METASTASI SCHELETRICHE DA TUMORI SOLIDI: **CARCINOMA PROSTATICO**

Cinzia Ortega

Oncologia Medica

IRCC

INSTITUTE FOR CANCER RESEARCH AND TREATMENT

Metastasi ossee nel PC: dimensioni del problema

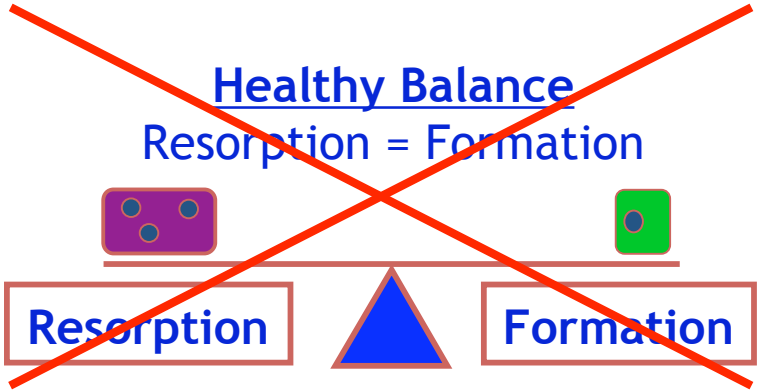
	5-year world prevalence, thousands[1]	Incidence of bone metastases in cancers[2]	Median survival, Months[2-4]
Myeloma	144	70 - 95	6 - 54
Renal	480	20 - 25	12
Melanoma	533	14 - 45	6
Bladder	1,000	40	6 - 9
Thyroid	475	60	48
Lung	1,394	30 - 40	6 - 7
Breast	3,860	65 - 75	19 - 25
Prostate	1,555	65 - 75	12 - 53

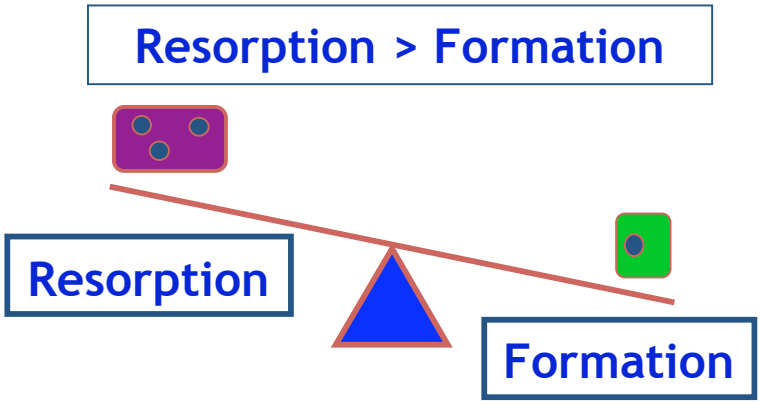
More lytic

More blastic

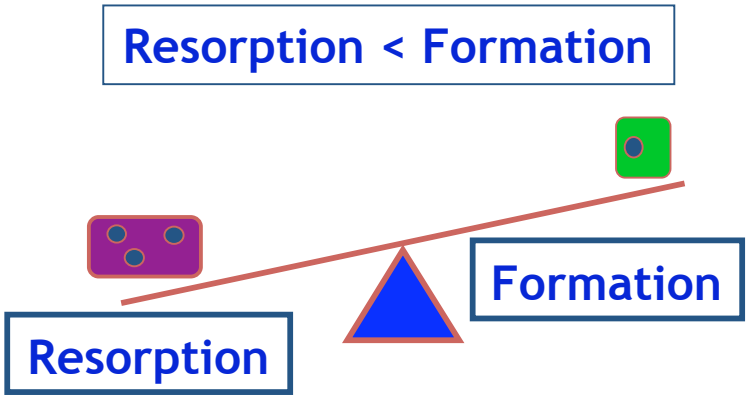
1. Ferlay J, et al. IARC Globocon 2000. Cancer Incidence, Mortality, and Prevalence.
2. Coleman RE. *Cancer Treat Rev*. 2001;27:165-176.
3. Coleman RE. *Cancer*. 1997;80:1588-1594.
4. Zekri J et al. *Int J Oncol.* 2001;19:379-382.

