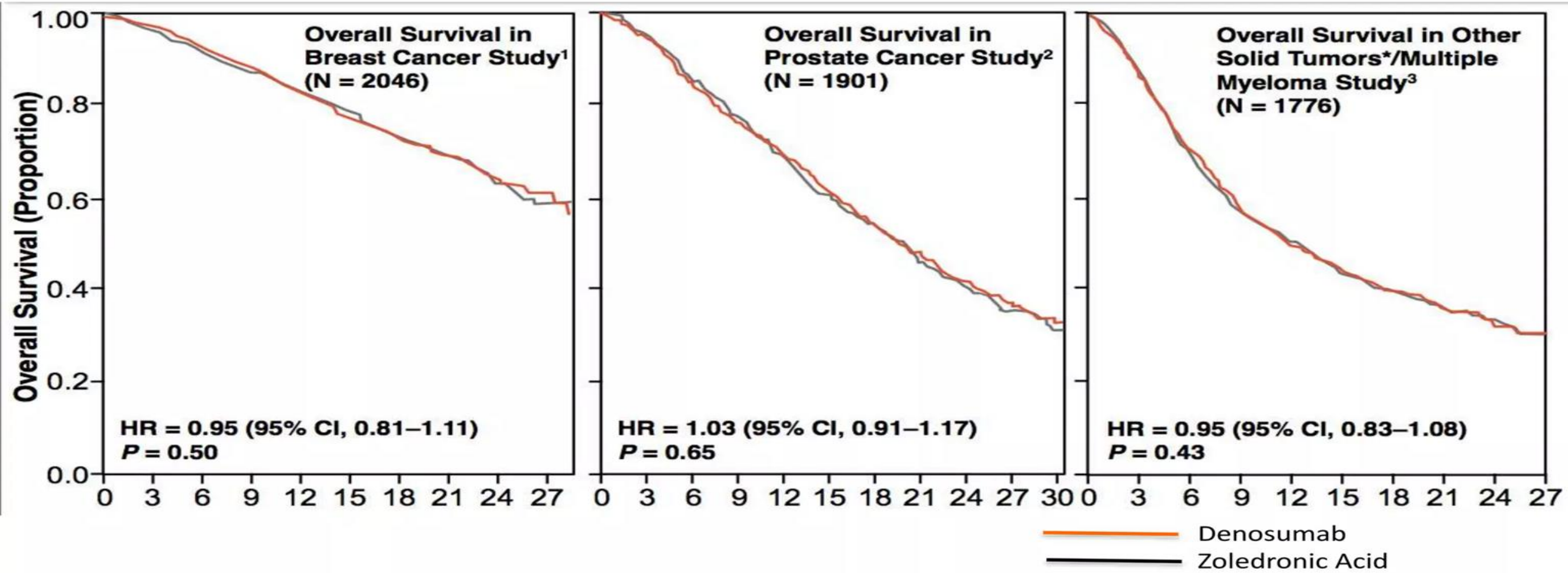
[a]Based on corrected calcium.
ONJ, osteonecrosis of the jaw confidence interval.

Supervivencia en avanzado

Cáncer de Próstata

Outcomes	Absolute effects and relative effects with 95% CIs. Main comparator: no treatment/placebo		
	Assumed risk with no treatment/placebo*	Corresponding risk with zoledronic acid	Corresponding risk with denosumab
Mortality (network based on 13 studies including 5494 participants; follow-up 12-60 months)	**484 per 1000** (48.4%)	**436 per 1000** (387 to 489)	**450 per 1000** (373 to 538)
		RR 0.90 (0.80 to 1.01)	**RR 0.93** (0.77 to 1.11)
		⊕⊕⊕⊖ **Moderate[1]**	⊕⊕⊕⊖ **Moderate[1]**

Overal Survival



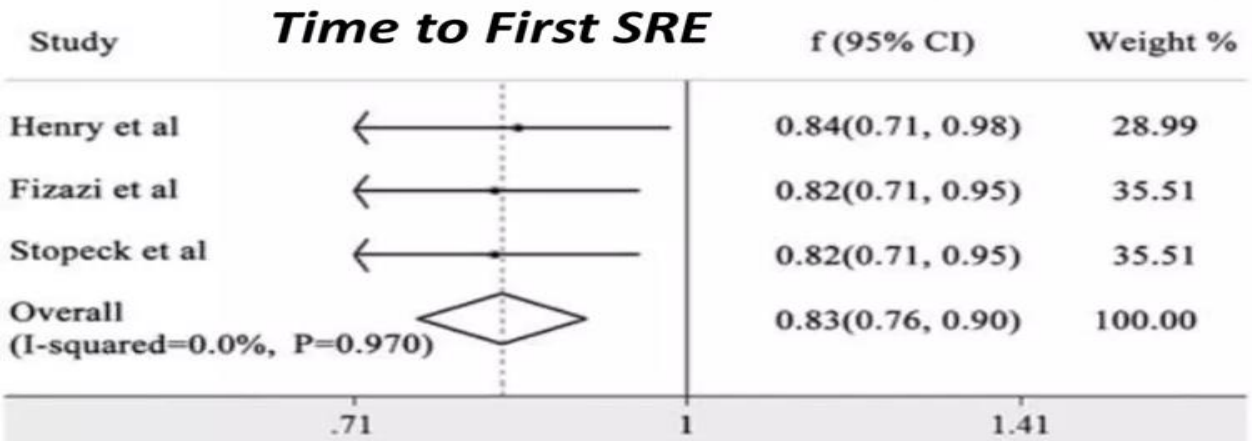
*Excluding breast and prostate.

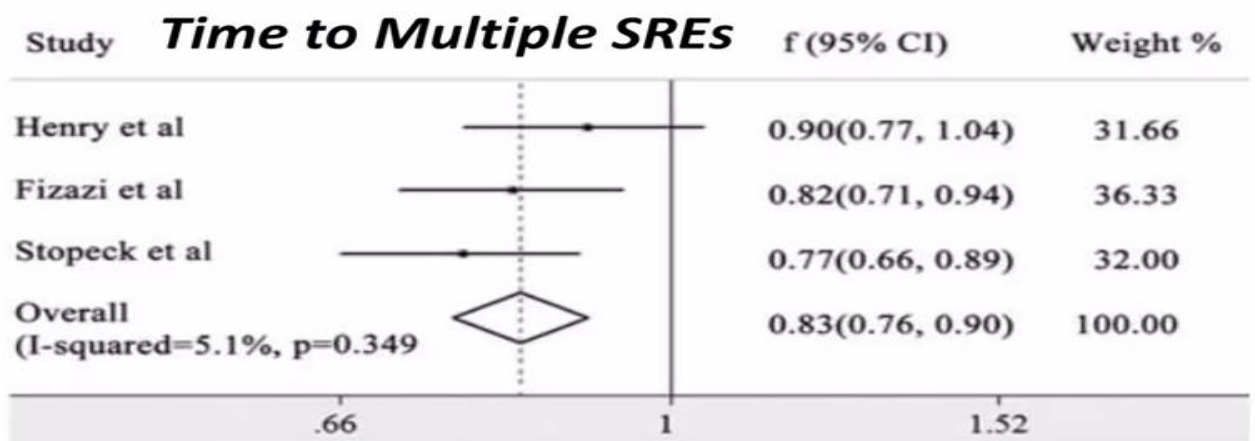
1. Stopeck AT, et al. J Clin Oncol. 2010;28:5132-5139. 2. Fizazi K, et al. Lancet. 2011;377:813-822. 3. Henry D, et al. J Clin Oncol. [Epub ahead of print] doi: 10.1200/JCO.2010.31.3304. 4. XGEVATM (denosumab) prescribing information, Amgen.

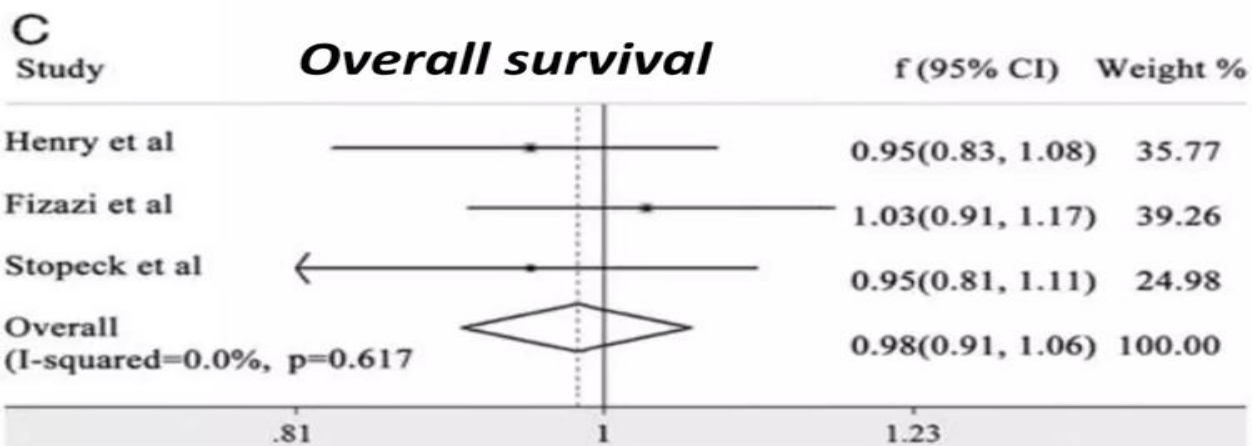
Efficacy and Safety of Denosumab Versus Zoledronic Acid in Patients With Bone Metastases

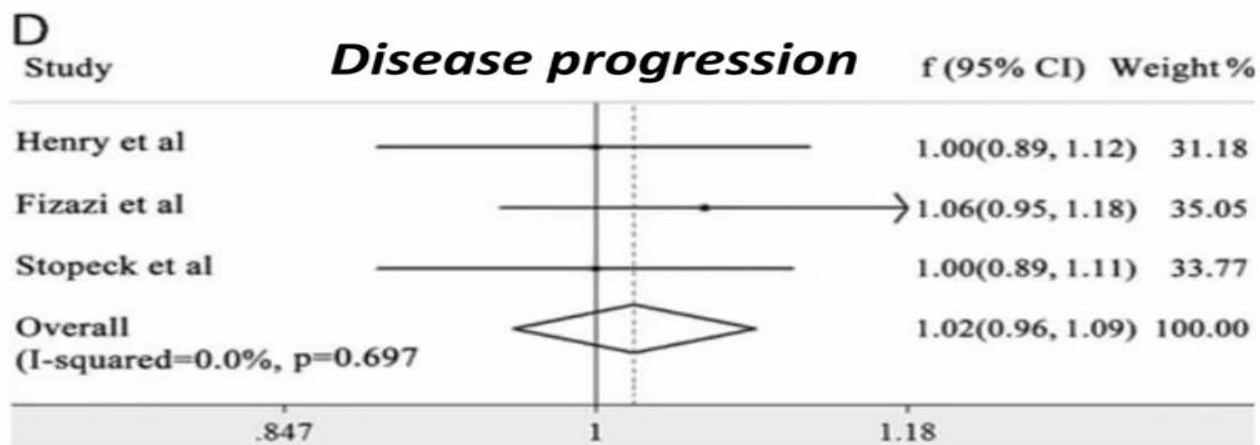
A Systematic Review and Meta-analysis

Lei Sun, MD and Shiying Yu, MD



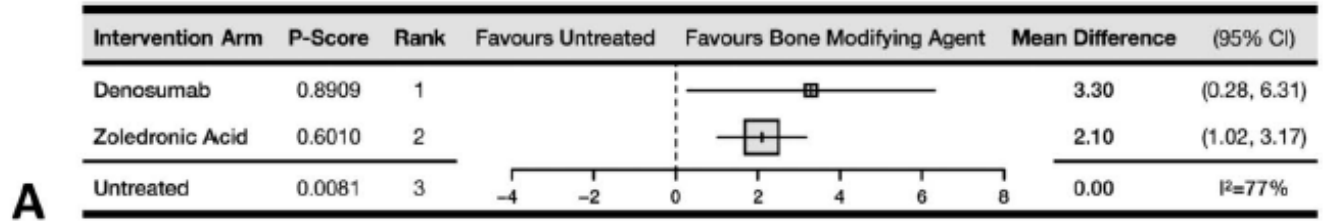






Sun L, Am J Clin Oncol 2013;36:399–403

Cáncer de Pulmón



Intervention Arm	P-Score	Rank	Mean Difference	(95% CI)
Denosumab	0.8909	1	3.30	(0.28, 6.31)
Zoledronic Acid	0.6010	2	2.10	(1.02, 3.17)
Untreated	0.0081	3	0.00	I^2=77%

A

OS:

Denosumab y Zoledronato prolongan la supervivencia en 3,3y 2,1 meses respectivamente comparados con pacientes no tratados

Adyuvancia

Bifosfonatos en Adyuvancia

Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

- 18 766 mujeres
- El beneficio en Riesgo de Recurrencia (RR 0·94, 95% CI 0·87–1·01; 2p=0·08), recurrencia a distancia (0·92, 0·85–0·99; 2p=0·03), y mortalidad por cáncer de mama (0·91, 0·83–0·99; 2p=0·04) estuvieron al borde de la significancia
- La reducción de la recurrencia ósea sí fue significativa (0·83, 0·73–0·94; 2p=0·004)

***Lancet* 2015; 386: 1353–61**

Bifosfonatos en Adyuvancia

Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

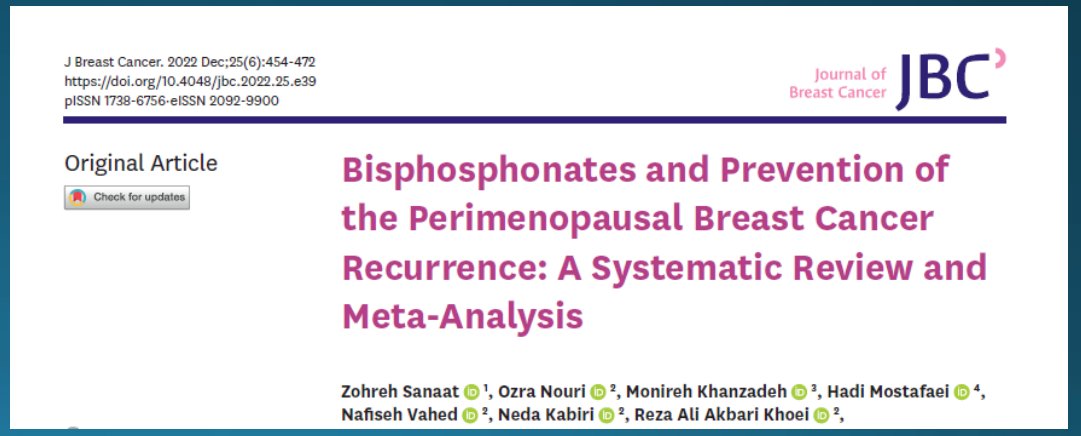
*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

- En el grupo de las 11 767 mujeres postmenopáusicas sí se observó una reducción altamente significativa en recurrencia (RR 0·86, 95% CI 0·78–0·94; 2p=0·002), recurrencia a distancia (0·82, 0·74–0·92; 2p=0·0003), recurrencia ósea (0·72, 0·60–0·86; 2p=0·0002), y mortalidad por cáncer de mama (0·82, 0·73–0·93; 2p=0·002)

