Utilizzo e beneficio dei bisfosfonati nel paziente oncologico: presente e futuro

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Osteonecrosi dei Mascellari (ONJ): Prevenzione, Diagnosi, Trattamento UPDATE 2009

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23 Giugno 2009

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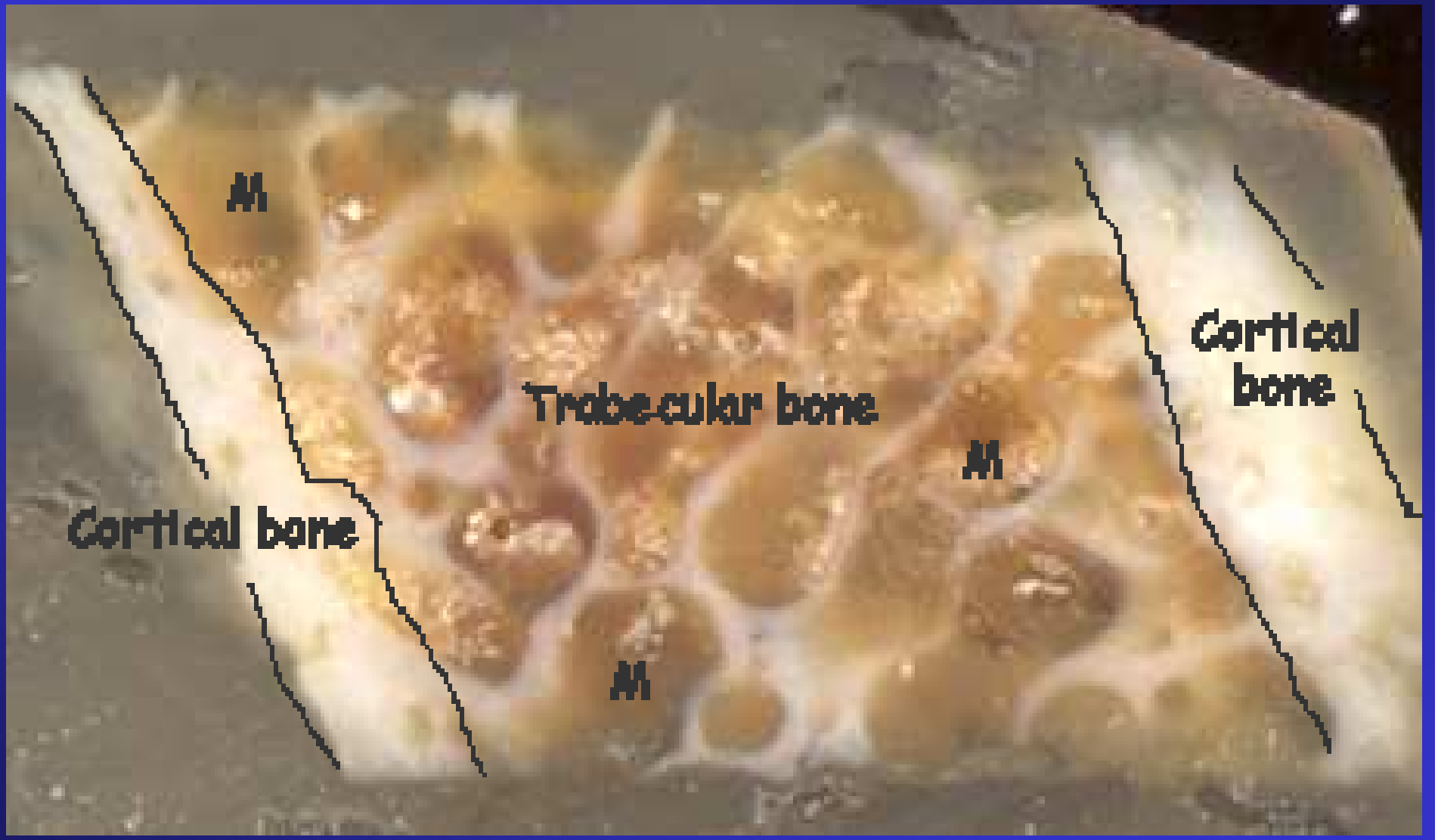
M
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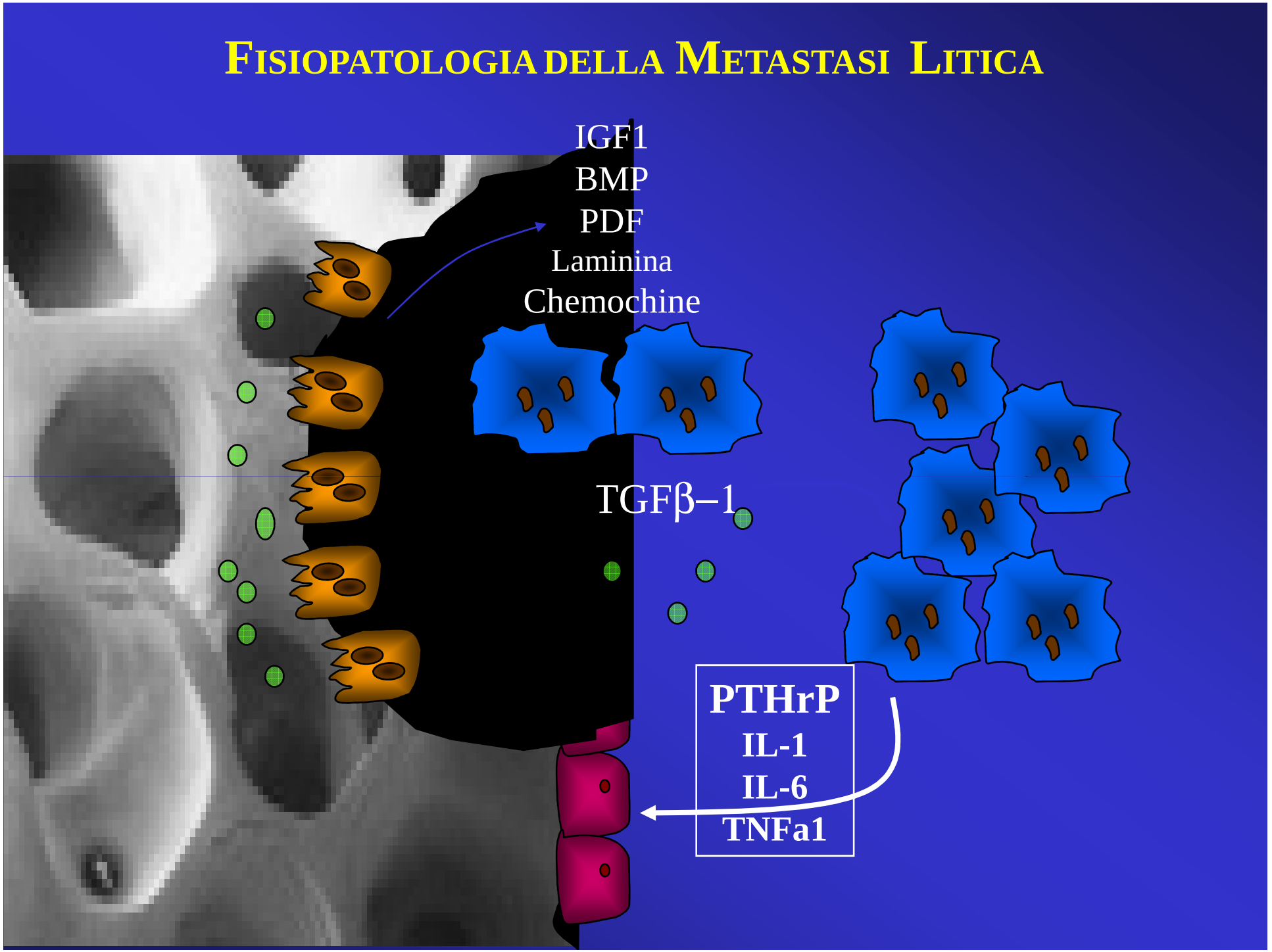
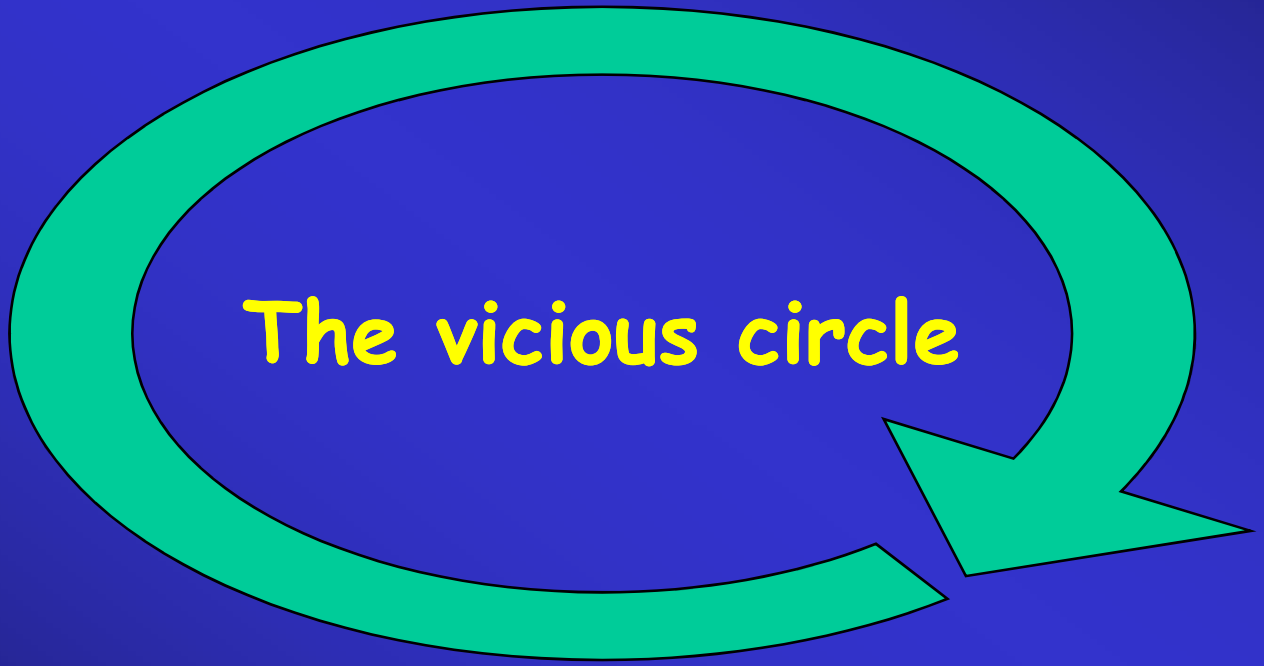
Trabecular bone
Cortical bone
Cortical bone