Metastasi ossee





OSTEOLYTIC METASTASIS

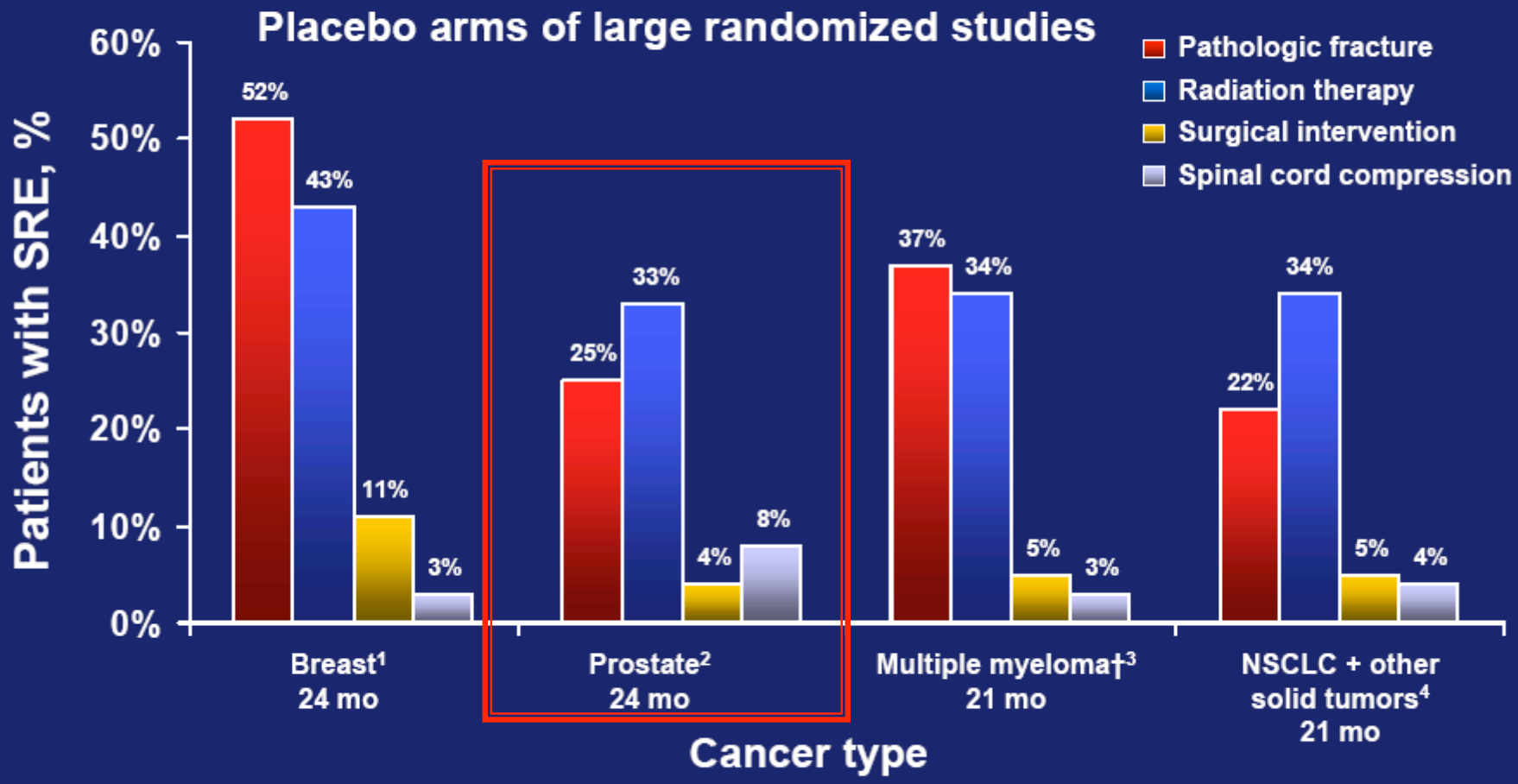


OSTEOBLASTIC METASTASIS

Pazienti con PC → ridotta “bone mineral density”

- Uomo anziano → fisiologico declino dei livelli ormonali che hanno un ruolo importante nel mantenere un “balanced bone remodelling system”
- Androgeno deprivazione (ADT)→ ulteriore “bone loss”
- I fattori prodotti dalle cellule tumorali di PC nel microambiente osseo (IL-1, IL-6, PTHrP, RANKL) → osteoclastogenesi e riassorbimento osseo

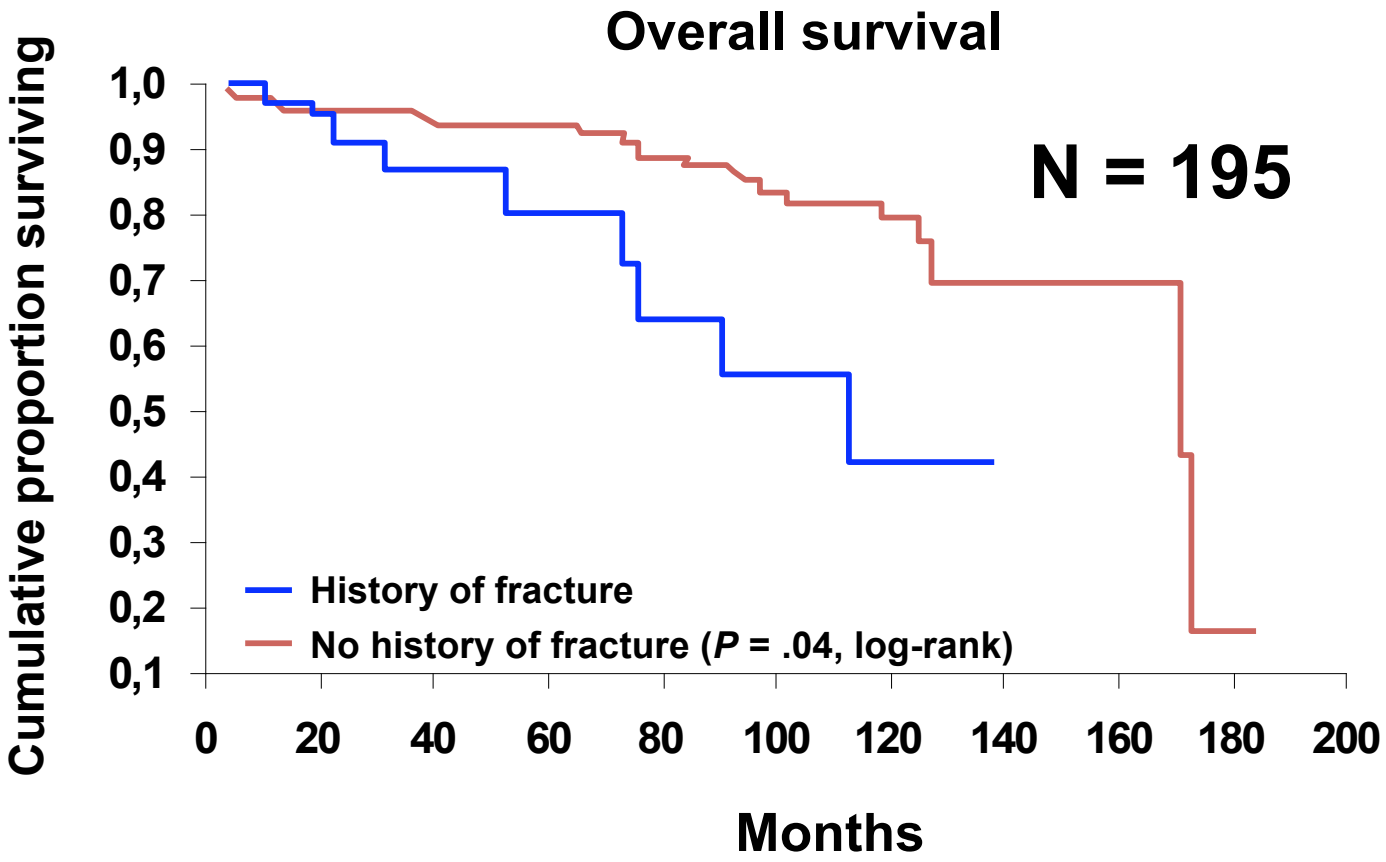
Patients With Bone Lesions Are at High Risk for Developing Skeletal Complications



†21-month data except for surgical intervention and spinal cord compression, for which only 9-month data are available.

1. Lipton A, et al. *Cancer*. 2000;88:1082-1090; 2. Saad F, et al. Presented at: 2003 AUA Annual Meeting. Abstract 1472; 3. Berenson JR, et al. *J Clin Oncol*. 1998;16:593-602; 4. Rosen LS, et al. *Cancer*. 2004;100:2613-2621.

Impatto sulla sopravvivenza
“Fractures Negatively Affect Survival”



Oefelein MG, et al. *J Urol*. 2002;168:1005-1007.

