

# Le terapie integrate nel carcinoma della prostata: passato, presente e futuro

Alfredo Berruti

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Brescia



Sistema Socio Sanitario

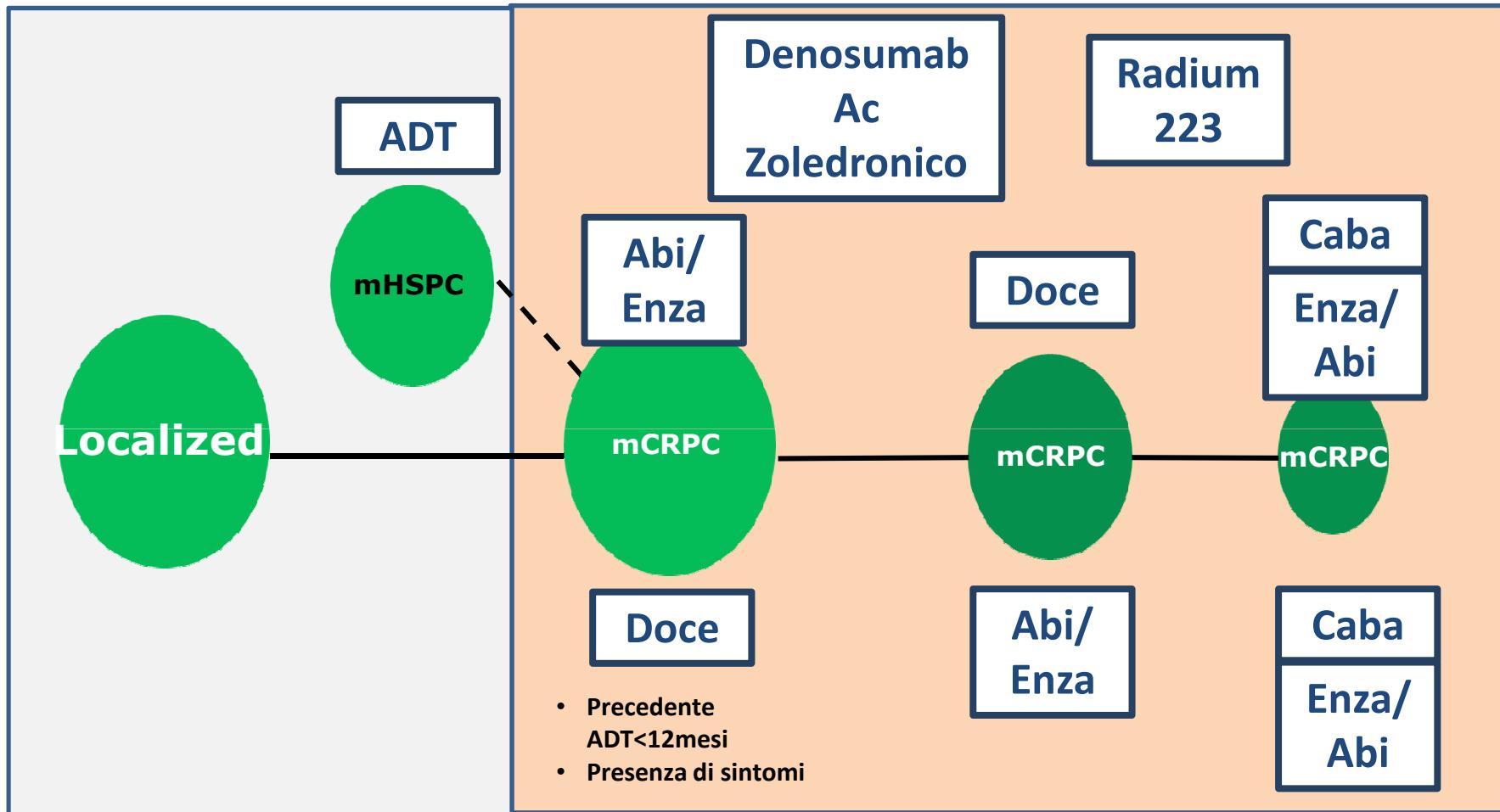


Regione  
Lombardia

ASST Spedali Civili



# Il trattamento del paziente con carcinoma prostatico



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## INCIDENCE OF SKELETAL COMPLICATIONS IN PATIENTS WITH BONE METASTATIC PROSTATE CANCER AND HORMONE REFRACTORY DISEASE: PREDICTIVE ROLE OF BONE RESORPTION AND FORMATION MARKERS EVALUATED AT BASELINE

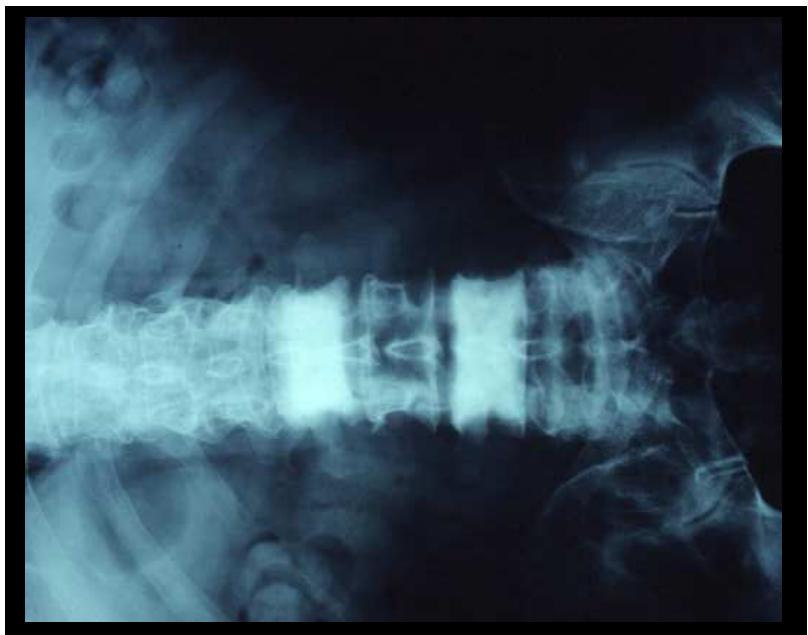
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ALFREDO BERRUTI, LUIGI DOGLIOTTI, RAFFAELLA BITOSSI, GIUSEPPE FASOLIS,  
GABRIELLA GORZEGNO, MAURIZIO BELLINA, MIRELLA TORTA, FRANCESCO PORPIGLIA,  
DARIO FONTANA AND ALBERTO ANGELI

*From the Dipartimento di Scienze Cliniche e Biologiche, Università di Torino, Clinica Medica, Oncologia Medica e Urologia, Azienda Ospedaliera San Luigi, Orbassano, Italy*

TABLE 3. *Skeletal complications*

	No. Pts. (%)
Vertebral body collapse	20 (17.9)
Spinal cord compression	7 (6.2)
Pathological fracture	10 (8.9)
Symptomatic hypercalcemia	1 (0.9)
Symptomatic hypocalcemia	1 (0.9)
Totals	34 (30.3)

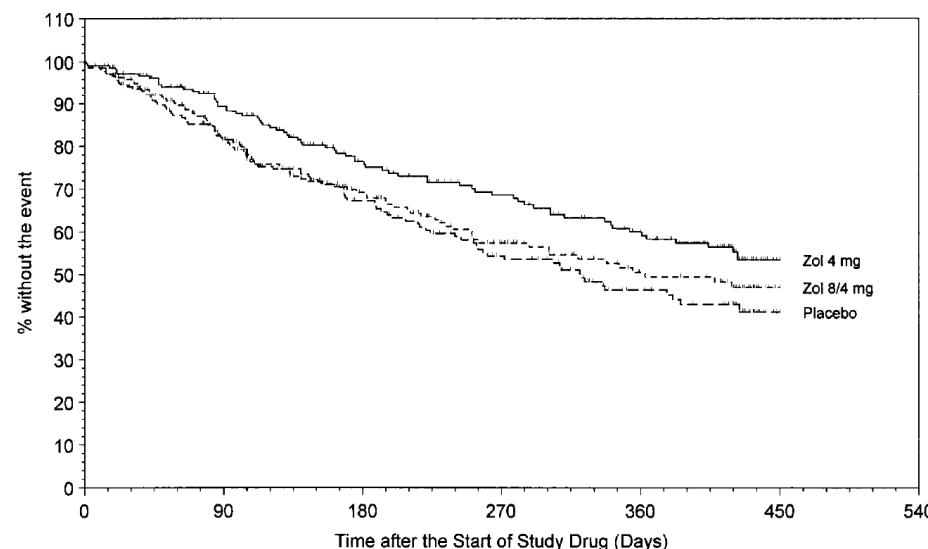


# A Randomized, Placebo-Controlled Trial of Zoledronic Acid in Patients With Hormone-Refractory Metastatic Prostate Carcinoma

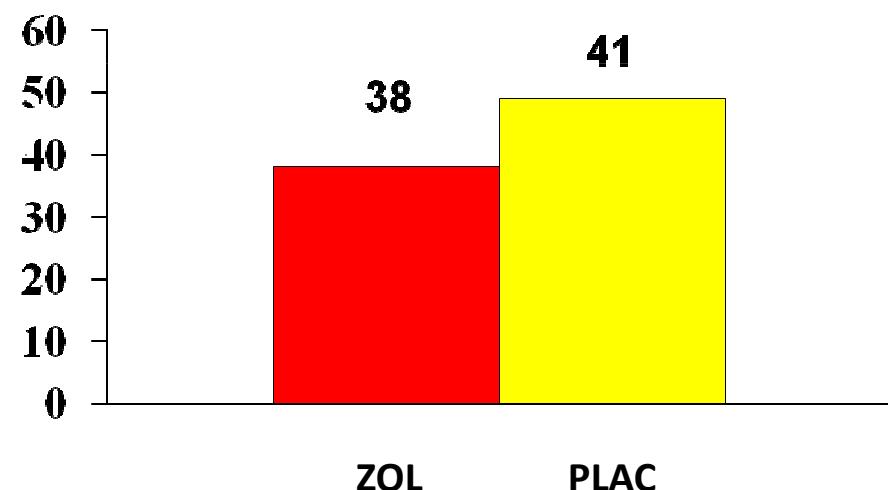
Fred Saad, Donald M. Gleason, Robin Murray, Simon Tchekmedyian,  
Peter Venner, Louis Lacombe, Joseph L. Chin, Jeferson J. Vinholes,  
J. Allen Goas, Bee Chen

