"IL TRATTAMENTO DELLE METASTASI OSSEE DA TUMORI SOLIDI"

Catania, 13 NOVEMBRE 2015
c/o NH Hotel Bellini

Il trattamento farmacologico: vecchi e nuovi farmaci

BREAST CENTRE
HUMANITAS CATANIA

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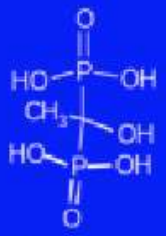
HUMANITAS
CENTRO CATANESE DI ONCOLOGIA

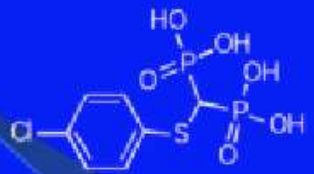
Different Classes of Bisphosphonates[1,2]

1 gen



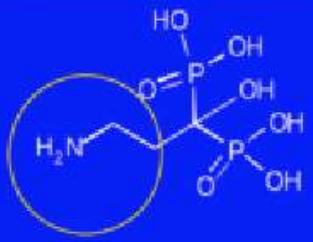
etidronate

clodronate

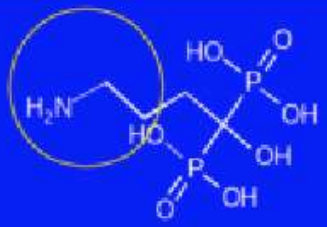


tiludronate

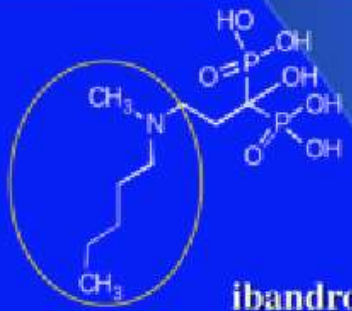
2 gen



pamidronate



alendronate



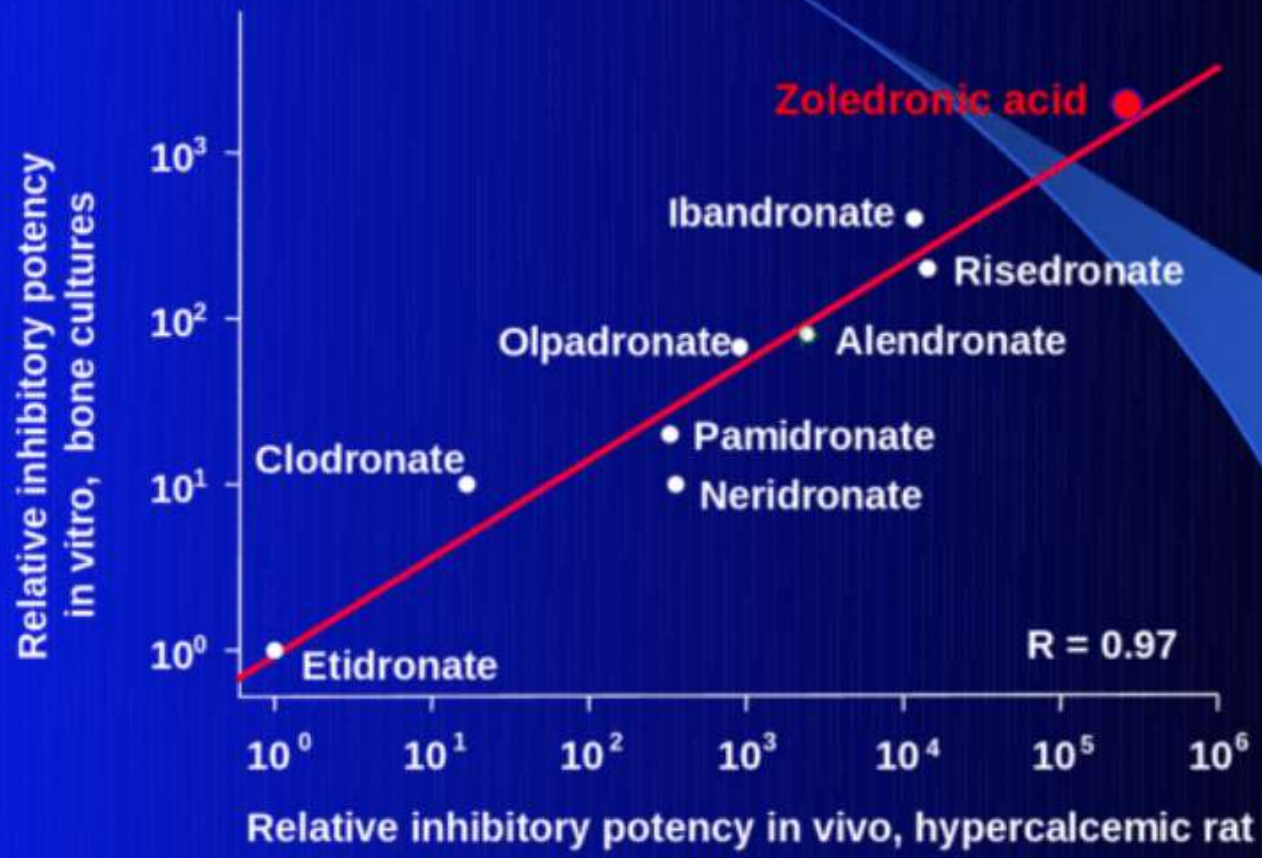
ibandronate

3 gen

zoledronic acid

1. Thurlimann B. *Bisphosphonates in Clinical Oncology: Focus on Pamidronate*. 1999.
2. Fleisch H. *Endocr Rev*. 1998.

Efficacia dei diversi bisfosfonati



Green JR, et al. *J Bone Miner Res*. 1994;9:745-751.

Ca. mammario: bisfosfonati vs. placebo

% pazienti con ≥1 SRE

	BP	placebo	% decrease
	value		
Pamidronate[1]	51	64	20%
	<0.001		
Oral Ibandronate[2]	45	52	13%
	0.122		
IV Ibandronate[3]	51	62	18%
	0.052		
Zoledronic acid[4]	30	50	40%
	0.003		

[1]Lipton, Cancer 2000; [2]Body, Ann Oncol 2003; [3]Body, Br J Cancer 2004; [4]Kohno

Coleman R, 5th International Conference on CIBD, Davos 2005

Ca. mammario: bisfosfonati vs. placebo

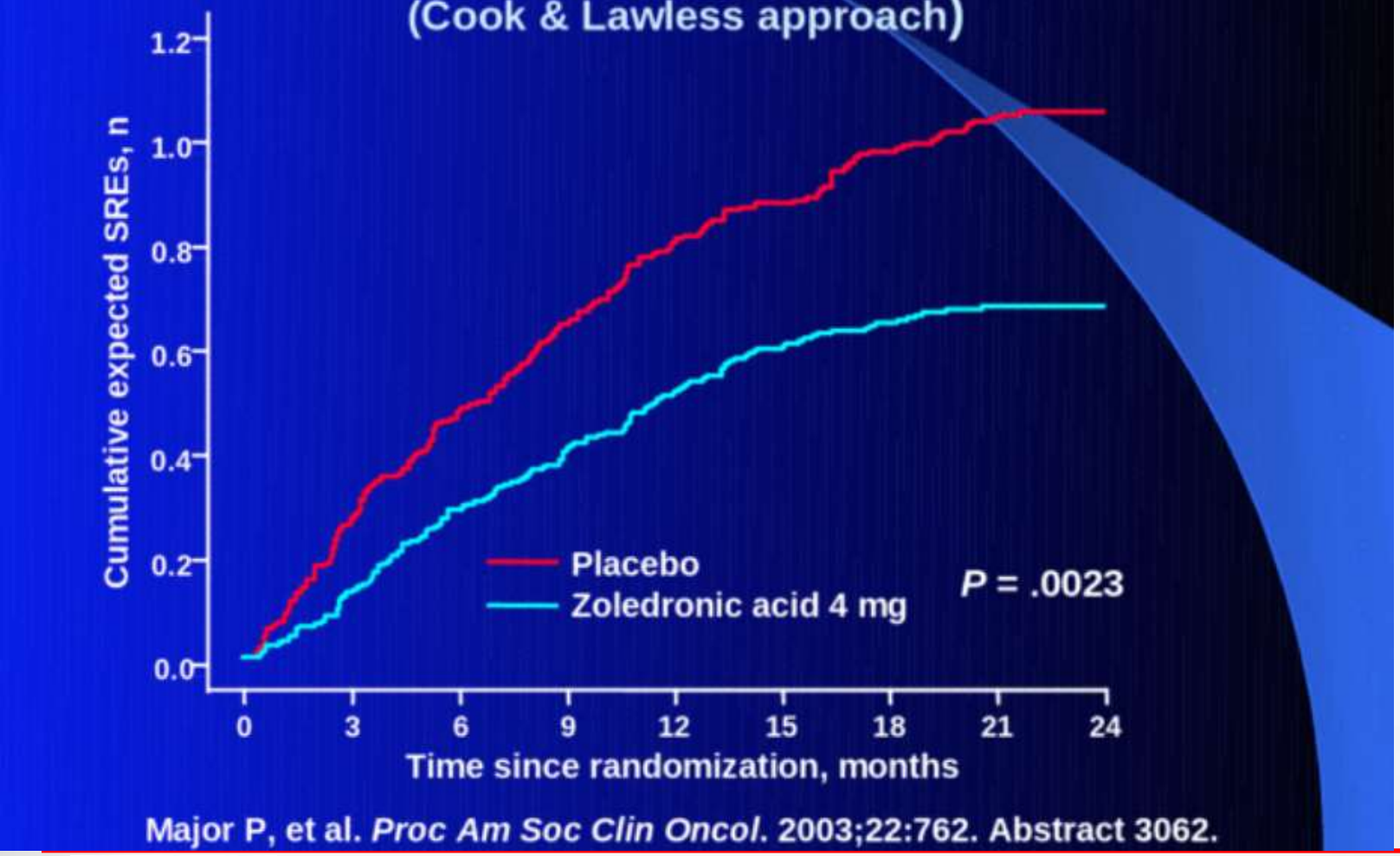
mediana del tempo a comparsa del primo SRE

	BP	placebo	% increase	P value
Clodronate[1]	9.4	5.6	68%	0.022
Pamidronate[2]	12.7	7.0	81%	0.001
Oral Ibandronate[3]	21.0	15.1	39%	0.089
IV Ibandronate[4]	11.8	7.7	53%	0.018
Zoledronic acid[5]	NR	12.0	110%*	0.007

[1]Pavlakis, Cochrane review 2004; [2]Lipton, Cancer 2000; [3]Body, Ann Oncol 2003; [4]Body, Br J Cancer 2004; [5]Kohno, J Clin Oncol 2005; *estimated

Coleman R, 5th International Conference on CIBD, Davos 2005

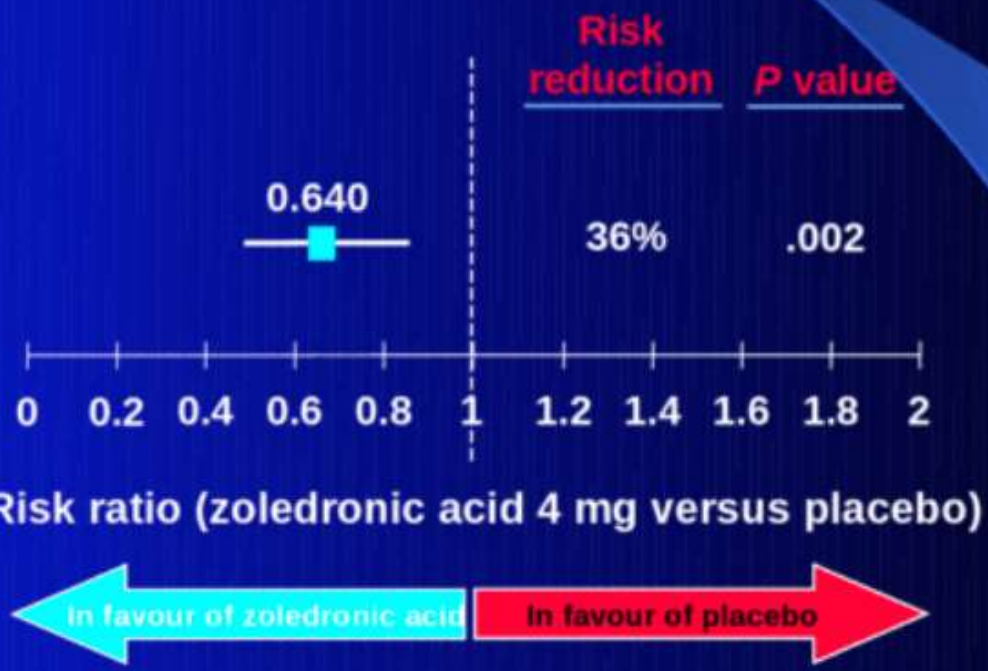
Ca. prostatico: A. Zoledronico vs. placebo



Major P, et al. *Proc Am Soc Clin Oncol*. 2003;22:762. Abstract 3062.

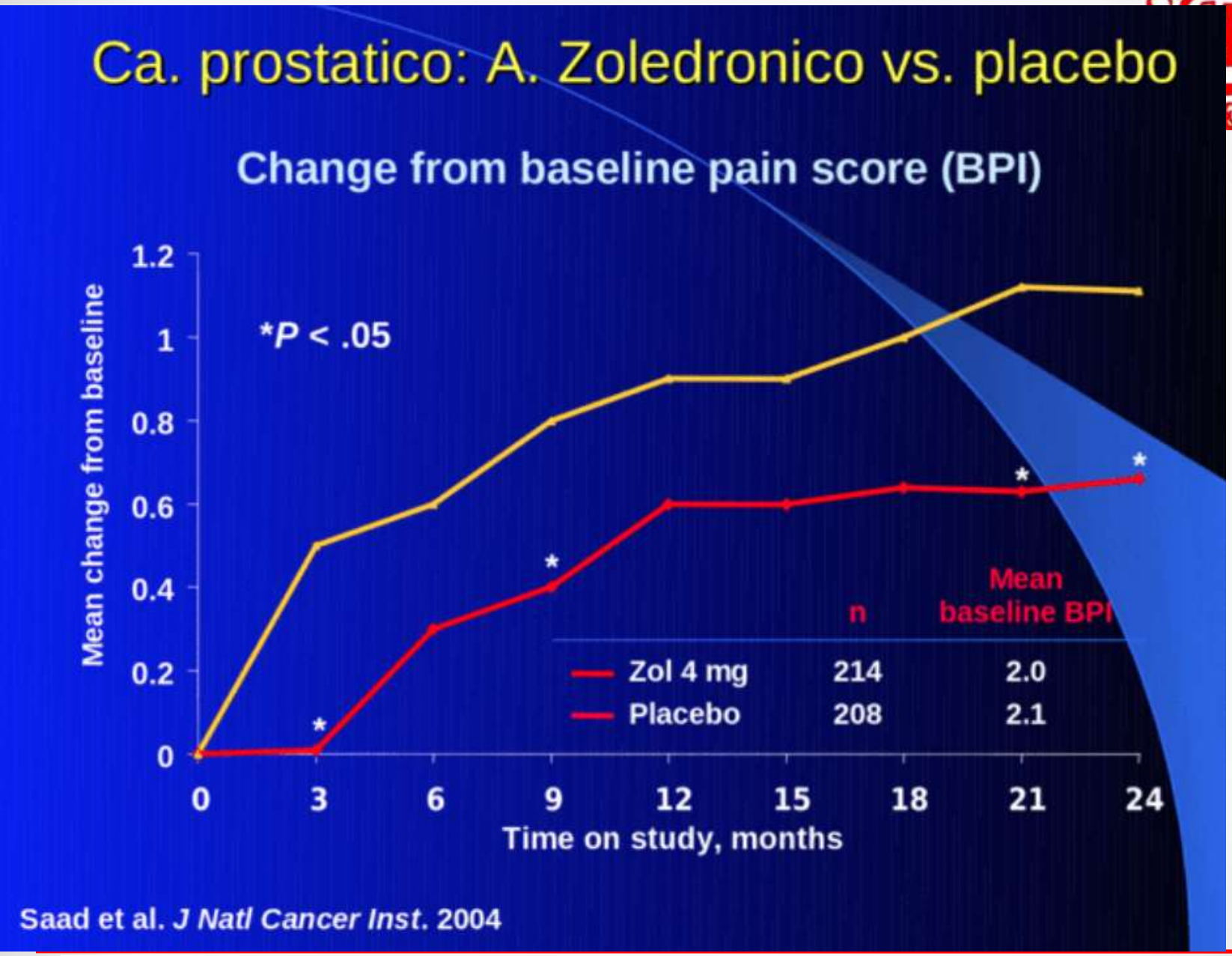
Ca. prostatico: A. Zoledronico vs. placebo

