La terapia medica delle metastasi ossee: nuovi sviluppi in oncologia

Daniele Santini MD, PhD
Università Campus Bio-Medico, Roma

Associazione Italiana Radioterapia Oncologica
Lazio Abruzzo Molise

Incontro scientifico regionale di aggiornamento dell' AIRO

Martedì 23 Ottobre 2012
Ore 17.00
Sede: Ospedale Sant'Andrea di Roma. Aula C piano 0.

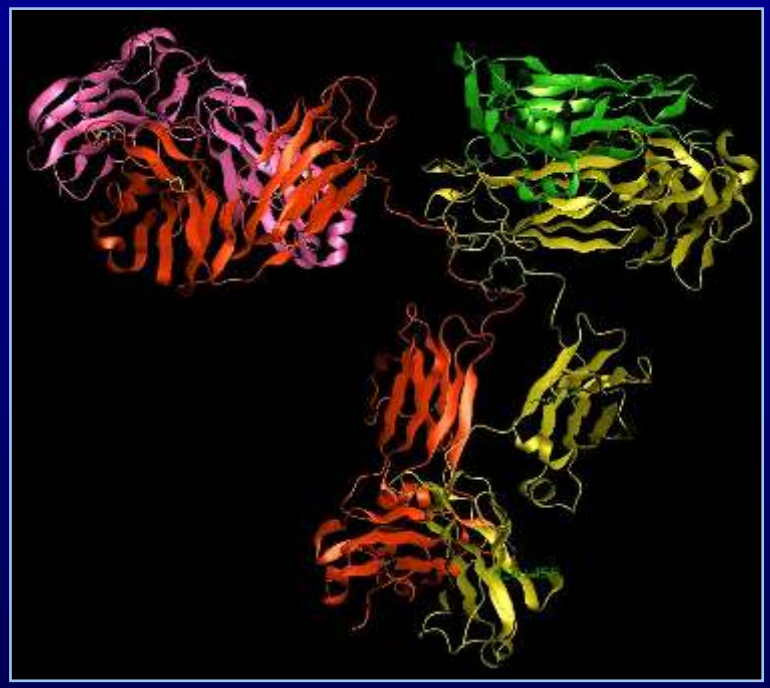
Overview:
bone health and new target molecules

- **Anti RANKL MoAb (Denosumab)**
- **Cathepsin K inhibitors (Odanacatib)**
- **Src inhibitors (Saracatinib, Dasatinib)**
- **New drugs in prostate cancer (Abiraterone, enzalutamide, cabozantinib, radium-223)**

Denosumab: anti RANKL MoAb

- Fully human monoclonal antibody
- IgG_2 isotype
- High affinity for human RANKL
- High specificity for RANKL
  - No detectable binding to TNFα, TNFβ, TRAIL, or CD40L
- No neutralizing antibodies detected in clinical trials to date

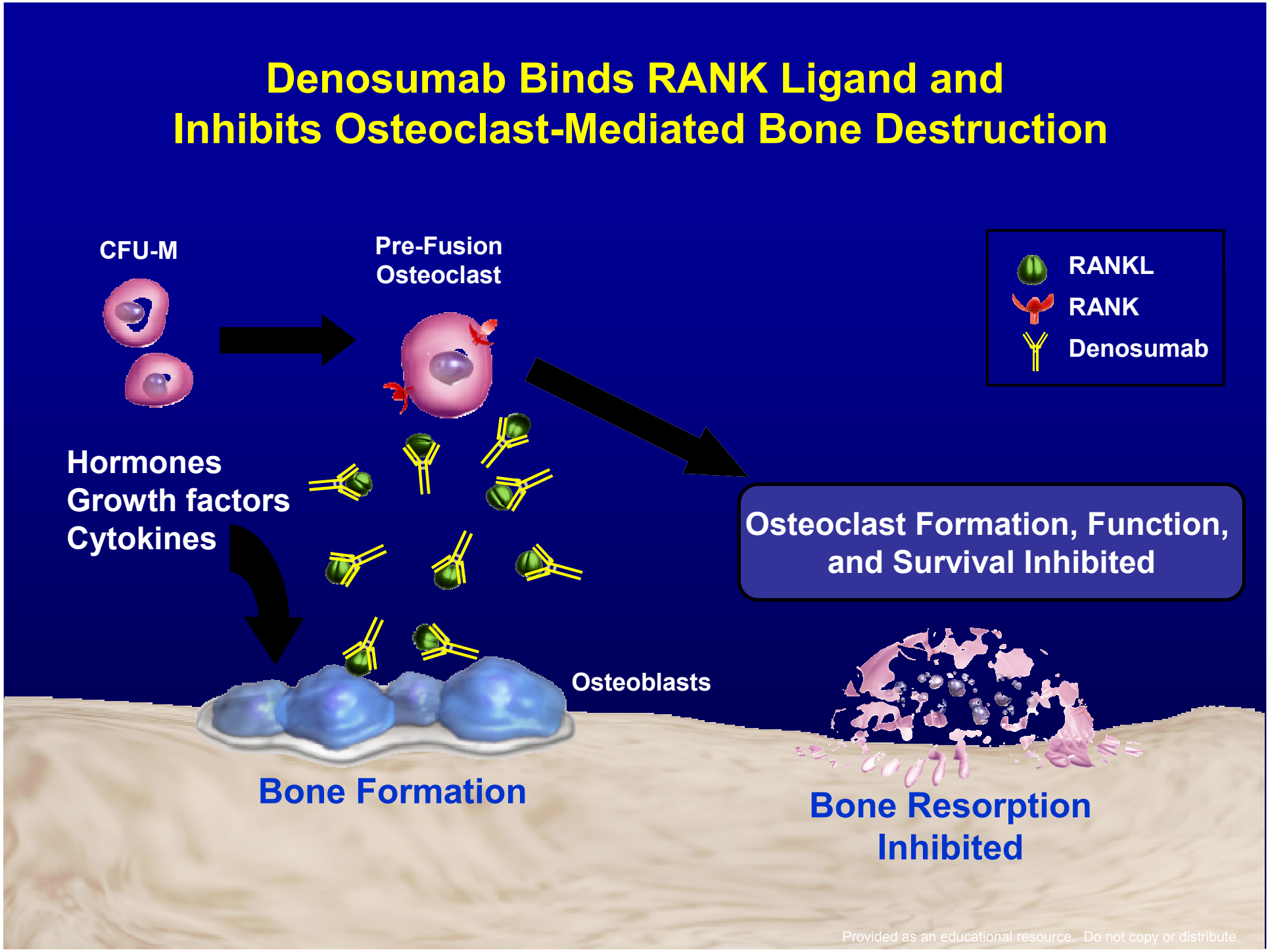
Model of Denosumab



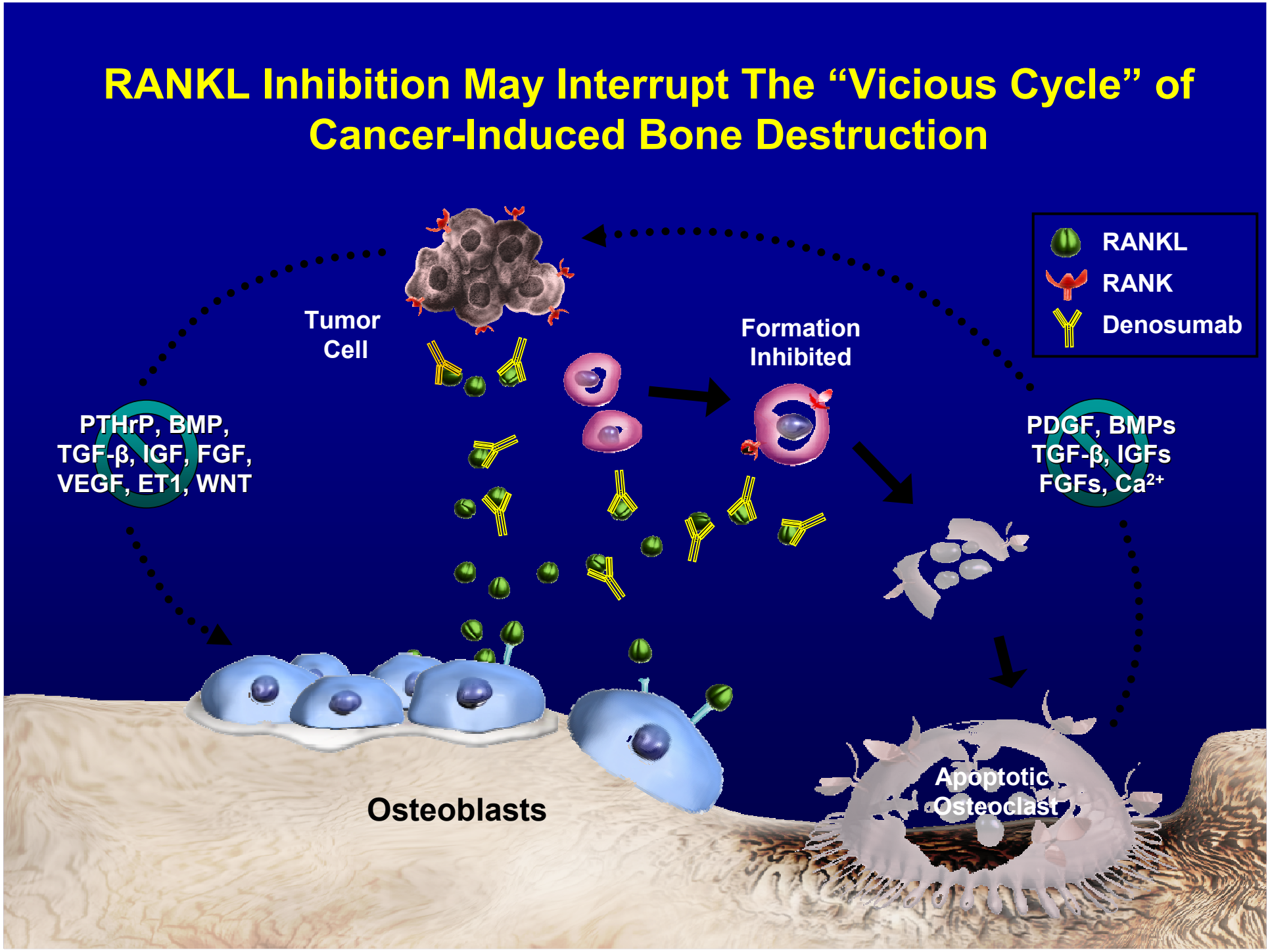
Bekker PJ, et al. *J Bone Miner Res.* 2004;19:1059-1066.
Data on file, Amgen.
Elliott R, et al. *Osteoporos Int.* 2007;18:S54. Abstract P149.
McClung MR, et al. *New Engl J Med*. 2006;354:821-31.

TNF = tumor necrosis factor;
TRAIL = TNFα-related apoptosis-inducing Ligand

Denosumab Binds RANK Ligand and Inhibits Osteoclast-Mediated Bone Destruction



RANKL Inhibition May Interrupt The "Vicious Cycle" of Cancer-Induced Bone Destruction



Phase III studies in solid tumours
Integrated analysis – Study Design

Key Inclusion Criteria

- **Adults with breast, prostate, other solid tumors, or multiple myeloma and ≥ 1 bone metastasis / lesion**

Key Exclusion Criteria

- No current or prior IV bisphosphonate administration for treatment of bone metastases

1:1

Denosumab 120 mg SC and Placebo IV* every 4 weeks (N = 2861)

Daily Supplements of Calcium and Vitamin D

Zoledronic acid 4 mg IV* and Placebo SC every 4 weeks (N = 2862)

