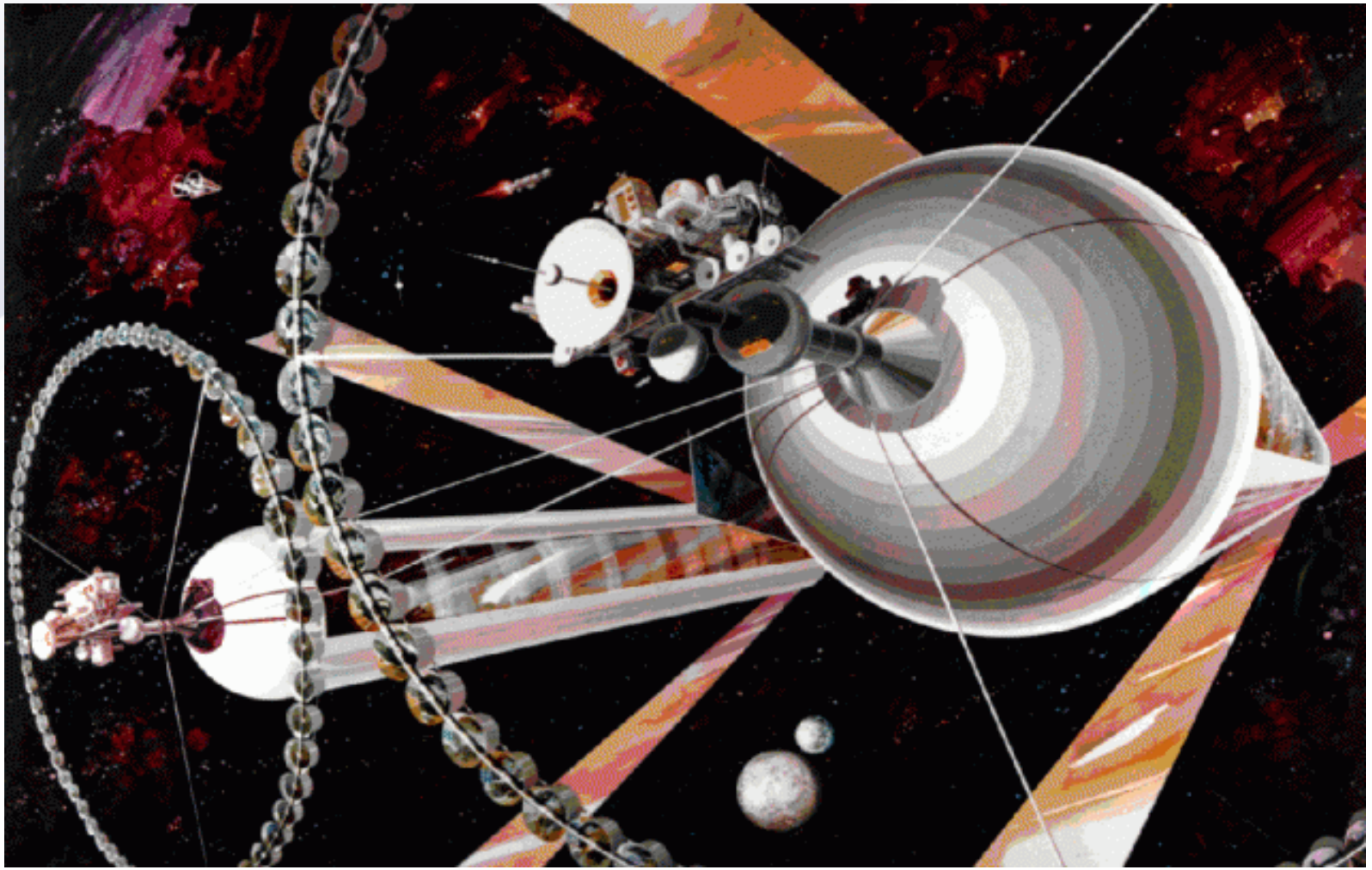
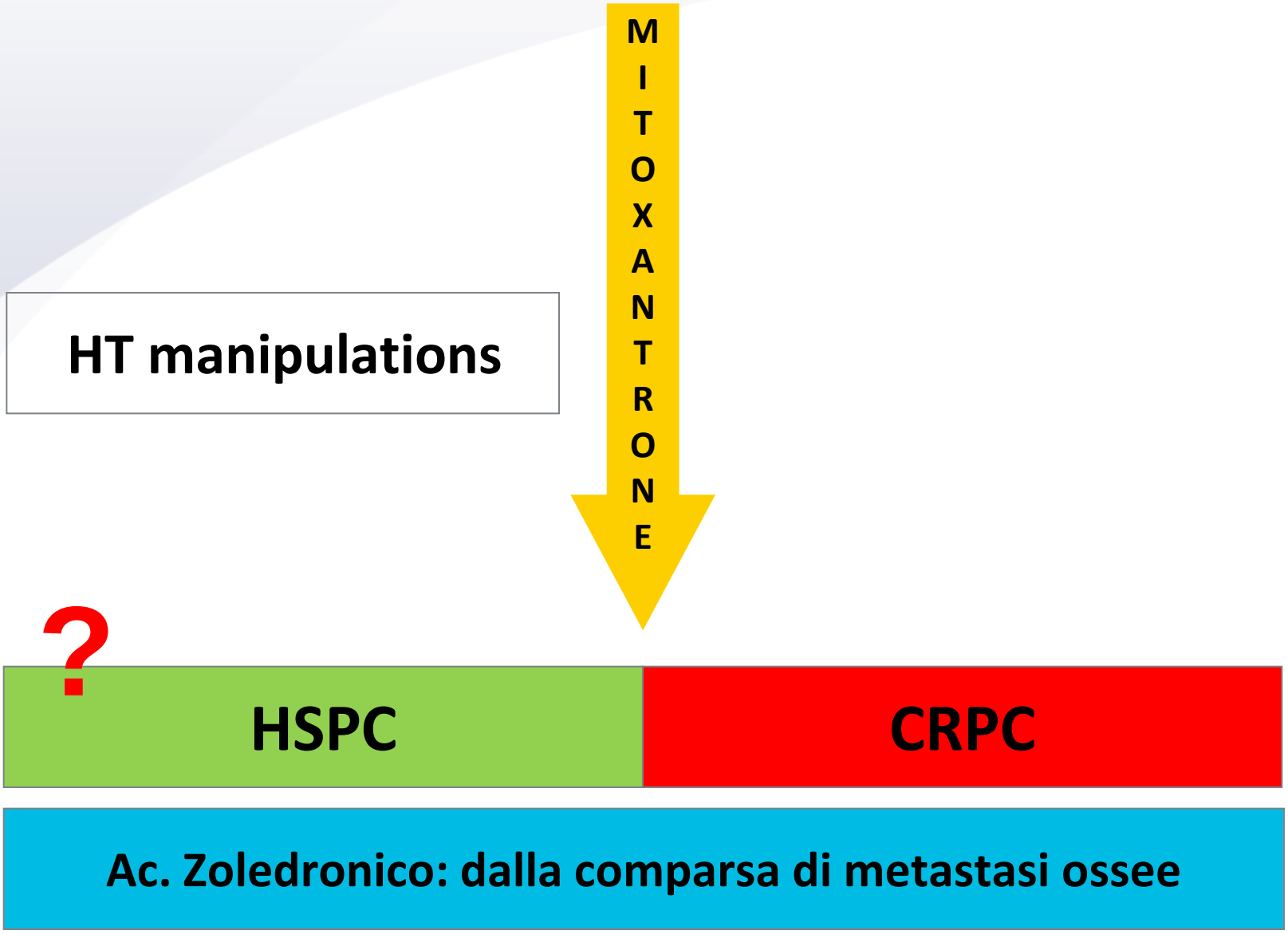
La gestione del paziente con metastasi ossee: nuovi approcci terapeutici

- Stato dell'arte del trattamento delle metastasi ossee nei tumori solidi sulla base delle più recenti Linee Guida
  Daniele Santini

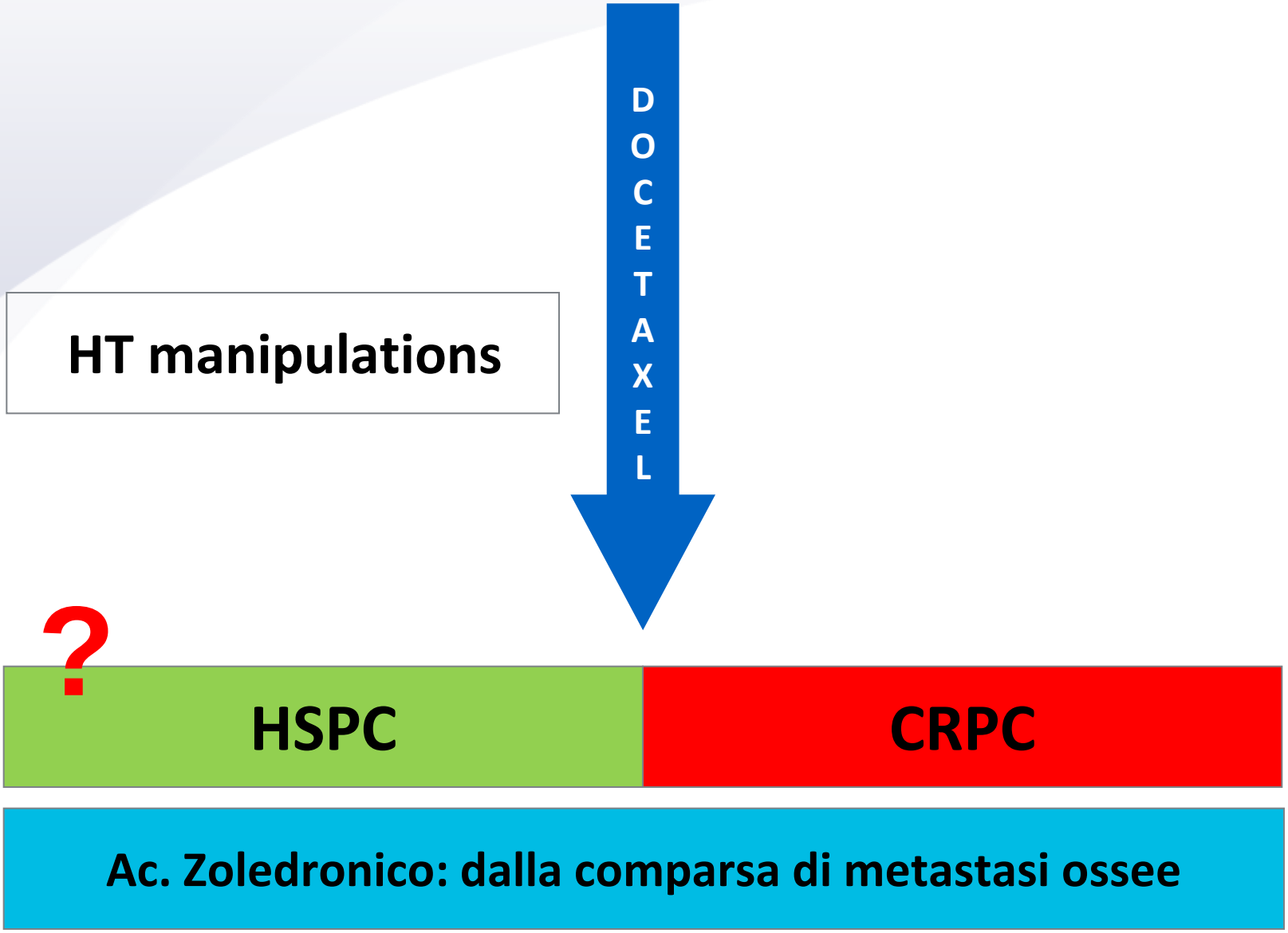
Il Rinascimento



2000 landscape



2004 landscape

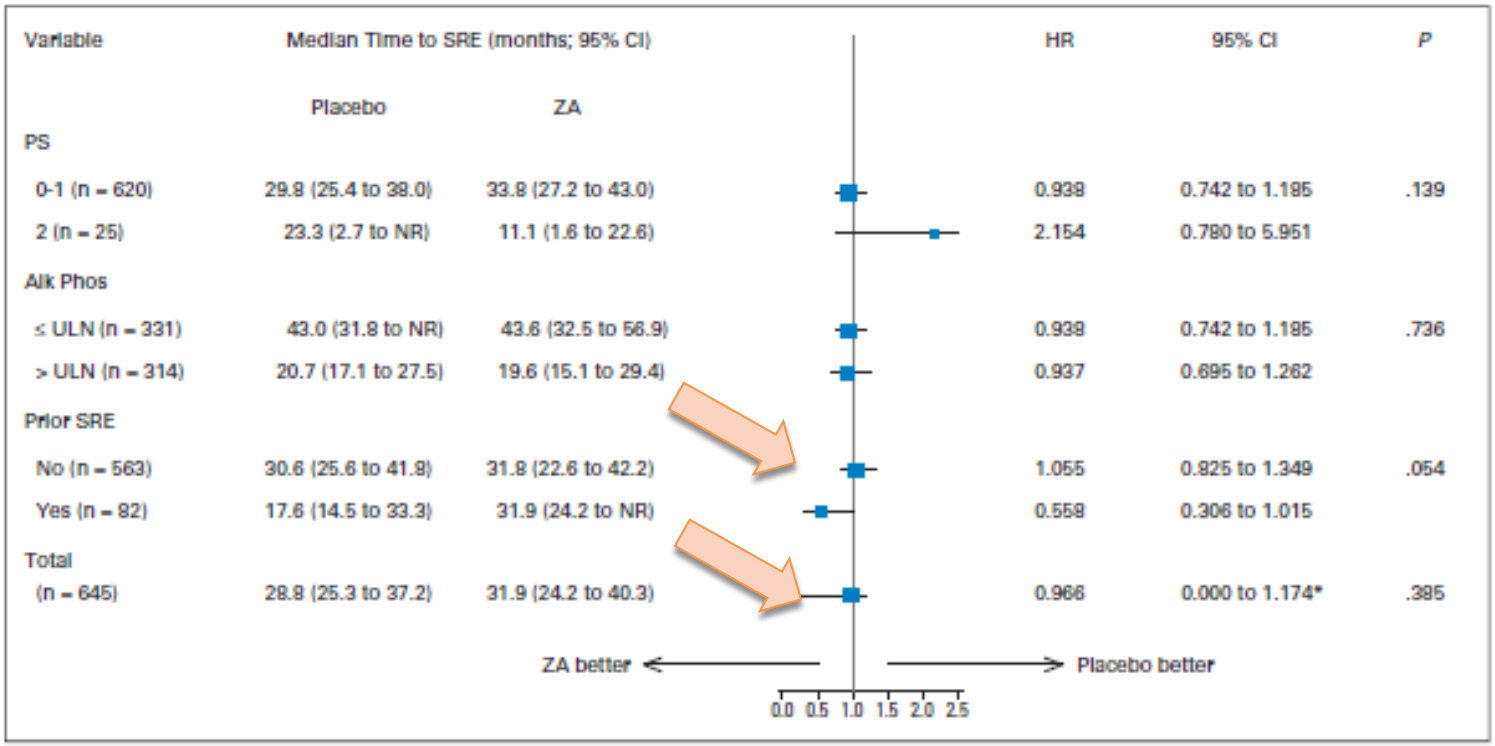


Published Ahead of Print on March 3, 2014 as 10.1200/JCO.2013.51.6500
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.51.6500