***Lancet* 2015; 386: 1353–61**

Bifosfonatos en Adyuvancia

- 21 estudios incluídos
- 3 estudios fase III randomizados, 3 estudios de cohorte, 2 retrospectivos y los demás abiertos o de fase II
- 10,238 pacients recibieron BPs
- 10,743 pacientes en el grupo control



J Breast Cancer. 2022 Dec;25(6):454-472
https://doi.org/10.4048/jbc.2022.25.e39
pISSN 1738-6756·eISSN 2092-9900

Journal of Breast Cancer JBC

Original Article

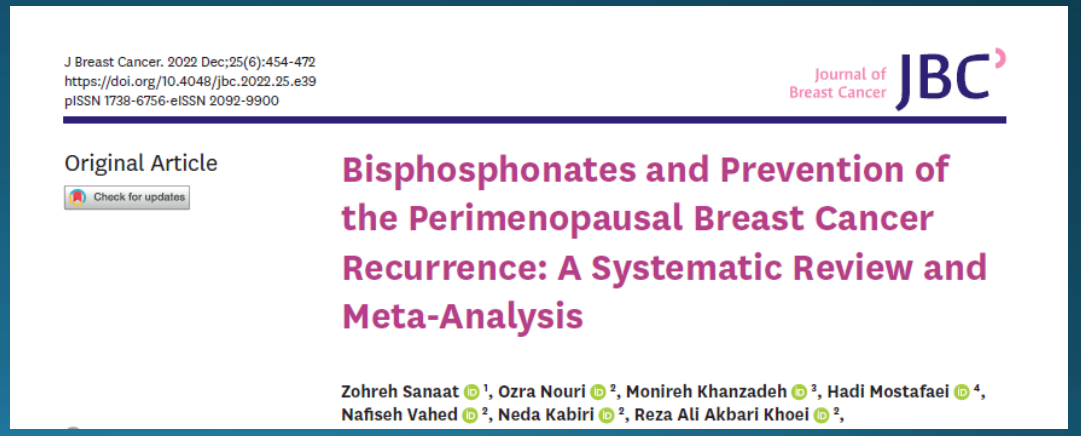
Check for updates

Bisphosphonates and Prevention of the Perimenopausal Breast Cancer Recurrence: A Systematic Review and Meta-Analysis

Zohreh Sanaat [1], Ozra Nouri [2], Monireh Khanzadeh [3], Hadi Mostafaei [4], Nafiseh Vahed [2], Neda Kabiri [2], Reza Ali Akbari Khoei [2],

Bifosfonatos en Adyuvancia

- HR para metástasis fue 0.77 (95% CI, 0.62–0.94; p = 0.01)
- HR para metásatasis óseas fue 0.74 (95% CI, 0.64–0.85; p < 0.0001)
- HR para OS fue 0.75 (95% CI, 0.63–0.89; p = 0.001)



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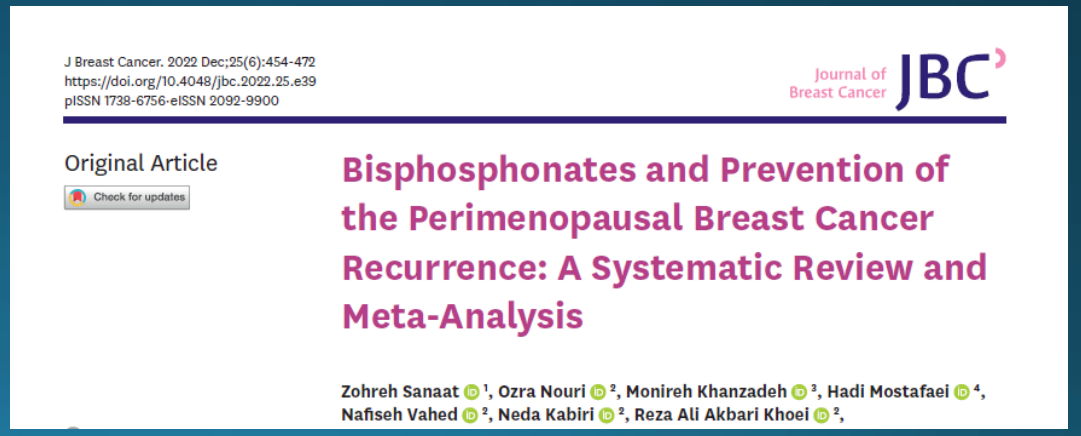
Bifosfonatos en Adyuvancia

- Limitaciones
- Estudios RCTs y de cohortes
- Los resultados ***sugieren*** un efecto beneficioso de BPs en DFS, OS, y metastasis locorregionales y a distancia en mujeres perimenopáusicas con cancer de mama



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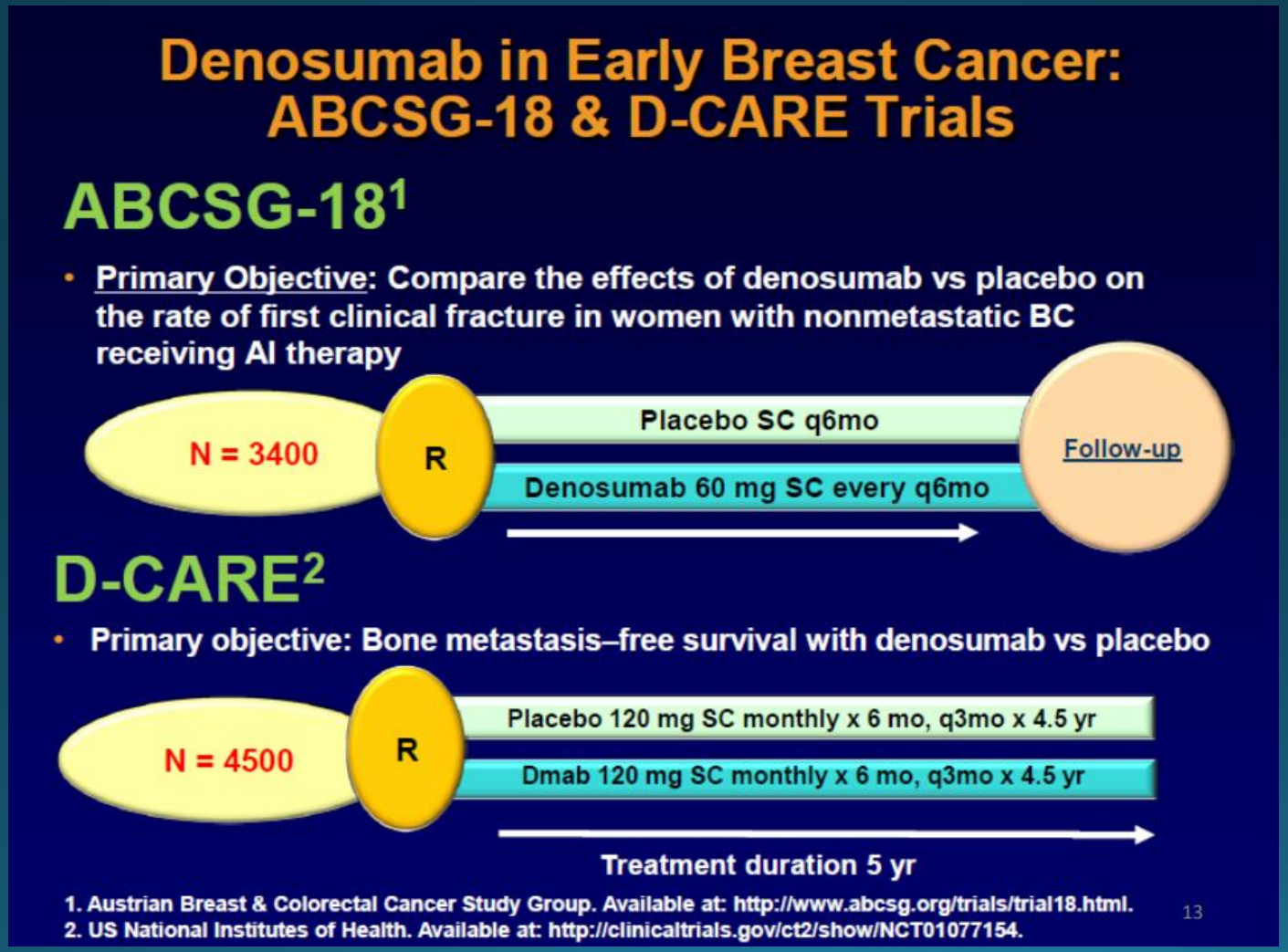
Denosumab en Adyuvancia



Denosumab en Adyuvancia

- ABCSG-18
  - 3420 pacientes postmenopáusicas EBC RH+ en adyuvancia con IAs

- D-CARE
  - 4509 pacientes con BC estadios II y III de alto riesgo (T3/T4 – N+), pre o postmenopáusicas con adyuvancia endócrina +/- QT y terapias HER

Denosumab en Adyuvancia

- ABCSG-18
  - Denosumab 60 mg sc cada 6 meses
  - El objetivo primario fue el Tiempo a la primera fractura
- D-CARE
  - Denosumab 120 mg sc mensual por 6 meses y luego cada 3 meses
  - El objetivo primario fue la Supervivencia libre de metastasis óseas (BMFS)

Denosumab en Adyuvancia

- ABCSG-18 trial
  - Demostró una prolongación significativa en el tiempo a la primer fractura comparado con placebo ([HR] 0.50 [95 % CI, 0.39–0.65], p <0.0001), (Objetivo primario) y de la supervivencia libre de metastasis óseas (HR, 0.81; 95 % CI, 0.65 to 1.00), (Objetivo secundario)

    POSITIVO

- D-CARE trial
  - No demostró diferencias contra placebo en BMFS (Objetivo primario) (HR 0.97, 95 % CI 0.82–1.14; p =0.709). Sí estuvo asociado a una reducción significativa de fracturas óseas (HR 0.76, CI 0.63–0.92, p- 0.0037), (Objetivo secundario)

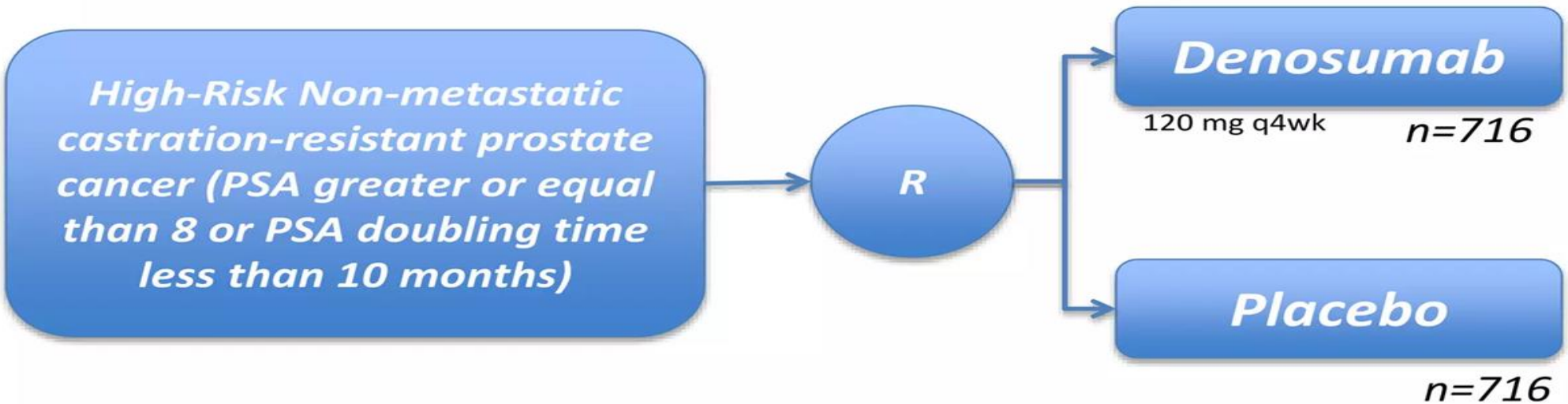
    NEGATIVO

Denosumab en Adyuvancia

- D-Care no pudo confirmar la eficacia de Denosumab en DFS reportada en el ABCSG-18
- Denosumab puede usarse durante la adyuvancia con IAs en mujeres post-menopásuicas con cancer de mama para preservación de la salud ósea a la dosis de 60 mg cada 6 meses
- Esa misma dosis podría tener un efecto en prevenir la recurrencia, por lo que no debería utilizarse para ese fin la dosis de 120 mg mensual

Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial

Matthew R Smith, Fred Saad, Robert Coleman, Neal Shore, Karim Fizazi, Bertrand Tombal, Kurt Miller, Paul Sieber, Lawrence Karsh, Ronaldo Damião, Teuvo L Tammela, Blair Egerdie, Hendrik Van Poppel, Joseph Chin, Juan Morote, Francisco Gómez-Veiga, Tomasz Borkowski, Zhishen Ye, Amy Kupic, Roger Dansey, Carsten Goessl

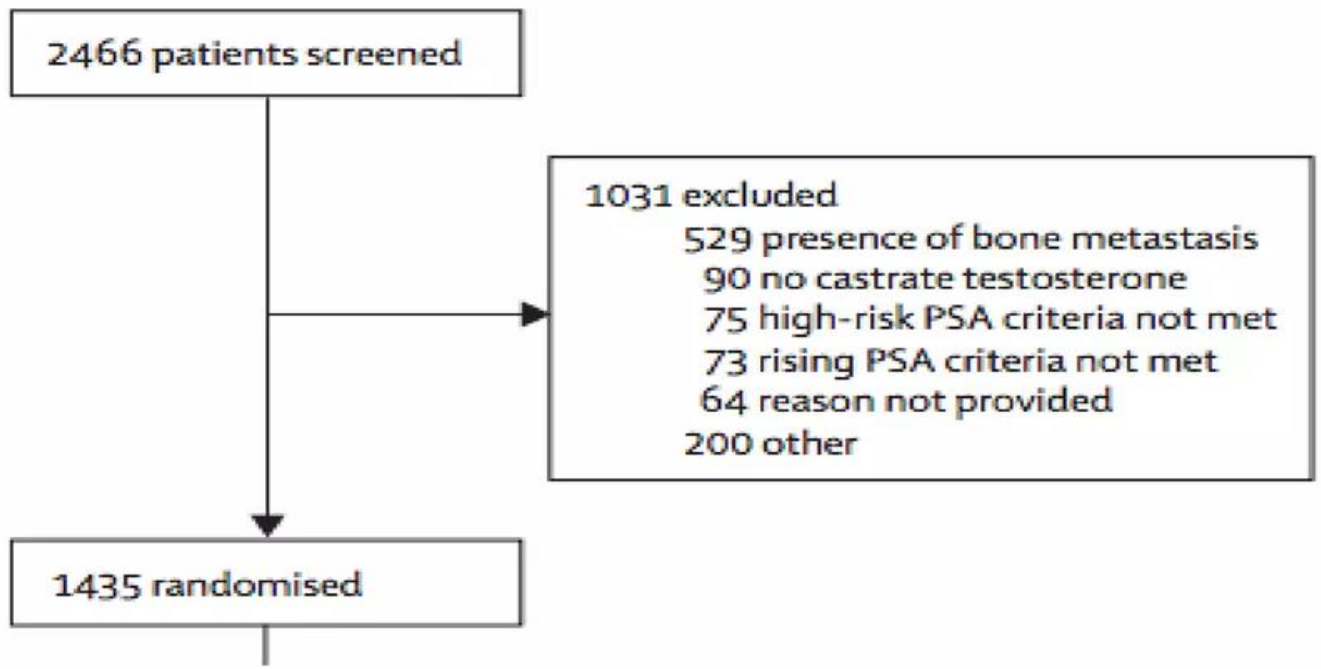


Composite endpoint determined by time to fi rst occurrence of bone metastasis (symptomatic or asymptomatic) or death from any cause