Fattori di rischio per lo sviluppo di metastasi ossee in PC

- elevati livelli di PSA basale
- “rising PSA” durante ADT
- elevata PSA velocity
- “short” PSADT

- PSA basale e PSA velocity sono fattori indipendenti predittivi del tempo alla comparsa di metastasi ossee e sopravvivenza
- PSA basale elevato e “short” PSADT sono associati ad una ridotta sopravvivenza libera da metastasi

L’uso dei fattori di rischio (cinetica del PSA) → precoce identificazione della malattia metastatica ossea

Smith JCO 2005

Terapia medica delle metastasi ossee da PC

- terapia medica sistemica
  - terapia antitumorale
    - Chemioterapia
    - Terapia ormonale
  - terapia antalgica

- **“bone targeting therapies’**
  - Bisfosfonati
  - Targeting RANK-RANK ligand
    - Denosumab
    - OPG
  - Targeting ET axis”
    - Atrasentan

Potential Targets for Bone Directed Therapy

Target	Potential Therapy	Stage of Development
Osteoclast function		
Inhibit osteoclast function	Bisphosphonates[24,25,28,29,66,67]	Phase III
RANK/RANKL signaling	Denosumab[38]	Phase III
	Synthetic OPG[68]	Being studied in osteoporosis, preclincal
MMPs	BMS-275291[41]	Phase II
Src tyrosine kinase	Src tyrosine kinase inhibitors[43,44]	Preclinical
Integrins	Cilengitide (EMD121974)[49]	Phase II
Osteoblast function		
ET axis	Atrasentan[57]	Phase III
BMPs	Increased noggin expression[70]	Preclinical
	AntiBMP antibodies[71]	Preclinical
Wnt signaling pathway[69]	Novel inhibitors of Wnt signaling	Preclinical
Exposed hydroxyapatite	Radiopharmaceuticals[34,35]	Phase III

“bone targeting therapies”

Bisfosfonati

Bifosfonati di prima generazione: “pain relief” in PC

Farmaco	N	Risultato	Autore
Etidronato vs placebo	57	No beneficio	Smith 1989
Clodronato vs placebo	75	No beneficio	Elomaa 1992
Mitox/Pred clodronato	204	No beneficio	Ernst 2003
Ibandronato	25	beneficio significativo	Heidenreich 2002

Bisfosfonati: studi di fase III

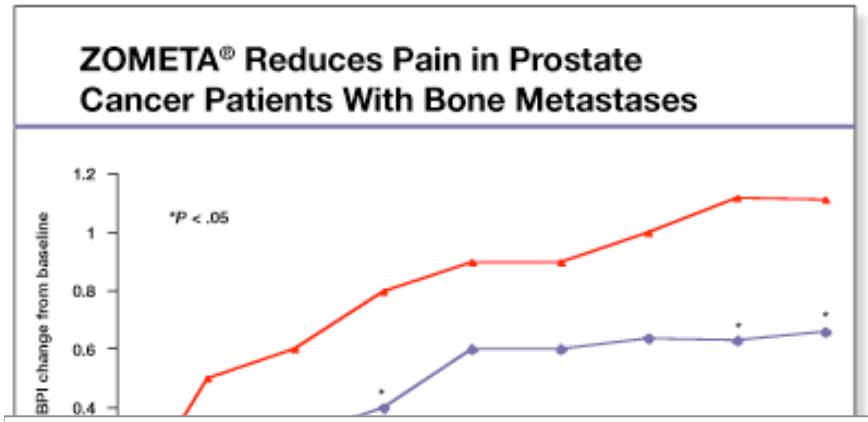
Completed phase III studies of bisphosphonates for PCa

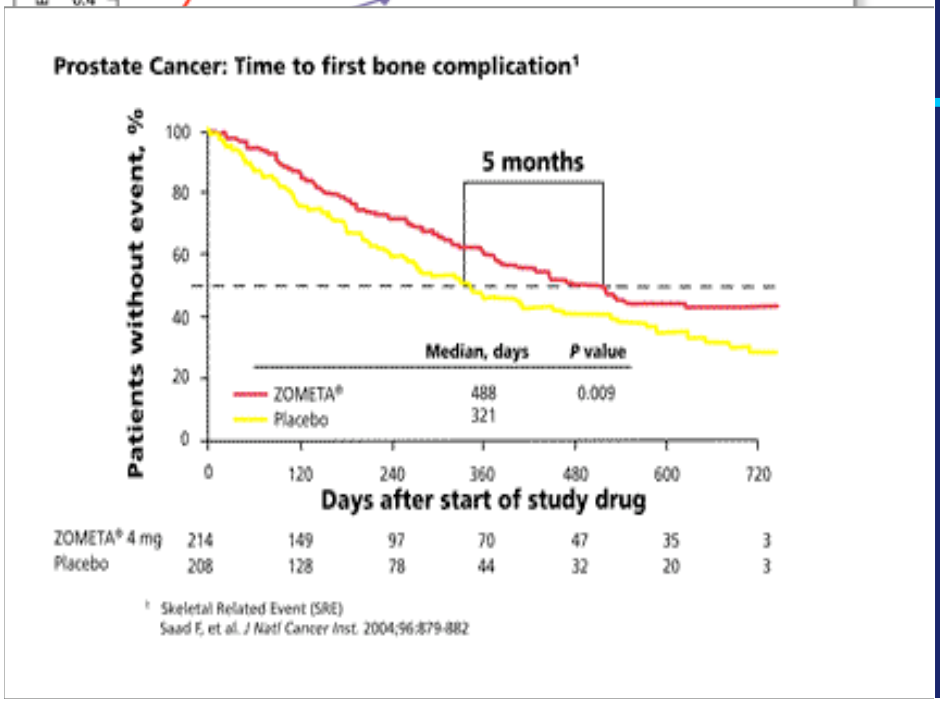
Trial	Regimen	No. Pts	Population	Primary End Point	Outcome
Zometa 039[24,25]	Zoledronic acid vs placebo (all pts continued hormone therapy, additional antineoplastics permitted)	643	Androgen independent prostate cancer with asymptomatic or minimally symptomatic bone metastases	Proportion of men experiencing 1 or more SREs by 15 mos	Significant decrease in No. + time to SREs
INT-05/CGP 032[66]	Pamidronate vs placebo (additional hormone therapy + chemotherapy were permitted)	350	Androgen independent prostate cancer with symptomatic bone metastases	Decreased bone pain + narcotic use	No significant difference in pain, analgesic use or SREs
Zometa 704[29]	Zoledronic acid vs placebo (gonadotropic hormone-releasing hormone agonists were continued, additional therapy at investigator discretion)	398	Progressive castrate, nonmetastatic	Time to first bone metastasis	Study was terminated early due to lower than expected event rate
MRC Pr05[67]	Clodronate vs placebo (standard hormone therapy was continued)	311	Androgen dependent, asymptomatic bone metastases	Symptomatic bone progression-free survival	Nonsignificant trend toward improved bone progression-free survival
MRC Pr04[28]	Clodronate vs placebo (standard hormone therapy was continued)	508	Standard treatment for stage T2–T4 disease with no evidence of bone metastases	Time to symptomatic bone metastases or PCa death	No significant difference in time to symptomatic bone metastases or overall survival