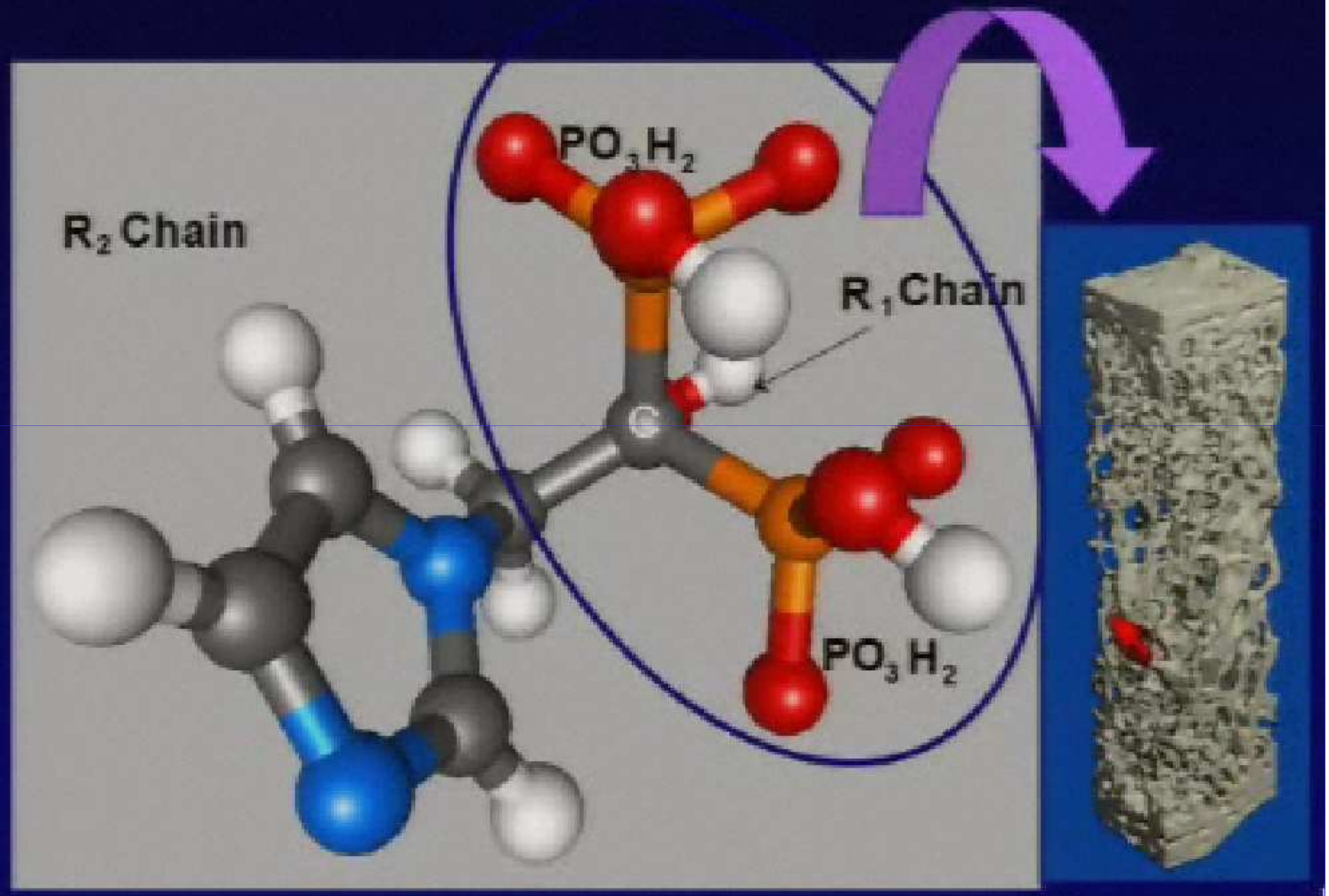
FISIOPATOLOGIA DELLA METASTASI LITICA



Cancer and the skeleton



Overall Structure of Bisphosphonates



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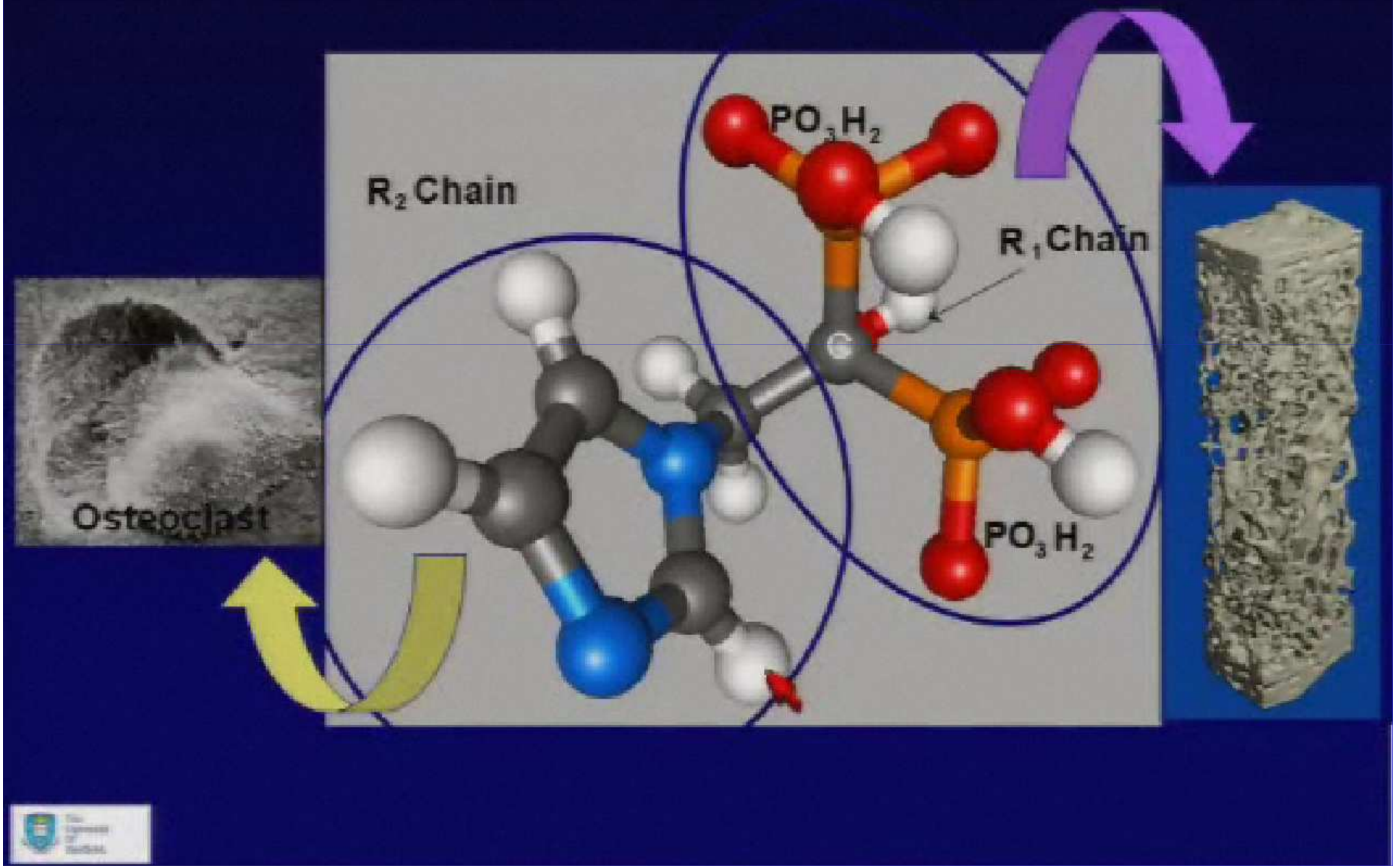