Multiple event analysis (Andersen-Gill)



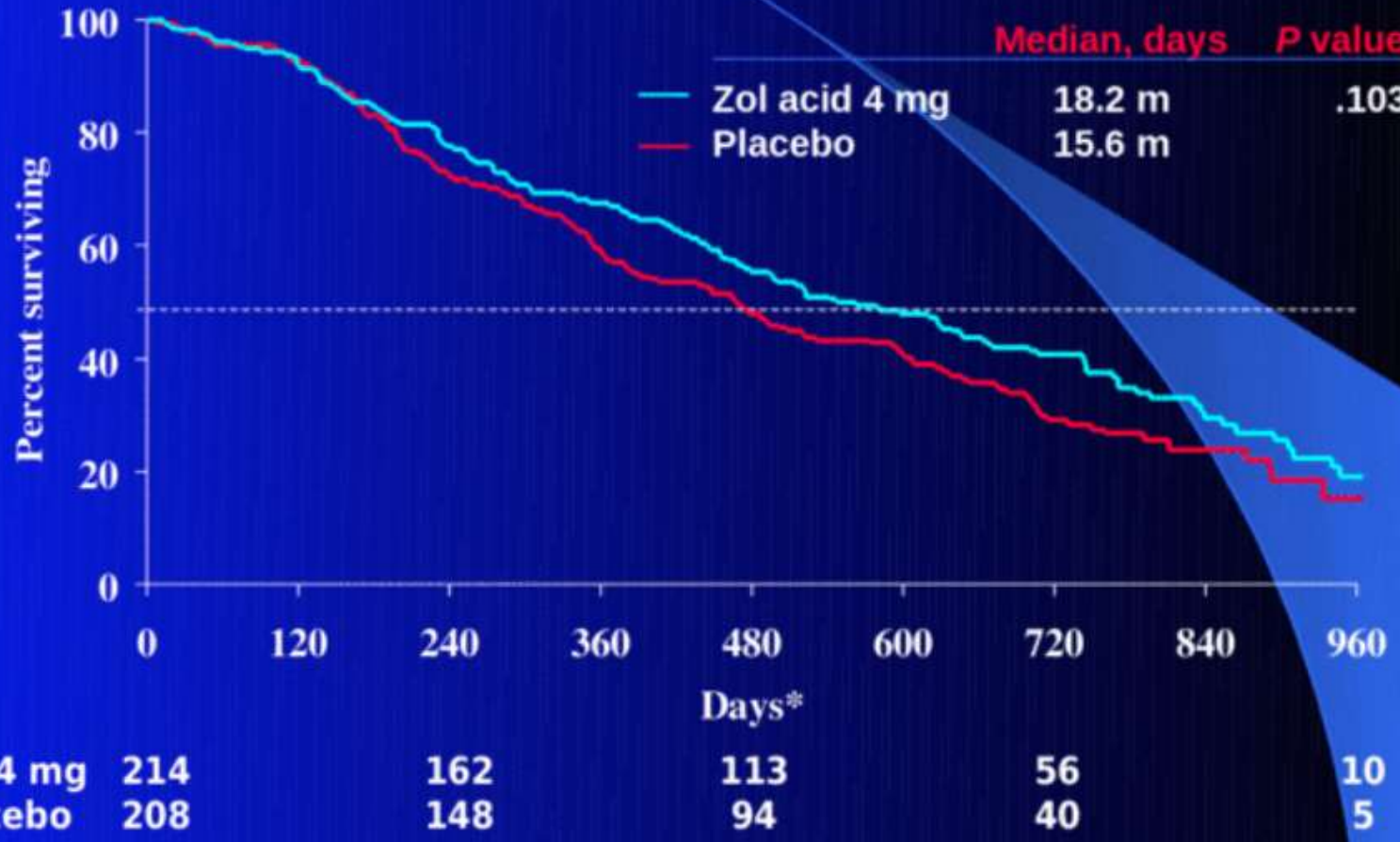
Saad et al. *J Natl Cancer Inst*. 2004

Ca. prostatico: A. Zoledronico vs. placebo



Saad et al. *J Natl Cancer Inst*. 2004

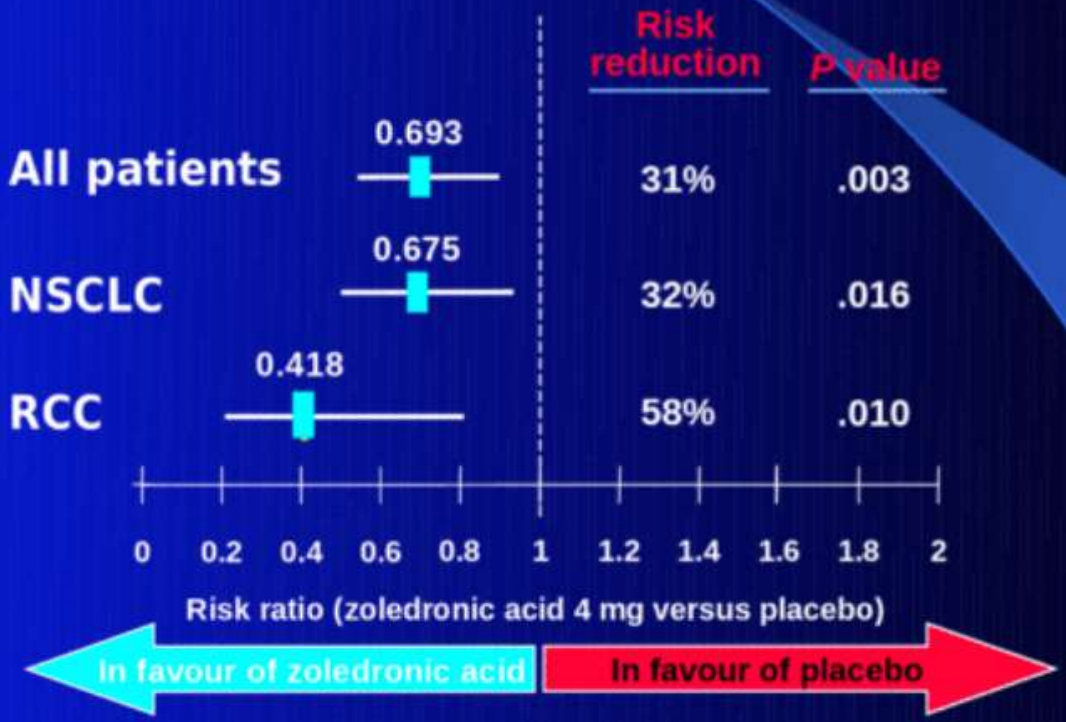
Overall Survival: Zoledronic Acid



Saad F, et al. *JNCI June 2004*

Altre neoplasie: A. Zoledronico vs. placebo

Multiple event analysis (Andersen-Gill)

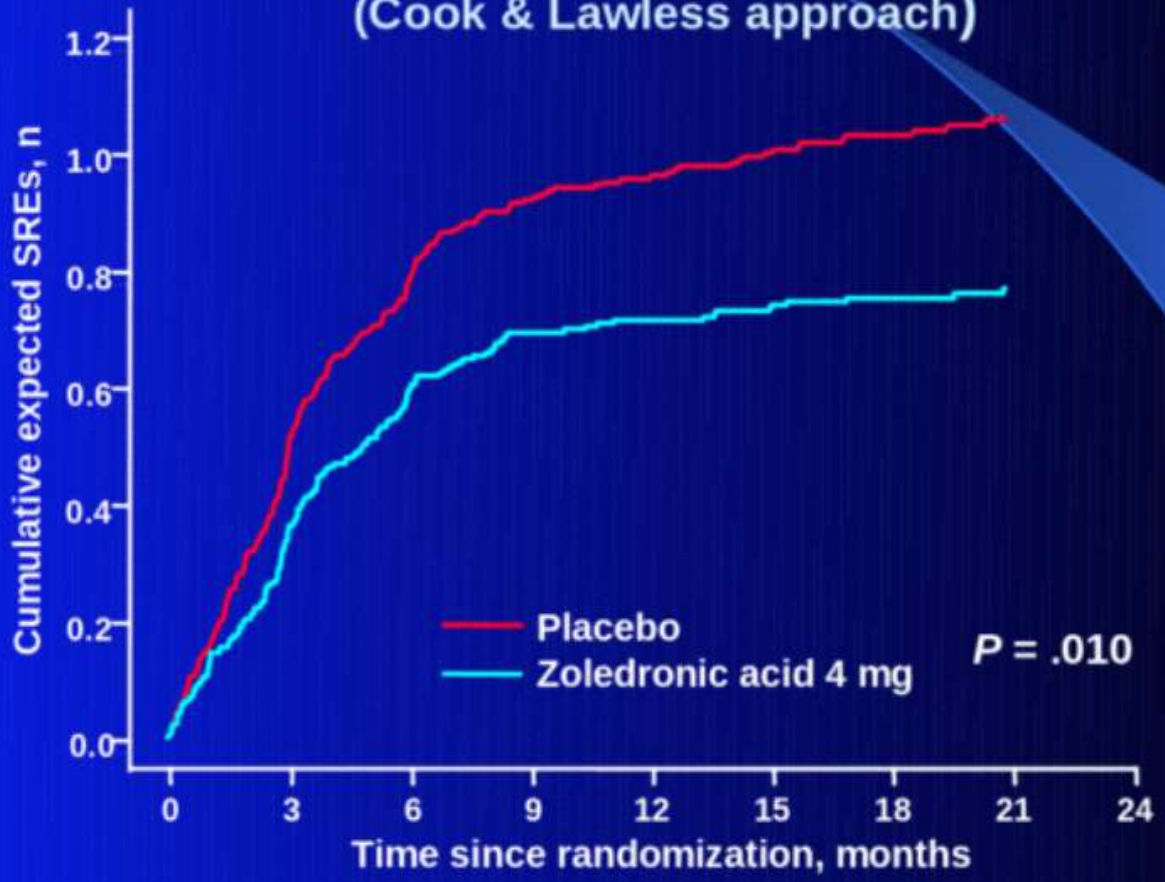


*Hypercalcemia of malignancy is included as a skeletal-related event.
Data from Rosen et al. *Cancer*. 2004;
RCC subset: Lipton A. *Cancer*. 2003;98:962-969.

Altre neoplasie (NSCLC, RCC)
A. Zoledronico vs. placebo

Independent Survival-Adjusted Multiple Event Analysis

(Cook & Lawless approach)



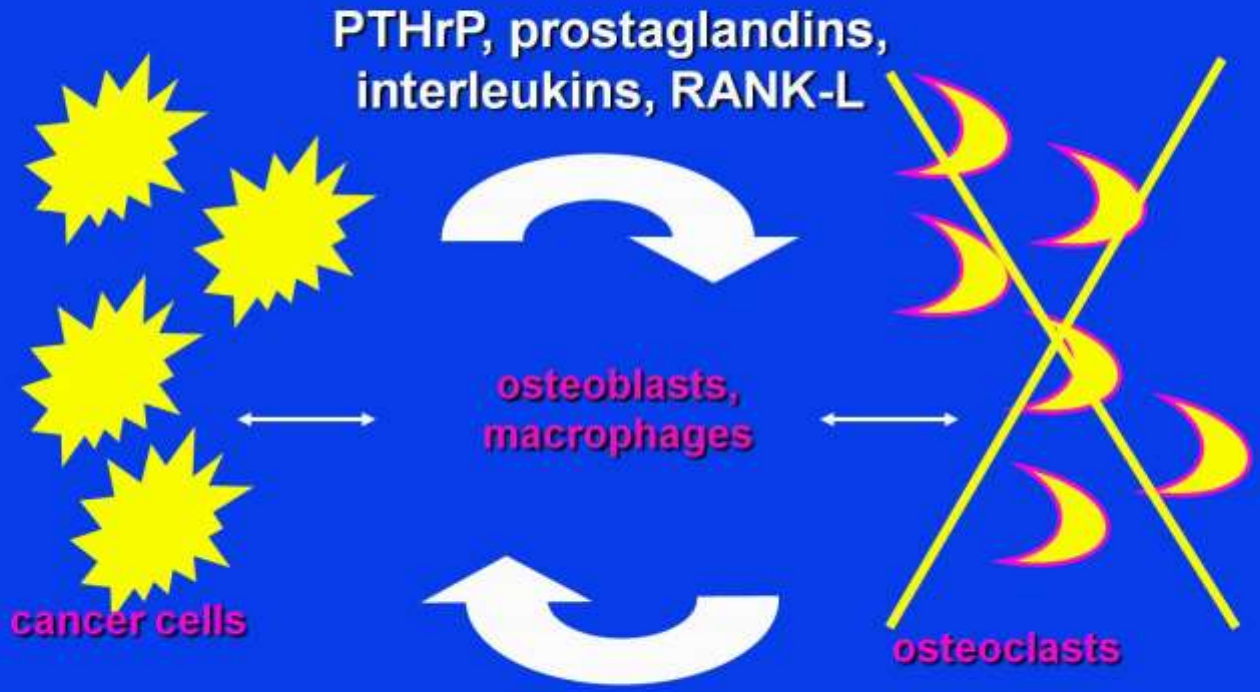
Major P, et al. *Proc Am Soc Clin Oncol*. 2003;22:762. Abstract 3062.

Tabella 1. Bifosfonati registrati in Italia per il trattamento delle metastasi scheletriche da carcinoma della mammella. Dosi e regimi terapeutici.

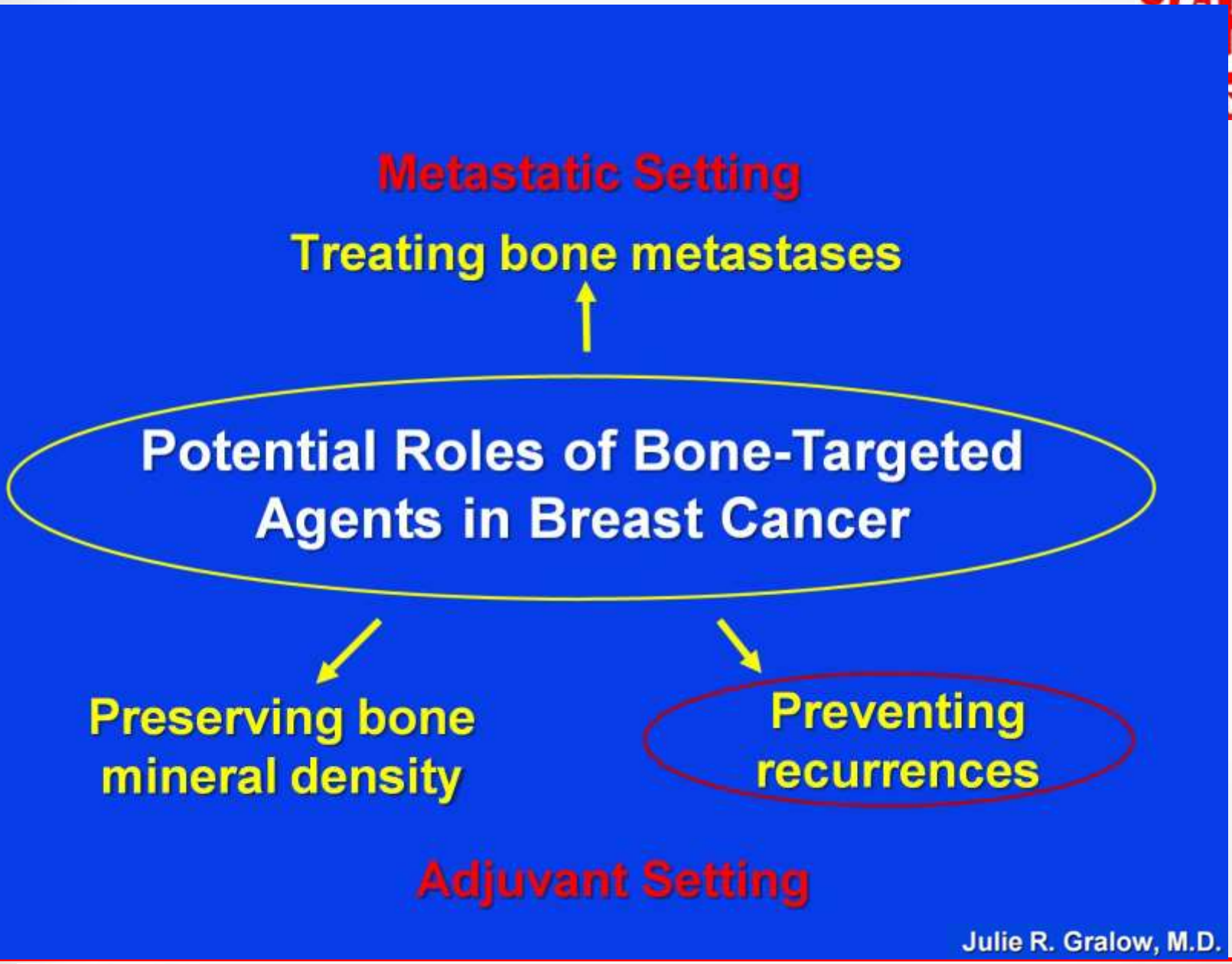
BISFOSFONATI	Classe	Via*	Dose	Frequenza
Clodronato	Non N-BP	OS	800 mg	2 cp/die
		I.V.	900mg	3-4 settimane
Pamidronato	N-BP 2° generazione	I.V.	90 mg	3-4 settimane
Ibandronato	N-BP 2° generazione	OS	50 mg	1cp/die
		I.V	6 mg	3-4 settimane
Ac zoledronico	N-BP 3° generazione	I.V	4 mg	3-4 settimane

* La somministrazione per os dei BP necessita, per un adeguato assorbimento, che vengano assunti al mattino a digiuno solo con acqua e venga rispettato il digiuno per circa un'ora in stazione eretta. La somministrazione endovenosa per clodronato e pamidronato richiede un tempo di infusione di 2 ore. Per ac zoledronico ed ibandronato infusione per 15 minuti.

