Novità nel trattamento delle metastasi ossee

Cinzia Ortega

Oncologia Medica

IRCC Candiolo

Fondazione del Piemonte per l'Oncologia

Multidisciplinary approach

- Medical treatment
  - Antineoplastic therapy
    - chemotherapy
    - “target therapies”
    - hormonal treatment
  - Analgesics
  - **“targeting bone metastasis”**
- Radiotherapy
- Surgical treatment
- Radiometabolic therapy
- Interventional radiology

Therapeutic strategies for treatment of bone metastases

Osteoclast inhibitors

Bisphosphonates
Anti RANK Ligand MoAB
Endothelin A inhibitors
Cathepsin K inhibitors
Src inhibitors
PTHrP antibody

Other Cellular Targets

Platelets: LPA
Endotelial cells: PDGFR, PIGF
Anti CTGF
CXCR4 antagonist
HDAC inhibitors
Cox-2
Proteosome inhibition
Anti-integrin
TGF-β inhibitors
ETRA
Wnt inhibitors

PTHrP, parathyroid hormone-related peptide; LPA, lysophosphatidic acid; PDGFR, platelet-derived growth factor receptor; PIGF, placental growth factor; CTGF, connective tissue growth factor; HDAC, histone deacetylase; TGFβ, trasforming growth factor-beta; ETRA, endothelin receptor A.

Therapeutic strategies for treatment of bone metastases

Osteoclast inhibitors

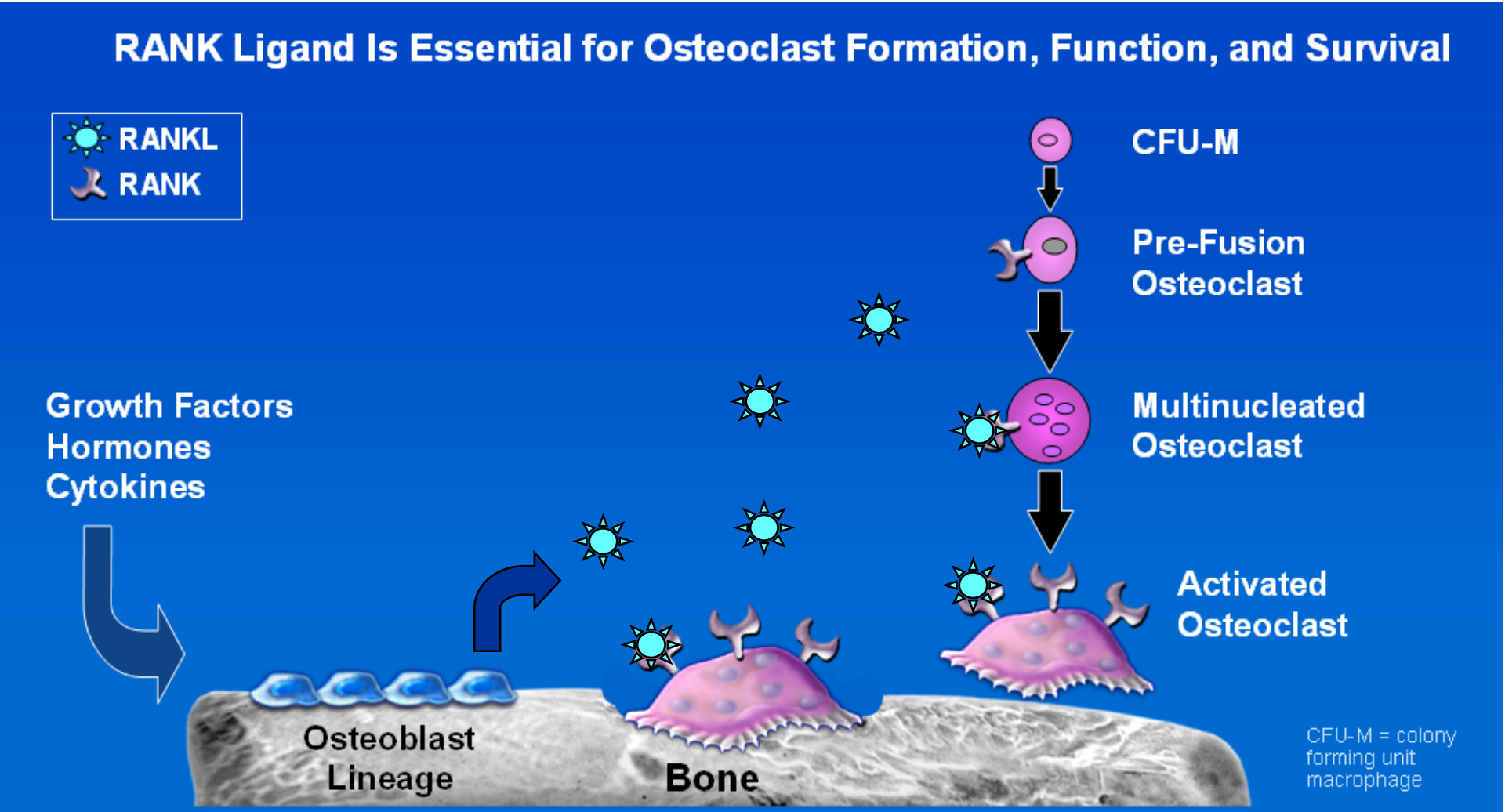
Bisphosphonates
Anti RANK Ligand MoAB
Endothelin A inhibitors
Cathepsin K inhibitors
Src inhibitors
PTHrP antibody

Other Cellular Targets

Platelets: LPA
Endotelial cells: PDGFR, PIGF
Anti CTGF
CXCR4 antagonist
HDAC inhibitors
Cox-2
Proteosome inhibition
Anti-integrin
TGF-β inhibitors
ETRA
Wnt inhibitors

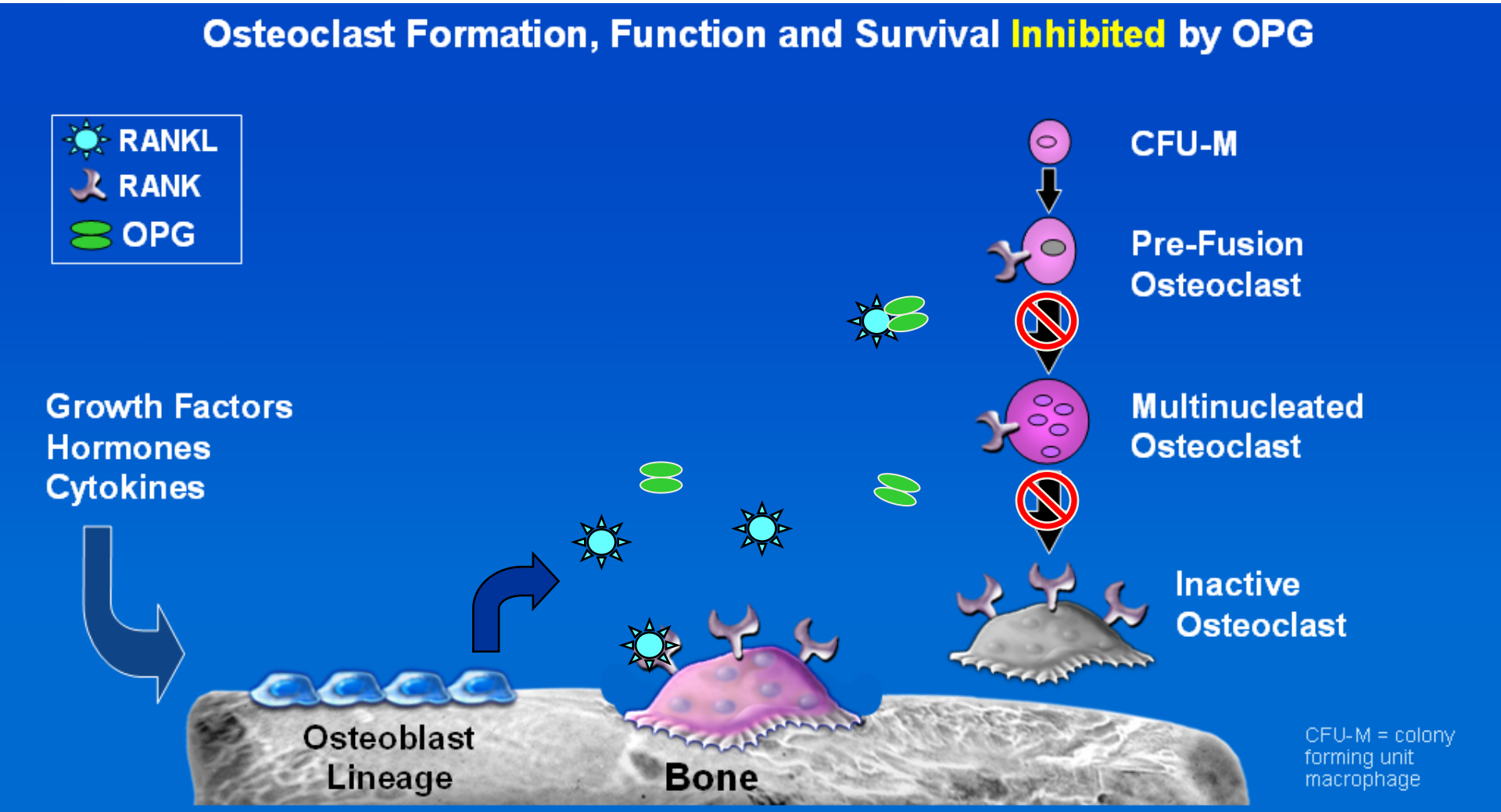
PTHrP, parathyroid hormone-related peptide; LPA, lysophosphatidic acid; PDGFR, platelet-derived growth factor receptor; PIGF, placental growth factor; CTGF, connective tissue growth factor; HDAC, histone deacetylase; TGFβ, trasforming growth factor-beta; ETRA, endothelin receptor A.

RANK Ligand, an Essential Mediator of Osteoclast Activity



Adapted from Boyle WJ et al. *Nature*. 2003;423:337-42.

Osteoprotegerin (OPG) neutralize effects of RANK Ligand



Adapted from Boyle WJ et al. *Nature*. 2003;423:337-42.

Denosumab: a RANK ligand inhibitor

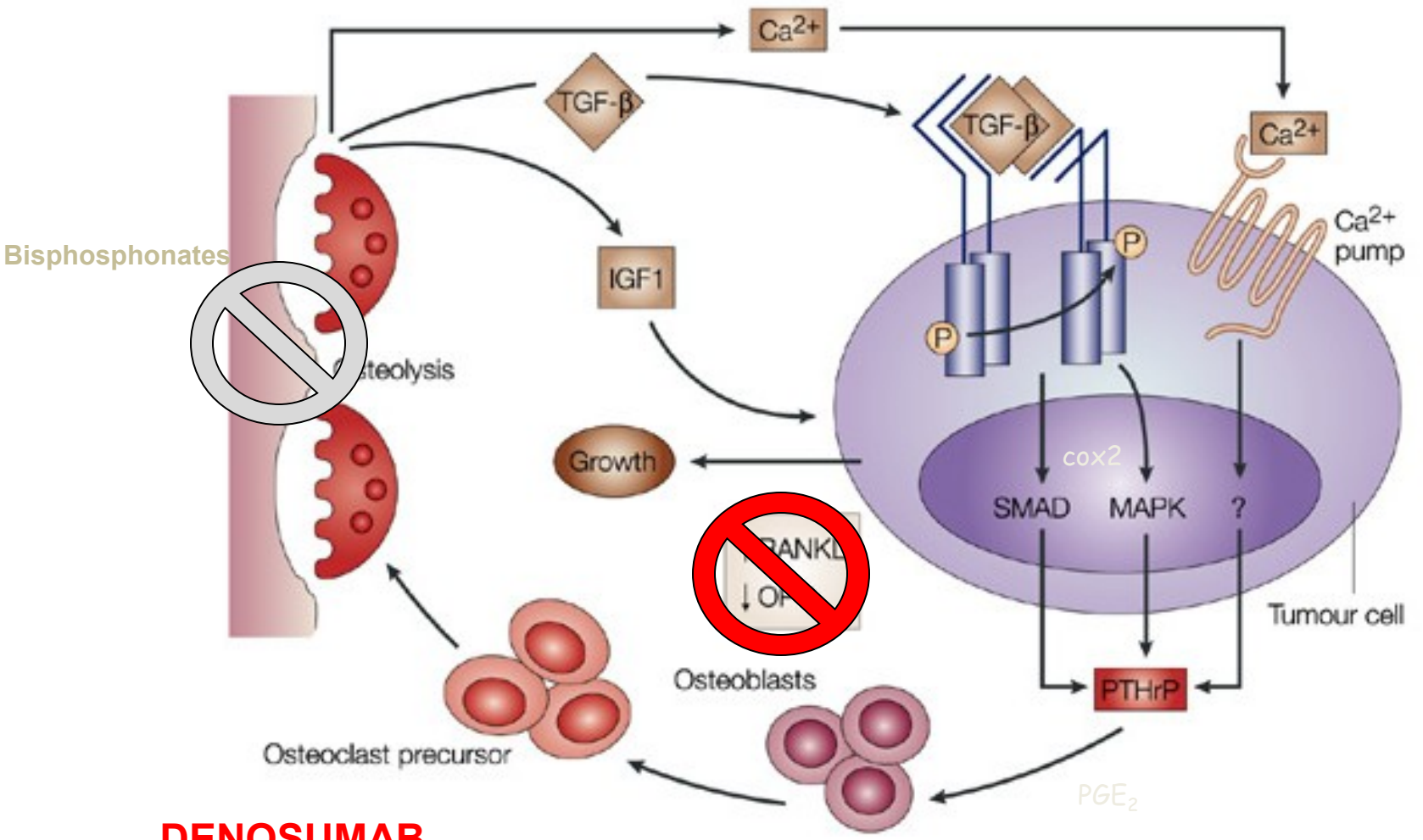
- **Fully human monoclonal antibody**
- **High affinity for human RANK Ligand**
- High specificity for RANK Ligand
  - No detectable binding to TNFα, TNFβ, TRAIL, or CD40L
- No neutralizing antibodies detected in clinical trials to date