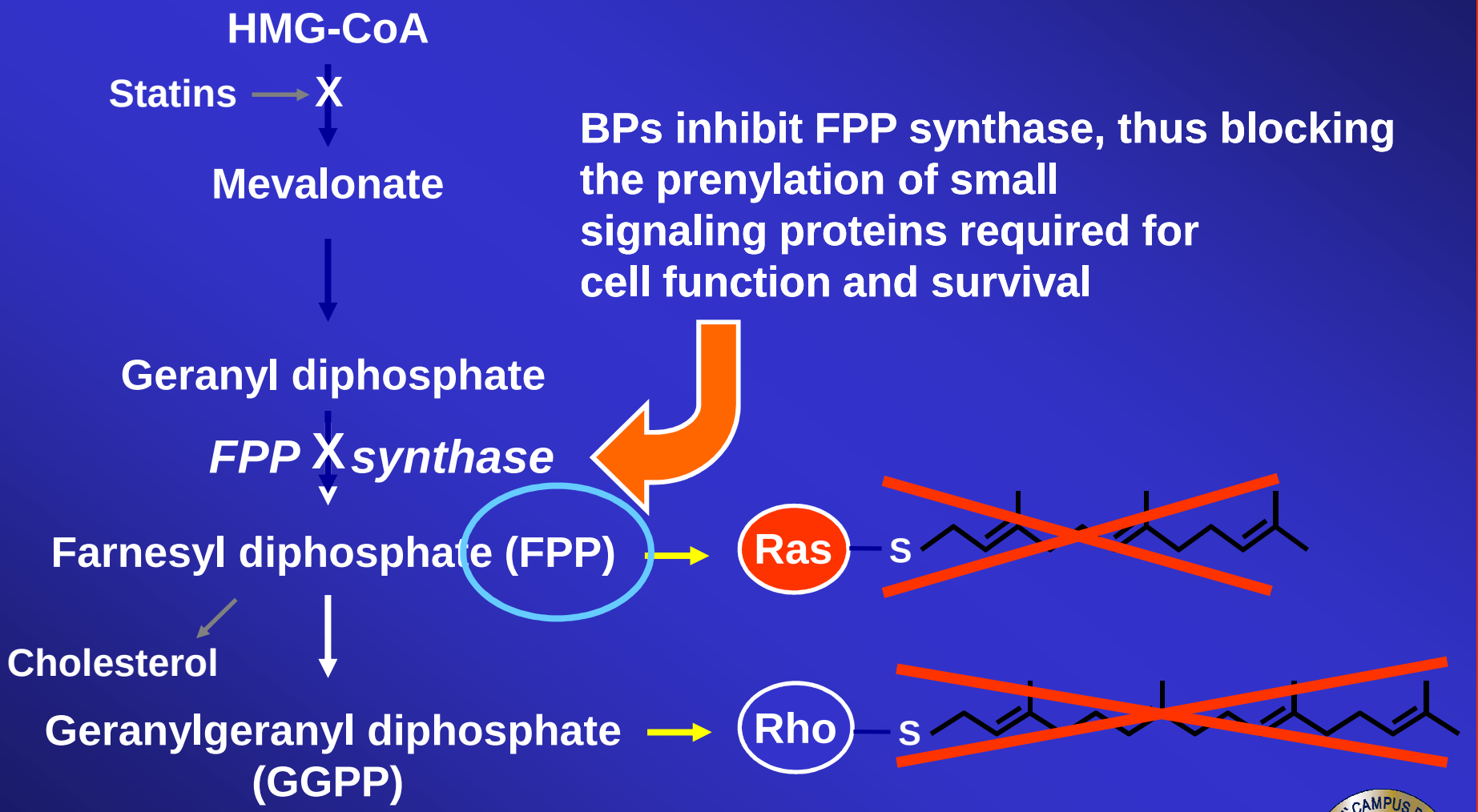
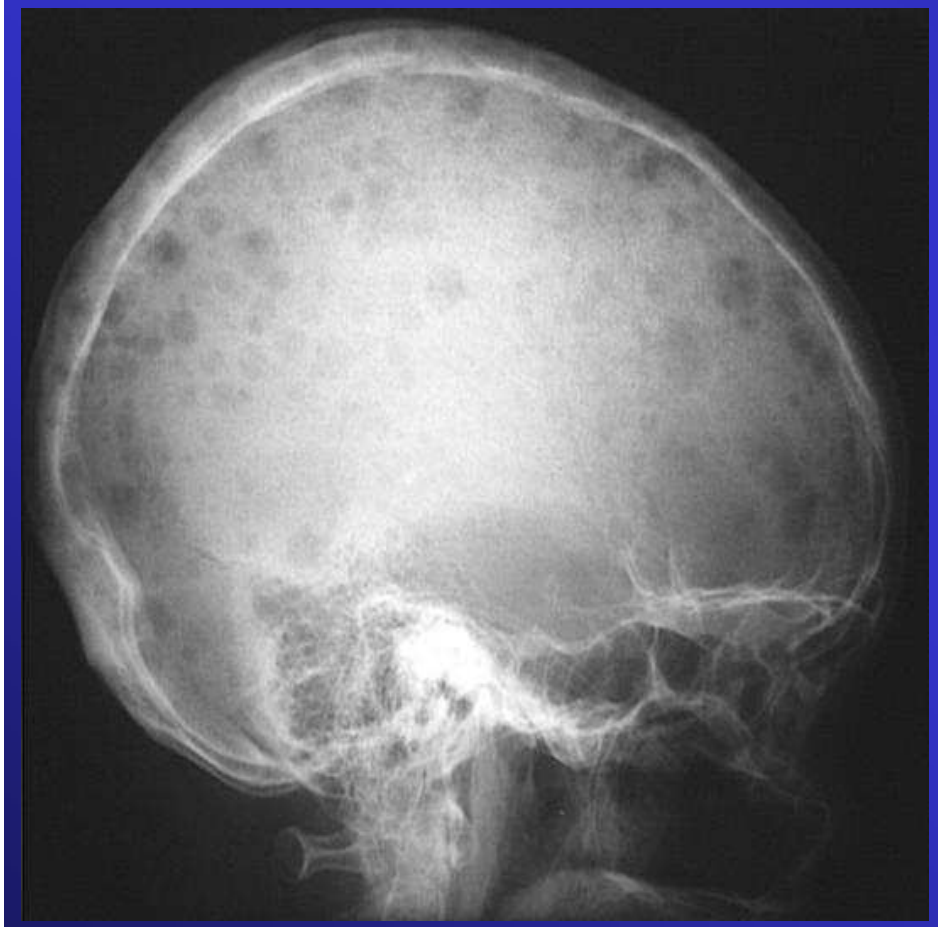
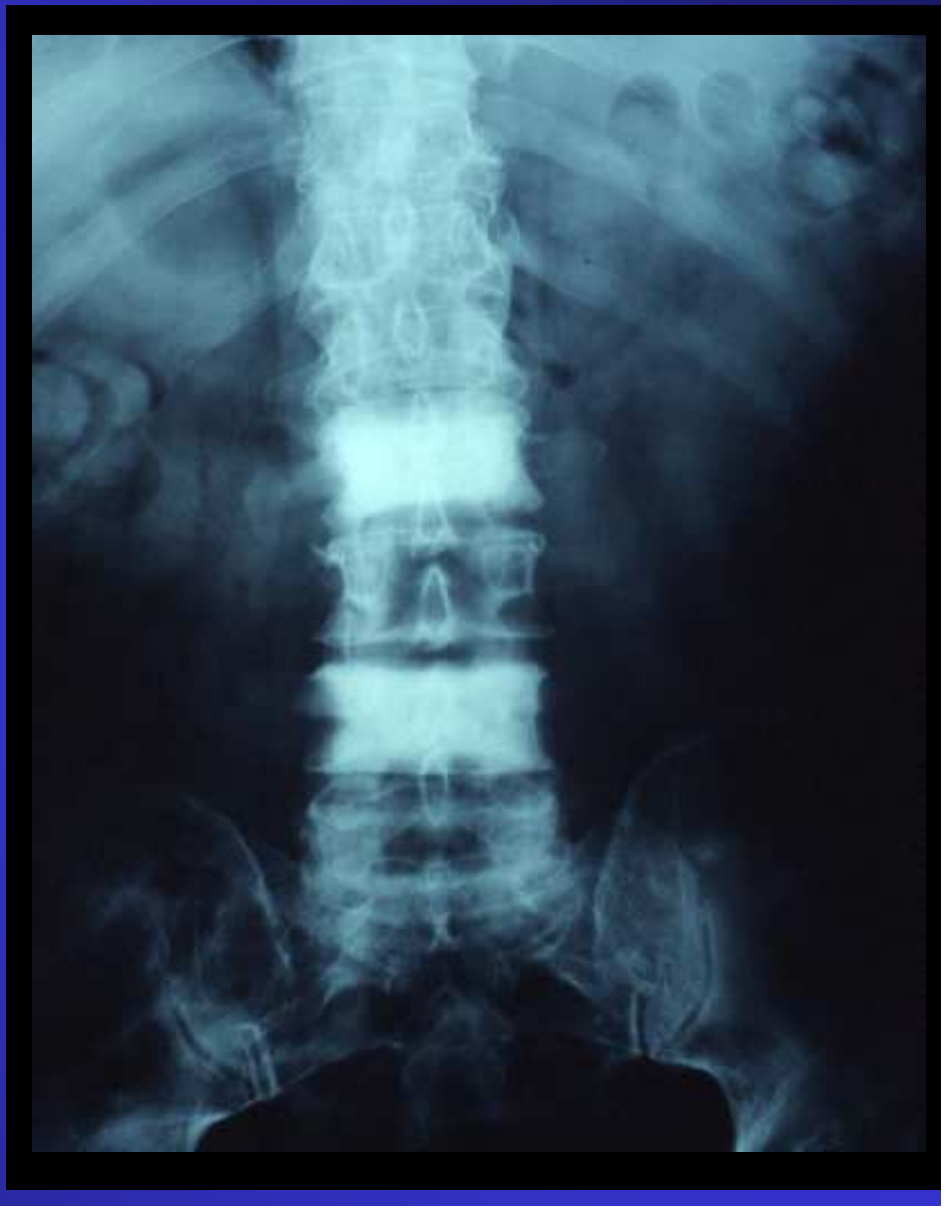


Molecular mechanism of action

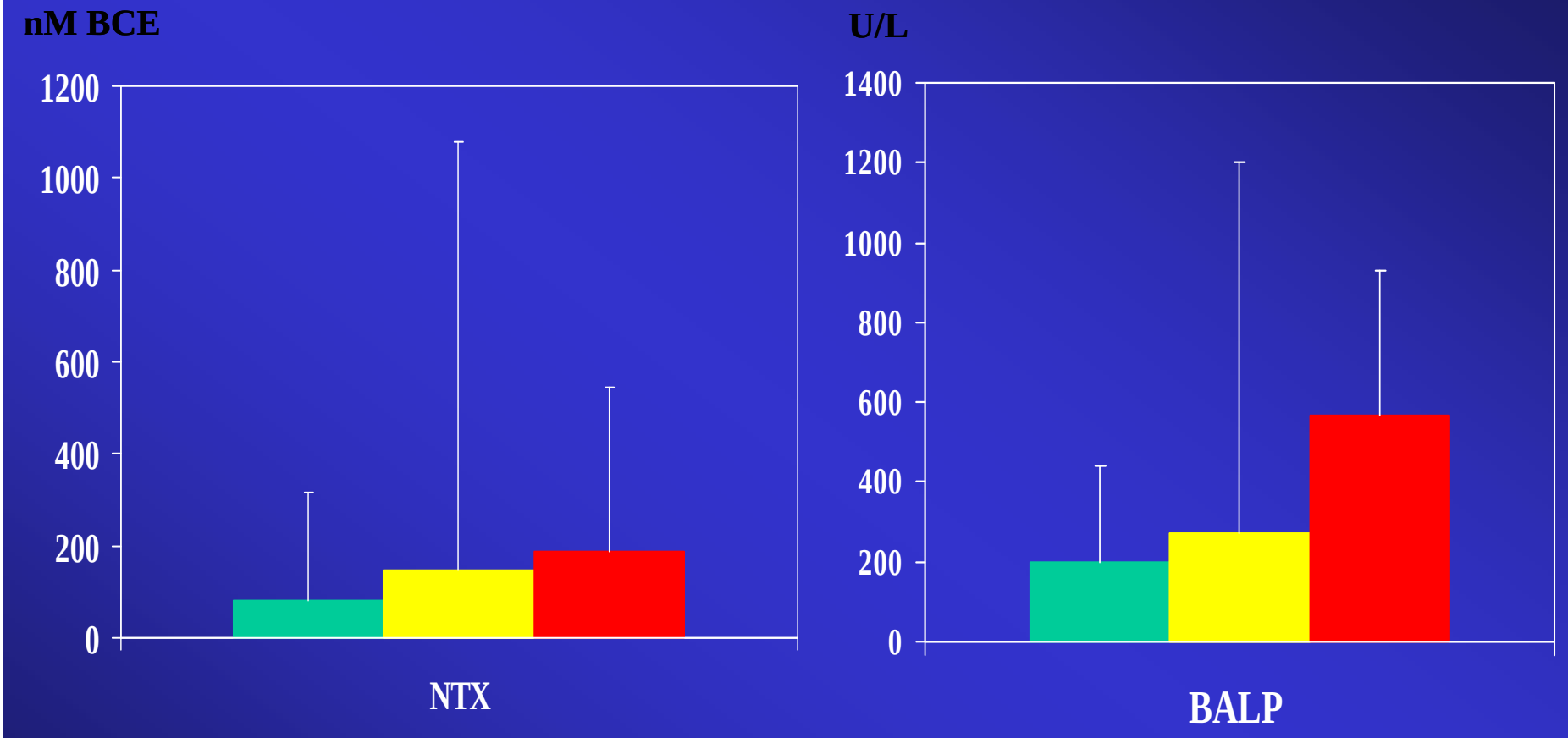


Bisfosfonati per quali pazienti?