Breast Cancer and the Bone Microenvironment



Julie R. Gralow, M.D.


Metastatic Setting
Treating bone metastases
Potential Roles of Bone-Targeted Agents in Breast Cancer
Preserving bone mineral density
Preventing recurrences
Adjuvant Setting
Julie R. Gralow, M.D.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Meta-Analysis of Randomized Adjuvant Bisphosphonate Studies

Lancet July 24, 2015 (epub ahead of print)
http://dx.doi.org/10.1016/S0140-6736(15)60908-4

- Individual patient data on 18,766 women with early stage breast cancer
- 26 randomized trials comparing adjuvant bisphosphonate versus no bisphosphonate/placebo for 2-5 years
  - Mean scheduled treatment duration 3.4 years
  - Median follow-up 5.6 years
- 5 trials evaluated oral clodronate
- 21 trials evaluated newer generation aminobisphosphonates (mostly zoledronic acid, some ibandronate)

Julie R. Gralow, M.D.

Meta-Analysis of Adjuvant Bisphosphonates

No bisphosphonate vs. bisphosphonate

10 year data	All Patients		Postmenopausal	
	- Bisphos	+ Bisphos	- Bisphos	+ Bisphos
Breast cancer recurrence	25.9%	24.9%	25.9%	22.8%
	P=0.08		RR 0.86, P=0.002	
Distant recurrence	21.8%	20.4%	21.2%	17.9%
	P=0.03		RR 0.82, P=0.003	
Bone recurrence	9.0%	7.8%	8.8%	6.6%
	P=0.004		RR 0.72, P=0.0002	

Julie R. Gralow, M.D.

Meta-Analysis of Adjuvant Bisphosphonates

No bisphosphonate vs. bisphosphonate

10 year data	All Patients		Postmenopausal	
	- Bisphos	+ Bisphos	- Bisphos	+ Bisphos
Breast mortality	18.4%	16.6%	18.0%	14.7%
	P=0.04		RR 0.82, P=0.002	
Overall mortality	22.3%	20.8%	23.5%	21.1%
	P=0.06		RR 0.86, P=0.005	

- For all women, significant reduction in bone recurrence and borderline reduction in breast cancer mortality
- In postmenopausal women, significant reduction in all recurrence, bone recurrence, distant recurrence, breast cancer mortality, overall mortality
  - RR 0.72 for bone recurrence (38% reduction)
  - RR 0.82 for breast cancer mortality (17% reduction)

Julie R. Gralow, M.D.

Meta-Analysis of Adjuvant Bisphosphonates

No bisphosphonate vs. bisphosphonate

10 year data	All Patients		Postmenopausal	
	- Bisphos	+ Bisphos	- Bisphos	+ Bisphos
Locoregional recurrence	5.7%	6.5%		
	P=0.25			
Contralateral breast cancer	2.8%	2.9%		
	P=0.79			
Distant recurrence outside bone	14.1%	13.6%	13.6%	12.1%
	P=0.69		RR 0.90, P=0.10	

- No significant effect on locoregional recurrence, contralateral breast cancer, or distant recurrence at extra-osseous sites

Julie R. Gralow, M.D.

Meta-Analysis of Adjuvant Bisphosphonates

No bisphosphonate vs. bisphosphonate

	All Patients		Postmenopausal	
	- Bisphos	+ Bisphos	- Bisphos	+ Bisphos
Fracture (5 years)	6.3%	5.1%	6.6%	5.3%
	RR 0.85, P=0.02		RR 0.83, P=0.03	

- Fractures were reduced with bisphosphonates

Julie R. Gralow, M.D.

Meta-Analysis of Adjuvant Bisphosphonates: Conclusions

- Effect of bisphosphonates greater in older women (> 55) and postmenopausal women
  - No effect on disease outcomes in pre-menopausal women, although those receiving ovarian suppression benefit (ABCSG-12: Gnant M et al, NEJM 2009)
- Risk reductions similar irrespective of ER status, lymph node status, tumor grade, use/non-use of chemotherapy
- Benefits similar for aminobisphosphonates (zoledronic acid, ibandronate) and clodronate
  - Effects similar in low intensity (6 month zoledronic acid) and high intensity (bone metastasis dosing) schedules
  - Effects similar in trials of different durations of treatment (2 yrs vs none, 3-5 years vs none)
- In postmenopausal women, reduction in bone recurrence, distant recurrence, breast cancer mortality, overall mortality

Bone Turnover Across the Menopausal Transition, the Role of Gonadal Inhibins

Nicks KM et al, Ann NY Acad Sci 1192:153-160, 2010

- Effects of bisphosphonates on bone recurrence emphasize importance of host microenvironment factors to metastasis
- Complex interactions between reproductive hormones, tumor biology, bone cell function, and bone marrow stem cells changes with menopause
  - Premenopausal setting: estradiol and inhibin of major importance in bones
  - Postmenopausal setting: activin and other members of the TGF-β superfamily become main regulators of bone cell metabolism

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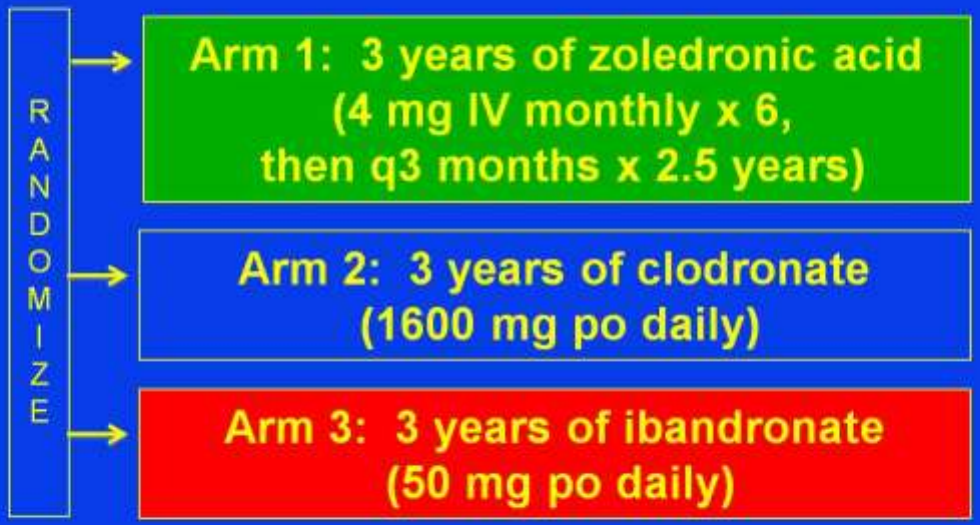
Comparison of Bisphosphonates

SWOG S0307: Phase III Trial of Bisphosphonates as Adjuvant Therapy in Primary Breast Cancer

Gralow J et al, ASCO 2015 abstract 503

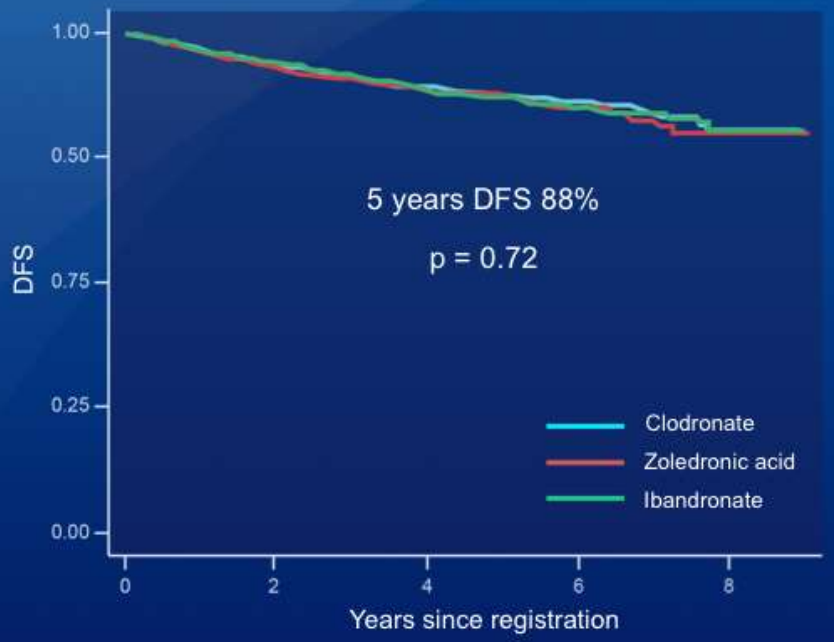


- Enrollment 11/05 - 2/10: 6,097 patients
- Eligibility: Stage I-III breast cancer patients s/p surgical resection, receiving adjuvant systemic therapy
- Primary Endpoint: DFS

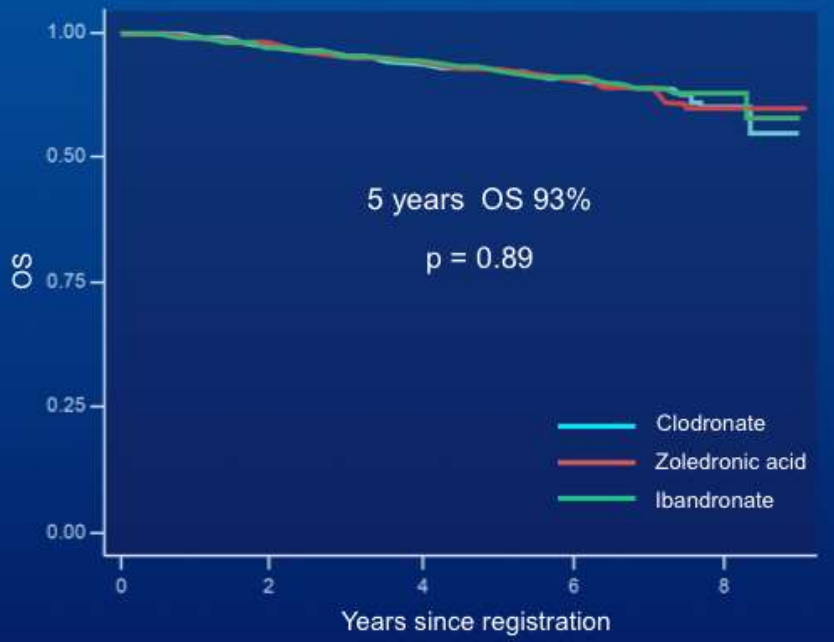
Julie R. Gralow, M.D.

S0307: DFS and OS

Disease-free survival by treatment
All patients



Overall survival by treatment
All patients



Mod. da Gralow J, et al. J Clin Oncol 33, 2015 (suppl; abstr 503)

Risks associated with adjuvant bisphosphonates

Generally well tolerated

- Low rate of troublesome GI adverse events with oral therapy
- Occasional bone pain and myalgia with IV aminobisphosphonates
- Low rate of ONJ
- Minimal rate of renal adverse events
- No reports of atypical femoral fractures in this disease setting

S0307	ONJ rate
Zoledronic acid	27/2094 (1.27%)
Clodronate	7/2151 (0.31%)
Ibandronate	11/1507 (0.71%)
p=0.003	

[1] AZURE – 26 (1.7%)

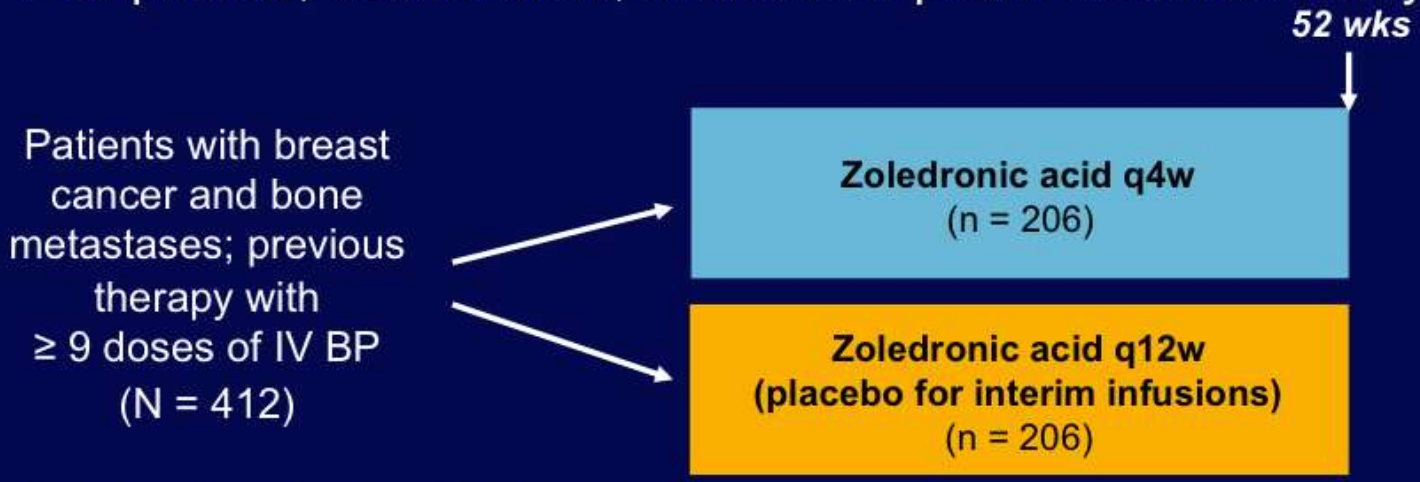
[2] NSABP-B34 – 1 (0.06%)

[3] GAIN – 2 (0.1%)

[1] Coleman et al Lancet Oncology 2014; [2] Paterson et al Lancet Oncology 2012; [3] von Minckwitz et al.J Clin Oncol 2013

OPTIMIZE-2 Study: Frequency of Continued Zoledronic Acid for Bone Mets

- Prospective, double-blind, multicenter phase III clinical study



- Primary endpoint: SRE rate
- Secondary endpoints: time to SRE, skeletal morbidity, safety, metabolic bone markers

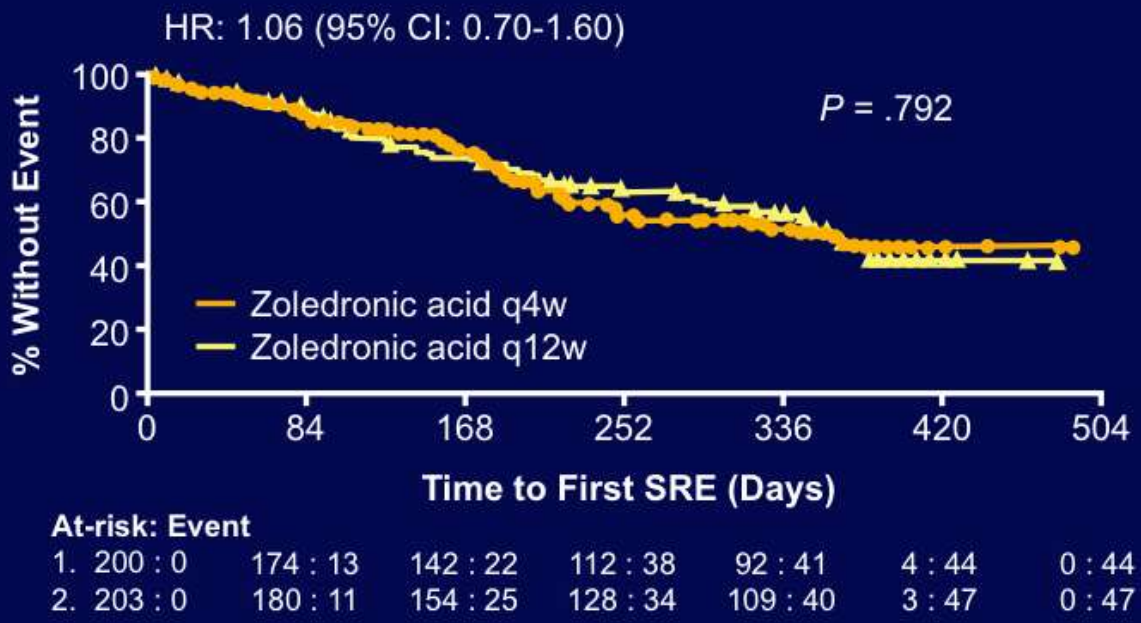
Protocol revisions during the course of the clinical trial

- Placebo arm was dropped early in the study secondary to poor accrual
- Sample size was reduced from 705 to 412, based on new data that became available (ZOOM trial)
- Statistical assumption of 10% noninferiority margin remained unchanged

Hortobagyi GN, et al. ASCO 2014. Abstract LBA9500.