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

HT manipulations

abiraterone

cabazitaxel

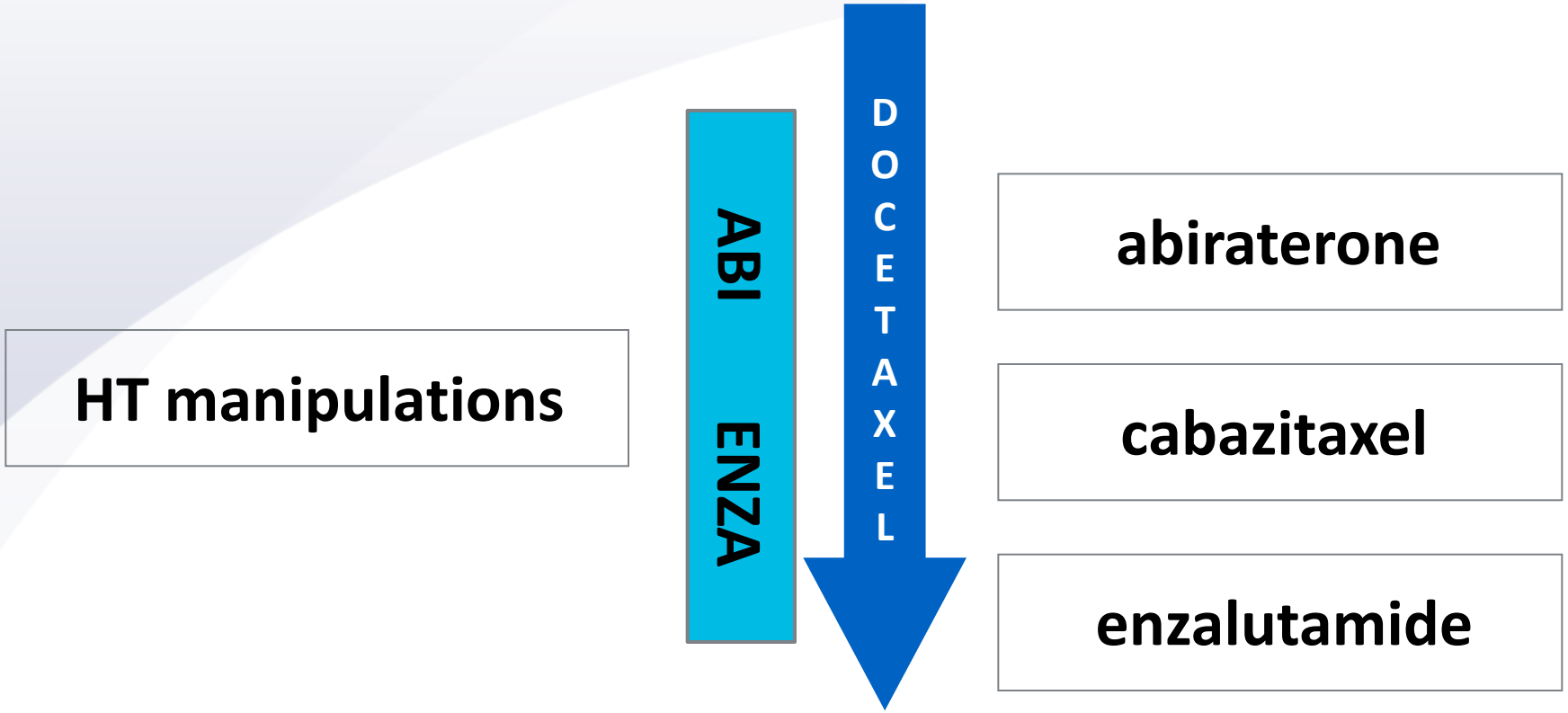
enzalutamide

Non esistono studi specifici di denosumab nel paziente in fase di ormonosensibilità

HSPC | **CRPC**

Denosumab: dalla comparsa di metastasi ossee

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.

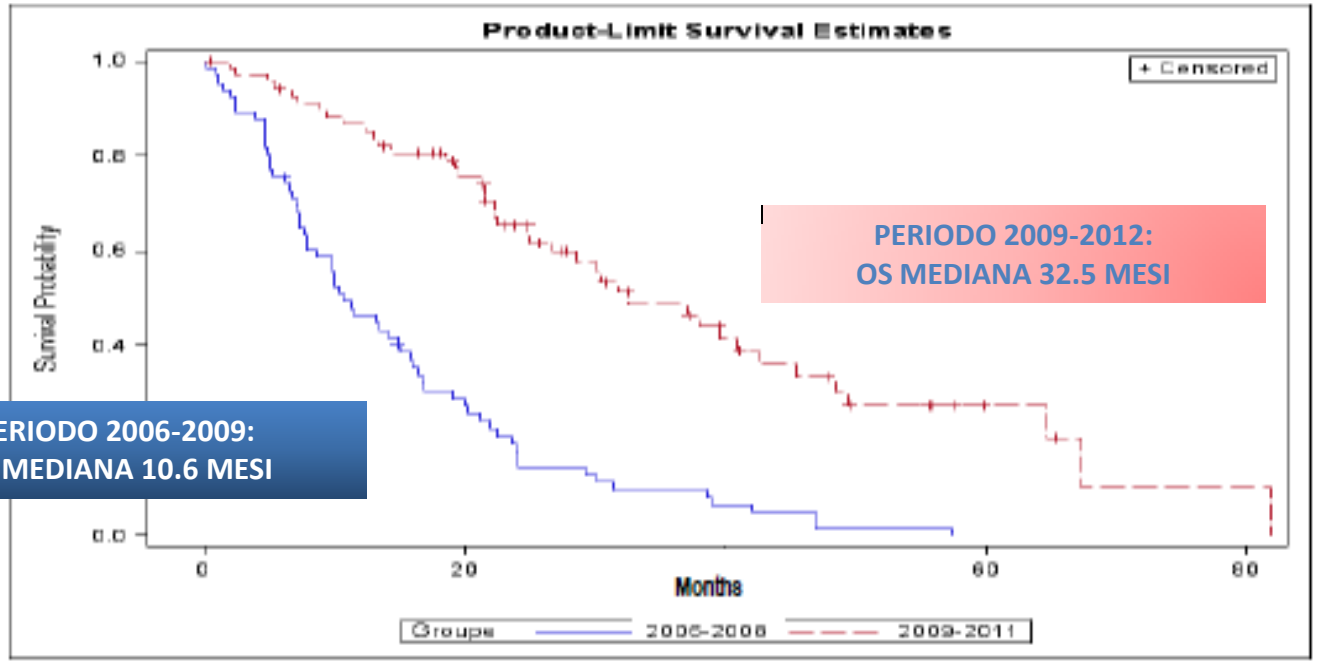


Figure 1 : Overall survival of mCRPC patients according to the period of treatment

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

Supplemental calcium and vitamin D strongly recommended

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

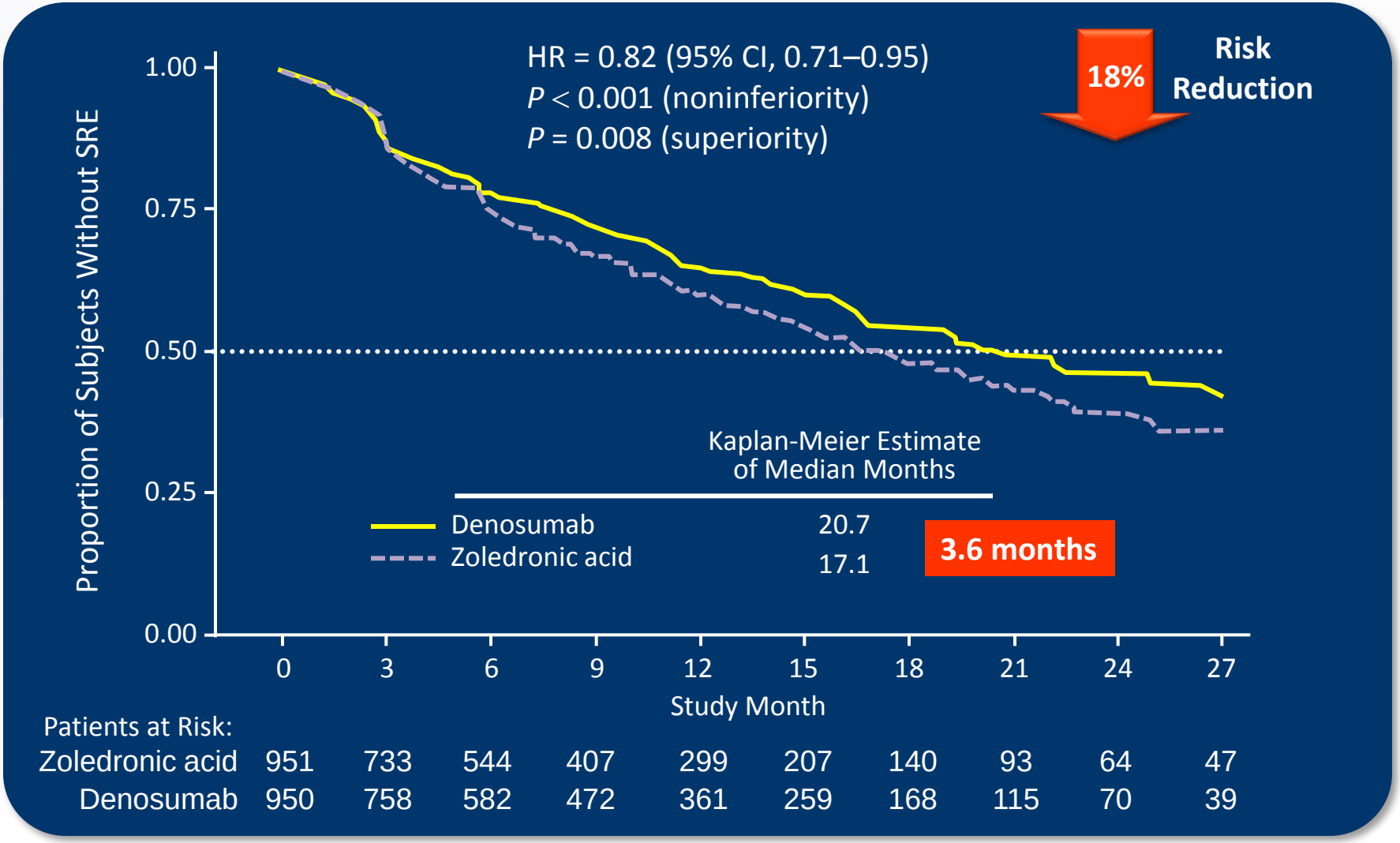
1° Endpoint
- **Time to first on-study SRE (non-inferiority)**