For the Zoledronic Acid Prostate Cancer Study Group

Time to SRE



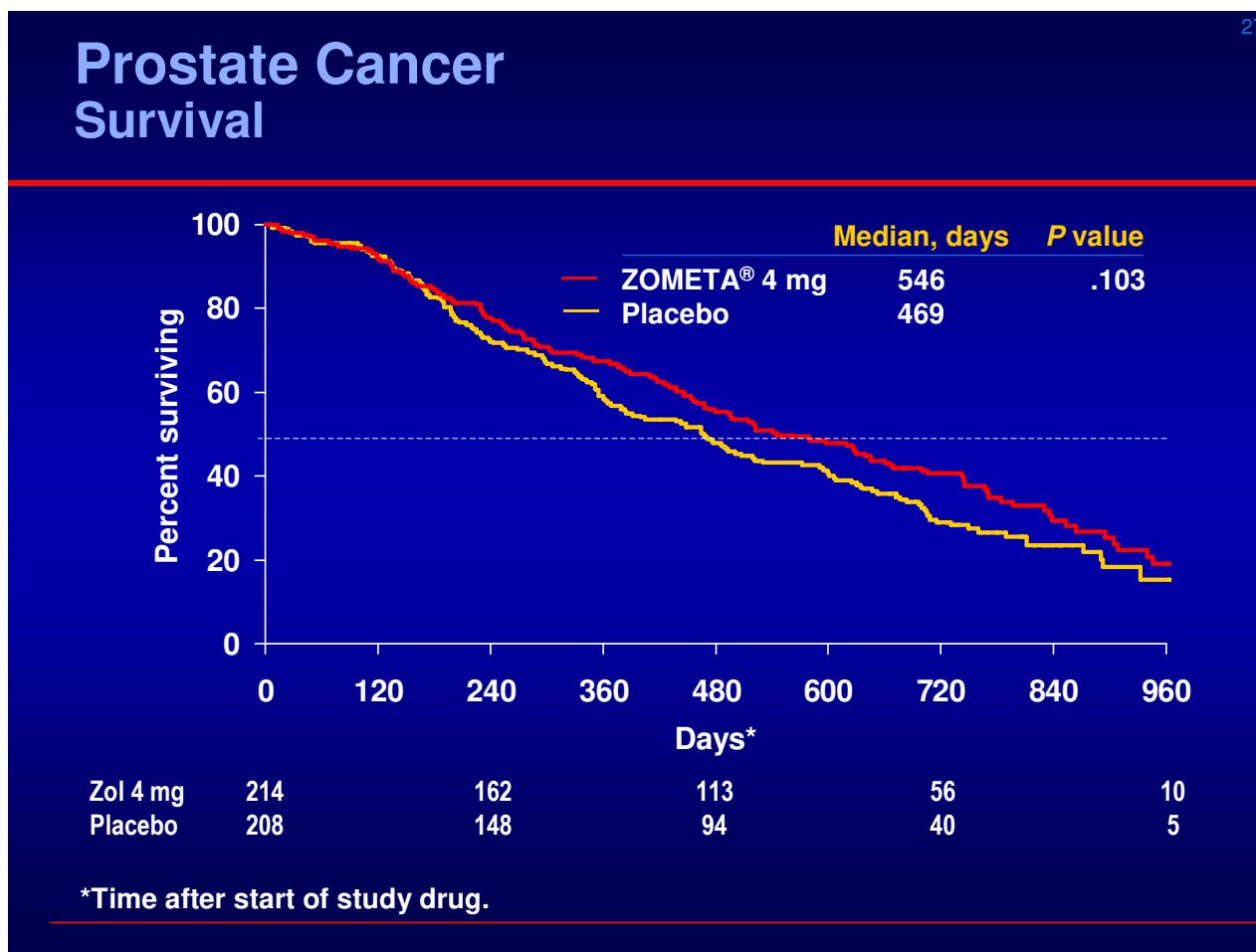
Proportion of SRE



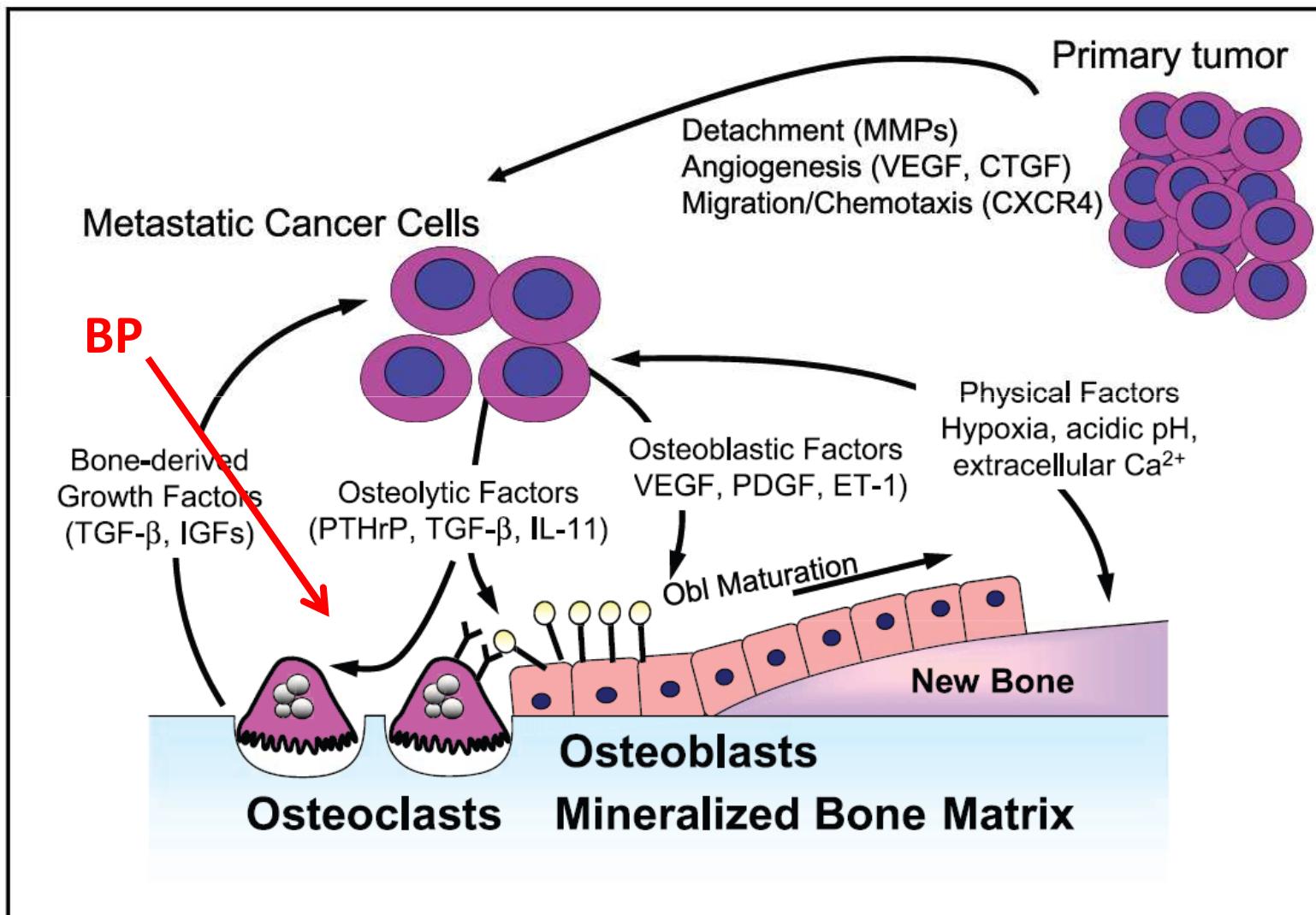
# A Randomized, Placebo-Controlled Trial of Zoledronic Acid in Patients With Hormone-Refractory Metastatic Prostate Carcinoma

Fred Saad, Donald M. Gleason, Robin Murray, Simon Tchekmedyian,  
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For the Zoledronic Acid Prostate Cancer Study Group



# THE VICIOUS CIRCLE

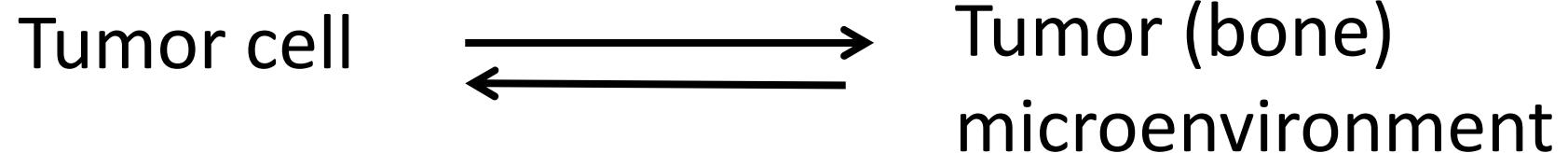


Kingsley LA et al Mol Cancer Ther 2007;6(10):2609–2617

## **Novel Therapies for Metastatic Castrate-Resistant Prostate Cancer**

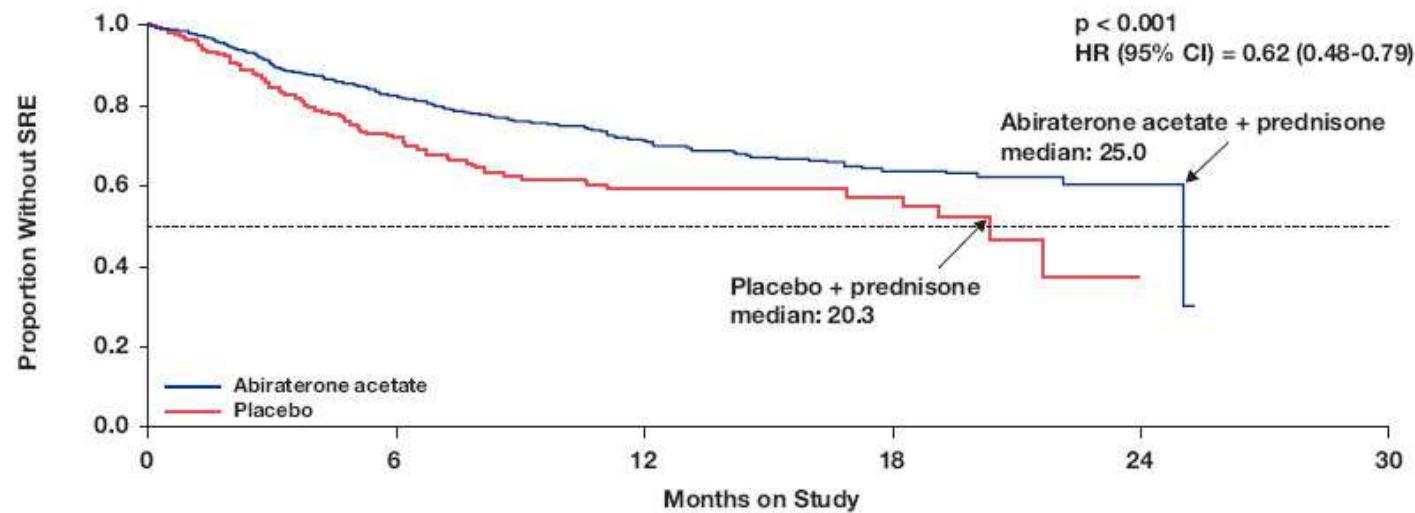
Farshid Dayyani, Gary E. Gallick, Christopher J. Logothetis, Paul G. Corn