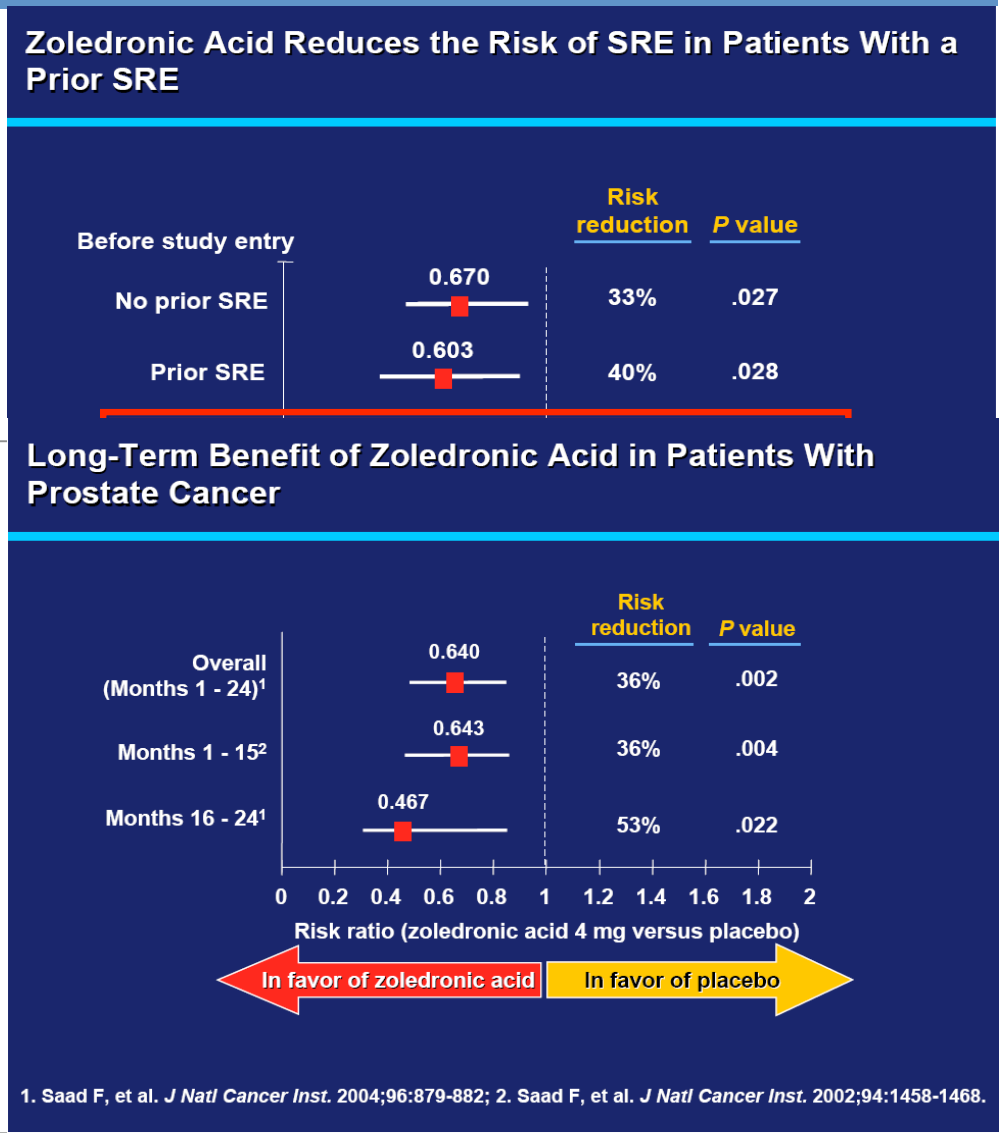
“Investigations of other bisphosphonates at different PCa stages has been disappointing as single agents and in combination with hormones and chemotherapy, and they currently have no role in standard treatment for Pca”