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.**

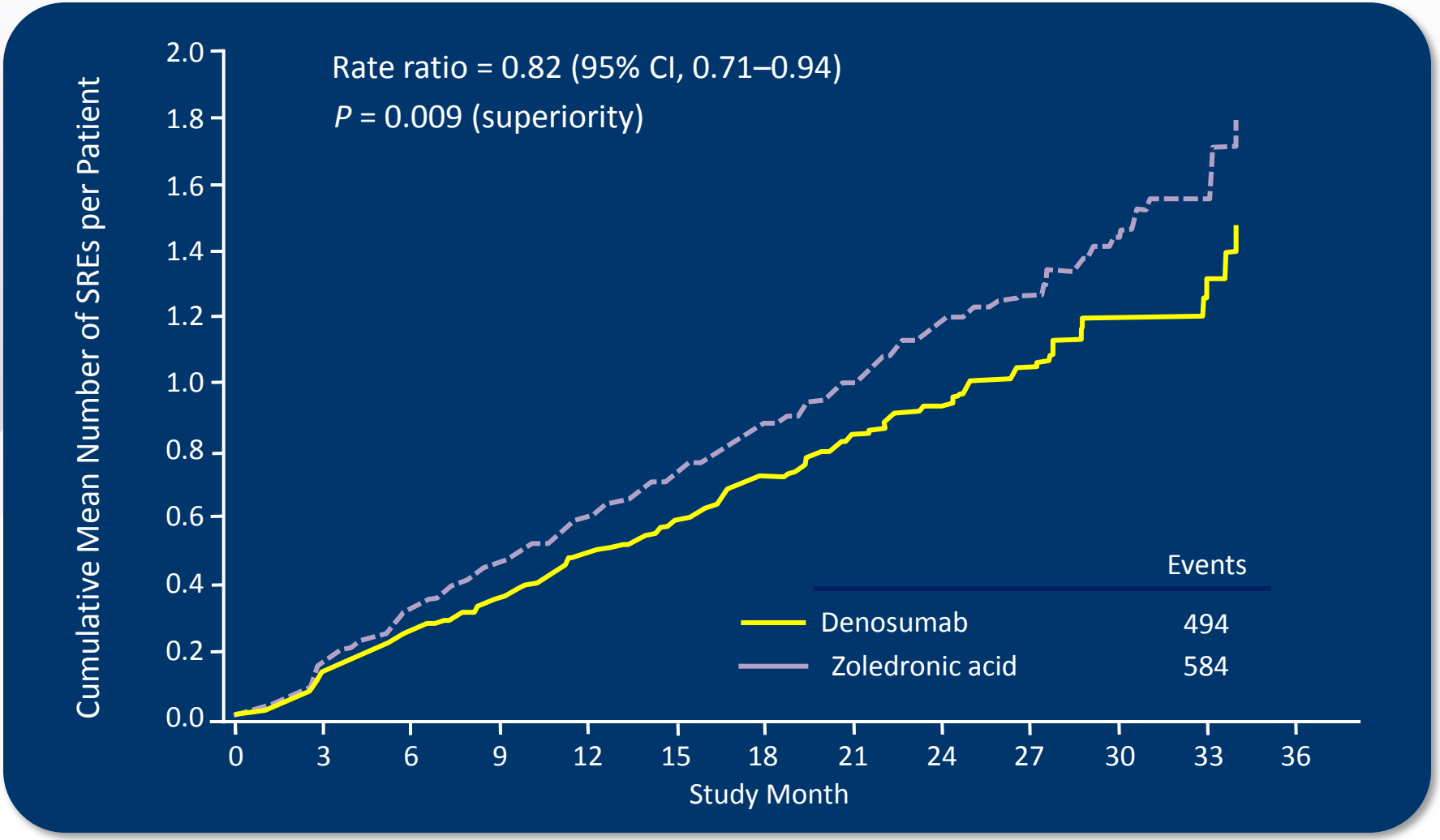
Fizazi K, et al. Lancet. 2011;377:813–822.

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.

Linee Guida - aggiornamento AIOM 2013
Carcinoma prostatico con metastasi ossee

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	L'uso dei bisfosfonati e di Denosumab è raccomandato in pazienti con metastasi ossee da carcinoma prostatico ormonorefrattario in quanto in grado di ritardare la comparsa di eventi scheletrici.	**Positiva forte**
B	Bisfosfonati e Denosumab possono trovare impiego per il controllo del dolore in pazienti con metastasi ossee da carcinoma prostatico ormonorefrattario, ma non possono sostituire i farmaci analgesici.	**Positiva debole**
B	? I bisfosfonati e il denosumab potrebbero essere impiegati nel paziente con metastasi ossee da carcinoma prostatico ormono-sensibile.	**Positiva debole**

Linee Guida - aggiornamento AIOM 2013
Carcinoma prostatico con metastasi ossee

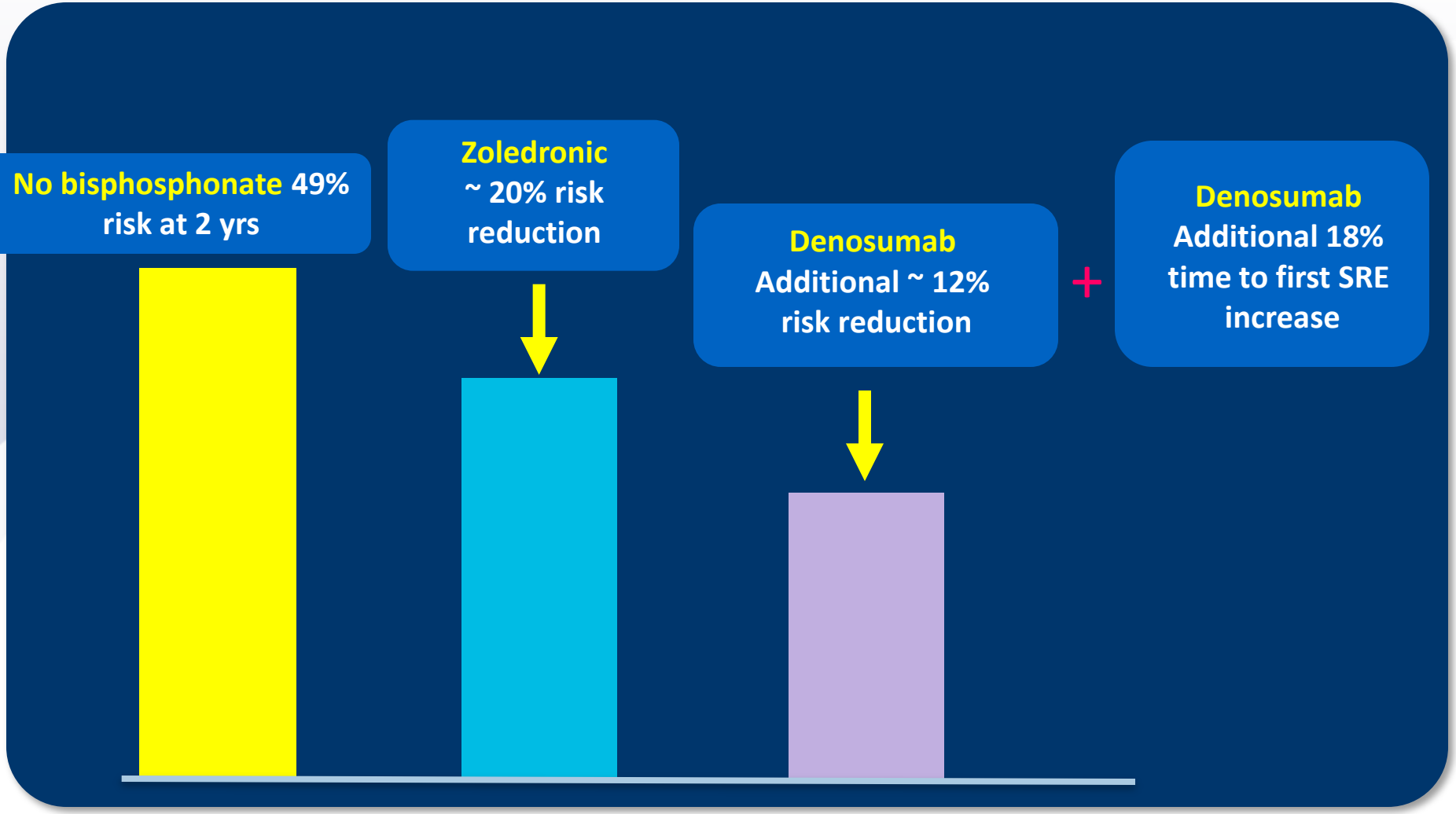
Tumore della prostata:

- Denosumab è una valida alternativa all'uso dell'acido zoledronico per quanto riguarda la prevenzione delle complicanze scheletriche nel paziente con malattia refrattaria alla ***(Livello di Evidenza SIGN 1++ A;*** *raccomandazione clinica nel capitolo specifico)*
- Il denosumab è superiore all'acido zoledronico in termini di tempo al primo SRE e di tempo al primo e ai successivi SRE ***(Livello di evidenza SIGN 1+ A****; raccomandazione clinica nel capitolo specifico)*

Linee Guida - aggiornamento AIOM 2013
La supplementazione con Vitamina D

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
D	In tutti i pazienti con metastasi ossee che debbano effettuare un trattamento con bisfosfonati o denosumab è raccomandabile una supplementazione di calcio e vitamina D.	**Positiva forte**
D	Si raccomanda di effettuare la supplementazione di calcio e vitamina D a dosi di almeno 1000-1200 UI al giorno di vitamina D e di 500 mg al giorno di calcio, possibilmente in formulazioni farmaceutiche separate.	**Positiva forte**
D	Si raccomanda di correggere ipocalcemie severe anche se asintomatiche durante trattamento con bisfosfonati o denosumab con dosi adeguate di vitamina D	**Positiva forte**

Skeletal Complication Risk: Incremental Benefits in Prostate Cancer



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

Do new ormonal agents affect bone disease?

Le molecole e il disegno degli studi

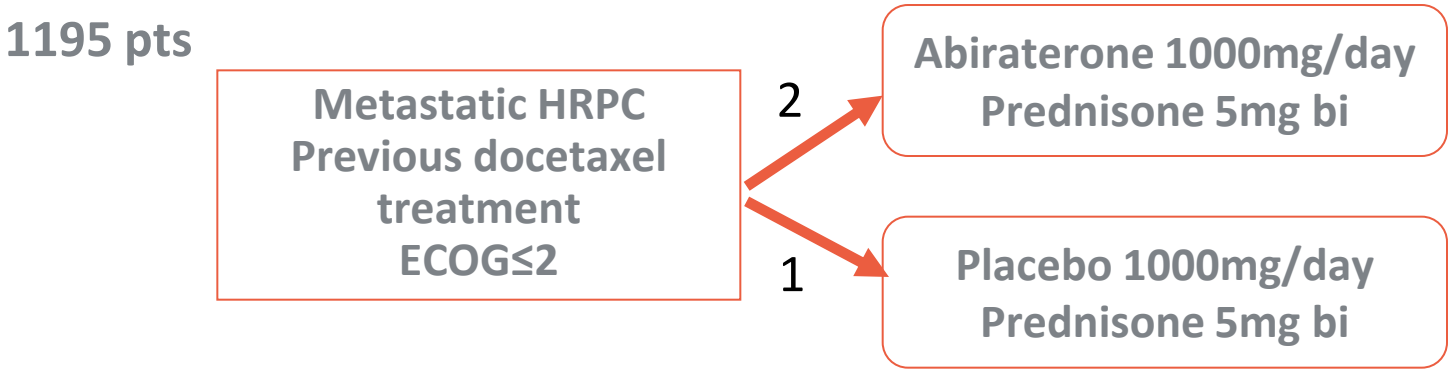
Disegno dello studio COU-AA-301

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 26, 2011 VOL. 364 NO. 21

Abiraterone and Increased Survival in Metastatic Prostate Cancer

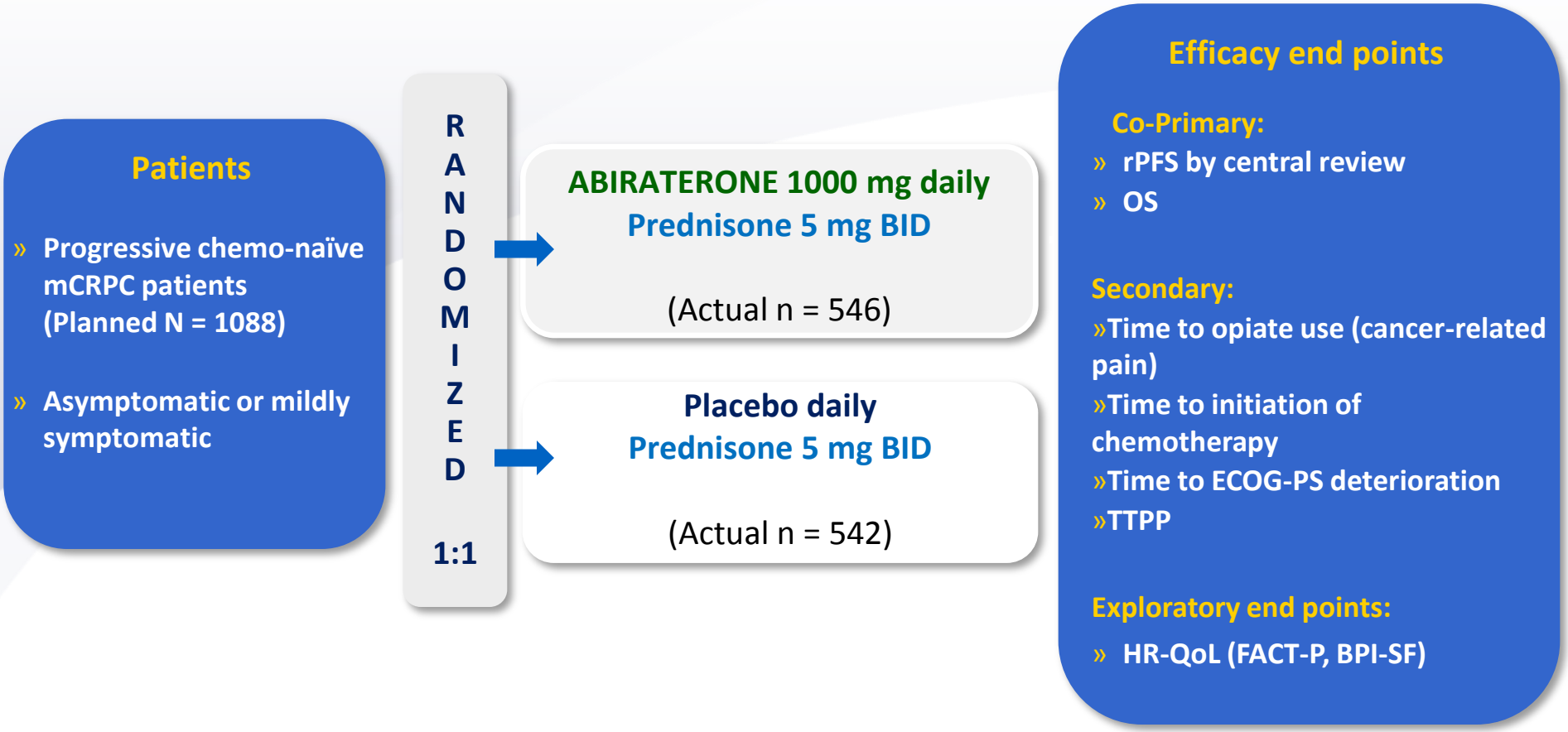
Johann S. de Bono, M.B., Ch.B., Ph.D., Christopher J. Logothetis, M.D., Arturo Molina, M.D., Karim Fizazi, M.D., Ph.D.,