Blinded Study Periods

Breast Cancer: April 2006 to March 2009

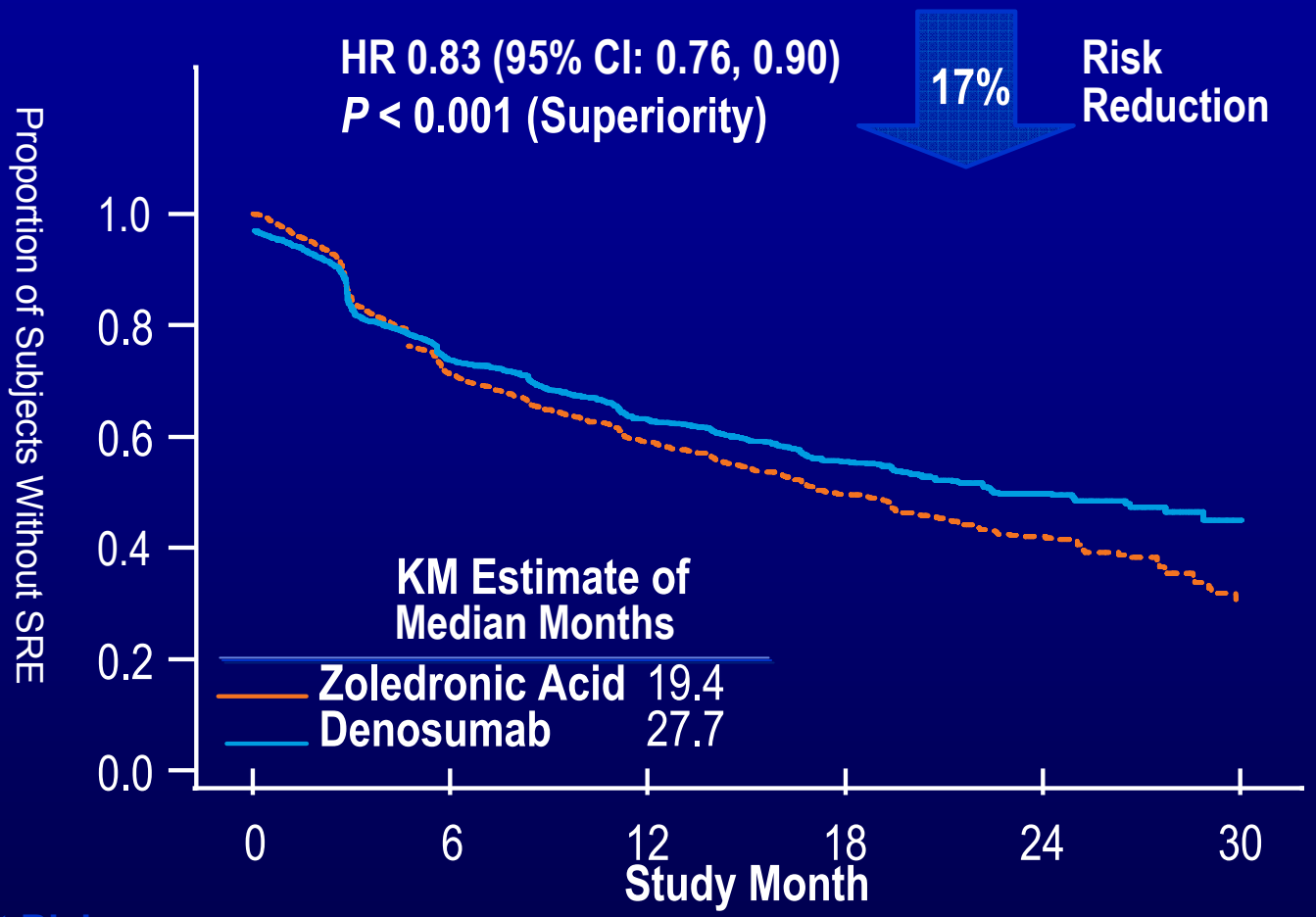
Prostate Cancer: May 2006 to October 2009

Other Solid Tumors and Multiple Myeloma: June 2006 to April 2009

* Per protocol and Zometa® label, IV product was dose adjusted for baseline creatinine clearance and subsequent dose intervals were determined by serum creatinine levels. No SC dose adjustments were required.

Lipton et al. ESMO, 2010

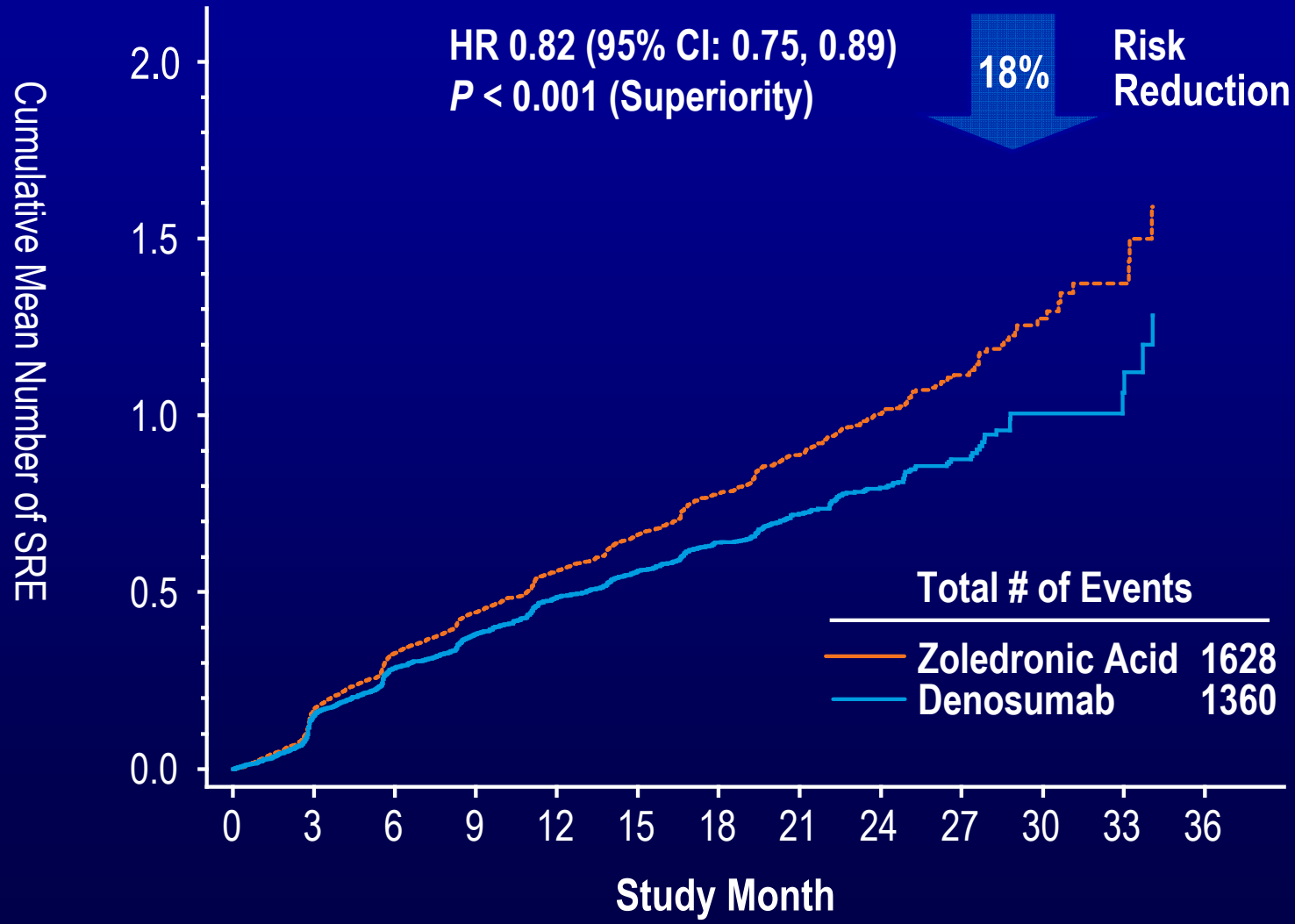
Time to First On-Study SRE



Patients at Risk:						
Zoledronic Acid	2861	1596	991	522	178	26
Denosumab	2862	1666	1077	570	197	22

Lipton et al. ESMO, 2010

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



Lipton et al. ESMO, 2010

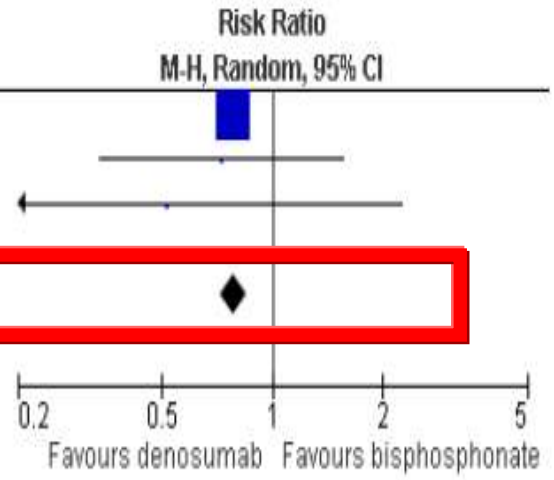
Bisphosphonates and other bone agents for breast cancer (Review)

Wong MHF, Stockler MR, Pavlakis N

Figure 3. Forest plot of comparison: 1 Breast cancer with bone metastases (BCBM), outcome: 1.3 Overall risk of skeletal events in BCBM: denosumab versus bisphosphonate

Study or Subgroup	denosumab Events	Total	bisphosphonate Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Stopeck 2010	491	1026	623	1020	98.6%	0.78 [0.72, 0.85]
Lipton 2008	25	212	7	43	1.1%	0.72 [0.33, 1.57]
Fizazi 2009 (1)	3	29	3	15	0.3%	0.52 [0.12, 2.26]
Total (95% CI)		**1267**		**1078**	**100.0%**	**0.78 [0.72, 0.85]**
Total events	519		633			

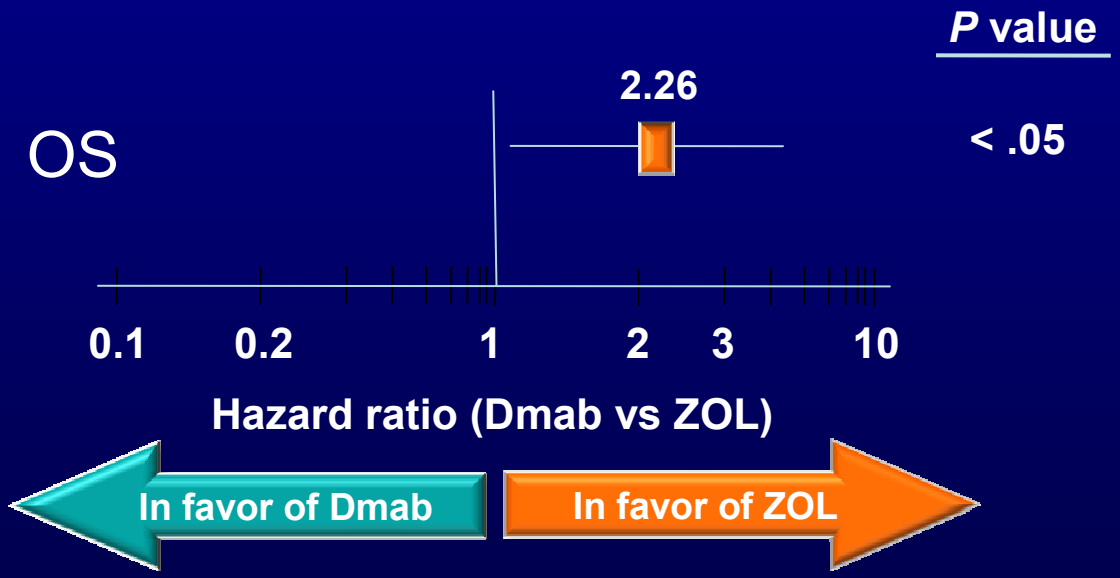
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 2 (P = 0.84); I² = 0%
Test for overall effect: Z = 6.03 (P < 0.00001)



(1) At 25 weeks follow-up; data provided by Amgen pharmaceutical

Denosumab ⬆ Mortality vs ZOL in MM Patients

- Dmab ⬆ the risk of death by 2.3-fold vs ZOL, and Dmab is not indicated for prevention of SREs in patients with MM (n = 180)[1]

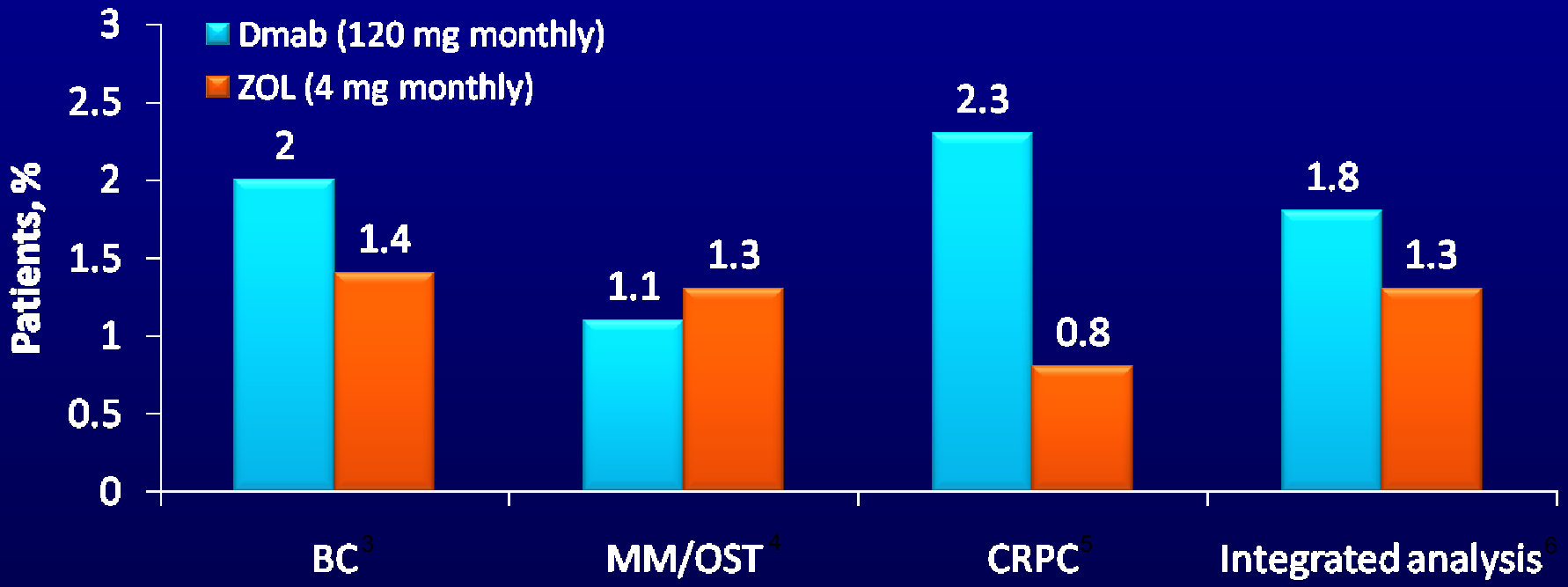


Abbreviations: Dmab, denosumab; MM, multiple myeloma; SRE, skeletal-related event; ZOL, zoledronic acid.