Bradley, J Urol 2007

Acido zoledronico *vs* placebo in HRPC: risultati studio 039

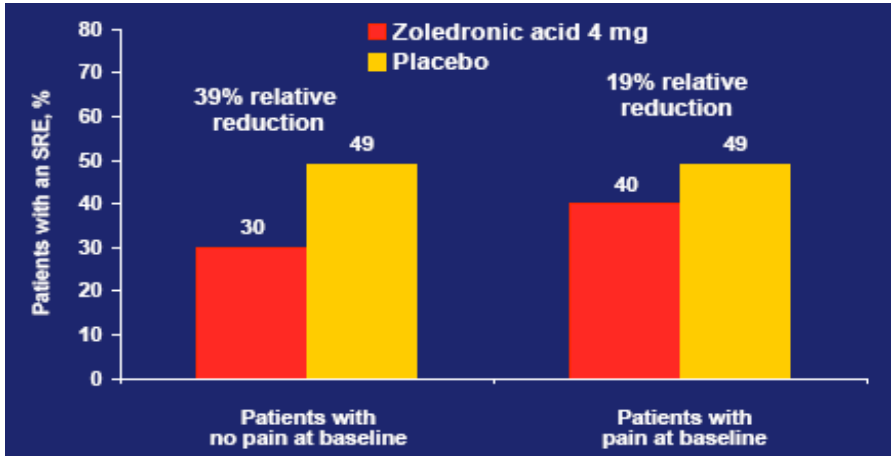




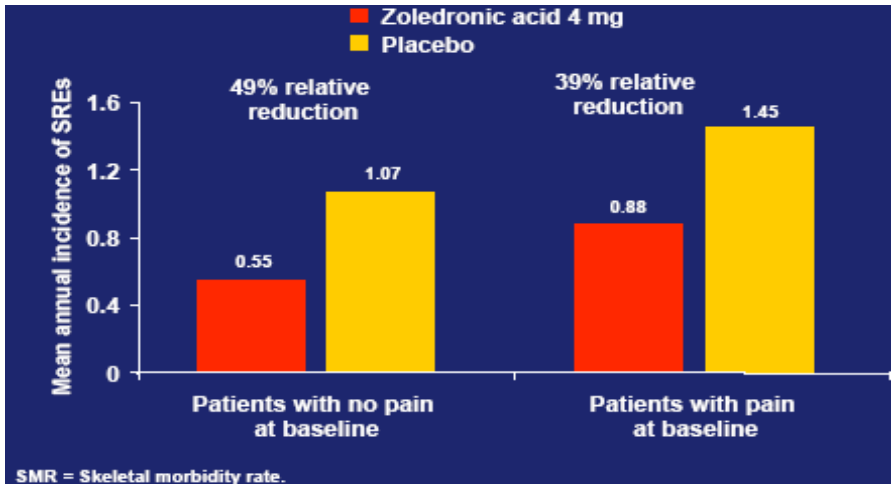


Acido zoledronico: “timing”

Il beneficio è maggiore se somministrato prima della comparsa del dolore



Il trattamento precoce potrebbe essere più efficace nel ridurre la SMR (skeletal morbidity rate)



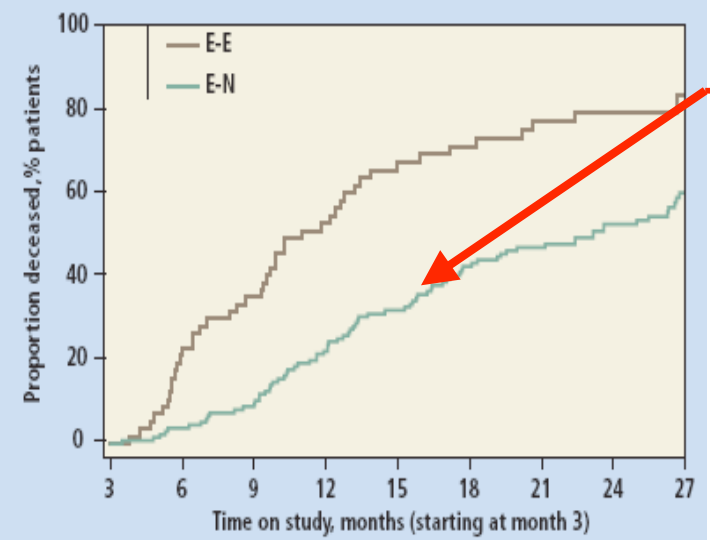
Saad F, et al. Eur Urol Suppl.2005;4:145.

Acido zoledronico e “survival”

Normalization of Elevated NTX Levels With Zoledronic Acid Treatment Correlates With a Survival Benefit in Patients With Bone Metastases From Prostate Can

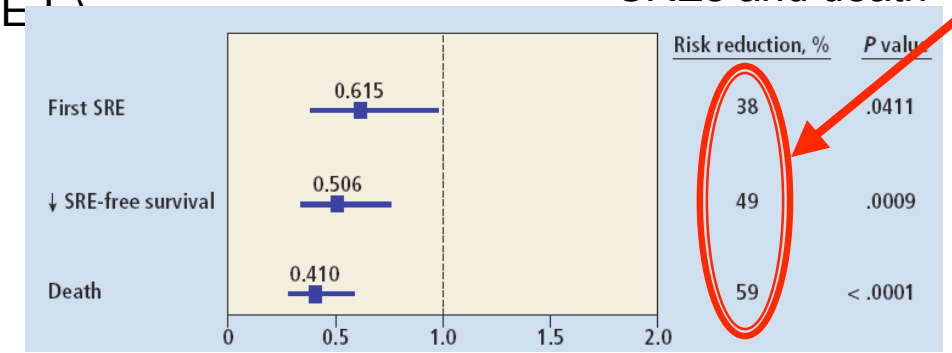
Saad et al. Presented at: American Society of Clinical Oncology 2007 Prostate Cancer Symposium: A Multidisciplinary Approach; February 22-24, 2007; Orlando, Florida. Abstract 235.

Retrospective exploratory analysis of patients with bone metastases from HRPC (n = 314) who received ZOL, stratified according to baseline NTX levels (Urinary NTX levels were measured at baseline and at month 3)



Normalization of NTX levels (E-N) correlated with increased overall survival compared with patients whose NTX levels remained elevated at 3 months (E-E)

Patients with elevated baseline NTX that normalized with ZOL had significantly lower risks of SREs and death



HRPC = Hormone-refractory prostate cancer; NTX = N-telopeptide of type I collagen; ZOL = Zoledronic acid

Bisfosfonati e PC: Linee guida 2007

The Cochrane Collaboration

- “bisphosphonates for advanced prostate cancer” (Review)
  - I bisfosfonati possono avere un ruolo nel ridurre il dolore e le complicanze scheletriche
  - Analisi statistica limitata dalle casistiche piccole e dall’eterogeneità dei disegni degli studi
  - Sono necessari studi ulteriori

→Ci sono dati insufficienti per guidare la scelta, la dose e la via di somministrazione dei bisfosfonati

Bisfosfonati e PC: raccomandazioni cliniche (1)

Annals of Oncology Advance Access published September 28, 2007

review

Annals of Oncology
doi:10.1093/annonc/mdm442

Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel

M. Aapro[1*], P. A. Abrahamsson[2], J. J. Body[3], R. E. Coleman[4], R. Colomer[5], L. Costa[6], L. Crinò[7], L. Dirix[8], M. Gnant[9], J. Gralow[10], P. Hadji[11], G. N. Hortobagyi[12], W. Jonat[13], A. Lipton[14], A. Monnier[15], A. H. G. Paterson[16], R. Rizzoli[17], F. Saad[18] & B. Thürlimann[19]

Based on the available evidence demonstrating a significantly lower incidence of skeletal complications as well as durable pain palliation, the opinion of the panel is that ZOL is presently the BP treatment of choice for patients with hormone refractory prostate cancer metastatic to bone. And it has been published that SRE reduction is greatest in patients without pain, thus patients should probably not have to wait for symptoms before starting ZOL therapy in this setting

Bisfosfonati e PC: raccomandazioni cliniche (2)

Condizione del paziente	Acido zoledronico
Scintigrafia negativa Tumore ormono-sensibile	No
Scintigrafia negativa Tumore ormono-refrattario	Uso dei bifosfonati a discrezione del medico. Monitorare attentamente il paziente
Scintigrafia positiva Tumore ormono-sensibile	La terapia con bifosfonati e.v. dovrebbe essere fortemente considerata
Scintigrafia positiva Tumore ormono-refrattario	SI