Smith MR, Lancet 2012; 379: 39–46

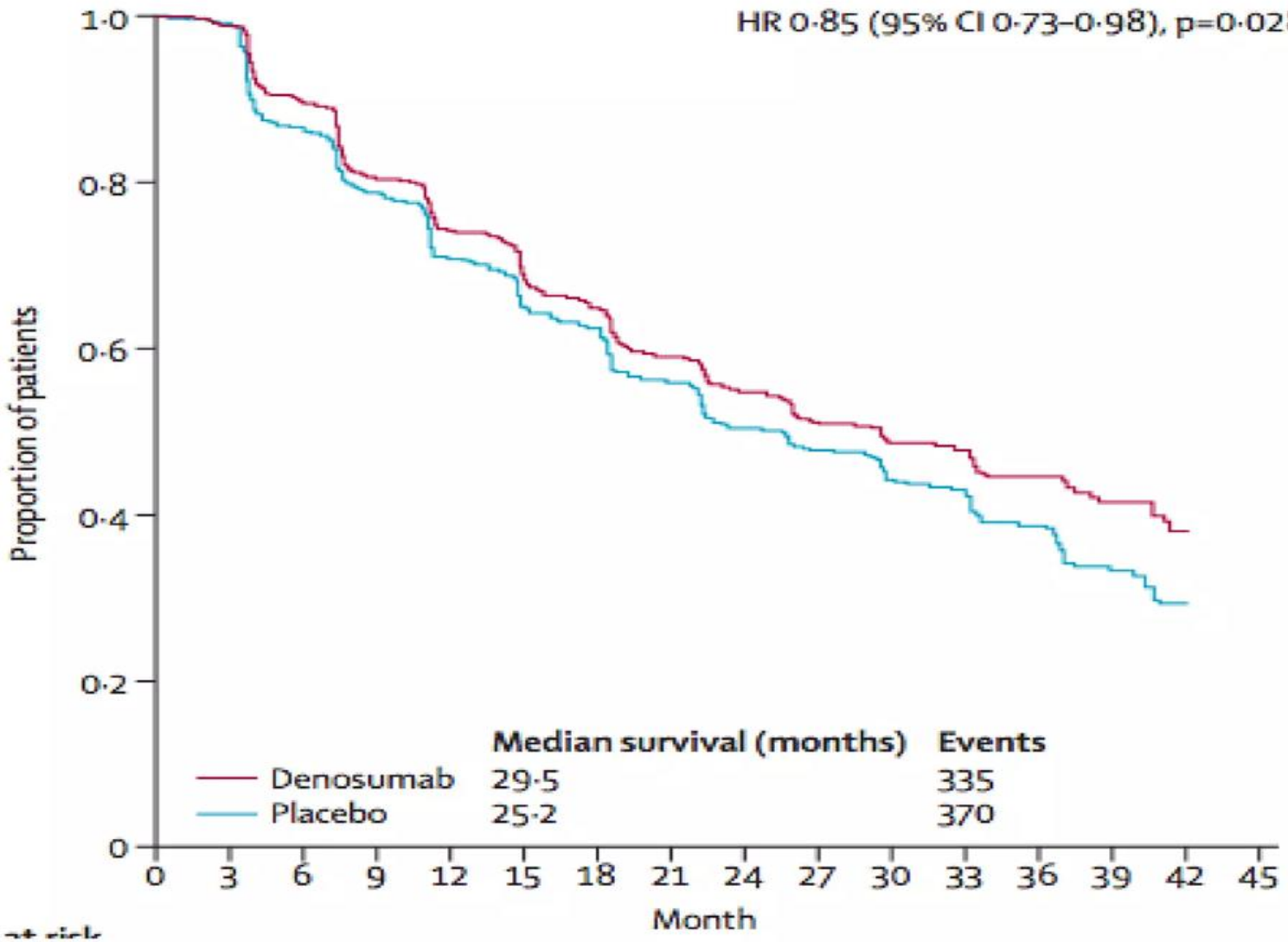
Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial

Matthew R Smith, Fred Saad, Robert Coleman, Neal Shore, Karim Fizazi, Bertrand Tombal, Kurt Miller, Paul Sieber, Lawrence Karsh, Ronaldo Damião, Teuvo L Tammela, Blair Egerdie, Hendrik Van Poppel, Joseph Chin, Juan Morote, Francisco Gómez-Veiga, Tomasz Borkowski, Zhishen Ye, Amy Kupic, Roger Dansey, Carsten Goessl



Smith MR, Lancet 2012; 379: 39–46

Bone-Metastasis-Free Survival



Smith MR, Lancet 2012; 379: 39–46

Nuevas terapias: CDKi - IO

- Estudios pre-clínicos demostraron que Denosumab tendría un efecto inmunomodulador sinérgico en combinación con inhibidores de checkpoint (ICIs)

- En modelos animales, la combinación mostró un efecto antitumoral mayor con aumento del reclutamiento y activación de linfocitos T infiltrantes CD4 + y CD8 +

Nuevas terapias: CDKi - IO

The Oncologist, 2025, **30**, oyaf134
https://doi.org/10.1093/oncolo/oyaf134
Advance access publication 23 June 2025
Original Article

OXFORD

Efficacy and immune-related adverse events of pembrolizumab with bone-modifying agents in female patients with breast cancer

Alexis LeVee[1], Esther Peluso[2], Melissa G. Lechner[3], Nora Ruel[4], Joanne Mortimer[1], Irene Kang[1], Karen Tsai[5]

- Estudio restrospectivo de cohortes
- 425 pacientes con cáncer de mama tratadas con pembrolizumab

Nuevas terapias: CDKi - IO

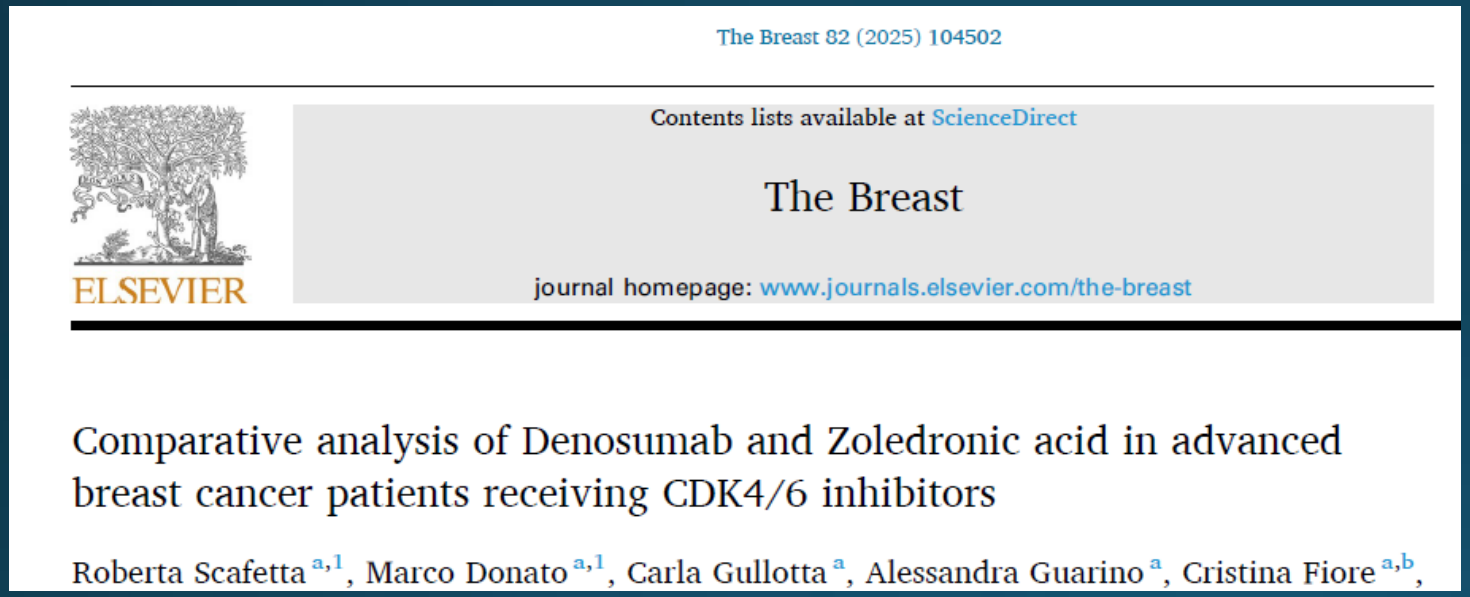
- Se observó un mayor índice de respuesta en pacientes con ABC tratadas con pembrolizumab y denosumab (48.0% [95% CI, 33.7-62.3]) comparadas con las que recibieron ZA (31.6% [95% CI, 8.6-54.6]) y las que sólo recibieron pembrolizumab (35.0% [95% CI, 24.3-45.7]), aunque sin significancia estadística (P = .3)

- La toxicidad fue mayor en los pacientes que recibieron Denosumab (21.8% vs 11.5%, P = .04)

Nuevas terapias: CDKi - IO

- Más allá de su acción antiresortiva, ZA produce activación de linfocitos T y modula la angiogenesis en el microambiente óseo
- También ha mostrado propiedades antitumorales favoreciendo la apoptosis de células neoplásicas y dificultando su adhesión a la matriz ósea
- CDK4/6is podrían generar un medio apropiado para el desarrollo de estas propiedades de ZA, lo que no ocurriría con Denosumab

Nuevas terapias: CDKi - IO



The Breast 82 (2025) 104502

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Comparative analysis of Denosumab and Zoledronic acid in advanced breast cancer patients receiving CDK4/6 inhibitors

Roberta Scafetta [a,1], Marco Donato [a,1], Carla Gullotta [a], Alessandra Guarino [a], Cristina Fiore [a,b],

Análisis retrospectivo de 864 pacientes con HR+/HER2-aBC y metástasis óseas tratadas con CDK4/6is más terapia endócrina

Nuevas terapias: CDKi - IO

- ZA se asocia con una prolongación significativa del tiempo al primer evento óseo (media 49.0 meses; 95 % CI:43.0–57.0) comparado con Denosumab (media 42 meses; 95 % CI:37.0–47.0) (HR =0.77, 95 % CI: 0.61–0.98, p =0.031)

- Sin diferencias significativas en PFS o OS

Conclusiones

- BMAs reducen el riesgo de SRE en pacientes con metástasis óseas, aunque no está claro que el beneficio sea para todos los tumores sólidos
- BMAs tiene un efecto beneficioso en el control del dolor por metástasis óseas en combinación con analgésicos y terapias oncológicas
- Denosumab en general ha mostrado ser superior a Zoledronato

Conclusiones

- Zoledronato podría tener indicación en algunos escenarios de cáncer de mama y pulmón, no lo tiene en cáncer de próstata, no sabemos en otros tumores sólidos

- Dosis menores e intervalos de administración más prolongados podrían tener igual efectividad y menor toxicidad, pero no está suficientemente investigado

- No hay evidencia definitiva de que los BMAs prolonguen la SV en estadios avanzados (Pulmón?)

Conclusiones

- BMAs reducen el riesgo de SRE en mujeres con cáncer de mama y adyuvancia con las
- Los resultados de BMAs en DFS y OS en EBC son contradictorios
- Denosumab podría prolongar OS en CRPC M0

Conclusiones

- No existe suficiente evidencia de los resultados de los BMAs asociados a las nuevas terapias con IO e CDKi
- Denosumab podría potenciar la actividad antitumoral de IO, pero también su toxicidad
- El potencial sinergismo entre CDKi y AZ podría reposicionar los BP en ABC


MUCHAS GRACIAS

Cochrane Library

Cochrane Database of Systematic Reviews

Bisphosphonates or RANK-ligand-inhibitors for men with prostate cancer and bone metastases: a network meta-analysis (Review)

Jakob T, Tesfamariam YM, Macherey S, Kuhr K, Adams A, Monsef I, Heidenreich A, Skoetz N

Toxicidad y Seguridad

- Manejo de complicaciones: Necrosis mandibular

Patient Incidence, n (%)	Denosumab (n=2755)	Zoledronic Acid (n=2744)
All adverse events (AEs)	2650 (96.2)	2654 (96.7)
CTCAE Grade 3, 4, or 5 AEs	1934 (70.2)	1941 (70.7)
Serious AEs	1549 (56.2)	1573 (57.3)
AEs leading to study discontinuation	261 (9.5)	270 (9.8)
Adverse events of interest		
Acute phase reactions (first 3 days)	241 (8.7)	561 (20.4)
ONJ (adjudicated)	48 (1.7)	35 (1.3)
Hypocalcemia*	261 (9.5)	131 (4.8)

n=the number of patients who received at least one dose of active drug
*Includes hypocalcemia, blood calcium decreased, calcium deficiency, and calcium ionized decreased

Richardson G, Siena S, Lipton A, et al. *COSA 2011*: abstract and oral presentation.

Denosumab does not require dose adjustments, regardless of renal function

	Zoledronic Acid	*Denosumab*
Cleared by the kidneys?	Yes	No
Dose adjustment required for baseline renal impairment?	Yes	No
Percentage of patients	17.7%	N/A
Dose withholding required for declining renal function during therapy?	Yes	No
Percentage of patients	9.8%	N/A

1. Lewiecki EM. Biologics. 2008;2:645-653. 2. Bekker PJ, et al. J Bone Miner Res. 2004;19:1059-1066. 3. Mould DR, Green B. BioDrugs. 2010;24:23-39. 4. Data on file, Amgen. 5. Zometa® Prescribing Information, Novartis.

Most Common Adverse Reactions Ocurring in More than 25% of Patients

	Denosumab	*Zoledronic Acid*
Nausea	31%	32%
Fatigue/asthenia	45%	46%
Hypophosphatemia*	32%	20%

*Laboratory-derived and below the central laboratory lower limit of normal (2.2–2.8 mg/dL [0.71–0.9 mmol/L] us).

Hypocalcemia

	Zoledronic Acid	*Denosumab*
All grades	9%	18%
Grade 3	1.2%	2.5%
Grade 4	0.2%	0.6%
Treatment discontinuation due to adverse event of hypocalcemia	< 0.1%	0.7%

Adverse events of hypocalcemia were predominantly transient and generally not associated with clinical consequences.

Most adverse events of hypocalcemia were single events that resolved with oral calcium or no action taken.