Primary endpoint: OS

Secondary endpoints: PSA response rate, Time to PSA progression, PFS

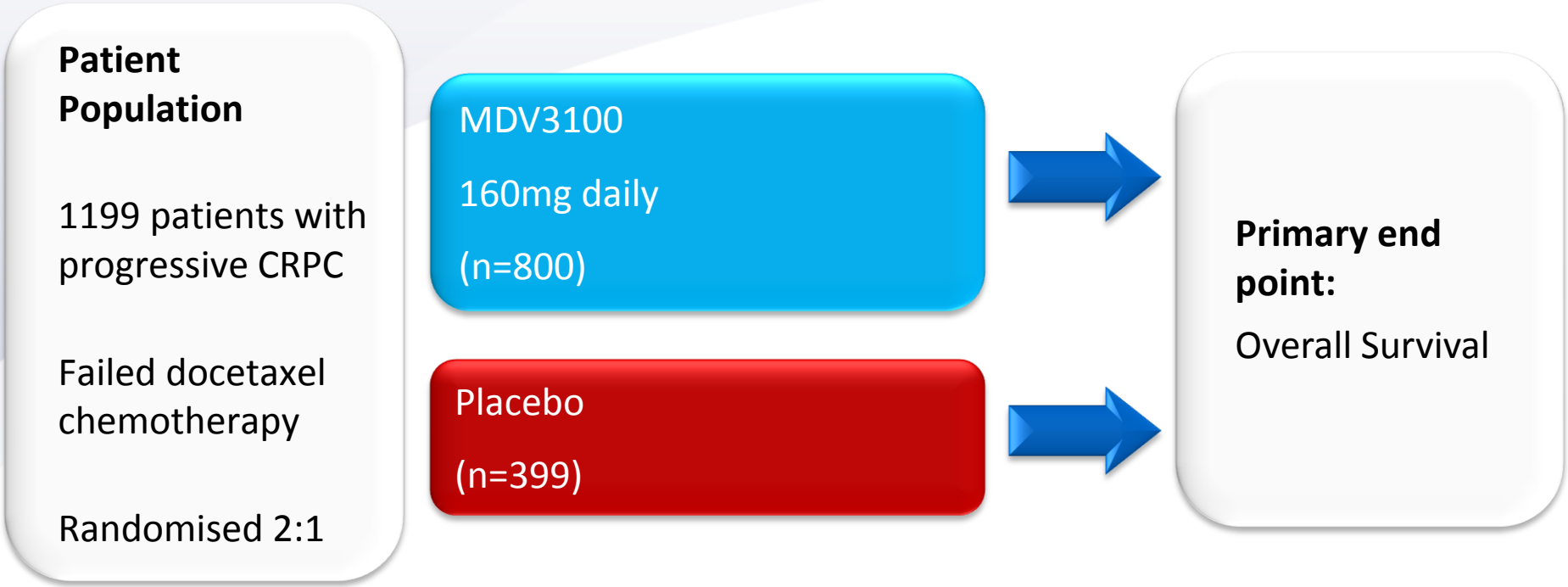
Disegno dello studio COU-AA-302



- Fase III multicentrico, randomizzato, in doppio cieco condotto in 151 centri in 12 paesi di USA, Europa, Australia, Canada
- Stratificazione alla randomizzazione in base all'ECOG PS 0 vs. 1

Ryan et al. N Engl J Med 2013; 368(2): 138-148

AFFIRM Phase III Trial of MDV3100 in Post-Chemotherapy treated CRPC

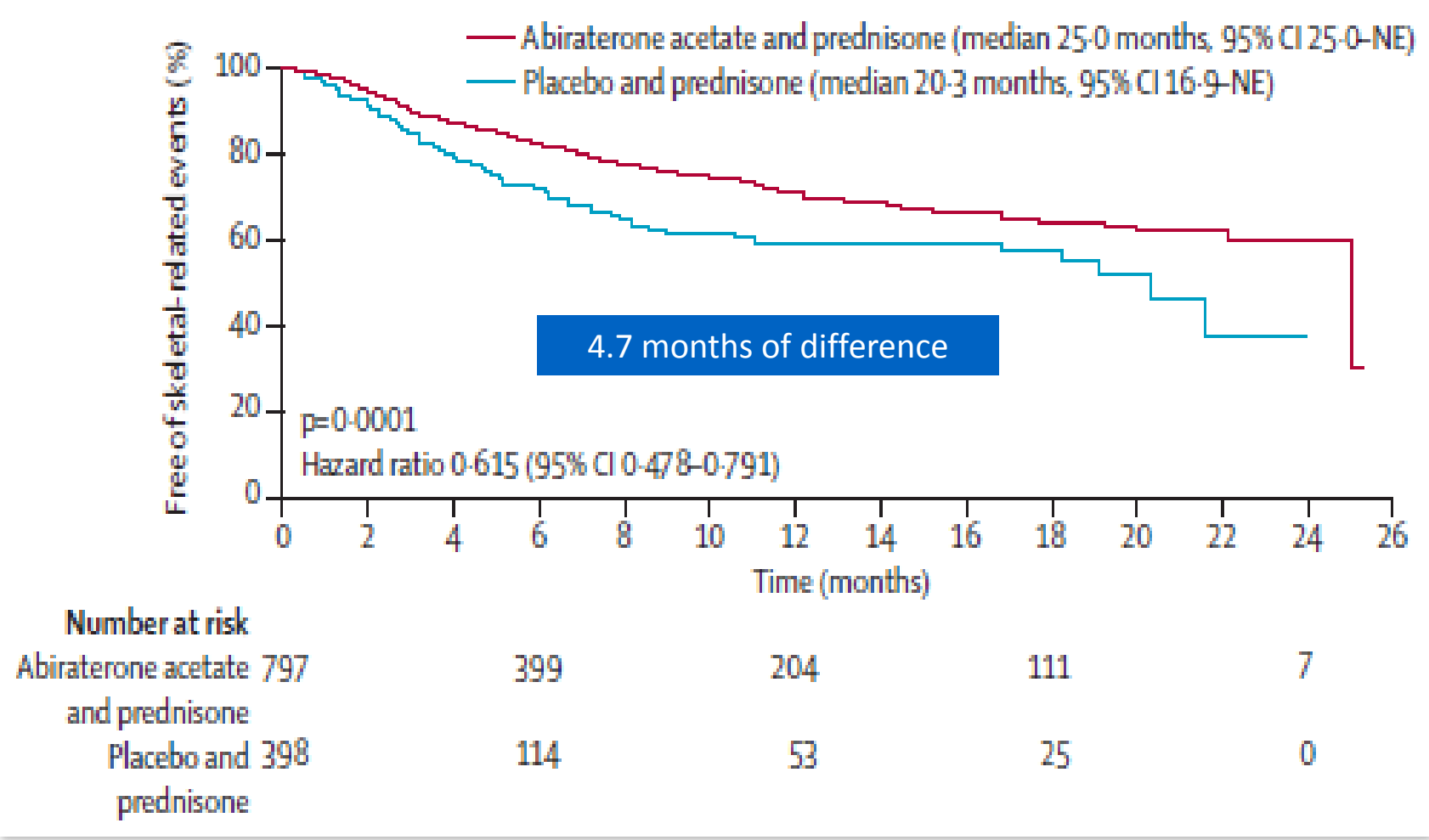


* Glucocorticoids were not required but allowed

Scher et al. ASCO GU Cancer Symposium 2012: LBA1 (oral presentation)

L’effetto sulle metastasi ossee - Gli SRE

Abiraterone post-docetaxel does delay SREs



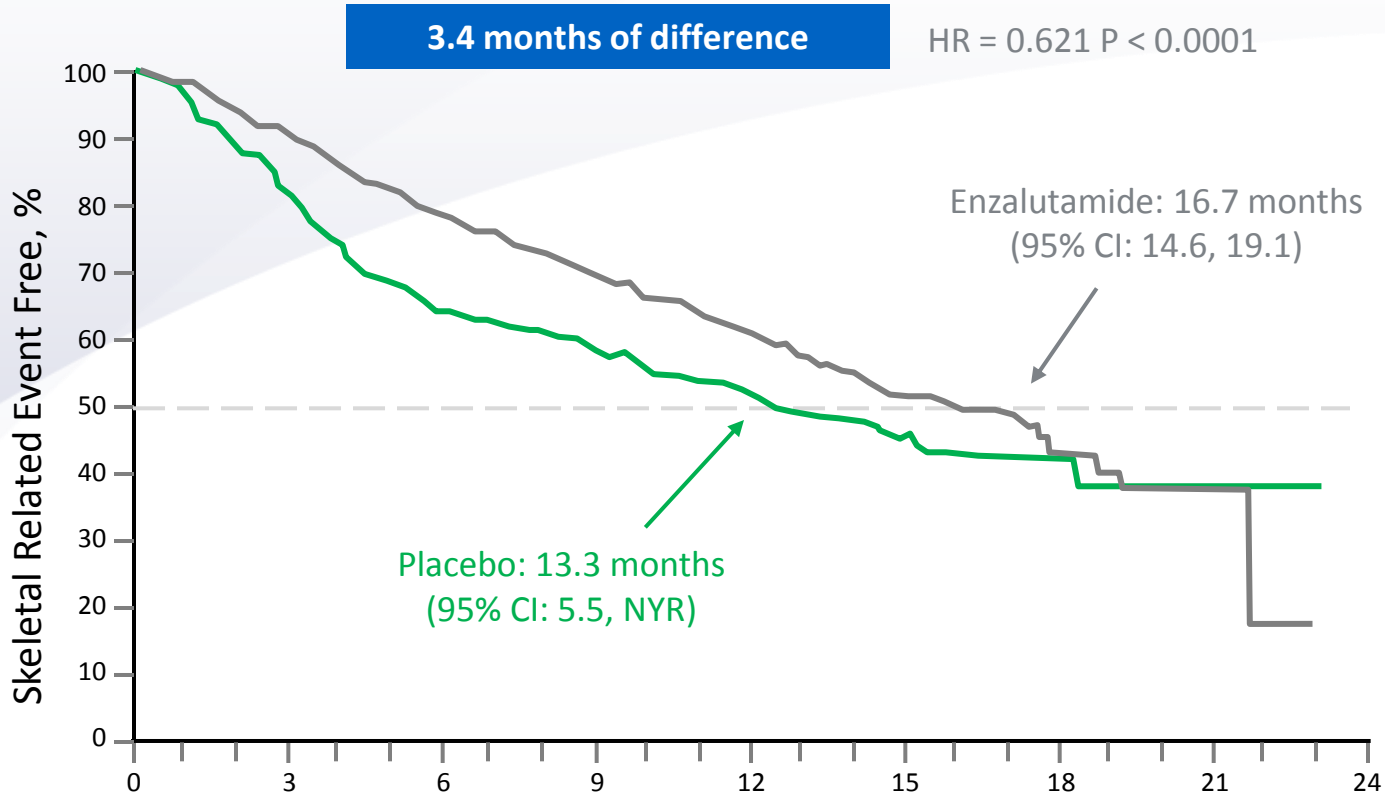
Logothetis et al. Lancet Oncology, 2012

Abiraterone post-docetaxel does delay SREs

SRE rate per 100 patients-years of exposure (%)*	38·9%	65·1%
Radiation to bone (%)	24·0%	46·1%
Pathological fracture (%)	6·0%	4·0%
Surgery to bone (%)	1·7%	1·0%
Spinal cord compression (%)	7·3%	14·0%