Saad, Eur Urol 2007

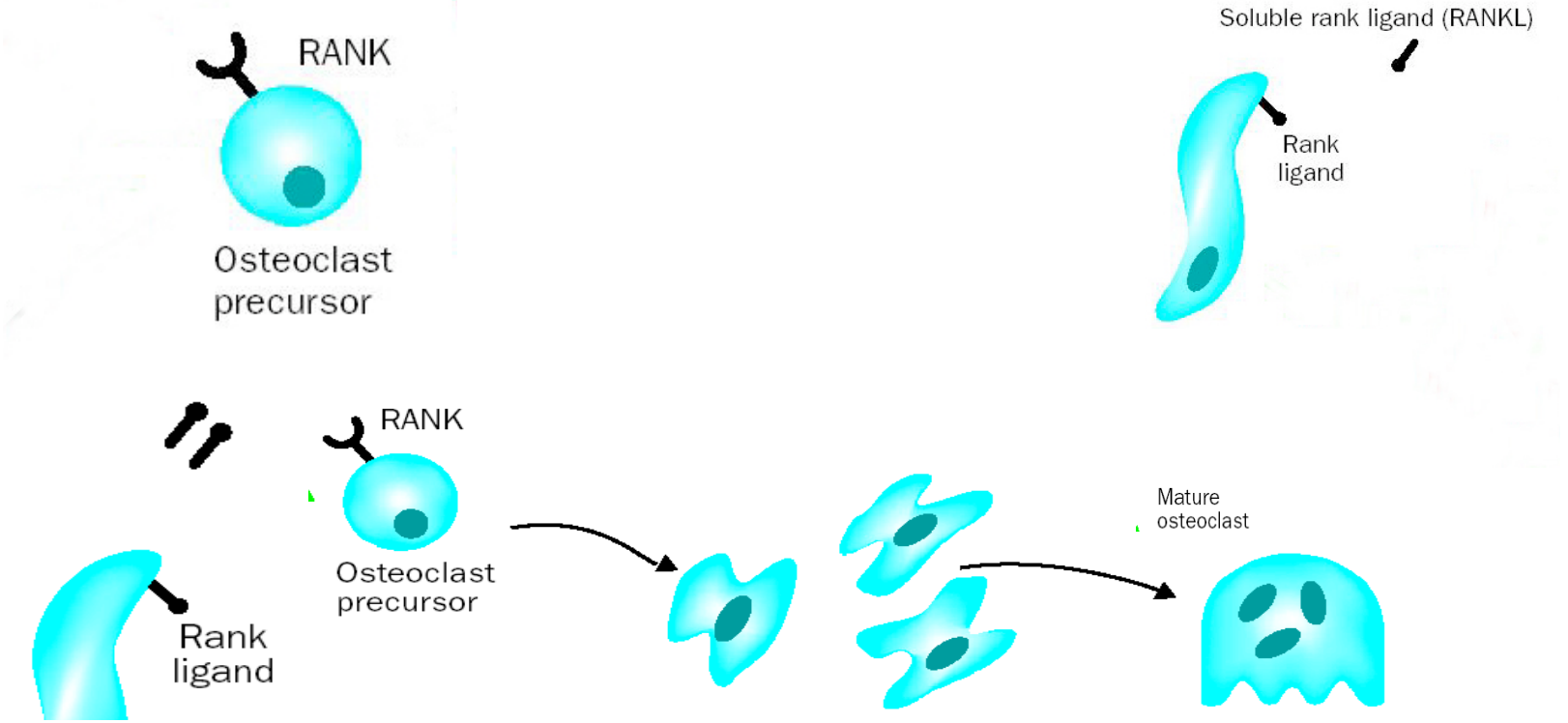
Nuovi farmaci

Targeting RANK-RANK ligand

Maturazione degli osteoclasti “regista” l’osteoblasta

I precursori degli Osteoclasti esprimono RANK, un membro della tumor necrosis factor receptor superfamily.

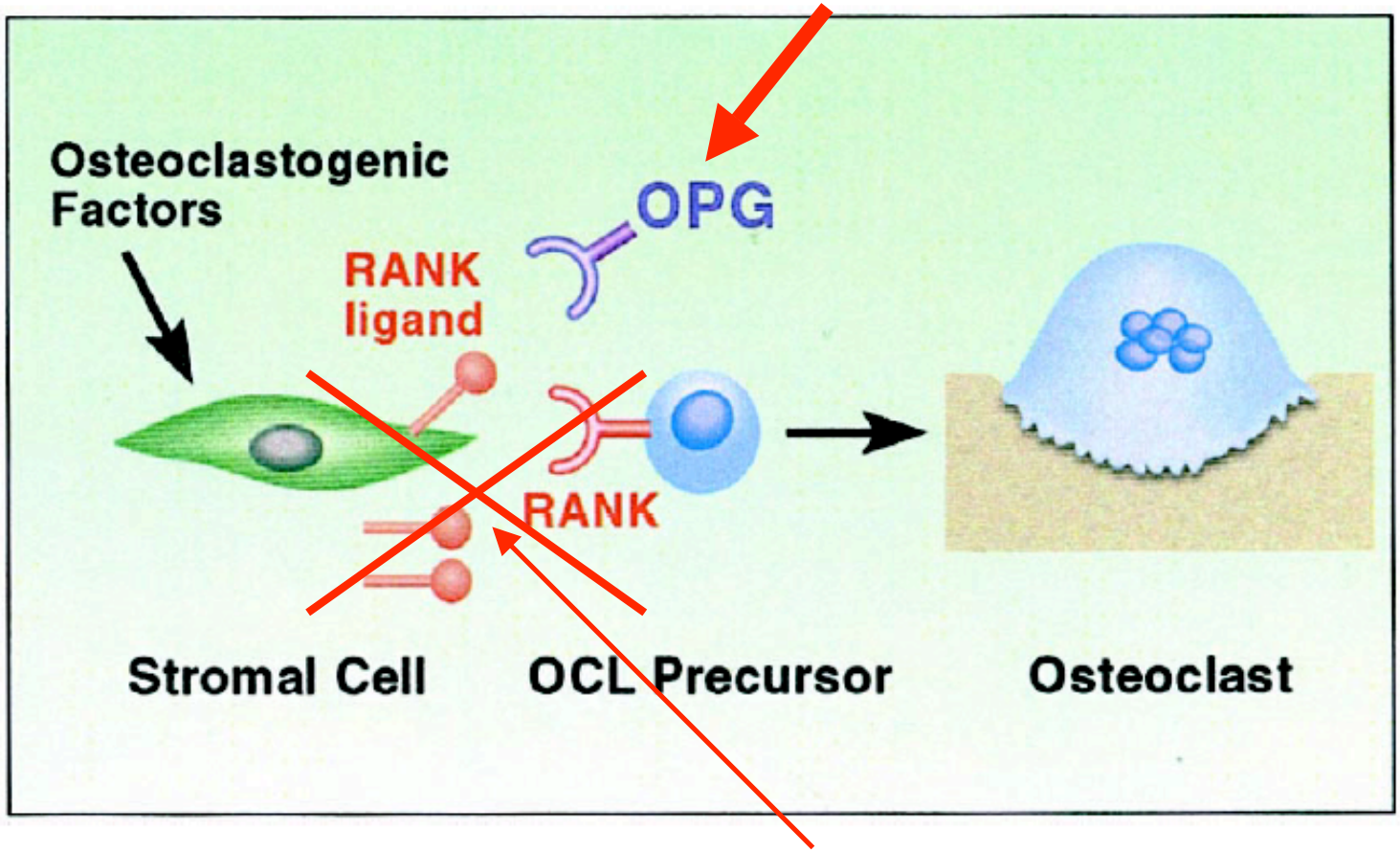
Osteoblasti, cellule stromali, cellule T attivate producono il ligando di RANK (RANK-L)