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

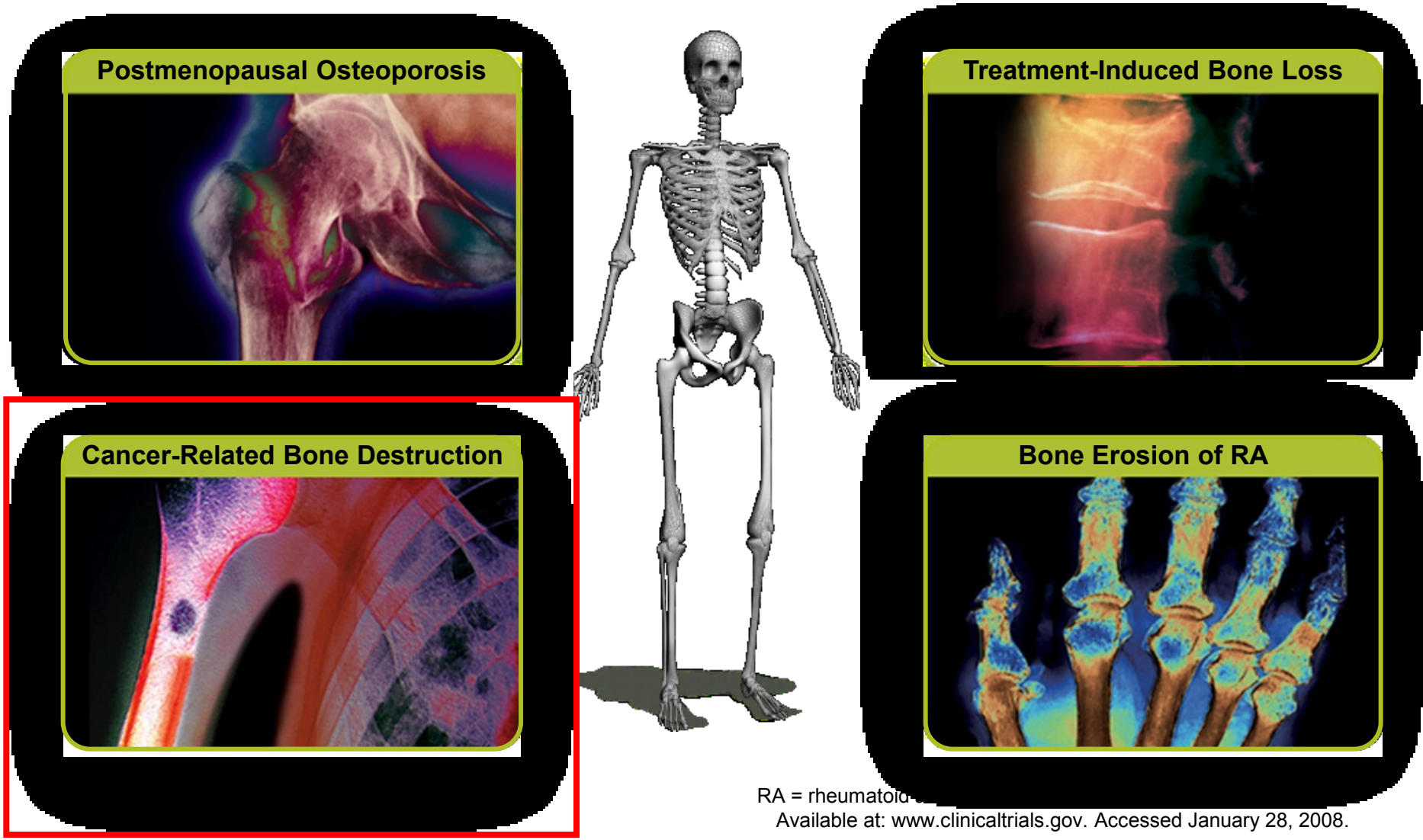
The "Vicious Circle" Hypothesis of Osteolytic Metastases



DENOSUMAB

Adapted from Mundy GR, et al. *Nat Rev Cancer*. 2002;2(8):584-593.

Denosumab Is Being Investigated in Several Conditions of Bone Loss and Destruction



RA = rheumatoid

Available at: www.clinicaltrials.gov. Accessed January 28, 2008.

Denosumab oncology programme overview

Phase 1	Phase 2	Phase 3
BrCa & MM - PK/PD	Breast cancer - PK/PD (Bisphosphonate naïve)[2]	Breast cancer – AI bone loss[7] 20040135 / 20050209 ABCSG
	Solid tumours & MM - PK/PD (Bisphosphonate treated)[3,4]	Prostate cancer – ADT bone loss 20040138
	Giant cell tumour[6]	Prostate cancer – delay of bone mets 20050147
	Multiple myeloma[5]	Breast cancer - SRE 20050136
		Prostate cancer – SRE 20050103
		Solid tumours & MM – SRE 200540244

SRE = skeletal-related event

[1]Body J J, *et al*. Clin. Cancer Res 2006; 12:1221-1228; [2]Lipton A, *et al*. J Clin Oncol 2007; 25:4431-4437; [3]Suarez T *et al*. J Clin Oncol 2006;24(S18):6S:8562; [4]Fizazi K, *et al*. J Clin Oncol 2008; 26:(176S):3596 and poster; [5]Vij *et al*. Blood 2007; 110(11):3604; [6]Thomas *et al*. CTOS, 2007:787; [7]Ellis G, *et al*. J Clin Oncol 2008:epub, Aug 25.

VOLUME 27 · NUMBER 10 · APRIL 1 2009

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Phase II Trial of Denosumab in Patients With Bone Metastases From Prostate Cancer, Breast Cancer, or Other Neoplasms After Intravenous Bisphosphonates

ABSTRACT

Purpose
Patients with bone metastases and elevated urinary N-telopeptide (uNTx), representing excessive bone resorption, are at increased risk for skeletal-related events (SREs), cancer progression, and death. Osteoclast-mediated bone resorption is regulated by RANKL. We evaluated the effect of denosumab, a fully human monoclonal antibody against RANKL, in patients with bone metastases and elevated uNTx levels despite ongoing intravenous (IV) bisphosphonate (BP) therapy.

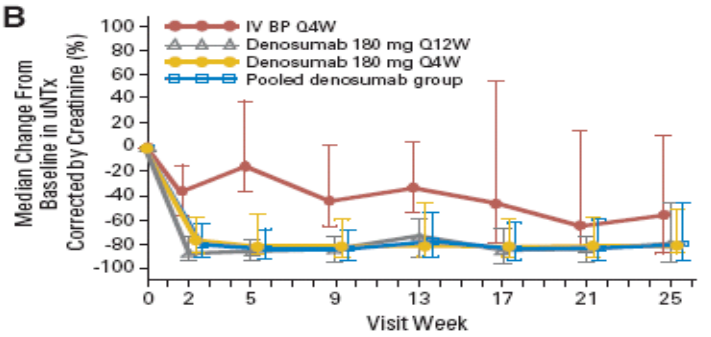
Patients and Methods
Eligible patients had histologically confirmed malignancy, ≥ 1 bone metastases, and uNTx levels higher than 50 nmol/L bone collagen equivalents (BCE)/mM creatinine despite IV BPs. They were stratified by tumor type and screening uNTx levels (50 to 100 or > 100 nmol/L BCE/mM creatinine), and randomly assigned to continue IV BPs every 4 weeks or receive subcutaneous denosumab 180 mg every 4 weeks or every 12 weeks.

Results
Among 111 patients accrued, the primary end point of uNTx levels lower than 50 nmol/L BCE/mM creatinine (uNTx < 50) at week 13 was achieved by 49 (71%) of 69 patients in the denosumab arms, compared with 10 (29%) of 35 patients in the IV BP arm ($P < .001$). The proportion of patients with uNTx lower than 50 was maintained at week 25 (64% denosumab arms; 37% IV BP arm; $P = .01$). The incidence of SREs was six (8%) of 73 and six (17%) of 35 in the denosumab group and IV BP group, respectively. Rates of adverse events were similar between treatment groups.

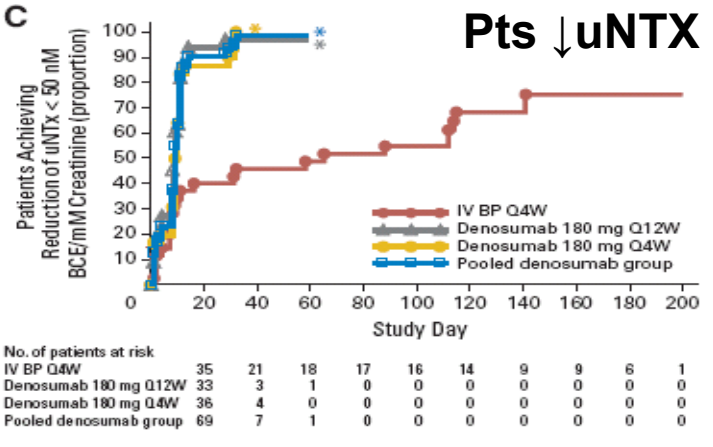
Conclusion
Among patients with elevated uNTx despite ongoing IV BP therapy, denosumab normalized uNTx levels more frequently than the continuation of IV BP. Fewer patients receiving denosumab experienced on-study SREs than those receiving IV BPs.

