AULA ORANGE 2

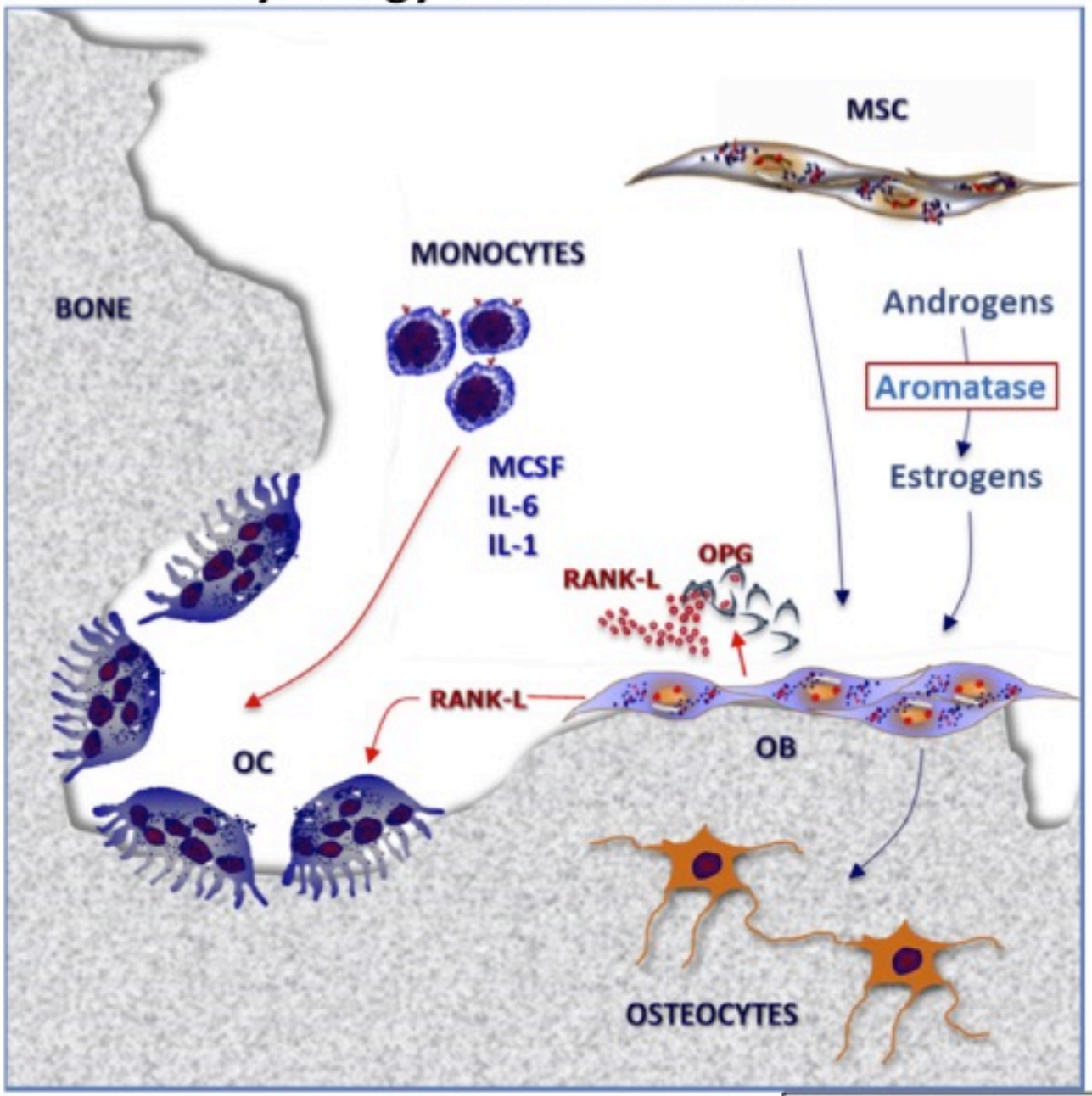
Meet the Expert 2

Osso e oncologia

Speaker:
A. Scillitani

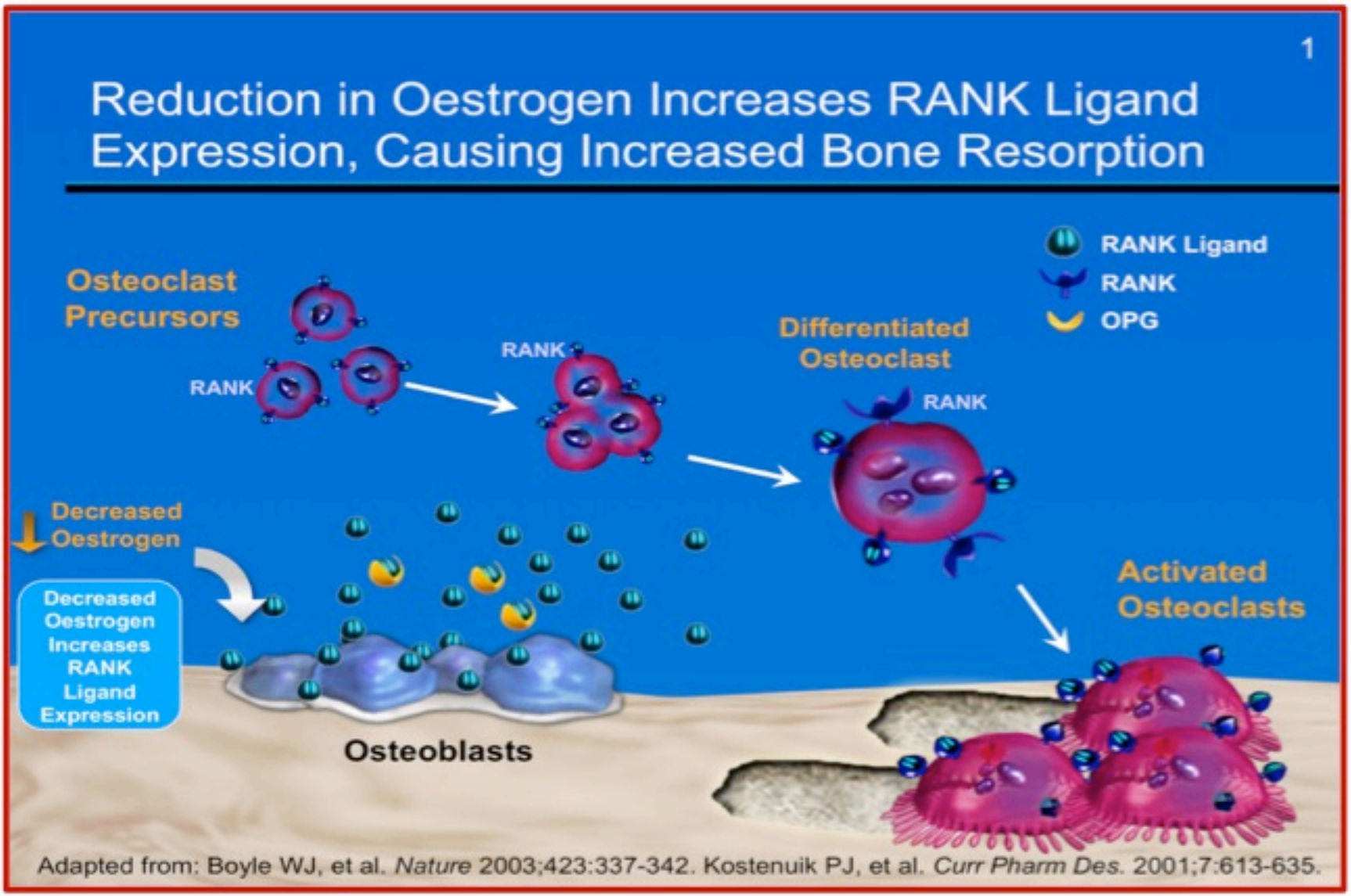