### Targeting



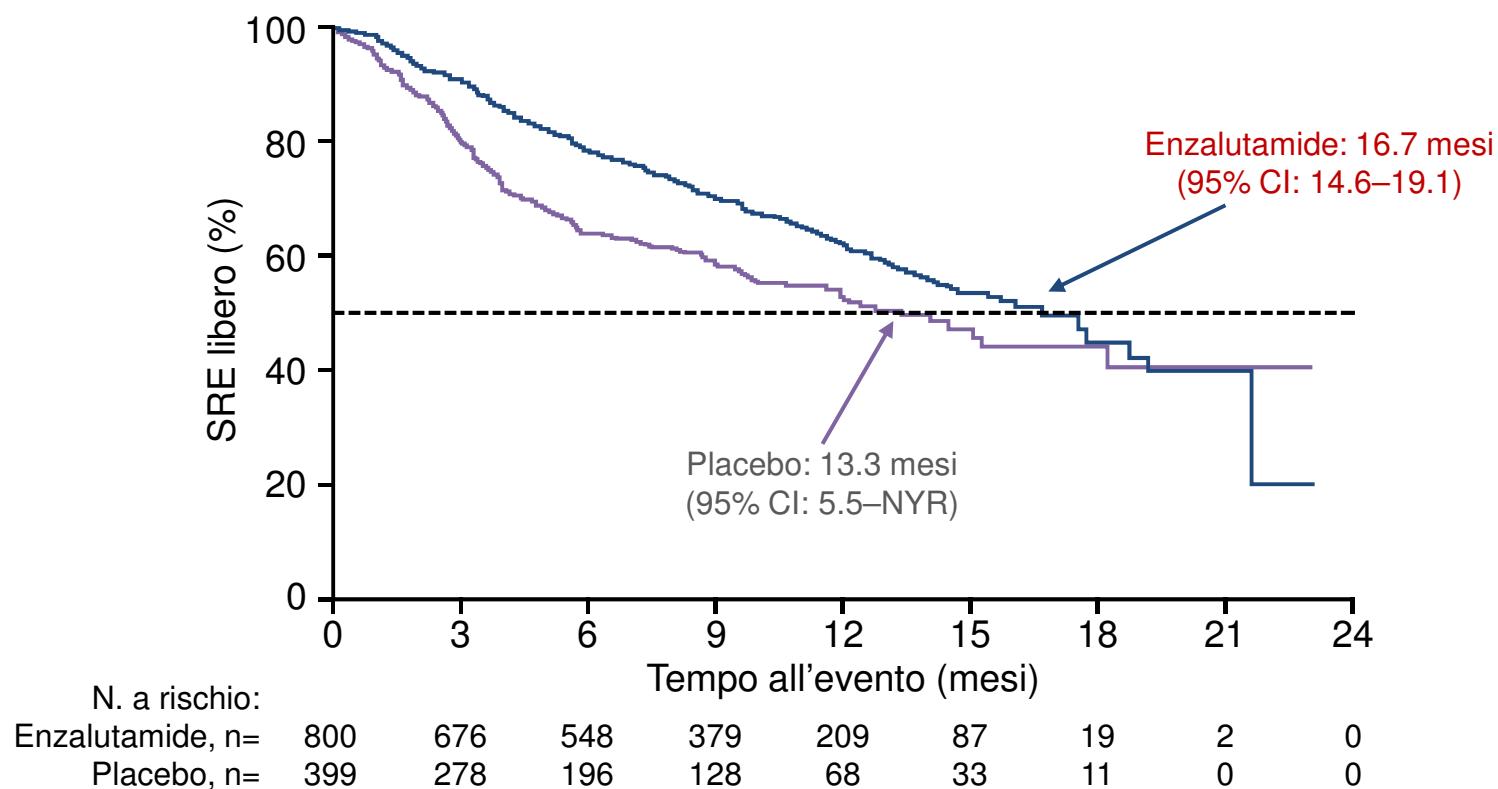
# Drugs targeting AR and SRE prevention

## Abiraterone



# Enzalutamide: Tempo al primo SRE

- Il tempo di insorgenza del primo SRE è stato significativamente ritardato da enzalutamide rispetto a placebo:
  - 16.7 versus 13.3 mesi (HR=0.69, 95% CI: 0.57–0.84; p<0.001)
  - 31% riduzione del rischio di SRE



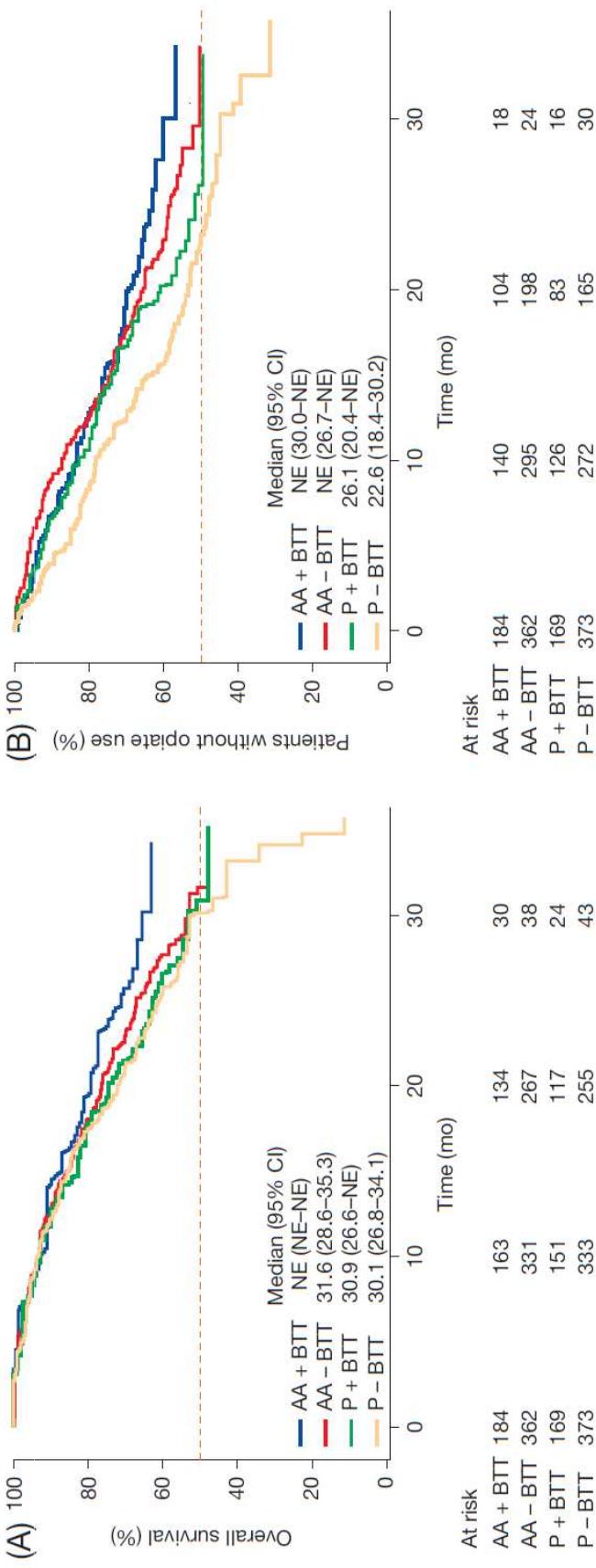
Tempo al primo SRE definito come il tempo di radioterapia, chirurgia ossea, fratture ossee patologiche, compressione del midollo spinale o il cambiamento di terapia antineoplastica per trattare il dolore osseo.

CI= intervallo di confidenza; HR= rapporto di rischio; NYR= non ancora raggiunto; SRE= eventi scheletrici correlati.

De Bono J, et al. Presented at ASCO 2012; Oral presentation 4519.

## Impact of Bone-targeted Therapies in Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer Patients Treated with Abiraterone Acetate: Post Hoc Analysis of Study COU-AA-302

Fred Saad<sup>a,\*</sup>, Neal Shore<sup>b</sup>, Hendrik Van Poppel<sup>c</sup>, Dana E. Rathkopf<sup>d</sup>, Matthew R. Smith<sup>e</sup>, Johann S. de Bono<sup>f</sup>, Christopher J. Logothetis<sup>g</sup>, Paul de Souza<sup>h</sup>, Karim Fizazi<sup>i</sup>, Peter F.A. Mulders<sup>j</sup>, Paul Mainwaring<sup>k</sup>, John D. Hainsworth<sup>l</sup>, Tomasz M. Beer<sup>m</sup>, Scott North<sup>n</sup>, Yves Fradet<sup>o</sup>, Thomas A. Griffin<sup>p</sup>, Peter De Porre<sup>q</sup>, Amit Londhe<sup>r</sup>, Thian Kheoh<sup>s</sup>, Eric J. Small<sup>t</sup>, Howard I. Scher<sup>d,u</sup>, Arturo Molina<sup>u</sup>, Charles J. Ryan<sup>t</sup>

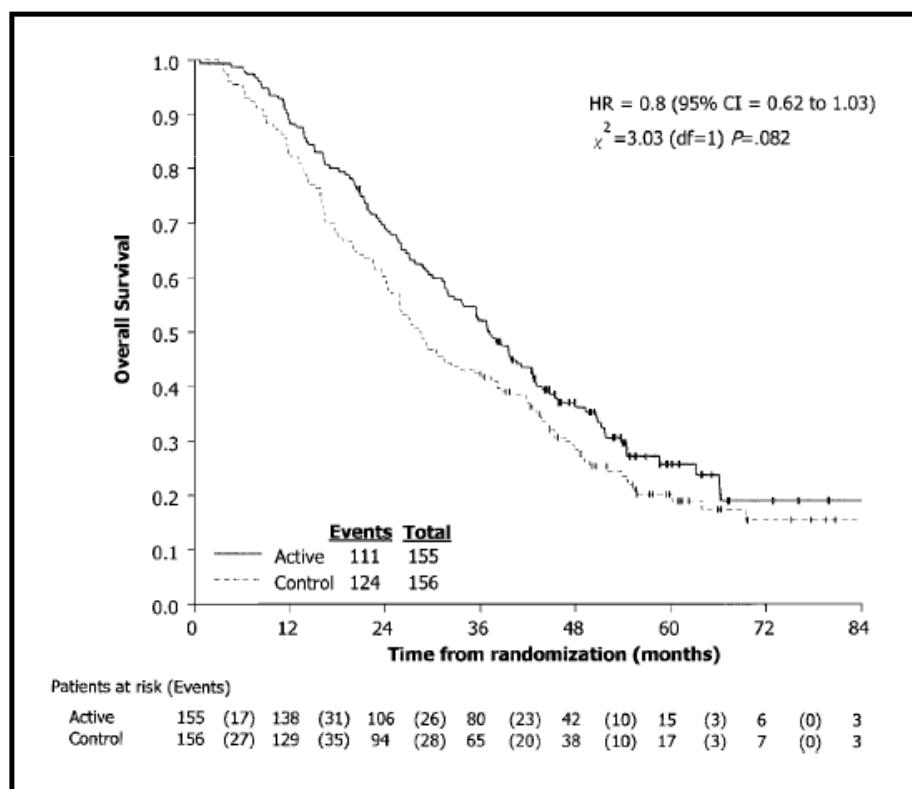
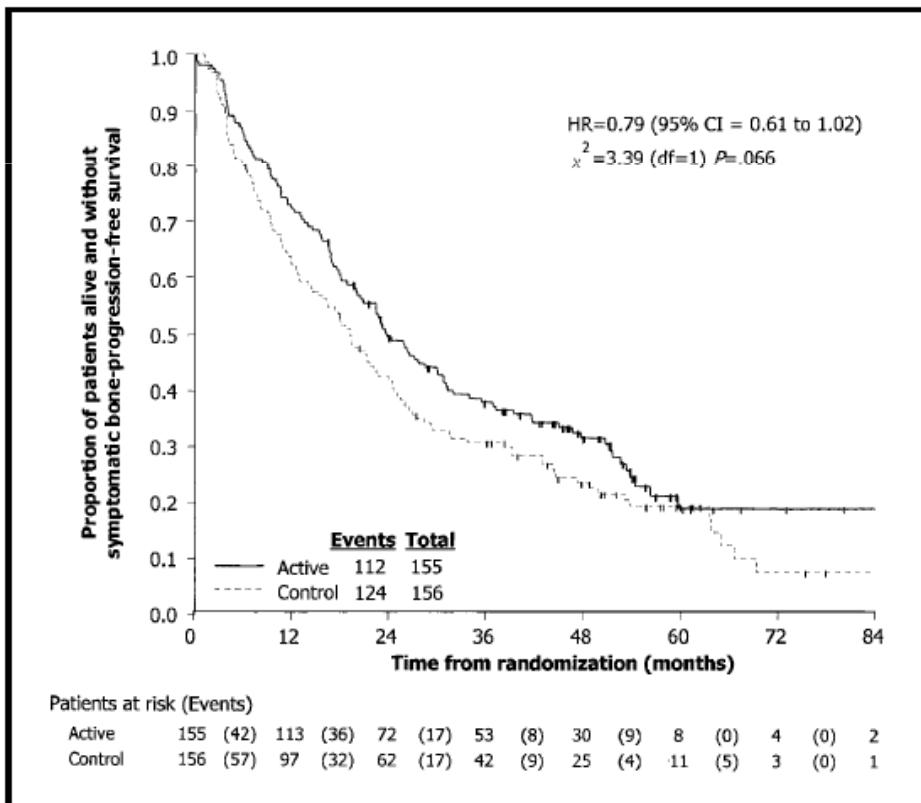