Bone turnover markers according to primary histology



Data are mean + SD

NOVARTIS file

Complications of bone metastases

- Bone pain
- Increased bone fragility - fractures
- Bone deformity
- Hypercalcemia
- Nerve compression syndromes
- Spinal cord injury

Bisphosphonates in the prevention of adverse skeletal events

BREAST CANCER

RR 0.83, 95% CI: 0.78 - 0.89; p <0.00001

Pavlakis N et al, Cochrane Rev 2005

PROSTATE CANCER

RR 0.79, 95% CI: 0.62 - 1.00; p = 0.05

Yuen KY et al, Cochrane Rev 2006

Bisphosphonates in the prevention of adverse skeletal events

BREAST CANCER

7 out 11 studies reported a significant pain reduction

Pavlakis N et al, Cochrane Rev 2005

PROSTATE CANCER

RR* 1.54, 95% CI: 0.97 - 2.44; p = 0.07

Yuen KY et al, Cochrane Rev 2006

***Pain reduction**

Linee guida AIOM 2008
Neoplasia mammaria metastatica

- **i BP sono in grado di ridurre il rischio di SRE e di ritardarne significativamente il tempo di comparsa.**
  EVIDENZA: I. GRADO DI RACCOMANDAZIONE: A
- **I BP hanno una documentato effetto sul dolore e migliorano la qualità della vita. Tuttavia non devono sostituire la terapia antalgica e non costituiscono la prima scelta nella terapia del dolore da metastasi scheletriche .**
  EVIDENZA: I. GRADO DI RACCOMANDAZIONE: A
- E' consigliabile sulla base delle evidenze utilizzare un aminobisfosfonato per via endovenosa.
  EVIDENZA: I. GRADO DI RACCOMANDAZIONE: A
- Lo zoledronato sembra essere più efficace del pamidronato. Mancano dati di riferimento diretto con l' ibandronato.
  EVIDENZA: II. GRADO DI RACCOMANDAZIONE: A

Linee guida AIOM 2008

Neoplasia prostatica metastatica

- **L'acido zoledronico si è dimostrato efficace nel ridurre le complicanze scheletriche di pazienti con metastasi ossee da carcinoma prostatico**

  Evidenza I; Grado di raccomandazione: A
- Ancorché vi sia un chiaro razionale, i dati disponibili non consentono di raccomandare fortemente l'uso dei bisfosfonati nel paziente con metastasi ossee da carcinoma prostatico ormonosensibile. L'uso di questi farmaci in questo contesto deve essere valutato caso per caso.

  Evidenza VI; grado di raccomandazione: B
- **I bisfosfonati possono essere efficaci nel controllo del dolore osseo**

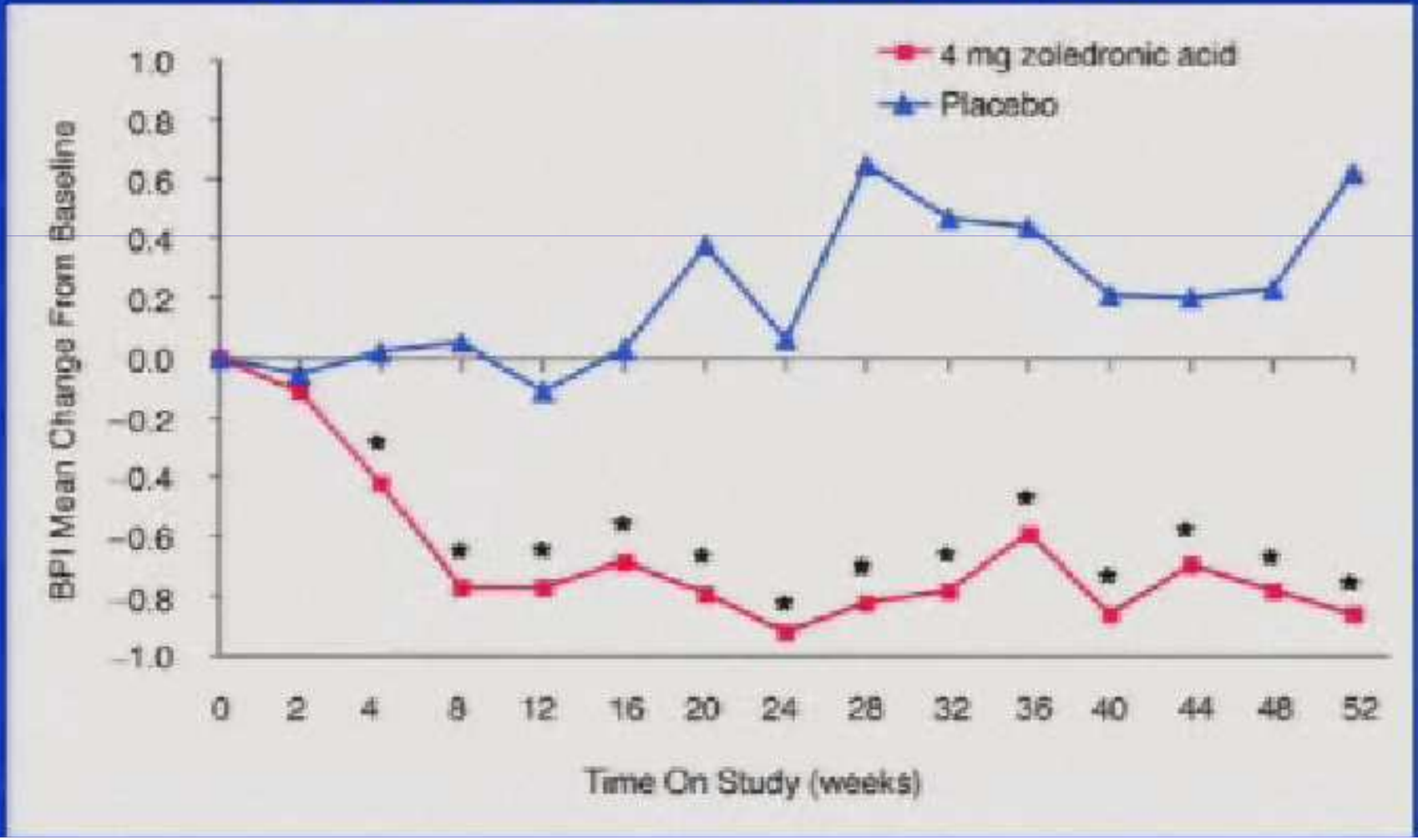
  Evidenza I; Grado di raccomandazione B

QUESITI APERTI

La schedula di somministrazione dei bisfosfonati e.v. ogni 21 o 28 giorni è quella ottimale?

Come migliorare l'efficacia dei bisfosfonati?

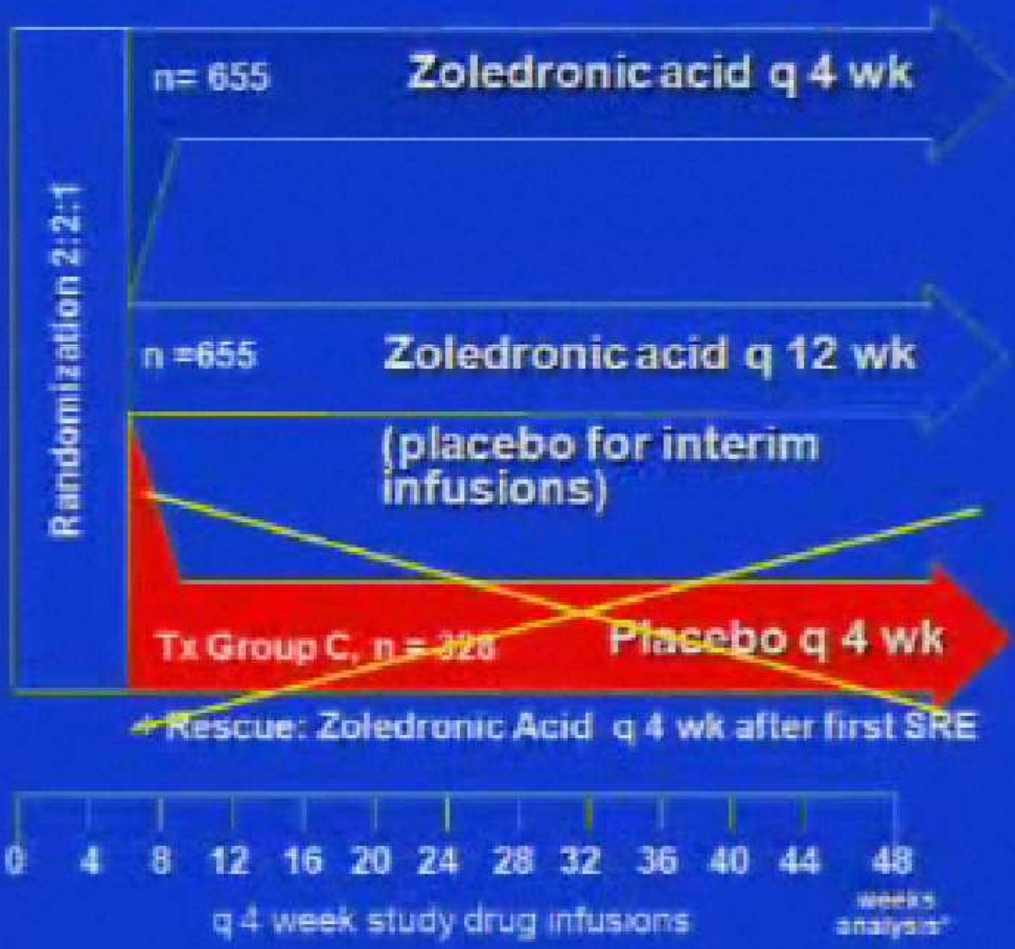
Zoledronic Acid vs. Placebo in Stage IV Breast Cancer
Pain Scores (Brief Pain Inventory)
Kohno N et al, J Clin Oncol 23, 2005