1. Data on file, Amgen. 2. XGEVA® (denosumab) prescribing information, Amgen.

- Manejo de complicaciones: Necrosis mandibular

Osteonecrosis of the Jaw (ONJ)

Denosumab: 1.8%

Zoledronic acid: 1.3% (NS)

Adverse Effects and Safety Profile

01 **Infections**

Increased risk of infections, particularly skin and urinary tract infections.

02 **Hypocalcemia**

Potential for severe hypocalcemia; monitor calcium levels during treatment.

03 **Skin Reactions**

Possible skin reactions, including dermatitis and cellulitis.

04 **Bone Pain**

Some patients may experience new or worsening bone pain.

05 **Osteonecrosis**

Risk of osteonecrosis of the jaw, especially after dental procedures.

06 **Gastrointestinal Issues**

Gastrointestinal issues like nausea and constipation may occur.

07 **Cardiovascular Events**

Potential for serious cardiovascular events; conduct regular risk assessments.

08 **Allergic Reactions**

Monitor for allergic reactions, which could manifest as rash or swelling.

Patient incidence, n (%)	Zoledronic acid (n = 2836)	Denosumab (n = 2841)
Adverse events (AEs), all grades	2745 (96.8)	2734 (96.2)
Most common AEs		
Nausea	895 (31.6)	876 (30.8)
Anaemia	859 (30.3)	771 (27.1)
Fatigue	766 (27.0)	769 (27.1)
Back pain	747 (26.3)	718 (25.3)
Decreased appetite	694 (24.5)	656 (23.1)
CTCAE grade 3, 4 or 5	2009 (70.8)	2000 (70.4)
AEs leading to study discontinuation	280 (9.9)	270 (9.5)

Lipton A, et al. Eur J Cancer 2012;48:3082–92.

CTCAE, common terminology criteria for adverse events.

Patient incidence, n (%)	Zoledronic acid (n = 2836)	Denosumab (n = 2841)
Infectious AEs	1218 (42.9)	1233 (43.4)
Infectious serious AEs	309 (10.9)	329 (11.6)
Acute phase reactions (first 3 days)	572 (20.2)	246 (8.7)
Cumulative rate of ONJ	37 (1.3)	52 (1.8)
Year 1	15 (0.5)	22 (0.8)
Year 2	28 (1.0)	51 (1.8)
Hypocalcaemia	141 (5.0)	273 (9.6)
New primary malignancy	18 (0.6)	28 (1.0)
AEs leading to study discontinuation	280 (9.9)	270 (9.5)

Lipton A, et al. Eur J Cancer 2012;48:3082–92.

ONJ, osteonecrosis of the jaw.

This analysis with over 5.700 patients with advanced malignant disease and bone metastases confirm the results of each single study.

Efficacy:

Denosumab has shown superiority versus zoledronic acid in terms of time to

- First complication of the bone (SRE)
- First and subsequent complication of the bone (SRE)

Tolerance

The most important adverse events that occurred in both treatment arms were ONJ, hypocalcemia, acute-phase-reactions and renal events:

- Hpocalcemia was more frequent in the denosumab arm.
- The frequency of ONJ was similar between both arms.
- Acute-phase-reactions and renal events were less frequent with denosumab compared to zoledronic acid.

Lipton A, Fizazi K, Stopeck AT, et al. *Eur J Cancer* 2012;48:3082-3092.

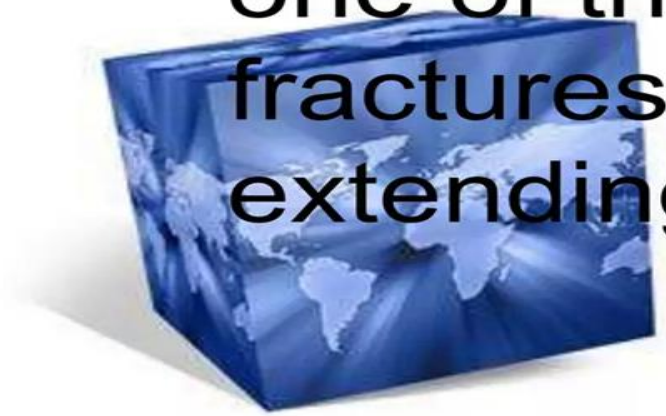
BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW

- AKA Phossy jaw
- American Academy of Oral and Maxillofacial Surgeons (AAOMS) proposed a definition for bisphosphonate-related ONJ that requires the satisfaction of the following criteria:
- (1) Current or prior use of bisphosphonate
- (2) An area of exposed bone within the maxillofacial region without healing for more than 8 weeks
- (3) Absence of history of radiation to the jaws

- It has been postulated that reduced bone remodeling associated with bisphosphonate use may lead to an increased risk of developing bone necrosis in select patients.
- The antiangiogenic effects of bisphosphonates may result in a reduction in the blood supply to the region and contribute to poor wound healing.
- Infection has also been implicated in the pathogenesis of ONJ

STAGES

- stage 1-were patients with asymptomatic necrotic bone
- stage 2-accompanied by infection with or without purulent drainage
- stage 3- patients with necrotic bone accompanied by infection, pain, and at least one of the conditions, including pathologic fractures, extraoral fistula, or osteolysis extending to the inferior border



- To assess the eHects of bisphosphonates and RANKL-inhibitors as supportive treatment for prostate cancer patients with bone metastases
- and to generate a clinically meaningful treatment ranking according to their safety and eHicacy using network meta-analysis
- We included randomized controlled trials
- Twenty-five trials fulfilled our inclusion criteria.

- Treatment with zoledronic acid probably neither reduces nor increases the proportion of participants with pain response
- Treatment with denosumab results in increased occurrence of the adverse event ONJ (RR 3.45, 95% CI 1.06 to 11.24; per 1000 participants30 more (1 more to 125 more)
- zoledronic acid probably neither reduces nor increases ONJ
- Compared to no treatment/placebo, treatment with zoledronic acid (RR 0.84, 95% CI 0.72 to 0.97) and denosumab (RR 0.72, 95% CI 0.54to 0.96) may result in a reduction of the total number of SREs
- Treatment with zoledronic acid and denosumab likely neither reduces nor increases mortality

Outcomes	Absolute effects and relative effects with 95% CIs. Main comparator: no treatment/placebo		
	Assumed risk with no treatment/placebo*	**Corresponding risk with zoledronic acid**	**Corresponding risk with denosumab**
Proportion of participants with pain response (network based on 4 studies including 1013 participants; follow-up 5-12 months)	**Response 265 per 1000** (26.5%)	**Response 386 per 1000** (246 to 614)	-
		RR 1.46 (0.93 to 2.32)	-
		⊖⊖⊖⊖ **Moderate[1]**	-

Outcomes	Absolute effects and relative effects with 95% CIs. Main comparator: no treatment/placebo		
	Assumed risk with no treatment/placebo*	Corresponding risk with zoledronic acid	Corresponding risk with denosumab
Adverse event: renal impairment (network based on 6 studies including 1769 participants; follow-up 5-36 months)	**124 per 1000** (12.4%)	**202 per 1000** (134 to 304)	-
		RR 1.63 (1.08 to 2.45)	-
		⊕⊕⊕⊖ **Moderate[2]**	-
Adverse event: osteonecrosis of the jaw (network based on 4 studies including 3006 participants; follow-up 5-24 months)	**12 per 1000** (1.2%)	**23 per 1000** (9 to 59)	**42 per 1000** (13 to 137)
		RR 1.88 (0.73 to 4.87)	**RR 3.45** (1.06 to 11.24)
		⊕⊕⊕⊖ **Moderate[1]**	⊕⊕⊕⊕ **High**

Outcomes	Absolute effects and relative effects with 95% CIs. Main comparator: no treatment/placebo		
	Assumed risk with no treatment/placebo*	Corresponding risk with zoledronic acid	Corresponding risk with denosumab
		Moderate[1]	High
Skeletal-related events total (network based on 12 studies including 5240 participants; follow-up 5-60 months)	**468 per 1000** (46.8%)	**393 per 1000** (337 to 454)	**337 per 1000** (253 to 449)
		RR 0.84 (0.72 to 0.97)	**RR 0.72** (0.54 to 0.96)
		⊕⊕⊝⊝ **Low[2,3]**	⊕⊕⊝⊝ **Low[2,3]**

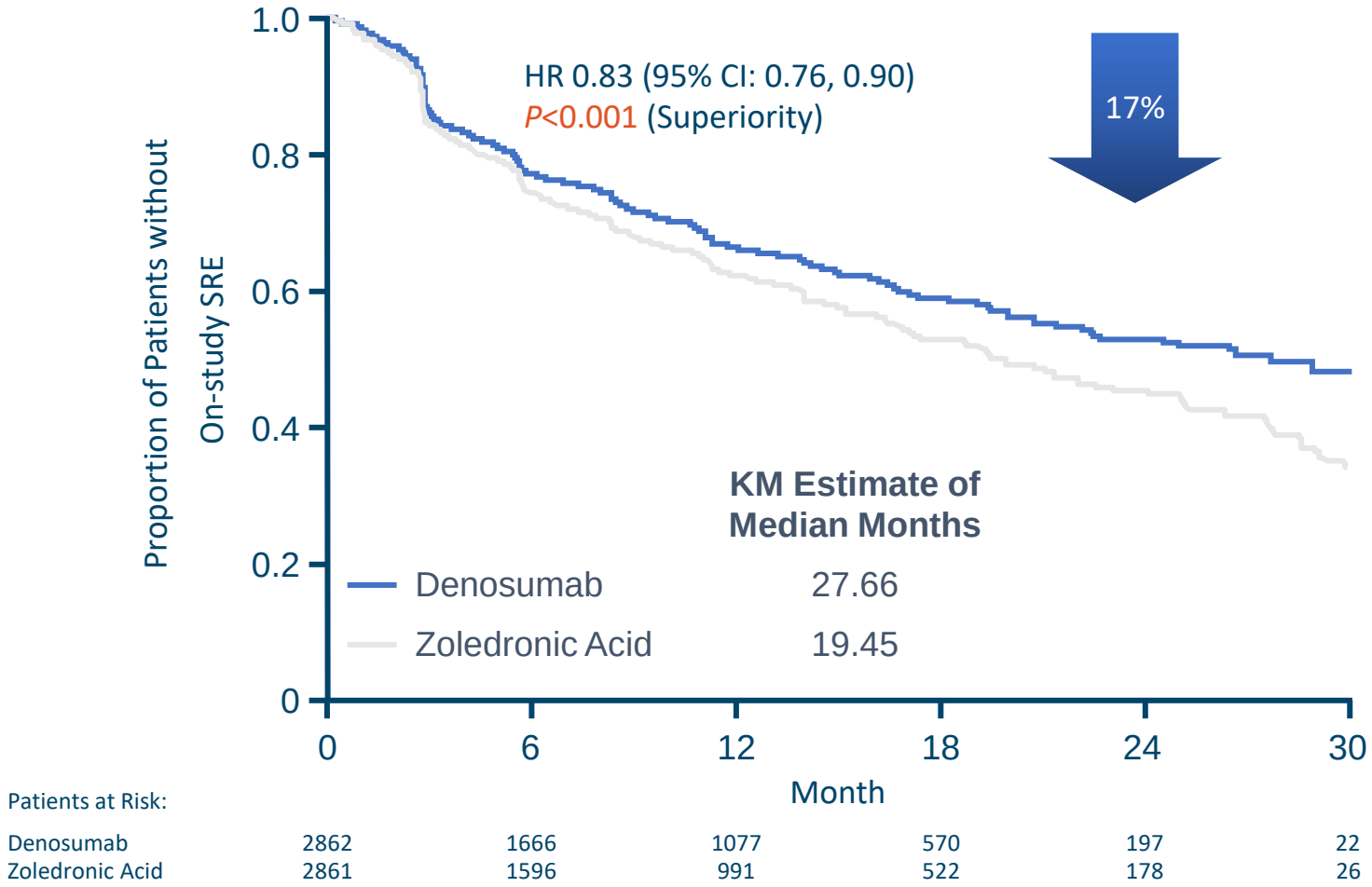
Prespecified Integrated Analysis: Baseline Demographics

Characteristics, n (%) or median	Zoledronic Acid (n = 2861)	Denosumab (n = 2862)
Women	1349 (47)	1316 (46)
Age (years)	63	63
ECOG performance status of 0 or 1	2546 (89)	2585 (90)
Previous SRE	1157 (40)	1112 (39)
Time from first bone metastasis to randomization (months): median (Q1, Q3)	2.3 (1.0, 7.6)	2.2 (1.0, 7.1)
Tumor type		
Breast	1020 (36)	1026 (36)
Prostate	951 (33)	950 (33)
Non-small-cell lung	352 (12)	350 (12)
Multiple myeloma	93 (3)	87 (3)
Renal	85 (3)	70 (2)
Small-cell lung	48 (2)	61 (2)
Other	312 (11)	318 (11)

ECOG = Eastern Cooperative Oncology Group.

1. Data on file, Amgen. 2. Lipton A, et al. Ann Oncol. 2010;21(suppl 8):382. Abstract 1249 and poster.

Int. analysis

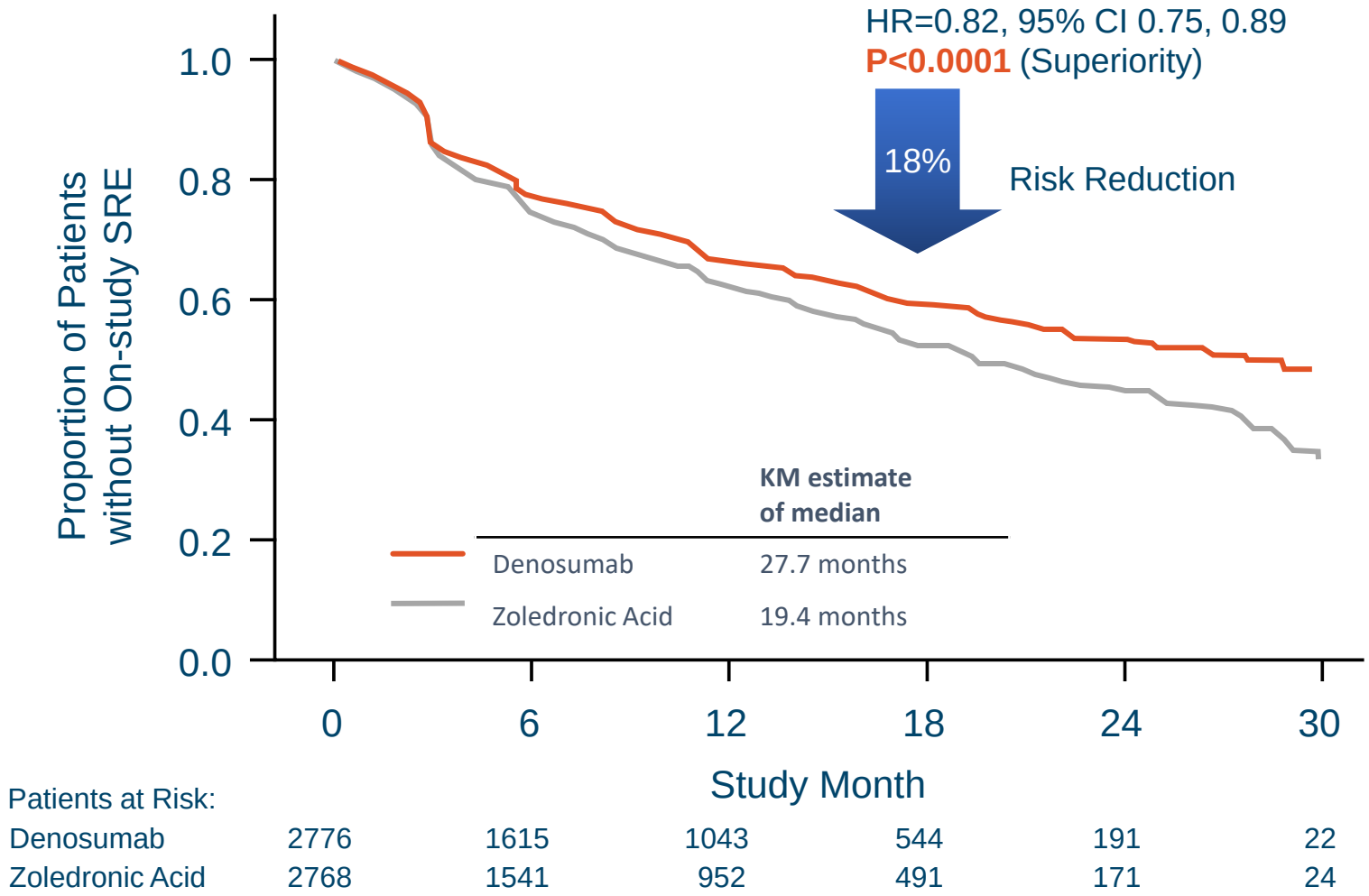


Lipton A, et al. *Eur J Cancer* 2012;48:3082-3092.