Discussants:
F. Angelini,
I. Chiodini

Physiology of bone turnover



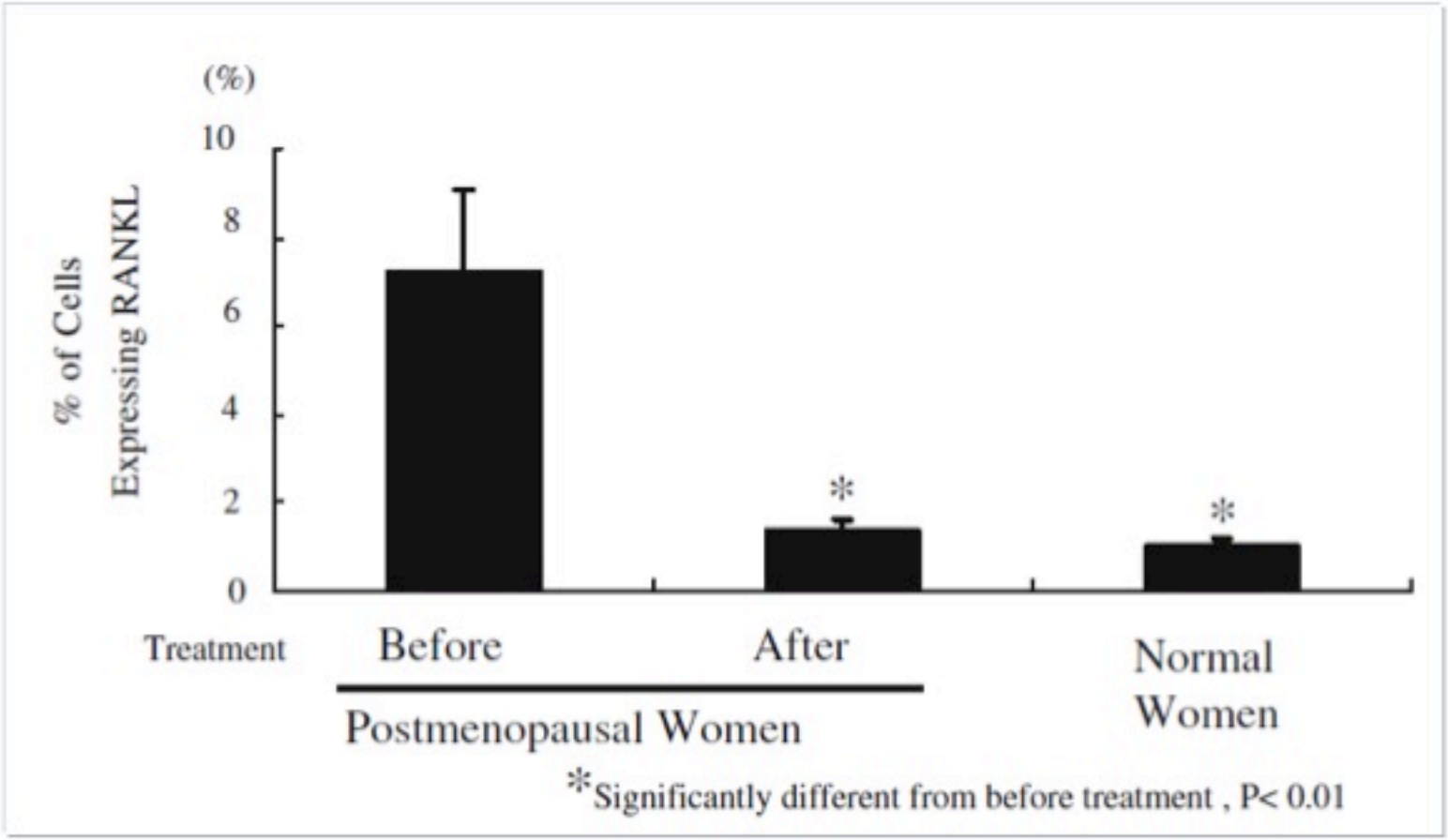
D'Oronzo S. et al. / Cancer Treatment Reviews 2015

Reduction in Oestrogen Increases RANK Ligand Expression, Causing Increased Bone Resorption