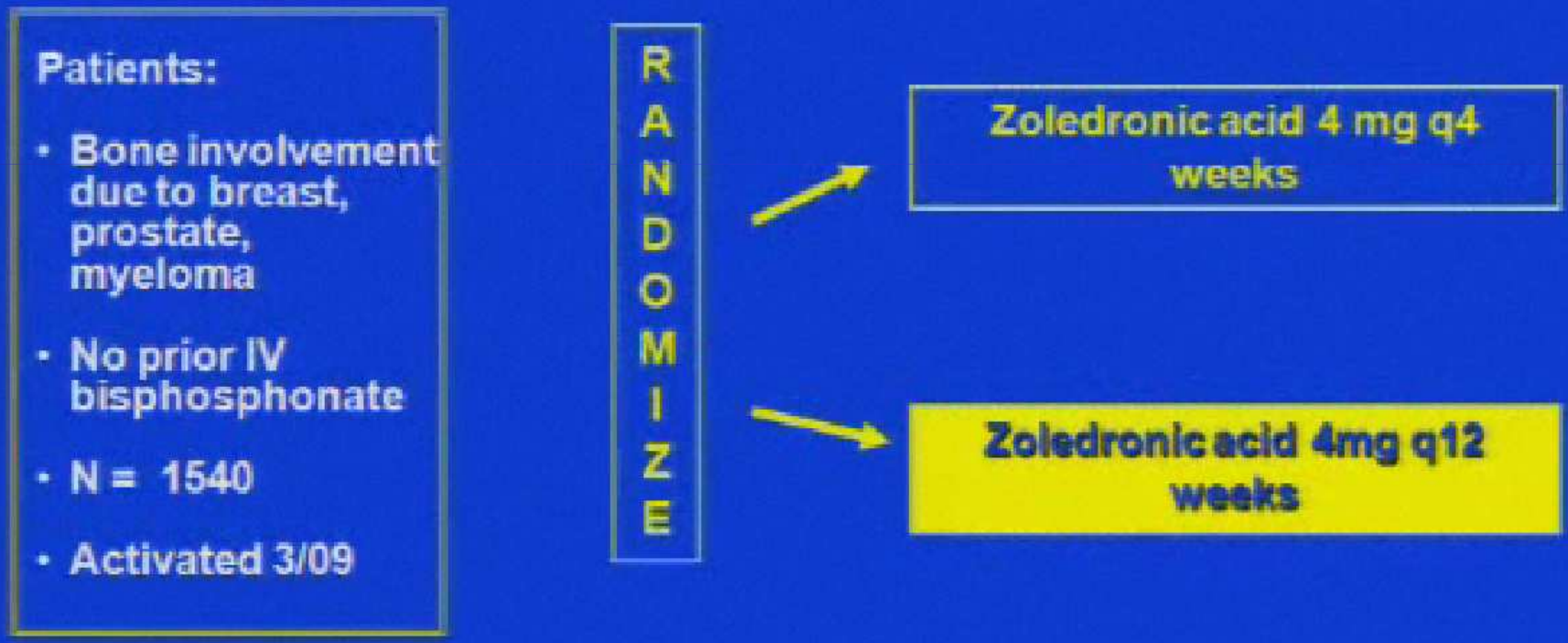
How To Dose Bisphosphonates Long-term?
OPTIMIZE-2 Study Design: Zoledronic Acid Dosing Intervals (Ongoing)

Patients:

- Breast cancer bone mets
- Zoledronic acid pretreated, 9-12 doses during previous year



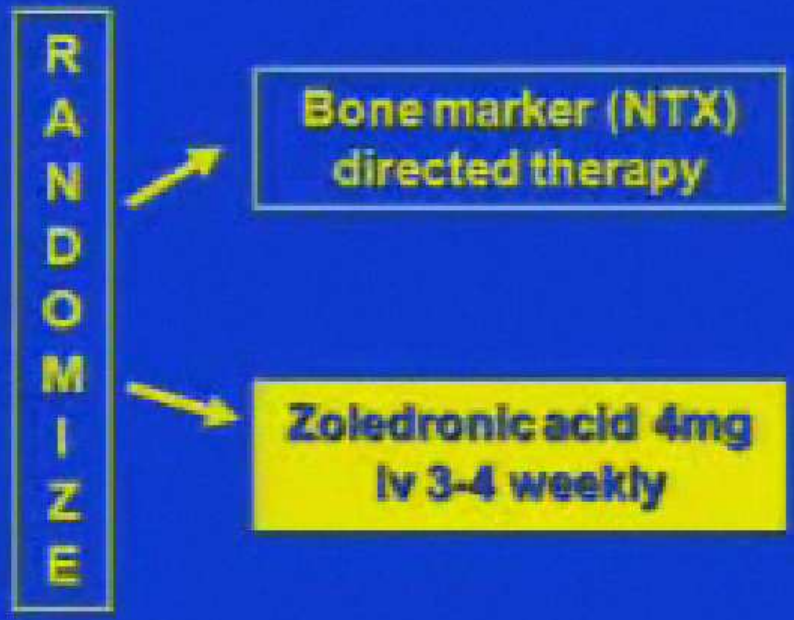
How To Dose Bisphosphonates?
CALGB 70604 Randomized Phase III Trial of Standard vs Longer Dosing Interval of Zoledronic Acid



Use of Bone Resorption Markers to Direct Therapy – BISMARK Trial (Ongoing)

P.I. R Coleman

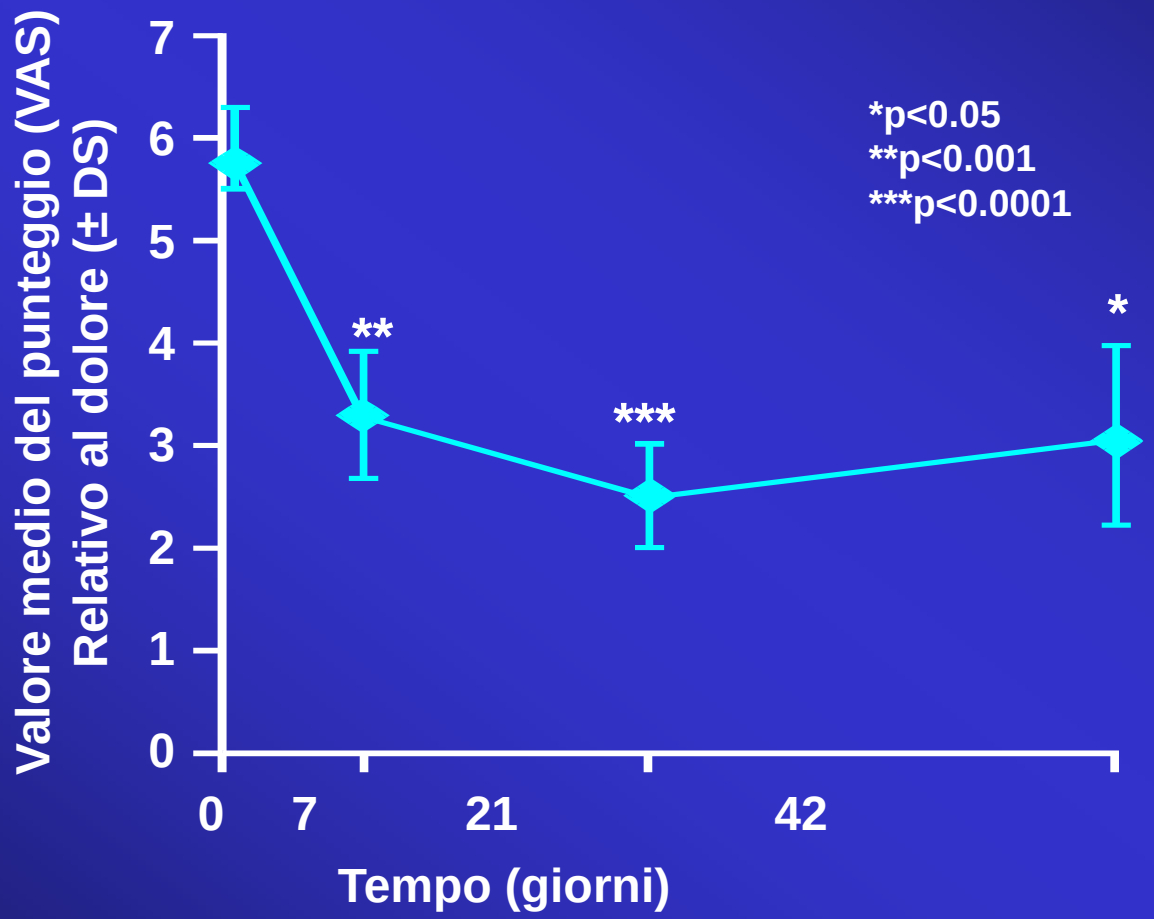
- Patients: 1400 patients with bone metastases from breast cancer
- Treatment: Randomized to "fixed" q3-4 weekly dosing vs "marker directed" dosing based on markers of bone turnover (measured every 15-16 weeks)
- Primary endpoint: Skeletal events



Marker directed schedule

- Ntx >100: zoledronic acid 4mg q3-4 wks
- Ntx 50-100: zoledronic acid 4 mg q8-9 wks
- Ntx <50: zoledronic acid 4mg q15-16 wks

Loading dose di Ibandronato (4 mg al dì per 5 giorni) e dolore osseo



Mancini I et al. *J Clin Oncol* 2004; 22: 3587-92

Activity and safety of a prolonged daily schedule of zoledronic in a patient with bone metastases from urothelial carcinoma

M. P. Brizzi, C. M. Sculli, F. Ragni, F. Porpiglia, M. Tampellini, G. Gorzegno, A. M. Priola, L. Dogliotti & A. Berruti*

Dipartimento di Scienze Cliniche e Biologiche, Università di Torino, Oncologia Medica, Urologia, Radiologia, Azienda Ospedaliera Universitaria San Luigi, Orbassano, Italy