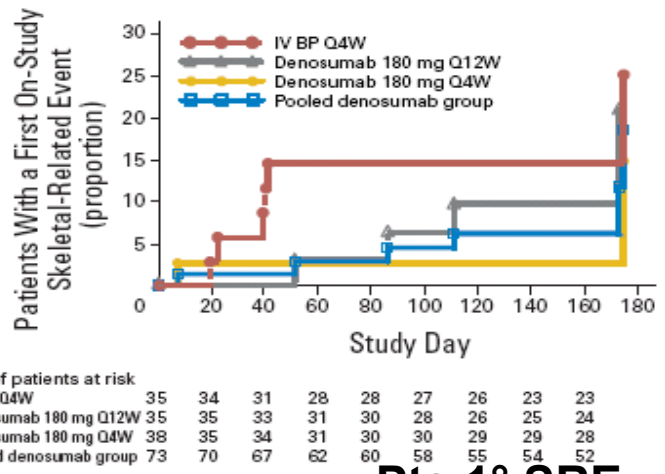
Fizazi, JCO 2009

↓ uNTX



Pts ↓uNTX





Pts 1° SRE

Denosumab Versus Zoledronic Acid for the Treatment of Breast Cancer Patients with Bone Metastases: Results of a Randomized Phase 3 Study

Stopeck A, et al. *Eur J Can Suppl.* 2009;7:2.
Abstract 2LBA and Oral Presentation ECCO 15/ESMO 34 2009

Key Inclusion

Adults with advanced breast cancer and confirmed bone metastases

Key Exclusion

Current or prior intravenous bisphosphonate administration

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

Supplemental Calcium and Vitamin D

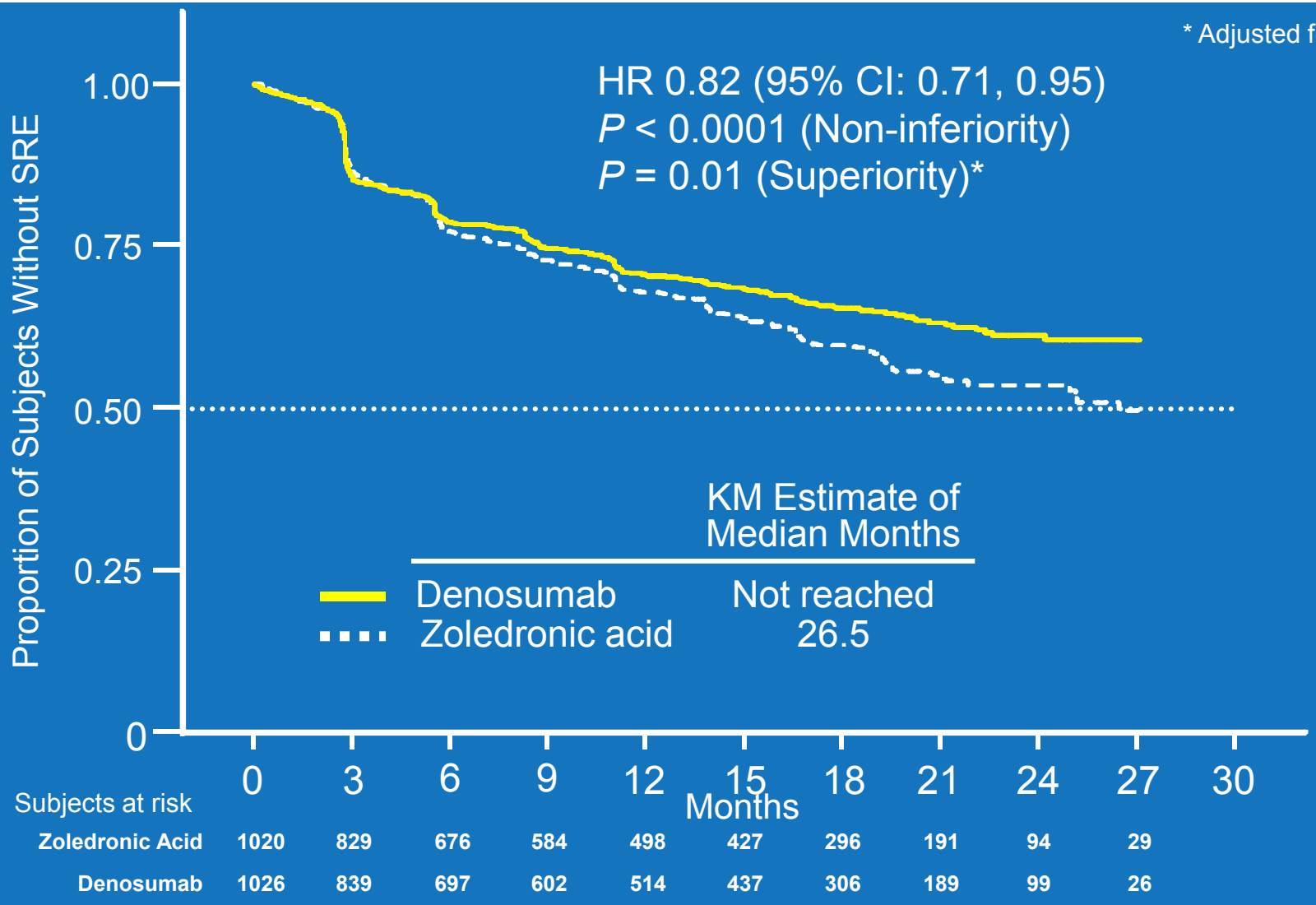
N = 1020 **Zoledronic acid 4 mg IV*** and SC placebo every 4 weeks

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)

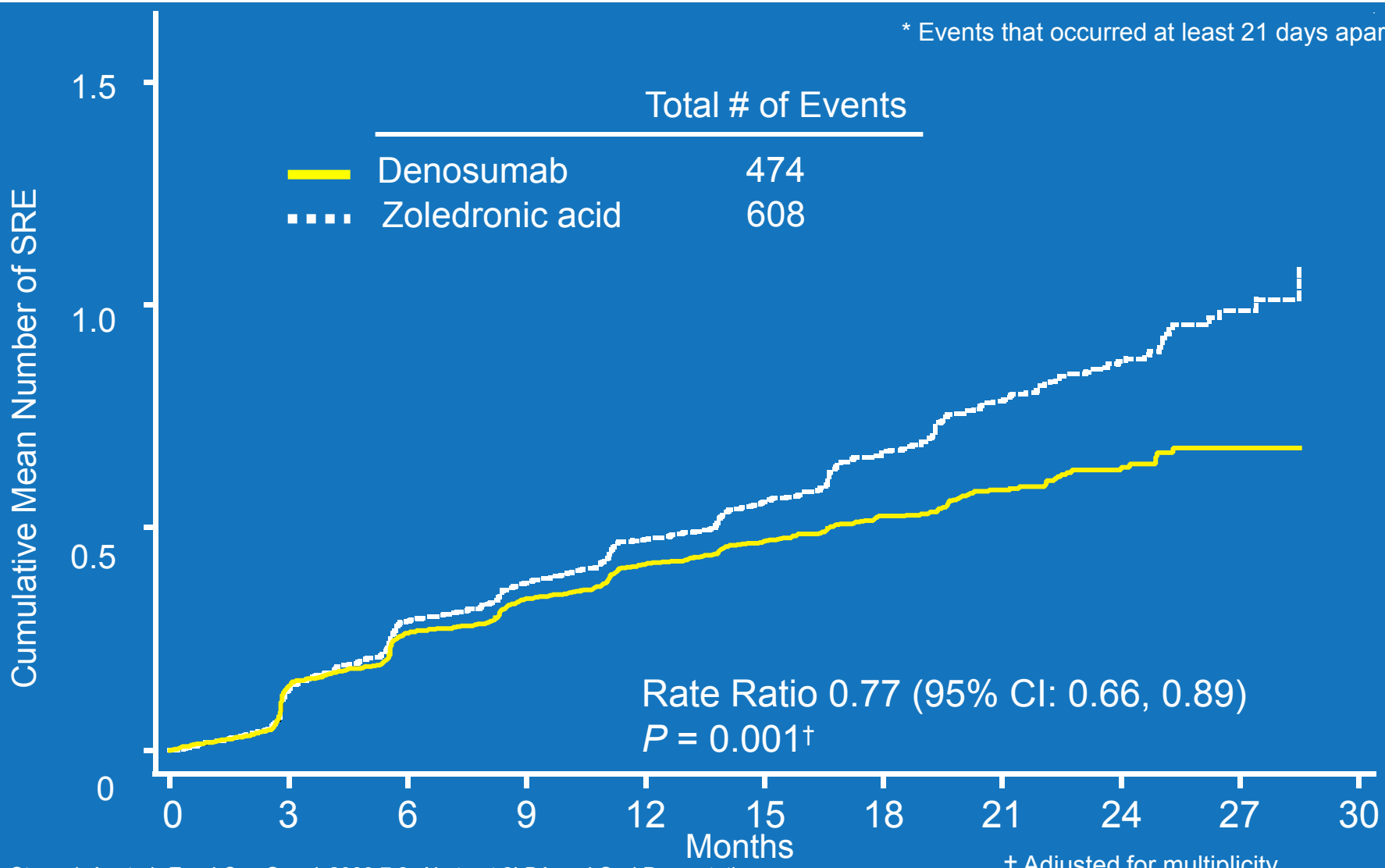
Denosumab is investigational and is not marketed anywhere in the world.

Time to First On-Study SRE



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

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



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

† Adjusted for multiplicity

Adverse Events of Interest

Event, n (%)	Zoledronic Acid (N = 1013)	Denosumab (N = 1020)
Infectious AEs	494 (48.8)	473 (46.4)
Infectious serious AEs	83 (8.2)	71 (7.0)
Acute phase reactions (first 3 days)	277 (27.3)	106 (10.4)
Potential renal toxicity AEs*	86 (8.5)	50 (4.9)
Renal failure	25 (2.5)	2 (0.2)
Acute renal failure	7 (0.7)	1 (< 0.1)
Cumulative rate of ONJ†	14 (1.4)	20 (2.0)
Year 1	5 (0.5)	8 (0.8)
Year 2	12 (1.2)	19 (1.9)
New primary malignancy	5 (0.5)	5 (0.5)

*Includes blood creatinine increased, hypercreatininemia, oliguria, renal impairment, proteinuria, renal failure, urine output decreased, creatinine renal clearance decreased, renal failure acute, renal function test abnormal, anuria, blood urea increased, renal failure chronic

No neutralizing anti-denosumab antibodies were detected

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

† $P = 0.39$

20050244 ST

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

Henry D, et al. *Eur J Can Suppl.* 2009;7:11.
Abstract 20LBA and Oral Presentation. ECCO 15/ESMO 34 2009

Key Inclusion

Adults with solid tumors and bone metastases (excluding breast and prostate) or multiple myeloma

Key Exclusion

Current or prior intravenous bisphosphonate administration

N = 886 **Denosumab 120 mg SC** and Placebo IV* every 4 weeks

Supplemental Calcium and Vitamin D

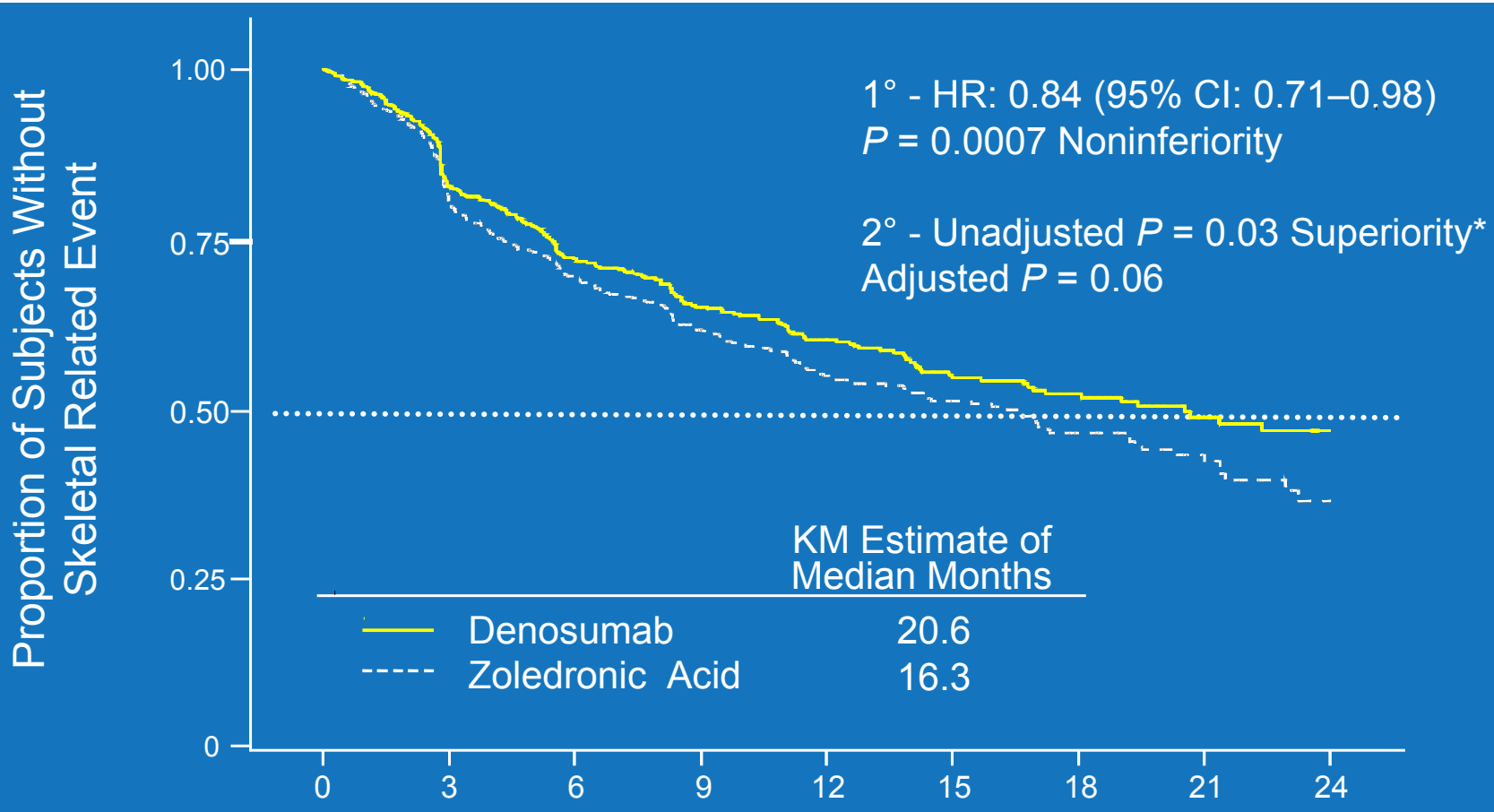
N = 890 **Zoledronic acid 4 mg IV*** and SC placebo every 4 weeks

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)

Denosumab is investigational and is not marketed anywhere in the world.