Logothetis et al. Lancet Oncology, 2012

Enzalutamide post-docetaxel does delay SREs

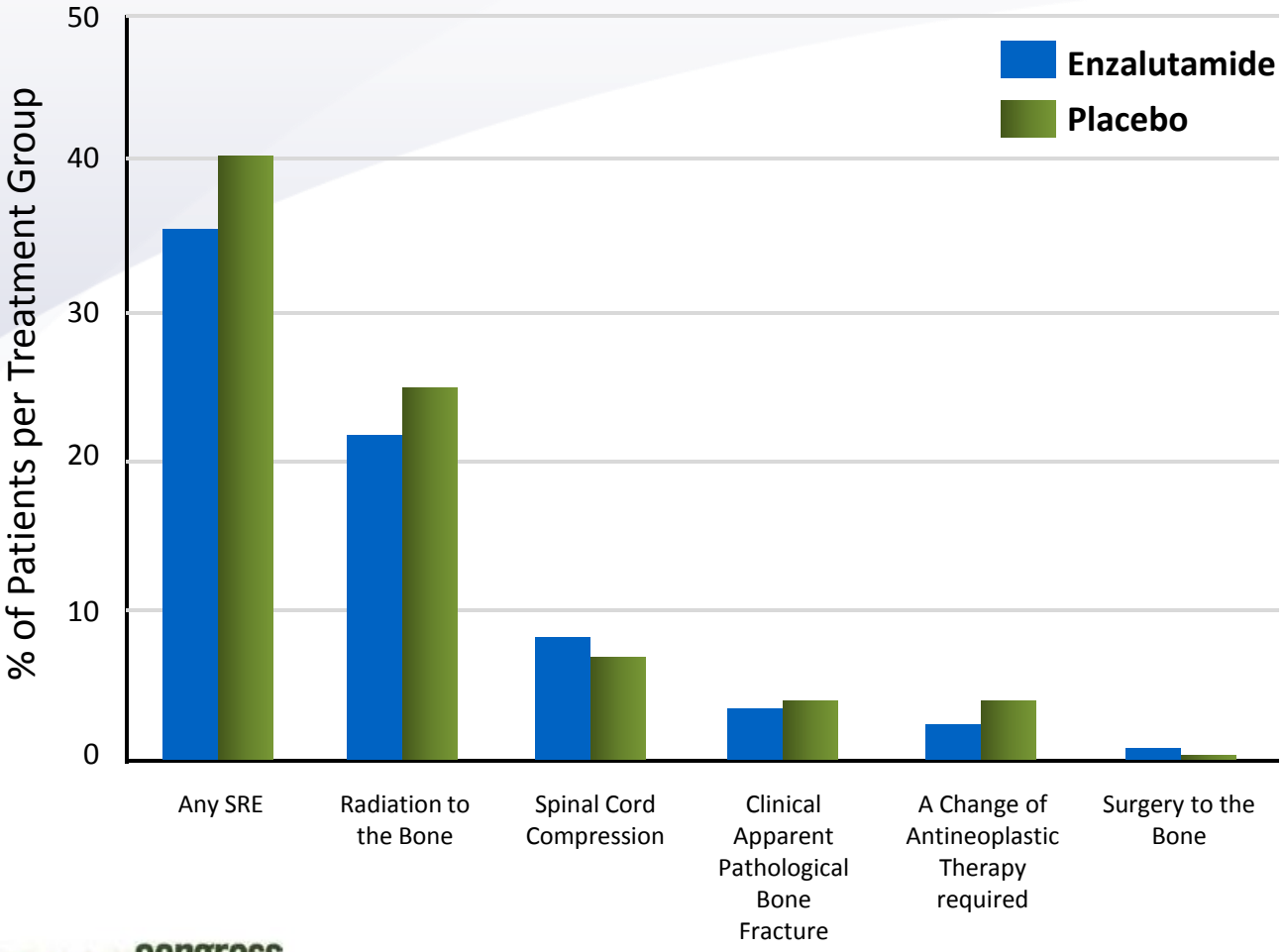


Pre-planned analysis

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

Enzalutamide post-docetaxel does reduce SREs



VIENNA 2012 ESMO congress

COU-AA-302: Miglioramento degli endpoint clinici

	Abiraterone	Prednisone		
	Median (months)	Median (months)	HR (95% CI)	p Value
Secondary end points				
Time to opiate use (cancer-related pain)	**NR**	**23.7**	**0.71 (0.59-0.85)**	**0.0002**
Time to chemotherapy initiation	**26.5**	**16.8**	**0.61 (0.51-0.72)**	**< 0.0001**
Time to ECOG PS deterioration	12.3	10.9	0.83 (0.72-0.94)	0.0052
Time to PSA progression	**11.1**	**5.6**	**0.50 (0.43-0.58)**	**< 0.0001**
Exploratory end points				
Time to BPI-SF pain interference progression	10.3	7.4	0.80 (0.68-0.93)	0.0049
Time to degradation in FACT-P (total score)	12.7	8.3	0.79 (0.67-0.93)	0.0046

IA3 data. Note: All secondary end points remain significant after adjusting for multiplicity testing.

Rathkopf et al. ASCO GU 2013; Abstract 5 (Oral Presentation)

L’effetto sulle metastasi ossee.
La progressione delle metastasi ossee

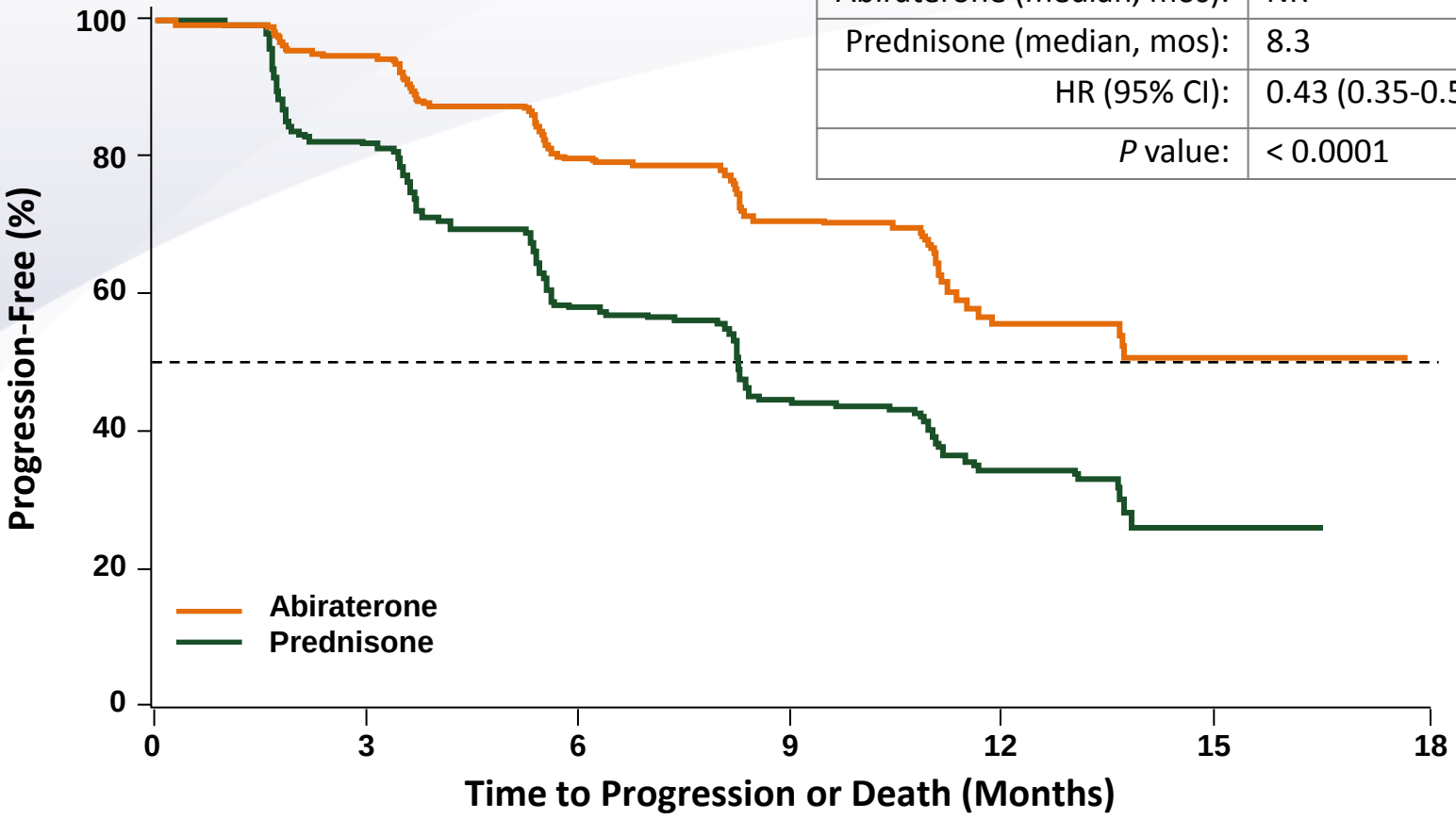
Abiraterone post-docetaxel does delay bone progression

	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

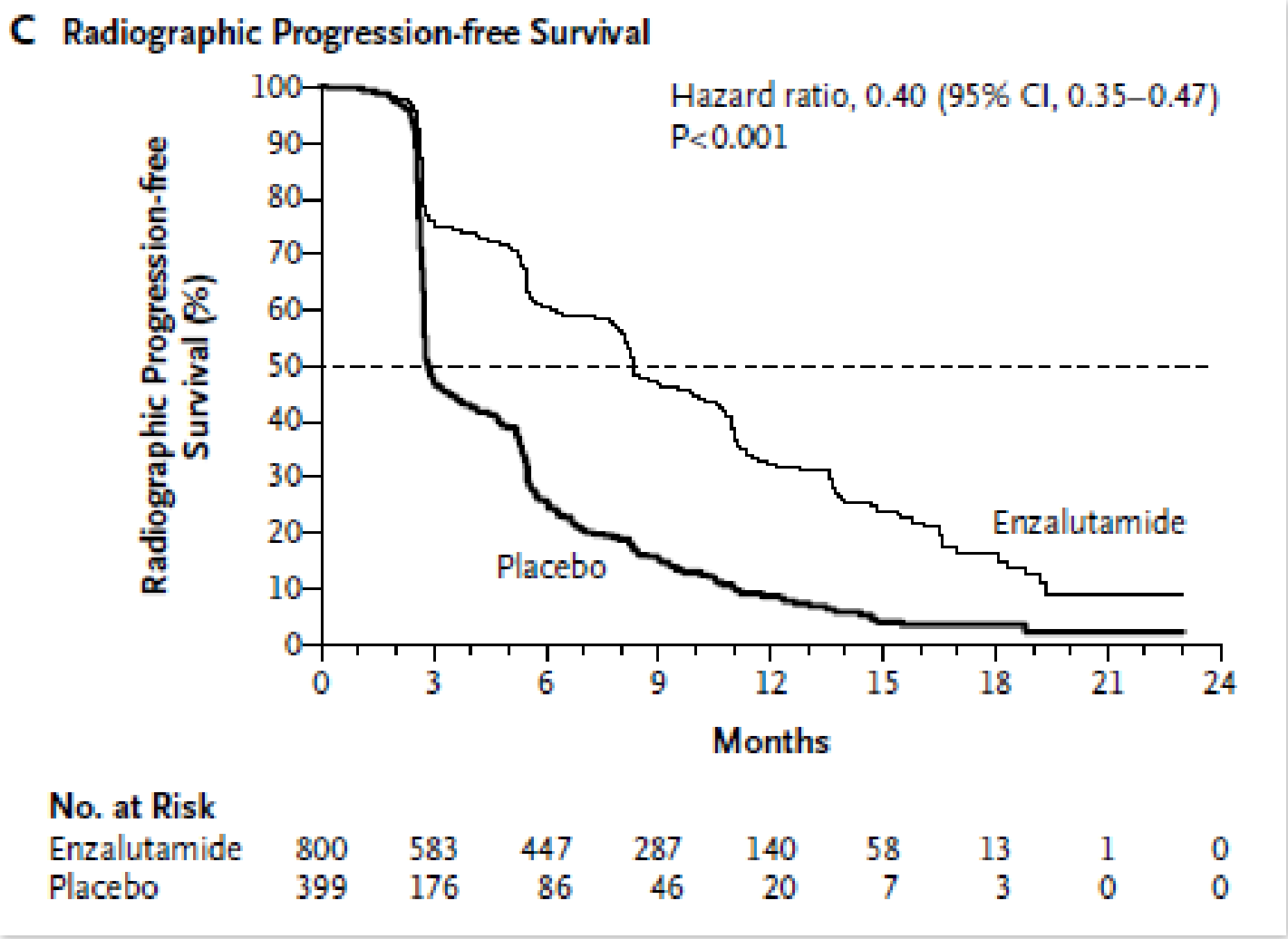
Abiraterone (median, mos):	NR
Prednisone (median, mos):	8.3
HR (95% CI):	0.43 (0.35-0.52)
P value:	< 0.0001