OPTIMIZE-2: SRE With Zoledronic Acid

	Zoledronic Acid q4w	Zoledronic Acid q12w	Proportion Difference, % (95% CI)	*P* Value
≥ 1 SRE, % (n/N)	22 (44/200)	23.2 (47/203)	1.2 (-7.5 to 9.8)	.724



Hortobagyi GN, et al. ASCO 2014. Abstract LBA9500. *Reprinted with permission.*

OPTIMIZE-2: Adverse Events With Zoledronic Acid Treatment

- Similar safety profiles for q4w or q12w dosing

Overall AEs, n (%)	Zoledronic Acid q4w (n = 198)	Zoledronic Acid q12w (n = 202)
AEs	189 (95.5%)	189 (93.6%)
Serious AEs	50 (25.3%)	51 (25.2%)
Grade 3/4 AEs	94 (47.5%)	86 (42.6%)
AEs leading to dose adjustment, interruption	21 (10.6%)	11 (5.4%)
AEs leading to study medication discontinuation	23 (11.6%)	18 (8.9%)
Deaths	10 (5.1%)	7 (3.5%)

AEs of Special Interest, n (%)	Zoledronic Acid q4w (n = 198)	Zoledronic Acid q12w (n = 202)
Renal AEs	19 (9.6%)	16 (7.9%)
ONJ (adjudicated) AEs	2 (1.0%)	0
Cardiac ischemic events	1 (0.5%)	2 (1.0%)
Atrial fibrillation events	1 (0.5%)	2 (1.0%)
Atypical subtrochanteric femoral fracture events (adjudicated)	0	0

- Median skeletal morbidity rate similar with q4w vs q12w dosing: 0.46 (SD: 1.063) vs 0.50 (SD: 1.500); *P* = .854

Hortobagyi GN, et al. ASCO 2014. Abstract LBA9500. *Reprinted with permission.*

OPTIMIZE-2: Conclusions

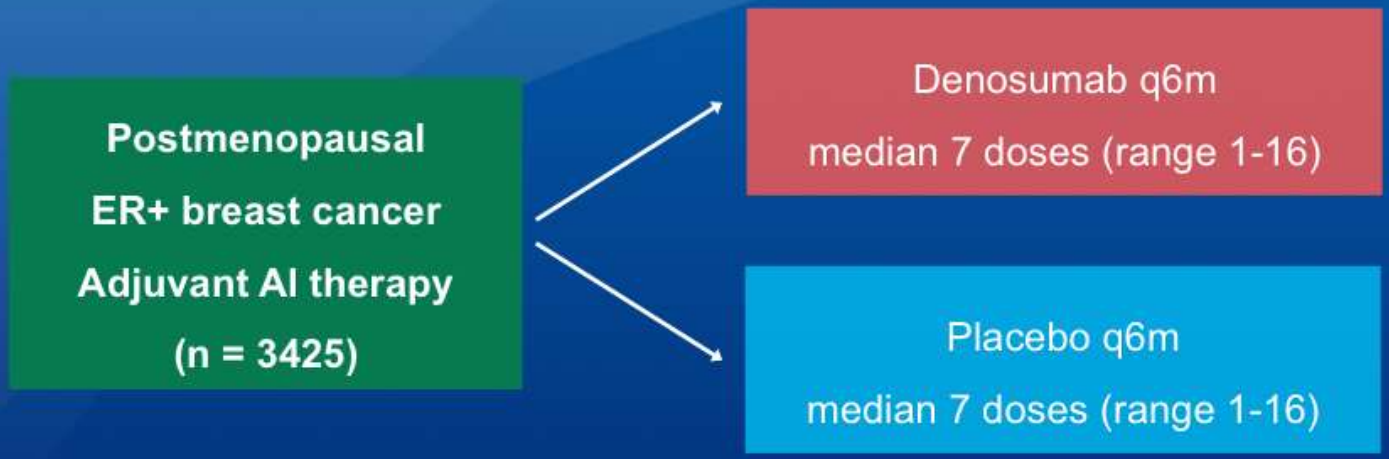
- Continuing zoledronic acid for an additional 1 yr at reduced dosing frequency of every 12 wks was noninferior to every 4 wks dosing (noninferiority margin: 10%)
- Similar safety profiles between the 2 arms
- Similar bone marker profiles between the 2 arms
- Results should be interpreted with caution due to study limitations, including:
  - Placebo arm dropped due to low accrual
  - Statistical concerns regarding noninferiority margin determination

Hortobagyi GN, et al. ASCO 2014. Abstract LBA9500.

Adjuvant denosumab in breast cancer: Results from 3,425 postmenopausal patients of the ABCSG 18 Trial

Gnant M, et al.

ABCSG 18: Study design

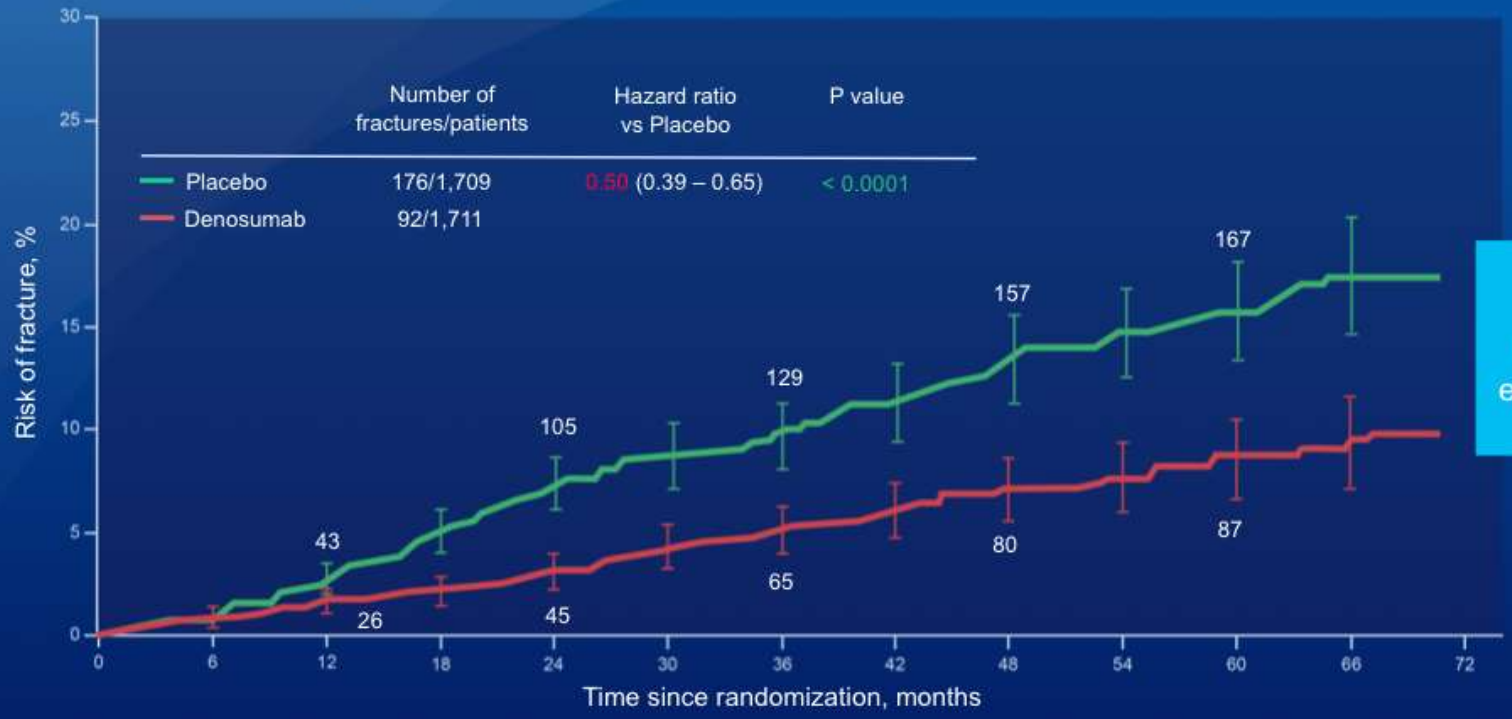


- Primary endpoints: Time to first clinical fracture
- Secondary endpoints: Change in BMD at 36 months
  Vertebral fractures (new/worsening)

Mod. da Gnant M. et al. J Clin Oncol 33, 2015 (suppl; abstr 504)

ABCSG 18: Risk of fractures

Median follow-up: 38 months

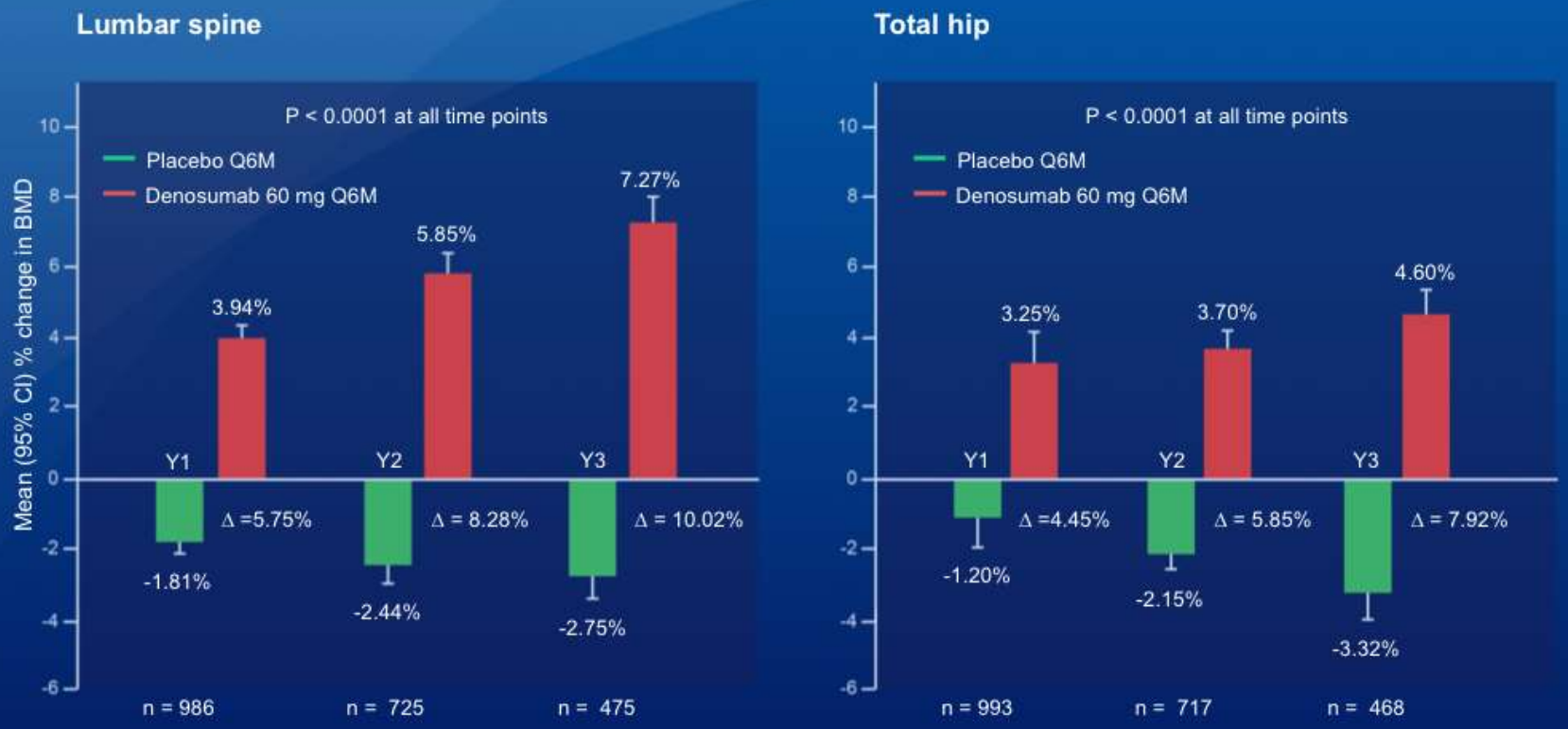


Only 17 disease recurrence events prior to a fracture

Fracture rate somewhat higher than expected (> 15% in placebo arm) at 5 years

Mod. da Gnant M. et al. J Clin Oncol 33, 2015 (suppl; abstr 504)

ABCSG 18 – Bone mineral density changes



Mod. da Gnant M, et al. J Clin Oncol 33, 2015 (suppl; abstr 504)

Study Design (20050136)

Key Inclusion: advanced breast cancer and confirmed bone metastases

Key Exclusion: current or prior intravenous BP administration

Stratified by previous SRE, prior oral BP, current chemotherapy, and geographic region (Japan vs others)