1. Xgeva™ (denosumab) injection, for subcutaneous use [package insert]. Thousand Oaks, CA; Amgen Inc; 2010.

Denosumab and ONJ risk

- Uncommon condition in cancer patients receiving complex treatment regimens such as BPs, Dmab, sunitinib, and bevacizumab[1-5]



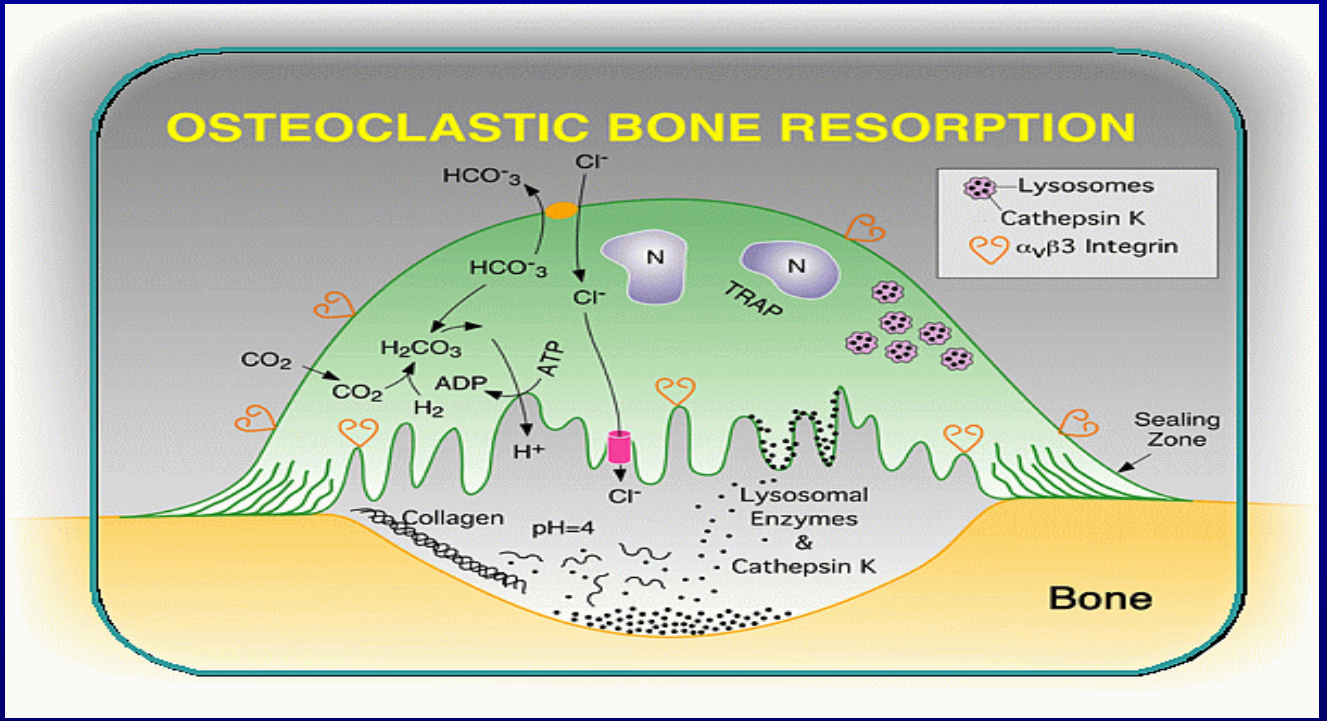
Abbreviation: AE, adverse event; BC, breast cancer; BP, bisphosphonate; CRPC, castrate-resistant prostate cancer; Dmab, denosumab; MM, multiple myeloma; ONJ, osteonecrosis of the jaw; OST, other solid tumors (not breast or prostate cancer); ZOL, zoledronic acid.

1. Hoff AO, et al. *JBMR* 2008;23(6):826-836; 2. McArthur HL, et al. ASCO 2008, abstract 9588; 3. Stopeck A, et al. *JCO.* 2010;28(35):5132-5139; 4. Henry D, et al. ECCO-ESMO 2009, abstract 20LBA; 5. Fizazi K, et al. ASCO 2010, abstract LBA4507; 6. Lipton A, et al. ESMO 2010, abstract 1249.

Overview:
bone health and target molecules

- Anti RANKL MoAb (Denosumab)
- Cathepsin K inhibitors (Odanacatib)
- Src inhibitors (Saracatinib, Dasatinib)
- New drugs in prostate cancer (Abiraterone, enzalutamide, cabozantinib, radium-223)

Cathepsin K inhibitors



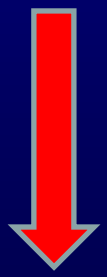
- Cathepsin K is a cysteine proteinase expressed predominantly in osteoclasts
- Cathepsin K plays a critical role in the degradation of bone
- Cathepsin K is expressed by cancer cells that metastasize to bone

Le Gall C and Clezardin P. **Curr Opin Support Palliat Care, 2008**

Data in metastatic bone disease

- Catk is highly expressed in breast and prostate tumors at comparable levels as osteoclast in human bone and osteoclastoma.

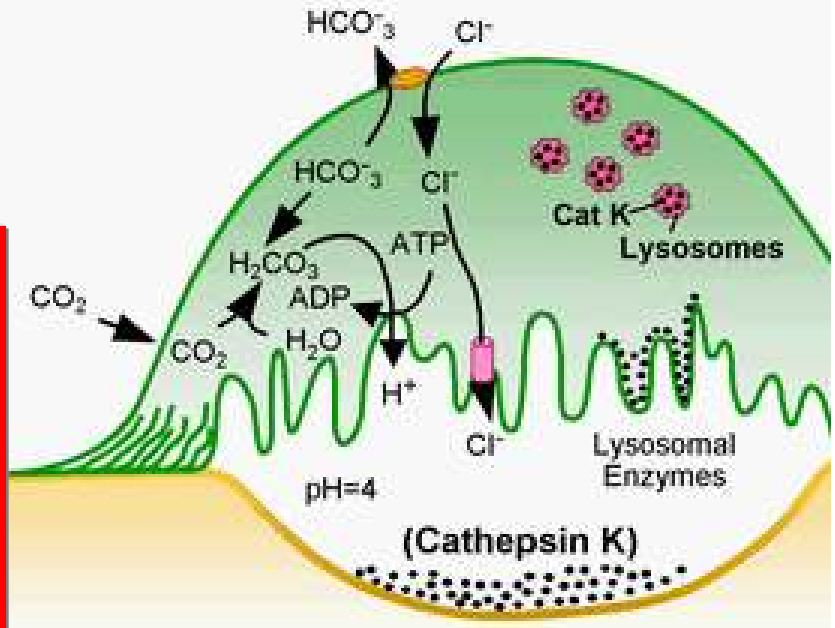
  - Role of CatK in tumor invasion



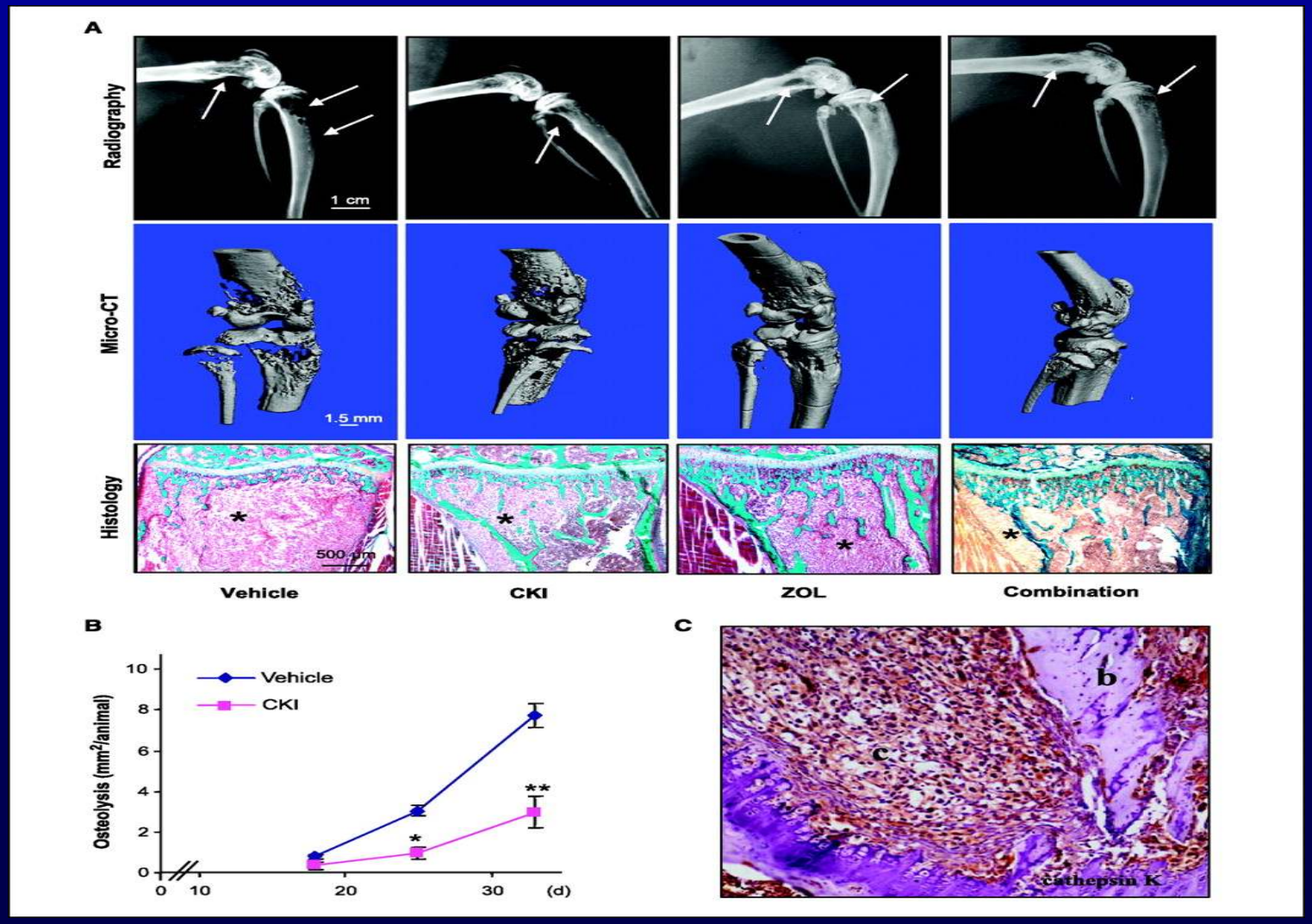
  - Potential therapeutic target in bone metastasis

Odanacatib (MK-0822): Cathepsin K Inhibitor for the Treatment of Osteoporosis

- Cathepsin K is a cysteine protease responsible for bone matrix degradation
- Odanacatib is a selective and reversible inhibitor of Cathepsin K
- Inhibition of Cathepsin K decreases bone resorption to a similar degree as the bisphosphonate, but decreases bone formation to a lesser extent[1]
- Increase in cortical bone thickness demonstrated in preclinical study[2]



L-006235: in vivo POC study for treatment of osteolysis and tumor growth in metastatic bone disease



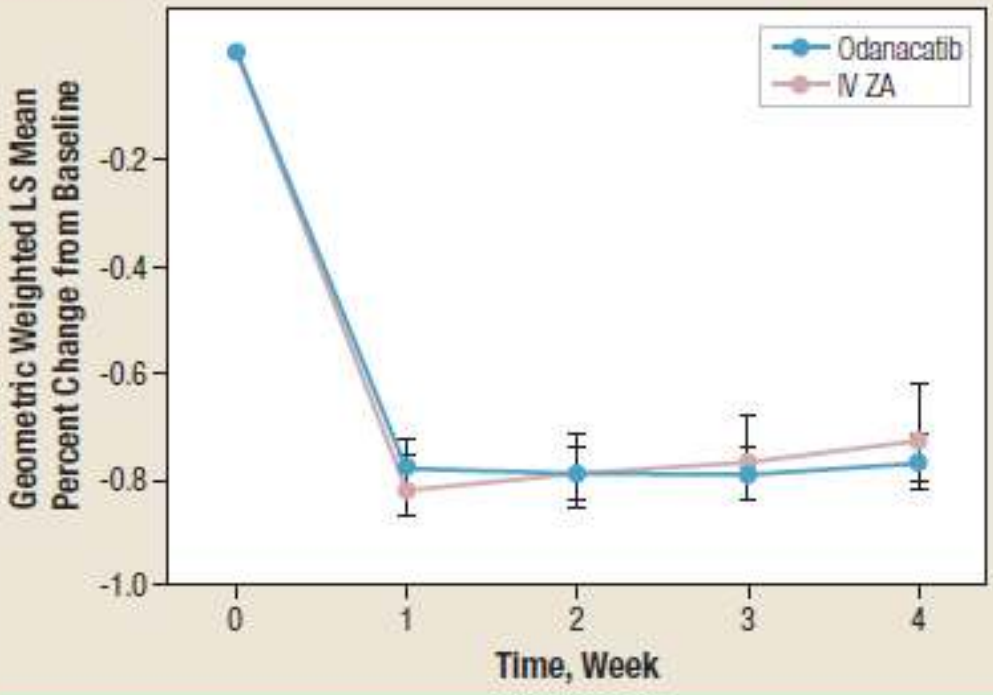
Le Gall, C. et al. Cancer Res 2007;67:9894-9902