# A Double-Blind, Placebo-Controlled, Randomized Trial of Oral Sodium Clodronate for Metastatic Prostate Cancer (MRC PR05 Trial)

David P. Dearnaley, Matthew R. Sydes, Malcolm D. Mason, Mark Stott,  
Christopher S. Powell, Anne C. R. Robinson, Peter M. Thompson, Leslie E. Moffat,  
Sharon L. Naylor, Mahesh K. B. Parmar

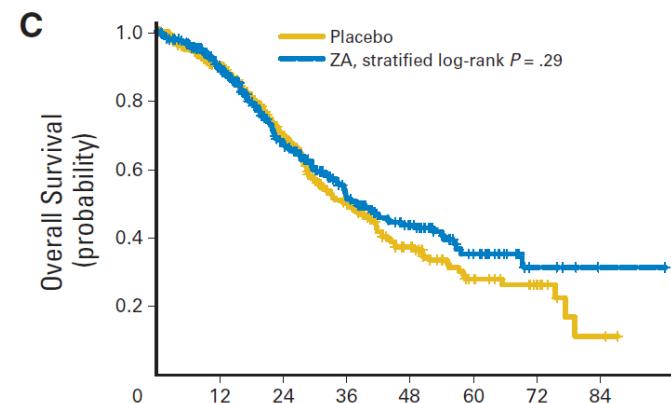
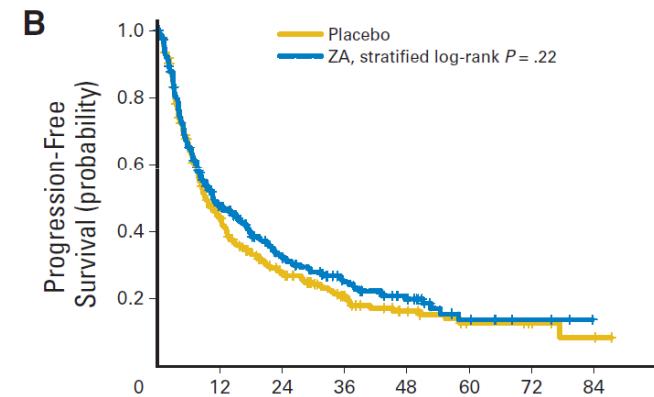
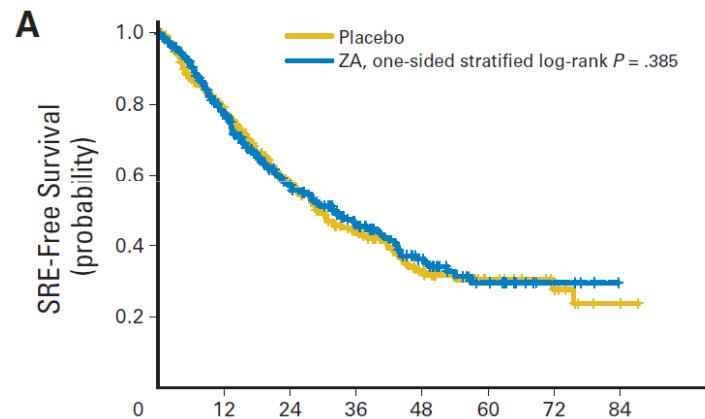
And the MRC PR05 Collaborators

J Natl Cancer Inst 2003;95:1300–11



## 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



**Is Time to First Skeletal-Related Event the Best Primary End Point in the Assessment of Bisphosphonate Efficacy in Patients With Castration-Sensitive Prostate Cancer?**

Smith et al, Z was planned to be administered to all patients at the onset of castration-resistant disease, but this was not the case with clodronate in the MRC study.

In the pivotal randomized clinical study in patients with castration-resistant prostate cancer and bone metastases,<sup>1</sup> Z administration was associated with a nonsignificant survival improvement compared with placebo. So the exposure to Z during the castration-resistant phase of patients who were randomly assigned to the placebo arm in the study by Smith et al<sup>2</sup> may have been responsible for the

**Francesca Valcamonico**

University of Brescia, Azienda Ospedaliera Spedali Civili, Brescia, Italy

**Fausto Petrelli**

Azienda Ospedaliera Treviglio, Treviglio, Italy

**Laura Ferrari, Vittorio Ferrari, and Salvatore Grisanti**

University of Brescia, Azienda Ospedaliera Spedali Civili, Brescia, Italy

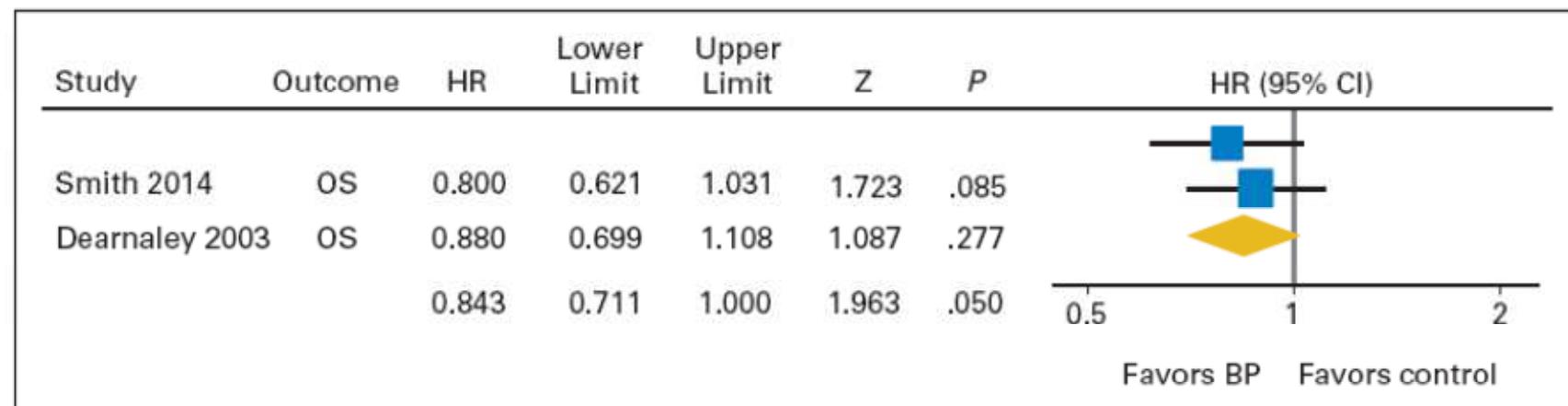
**Sandro Barni**

Azienda Ospedaliera Treviglio, Treviglio, Italy

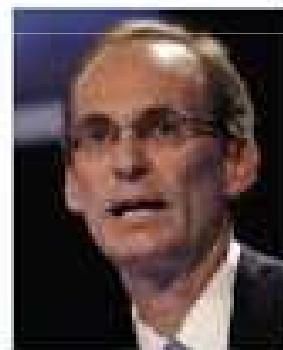
**Alfredo Berruti**

University of Brescia, Azienda Ospedaliera Spedali Civili, Brescia, Italy

**September 2014**



I absolutely  
disagree!!



*Matthew Smith  
MD, PhD*

## Zoledronic acid: Survival



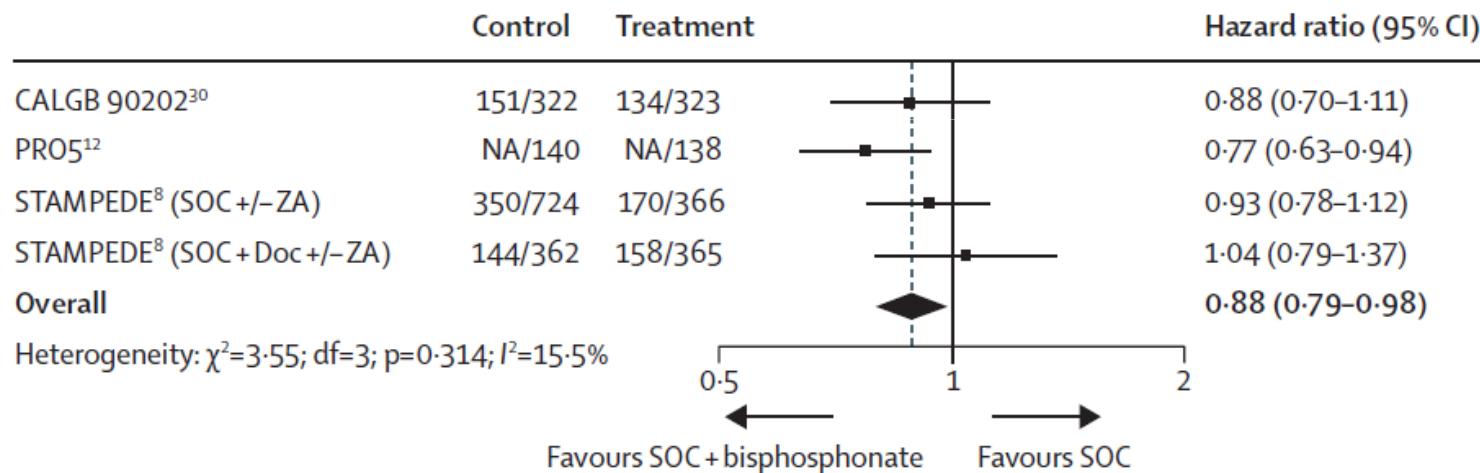
# Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data