Abiraterone	546	489	340	164	46	12	0
Prednisone	542	400	204	90	30	3	0

Ryan et al. NEJM, 2013

Enzalutamide post-docetaxel does delay bone progression



Scher HI et al, NEJM, 2012

Le nuove molecole: abiraterone

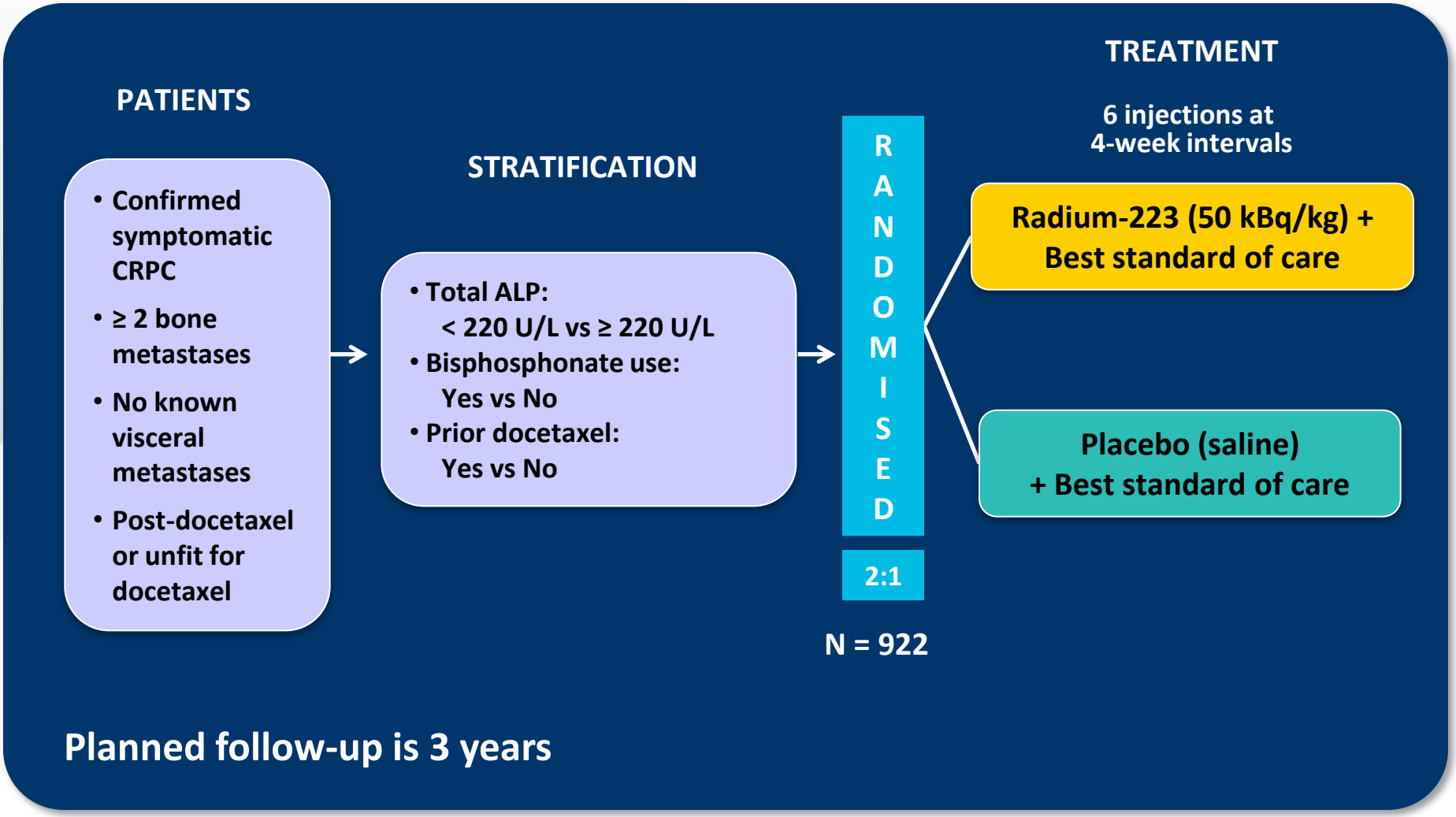
L’abiraterone è capace, quando somministrato dopo il docetaxel, nei pazienti affetti da tumore della prostata metastatico allo scheletro in fase di resistenza alla castrazione, di ritardare la comparsa degli SRE e la progressione scheletrica
Livello di evidenza: 1+B; raccomandazione **clinica**: POSITIVA FORTE

Le nuove molecole: enzalutamide

L’enzalutamide è capace, quando somministrato dopo il docetaxel, nei pazienti affetti da tumore della prostata metastatico allo scheletro in fase di resistenza alla castrazione, di ritardare la comparsa degli SRE e la progressione scheletrica
Livello di evidenza: 1+B; raccomandazione **clinica**: POSITIVA FORTE

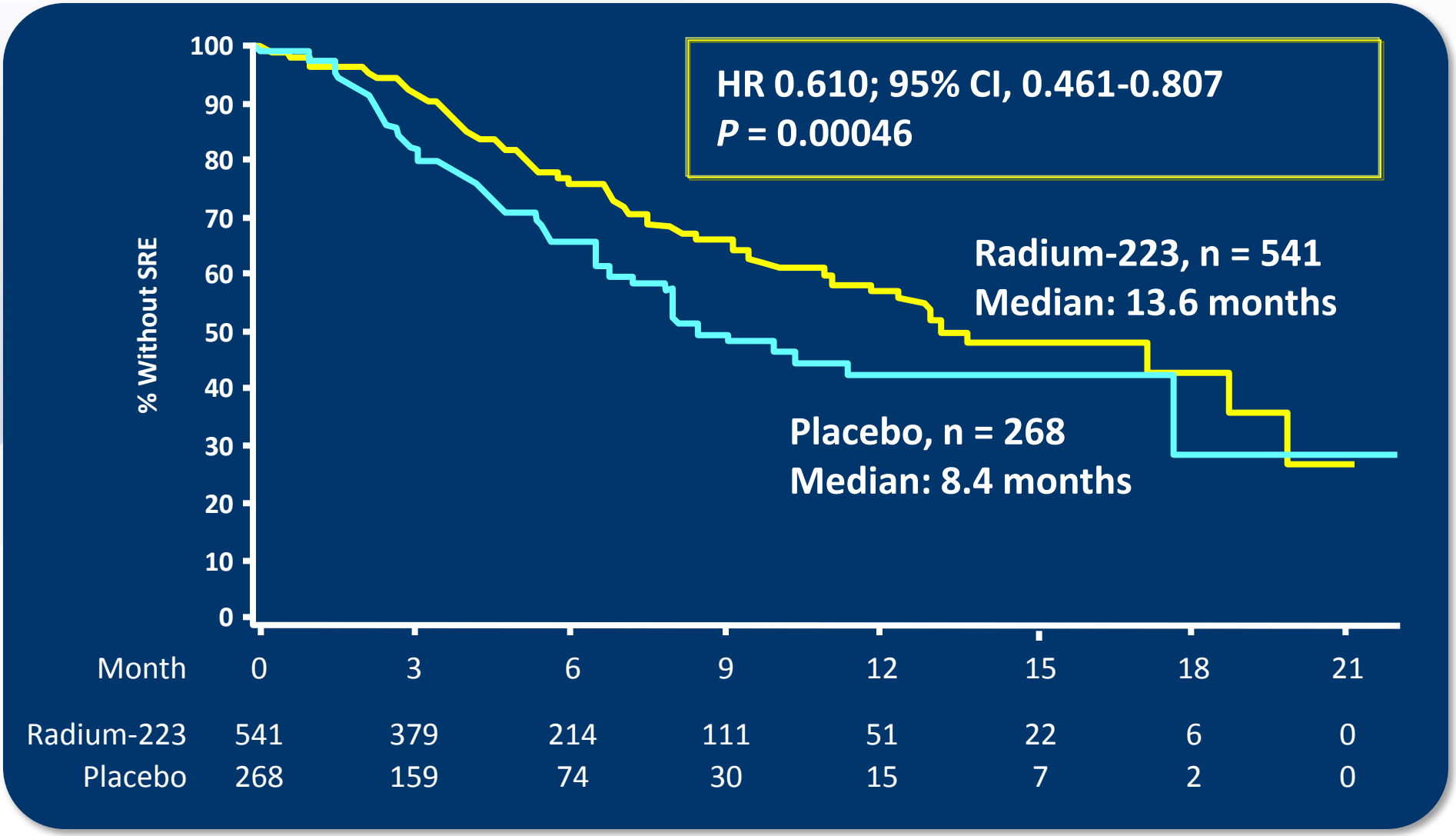
…c’è qualcos’altro di cui parlare?

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

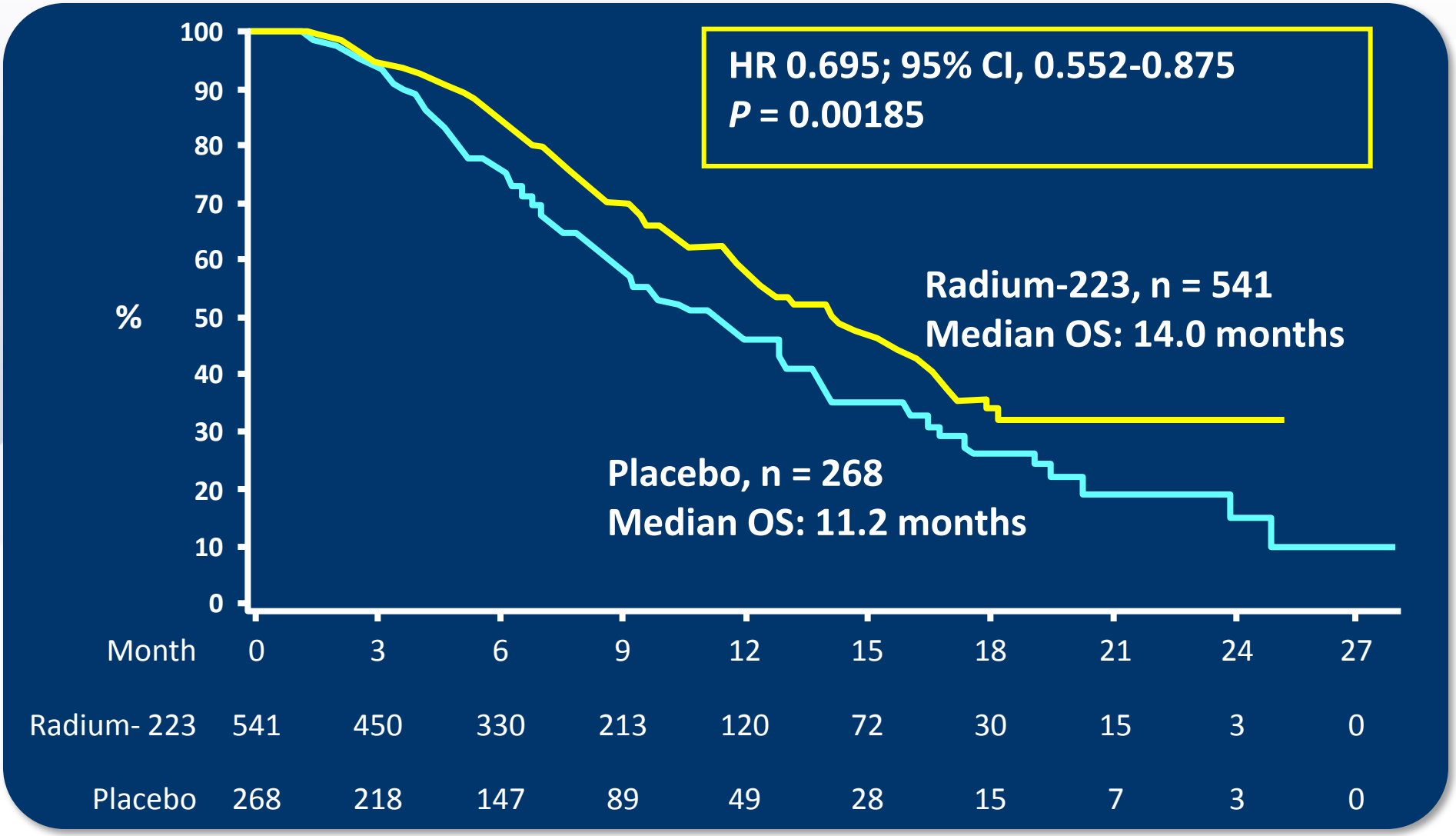


Clinicaltrials.gov identifier: NCT00699751.

ALSYMPCA Time to First Skeletal-Related Event



ALSYMPCA Overall Survival



… riepilogando

Improve overal survival	**YES**
Improve quality of life	**YES**
Delay SRE	**YES**
Delay bone progression	**YES**

News in breast cancer bone disease

Il Rinascimento

Il Presente

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

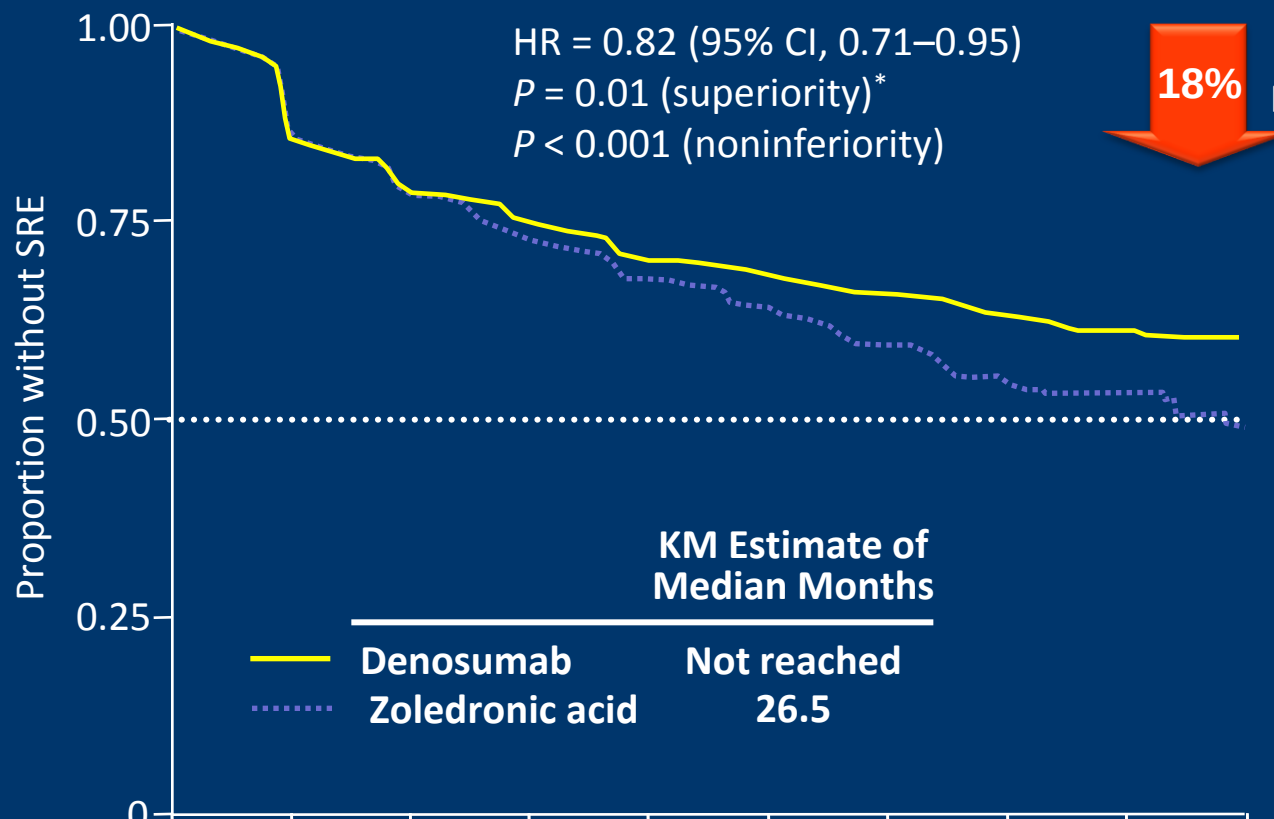
1° Endpoint
- **Time to first on-study SRE (non-inferiority)**