Time to First On-Study SRE

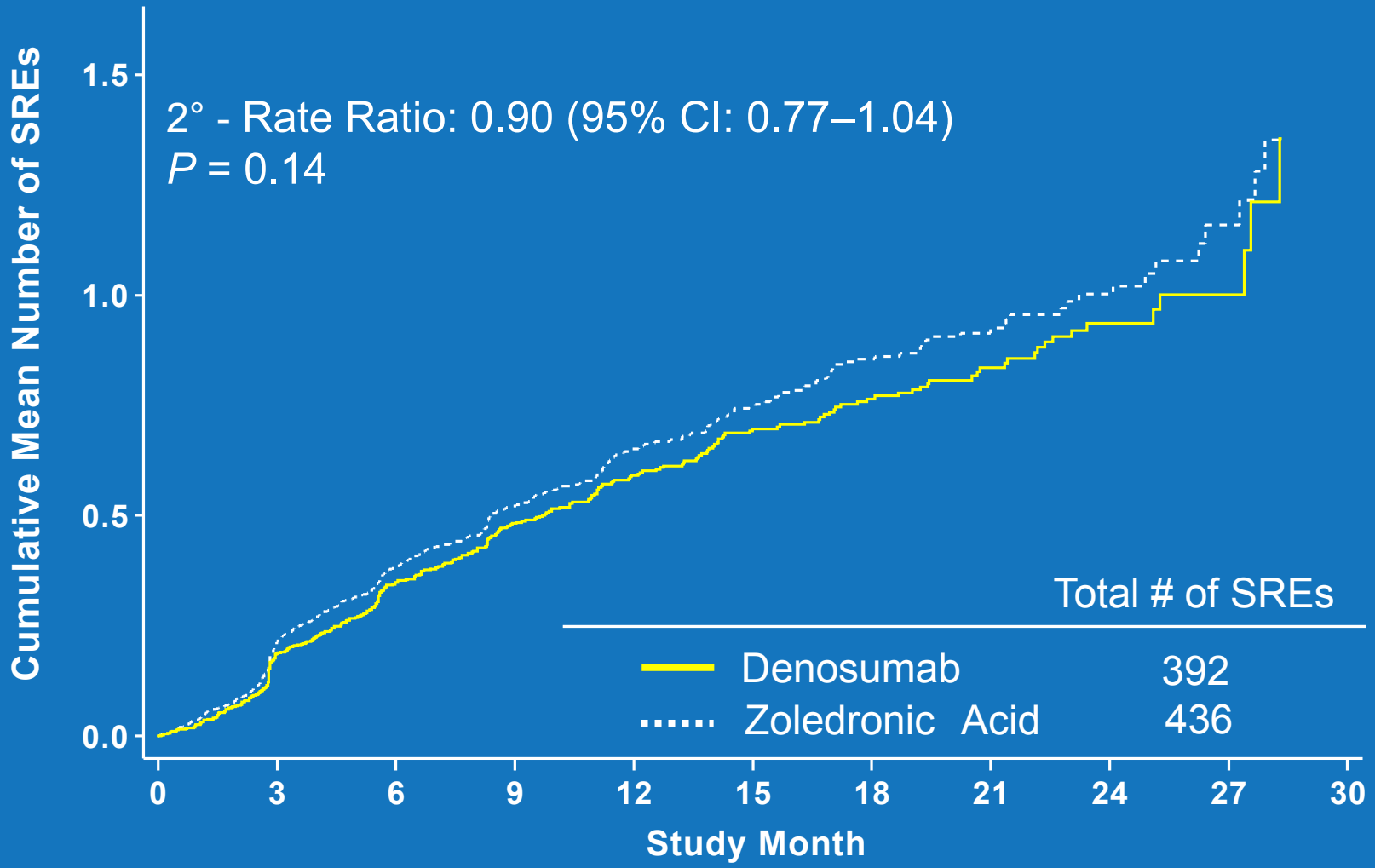


Subjects at Risk								
Zoledronic Acid	890	578	376	261	194	126	86	47
Denosumab	886	582	387	266	202	134	96	55

*Due to multiplicity adjustment

Henry D, et al. *Eur J Can Suppl.* 2009;7:11. Abstract 20LBA and Oral Presentation.

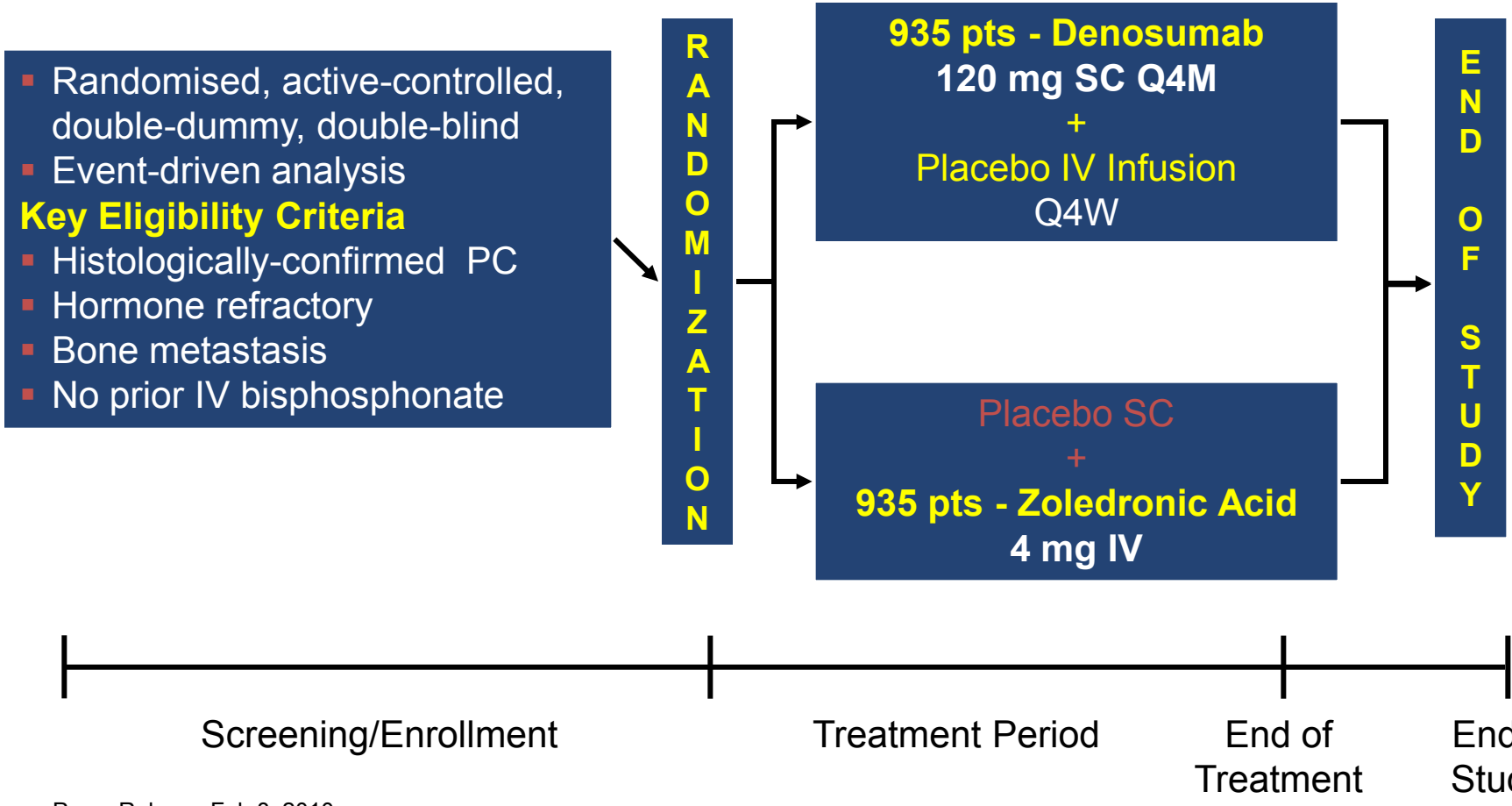
Time to First-and-Subsequent On-Study SRE (Multiple Event Analysis)



Henry D, et al. *Eur J Can Suppl.* 2009;7:11. Abstract 20LBA and Oral Presentation.

Study Schema

20050103: Advanced Prostate Cancer – delay of SRE



Amgen Press Release Feb 8, 2010

*Event-driven

Ibrahim T, Personal communication , Milan 2010

Phase 3 Study Comparing Denosumab with Zoledronic Acid in the Treatment of Bone Metastases in Patients with Advanced Prostate Cancer: Results

- Study met primary and secondary endpoints
- Denosumab demonstrated superiority for both delaying the time to the first on-study SRE and delaying of time to the first-and-subsequent SREs
- Both results were statistically significant

Endpoint	HR (95% CI)
Delaying the time to first on-study SRE	0.82 (0.71,0.95)
Delaying the time to first-and-subsequent SREs	0.82 (0.71,0.94)

Amgen Press Release Feb 8, 2010

"Denosumab is investigational and is not marketed anywhere in the world"

Ibrahim T, Personal communication , Milan 2010

Therapeutic strategies for treatment of bone metastases

Osteoclast inhibitors

Bisphosphonates
Anti RANK Ligand MoAB
Endothelin A inhibitors
Cathepsin K inhibitors
Src inhibitors
PTHrP antibody