The Cathepsin K Inhibitor Odanacatib Suppresses Bone Resorption in Women With Breast Cancer and Established Bone Metastases: Results of a 4-Week, Double-Blind, Randomized, Controlled Trial

Anders Bonde Jensen,[1] Christopher Wynne,[2] Guillermo Ramirez,[3] Weili He,[4] Yang Song,4 Yuliya Berd,[4] Hongwei Wang,[4] Anish Mehta,[4] Antonio Lombardi[4]

Clinical Breast Cancer, Vol. 10, No. 6, 452-458, 2010; DOI: 10.3816/CBC.2010.n.059

Figure 1 Geometric Mean Percent Change From Baseline in uNTx/Creatinine Ratio (Least Square Mean ± 95% CI)



This figure demonstrates comparable reduction of uNTx for both study medications.
Abbreviations: I.V. ZA = intravenous zoledronic acid; LS = least square mean; uNTx = urinary N-telopeptide of type 1 collagen

L-006235: as an add-on therapy in metastatic bone disease

- CatK inhibitors as an add-on therapy to Breast cancer already on ZA therapy

Sequential treatment ZA (12ug/kg) plus L235 (30 and 100) demonstrated additive efficacy:

-Protection osteolysis

- Tumor volume (CT)

	ZA 12 ug/kg plus L235 30 mg/kg	ZA12ug/kg
% normal bone	100%	90%

Overview:
bone health and target molecules

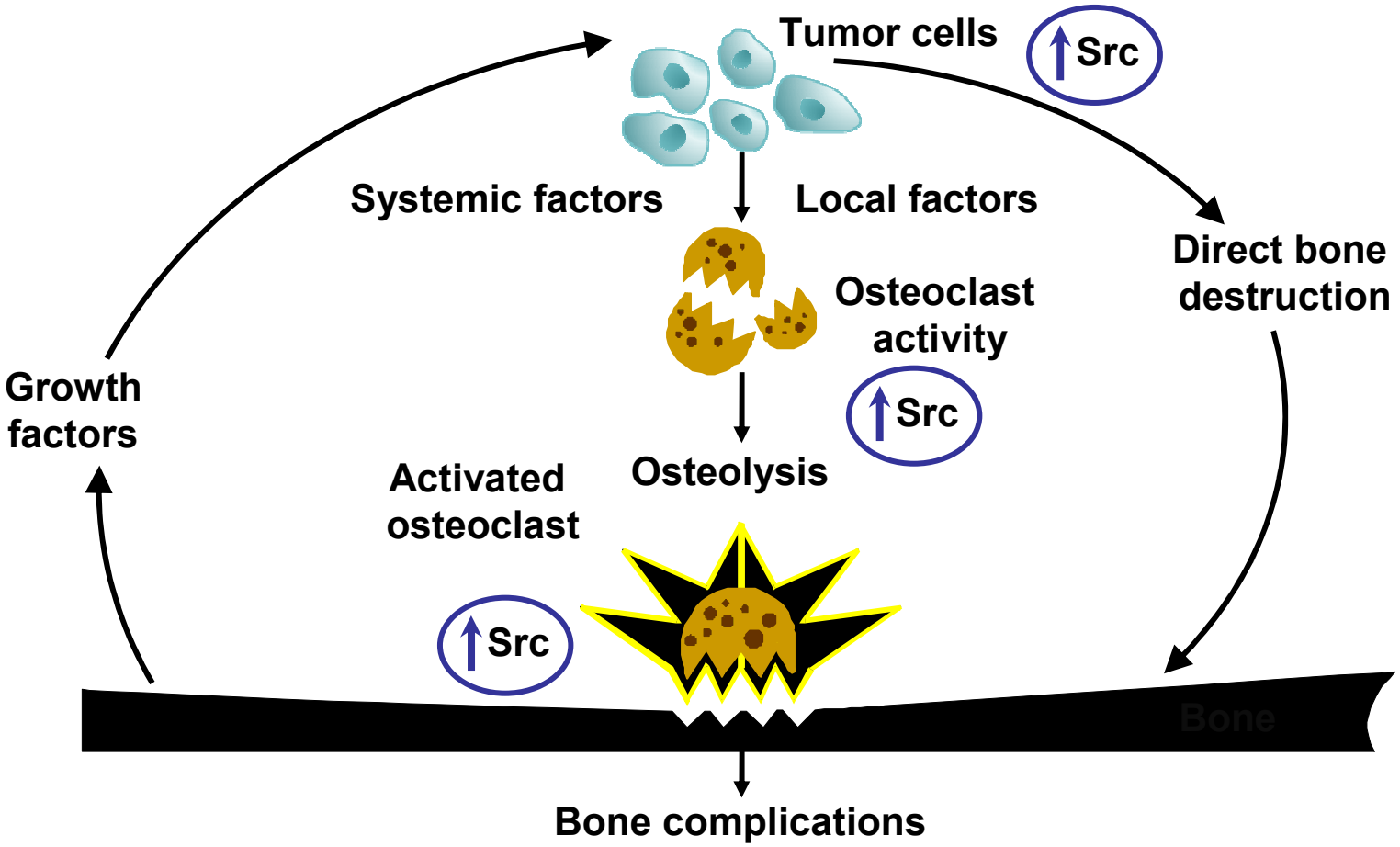
- Anti RANKL MoAb (Denosumab)
- Cathepsin K inhibitors (Odanacatib)
- Src inhibitors (Saracatinib, Dasatinib)
- New drugs in prostate cancer (Abiraterone, enzalutamide, cabozantinib, radium-223)

Evidence for a Role of Src in Bone Metabolism and Metastatic Bone Disease

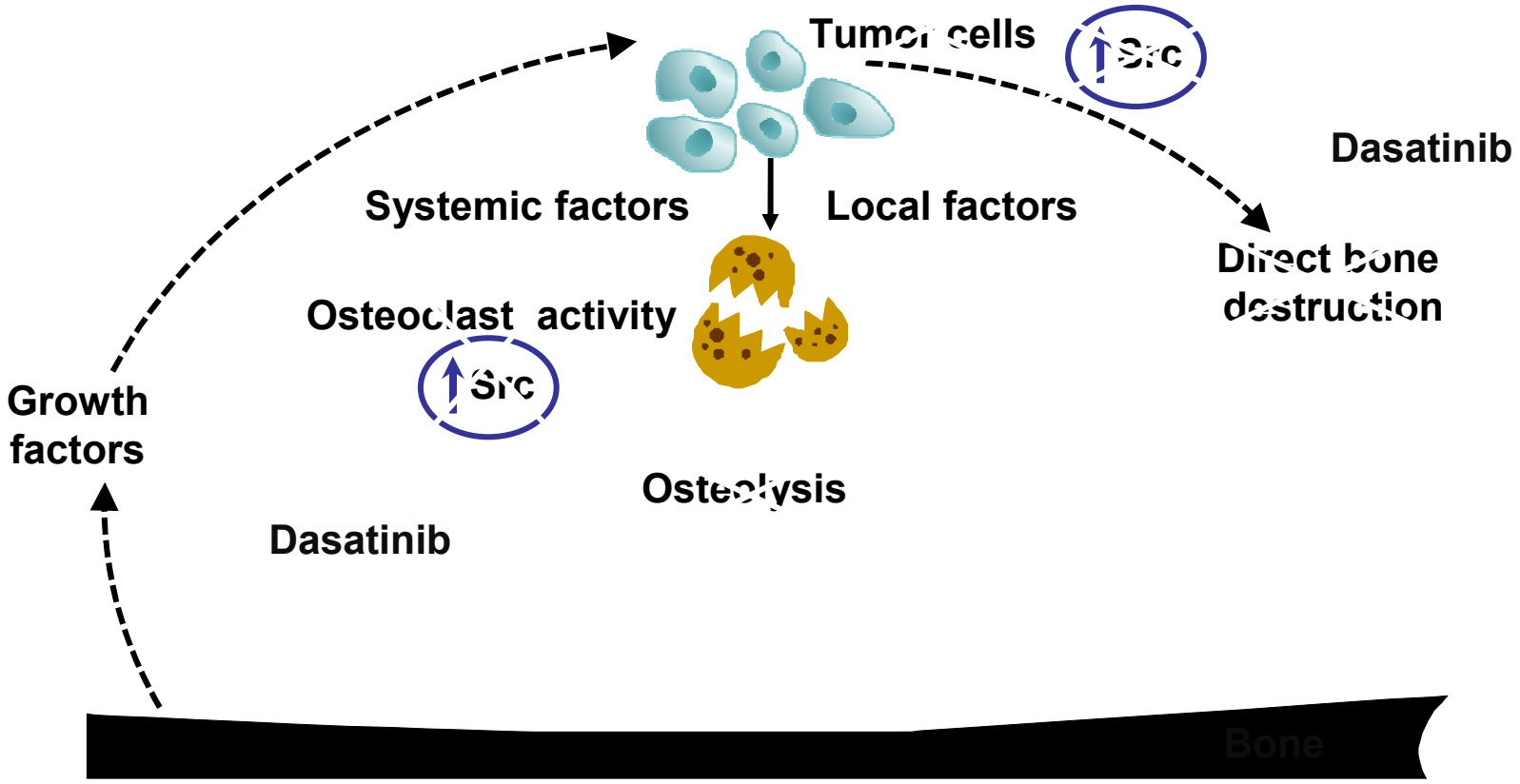
- Src kinase is a nonreceptor tyrosine kinase, highly expressed in normal osteoclasts[1,2]
- Src plays an essential role in RANKL-mediated osteoclast activation[3] and perhaps survival[4]
- Src knockout mice are osteopetrotic[5]
- Src may be critical for tumor cell survival in bone microenvironment[6]

1. Horne WC, et al. *J Cell Biol*. 1992;119(4):1003-1013; 2. Tanaka S, et al. *FEBS Lett*. 1992;313(1):85-89;
3. Boyce BF, et al. *J Clin Invest*. 1992;90(4):1622-1627; 4. Wong BR, et al. *Mol Cell*. 1999;4(6):1041-1049;
5. Lowe C, et al. *Proc Natl Acad Sci U S A*. 1993;90(10):4485-4489; 6. Zhang XH, et al. *Cancer Cell*. 2009;16(1):67-78.

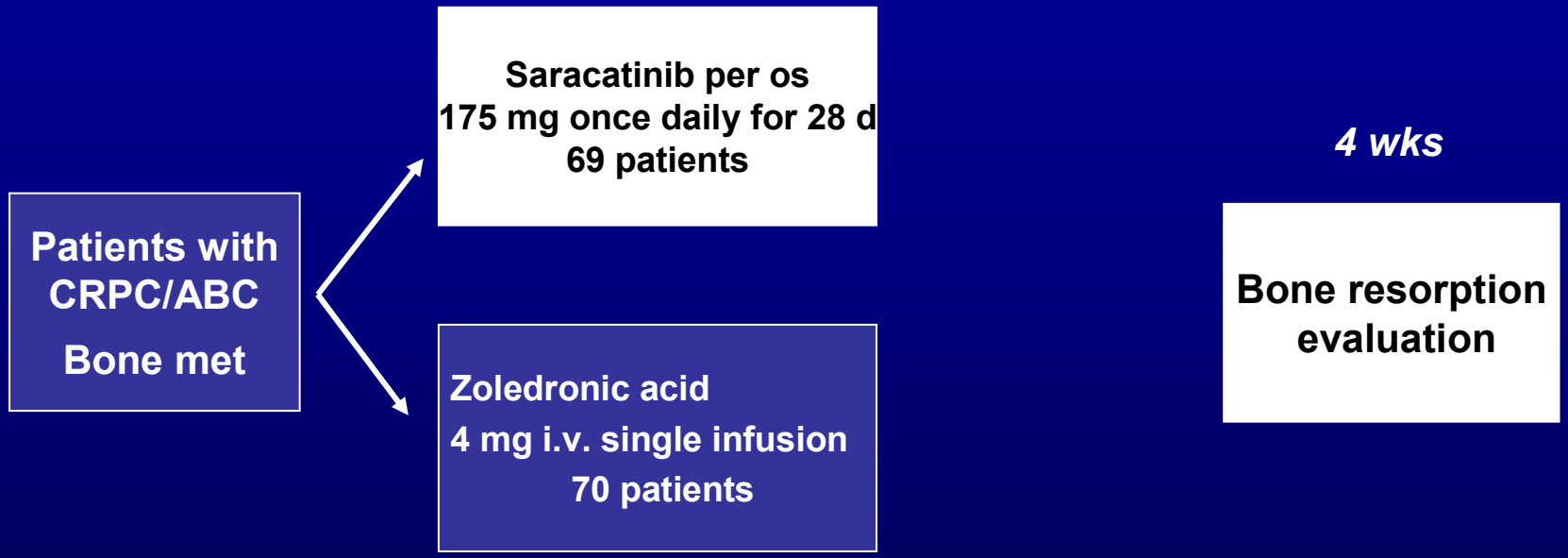
Role of Src in Prostate Tumor Cell and Osteoclast Activities