N = 1026 Denosumab 120 mg SC and Placebo IV* every 4 weeks

Supplemental Calcium and Vitamin D

N = 1020 Zoledronic acid 4 mg IV* and SC placebo every 4 weeks

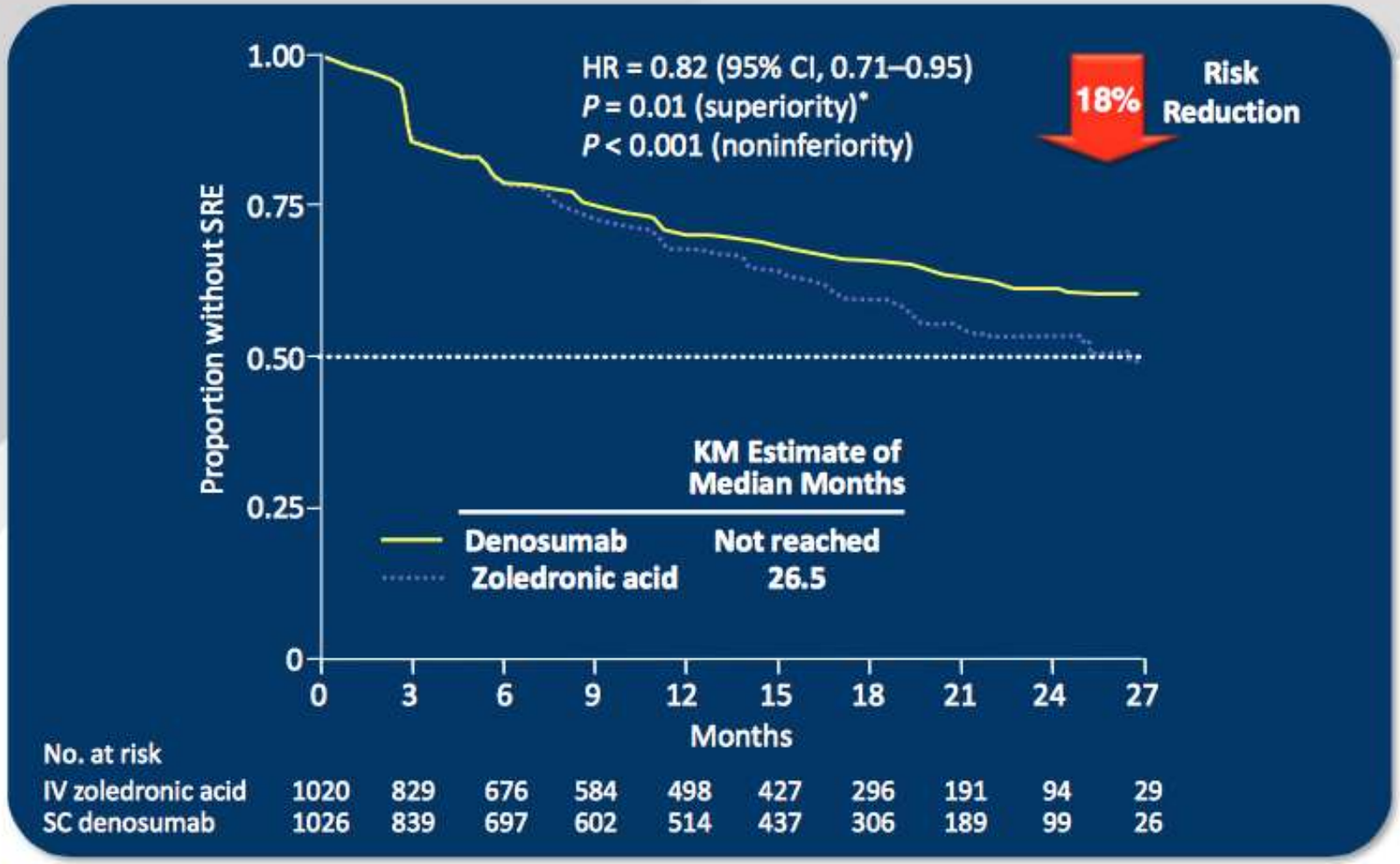
1° Endpoint
- Time to first on-study SRE (non-inferiority)

2° Endpoints
- Time to first on-study SRE (superiority)
- Time to first and subsequent on-study SRE (superiority)

*IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine (per Zometa® label)

Stopeck A, et al. Eur J Can Suppl. 2009;7:2. Abstract 2LBA and Oral Presentation.

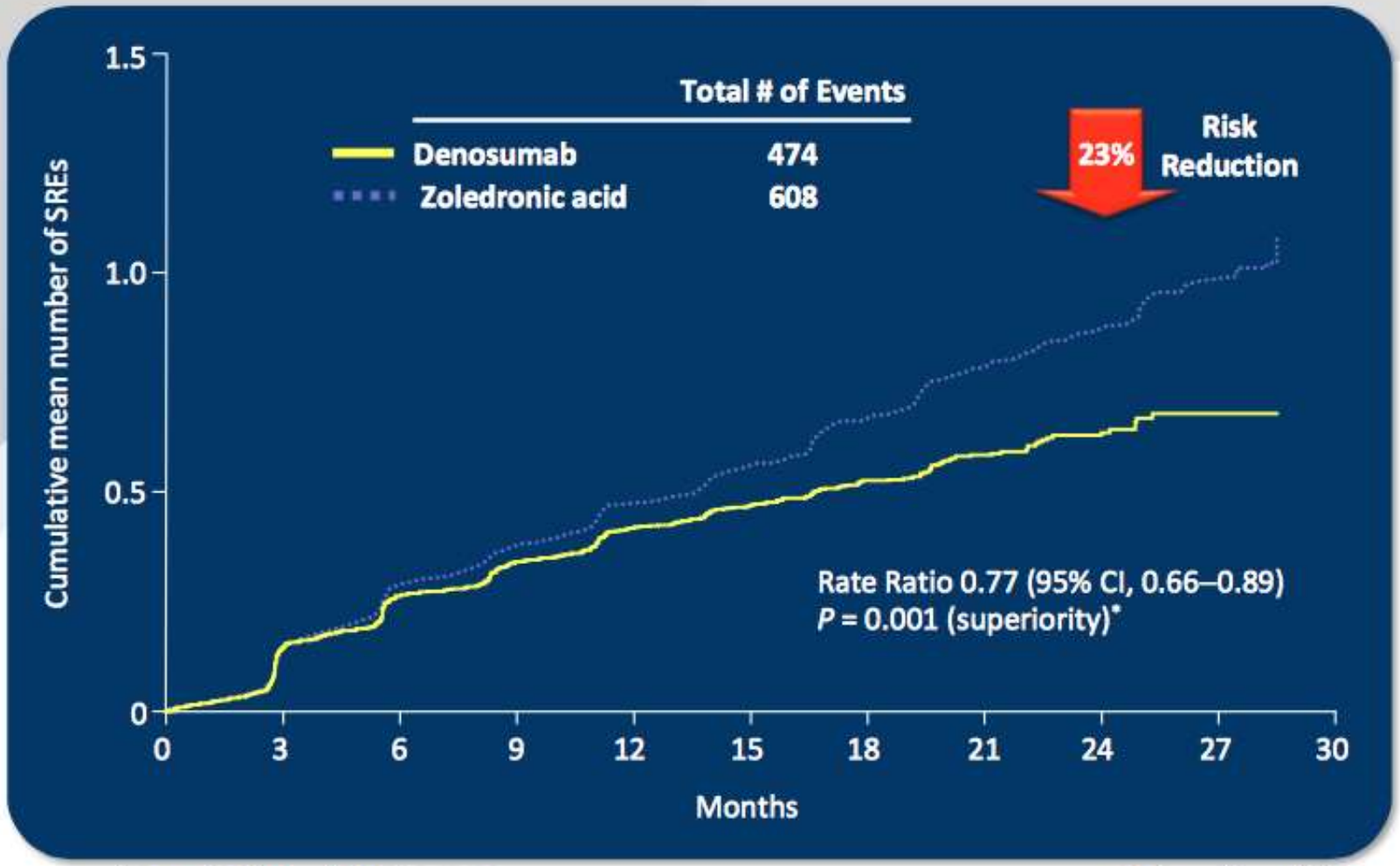
Primary endpoint: Time to First On-Study SRE



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

*Adjusted for multiplicity

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



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

*Adjusted for multiplicity

Ca. prostatico

2000 landscape

MITOXANTRONE

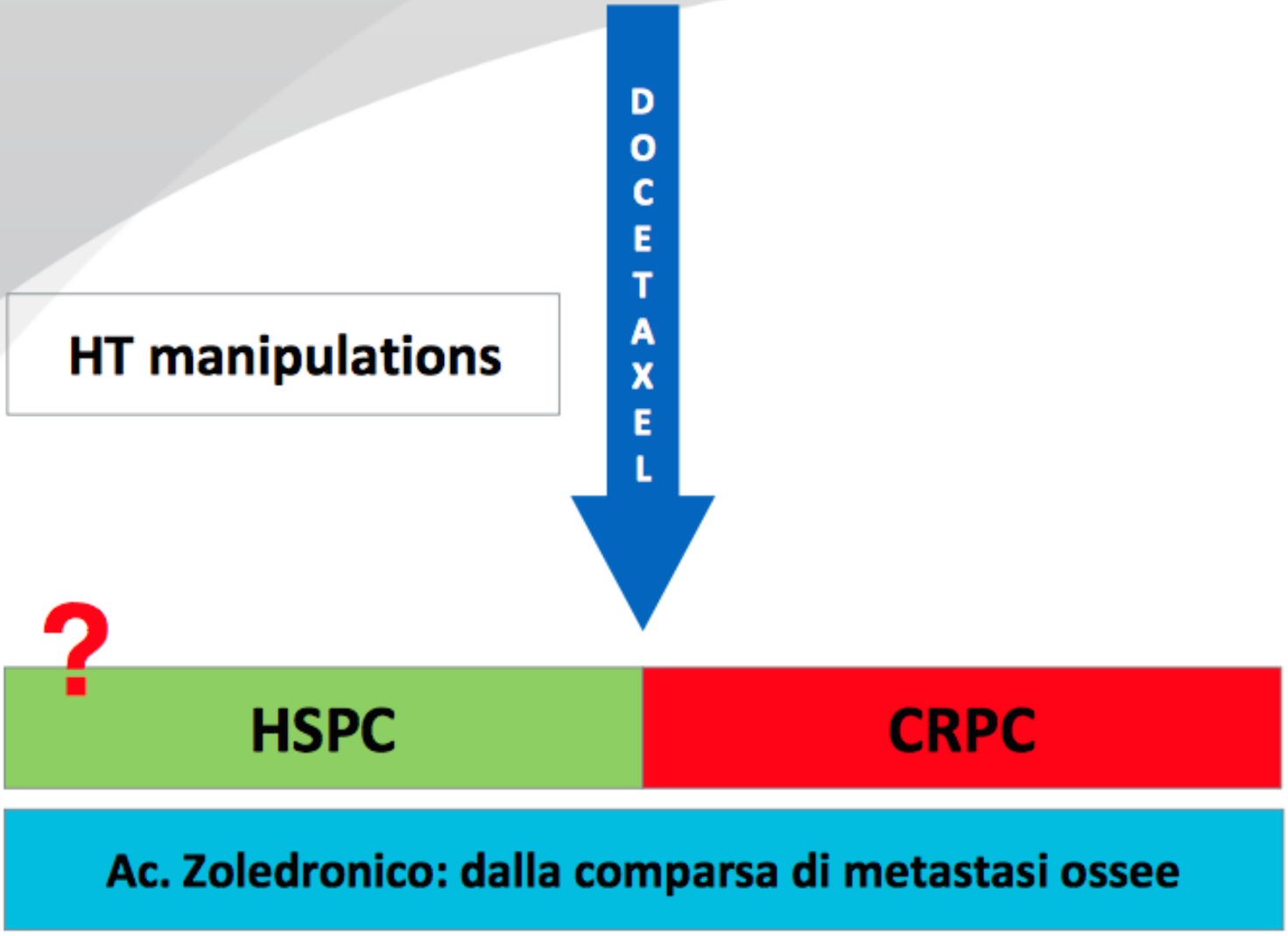
HT manipulations

?

HSPC | CRPC

Ac. Zoledronico: dalla comparsa di metastasi ossee

2004 landscape

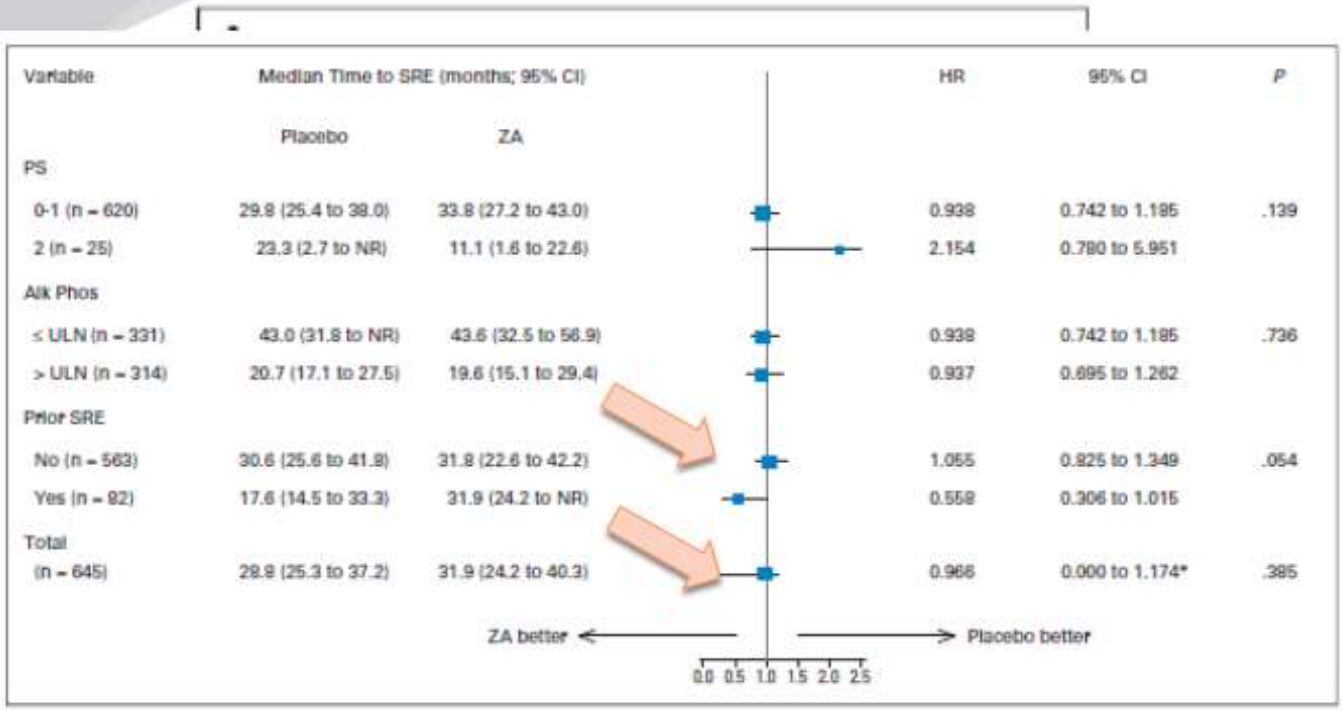


Published Ahead of Print on March 3, 2014 as 10.1200/JCO.2013.51.6500
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.51.6500

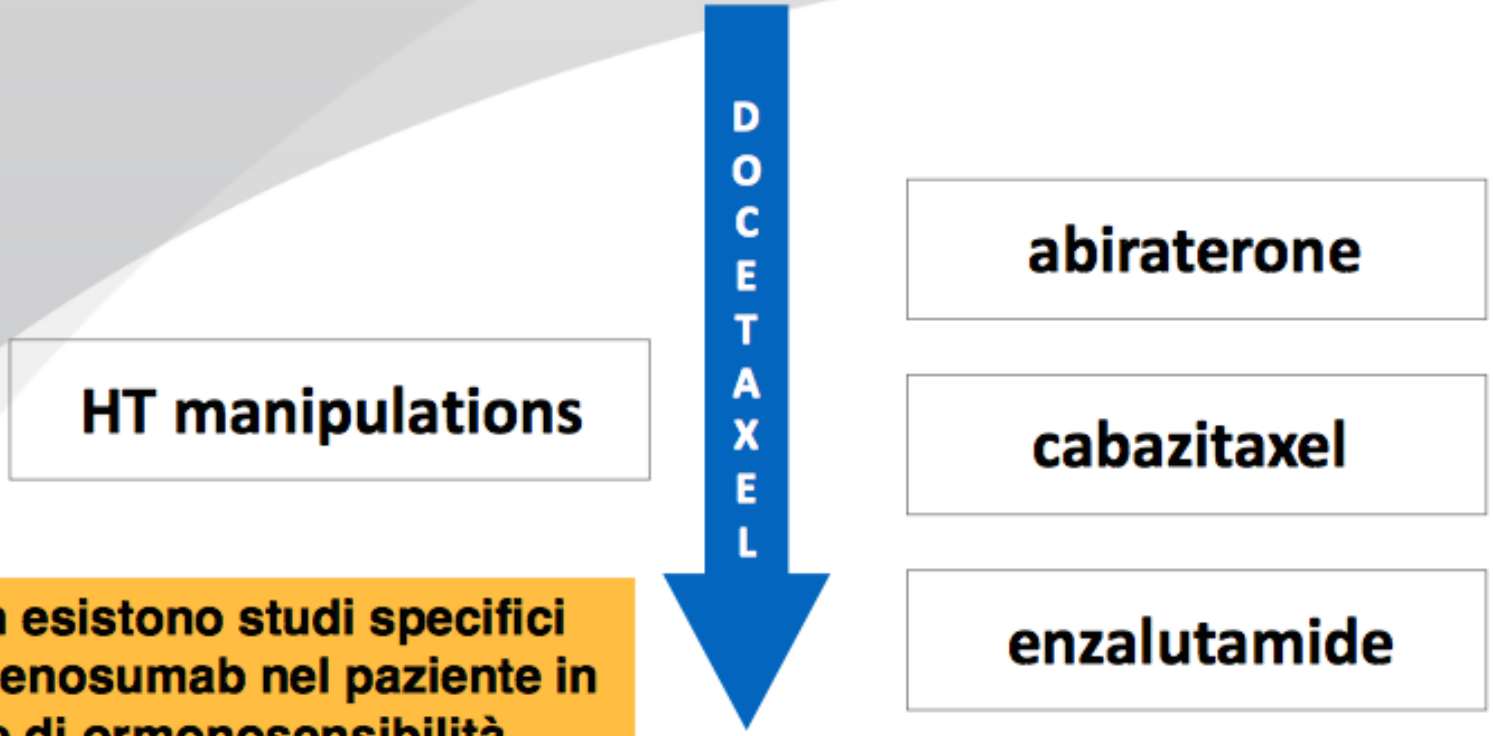
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Randomized Controlled Trial of Early Zoledronic Acid in Men With Castration-Sensitive Prostate Cancer and Bone Metastases: Results of CALGB 90202 (Alliance)