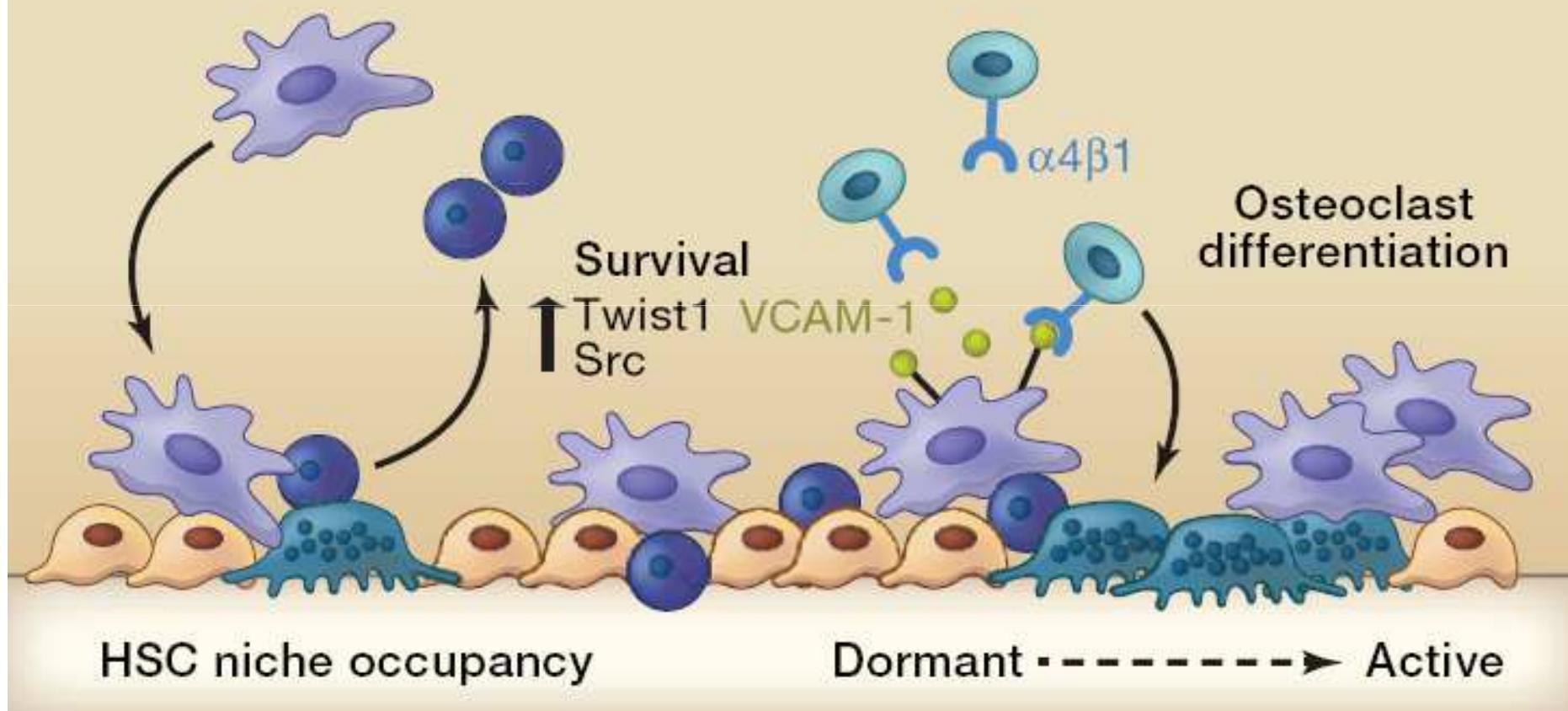
Claire L Vale\*, Sarah Burdett\*, Larysa H M Rydzewska, Laurence Albiges, Noel W Clarke, David Fisher, Karim Fizazi, Gwenaelle Gravis, Nicholas D James, Malcolm D Mason, Mahesh K B Parmar, Christopher J Sweeney, Matthew R Sydes, Bertrand Tombal, Jayne F Tierney, for the STOpCaP Steering Group



A



## Dormancy and relapse



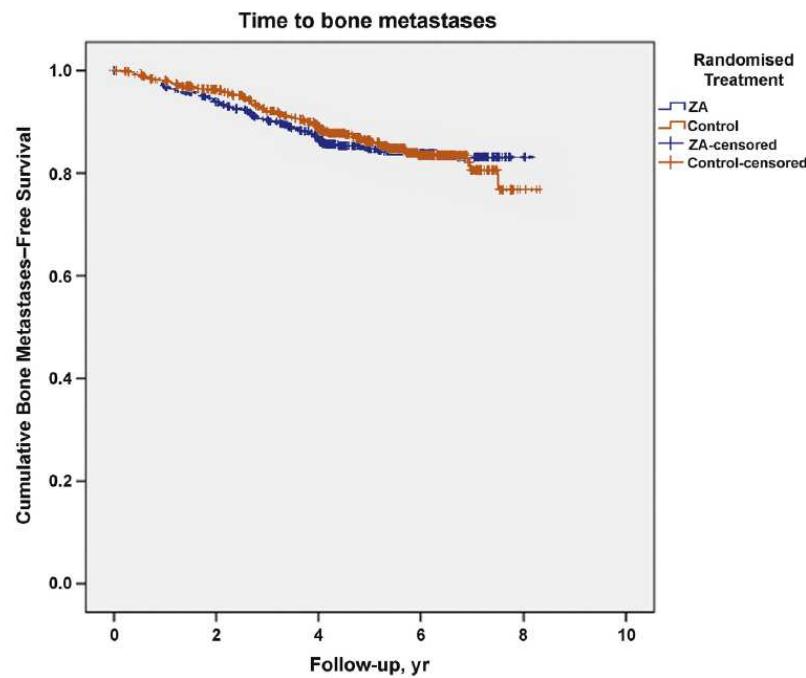


Platinum Priority – Prostate Cancer  
*Editorial by XXX on pp. x–y of this issue*

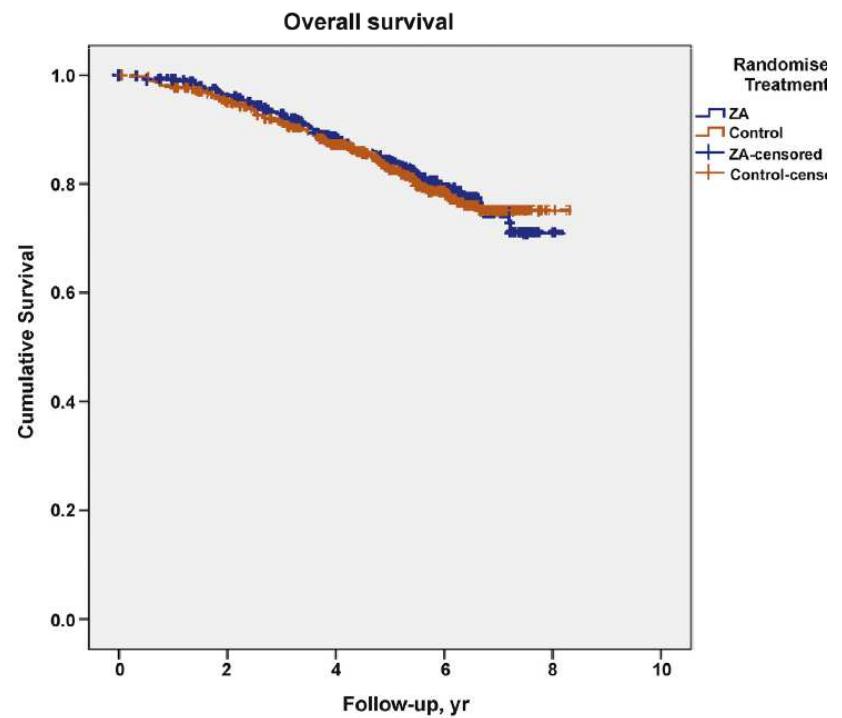
## Prevention of Bone Metastases in Patients with High-risk Nonmetastatic Prostate Cancer Treated with Zoledronic Acid: Efficacy and Safety Results of the Zometa European Study (ZEUS)

Manfred Wirth<sup>a</sup>, Teuvo Tammela<sup>b</sup>, Virgilio Cicalese<sup>c</sup>, Francisco Gomez Veiga<sup>d</sup>, Karl Delaere<sup>e</sup>, Kurt Miller<sup>f</sup>, Andrea Tubaro<sup>g</sup>, Matthias Schulze<sup>h</sup>, Frans Debruyne<sup>i</sup>, Hartwig Huland<sup>j</sup>, Anup Patel<sup>k</sup>, Frederic Lecouvet<sup>k</sup>, Christien Caris<sup>l</sup>, Wim Witjes<sup>l,\*</sup>

<sup>a</sup>University Clinic Carl Gustav Carus, Urology, Dresden, Germany; <sup>b</sup>Tampere University Hospital and University of Tampere, Urology, Tampere, Finland; <sup>c</sup>Azienda Ospedaliera "S. Giuseppe Moscati", Urology, Avellino, Italy; <sup>d</sup>A Coruña University Hospital, Urology, A Coruña, Spain; <sup>e</sup>Atrium Medisch Centrum, Urology, Heerlen, The Netherlands; <sup>f</sup>Charité, Universitätsmedizin, Urology, Berlin, Germany; <sup>g</sup>"San'Andrea Hospital", Urology, Rome, Italy; <sup>h</sup>Private Practice Schulze, Markkleeberg, Germany; <sup>i</sup>Andros Clinic, Urology, Arnhem, The Netherlands; <sup>j</sup>University Krankenhaus Eppendorf, Urology, Hamburg, Germany; <sup>k</sup>Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Radiology, Brussels, Belgium; <sup>l</sup>European Association of Urology, Research Foundation, Arnhem, The Netherlands



Eur Urol 2014

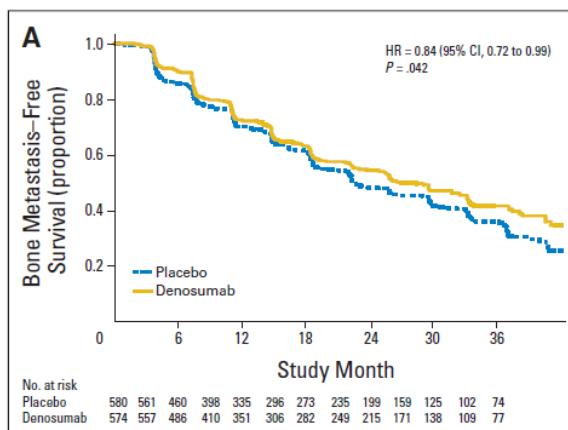


Denosumab and Bone Metastasis-Free Survival in Men  
With Nonmetastatic Castration-Resistant Prostate Cancer:  
Exploratory Analyses by Baseline Prostate-Specific Antigen  
Doubling Time

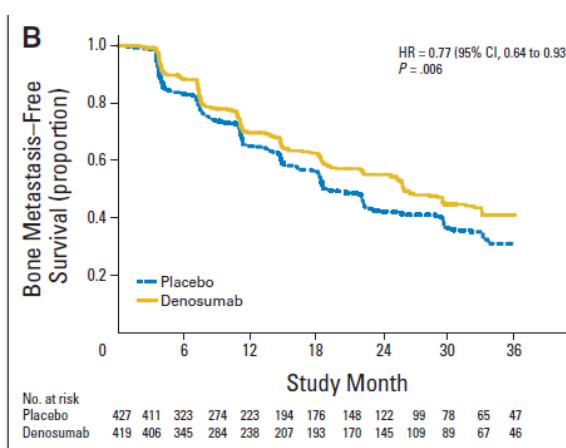
Matthew R. Smith, Fred Saad, Stephane Oudard, Neal Shore, Karim Fizazi, Paul Sieber, Bertrand Tombal,  
Ronaldo Damiao, Gavin Marx, Kurt Miller, Peter Van Veldhuizen, Juan Morote, Zhishen Ye, Roger Dansey,  
and Carsten Goessl