Dasatinib in PC: Inhibition of Tumor Cells and Osteoclast Activity Through Src



A Phase II, randomized, open-label, pilot study to evaluate the safety and the effects on bone resorption of SARACATINIB (AZD0530) in patients with prostate cancer or breast cancer with metastatic bone disease



Results

CTX decrease: by 74% from baseline (SAR) versus 68% (ZOL)

The CTX decrease was acute for ZOL, slower for SAR

Nausea (24%); GOT/GPT increase (6%); creatinine increase (6%)

Aklilu M et al. CIBD 2010

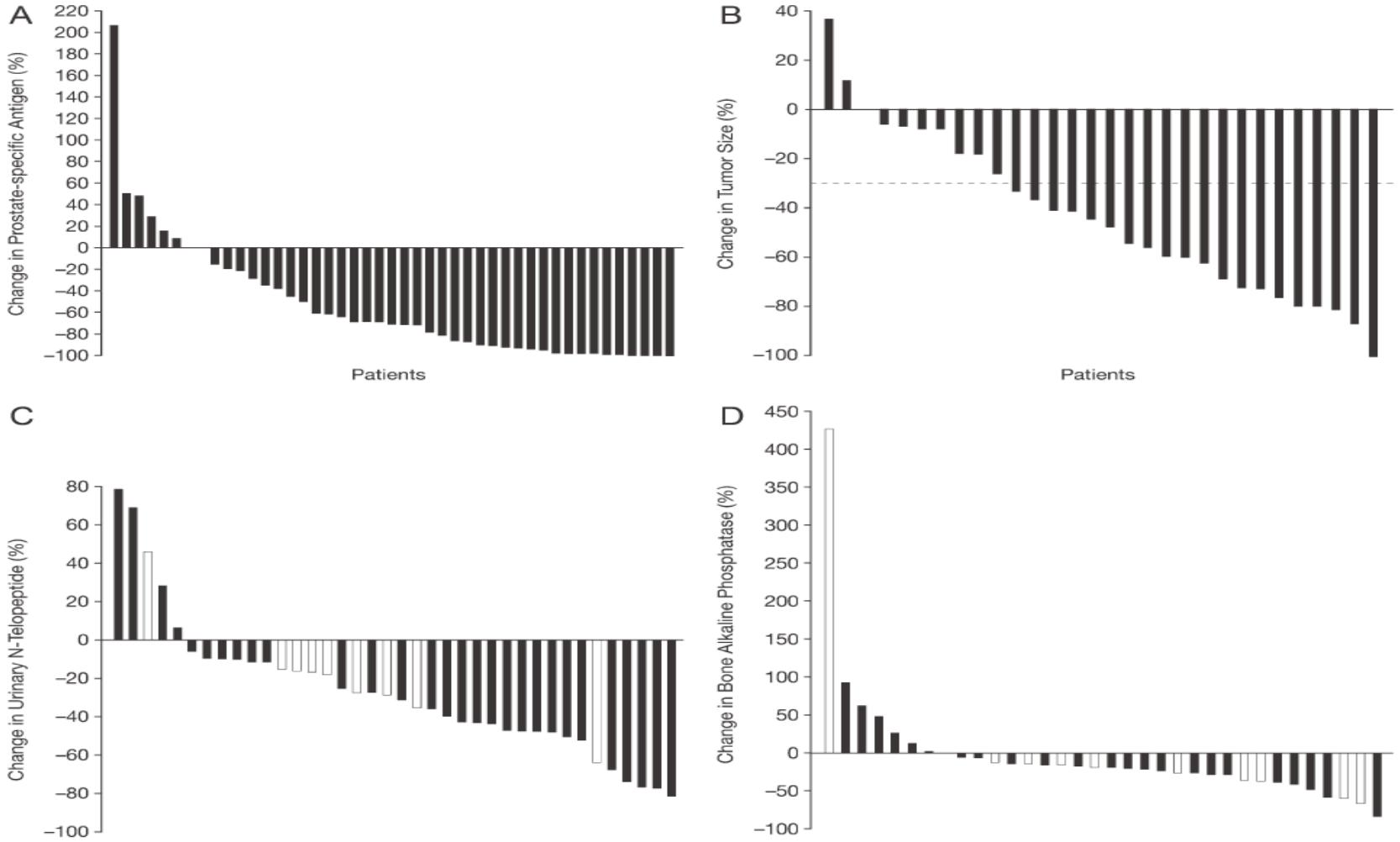
Original Article

Dasatinib Combined With Docetaxel for Castration-Resistant Prostate Cancer

Results From a Phase 1-2 Study

Cancer January 1, 2012

John C. Araujo, MD[1]; Paul Mathew, MD[2]; Andrew J. Armstrong, MD[3]; Edward [illegible]; Mathew Lonberg, MD[6]; Gary E. Gallick, PhD[1]; Géralyn C. Trudel, PhD[7]; Prashni Paliwal, PhD[8]; Shruti Agrawal, PhD[9]; and Christopher J. Logothetis, MD[1]



Phase III study: READY (ongoing)

(metastatic hormonorefractory prostate cancer patients)

Doc + P vs Doc + P + DASATINIB

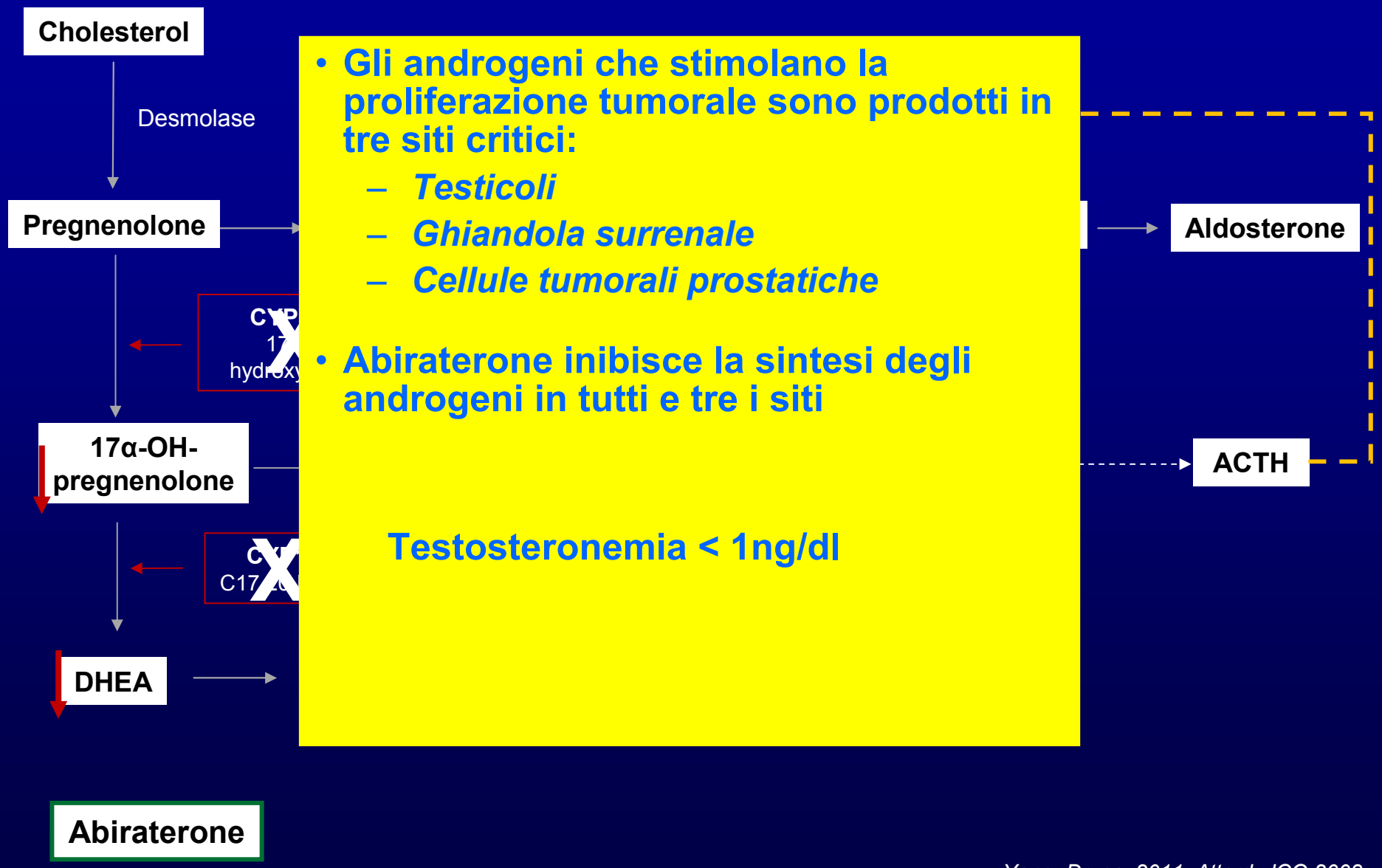
Preliminary results:

- 4.8 months OS improvement with the combination
- Longer PFS with the combination
- Median time to SRE longer (7.5 vs. 6.0 months)

Overview: bone health and target molecules

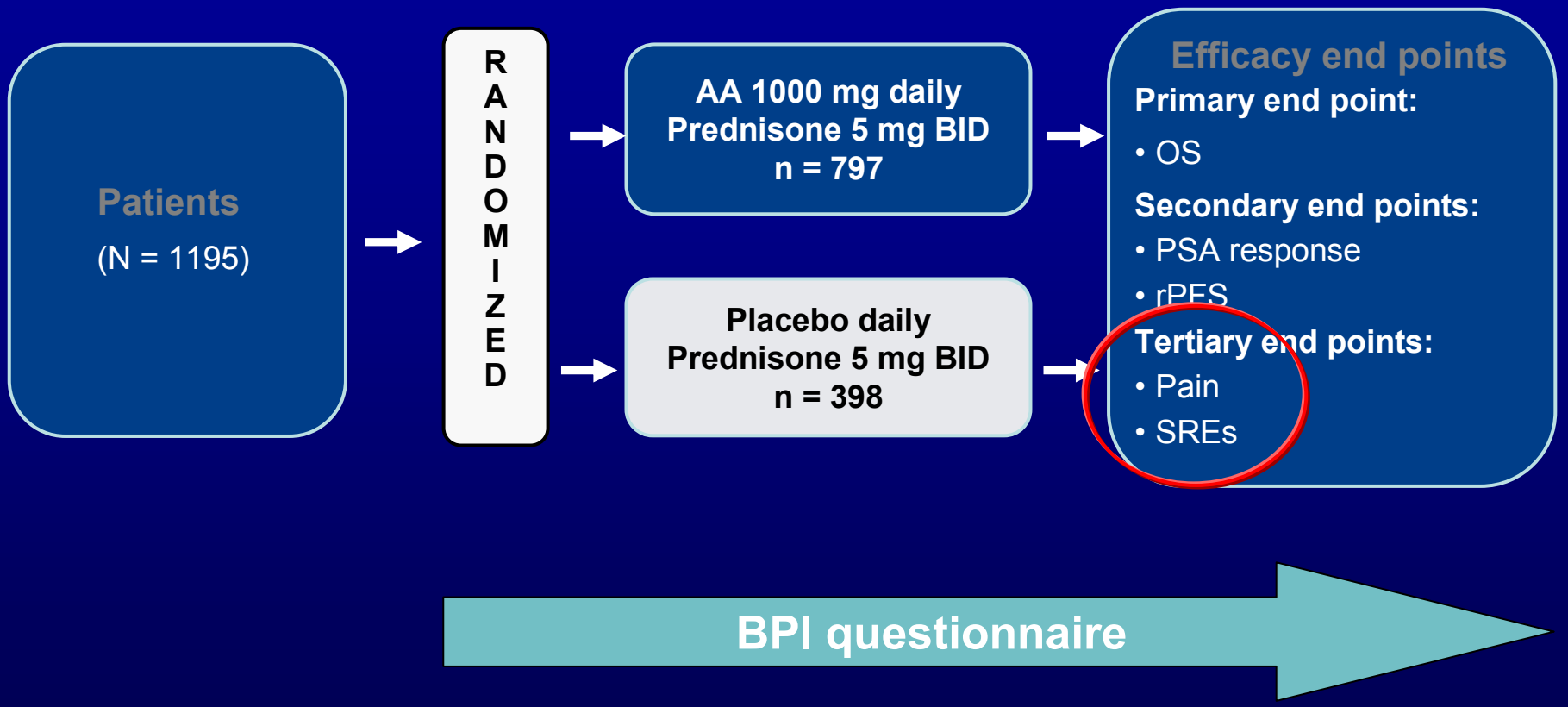
- Anti RANKL MoAb (Denosumab)
- Cathepsin K inhibitors (Odanacatib)
- DKK inhibitors and WNT/beta-catenin agonist (mAbs)
- Src inhibitors (Saracatinib, Dasatinib)
- New drugs in prostate cancer (Abiraterone, enzalutamide, cabozantinib, radium-223)