Post-hoc-analysis of the subgroup “solid tumors”

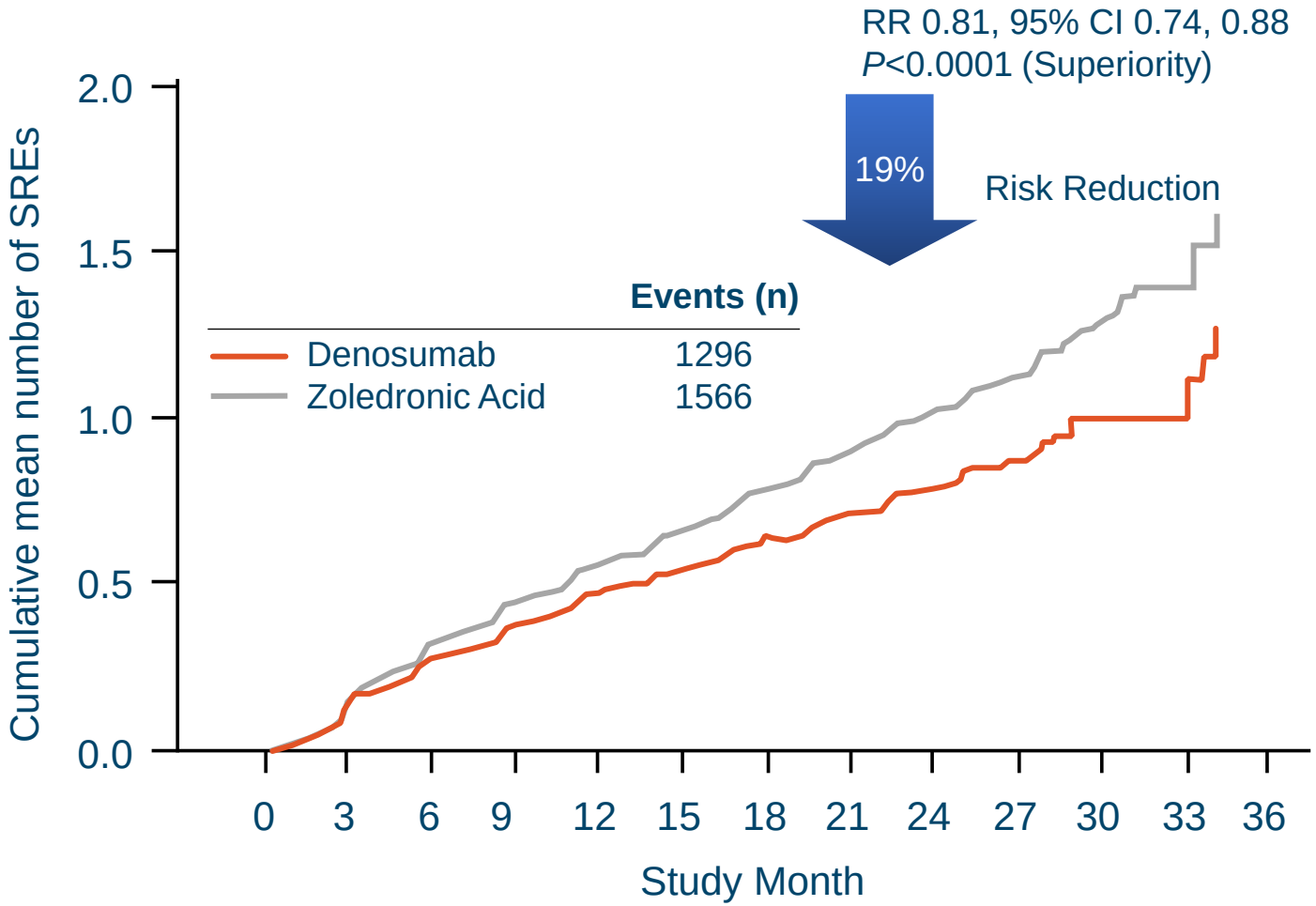
Richardson G, Siena S, Lipton A, et al. *COSA 2011*: abstract and oral presentation.
von Moos R, Stopeck A, Fizazi K, et al. *ECC* 2013: abstract P079 and poster presentation.

Int. analysis solid tumors



Richardson G, Siena S, Lipton A, et al. *COSA 2011*: abstract and oral presentation.

Int. analysis
solid tumors



Richardson G, Siena S, Lipton A, et al. *COSA 2011*: abstract and oral presentation.

Table 1
Patient demographics and baseline characteristics.

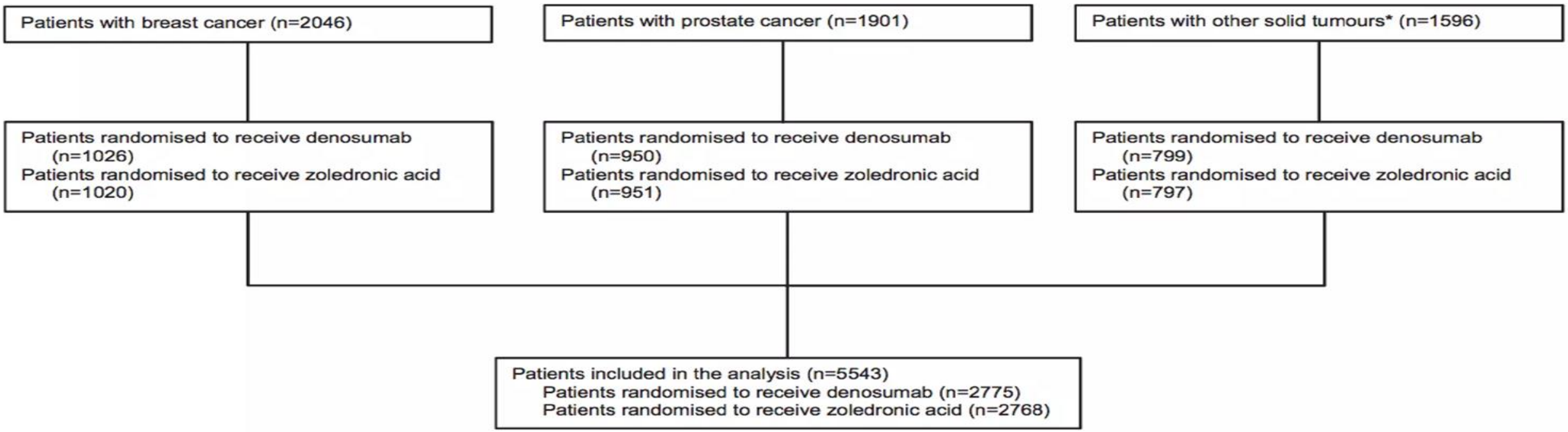
Characteristic	Zoledronic acid (n = 2768)	Denosumab (n = 2775)
Tumour type, n (%)		
Breast	1020 (37)	1026 (37)
Prostate	951 (34)	950 (34)
Other solid tumours	797 (29)	799 (29)
ECOG performance status,[a] n (%)		
0	1120 (41)	1141 (41)
≥1	1640 (59)	1631 (59)
Location of bone metastases,[b,c] n (%)		
Axial only	672 (24)	706 (25)
Appendicular only	345 (13)	387 (14)
Axial and appendicular	833 (30)	804 (29)
Number of bone metastases, n (%)		
<2	1696 (61)	1689 (61)
≥2	1072 (39)	1086 (39)
Presence or absence of visceral metastasis, n (%)		
Yes	1152 (42)	1185 (43)
No	1616 (58)	1590 (57)
Median uNTx level,[d] n (%)		
≥43.7 nmol/mmol	1222 (44)	1254 (45)
<43.7 nmol/mmol	1246 (45)	1229 (44)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; uNTx, urinary N-telopeptide.

Lipton A. Eur Journal of Cancer 53 (2016) 75-83

Effect of denosumab versus zoledronic acid in preventing skeletal-related events in patients with bone metastases by baseline characteristics

A. Lipton [a,*], K. Fizazi [b], A.T. Stopeck [c], D.H. Henry [d], M.R. Smith [e], N. Shore [f], M. Martin [g], S. Vadhan-Raj [h], J.E. Brown [i], G.E. Richardson [j], F. Saad [k], D.A. Yardley [l], K. Zhou [m], A. Balakumaran [m,1], A. Braun [m,2]



Lipton A. Eur Journal of Cancer 53 (2016) 75-83

Is denosumab COST-EFFECTIVE when compared to (active) bisphosphonates in solid tumors?

EXPERT REVIEWS

Health-economic review of zoledronic acid for the management of skeletal-related events in bone-metastatic prostate cancer

Expert Rev. Pharmacoecon. Outcomes Res. 12(4), 425–437 (2012)

Expert commentary

Zoledronic acid and denosumab are SRE-limiting agents proven effective in patients with bone-metastatic prostate cancer. As was presented in this article, denosumab has been compared with zoledronic acid from USA, UK and Dutch payer perspectives, and zoledronic acid has been compared with pamidronate and no therapy across Europe and North America. Zoledronic acid was found to be cost effective across Europe and Canada but not in the USA, while denosumab was found to be cost effective in The Netherlands, the UK and the USA in certain analyses, but cost ineffective in other analyses in the UK and the USA. Across the reviewed analyses, by far the most robust driver of modeled outcomes was drug acquisition cost.

Carter JA, Botteman MF. Health-economic review of zoledronic acid for the management of skeletal-related events in bone-metastatic prostate cancer. Expert Rev Pharmacoecon Outcomes Res. 2012;12:425–437

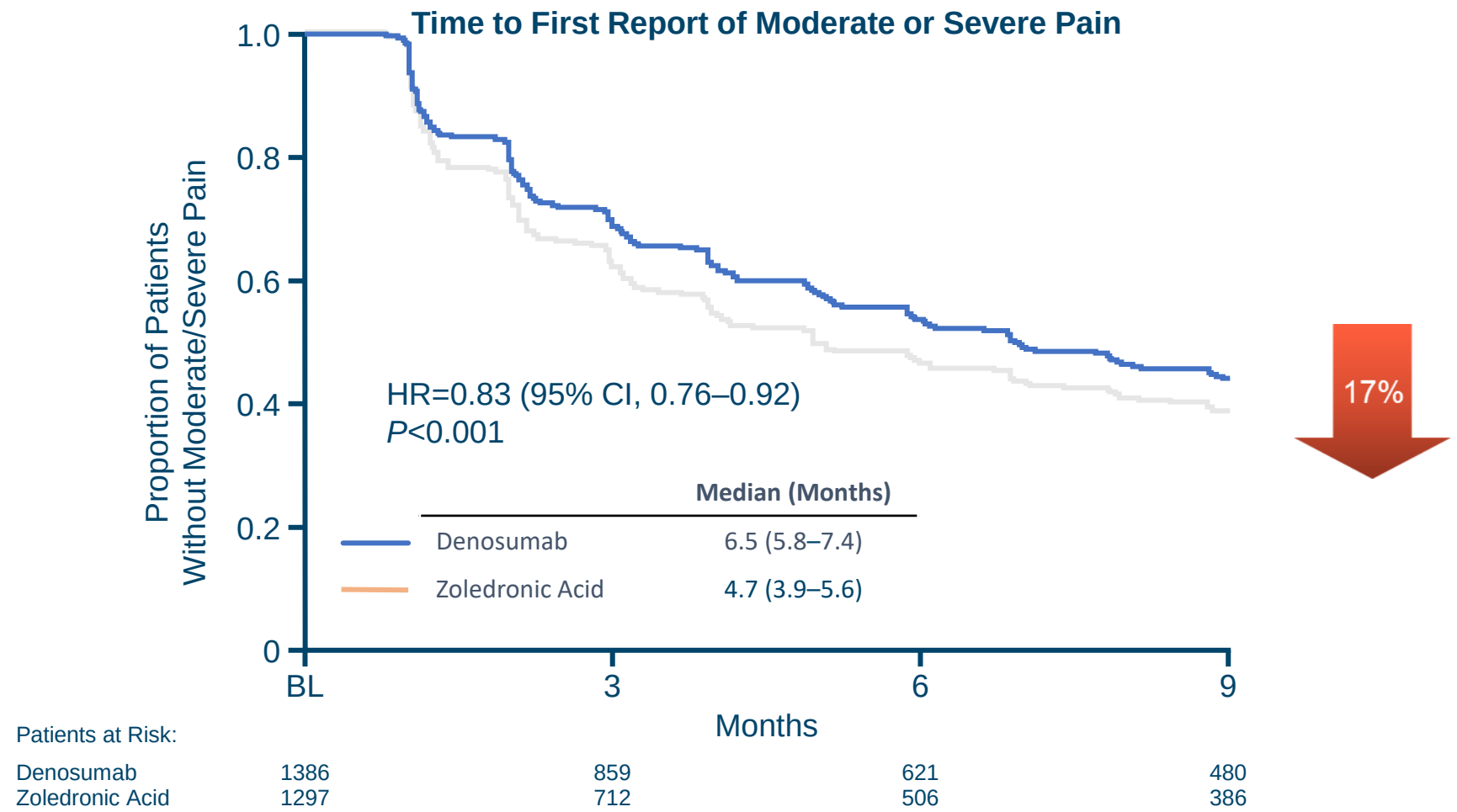
- Pain occurs in the vast majority of cancer patients with bone metastases and worsens to (moderate/strong) over the course of their disease
- Denosumab delayed worsening of pain compared with zoledronic acid
- A lower proportion of patients receiving denosumab experienced worsening of pain than patients receiving zoledronic acid at the majority of time points
- A lower proportion of patients receiving denosumab required increasing analgesic use over time

Cleeland CS, Patrick DL, Fallowfield L, et al. *ESMO 2010*: Abstract 1248P und Poster.