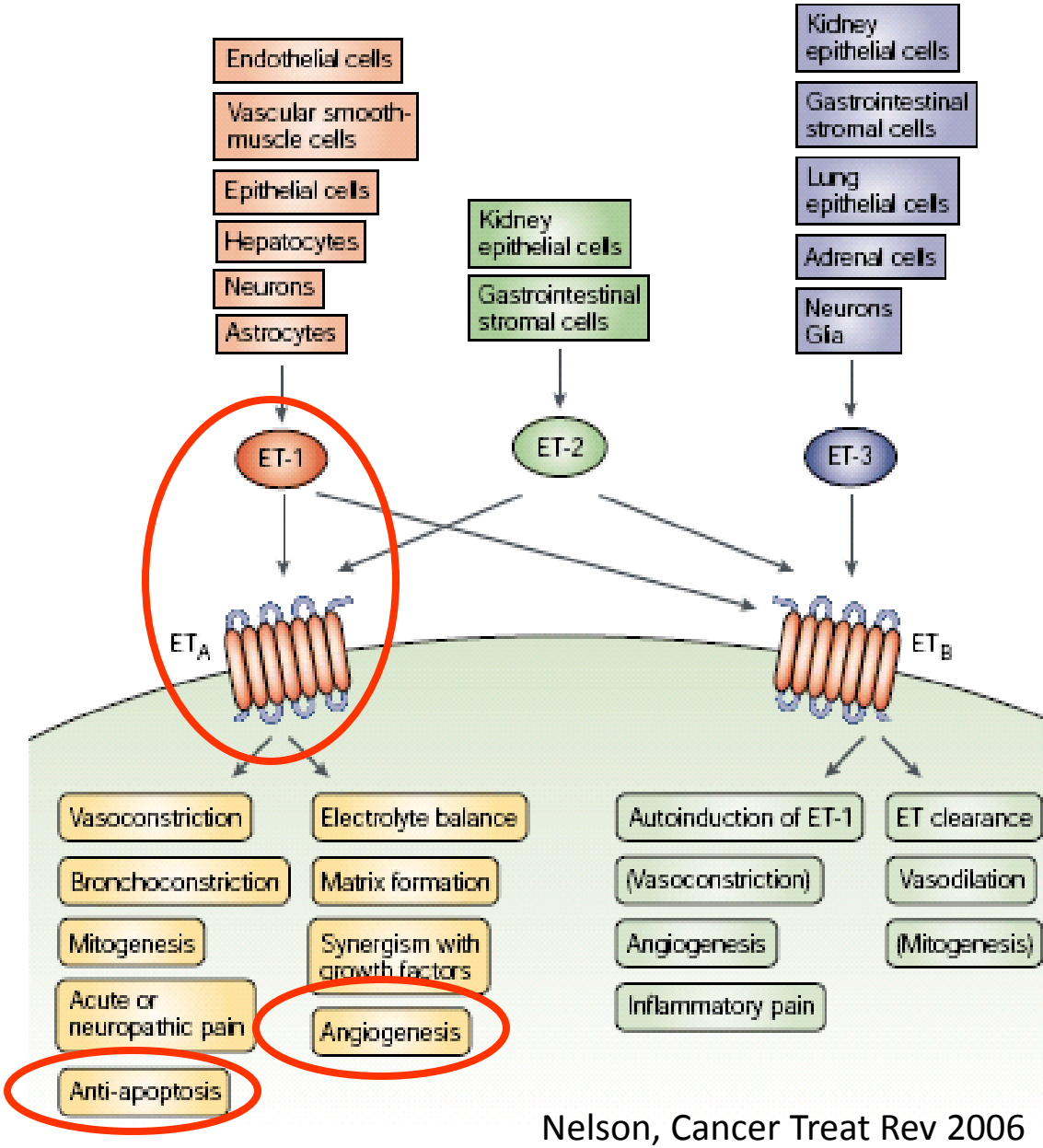
Other Cellular Targets

Platelets: LPA
Endotelial cells: PDGFR, PIGF
Anti CTGF
CXCR4 antagonist
HDAC inhibitors
Cox-2
Proteosome inhibition
Anti-integrin
TGF-β inhibitors
ETRA
Wnt inhibitors

PTHrP, parathyroid hormone-related peptide; LPA, lysophosphatidic acid; PDGFR, platelet-derived growth factor receptor; PIGF, placental growth factor; CTGF, connective tissue growth factor; HDAC, histone deacetylase; TGFβ, trasforming growth factor-beta; ETRA, endothelin receptor A.

Endothelin axis

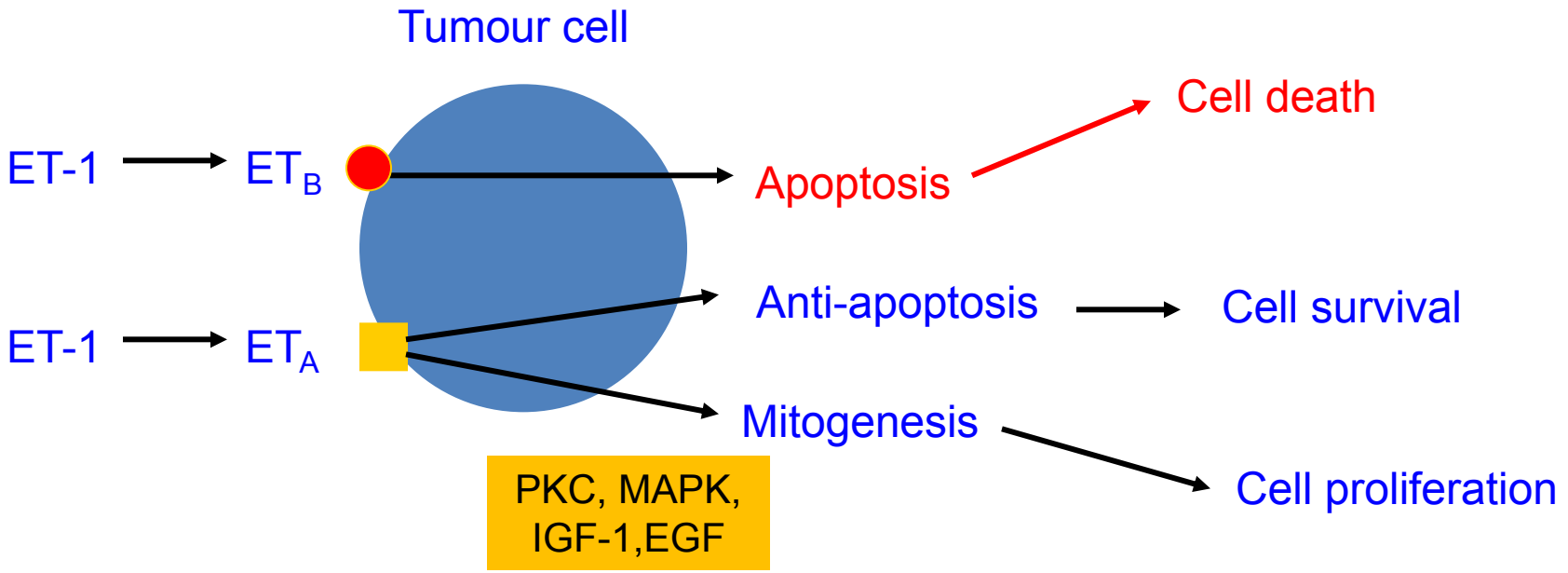
- The endothelins (ETs) comprise a family of three small (21-amino-acid) peptides: ET-1, ET-2 and ET-3.
- ET-1 is a potent endogenous vasoconstrictor and a progression factor in many tumour types
- **ET_A-receptor activation by ET-1 contributes to tumour growth and progression**
- ET_B: decoy receptor for ET1 and clearance mechanism
- ET_A-receptor blockade might improve cancer treatment



Nelson, Cancer Treat Rev 2006

Endothelin A (ET-1) receptor antagonist

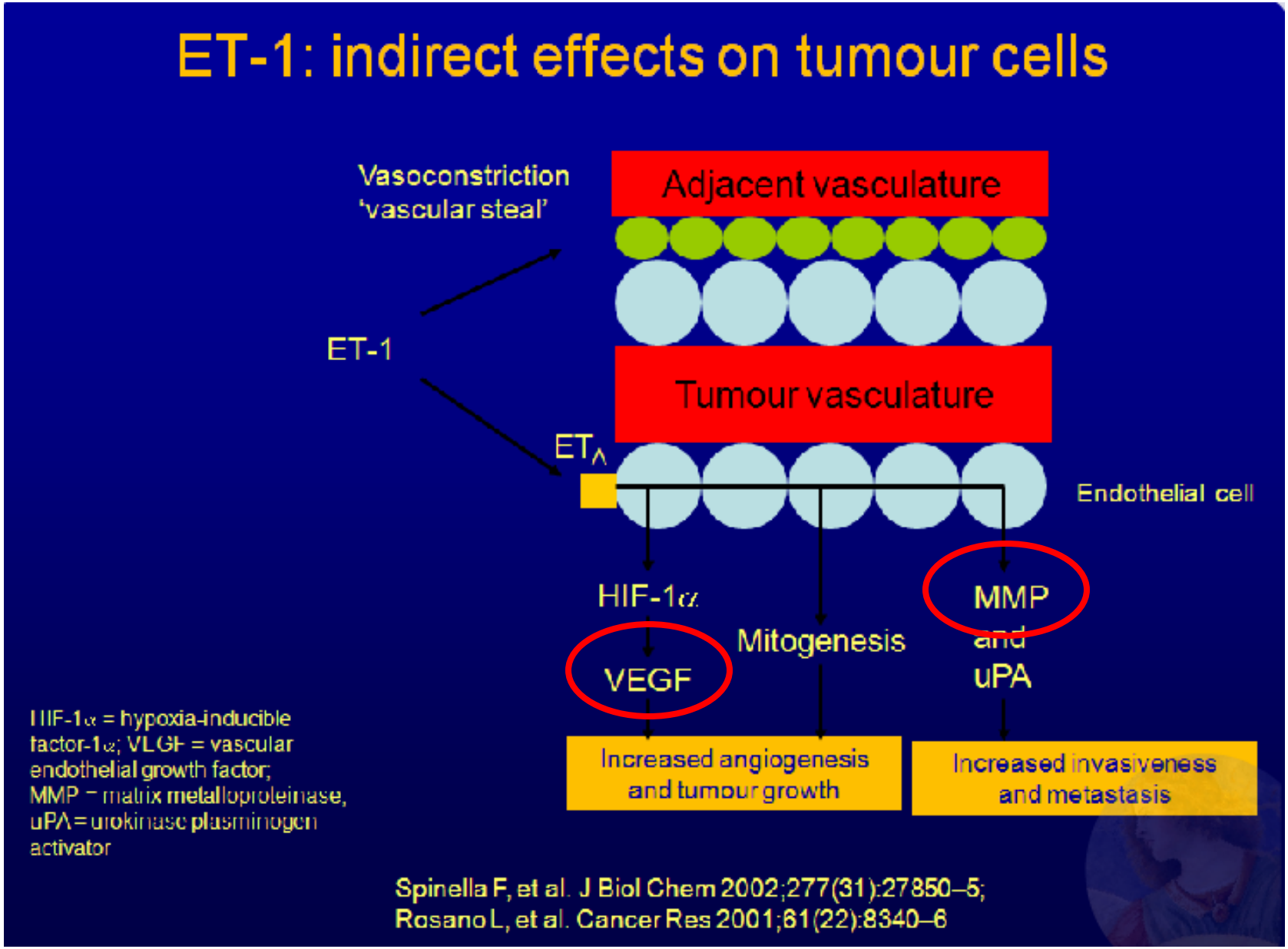
ET-1: direct effects on tumour cells



ET_A = endothelin receptor A;
ET_B = endothelin receptor B

Nelson JB, et al. Nat Med 1995;1(9):944–9;
Okazawa M, et al. J Biol Chem 1998;273(20):12584–92;
Del Bufalo D, et al. Mol Pharmacol 2002;61(3):524–32