Meccanismo azione abiraterone



Yang, Drugs. 2011; Attard, JCO 2008

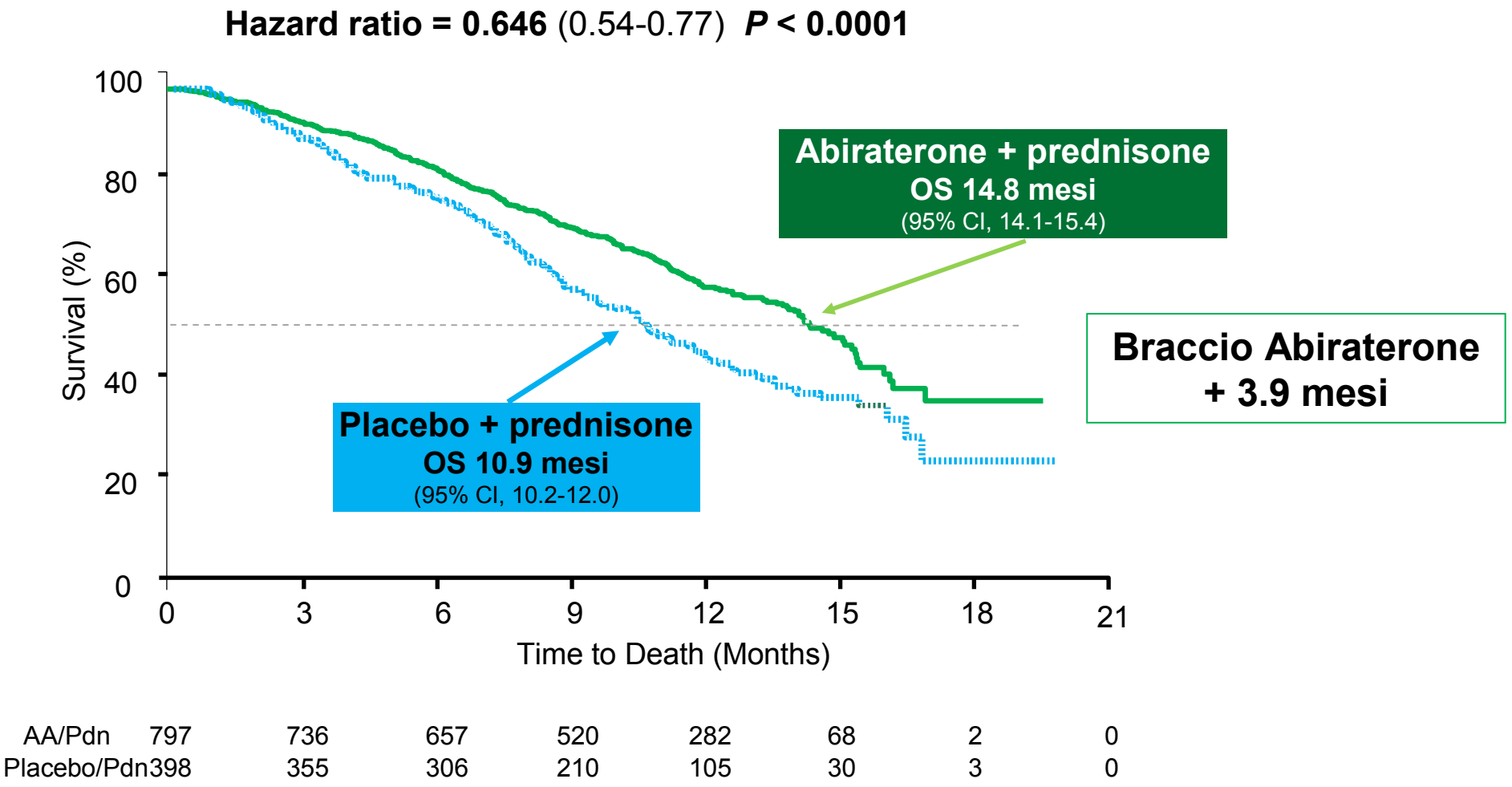
Overall Study Design



Baseline, Cycle 1 (Day 15), subsequent treatment cycles (Day 1)

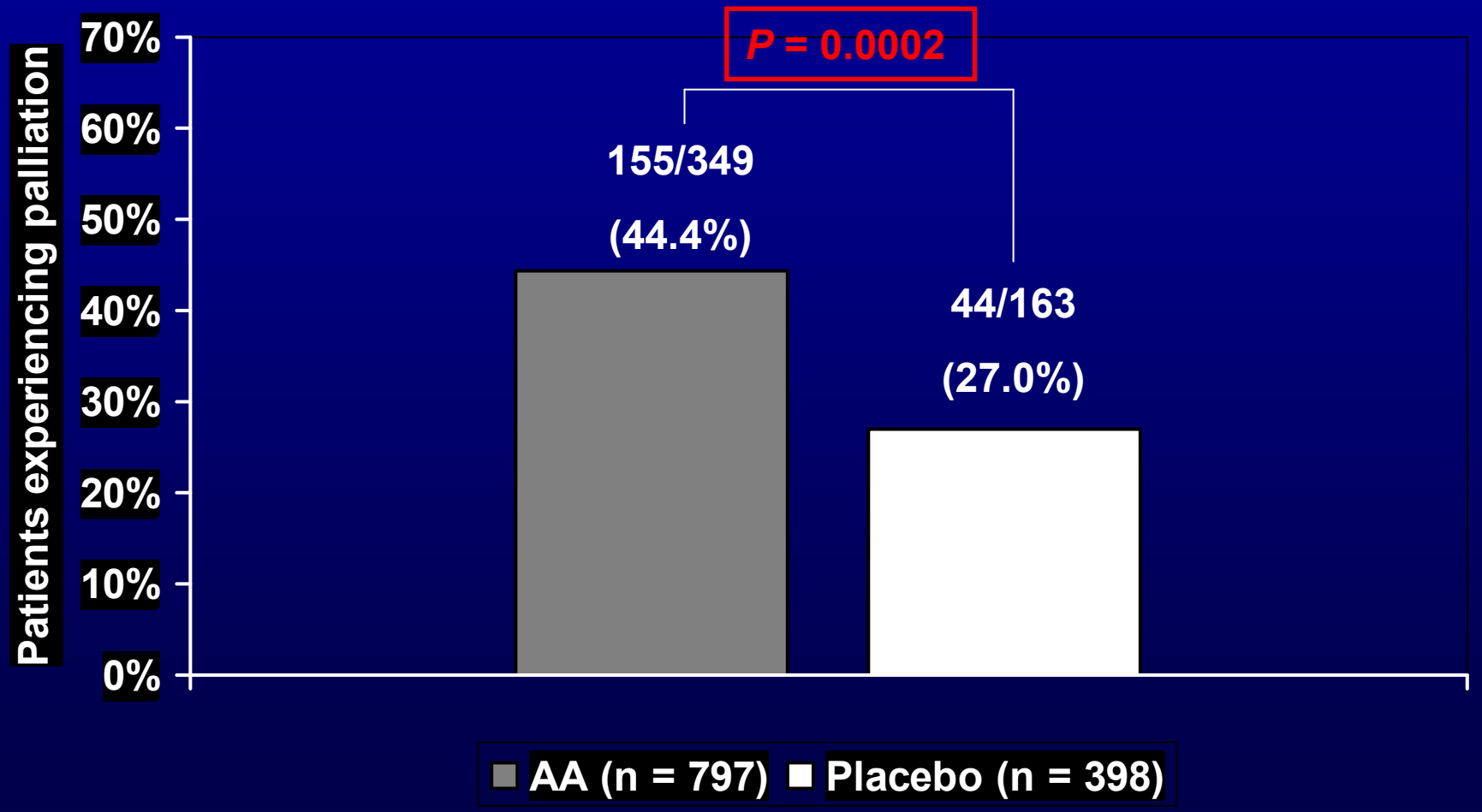
de Bono et al. NEJM 2011

Overall survival



de Bono et al. NEJM 2011

Symptomatic Improvement - Pain Intensity Palliation

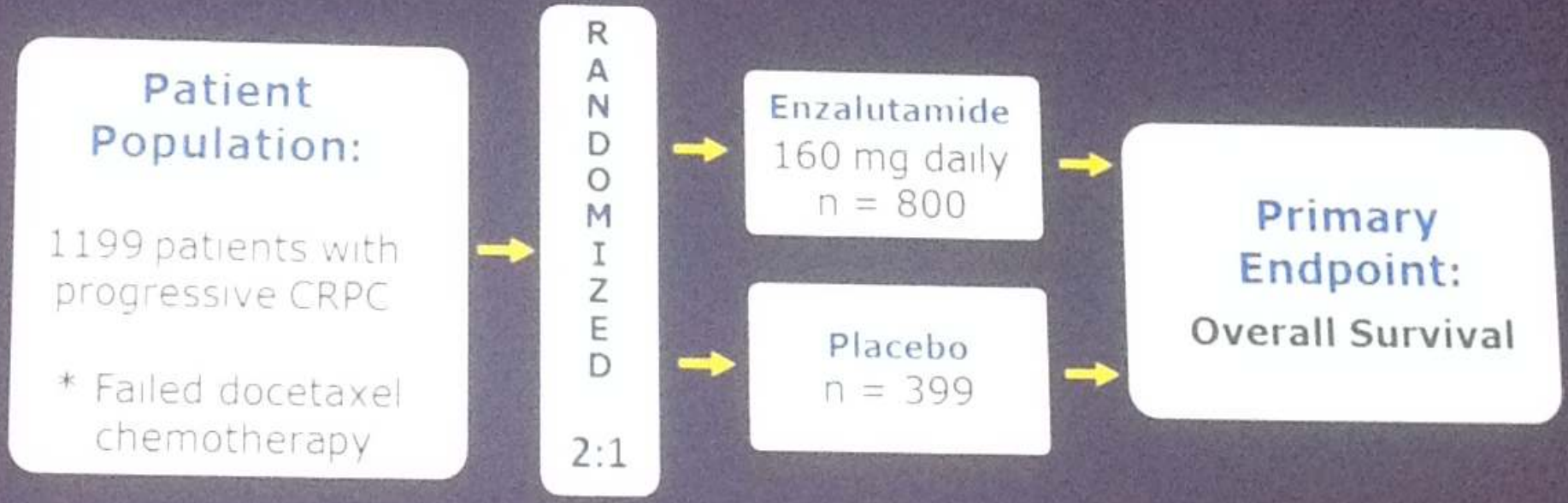


Results

	AA (n = 797)	Placebo (n = 398)	*P* Value
Overall survival			
Median, months	14.8	10.9	< 0.0001
PSA response rate			
Total	38.0%	10.1%	< 0.0001
Confirmed	29.1%	5.5%	< 0.0001
Radiographic PFS			
Median, months	5.6	3.6	< 0.0001
Time to first SRE (pathologic fracture/spinal cord compression/ palliative radiation/bone surgery)			
25th percentile, days	301.0	150.0	< 0.0001

Logothetis et al. JCO 2011; 29 (Suppl): Abst4520 (oral)

AFFIRM Trial Design



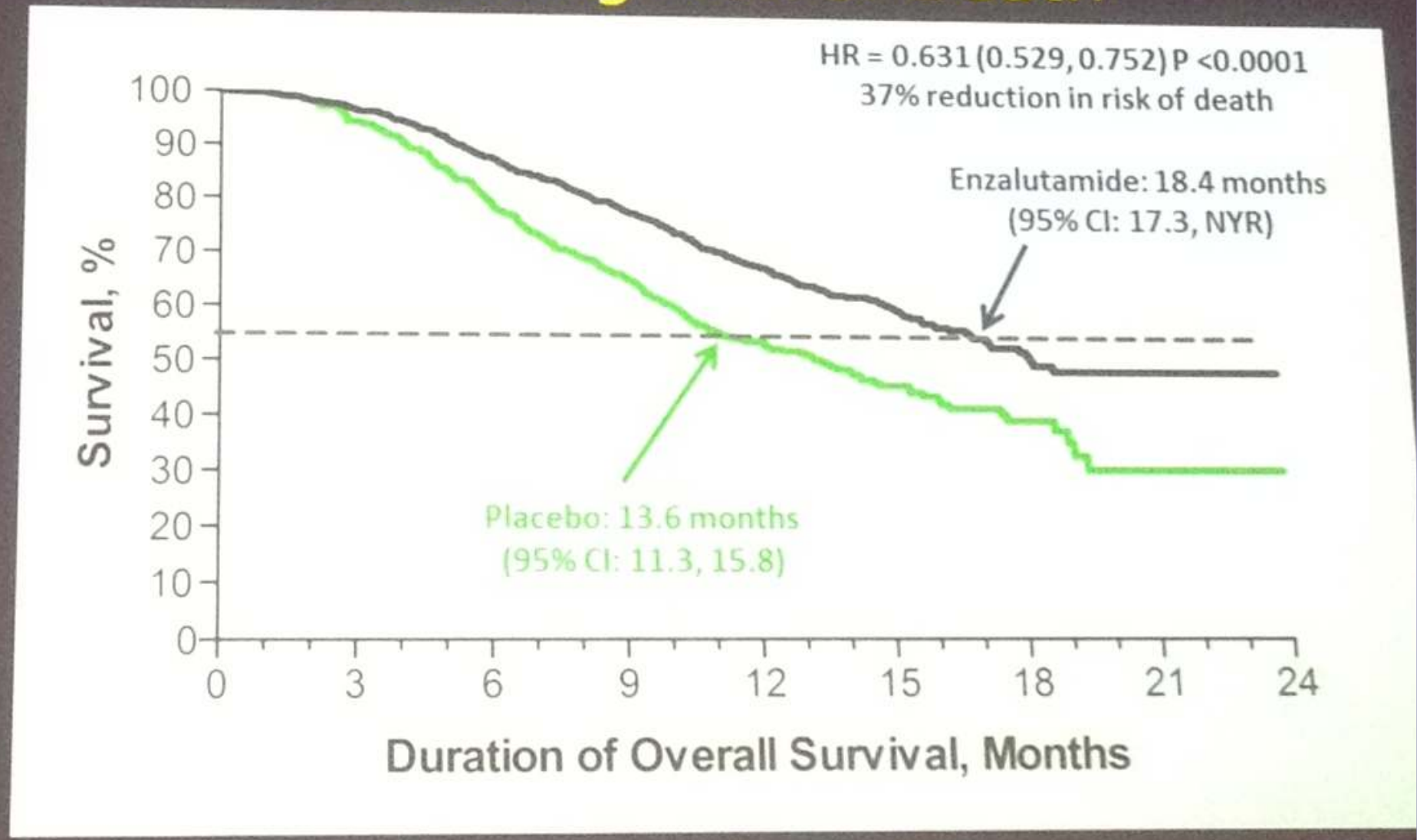
Glucocorticoids were not required but allowed.