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

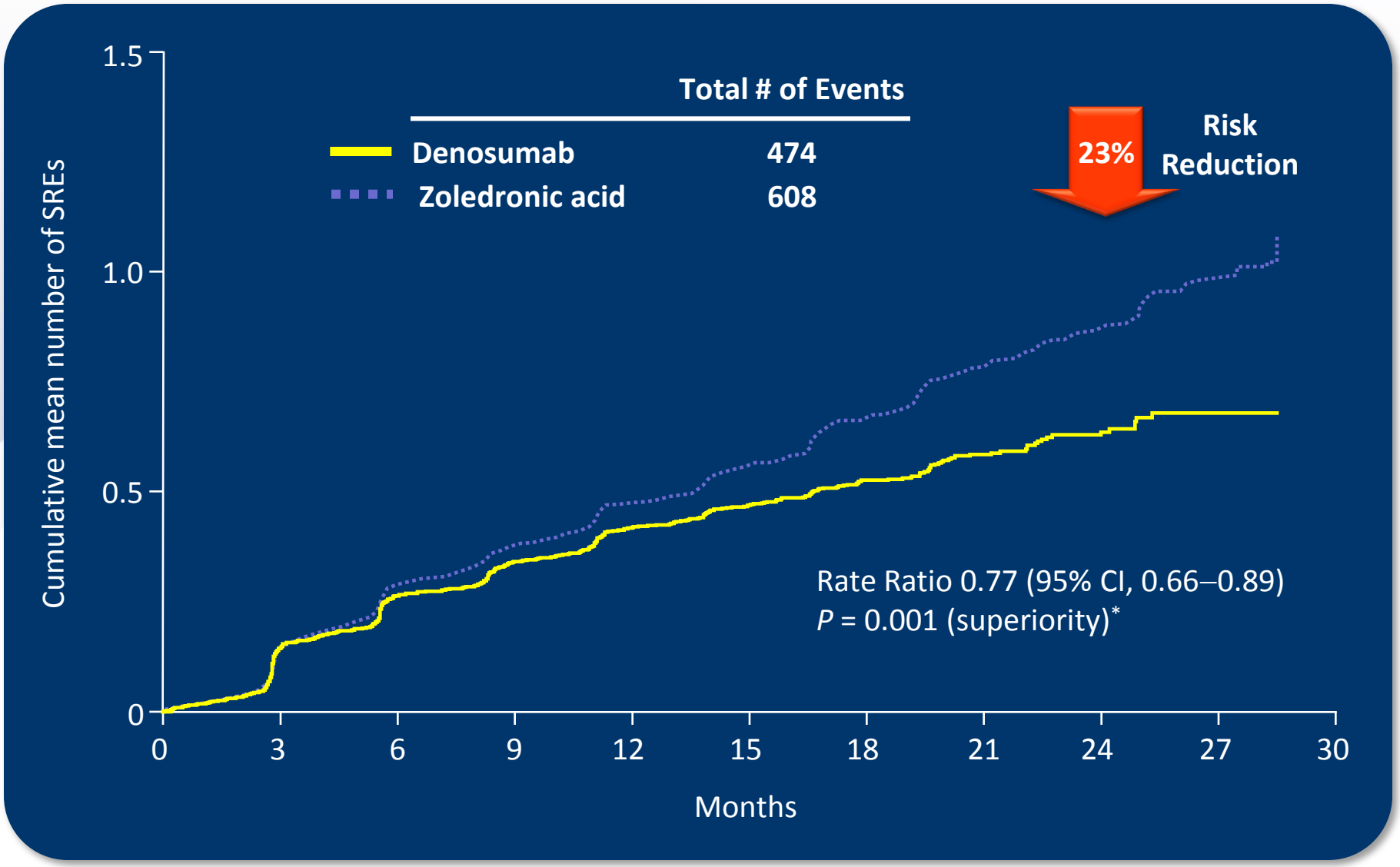


No. at risk										
IV zoledronic acid	1020	829	676	584	498	427	296	191	94	29
SC denosumab	1026	839	697	602	514	437	306	189	99	26

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

Linee Guida - aggiornamento AIOM 2013
Carcinoma mammario con metastasi ossee

Qualità Globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	Nelle pazienti affetta da carcinoma mammario con metastasi ossee alla prima diagnosi il trattamento con denosumab può essere utilizzato. **La valutazione complessiva della qualità delle evidenze ad oggi disponibili circa "l'efficacia di denosumab in pazienti affetta da carcinoma mammario con metastasi ossee alla prima diagnosi", la valutazione del rapporto tra i benefici ed i danni correlati e la formulazione della raccomandazione relativa al quesito posto, sono state analizzate secondo metodologia GRADE (vedere capitolo 12).*	**Positiva debole**

Il Denosumab è non inferiore ai bisfosfonati per quanto riguarda la prevenzione delle complicanze scheletriche Livello di Evidenza: 1++; Raccomandazione: clinica POSITIVA FORTE

Il denosumab è superiore all'acido zoledronico in termini di tempo al primo SRE e di tempo al primo e ai successivi SRE (Livello di evidenza 1+; Raccomandazione clinica: POSITIVA FORTE)

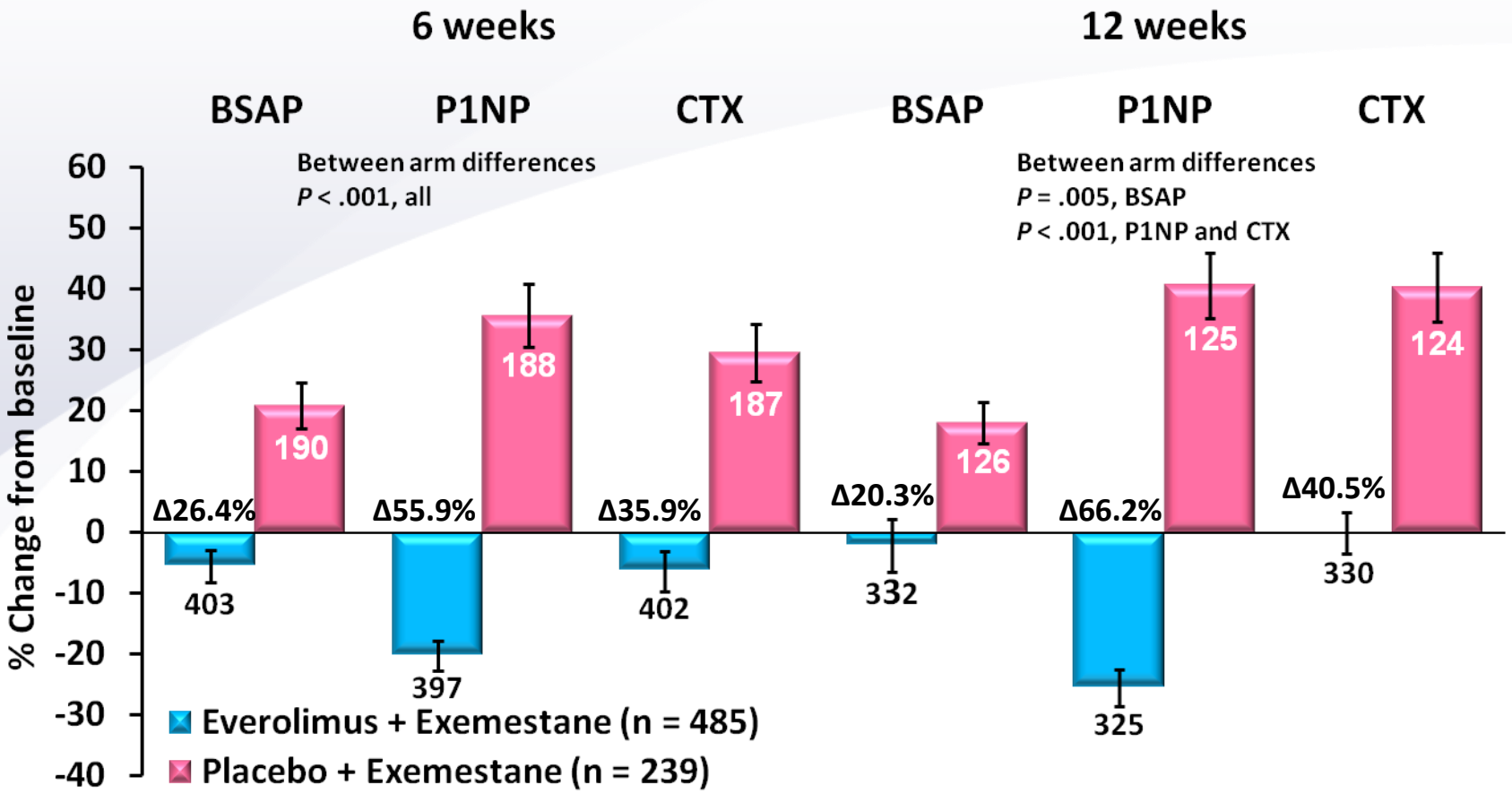
Take home message: I bisfosfonati sono efficaci nel ridurre le complicanze scheletriche, nel ritardare il tempo di comparsa delle complicanze scheletriche e nel ridurre il dolore osseo in pazienti con metastasi ossee secondarie a carcinoma mammario. Il Denosumab è una valida alternativa all'uso dei bisfosfonati per quanto riguarda la prevenzione delle complicanze scheletriche. Il Denosumab è superiore all'acido zoledronico in termini di ritardo della comparsa del primo e dei successivi SRE.

Effect of Everolimus on Bone Marker Levels and Progressive Disease in Bone in BOLERO-2

Michael Gnant, Jose Baselga, Hope S. Rugo, Shinzaburo Noguchi, Howard A. Burris, Martine Piccart, Gabriel N. Hortobagyi, Janice Eakle, Hirofumi Mukai, Hiroji Iwata, Matthias Geberth, Lowell L. Hart, Peyman Hadji, Mona El-Hashimy, Shantha Rao, Tetiana Taran, Tarek Sahmoud, David Lebwohl, Mario Campone, Kathleen I. Pritchard

Gnant M, et al. *JNCI*. 2013 February 19 Epub, doi: 10.1093/jnci/djt026.