RANK-L lega il RANK receptor sui precursori degli OC → maturazione di OC

Osteoprotegerina (OPG)

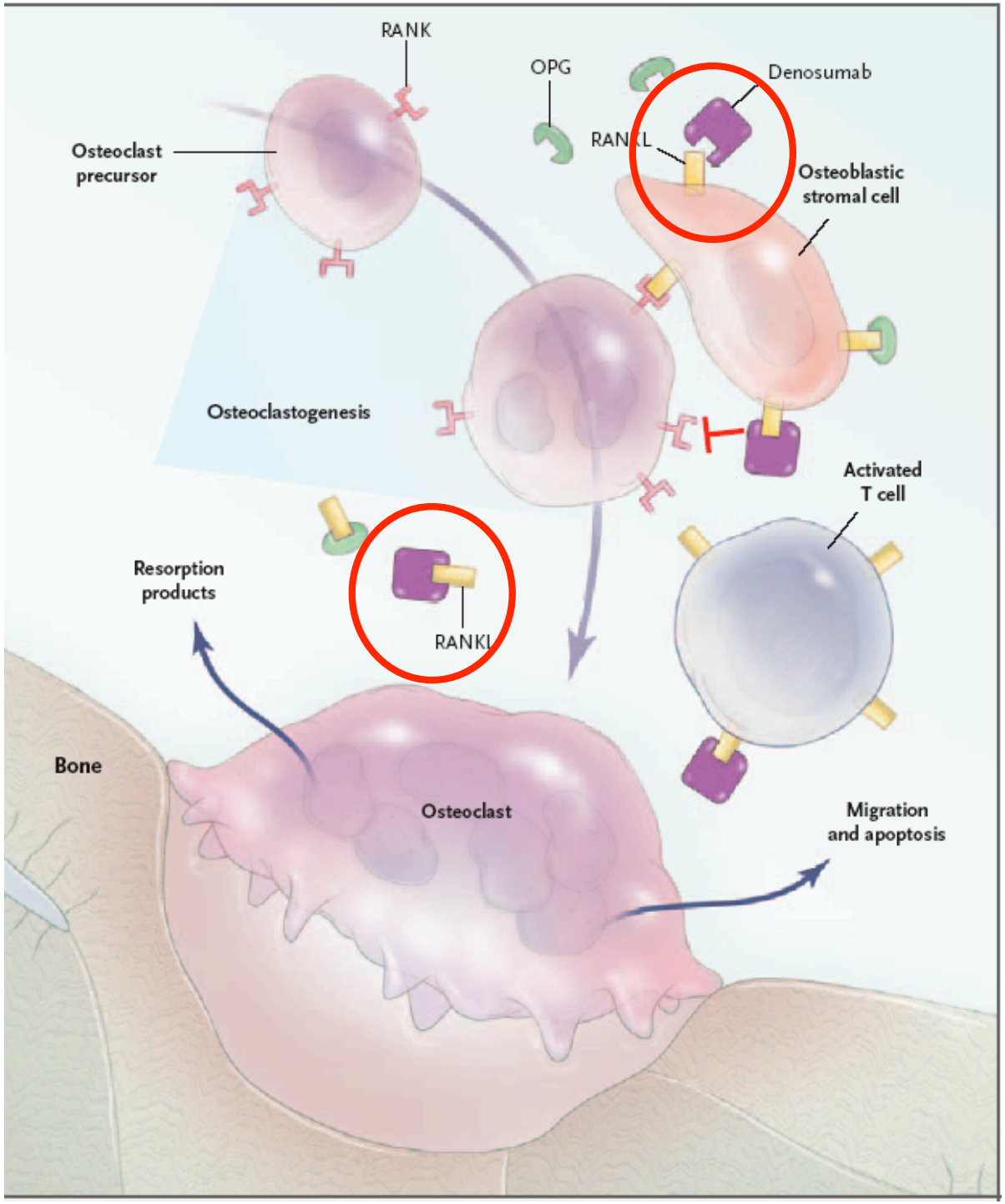
OPG: “decoy receptor” (= ESCA) solubile per RANKL → blocca interazione RANKL/RANK→ inibizione di OC e del riassorbimento osseo



AMG 162 (denosumab)

AMGN-0007 (recombinant-OPG)

Roodman, N Engl J Med 2004



Skeletal action of denusumab (RANKL inhibitor)

- ❑ Fully human monoclonal antibody
- ❑ Potent inhibitor of bone resorbtion
- ❑ Is being evaluated in osteoporosis and bone mets

Whyte, NEJM 2006

American Society of Clinical Oncology

K. Fizazi, L. Bosserman, A. Lipton, Y. Rahim, T. Suarez, M. Fan, L. Wu, R. Markus (abs N° 272)

Phase II randomized trial of denosumab in patients with bone metastases from prostate cancer and elevated urine N- telopeptide levels after receiving zoledronic acid

- **interim analysis comparing suppression of bone turnover markers (BTMs) in 24 pts with CaP treated with denosumab or ZA:**
  - Denosumab suppressed BTMs, with a trend to greater reduction of BTMs compared with ZA
  - Common adverse events were bone pain, anemia, and nausea.