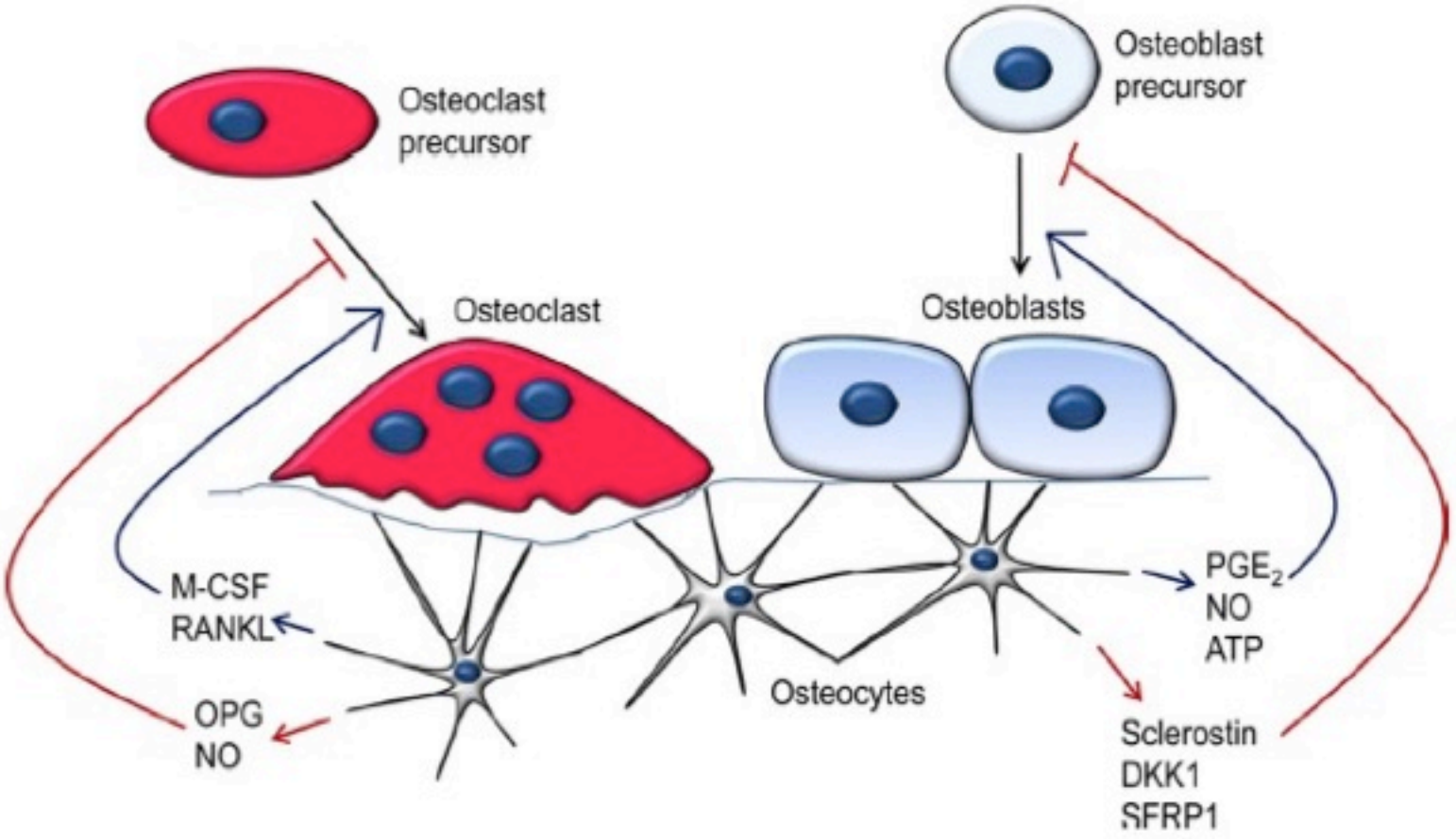
Adapted from: Boyle WJ, et al. *Nature* 2003;423:337-342. Kostenuik PJ, et al. *Curr Pharm Des.* 2001;7:613-635.