Pain and Pain Interference, analgetics use and Quality of life

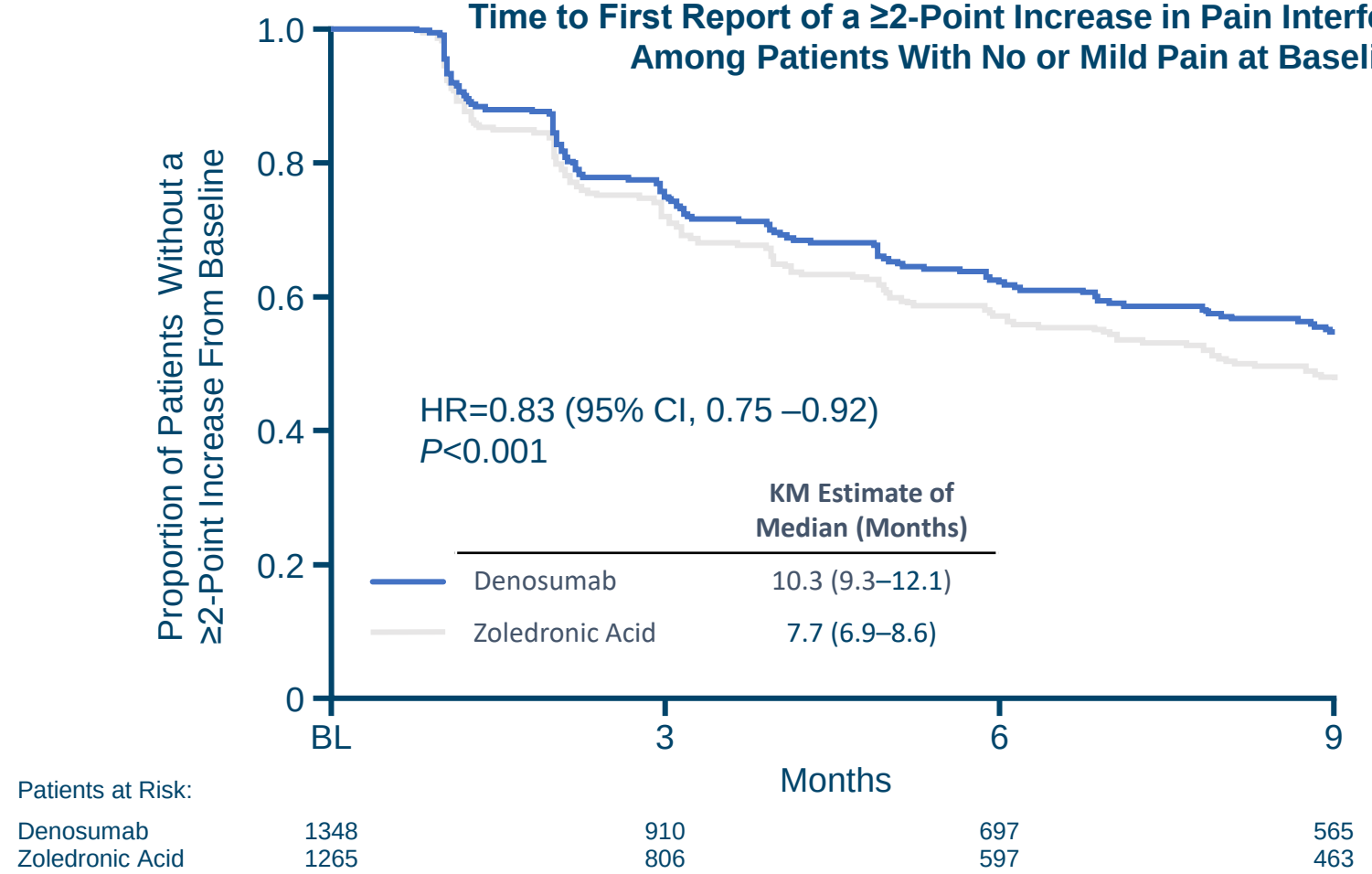
Post-hoc-Analysis of the subgroup “solid tumors”

von Moos R, Body JJ, Egerdie B, et al. *Support Care Cancer* 2013; doi 10.1007/s00520-013-1932-2.
von Moos R, et al. *ECC 2013*: abstract P081 and poster presentation.



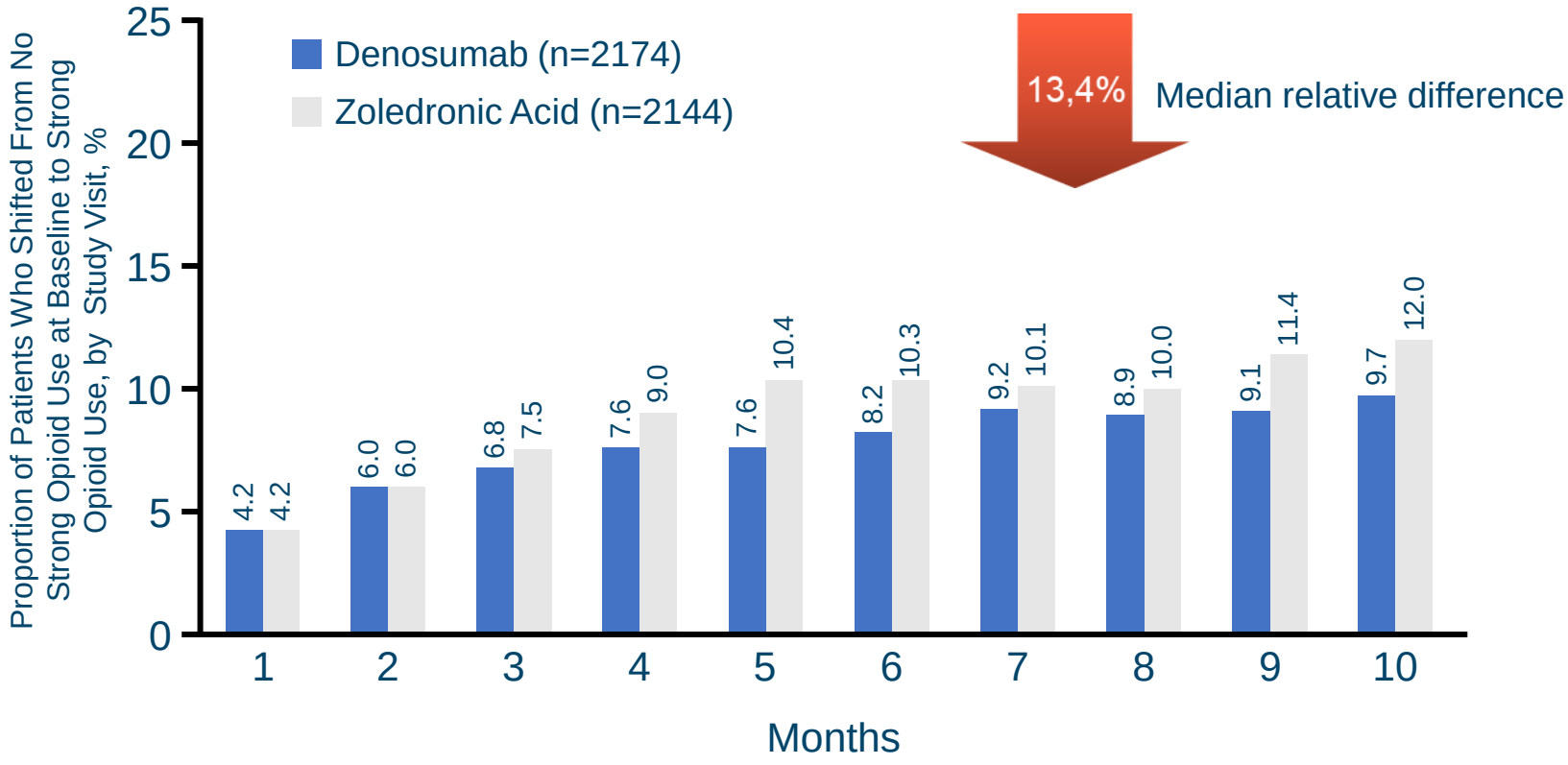
von Moos R, Body JJ, Egerdie B, et al. *Support Care Cancer* 2013; doi 10.1007/s00520-013-1932-2.

Time to First Report of a ≥2-Point Increase in Pain Interference Score Among Patients With No or Mild Pain at Baseline



von Moos R, Body JJ, Egerdie B, et al. *Support Care Cancer* 2013; doi 10.1007/s00520-013-1932-2.

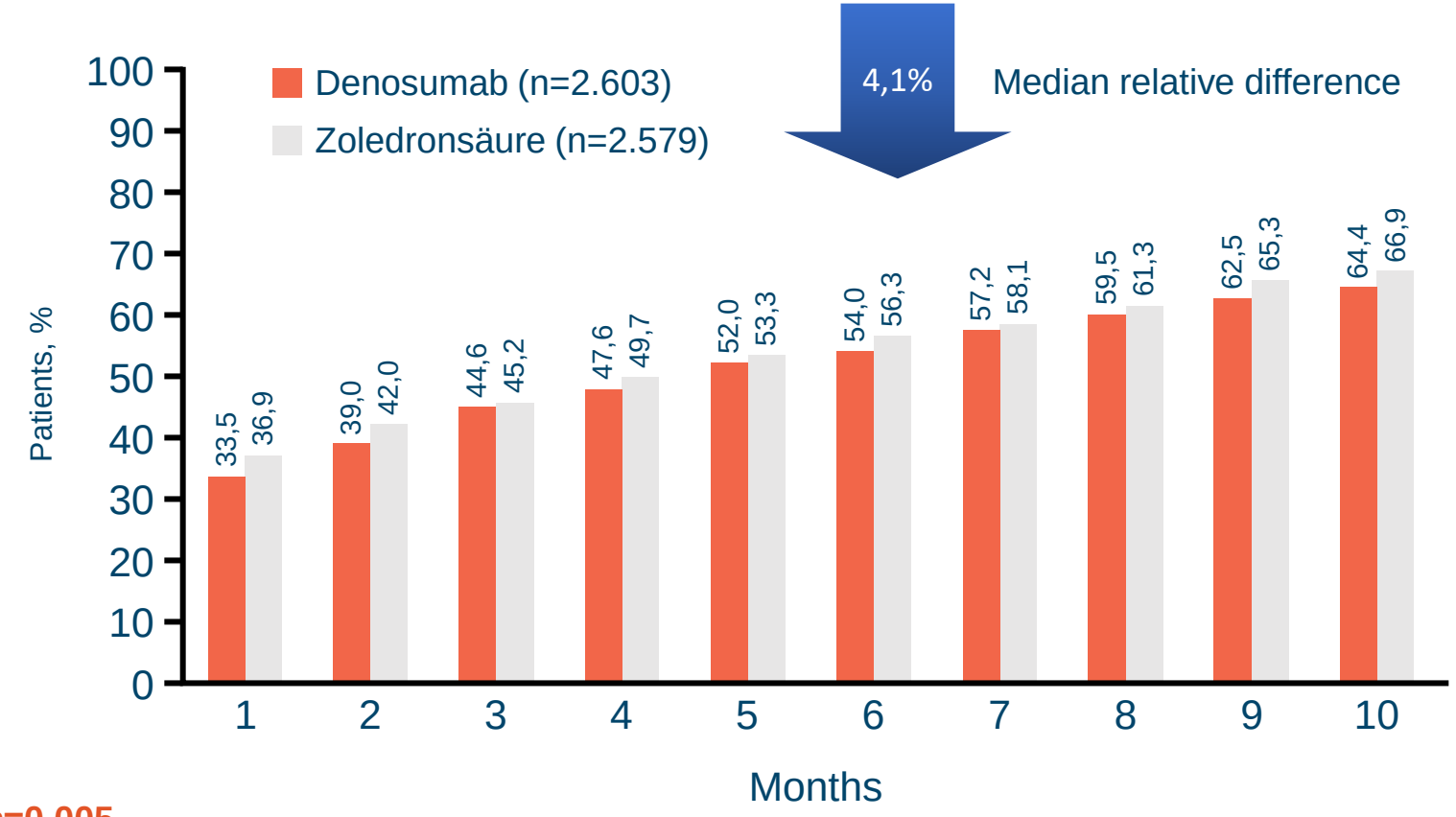
Proportion of Patients Who Shifted From Baseline Use of No Analgesic, Non-Opioid Analgesics or Weak Opioids to Use of Strong Opioids on Study



Average relative difference, –13.4%
P=0.041 overall, denosumab vs. zoledronic acid by Generalized Estimating Equation

von Moos R, Body JJ, Egerdie B, et al. *Support Care Cancer* 2013; doi 10.1007/s00520-013-1932-2.

Patients (%) with a reduction in quality of life through the FACT[1]-G-total score of ≥5 points versus baseline



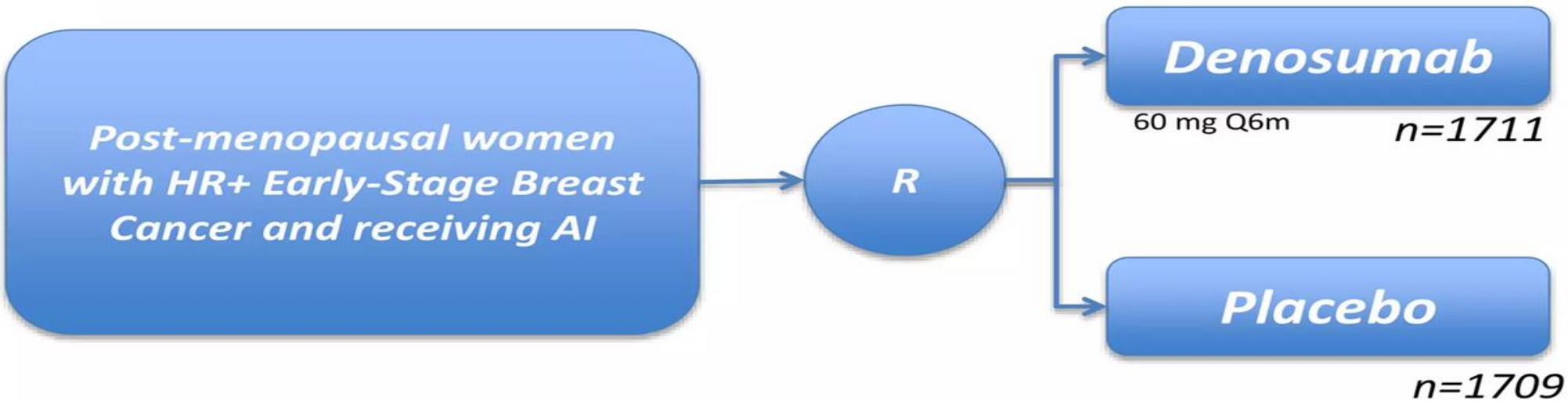
***p*=0,005**

[1] Function Assessment of Cancer Therapy

von Moos R, Body JJ, Egerdie B, et al. Support Care Cancer 2013; doi 10,1007/s00520-013-1932-2.