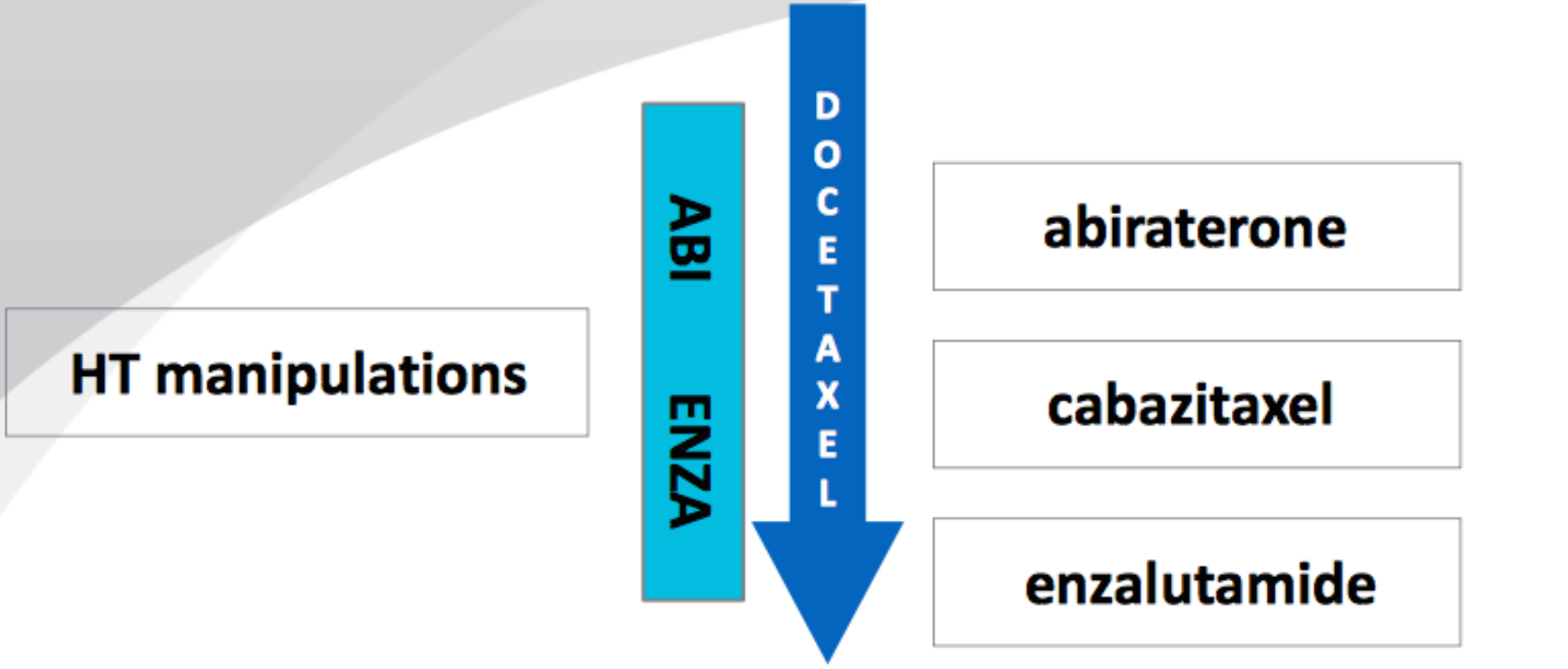
Matthew R. Smith, Susan Halabi, Charles J. Ryan, Arif Hussain, Nicholas Vogelzang, Walter Stadler, Ralph J. Hauke, J. Paul Monk, Philip Saylor, Nirmala Bhoopalam, Fred Saad, Ben Sanford, W. Kevin Kelly, Michael Morris, and Eric J. Small



2013-4 landscape



2014-5 landscape



HSPC | **CRPC**

Denosumab: dalla comparsa di metastasi ossee

Impact of news drugs in the median overall survival of patients with metastatic castration resistant prostate cancer (mCRPC)

N. Chaumard-Billotey [1], M. Aitichou [1], S. Chabaud [2], H. Boyle [3], B. Favier [1], Y. Devaux [3], JP. Droz [3], A. Fléchon [3]
[1] Pharmacy department, [2] Biostatistical unit, [3] Department of Oncology - Centre Léon Bérard, 28 Rue Laennec, Lyon 69008, France.

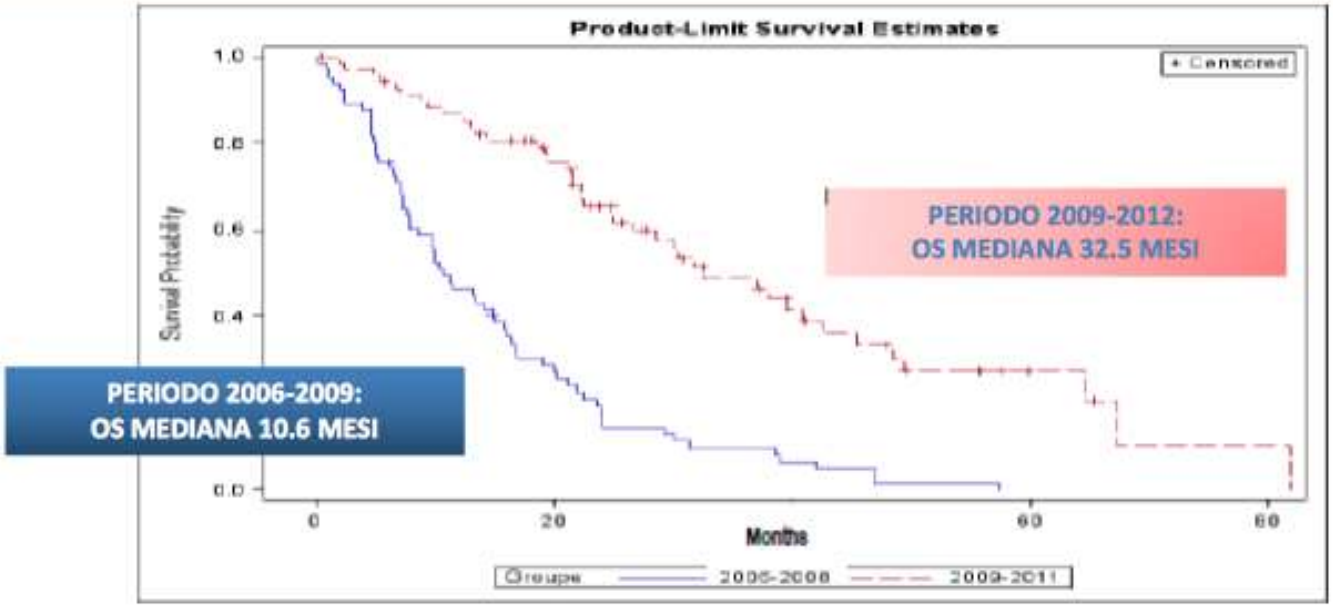


Figure 1 : Overall survival of mCRPC patients according to the period of treatment

Patient characteristics remained comparable during the two periods. Nevertheless, over time, survival has improved obviously, probably through earlier management, more intensive schedules of docetaxel and use of new drugs

Study design

Key Inclusion Criteria

Castration-resistant prostate cancer and > 1 bone metastases

Key Exclusion Criteria

Current or prior IV bisphosphonate treatment

N = 950 denosumab 120 mg SC and placebo IV Q4W

N = 951 zoledronic acid 4 mg IV* and placebo SC Q4W

Supplemental calcium and vitamin D strongly recommended

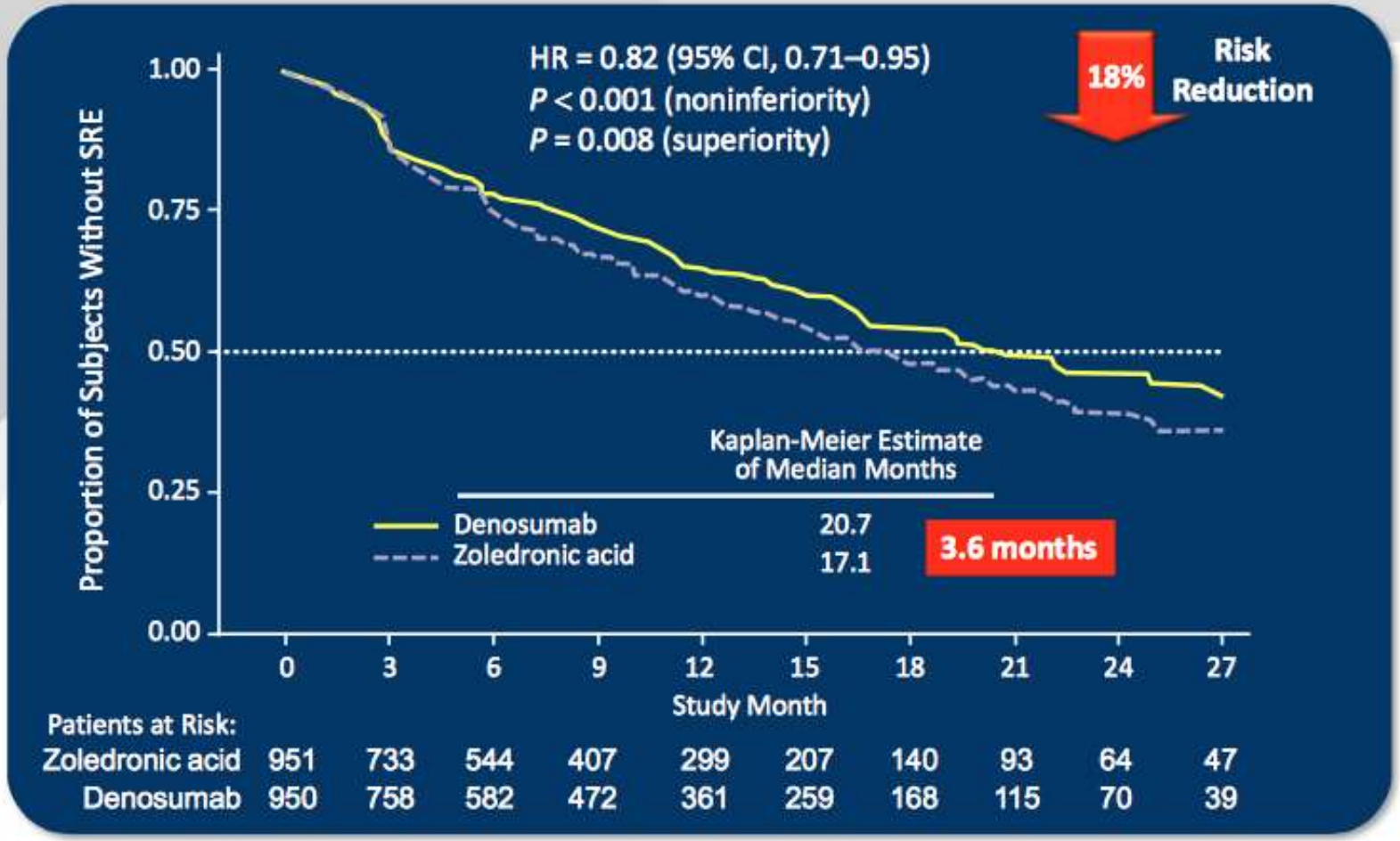
1° Endpoint
- Time to first on-study SRE (non-inferiority)

2° Endpoints
- Time to first on-study SRE (superiority)
- Time to first and subsequent on-study SRE (superiority)

*Per protocol and Zometa® label, IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine. No SC dose adjustments made due to increased serum creatinine.

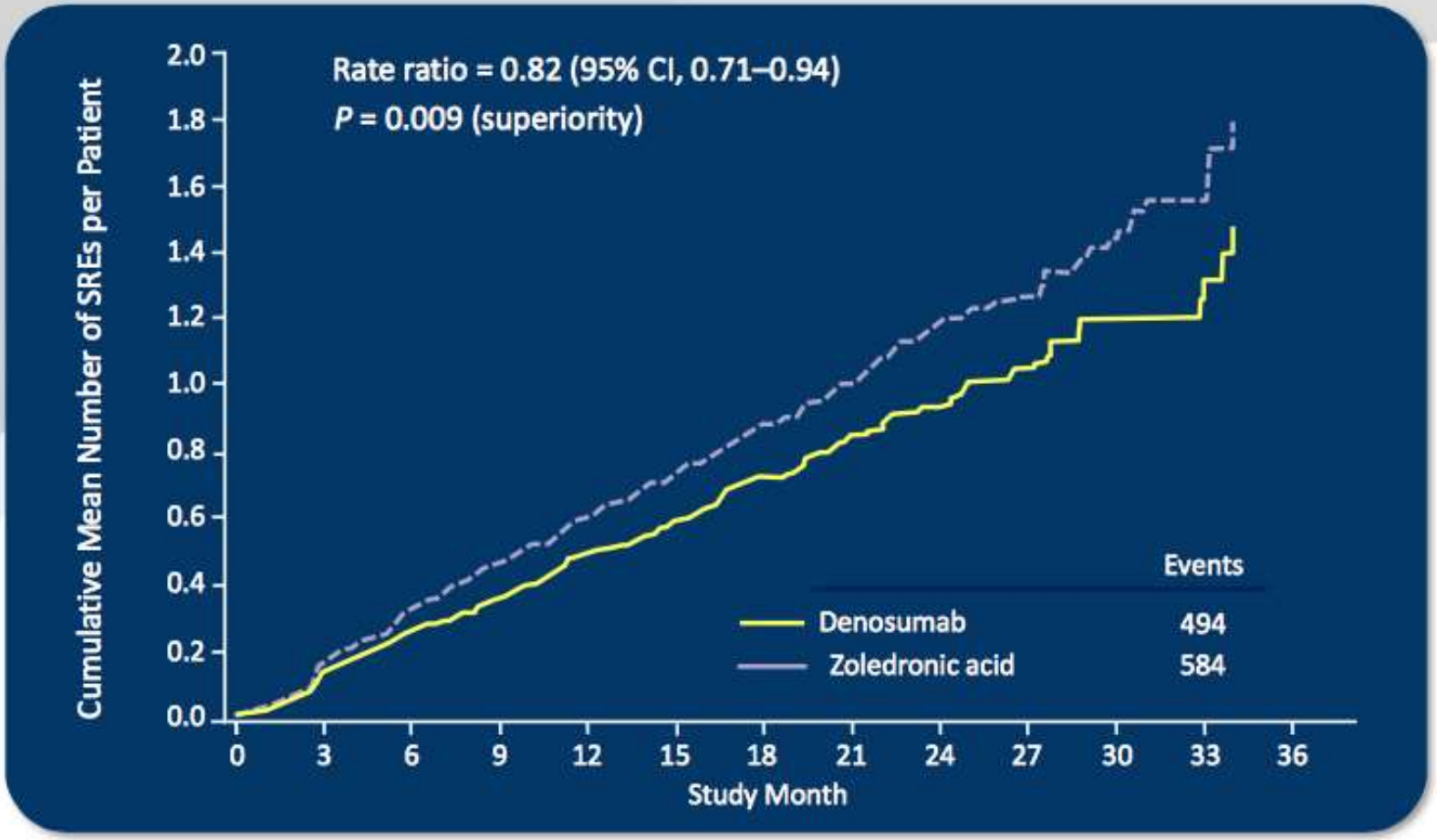
Fizazi K, et al. Lancet. 2011;377:813–822.