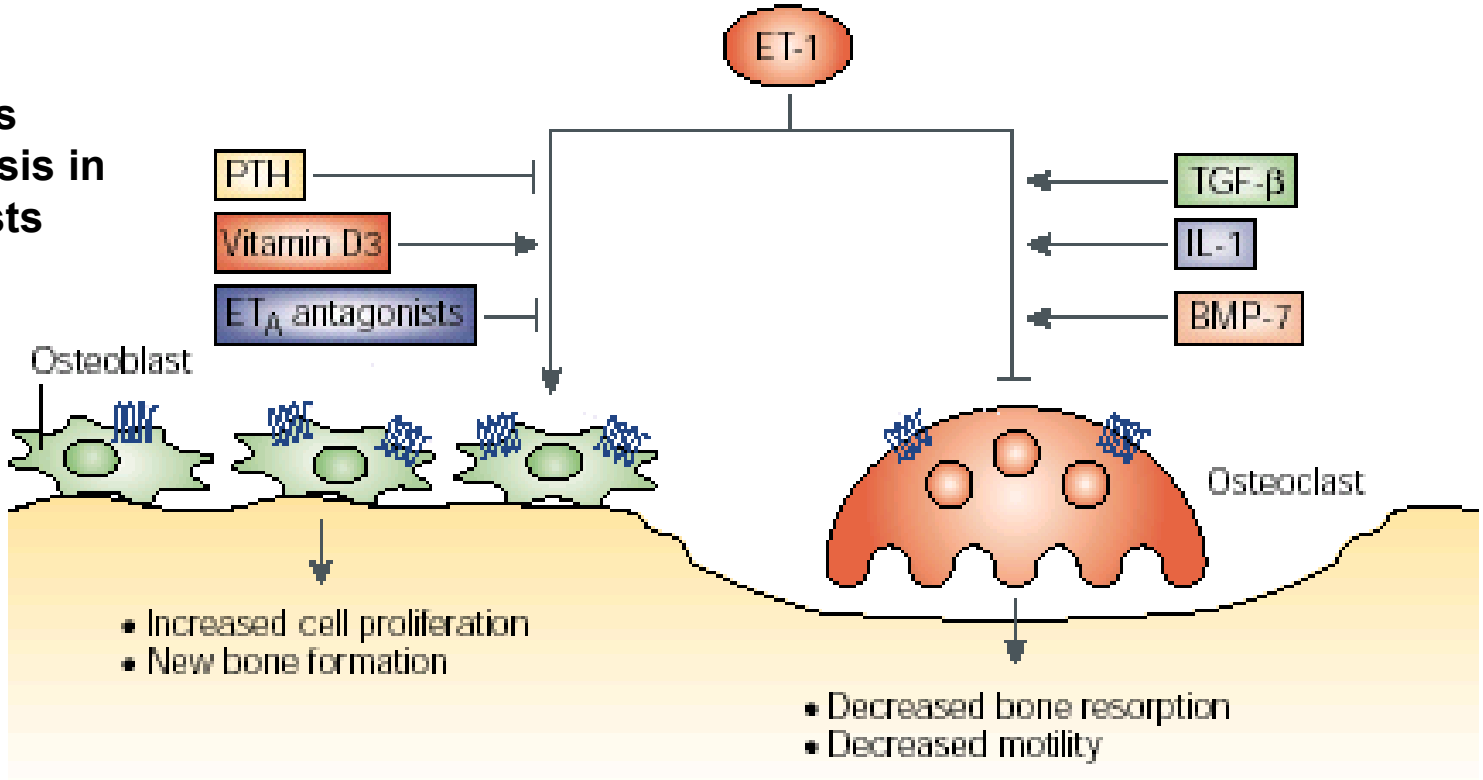
ET-1: indirect effects on tumour cells



Galluzzo S., Personal communication, Forlì 2009

ET1 activity in bone remodelling

ET-1 stimulates mitogenesis in osteoblasts



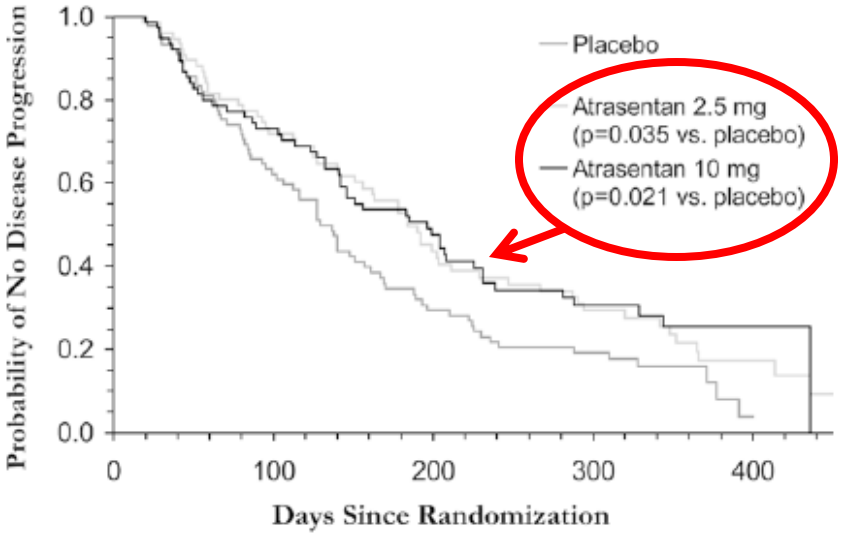
- ET-1 increases in the circulation of some patients with PC
- Both ET1 and ET_A are overexpressed in PC cells and bone mets
- *In vivo* : ET_A antagonists inhibit experimental models of bone mets

Nelson, Cancer Treat Rev 2006

Endothelin A (ET-1) receptor antagonist: atrasentan

- M96-594: Fase II Atrasentan (2.5 mg/10mg) vs placebo 288 pz con HRPC asintomatici + M1 → ↑ TTP

Carducci, JCO 2003



- M00211: Fase III Atrasentan (10mg) vs placebo 809 pz. con HRPC asintomatici + M1→ ↑ TTP (significativo solo in M1 ossee)

Carducci, JCO 2004

- Studio combinato M96-594/ M00211: 1002 pz (10 mg) →↑ TTP; ↑ TT"bone pain"; ↑ TT "PSA progression"

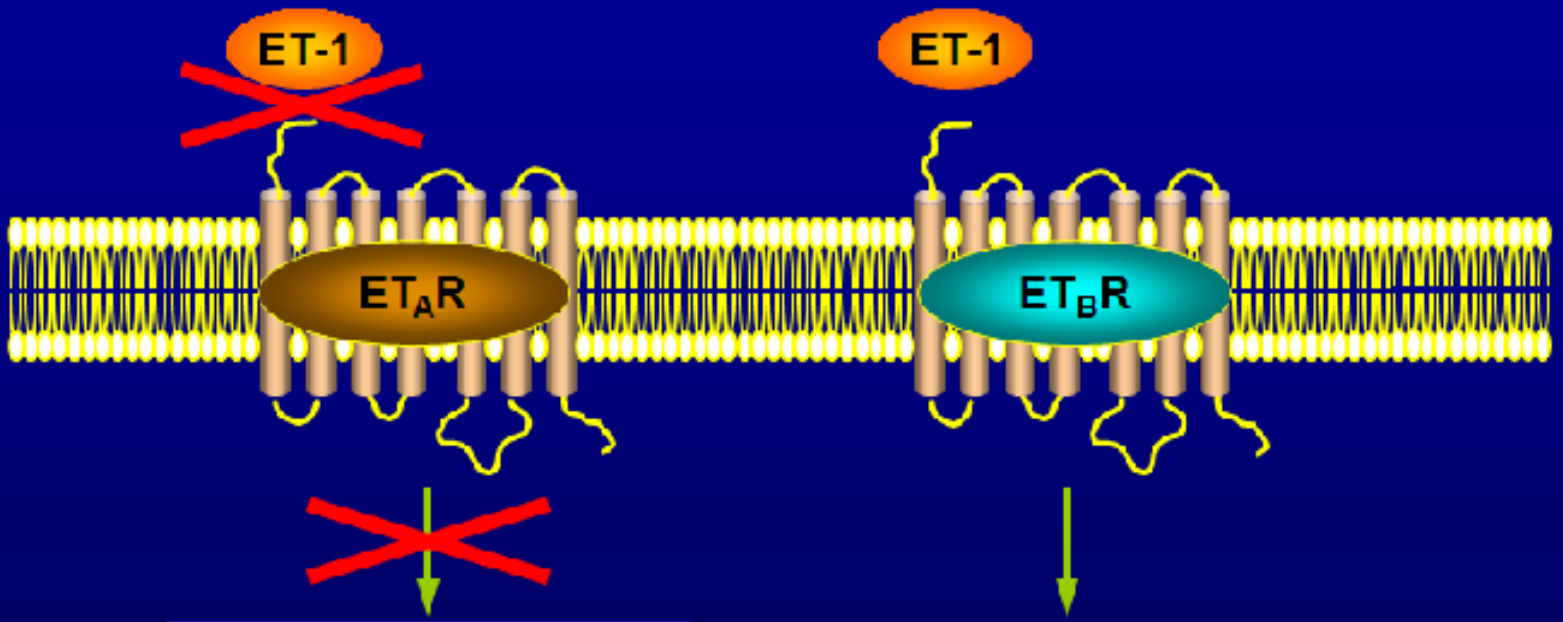
Vogelzang, JCO 2005

ONGOING:

M00244: Fase III, in non M1 PC con "rising PSA" → TTP

SWOG 0421: Fase III Atrasentan + TXT vs placebo + TXT → OS + TTP **CHIUSO 1/2010**

ZD4054 (zibotentan)– a specific-ET_AR antagonist



ZD4054 specifically blocks ET_AR, with no detectable activity at ET_BR

Morris CD *et al. Br J Cancer* 2005;92:2148–2152

Galluzzo S., Personal communication, Forlì 2009

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

Safety and Efficacy of the Specific Endothelin-A Receptor Antagonist ZD4054 in Patients with Hormone-Resistant Prostate Cancer and Bone Metastases Who Were Pain Free or Mildly Symptomatic: A Double-Blind, Placebo-Controlled, Randomised, Phase 2 Trial☆

*** Composite endpoint**

Clinical progression (requiring surgery or radiotherapy)
Pain requiring opiates
Soft tissue metastases
Death in absence of progression

Asymptomatic or mildly symptomatic HRPC patients with bone metastases receiving castration therapy

No prior chemotherapy

→ **Double blind randomisation**

→ **ZD4054 10mg orally once daily**

ZD4054 15mg orally once daily

Placebo orally once daily

→ **Time to Progression ***

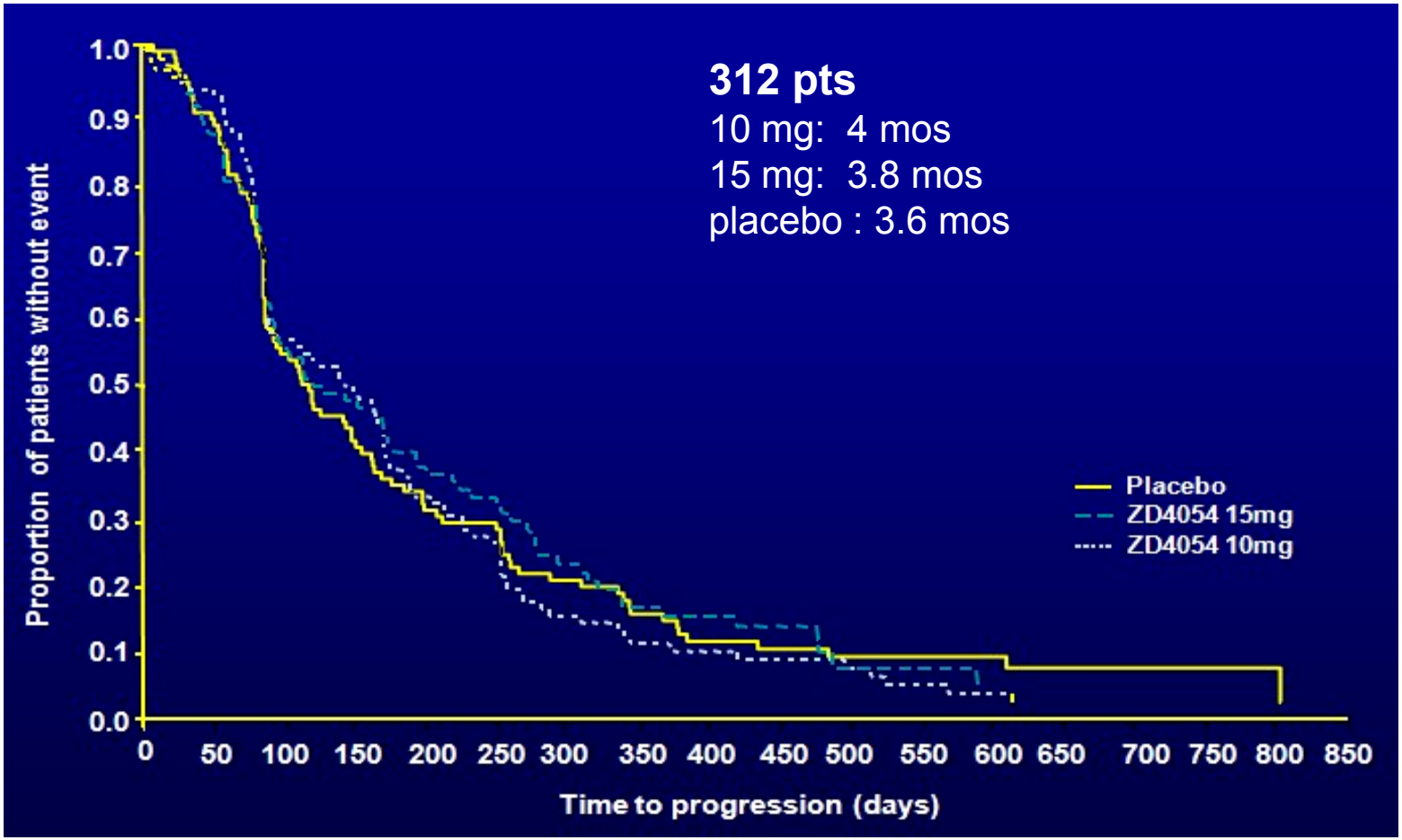
→ **Survival ****

* Primary Endpoint
** Secondary Endpoint (along with safety, PSA progression)
Study sized around alpha level of 0.2 for phase II setting