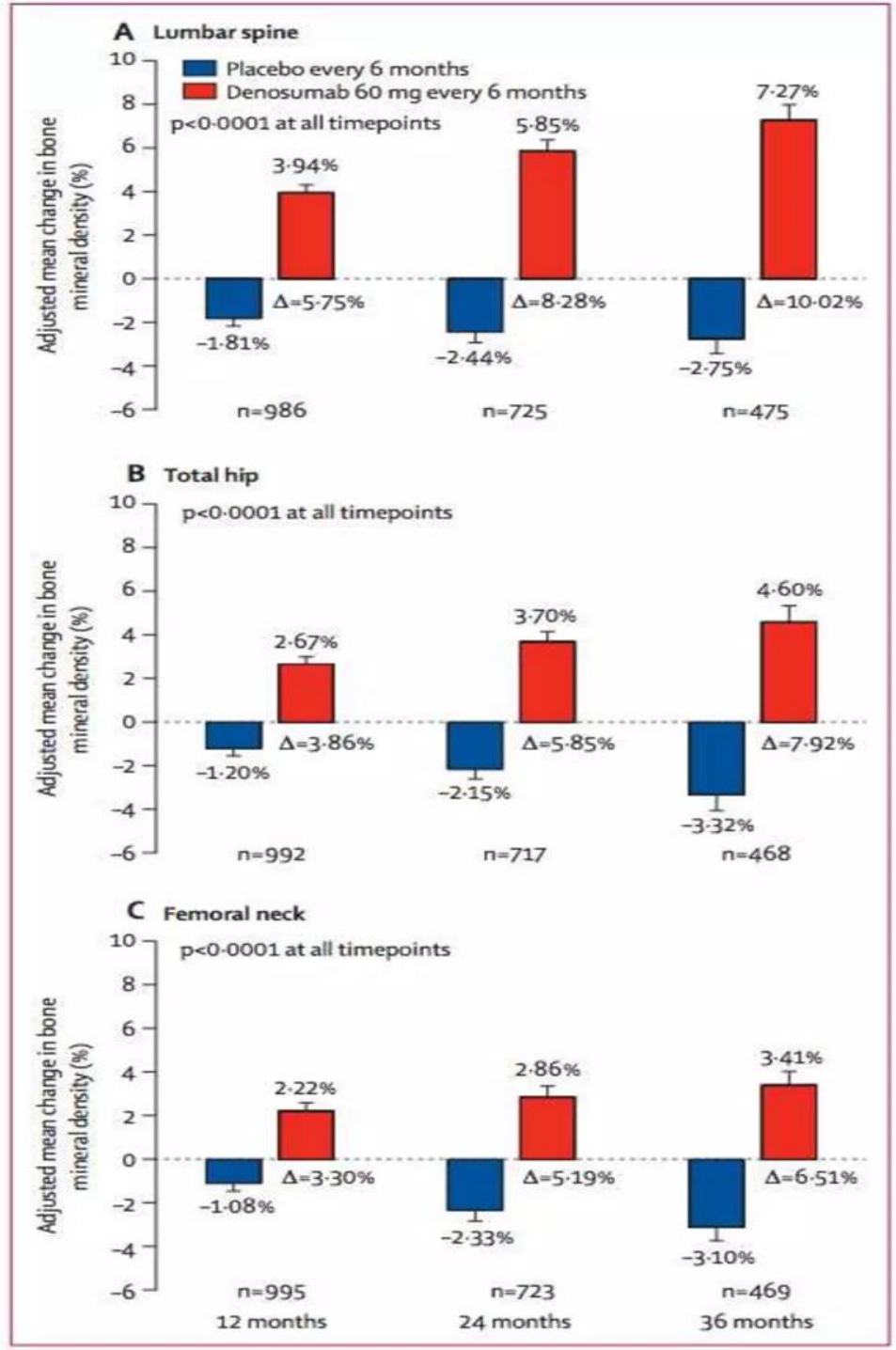
Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial

*Michael Gnant, Georg Pfeiler, Peter C Dubsky, Michael Hubalek, Richard Greil, Raimund Jakesz, Viktor Wette, Marija Balic, Ferdinand Haslbauer, Elisabeth Melbinger, Vesna Bjelic-Radisic, Silvia Artner-Matuschek, Florian Fitzal, Christian Marth, Paul Sevelda, Brigitte Mlineritsch, Günther G Steger, Diether Manfreda, Ruth Exner, Daniel Egle, Jonas Bergh, Franz Kainberger, Susan Talbot, Douglas Warner, Christian Fesl, Christian F Singer, on behalf of the Austrian Breast and Colorectal Cancer Study Group**