Time to First On-Study SRE



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

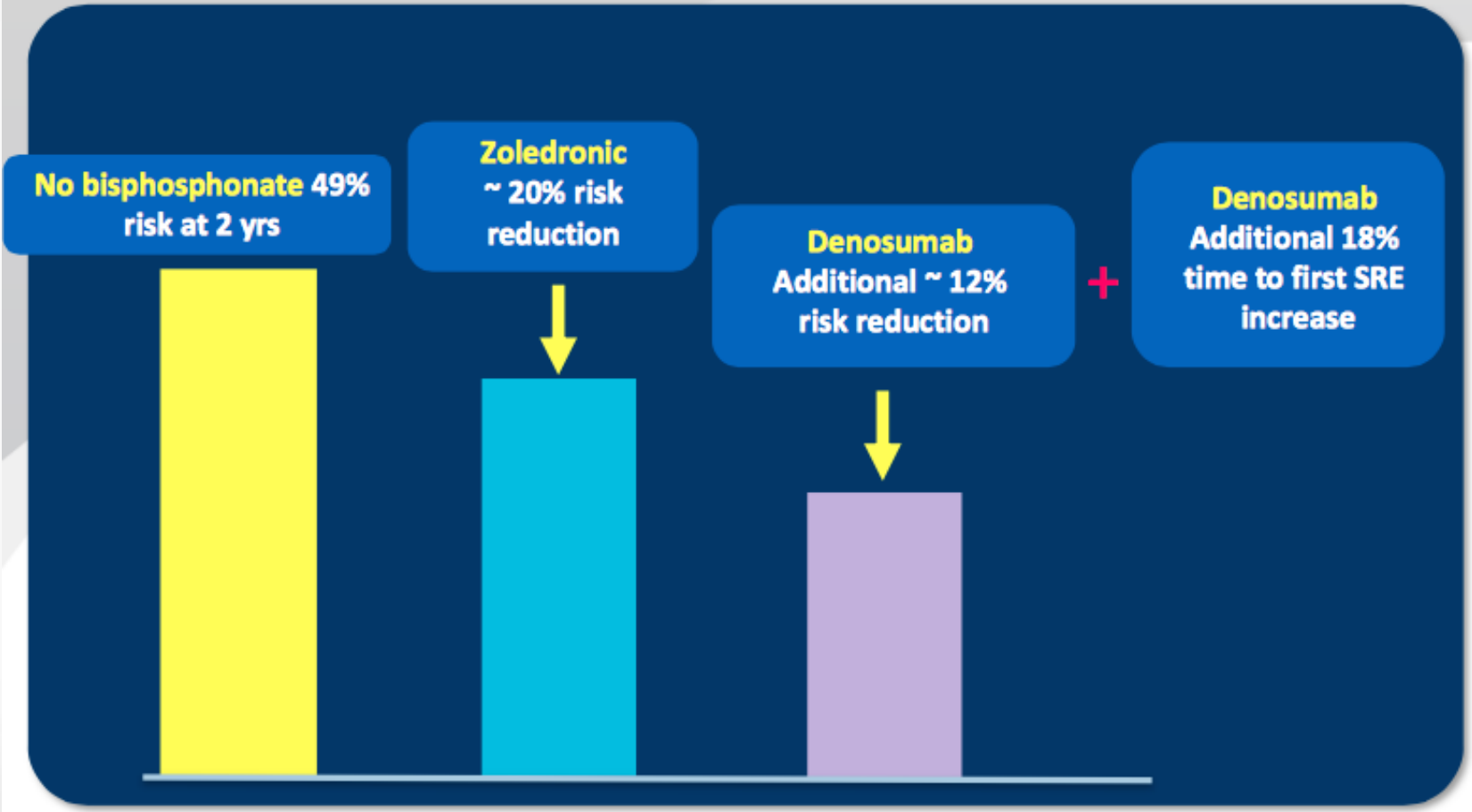
Time to First and Subsequent On-Study SRE (Multiple Event Analysis)



*Events occurring at least 21 days apart.

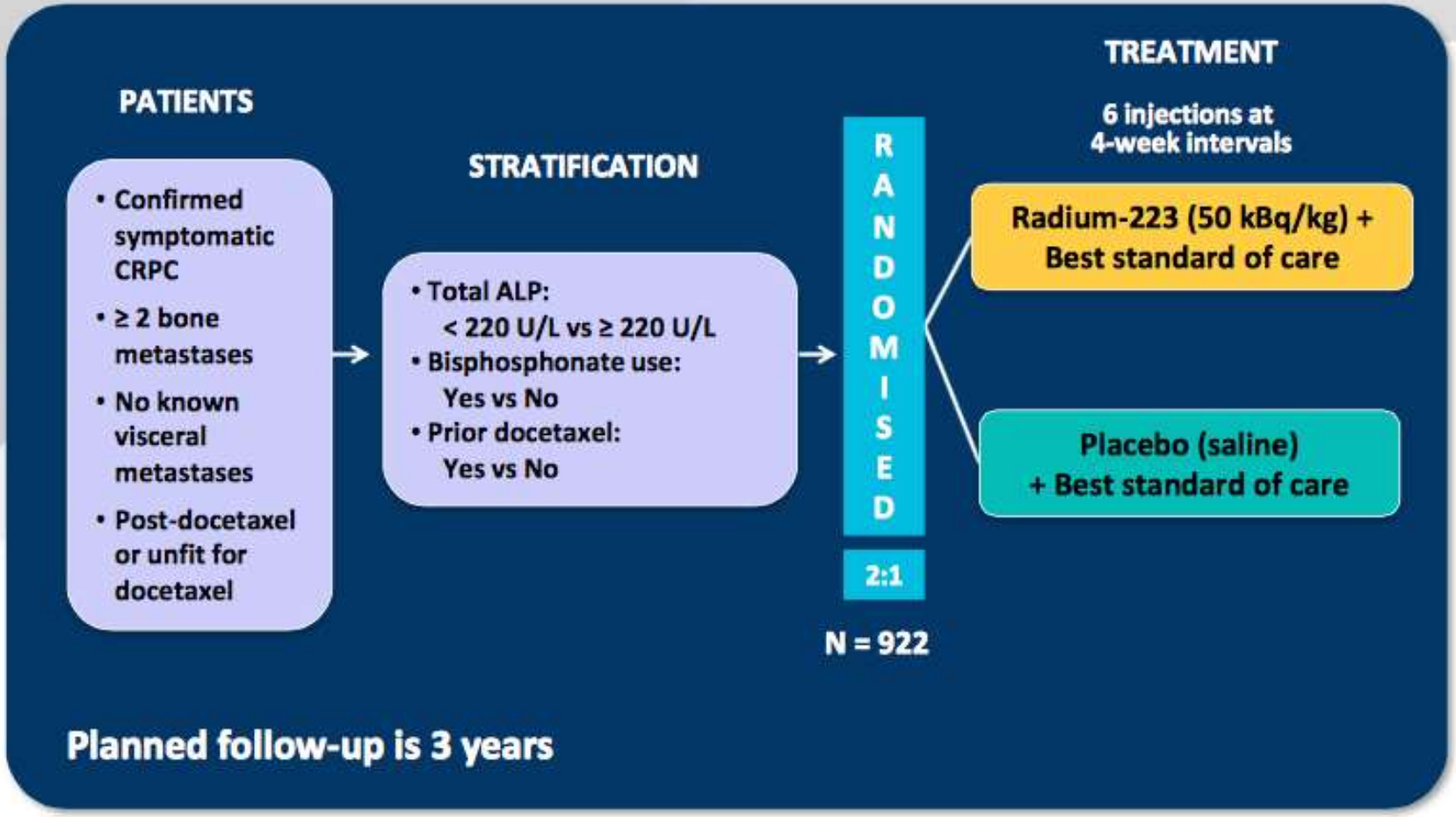
Fizazi K, et al. Lancet. 2011;377:813–822.

Skeletal Complication Risk: Incremental Benefits in Prostate Cancer



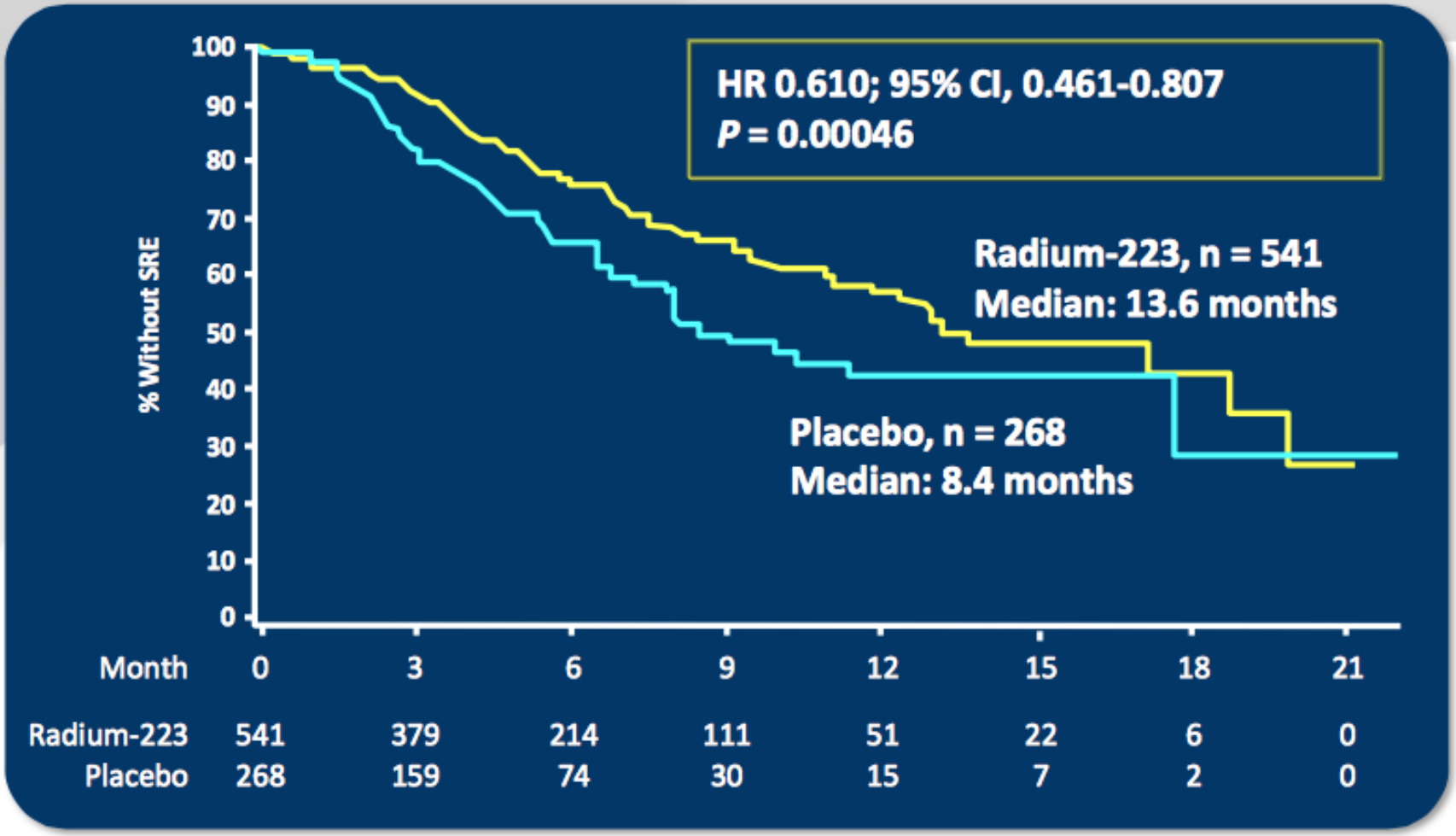
Saad F, JNCI, 2004, Fizazi K, Lancet, 2011.

ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design

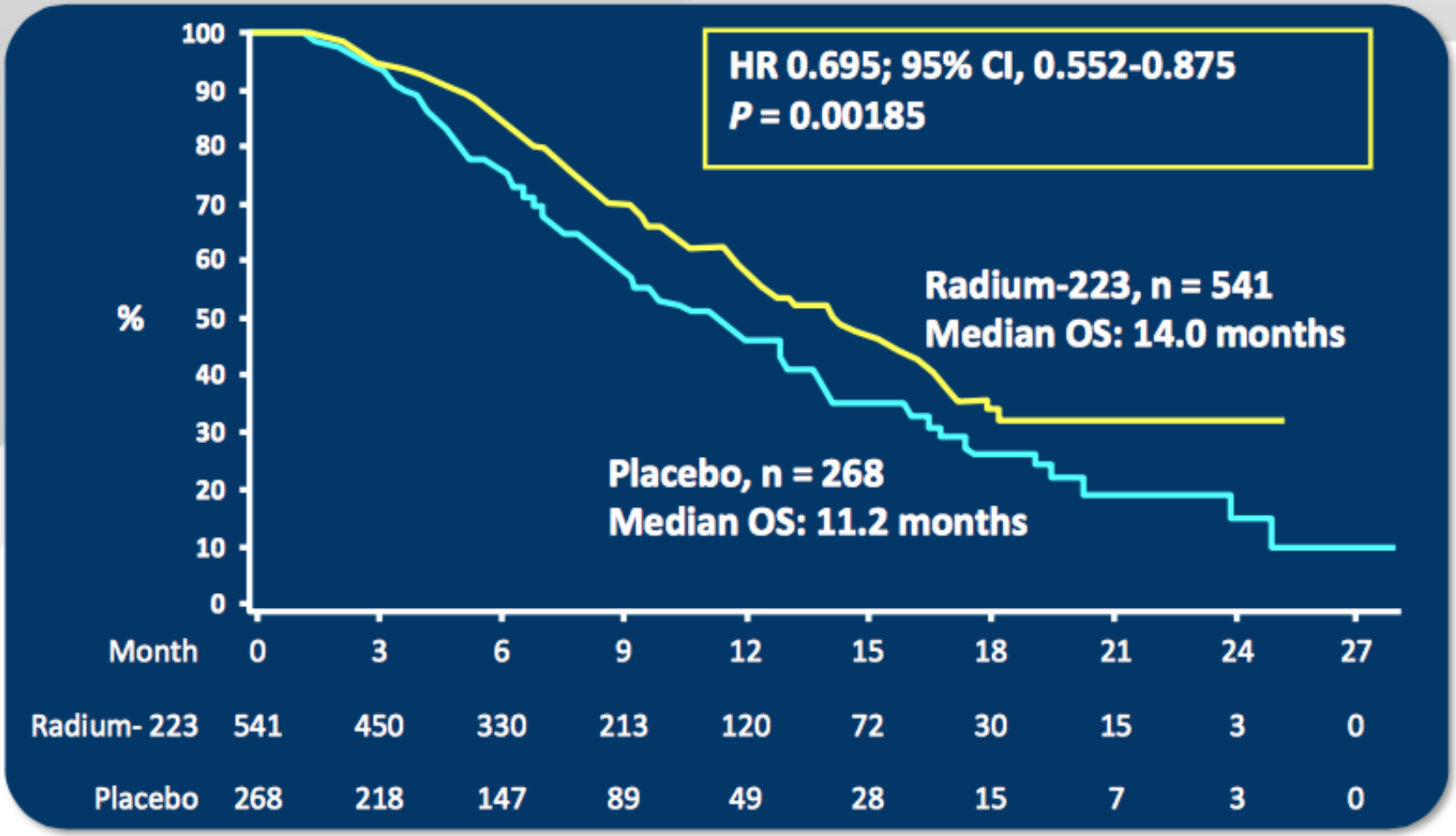


Clinicaltrials.gov identifier: NCT00699751.