Estradiol rapidly inhibits osteoclastogenesis and RANKL expression in bone marrow cultures in postmenopausal women: a pilot study



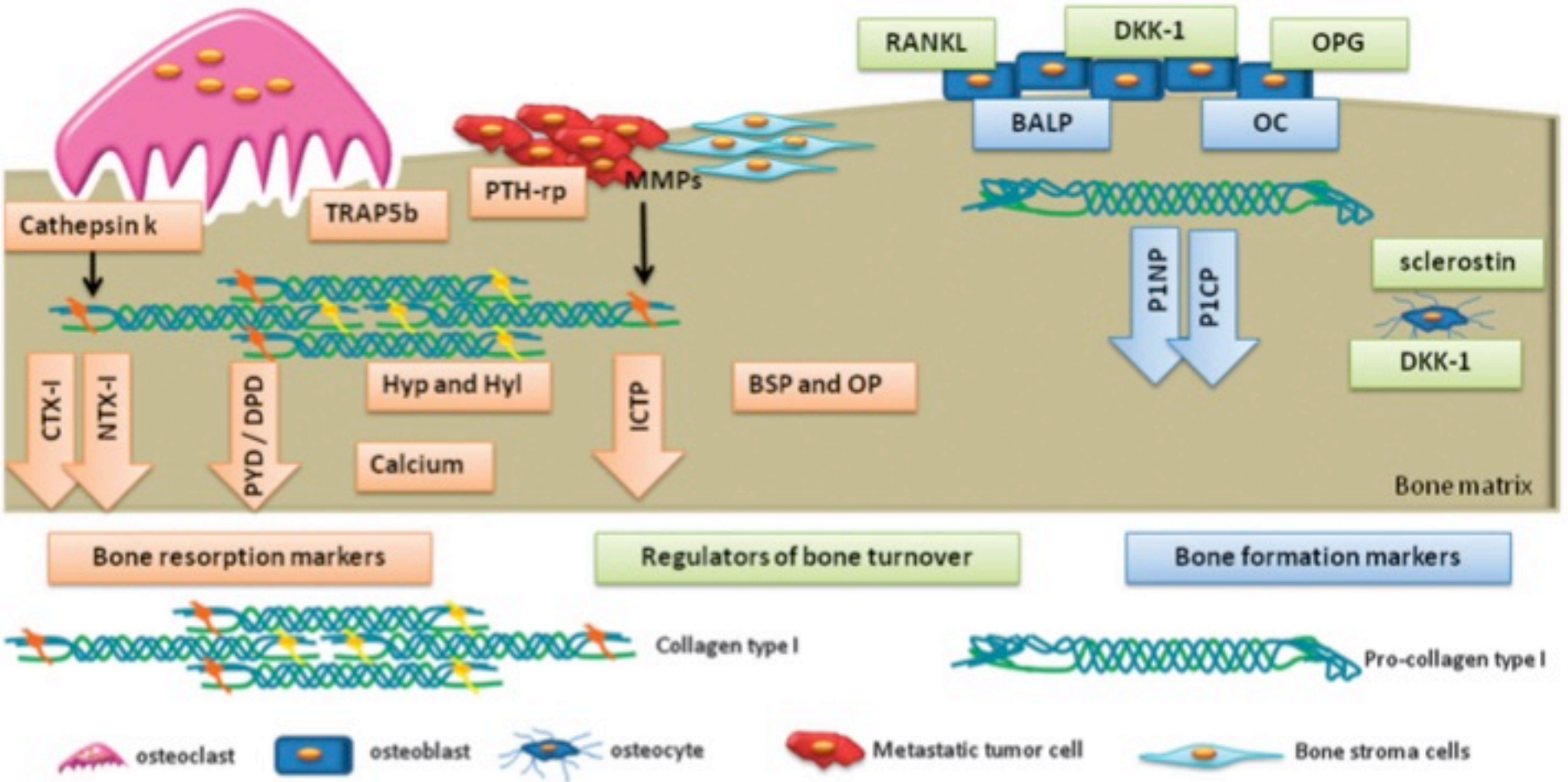
Taxel P et al, Osteoporos Int 2008

Osteocyte regulation of bone remodeling



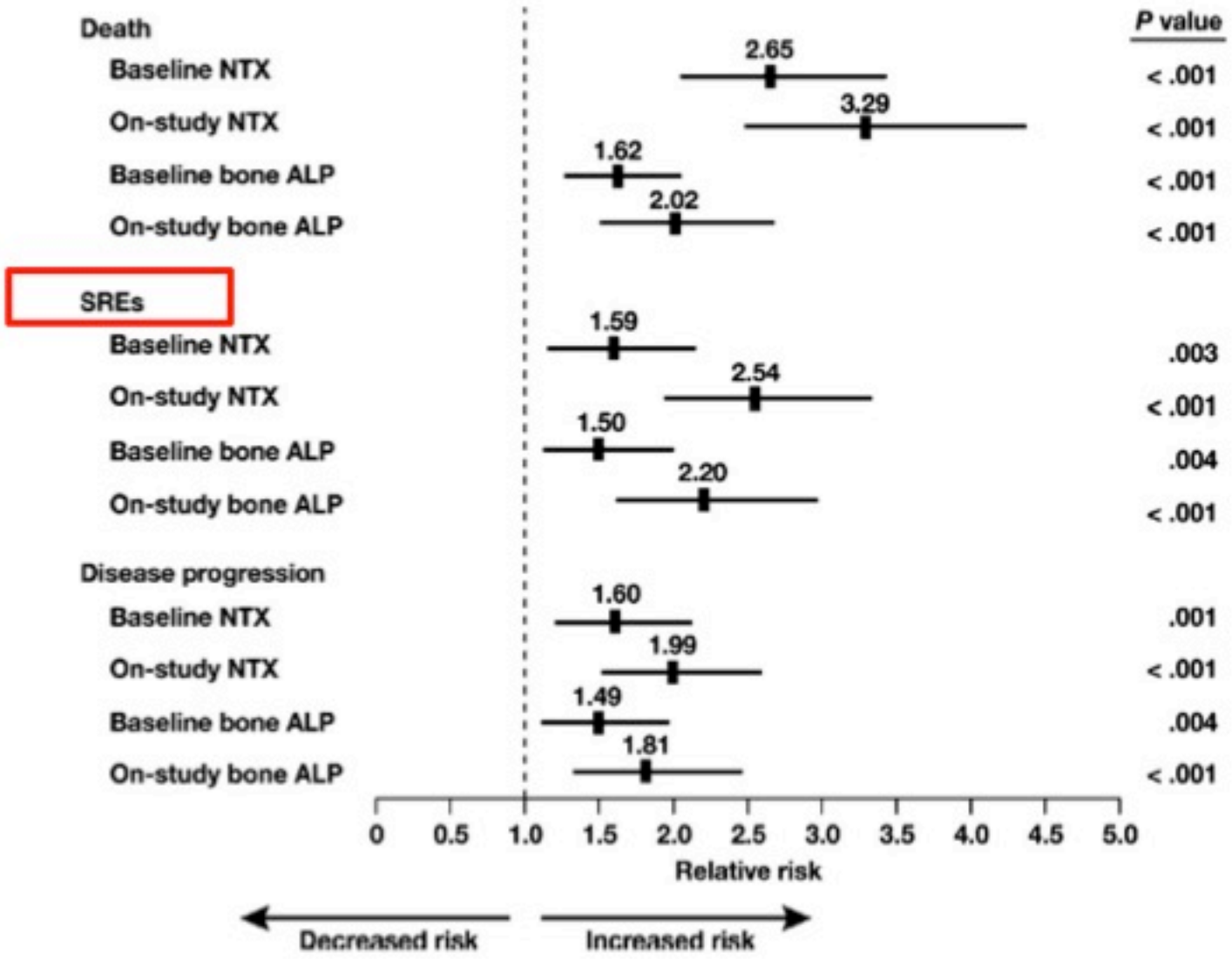