312 pts

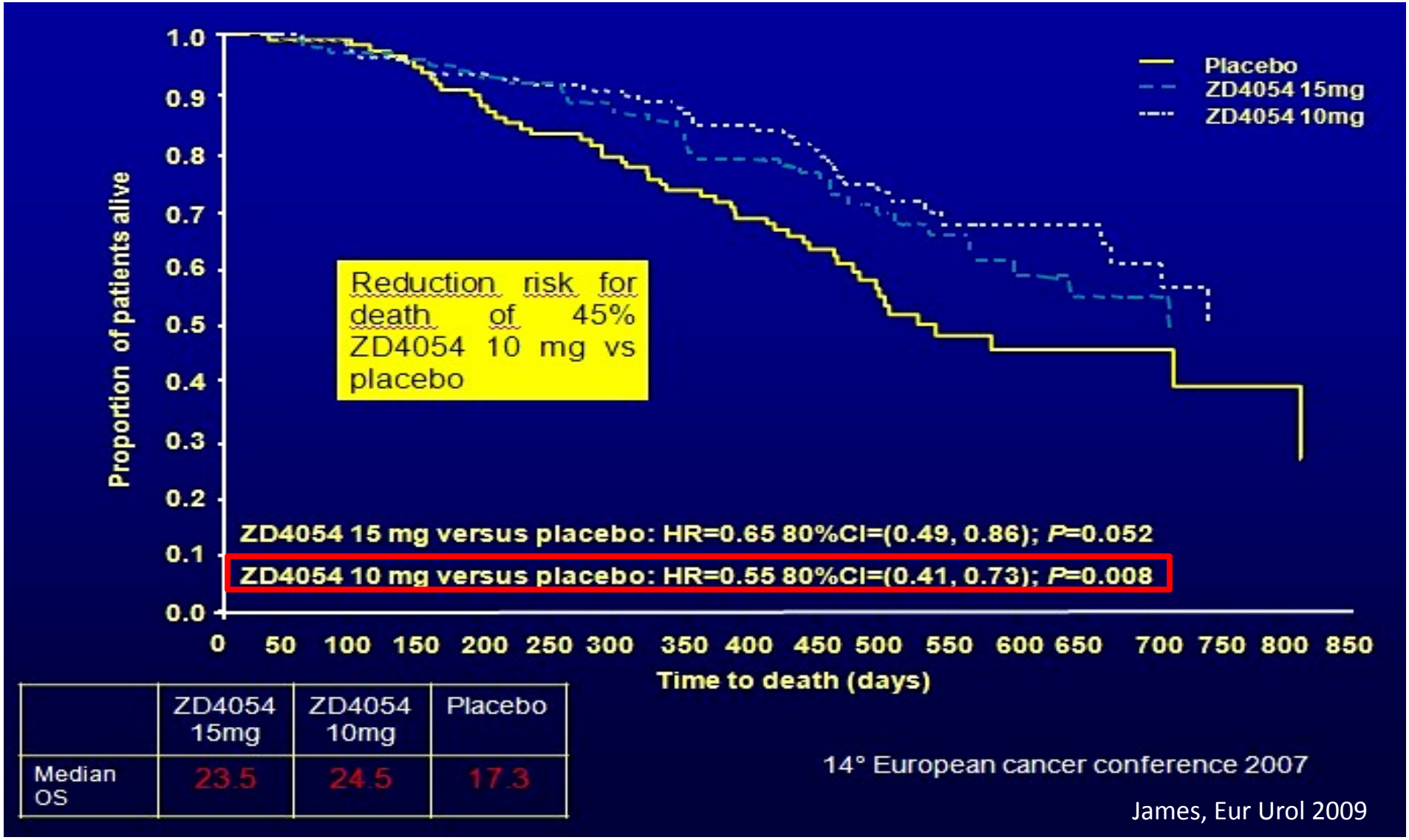
James, Eur Urol 2009

Primary endpoint: Progression-free survival
Updated analysis



James, Eur Urol 2009

Updated analysis
Secondary endpoint: OS



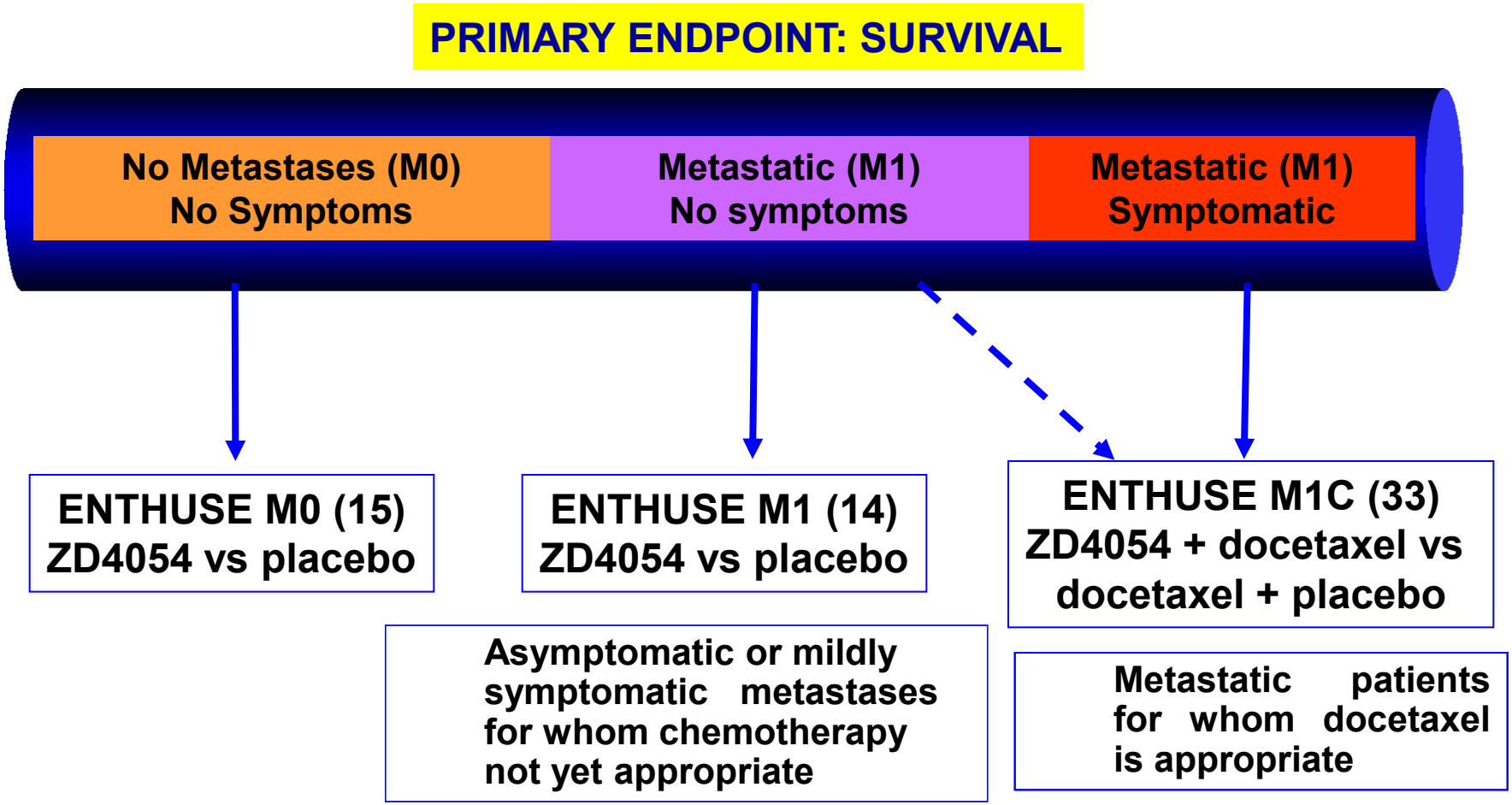
	ZD4054 15mg	ZD4054 10mg	Placebo
Median OS	23.5	24.5	17.3

14° European cancer conference 2007

James, Eur Urol 2009

ENTHUSE (Endothelin A receptor Antagonist Use)

The Phase III Clinical Trials to Evaluate a Specific Endothelin A Receptor Antagonist (ZD4054) in Hormone Resistant Prostate Cancer (rising PSA on a background of stable castration therapy for whom no curative treatment is indicated)



Therapeutic strategies for treatment of bone metastases

Osteoclast inhibitors

Bisphosphonates
Anti RANK Ligand MoAB
Endothelin A inhibitors
Cathepsin K inhibitors
Src inhibitors
PTHrP antibody

Other Cellular Targets

Platelets: LPA
Endotelial cells: PDGFR, PIGF
Anti CTGF
CXCR4 antagonist
HDAC inhibitors
Cox-2
Proteosome inhibition
Anti-integrin
TGF-β inhibitors
ETRA
Wnt inhibitors

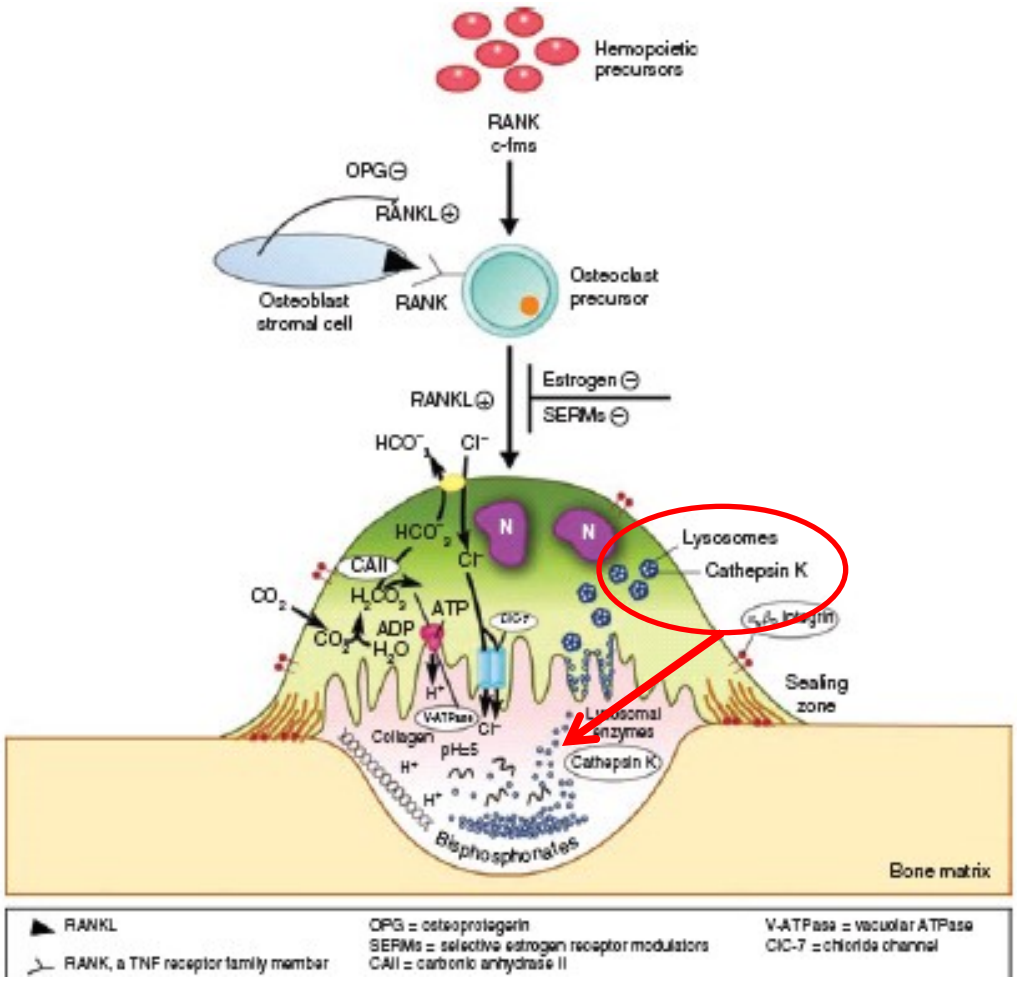
PTHrP, parathyroid hormone-related peptide; LPA, lysophosphatidic acid; PDGFR, platelet-derived growth factor receptor; PIGF, placental growth factor; CTGF, connective tissue growth factor; HDAC, histone deacetylase; TGFβ, trasforming growth factor-beta; ETRA, endothelin receptor A.