**PSA DT**

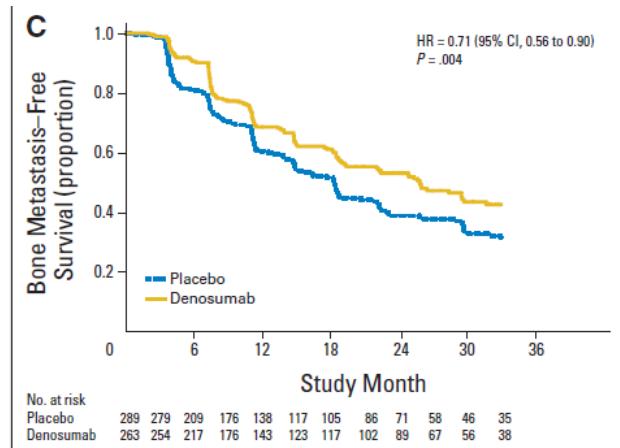
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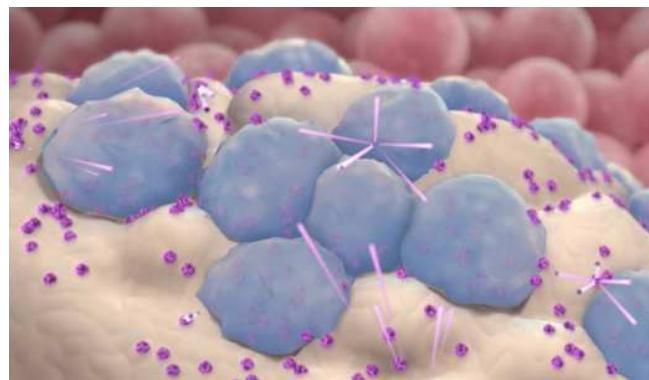
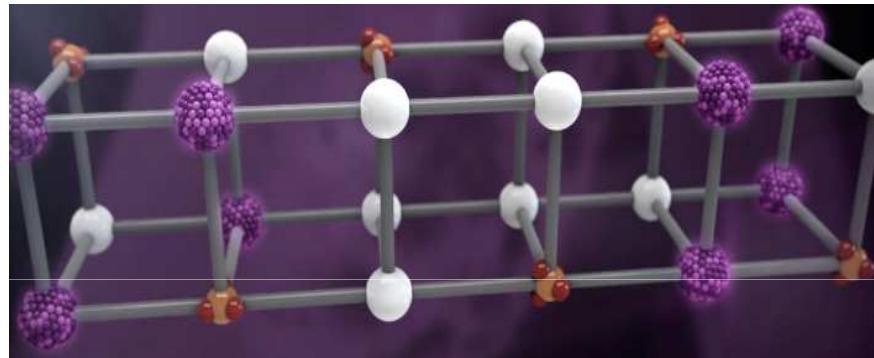
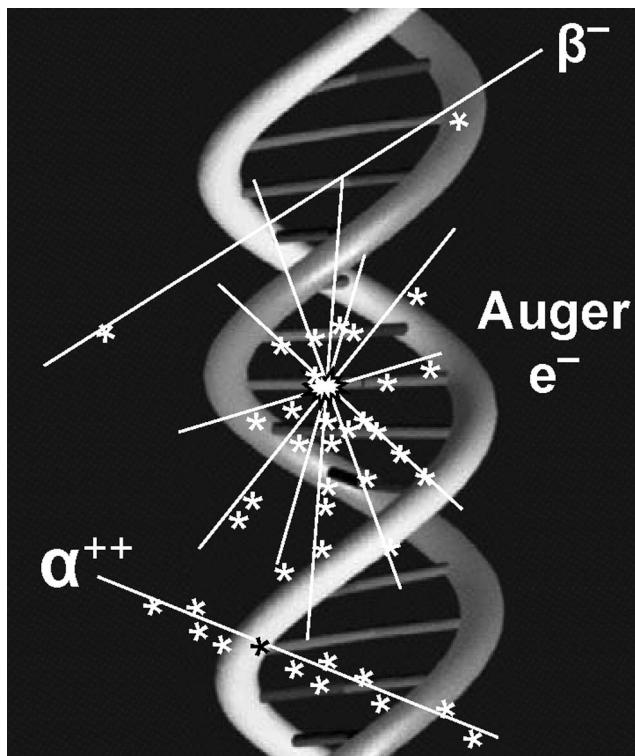


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# Mechanism of action of Radium-223

1. R223 mimics calcium and is incorporated in areas of new bone formation (complexes of hydroxyapatite)
2. R223 emits alpha-particles with high efficiency (multiple double-strands DNA breaks) and in a short range (<10 cell diameter)



# INCREMENTO IN SOPRAVVIVENZA

The NEW ENGLAND  
JOURNAL of MEDICINE

ESTABLISHED IN 1821

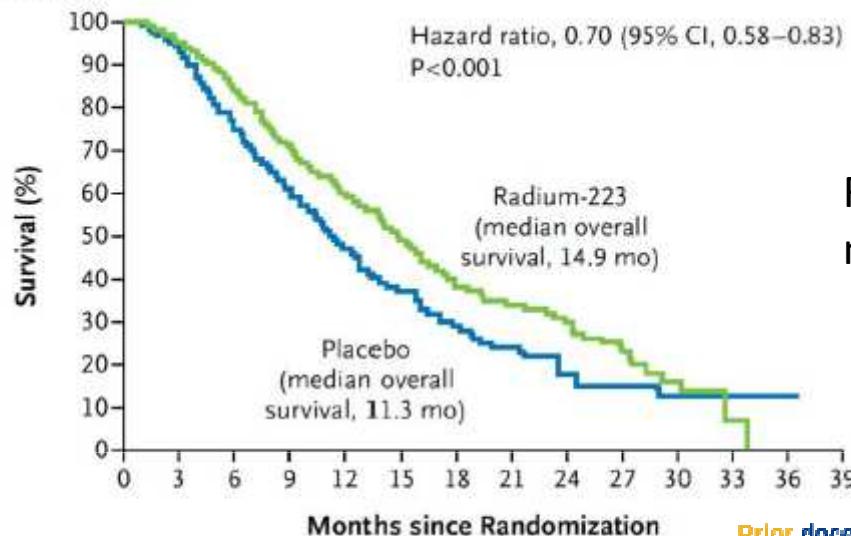
JULY 18, 2013

VOL. 309 NO. 3

## Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

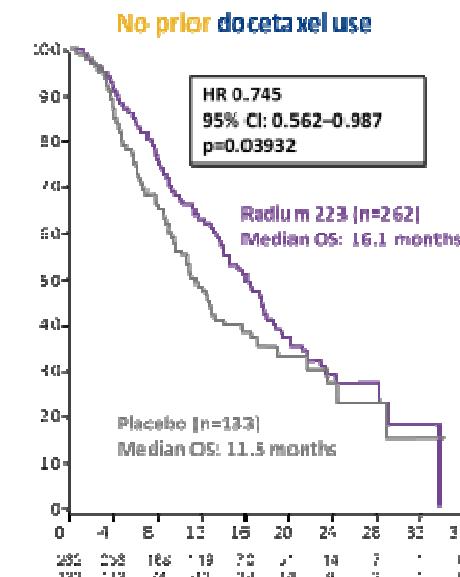
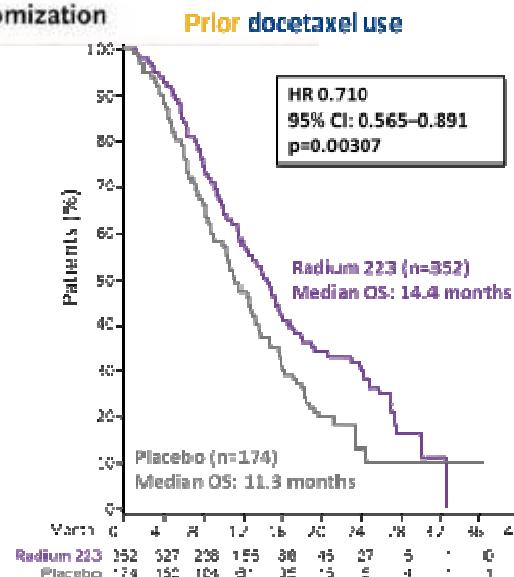
C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Tossi, A. Chodacki, P. Wieschno, J. Logue, M. Seike, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottsmaier, N.D. James, A. Sollberg, I. Syridius, J. Klement, S. Wedel, S. Boermer, M. Dall'Oglio, L. Franzen, R. Coleman, N.J. Vogelzang, C.G. O'Strian-Tean, K. Staudacher, J. Garcia-Vargas, M. Shan, O.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators<sup>a</sup>

### A Overall Survival



Riduzione del 30% del rischio di morte

Efficacia sia in pre- che post-docetaxel



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

Vogelzang NJ, et al. J Clin Oncol. 31, 2013 (suppl; abstr 5068).

# Fattori predittivi di efficacia in corso di Radium 223

## Median change from baseline to 4 weeks after last injection (week 16)

	Radium 223	Placebo	P
Bone ALP*	-66%	+9%	< 0.0001
Total ALP*	-46%	+31%	< 0.0001
PINP*	-63%	+38%	< 0.0001
CTX-I†	-31%	+32%	0.002
ICTP†	+15%	+43%	0.011
PSA‡	-24%	+45%	0.003

ALP, alkaline phosphatase; CTX-I, cross-linked C-terminal telopeptides of type I collagen; ICTP, C-terminal telopeptides of type I collagen; PINP, amino-terminal procollagen propeptides of type.

\*Bone formation marker.

†Bone resorption marker.

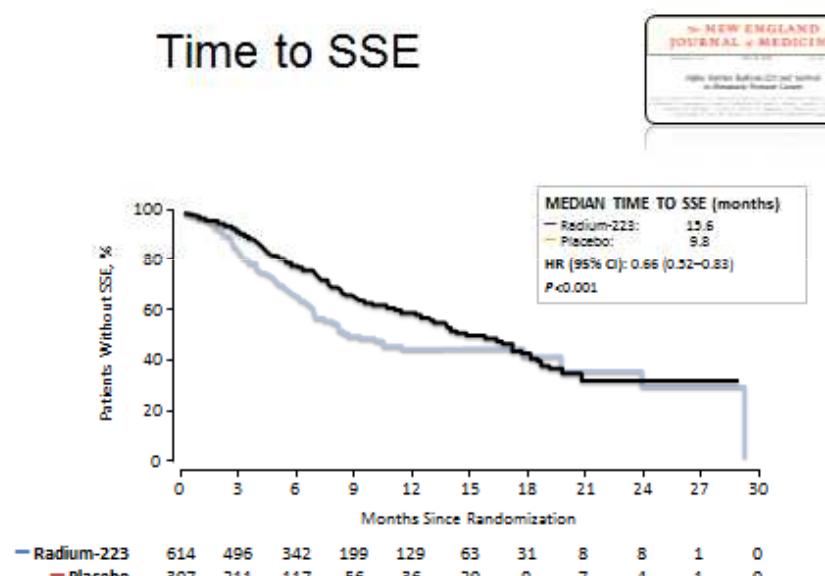
‡Prostate tumor growth marker.

Nilsson S, et al. *Lancet Oncol* 2007;8:587-594.