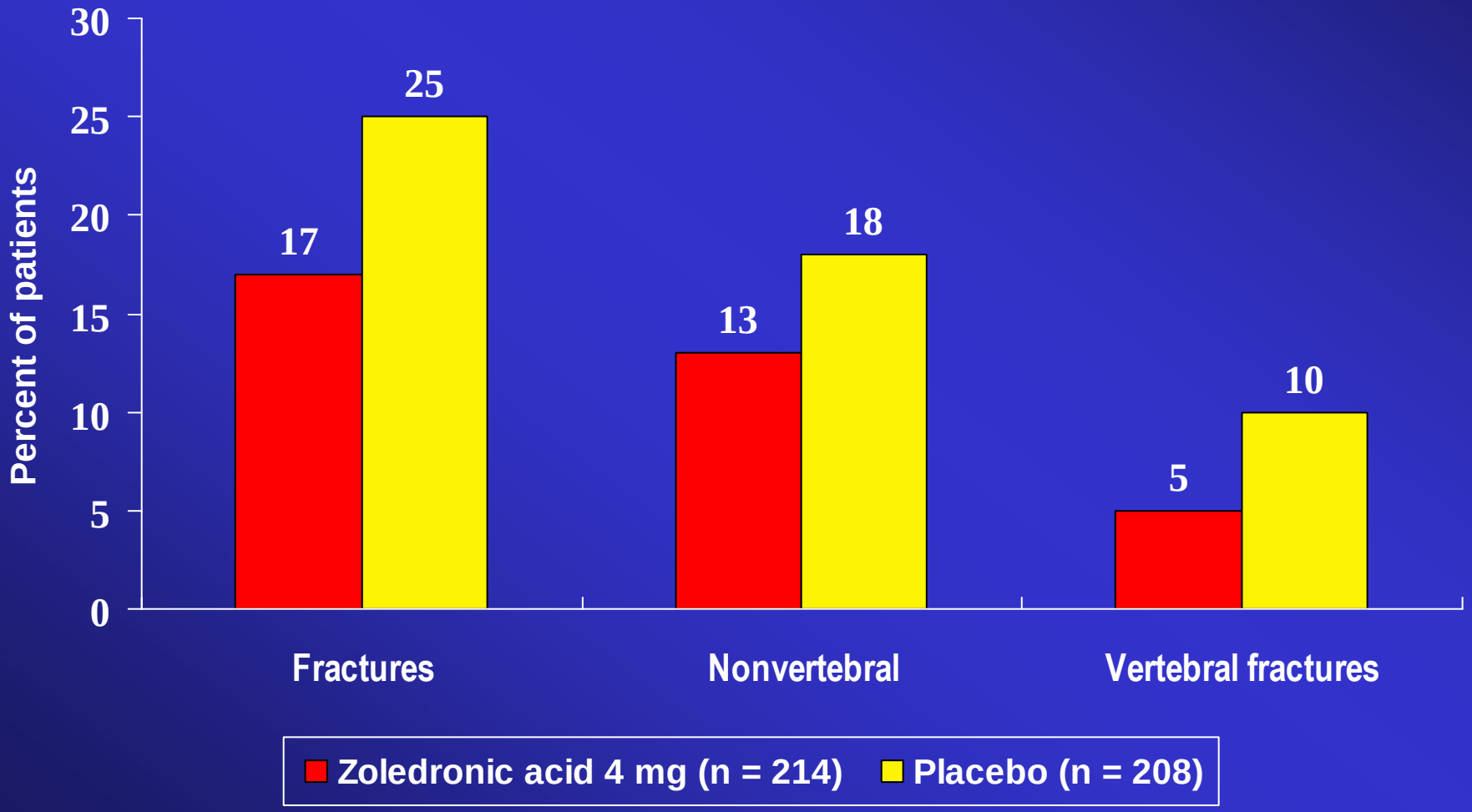
Ann Oncol 2009

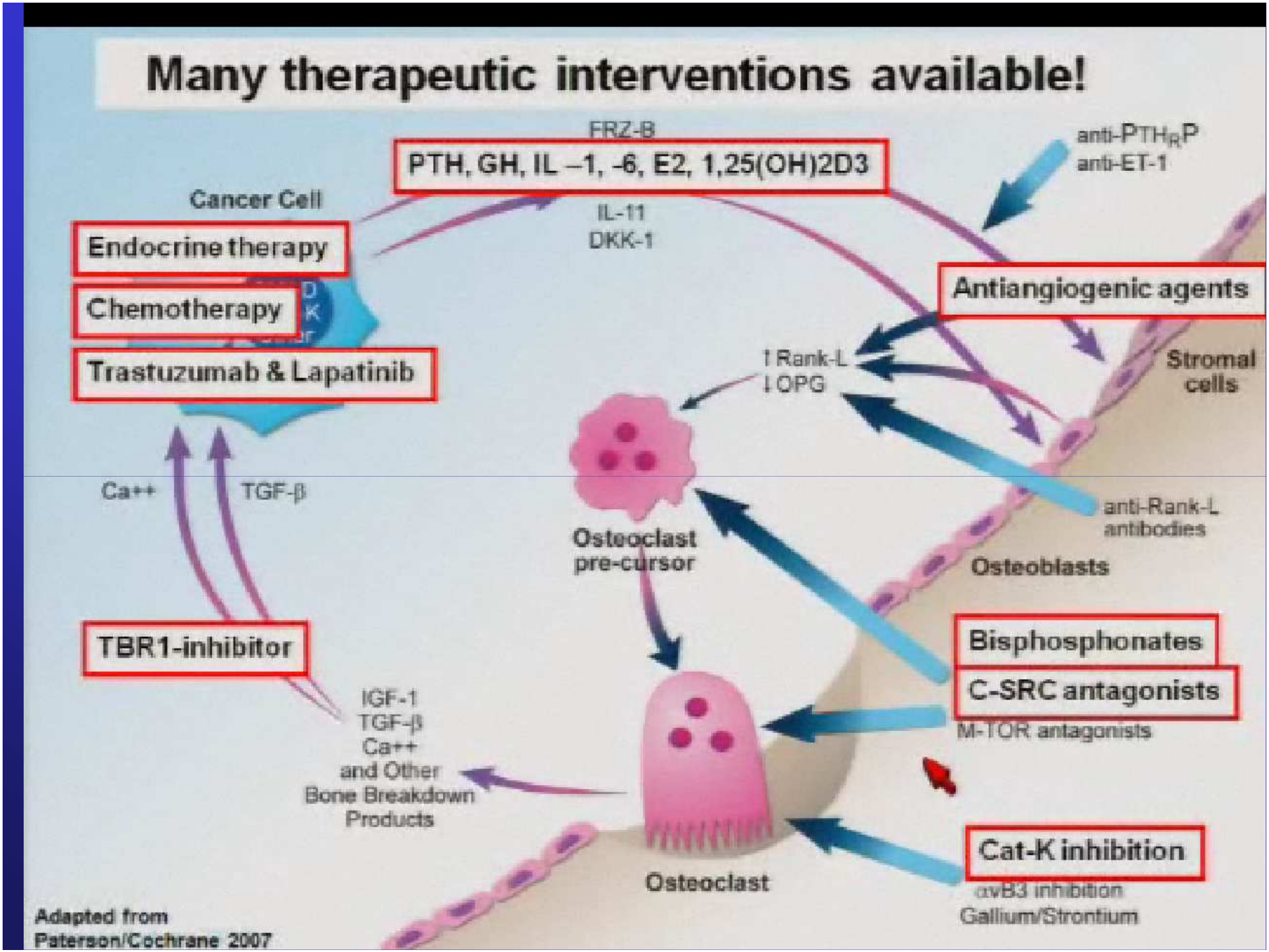
Acido zoledronico somministrato per errore alla schedule di 4 mg ev al giorno per 21 giorni

Netto miglioramento del dolore e del PS in una paziente allettata sottoposta a morfina a dosaggi elevati

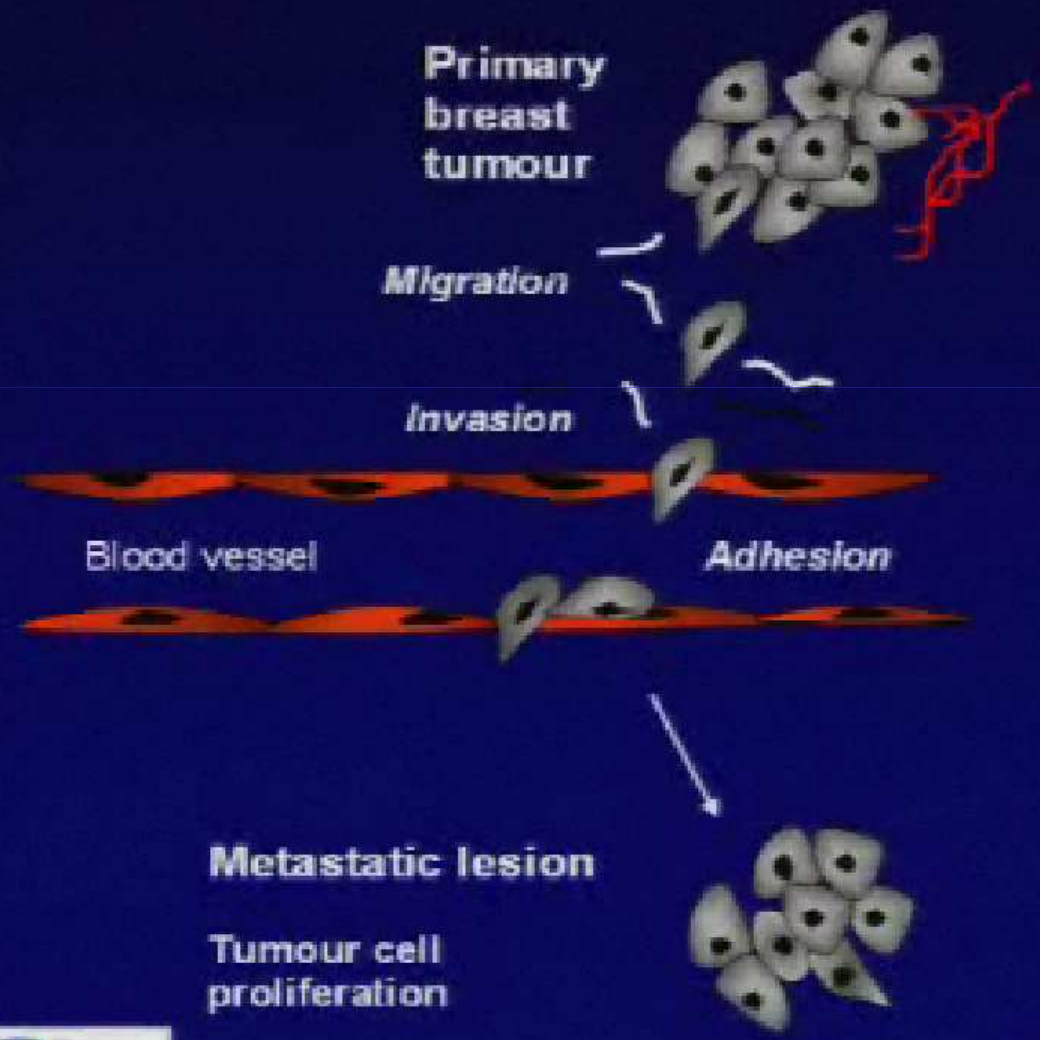
Prostate Cancer
Proportion (%) of Patients With Fractures