PCWG2 criteria used (continue therapy through minor PSA changes; confirm bone scan 'progression'; focus on benefit not response).*

Recruitment in 156 centers from 15 countries and 5 continents.
Enrollment between September 2009 and November 2010.

HI SCHER, NEJM, 2012

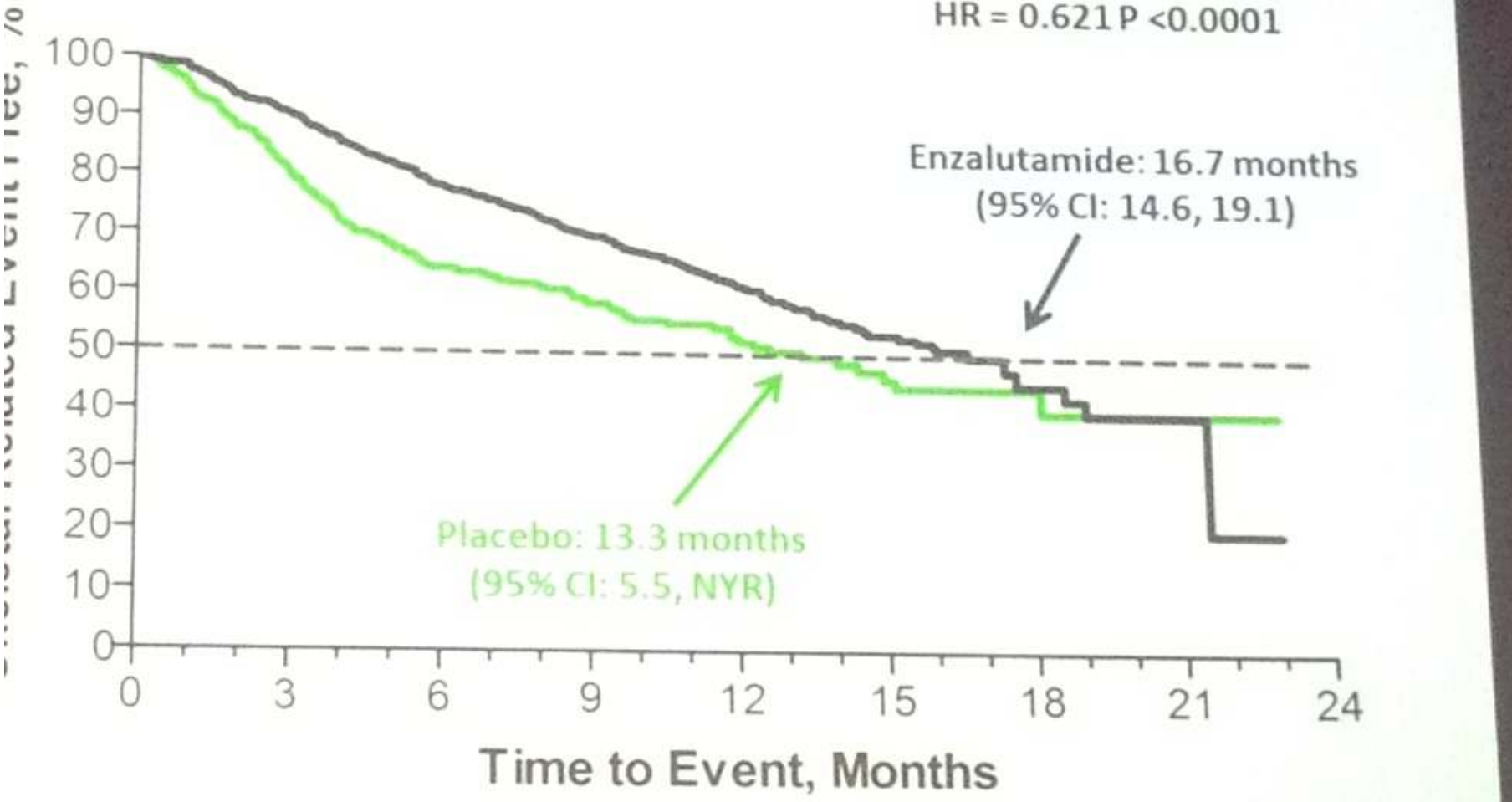
Enzalutamide Prolonged Survival, Reducing Risk of Death



Enzalutamide	800	775	701	627	400	211	72	7	0
Placebo	399	376	317	263	167	81			

HI SCHER, NEJM, 2012

Time to First Skeletal Related Event

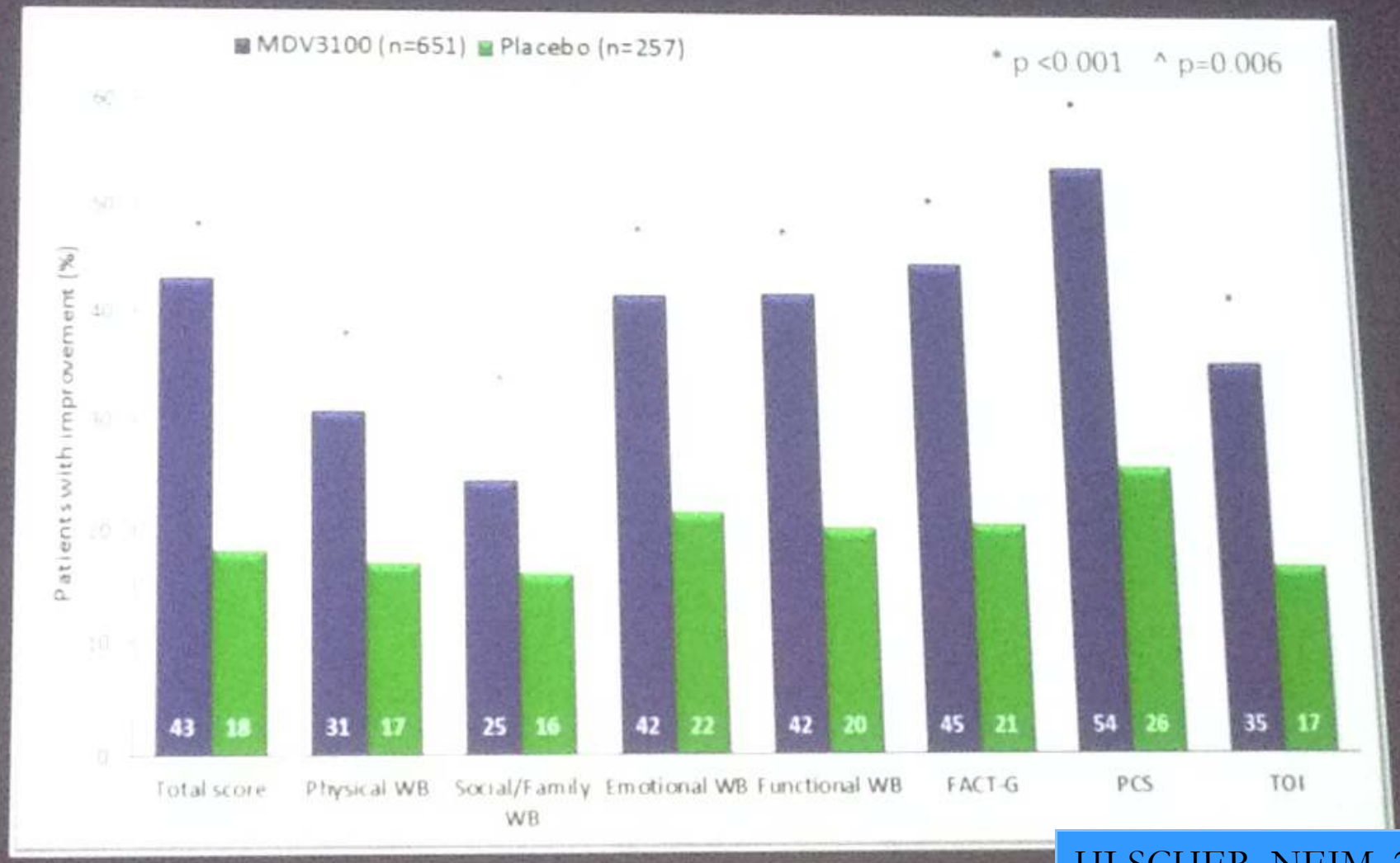


amide	800	676	548	379	209	87	19	2	0
bo	399	278	196	128	68	33	11	0	0

HI SCHER, NEJM, 2012

Quality-of-Life Responses by FACT-P

Analysis includes all patients with baseline and post-baseline values.



HI SCHER, NEJM, 2012

Abstract 4513

Cabozantinib (XL184) in chemotherapy-pretreated metastatic castration resistant prostate cancer (mCRPC): Results from a phase II nonrandomized expansion cohort (NRE).

Autori, Matthew Raymond Smith, Christopher Sweeney, Dana E. Rathkopf, Howard I. Scher, Christopher Logothetis, Daniel J. George, Celestia S. Higano, Evan Y. Yu, Andrea Lynne Harzstark, Eric Jay Small, A. Oliver Sartor, Michael S. Gordon, Nicholas J. Vogelzang, David C. Smith, Maha Hussain, Johann Sebastian De Bono, Naomi B. Haas, Christian Scheffold, Yihua Lee, Paul G. Corn;

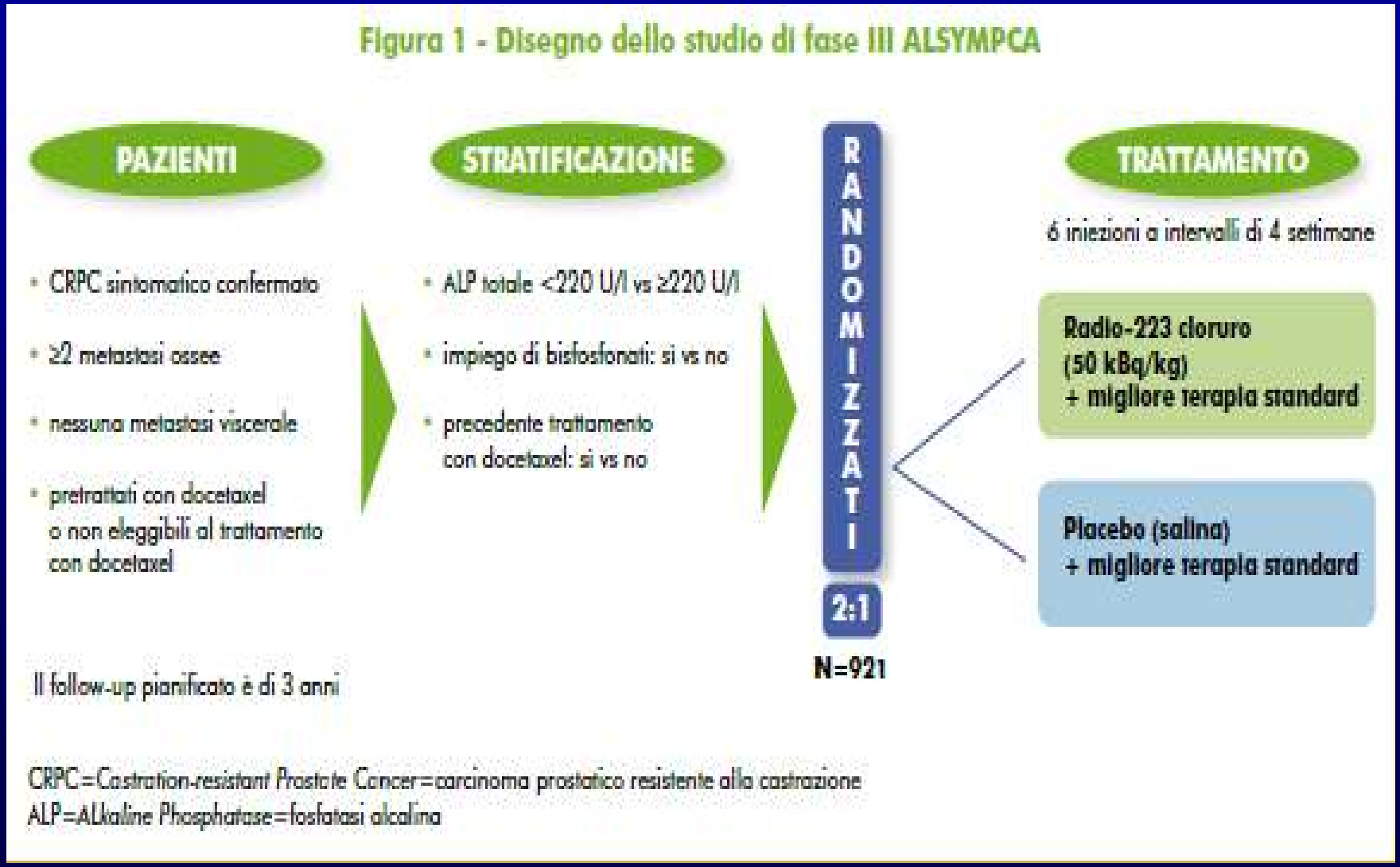
ASCO 2012

Risposta sulle lesioni ossee (revisione indipendente)