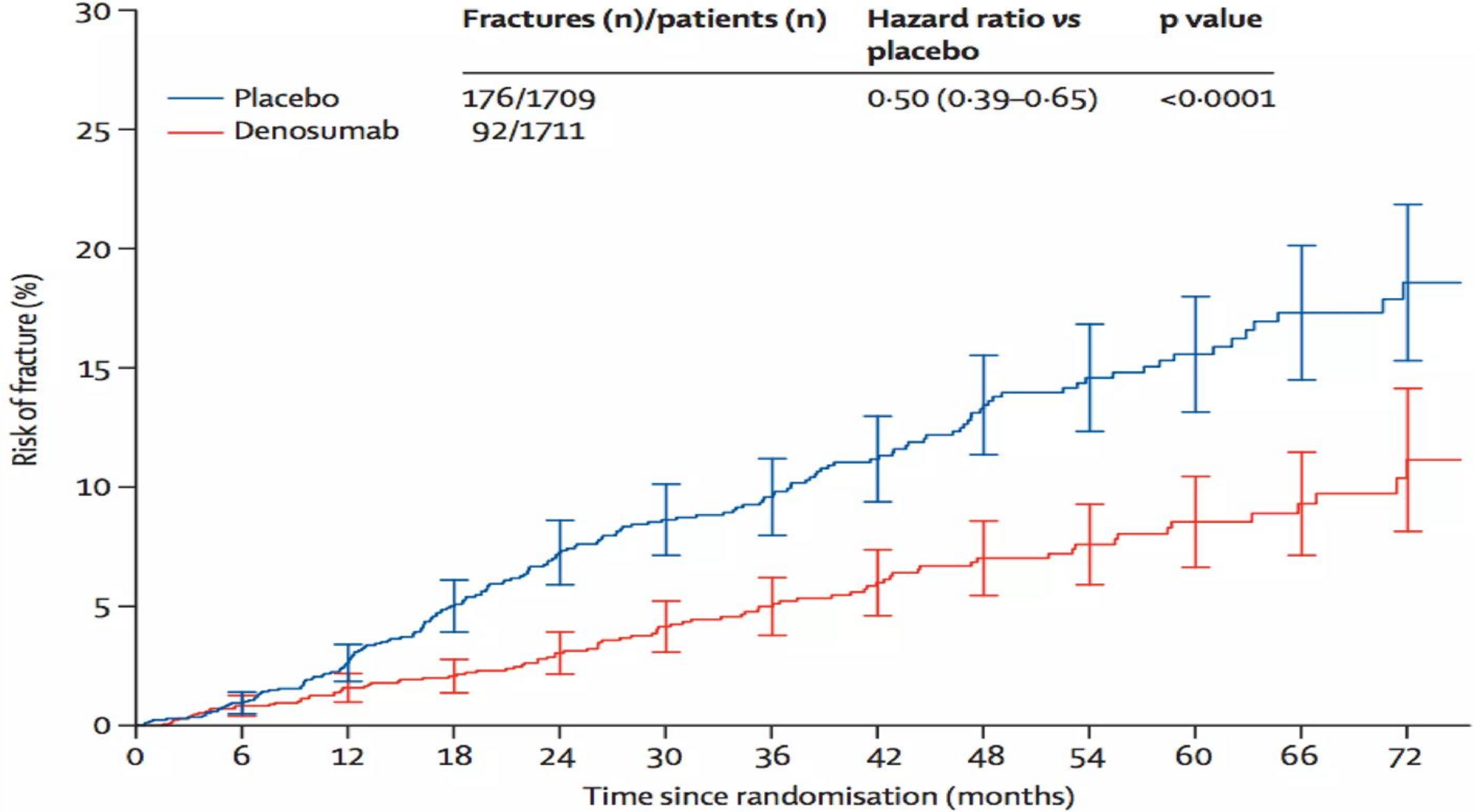


Time from randomization to first fracture

Gnant M, Lancet Oncol 2015

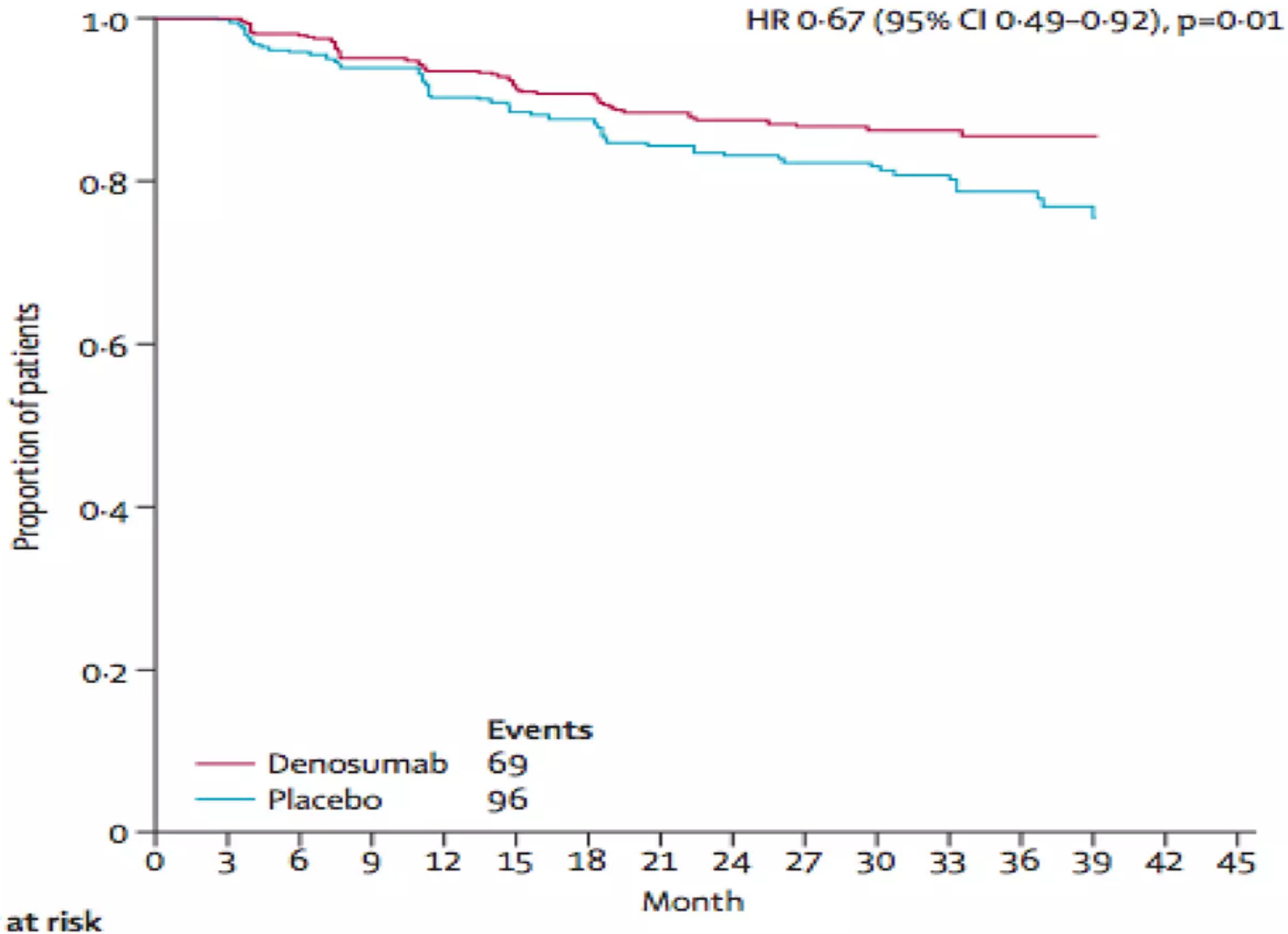


Gnant M, Lancet Oncol 2015



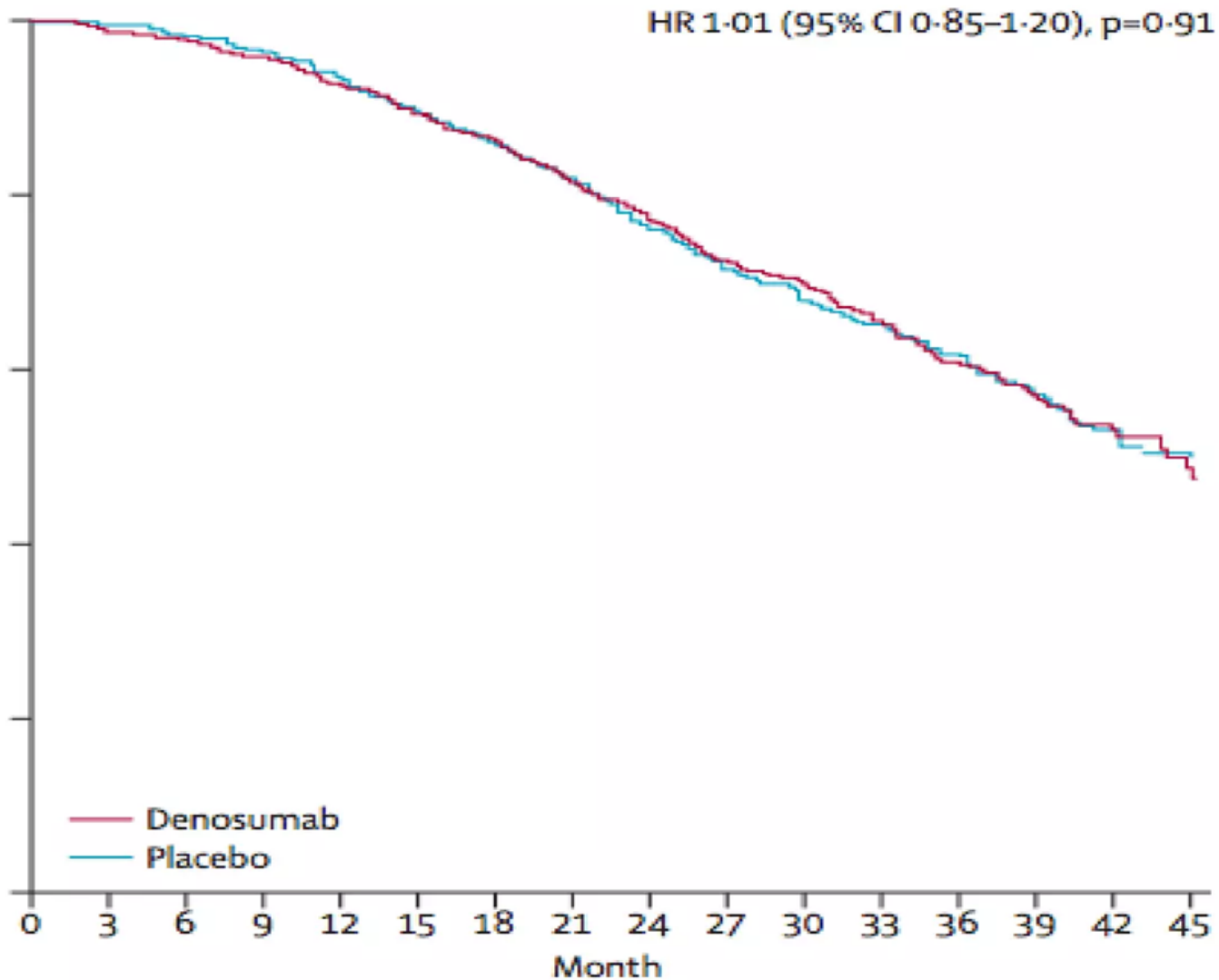
Ghant M, Lancet Oncol 2015

Time to symptomatic bone metastases



Smith MR, Lancet 2012; 379: 39–46

Time to symptomatic bone metastases



Smith MR, Lancet 2012; 379: 39–46

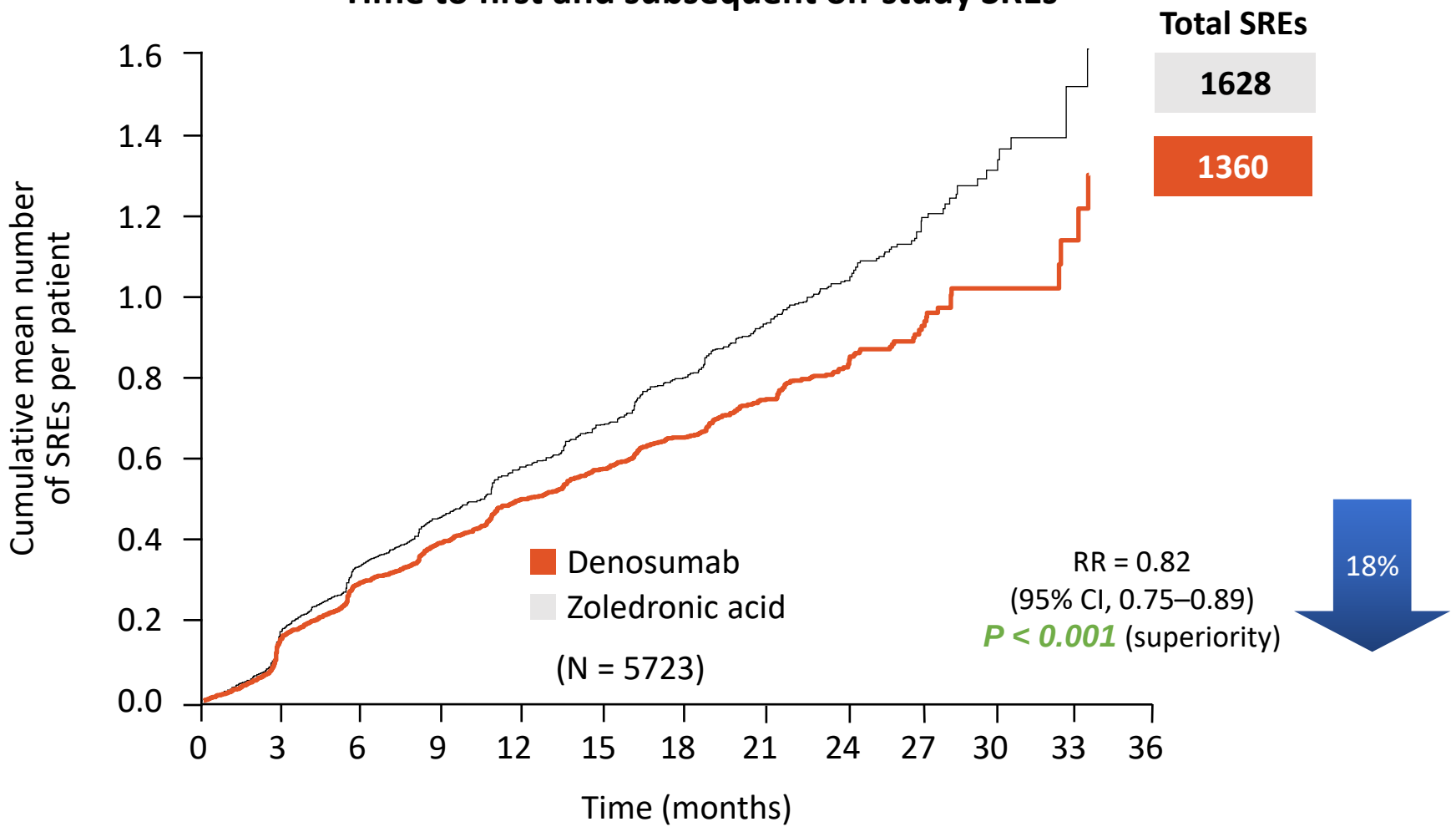
	Placebo (n=705)	Denosumab (n=720)
Any adverse event	655 (93%)	676 (94%)
Most common adverse events		
Back pain	156 (22%)	168 (23%)
Constipation	119 (17%)	127 (18%)
Arthralgia	112 (16%)	123 (17%)
Diarrhoea	102 (14%)	111 (15%)
Urinary tract infection	96 (14%)	108 (15%)
Serious adverse events	323 (46%)	329 (46%)
Most common serious adverse events		
Urinary retention	31 (4%)	54 (8%)
Haematuria	24 (3%)	35 (5%)
Prostate cancer	21 (3%)	15 (2%)
Anaemia	12 (2%)	22 (3%)
Urinary tract infection	14 (2%)	15 (2%)
Grade 3, 4, or 5 adverse events	353 (50%)	381 (53%)
Adjudicated positive osteonecrosis of the jaw	0	33 (5%)
Hypocalcaemia	2 (<1%)	12 (2%)

Data are n (%).

***Table 2:* Adverse events**

Smith MR, Lancet 2012; 379: 39–46

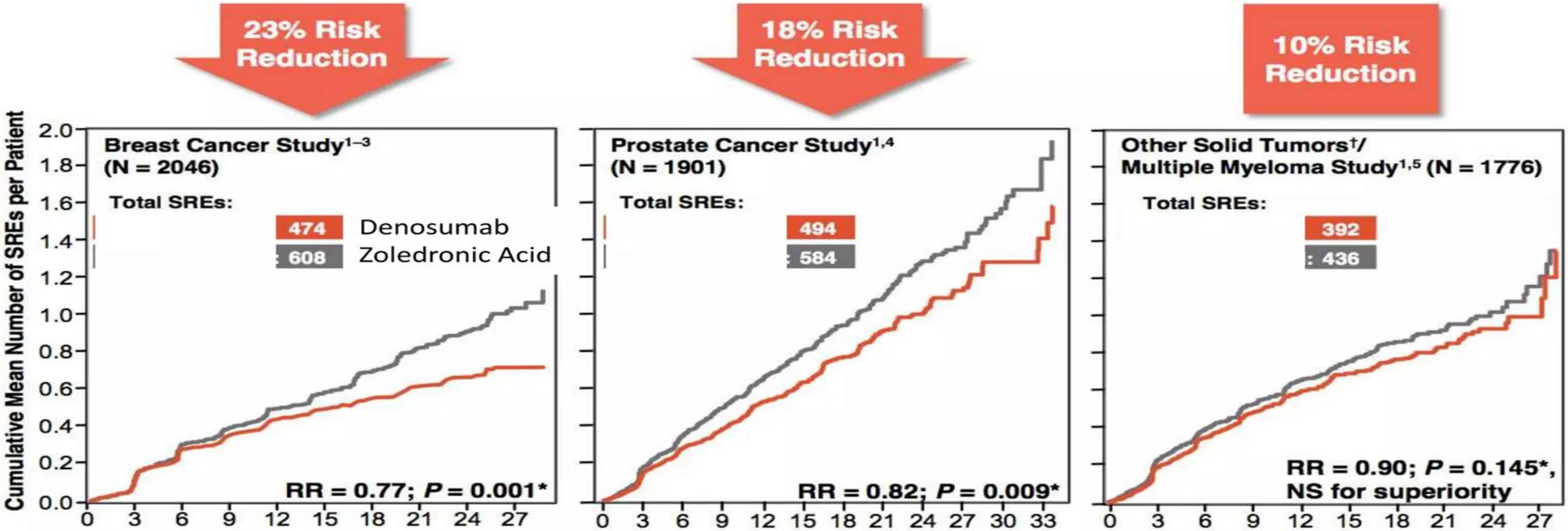
Time to first and subsequent on-study SREs



Events occurring at least 21 days apart (multiple event analysis).
RR, rate ratio.

Lipton A, et al. Eur J Cancer 2012;48:3082–92.

Denosumab Was Superior to Zoledronic Acid: 18% Risk Reduction in First and Subsequent SREs



*P value for superiority. †Excluding breast and prostate. Study Month

1. Denosumab prescribing information, Amgen. 2. Stopeck A, et al. Presentation at: ECCO/ESMO Multidisciplinary Congress. Sept 20-24, 2009; Berlin, Germany. 3. Stopeck AT, et al. J Clin Oncol. 2010;28:5132- 5139. 4. Fizazi K, et al. Lancet. 2011;377:813-822. 5. Henry D, et al. J Clin Oncol. [Epub ahead of print] doi: 10.1200/JCO.2010.31.3304.

Denosumab: Superior Efficacy

	Risk Reduction in Time to First SRE	*P*-value	Risk Reduction in Time to First and Subsequent SREs	*P*-value
Integrated analysis[1,7]	17%	< 0.0001, superiority	18%	< 0.0001, superiority
Breast cancer[2]	18%	0.010, superiority	23%	0.001, superiority
Prostate cancer[2]	18%	0.008, superiority	18%	0.009, superiority
Other solid tumors* or multiple myeloma[2]	16%	< 0.001, noninferiority 0.060, NS for superiority	10%	0.145, NS for superiority
Subanalysis of other solid tumors*[3]	19%	0.034, superiority	15%	0.048, superiority

*Excluding breast and prostate.

1. Data on file, Amgen. 2. XGEVATM (denosumab) prescribing information, Amgen. 3. Henry D, et al. Presentation at: ASCO Annual Meeting. June 4-8, 2010; Chicago, ILL. 4. Stopeck A, et al. Presentation at: ECCO/ESMO. Sept 20-24, 2009; Berlin, Germany. Abstract 2LBA. 5. Fizazi K, et al. Lancet. 2011;377:813-822. 6. Henry D, et al. J Clin Oncol. [Epub ahead of print] doi: 10.1200/JCO.2010.31.3304. 7. Lipton A, et al. Ann Oncol. 2010;21(suppl 8):382. Abstract 1249 and poster.

Efficacy and Safety of Denosumab Versus Zoledronic Acid in Patients With Bone Metastases

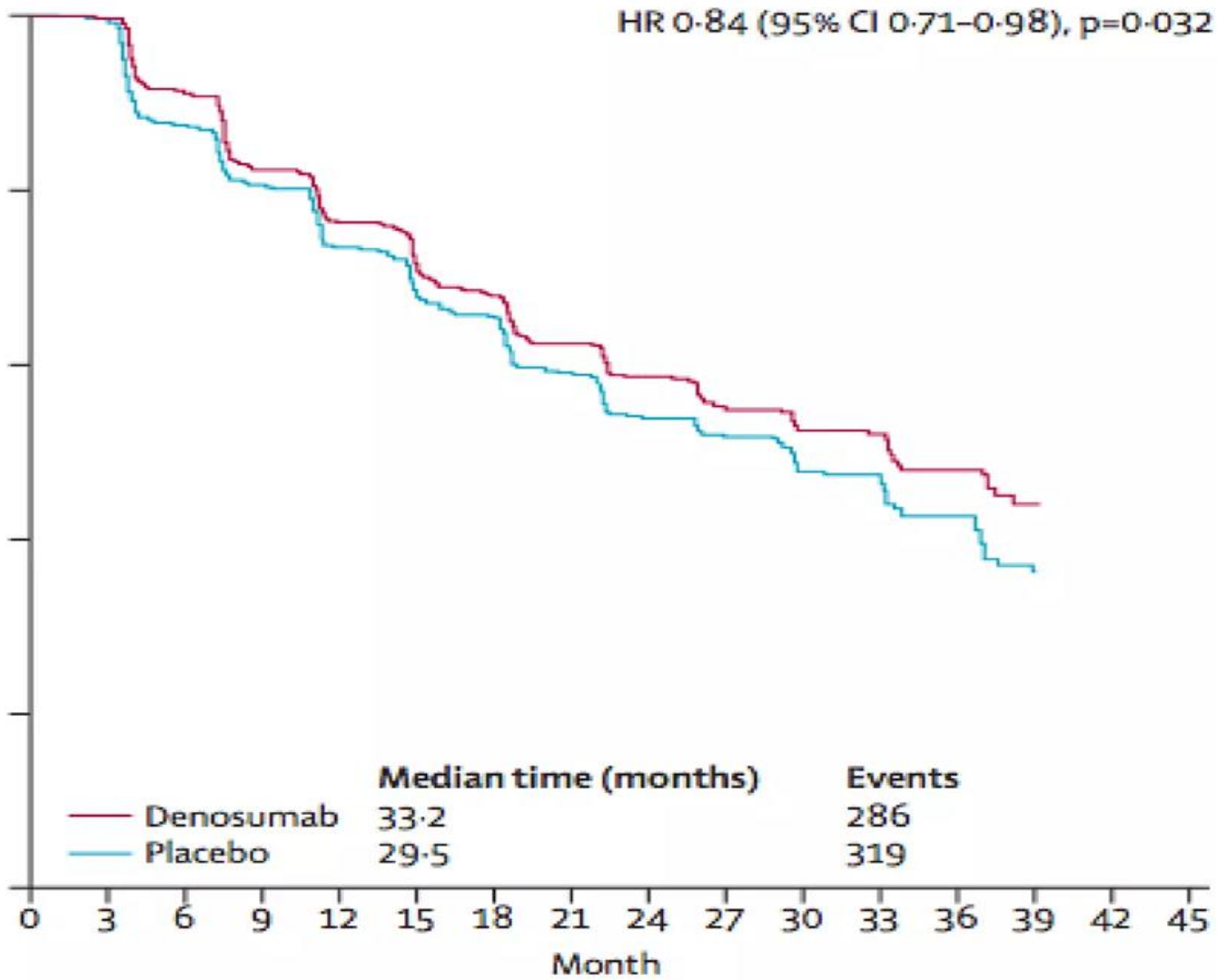
A Systematic Review and Meta-analysis

Lei Sun, MD and Shiying Yu, MD

This meta-analysis indicates that denosumab is more effective than ZA in reducing morbidity for patients with bone metastases. In addition, the risk of relative serious AEs was not significantly increased in patients receiving denosumab compared with those given ZA

Sun L, Am J Clin Oncol 2013;36:399–403

Time to bone metastases



Smith MR, Lancet 2012; 379: 39–46