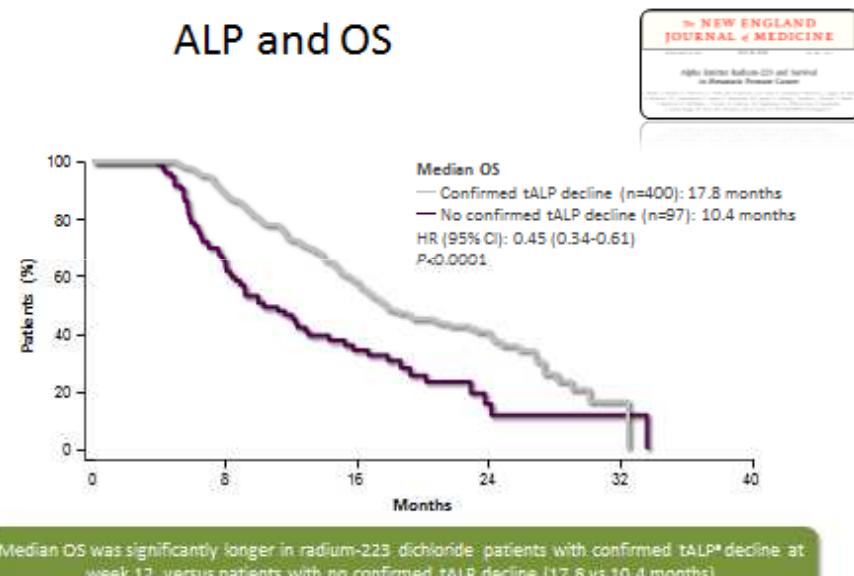
Nilsson S et al. *Lancet Oncology* 2007

# SECONDARY ENDPOINTS

Time to SSE



ALP and OS



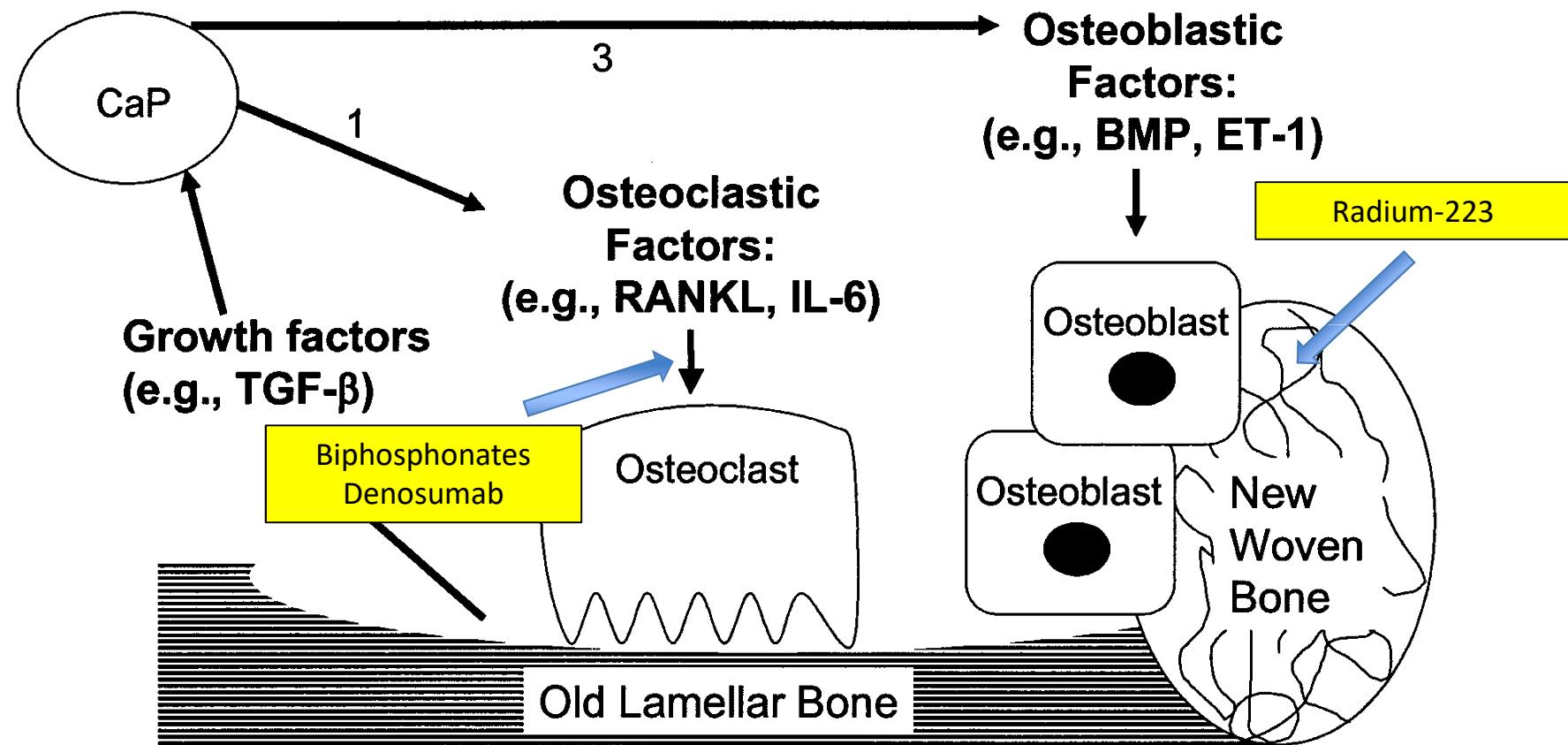
SSE: standard of care; CI, confidence interval; HR, hazard ratio; SSE, symptomatic skeletal event.

\* Confirmed tALP decline was defined as any decrease from baseline at week 12, confirmed at week later.

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

Sator O, et al. J Clin Oncol. 2013;31(suppl). Abstract 5000.

## Mechanism of action of Radium-223

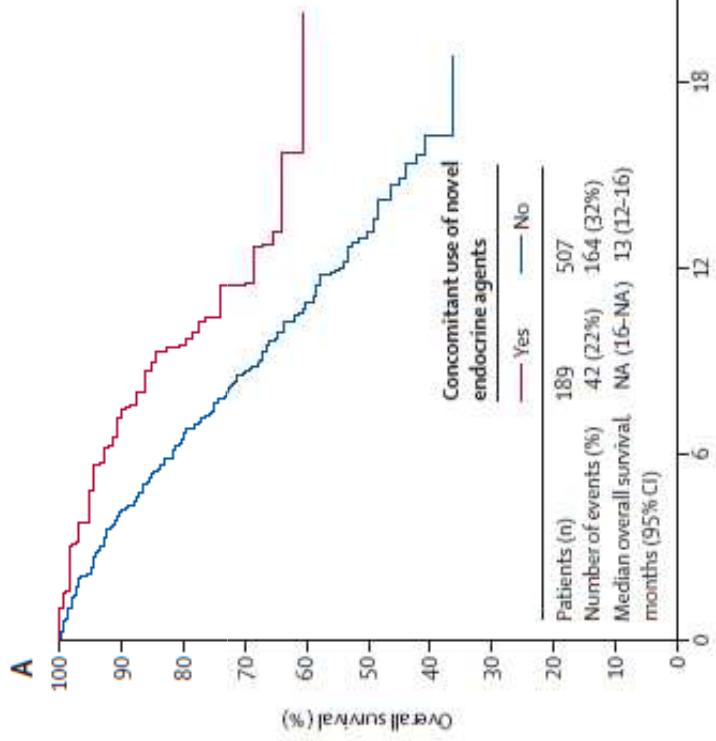




# Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial

Fred Saad, Joan Carles, Silke Gilissen, Axel Heidenreich, Daniel Heinrich, Jeremy Gratt, Jérémie Lévy, Kurt Miller, Sten Nilsson, Oana Petreniciuc, Marcello Tucci, Manfred Wirth, Judith Federhofer, Joe M O'Sullivan, for the Radium-223 International Early Access Program Investigators\*

Lancet Oncol 2016; 17:1306-16



## EORTC protocol 1333-GUCG – PEACE III

"Studio randomizzato di fase 3 che confronta enzalutamide vs. la combinazione di Ra223 e enzalutamide in pazienti mCRPC con metastasi ossee, sintomatici o lievemente sintomatici".

Disegno dello Studio:

Fase 3, globale, multicentrico, prospettico,  
enzalutamide + Radium 223 vs enzalutamide

Pazienti:

Sample size stimato: 560 pazienti

Data prevista di fine studio:

Aprile 2021

### Obiettivi dello Studio

- Primary Endpoints:

- Valutare se la combinazione di ENZALUTAMIDE e Ra223 migliora il tempo alla progressione radiologica (rPFS1) rispetto ad ENZALUTAMIDE come agente singolo

- Secondary endpoints:

- Valutare se la combinazione ENZALUTAMIDE e Ra223 offre vantaggi rispetto al solo ENZALUTAMIDE in termini di endpoint secondari di efficacia (OS, SSE ed altri), confrontare il profilo di sicurezza dei due approcci e documentare il loro impatto sul paziente: dolore e qualità della vita.



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### Radium-223 Dichloride and Abiraterone Acetate Compared to Placebo and Abiraterone Acetate for Men With Cancer of the Prostate When Medical or Surgical Castration Does Not Work and When the Cancer Has Spread to the Bone, Has Not Been Treated With Chemotherapy and is Causing no or Only Mild Symptoms (ERA 223)

This study is ongoing, but not recruiting participants.

Sponsor:

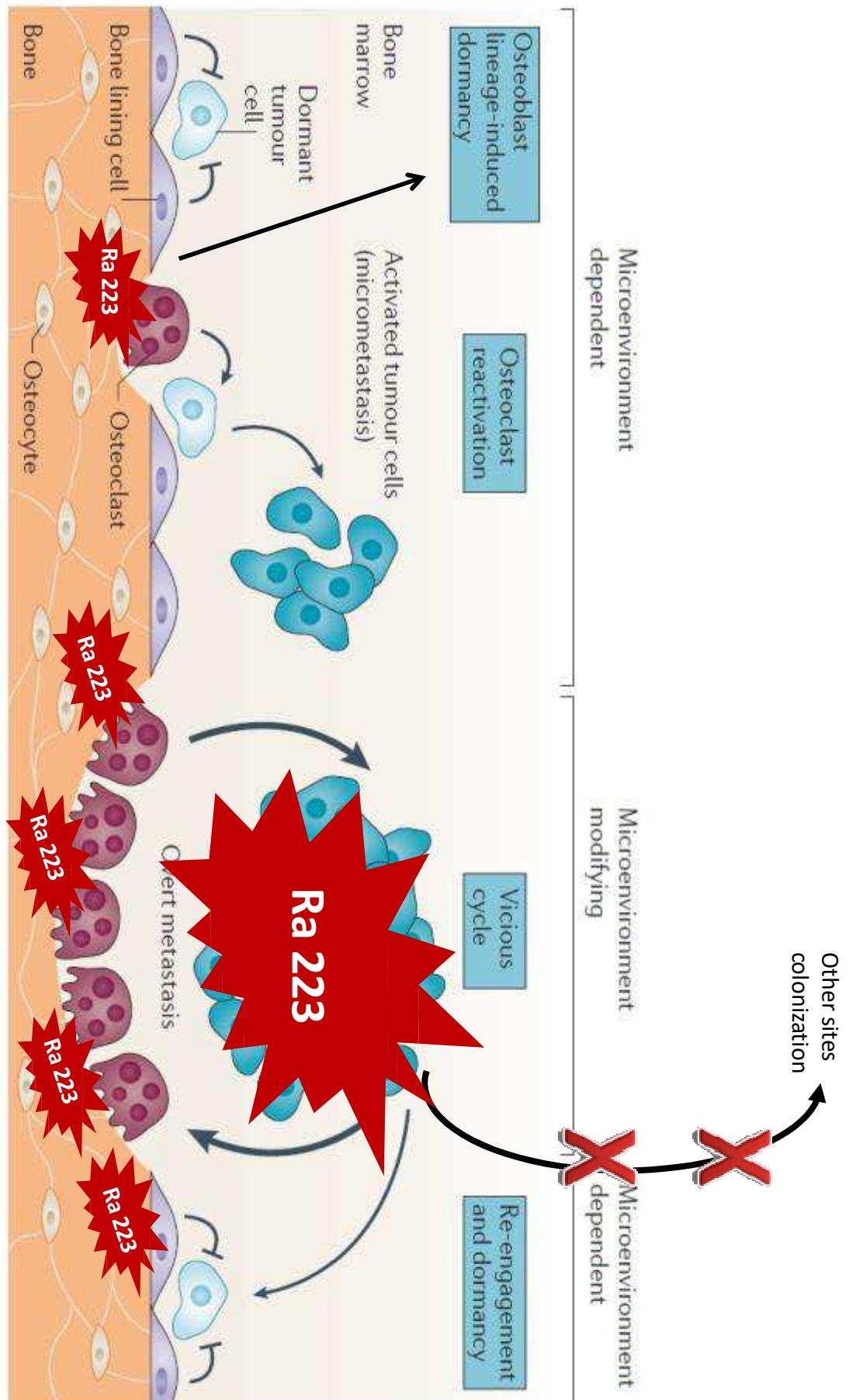
Bayer

ClinicalTrials.gov Identifier:

NCT02043678

First Posted: January 23, 2014

Last Update Posted: September 7, 2017





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## Phase IV Study to Evaluate Bone Mineral Density in No-bone Metastatic Prostate Cancer Treated With Degarelix (BLADE)

This study is currently recruiting participants.