Zoledronic acid consistently reduced the incidence of fractures




Many therapeutic interventions available!
FRZ-B
PTH, GH, IL –1, -6, E2, 1,25(OH)2D3
anti-PTHRP
anti-ET-1
Cancer Cell
IL-11
DKK-1
Endocrine therapy
Chemotherapy
Trastuzumab & Lapatinib
Antiangiogenic agents
↑Rank-L
↓OPG
Stromal cells
Ca++
TGF-β
anti-Rank-L antibodies
Osteoclast pre-cursor
Osteoblasts
TBR1-inhibitor
Bisphosphonates
C-SRC antagonists
M-TOR antagonists
IGF-1
TGF-β
Ca++
and Other
Bone Breakdown
Products
Cat-K inhibition
Osteoclast
αvB3 inhibition
Gallium/Strontium
Adapted from
Paterson/Cochrane 2007

Schematic Illustration of the Anti-tumour Activity of Zoledronic Acid



- Inhibition of angiogenesis
- Inhibition of invasion and adhesion
- Induction of tumour cell apoptosis
- Inhibition of tumour cell proliferation
- Synergistic anti-tumour activity with cytotoxic drugs

Adapted from Winter et al. Cancer Treatment Reviews. 2008; 34: 453-475

Doxorubicin and Zoledronic Acid In Vivo Effects

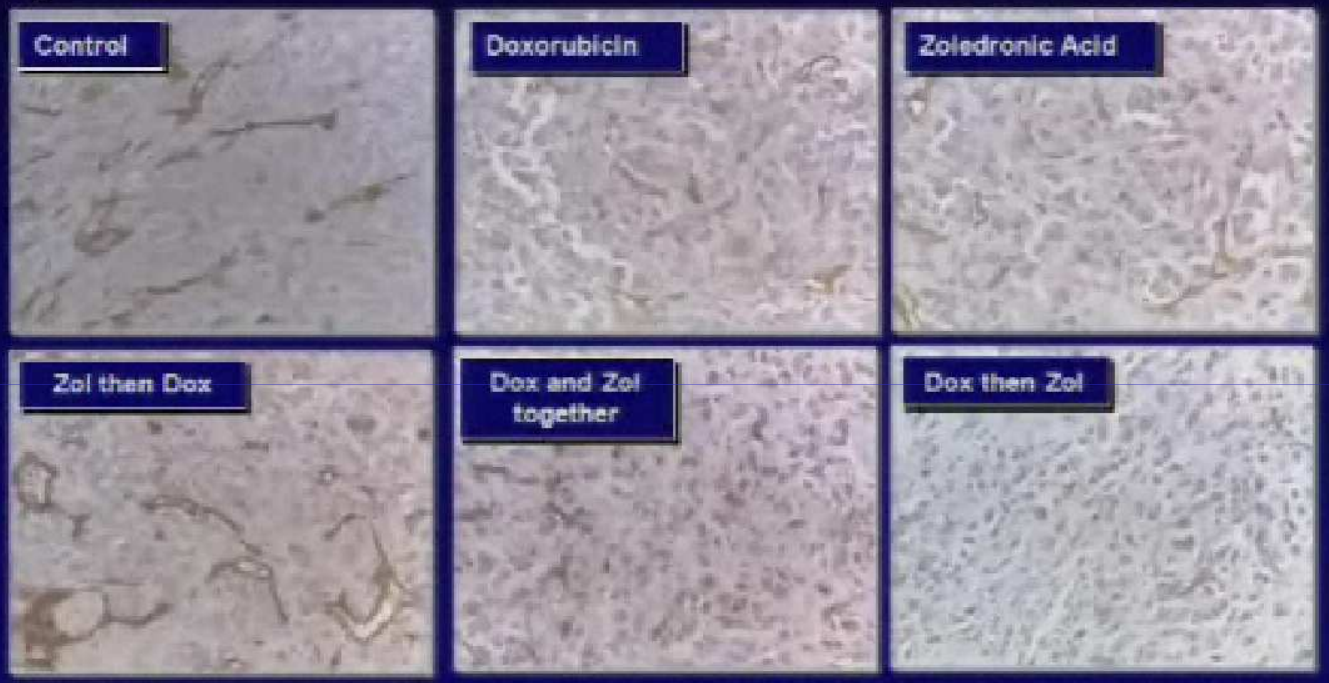
Dox followed by zol **increases** tumour cell apoptosis and **inhibits** tumour cell proliferation—sequential treatment is **superior to combined**

PD Ottewell JNCI (2008) 100(16):1167-78

14:23/23:58

Doxorubicin and Zoledronic Acid In Vivo - Effects on Tumour Vascularisation

CD34 staining

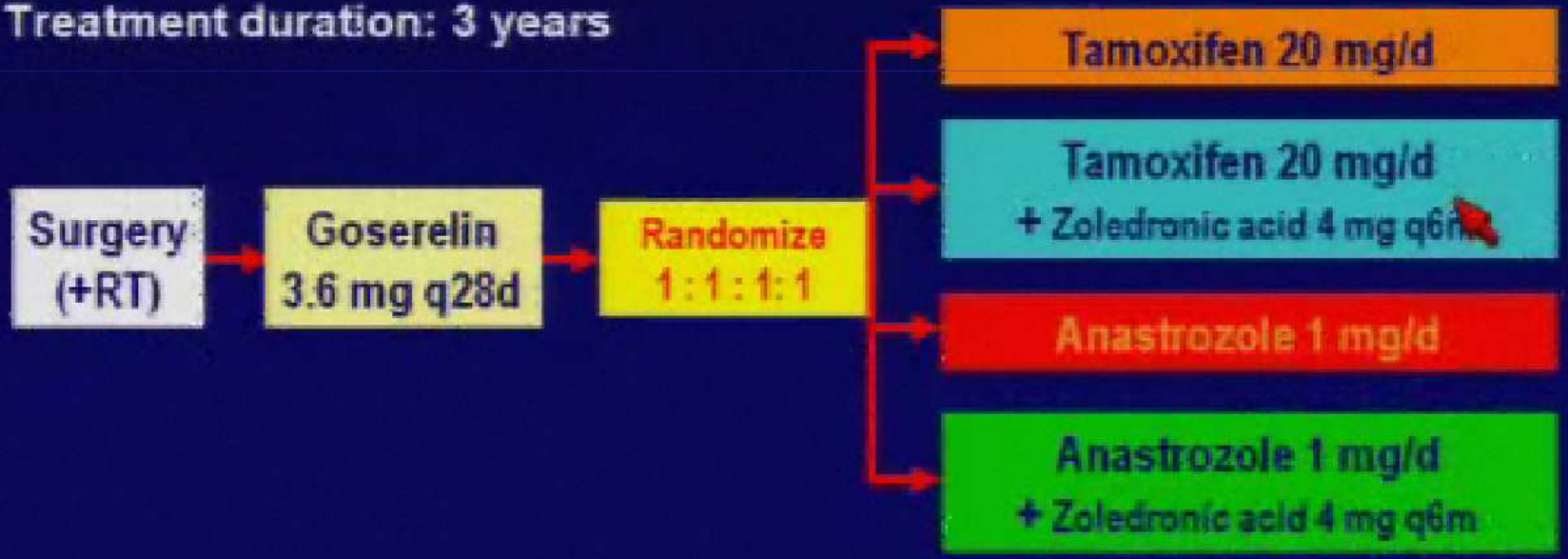


Dox followed by Zol decreases vascularisation of sc breast tumours

PD Ottewell JNCI (2008) 100(16):1167-78

ABCSG-12 Trial Design

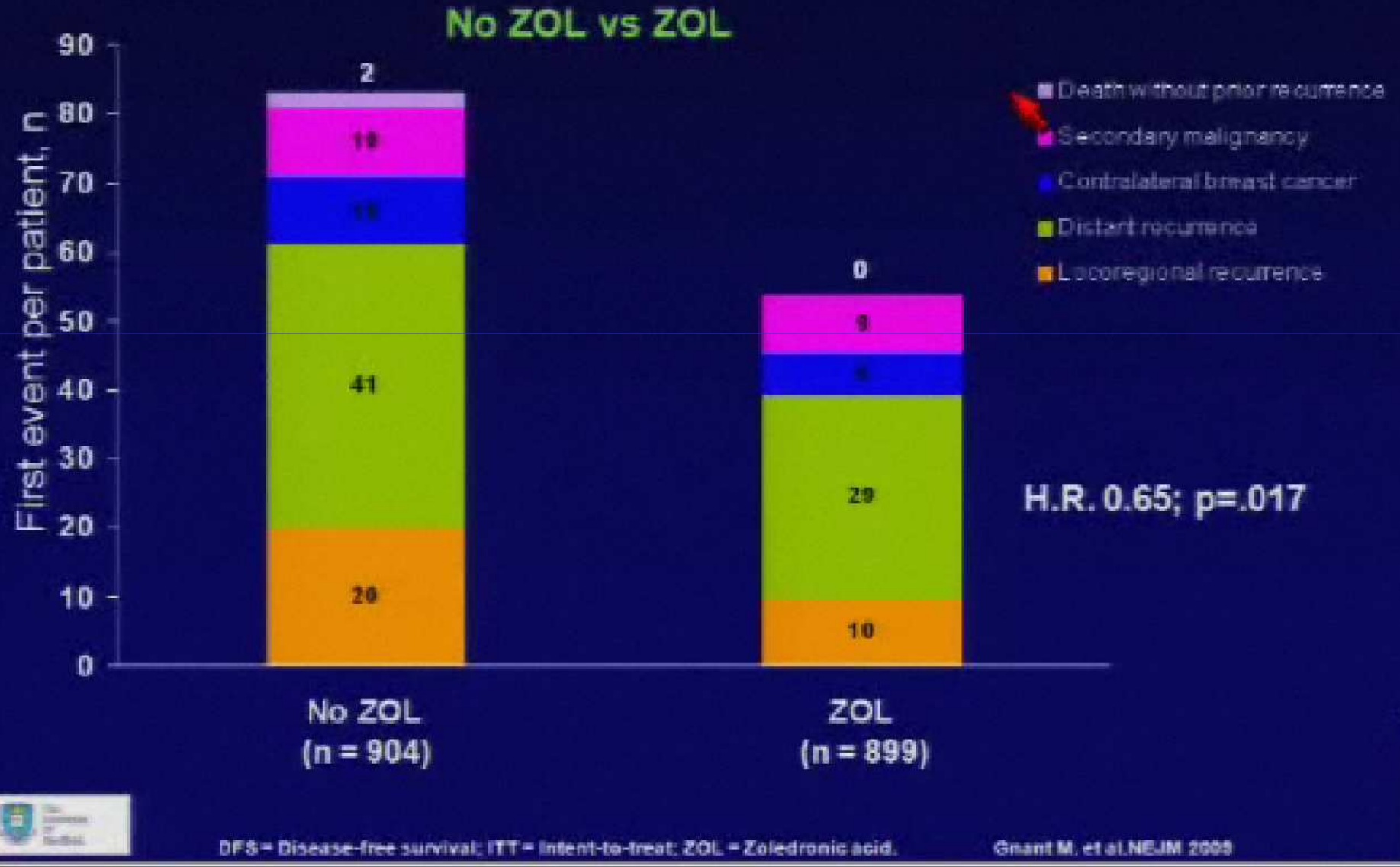
- Accrual 1999-2006
- 1,803 premenopausal breast cancer patients
- Endocrine-responsive (ER and/or PR positive)
- Stage I&II, <10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years