Valutazione della BSLA tramite CAD	
Pazienti complessivi (n=93)[a]	n (%)
Risposta delle lesioni ossee	62 (67)
Completa (100% riduzione della BSLA)	4 (4)
Parziale (≥30% di riduzione della BSLA)	58 (62)
Stabile	15 (16)
Progressione	7 (8)
Durata mediana della risposta, mesi (range)	5,4 (5,0 - 6,9)

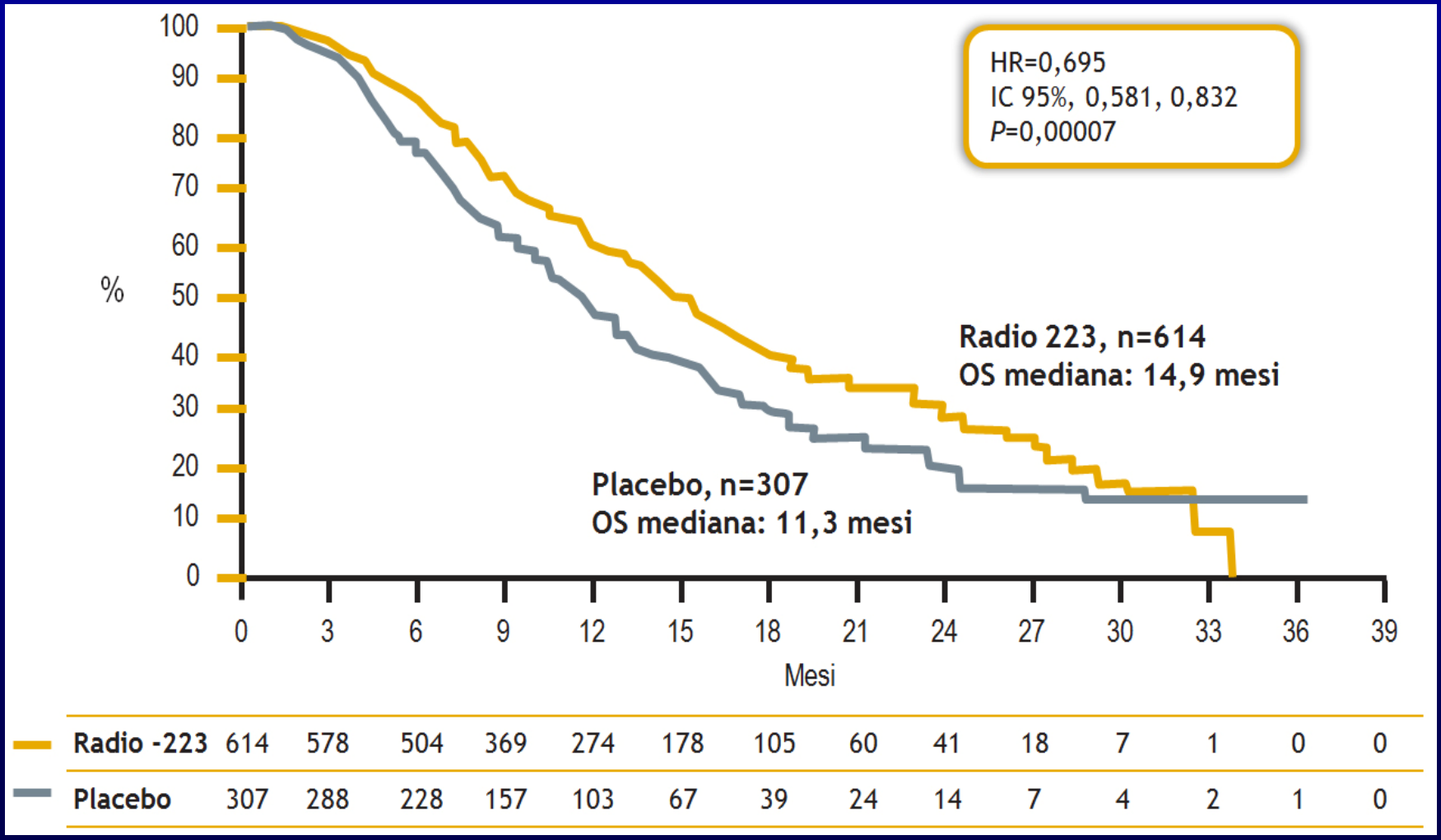
[a] scansioni ossee successive al basale erano disponibili solo per 84 pazienti

Radio-223



A.O. Sartor et al, ASCO GU, 2012

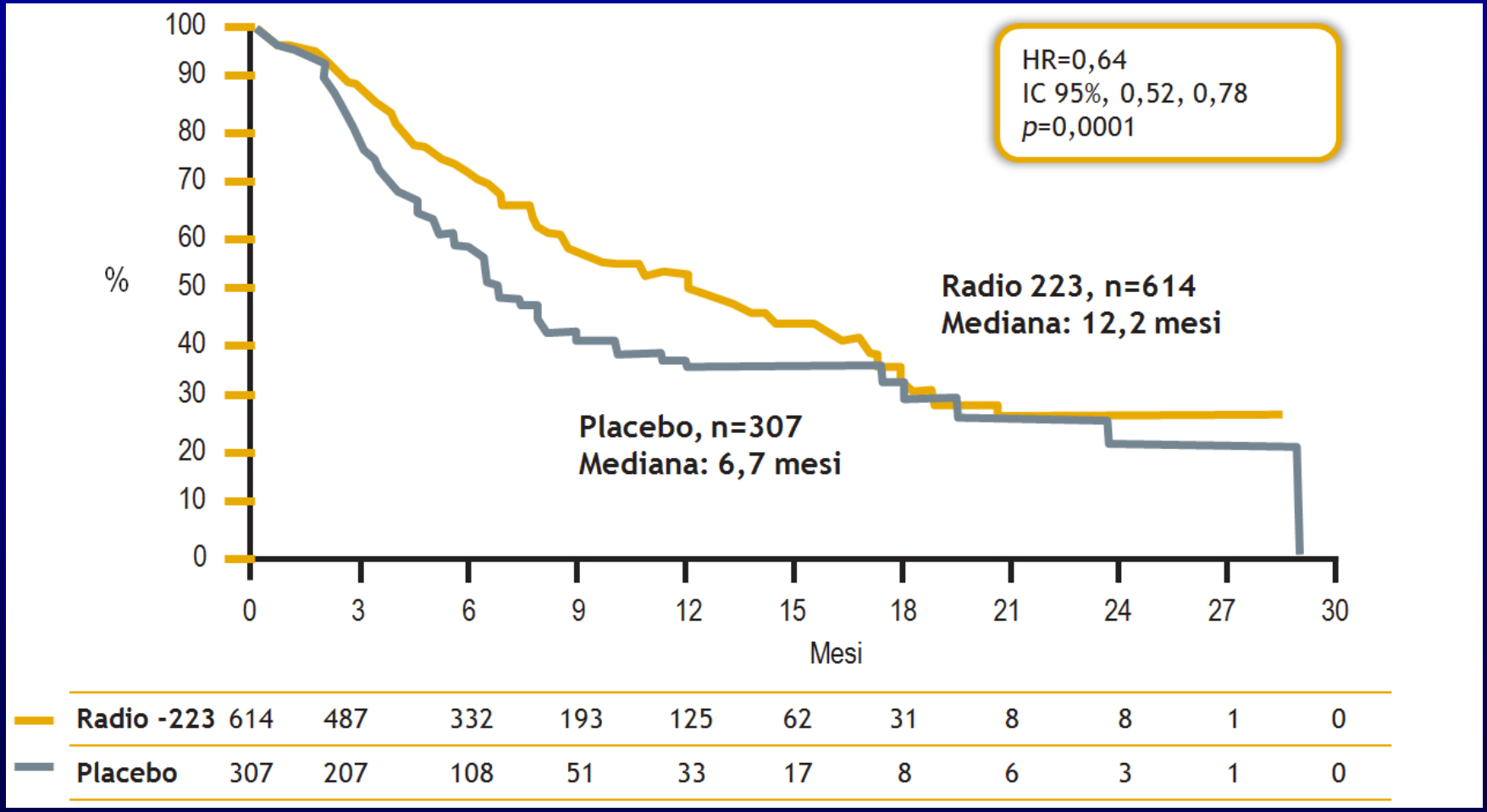
Analisi aggiornata della sopravvivenza globale



Radio -223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

C Parker et al, ASCO, 2012

Analisi aggiornata del tempo allo sviluppo del primo evento scheletrico



Radio -223	614	487	332	193	125	62	31	8	8	1	0
Placebo	307	207	108	51	33	17	8	6	3	1	0

C Parker et al, ASCO, 2012

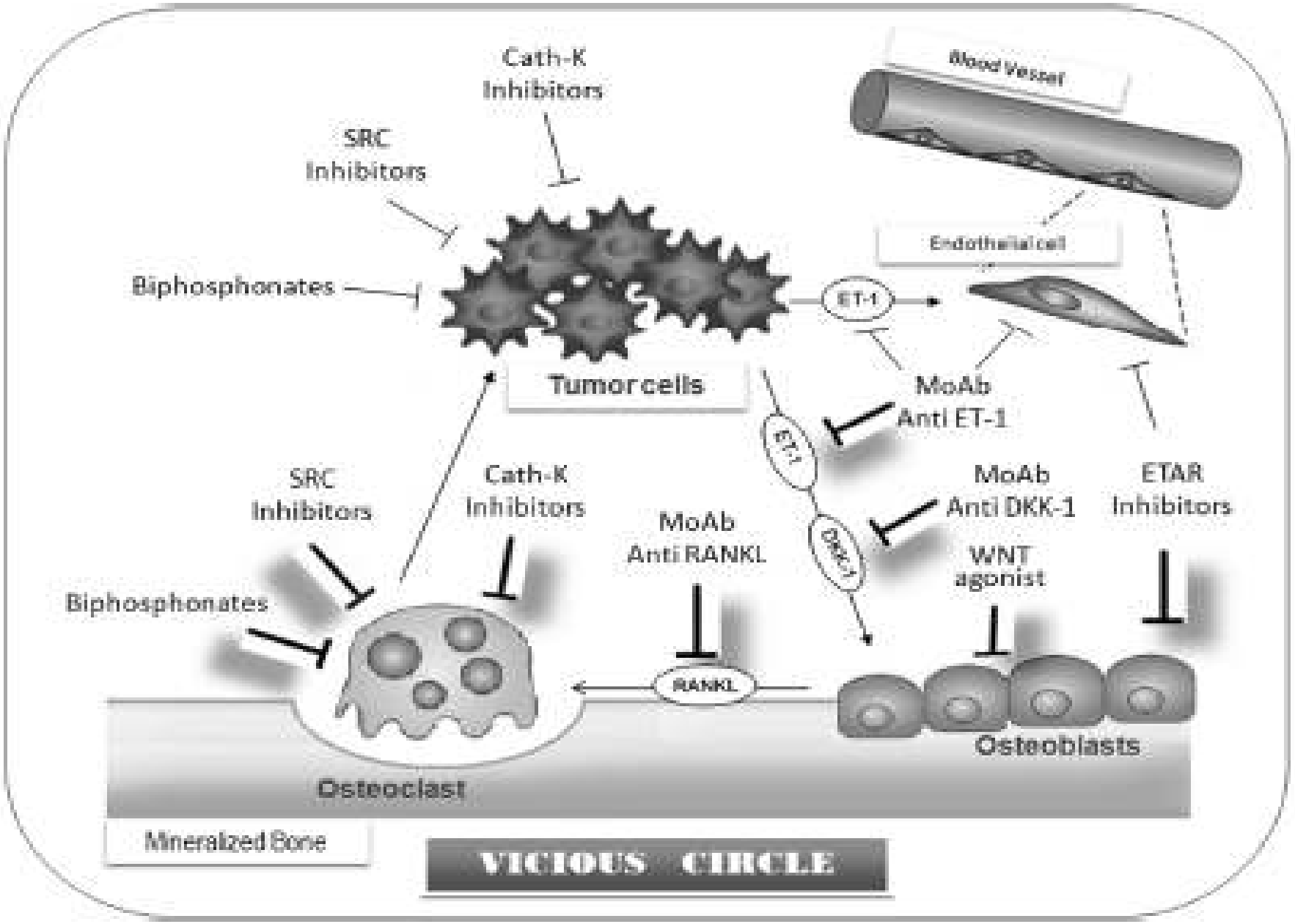


Fig. 1. Vicious circle pathways and/or molecules potential candidates in targeting bone metastases.

Santini D et al. Cancer Treat Reviews, 2010

Thank you very much for your attention