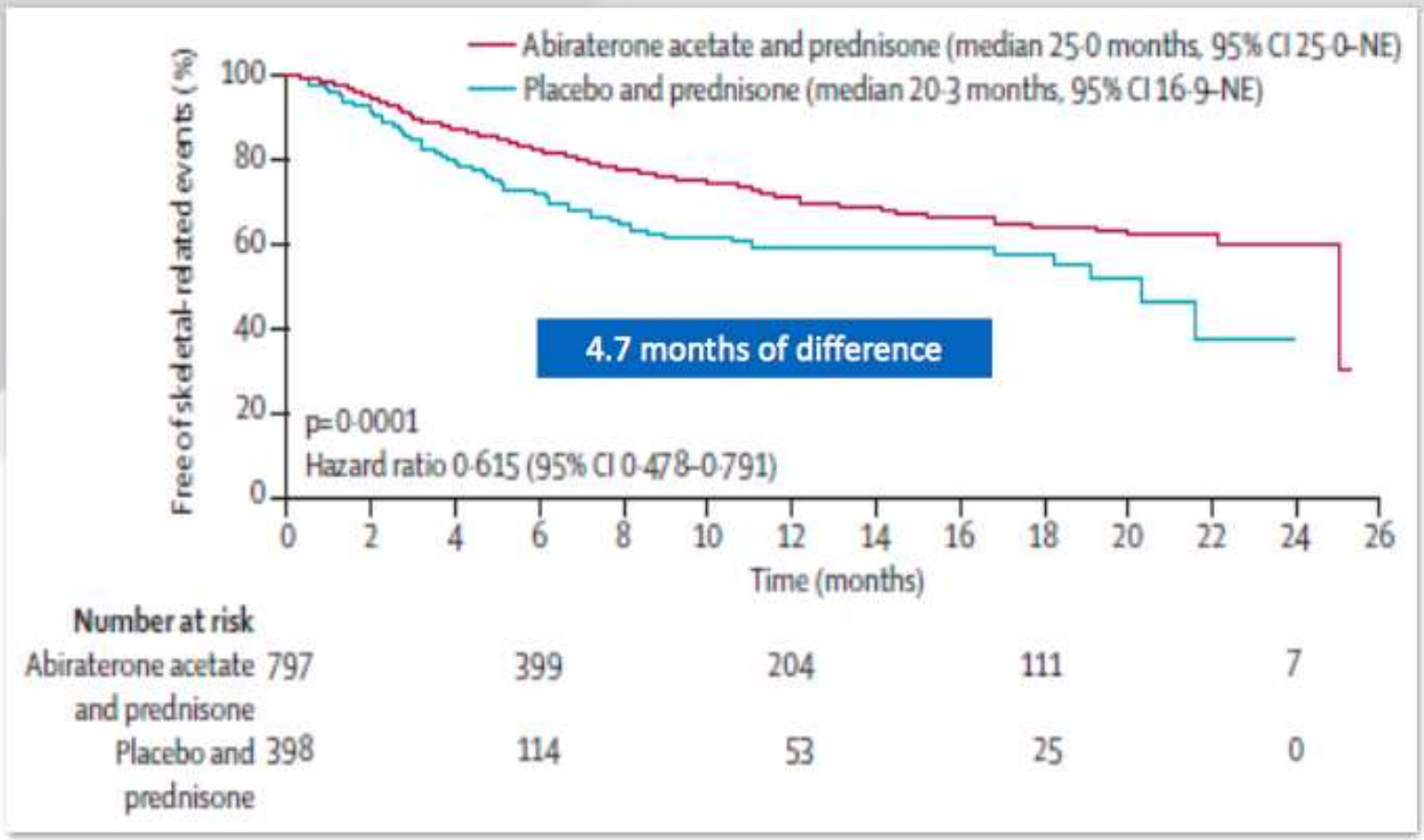
ALSYMPCA Time to First Skeletal-Related Event



ALSYMPCA Overall Survival

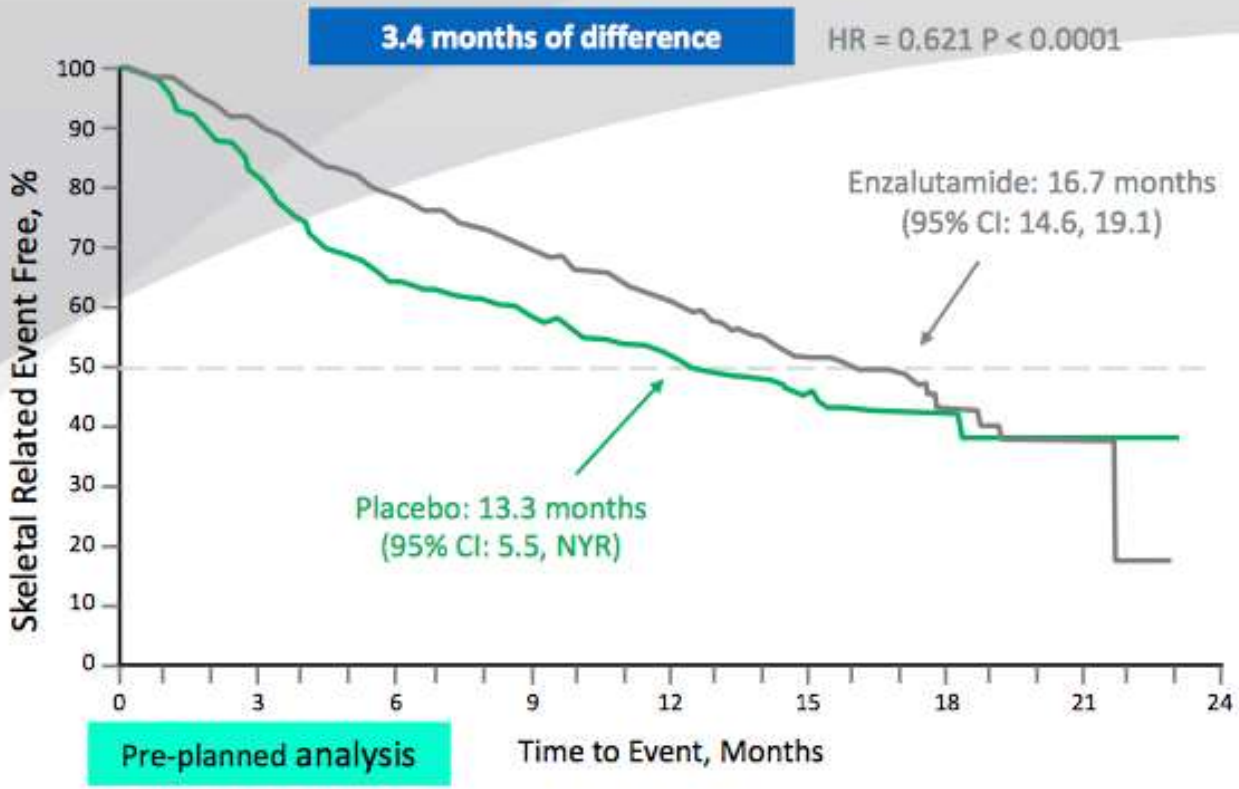


Abiraterone post-docetaxel does delay SREs



Logothetis et al. Lancet Oncology, 2012

Enzalutamide post-docetaxel does delay SREs



Enzalutamide	800	676	548	379	209	87	19	2	0
Placebo	399	278	196	128	68	33	11	0	0

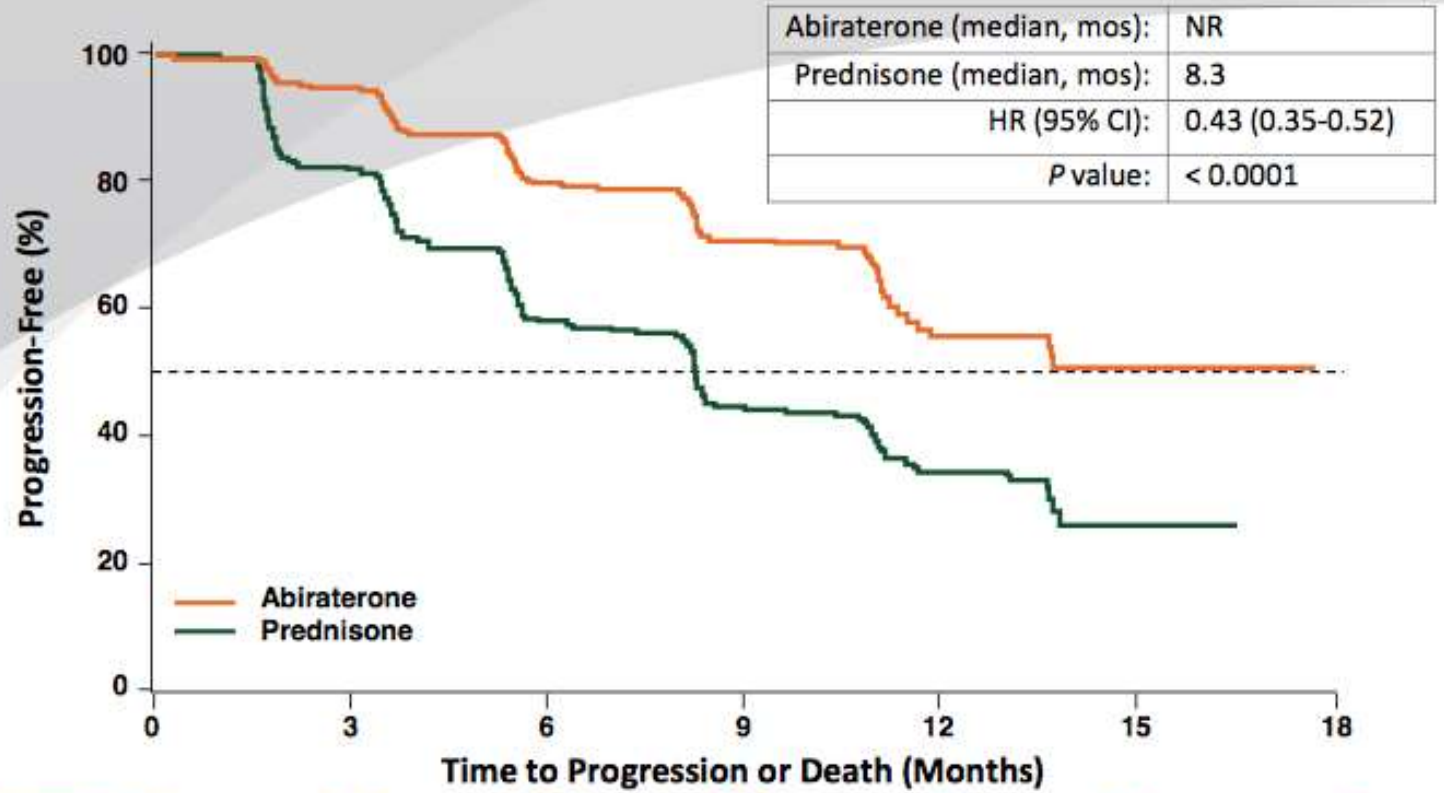
JS De Bono, ASCO, 2012

Abiraterone post-docetaxel does delay bone progression

	Abiraterone + Prednisone (n = 797)	Placebo + Prednisone (n = 398)	*P* Value
Time to progression (months) 25th percentile (95% CI)	9.27 (7.39-12.88)	4.57 (2.79-6.47)	0.0019

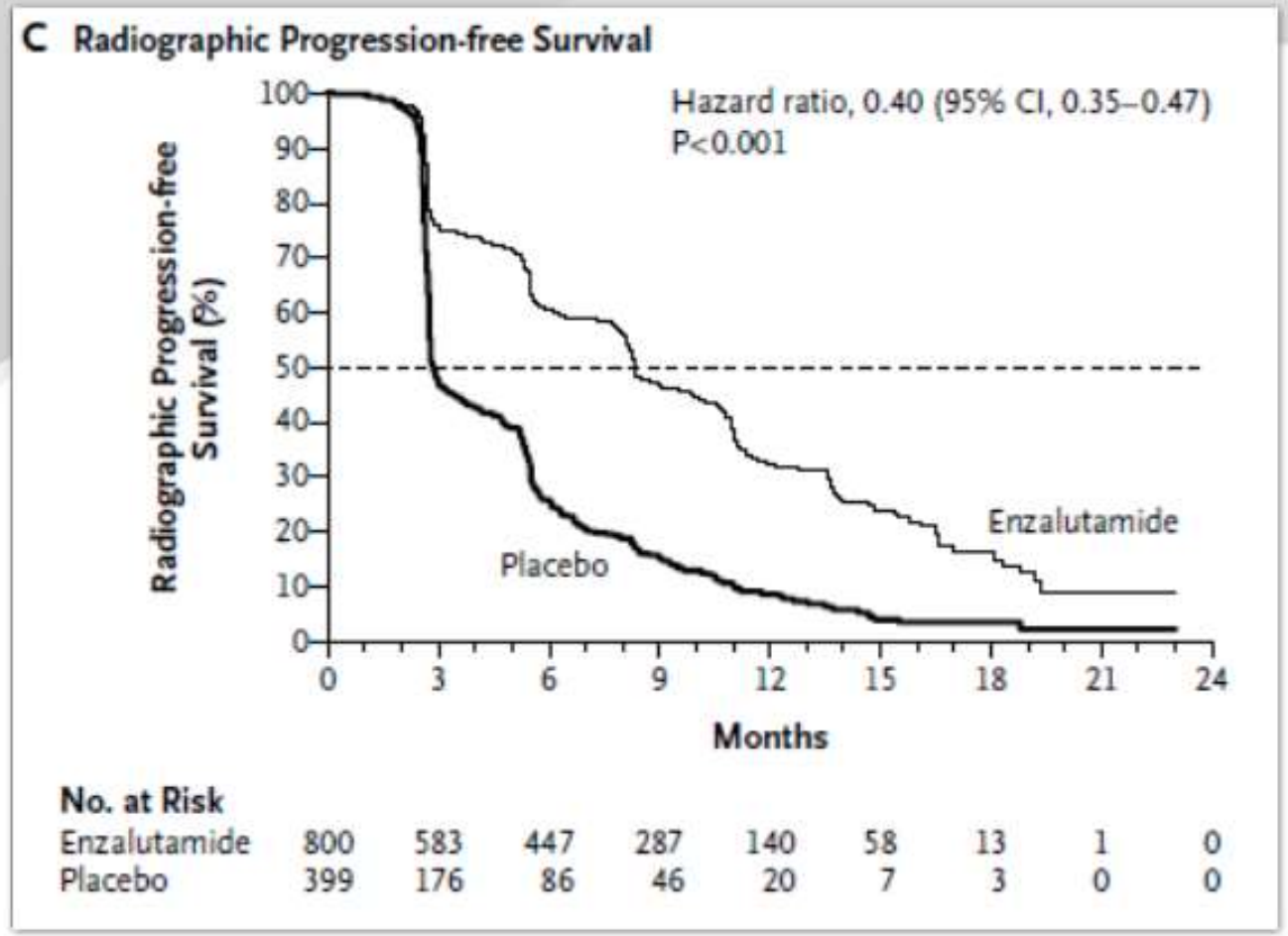
Logothetis et al. J Clin Oncol 2011; 29 (Suppl): Abstract 4520 (oral presentation)

Abiraterone pre-docetaxel does delay bone progression



Ryan et al. NEJM, 2013

Enzalutamide post-docetaxel does delay bone progression



Scher HI et al, NEJM, 2012

ESMO clinical practice guidelines 2014

Bone health

Initiation	Agents(s) and dosing	Monitoring
Bone targeted therapy should be started at the diagnosis of metastatic bone disease It is recommended to start zoledronic acid or denosumab in all patients with breast cancer and bone metastases or CRPC and bone metastases, whether they are symptomatic or not Patients with advanced lung cancer, renal cancer and other solid tumours (non-breast or non-prostate) and bone metastases should be selected for zoledronic acid or denosumab if they have a life expectancy > 3 months and are considered at high risk of SREs	Zoledronic acid – Most effective bisphosphonate for prevention of morbidity from metastatic bone disease Denosumab – More effective than zoledronic acid for prevention of skeletal morbidity from solid tumours Calcium and vitamin D strongly recommended	Serum calcium (regularly) Skeletal radiography assesses response to treatment but information is delayed and method insensitive Isotopic bone scanning is not useful in assessing treatment response Biochemical markers of bone metabolism may provide information on prognosis and response to bone-specific treatment but are not recommended routinely Assesment of symptoms and activity status is essential

ESMO clinical practice guidelines 2014

Bone health

Key quotes:[1]

"The choice of the bone-targeting agent to be administered remains open. The recent guidelines from the American Society of Clinical Oncology (ASCO) state that there is insufficient evidence to recommend one bone-modifying agent (zoledronic acid, pamidronate, denosumab) over another in the management of metastatic bone disease in breast cancer.[2] However, while the greater efficacy of zoledronic acid compared with pamidronate in breast cancer could only be shown by post hoc multiple event analyses,[3] this is not the case for the comparisons between zoledronic acid and denosumab, in which the greater efficacy of the latter was demonstrated in various classical pre-specified end points"

If you smoke, quit now

If your diet is high in fat, work to eat more healthfully

Adopt a regular exercise routine, since exercise has been shown to lower the risk of cancer