[See ▲ Contacts and Locations](#)

*Verified June 2017 by Alessandro Antonelli, Azienda Ospedaliera Spedali Civili di Brescia*

Sponsor:

Azienda Ospedaliera Spedali Civili di Brescia

ClinicalTrials.gov Identifier:

NCT03202381

First Posted: June 28, 2017

Last Update Posted: June 28, 2017

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**ClinicalTrials.gov**

**Luteinizing Hormone-releasing Hormone Analogue and Enzalutamide +/- Zoledronic Acid in Prostate Cancer Patients (BonEnza)**

This study is not yet open for participant recruitment.

[See ▲ Contacts and Locations](#)

*Verified November 2017 by Alfredo Berutti, Azienda Ospedaliera Spedali Civili di Brescia*

Sponsor:

Azienda Ospedaliera Spedali Civili di Brescia

ClinicalTrials.gov Identifier:

NCT03336983

First Posted: November 8, 2017

Last Update Posted: November 9, 2017

Save this study [Saved Studies \(0\)](#)

# **A PILOT PHASE IV STUDY TO EVALUATE VARIATION IN BONE MINERAL DENSITY, LEAN AND FAT BODY MASS MEASURED BY DUAL-ENERGY X-RAY ABSORPTIOMETRY IN PATIENTS WITH PROSTATE CANCER WITHOUT BONE METASTASES TREATED WITH DEGARELIX**

**PROTOCOL SIGLE: BLADE: : BONE MINERAL MASS DEXA DEGARELIX**

**Principal investigator:** Alessandro Antonelli, MD, Urology Unit University of Brescia, ASST-Spedali Civili, Brescia

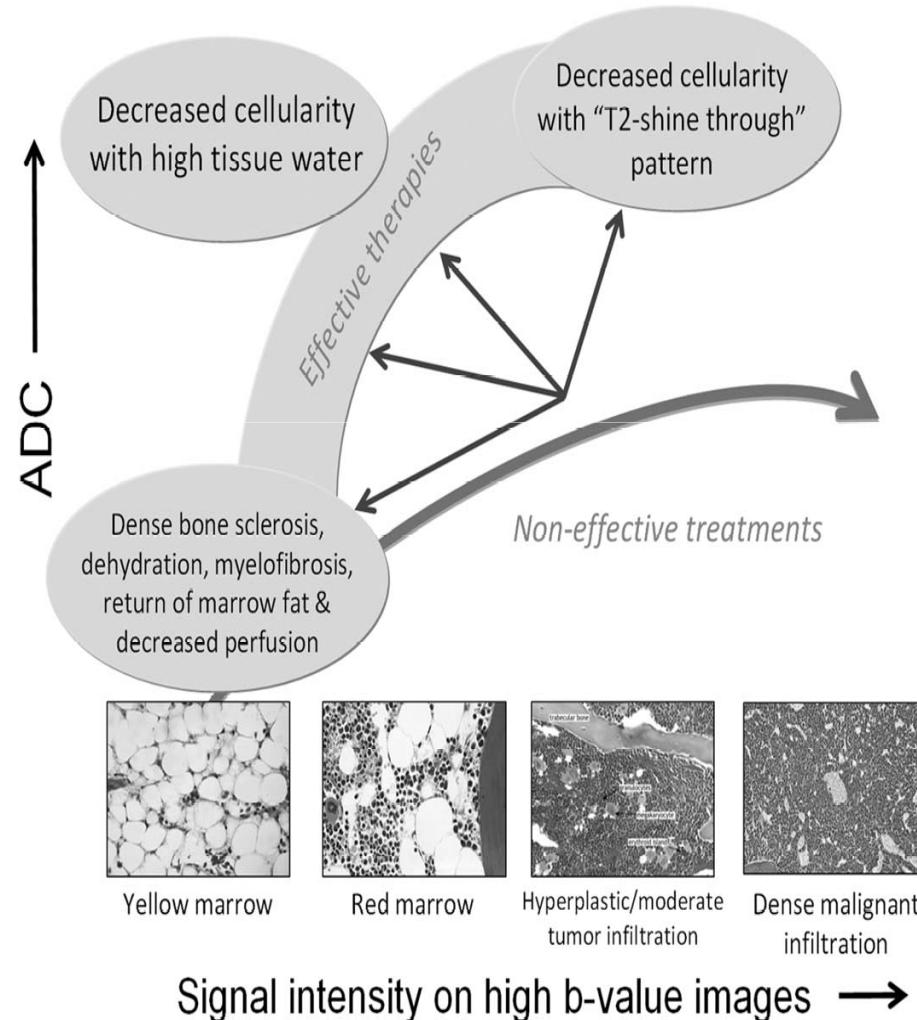
## **Primary Objective**

To determine changes in fat body mass after 12 months Degarelix administration.

## **Secondary Objectives**

- to assess changes in lean body mass and bone mineral density after 12 months of therapy;
- to assess changes in fasting serum lipids after 12 months of therapy;
- to assess changes in bone turn-over markers after 12 months of therapy;
- to assess changes in insulin sensitivity after 12 months of therapy;
- to assess changes in serum FSH levels after 12 months of therapy;
- to correlate changes in serum FSH with changes in body composition.

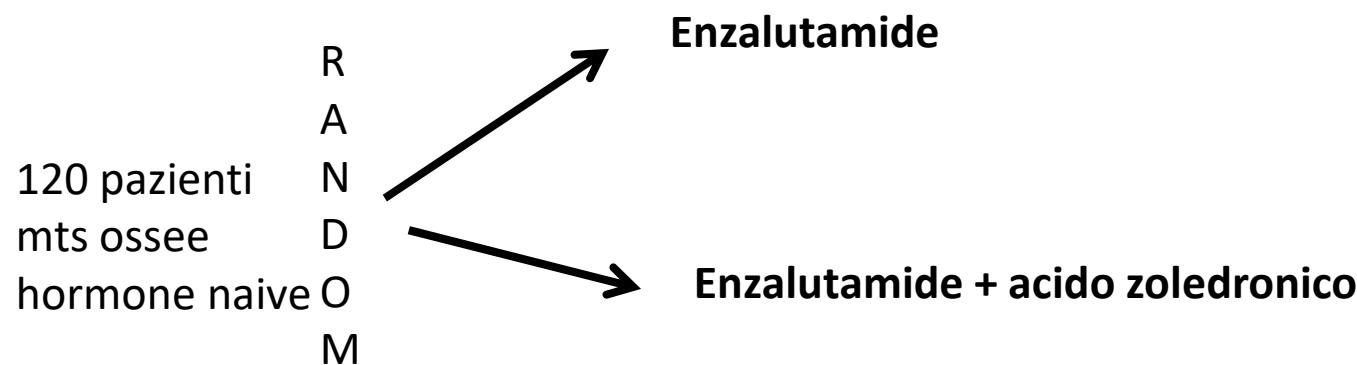
# Response monitoring with WB-DWI



Padhani et al; J Magn Res Im 2014

**VALUTAZIONE DELLA RISPOSTA OSSEA DOPO LHRH-ANALOGO IN ASSOCIAZIONE  
AD ENZALUTAMIDE CON O SENZA ACIDO ZOLEDRONICO IN PAZIENTI CON  
METASTASI OSSEE DA CARCINOMA PROSTATICO ORMONO SENSIBILE: STUDIO  
PROSPETTICO DI FASE II RANDOMIZZATO MULTICENTRICO .**

**Studio Bonenza**

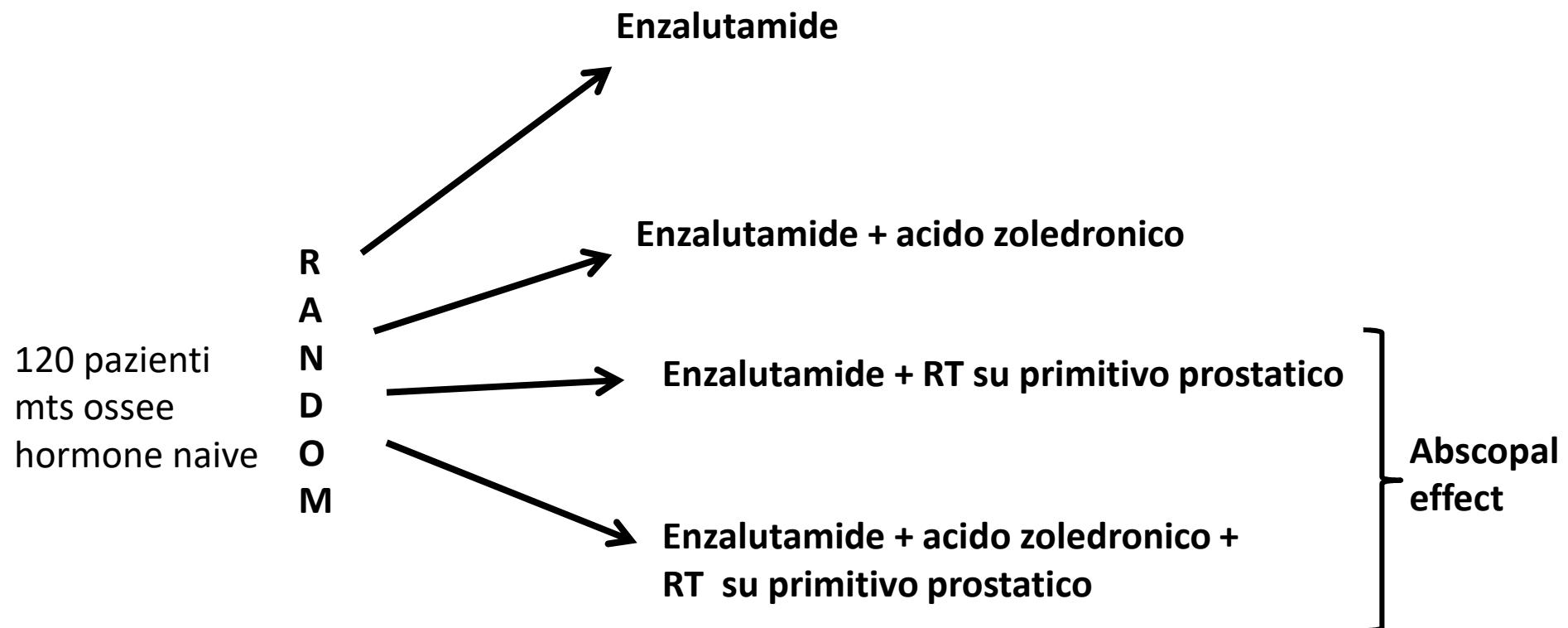


**Obiettivo primario**

Valutazione dell'attività di LHRH analogo ed Enzalutamide con o senza acido zoledronico in termini di risposta ossea valutata con *Whole body diffusion MRI* nei pazienti affetti da metastasi ossee da carcinoma della prostata ormono-sensibile.

**VALUTAZIONE DELLA RISPOSTA OSSEA DOPO LHRH-ANALOGO IN ASSOCIAZIONE  
AD ENZALUTAMIDE CON O SENZA ACIDO ZOLEDRONICO IN PAZIENTI CON  
METASTASI OSSEE DA CARCINOMA PROSTATICO ORMONO SENSIBILE: STUDIO  
PROSPETTICO DI FASE II RANDOMIZZATO MULTICENTRICO .**

**Studio Bonenza emendato**



**Obiettivo primario**

Valutazione dell'attività di LHRH analogo ed Enzalutamide con o senza acido zoledronico +/- RT su primitivo prostatico in termini di risposta ossea valutata con *Whole body diffusion MRI* nei pazienti affetti da metastasi ossee da carcinoma della prostata ormono-sensibile.