EVE ⬇ Bone Turnover Marker Levels at 6 and 12 Weeks (Overall Population)

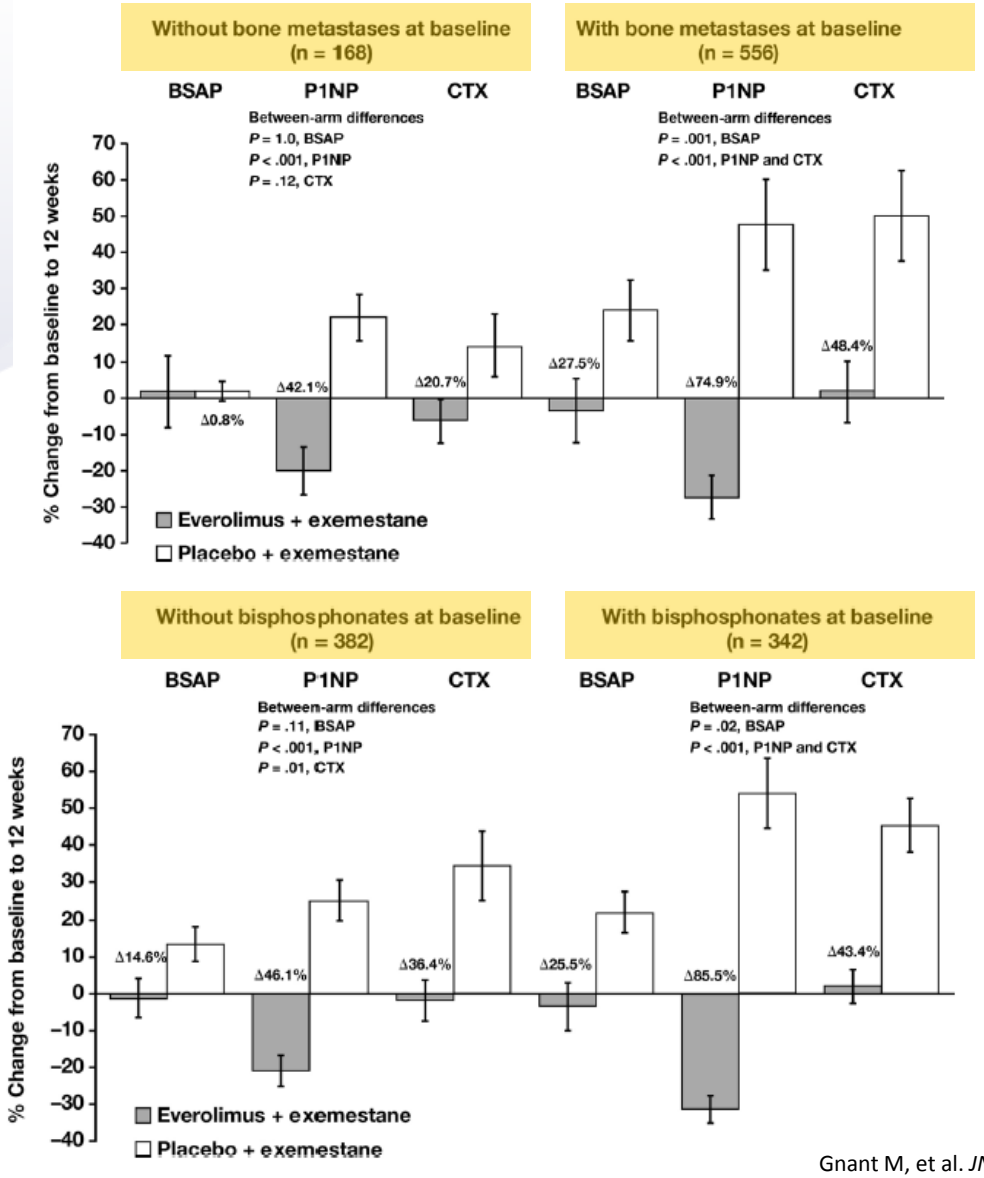


Data from full analysis set.
Proportions of patients with bone metastases or bisphosphonate use reflect the status at study entry among patients with baseline bone marker assessments.

Abbreviations: BSAP, bone-specific alkaline phosphatase; CTX, C-terminal cross-linking telopeptide of type I collagen; P1NP, amino-terminal propeptide of type I collagen.

Gnant M, et al. *JNCI*. 2013 February 19 Epub, doi: 10.1093/jnci/djt026.

Effect of Everolimus on Bone Marker Levels and progressive Disease in Bone in BOLERO-2



Gnant M, et al. *JNCI*. 2013 February 19 Epub, doi: 10.1093/jnci/djt026.

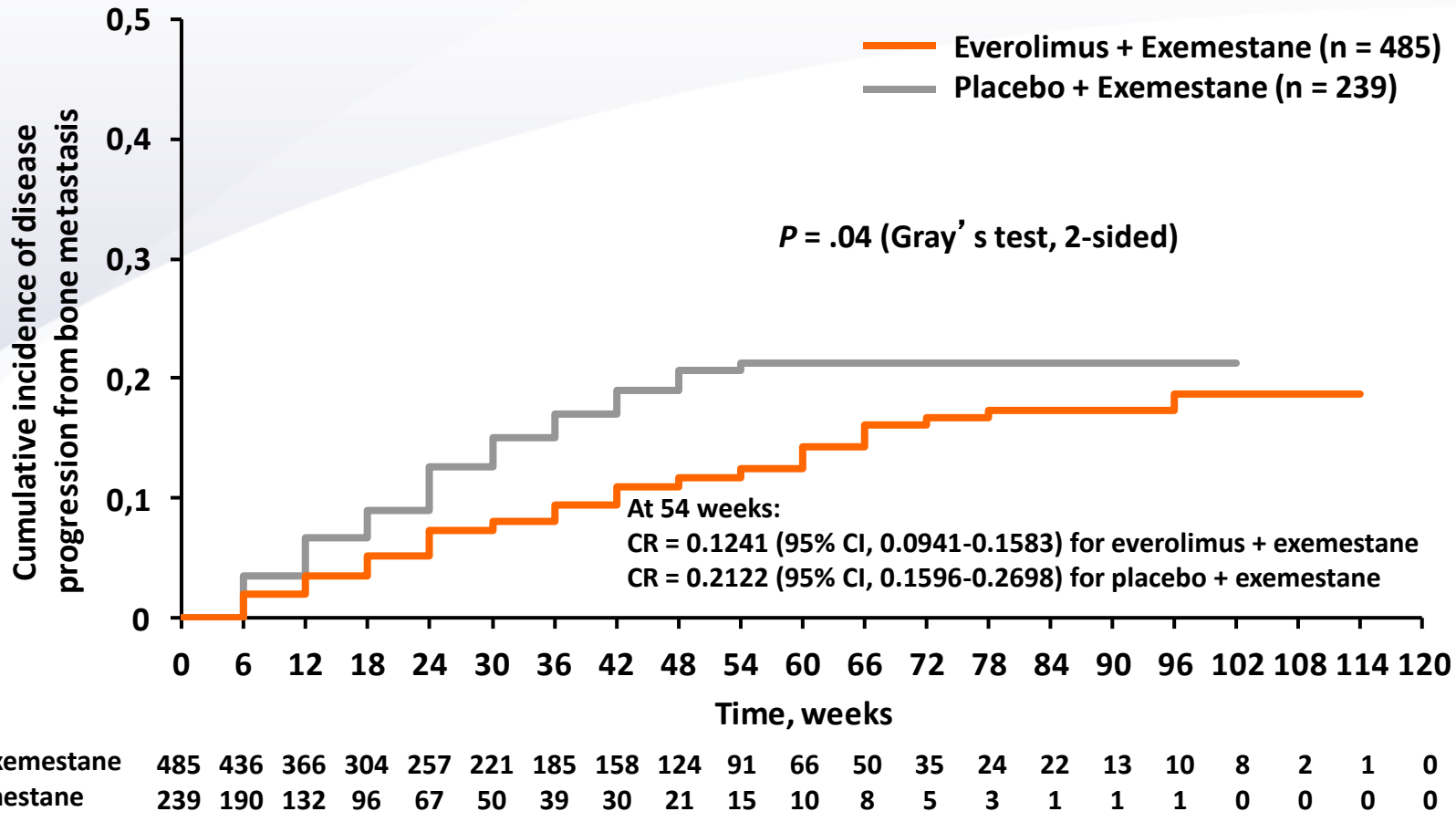
Bone-Related AEs at 18 Months' Follow-up
(Safety Population)

Adverse Event	Everolimus + Exemestane, n (%) (n = 482)		Placebo + Exemestane, n (%) (n = 238)	
	All Grades	Grade 3[a]	All Grades	Grade 3[a]
Any	16 (3.3)	0	10 (4.2)	4 (1.7)
Fractures	**2.3%**		**3.8%**	
Pathologic	0	0	3 (1.3)	1 (0.4)
Femur	0	0	2 (0.8)	2 (0.8)
Hip	0	0	1 (0.4)	1 (0.4)
Rib	7 (1.5)	0	1 (0.4)	0
Spinal	1 (0.2)	0	0	0
Spinal compression	2 (0.4)	0	0	0
Wrist	1 (0.2)	0	0	0
Pubis	0	0	1 (0.4)	0
Osteonecrosis	2 (0.4)	0	0	0
Osteonecrosis of the jaw[b]	2 (0.4)	0	1 (0.4)	0
Osteoporosis	2 (0.4)	0	0	0

[a] No grade 4 events were reported in either treatment arm.
[b] 1 of 3 patients who developed osteonecrosis of the jaw had received bisphosphonate treatment.

Abbreviation: AEs, adverse events.
Gnant M, et al. *JNCI*. 2013 February 19 Epub, doi: 10.1093/jnci/djt026.

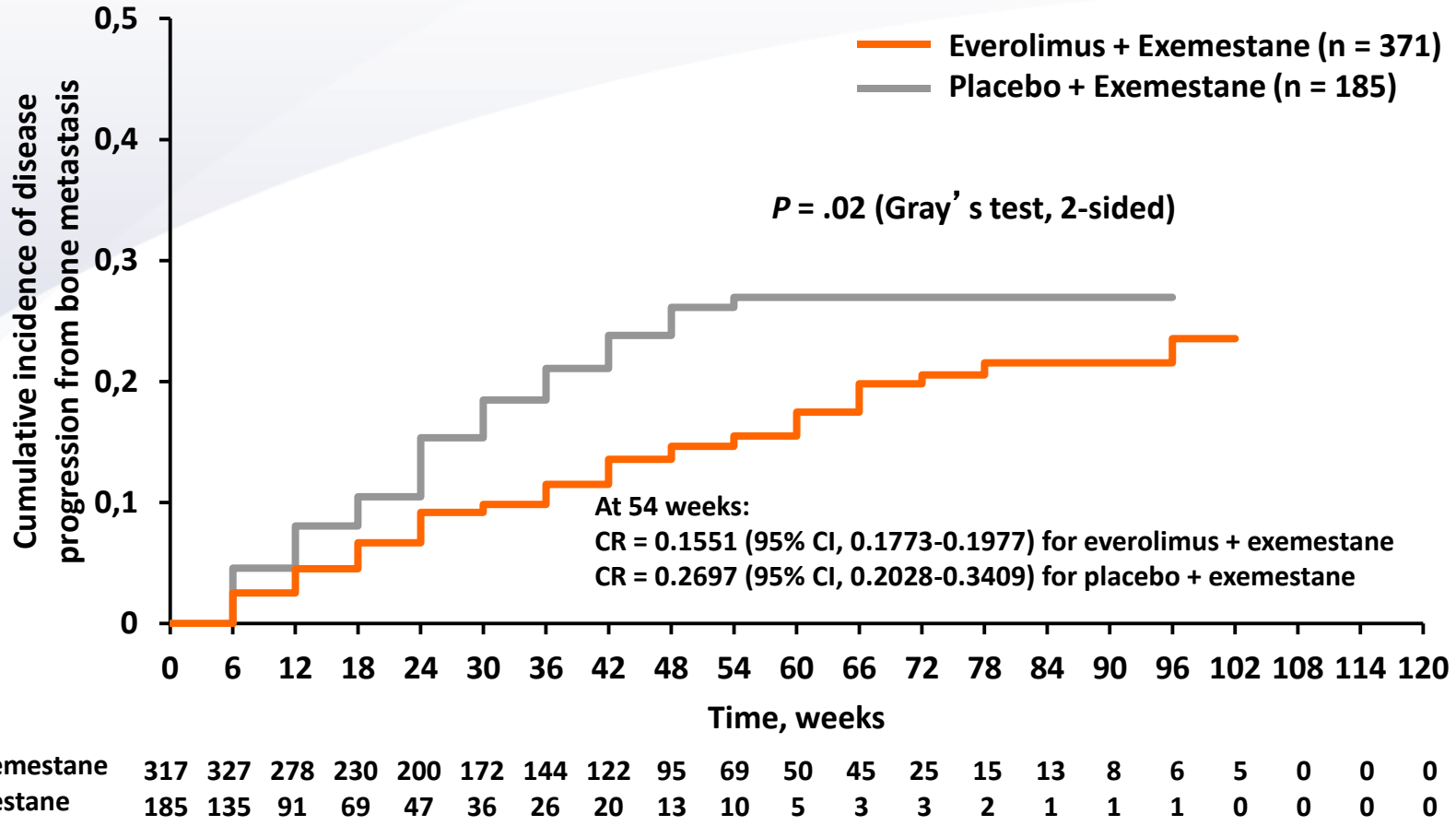
EVE ⬇ Disease Progression in Bone: Overall Population (N = 724)



Patients at risk																				
Everolimus + Exemestane	485	436	366	304	257	221	185	158	124	91	66	50	35	24	22	13	10	8	2	1	0
Placebo + Exemestane	239	190	132	96	67	50	39	30	21	15	10	8	5	3	1	1	1	0	0	0	0

Cumulative incidence of disease progression was determined using the competing risk method; exploratory P = .036 by Gray's test.
Abbreviations: CI, confidence interval; CR, competing risk estimate.
Gnant M, et al. JNCI. 2013 February 19 Epub, doi: 10.1093/jnci/djt026.

EVE ⬇ Disease Progression in Bone: Patients With Bone Metastases at Baseline (n = 556)



Patients at risk																				
Everolimus + Exemestane	317	327	278	230	200	172	144	122	95	69	50	45	25	15	13	8	6	5	0	0	0
Placebo + Exemestane	185	135	91	69	47	36	26	20	13	10	5	3	3	2	1	1	1	0	0	0	0

Cumulative incidence of disease progression was determined using the competing risk method; exploratory P = .0165 by Gray's test.
Abbreviations: CI, confidence interval; CR, competing risk estimate.
Gnant M, et al. JNCI. 2013 February 19 Epub, doi: 10.1093/jnci/djt026.

Nuove terapie ormonali e bone targeted therapies

- L'effetto "scheletrico" di abiraterone/enzalutamide/radio 223 come si inserisce con l'effetto "scheletrico" delle bone targeted therapies
- L'uno sostituisce l'altro?
- Esiste un razionale nell'associare l'utilizzo di entrambi?

Everolimus e bone targeted therapies

- L’effetto “scheletrico” dell’everolimus come si inserisce con l’effetto “scheletrico” delle bone targeted therapies
- L’uno sostituisce l’altro?
- Esiste un razionale nell’associare l’utilizzo di entrambi?

Grazie per la vostra attenzione