Cathepsin K inhibitors

Cathepsin K:

- is a cysteine protease expressed by the osteoclast (OC)
- is capable of degrading type-1 collagen
- The enzyme can be detected:
  - extracellularly in bone resorption lacunae
  - intracellularly (OC) in vesicles, granules, and vacuoles
- is often upregulated in many tumors

Animal studies have shown that **inhibition of cathepsin K → dose dependent reduction in bone resorption (↓sCTX)**



Stoch SA Clin Pharmacol & Therapeutics 2008

odanacatib (Cathepsin K Inhibitor)

- Preclinical studies in in breast cancer models:
  - Catepsine K is expressed also by bone-resident cancer cells
  - Increased Cat K expression in BC is associated with tumor invasiveness and increased risk of bone metastases
  - **Cathepsine K inhibitors reduce the breast cancer-induced osteolysis and skeletal tumor burden**

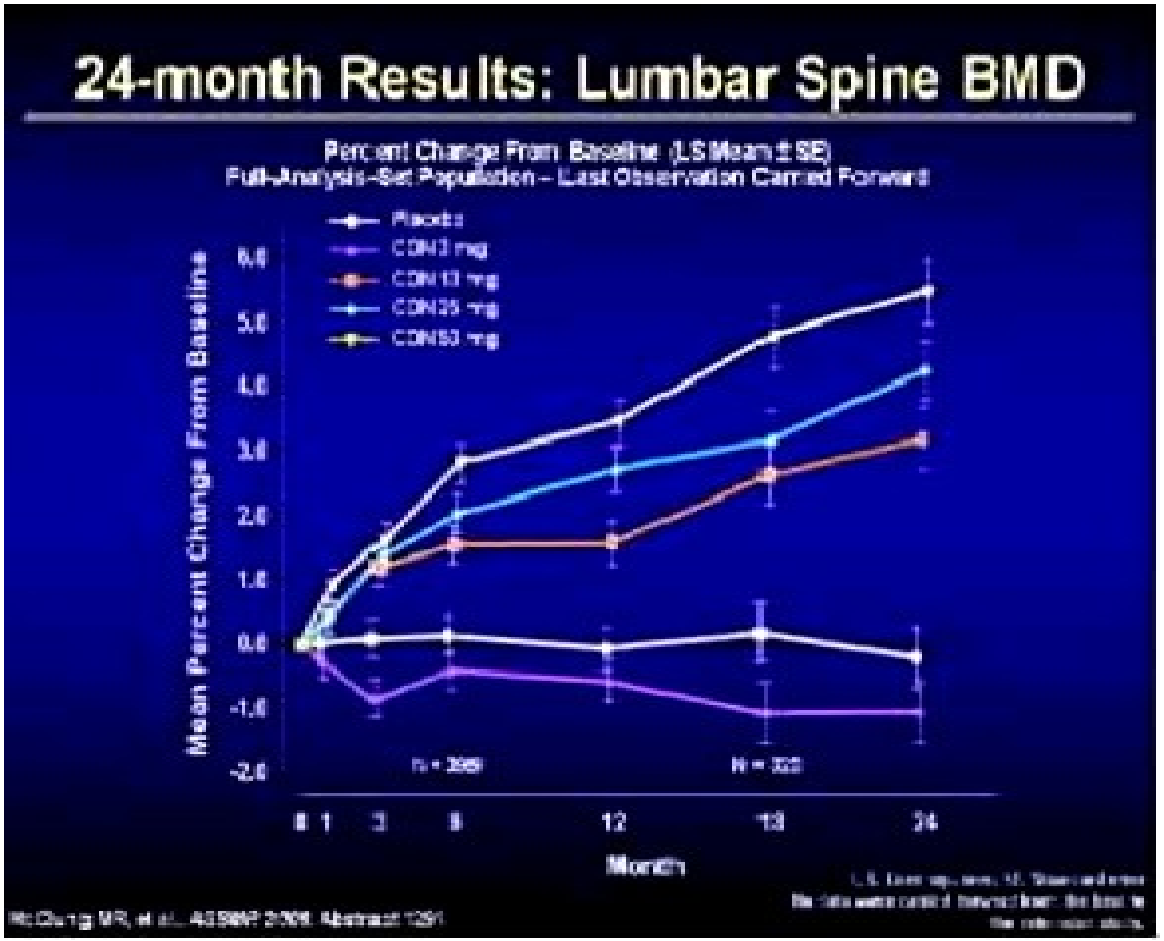
    DUAL BENEFIT in OSTEOLYIC BONE METS

    (Le Gall C, Clezardin P, Cancer Res 2007)

- Reductions in bone resorption markers and increases in BMD in humans

odanacatib (Cathepsin K Inhibitor)

A Randomized, Double-Blind, Placebo-Controlled Study of Odanacatib (MK-822) in the Treatment of Postmenopausal Women With Low Bone Mineral Density: 24-Month Results. Abstract 1291



American Society for Bone and Mineral Research (ASBMR) 30th Annual Meeting, 2008,

BMD, bone mineral density

odanacatib (Cathepsin K Inhibitor)

nature publishing group ARTICLES

Effect of the Cathepsin K Inhibitor Odanacatib on Bone Resorption Biomarkers in Healthy Postmenopausal Women: Two Double-Blind, Randomized, Placebo-Controlled Phase I Studies

SA Stoch[1], S Zajic[1], J Stone[1], DL Miller[1], K Van Dyck[1], MJ Gutierrez[2], M De Decker[3], L Liu[1], Q Liu[1], BB Scott[1], D Panebianco[1], B Jin[1], LT Duong[1], K Gottesdiener[1] and JA Wagner[1]

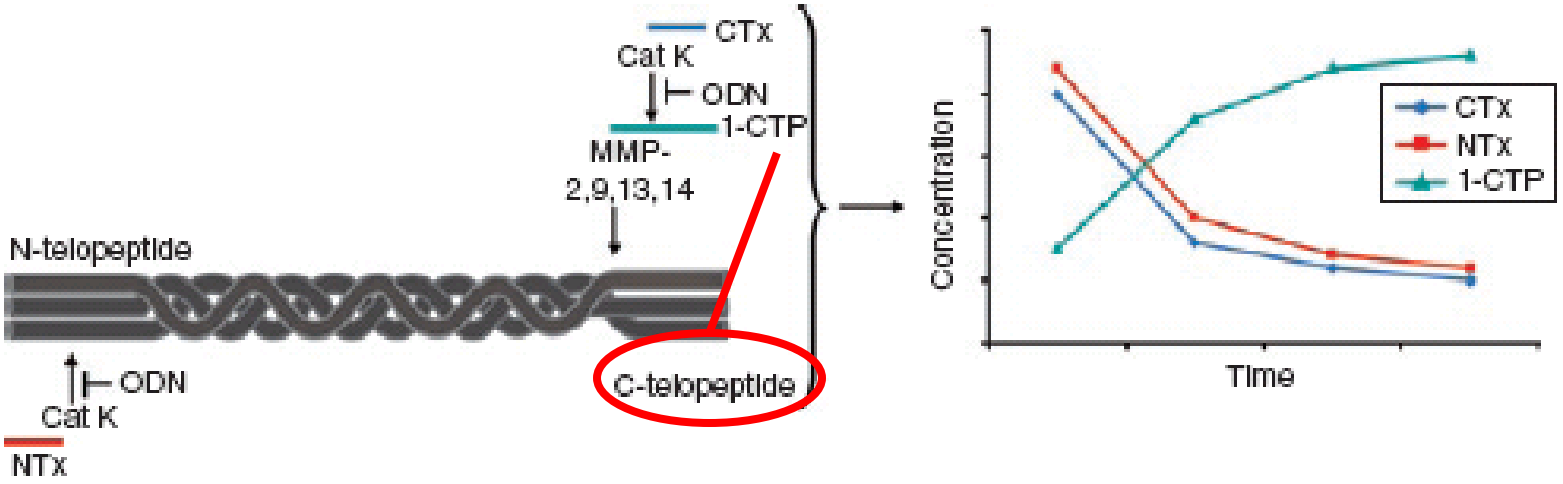
79 pts

- 49 once a week (5, 25,50, 100 mg)
- 30 daily (0.5, 2.5, 10 mg)

➢ **Pronounced reductions in C-terminal telopeptide of type I collagen** and **N-terminal telopeptide of type I collagen** →weekly administration.

➢ **Robust reductions in CTx and NTx** →daily administration.

➢ **ODN exhibits robust and sustained suppression of bone resorption biomarkers (CTx and NTx/Cr) at weekly doses ≥25 mg and daily doses ≥2.5 mg.**



Phase II of odanacatib in metastatic bone disease

Odanacatib 5 mg (once daily)

	Baseline	Wk 4%	Change (95% C.I.)
uNTx	140	48	-77 (-82, -71)
uDPD	18	13	-30 (-43, -15)
sBSAP	27	25	-9 (-17, -2)
S-1CTP	10	20	+93 (+70, +119)

Similar effects on uNTX, DpD and BSAP to zoledronic acid 4 mg

uNTX, urinary N-telopeptide of type I collagen
DPD, deoxypyridinoline
BSAP, Bone-Specific Alkaline Phosphatase

Adapted from Wynne et al ASCO 2008

Effect of Cathepsin K Inhibition on Suppression of Bone Resorption in Women with Breast Cancer and Established Bone Metastases in a 4-Week, Double-Blind, Randomized Controlled Trial

Anders Bonde Jensen[1] Nina Olmeo[2] Christopher Wynne[3] Guillermo Ramirez[4] Antje Lebrecht[5] Anish Mehta[6] Weili He[6] Yang Song[6] Yuliya Berd[6] Antonio Lombardi[6]

Study Design

- Randomized, double-blind, parallel-arm, active comparator-controlled, multicenter study.
- Treatment period: 4-week study, with a 2-week follow-up period.
- A 2:1 randomization to odanacatib or zoledronic acid (ZA) was performed.

Treatment

- Regimen A: Odanacatib 5 mg qd orally day 1-28 (N=29).
- Regimen B: IV ZA 4 mg on day 1 (N=14).

Primary Endpoints

➢ Markers of Bone Resorption

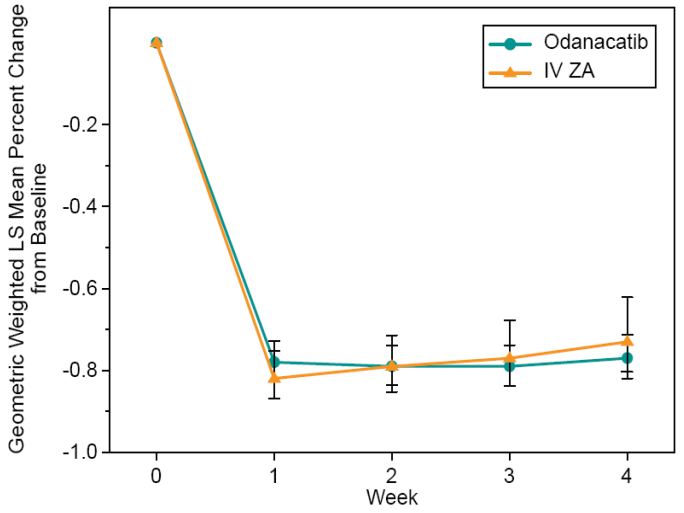
➢uNTx corrected for creatinine

➢Odanacatib, significantly suppressed markers of bone resorption

➢The effects on bone resorption were similar to IV zoledronic acid 4 mg.

➢ In this study, odanacatib was safe and well tolerated.

Figure 1. Geometric Mean Percent Change from Baseline in u-NTx/Creatinine Ratio (Least Square Mean ±95% CI)



New drugs: conclusions

- Denosumab is a promising agent for standard therapy of patients with bone mets.

- Further clinical trials are needed to evaluate if Denosumab as well as bisphosphonates may be effective not only in preventing bone loss, but also in preventing the development of bone metastases (phase II ongoing)

- Cathepsin K Inhibitors and Endothelin A receptor antagonists are potentially important novel therapeutic approaches for treating bone metastases, and further studies are warranted

- The activity of each drug has to be confirmed with a “head to head” comparison with potent bisphosphonates (i.v. zoledronic acid)

- Next studies will be focused on the evaluation of concomitant or sequential administration of different bone-targeted drugs