Denosumab appeared to reduce BTMs to a similar or greater extent than ZA in CaP pts with bone metastases and elevated BTMs.

ONGOING TRIALS

- **Denosumab sc Q4W vs Zoledronic acid i.v. Q4w in HRPC with bone mets.**
  - Randomized, double blind, multicenter phase III trial, 1700 pts, SRE evaluation

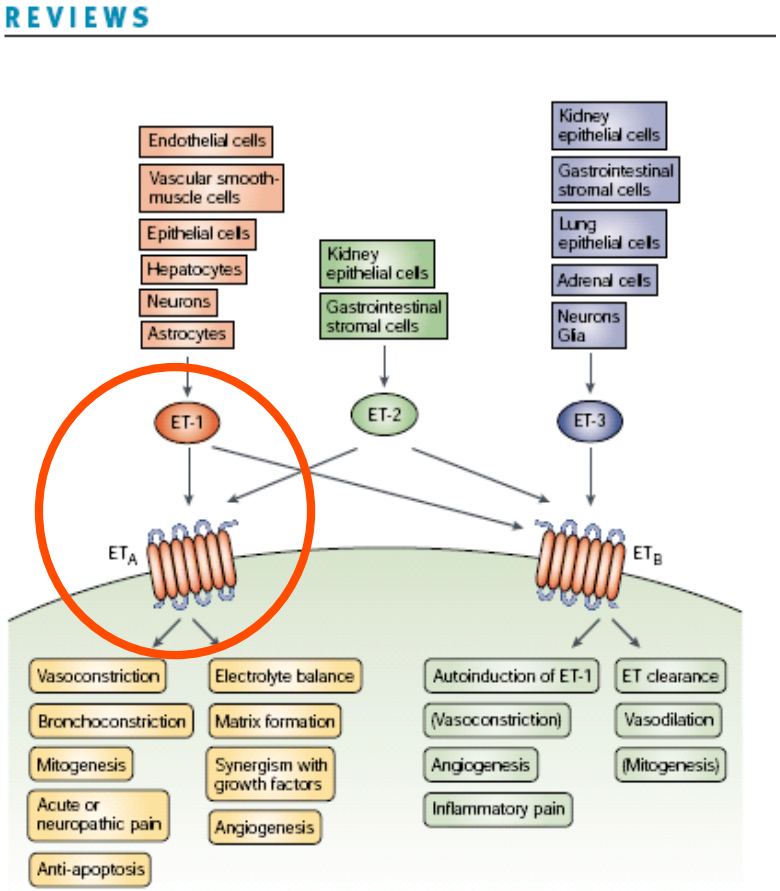
- **Denosumab vs Placebo in castrate non metastatic disease:** 1400 pts,Metastasis-free survival evaluation
- **Denosumab vs placebo in ADT pts:** 1400 pts; BMD evaluation and incident fracture rate

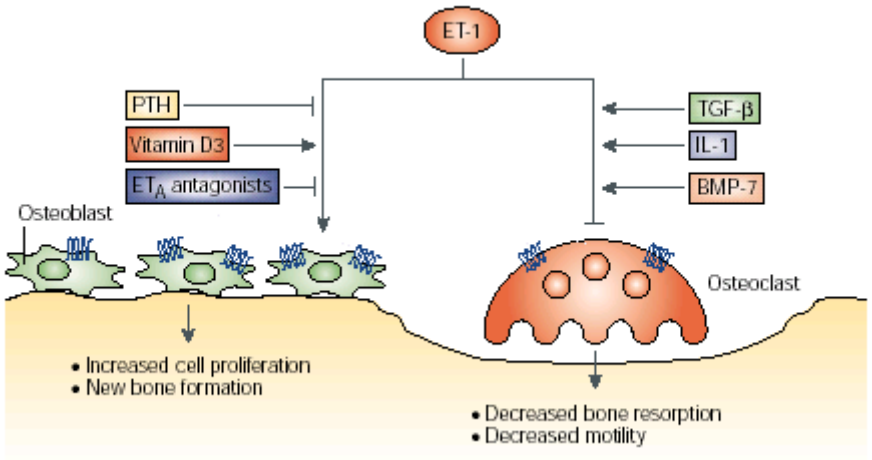
Atrasentan: ET_A-receptor antagonists

oral administration, once a day
favourable tolerability profile

- The endothelins (ETs) comprise a family of three small (21-amino-acid) peptides: ET-1, ET-2 ,ET-3
- ET-1 is a potent endogenous vasoconstrictor and progression factor in many tumour types
- ET1 binds to ET_A receptors
- Both ET1 and ET_A are overexpressed in PC cells and bone mets
- ET_A-receptor activation by ET-1 contributes to tumour growth and progression
- ET_A-receptor blockade might improve cancer treatment
- Ectopic secretion of ET-1 by metastatic PC cells could directly induce pain

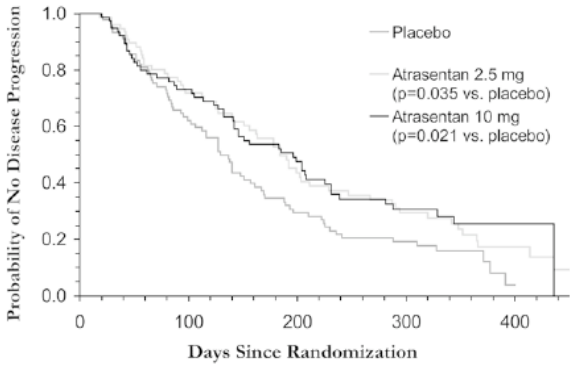
Nelson, Cancer Treat Rev 2003





Atrasentan: studi clinici

- M96-594: Fase II Atrasentan (2.5 mg/10mg) vs placebo 288 pz (244 valutabili) → ↑ TTP (p=0.002)



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 TRIALS:**
  - **M00244: Fase III, in non M1 PC con "rising PSA" → TTP**
  - **SWOG 0421: Fase III Atrasentan + TXT vs placebo + TXT → OS + TTP**

CONCLUSIONI

- Lo standard di trattamento medico delle metastasi ossee da PC, oltre alla terapia specifica antitumorale, é l'acido zoledronico
- La conoscenza delle interazioni fra cellule neoplastiche e microambiente osseo permette di identificare nuovi target terapeutici
- RANKL ed il recettore ETA rappresentano nuovi "target" terapeutici
- Il miglior modo per combinare le "target therapies" con altri trattamenti antitumorali deve ancora essere definito e richiede studi clinici disegnati "ad hoc"