Gnant M et al. NEJM 2008

16:33/23:58

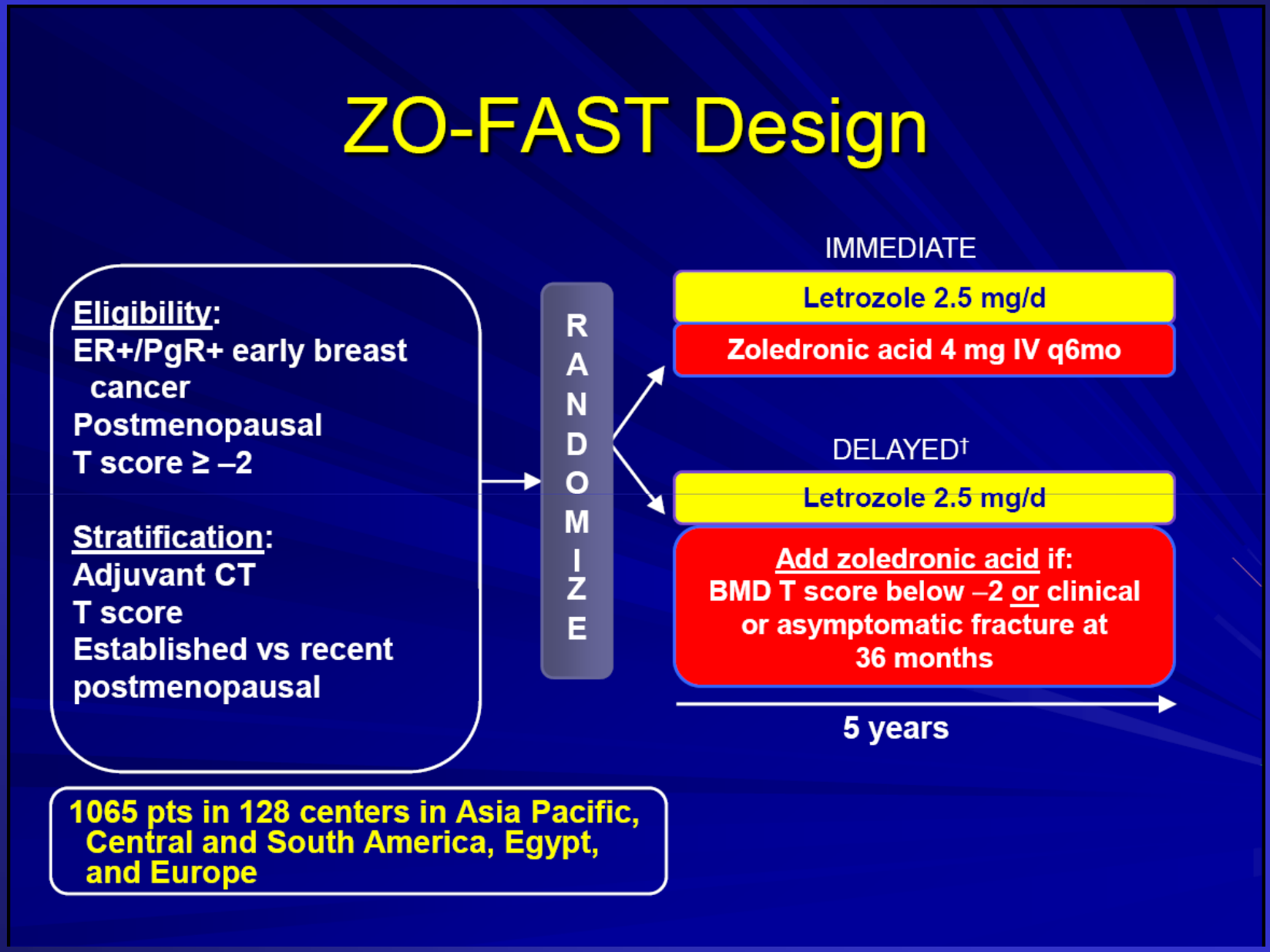
First DFS Events (ITT Population)



DFS = Disease-free survival; ITT = Intent-to-treat; ZOL = Zoledronic acid.

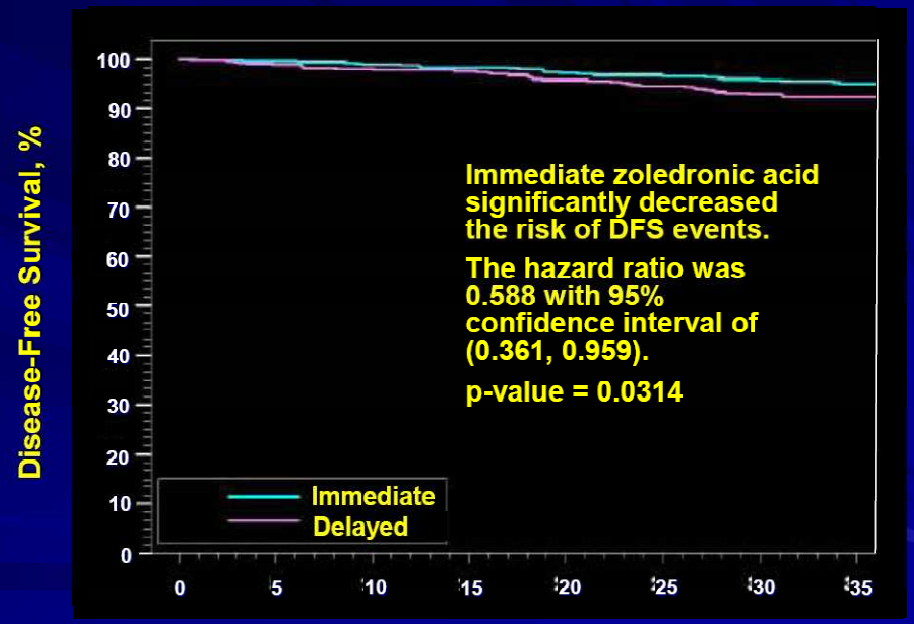
Gnant M. et al.NEJM 2009

ZO-FAST Design



Kaplan Meier Plot of Disease-Free Survival by Treatment Group

All Randomized Patients



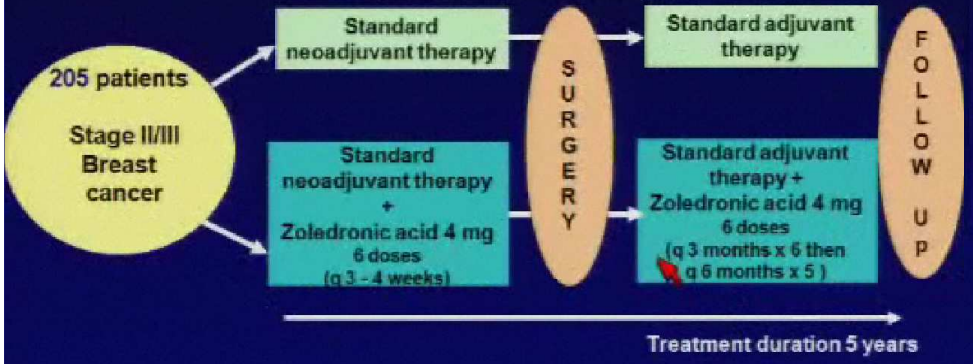
Sites of Disease Recurrence at Month 36

	Immediate N=532 No. of Patients (%)	Delayed N=532 No. of Patients (%)
Local	2 (0.4)	10 (1.9)
Distant*	20 (3.8)	30 (5.6)
Bone	9 (1.7)	17 (3.2)
Brain	4 (0.8)	3 (0.6)
Lymph node	5 (0.9)	3 (0.6)
Liver	5 (0.9)	3 (0.6)
Lung	4 (0.8)	6 (1.1)
Skin	0	7 (1.3)
Other	7 (1.3)	12 (2.3)

*Patient could have multiple sites reported

AZURE: (Neo) Adjuvant Zoledronic Acid in Breast Cancer?

Sub-set of 3360 patients included in AZURE who received neoadjuvant chemotherapy



Zoledronic Acid (ZA) Plus Chemotherapy in the Neoadjuvant Treatment of Breast Cancer

- 205 patients (6.1%) received neoadjuvant therapy

	N	CT alone	CT + ZA	P-Val
Mean residual tumour size	171	42.4 mm	28.2 mm	.002
Pathologic complete response	180	5.8%	10.9%	.03

CT vs. CT+ZA: 78% vs. 65% of patients requiring mastectomy

Possible antitumour effect of ZA in the neoadjuvant setting

Winter, SABCS 2008, Abstract 5101

Ongoing Studies for the Prevention of Bone Metastasis

SKELETAL & BONE HEALTH

Cancer type	Study	Treatment
Breast	AZURE	Standard treatment ± zoledronic acid
	NSABP-B-34	
	Intergroup S0307	Zoledronic acid vs clodronate vs ibandronate
	SUCCESS	Zoledronic acid 2 years vs 5 years
Prostate	ZEUS	Zoledronic acid vs control group
Lung	2419	Zoledronic acid vs control group

First interim analysis expected 2009