Dallas SL et al. Endocr Rev, 2013

Bone remodeling markers and bone metastases

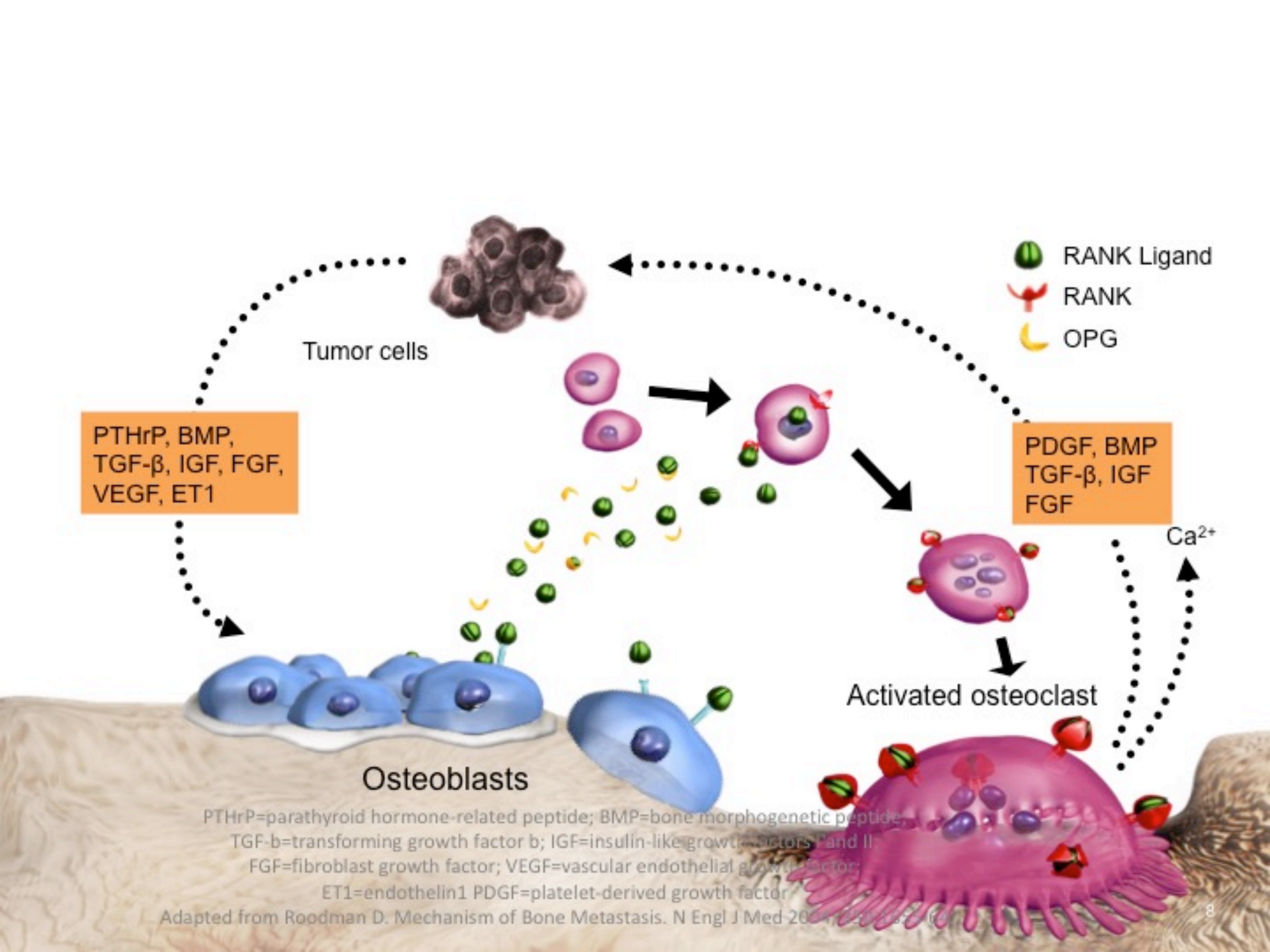


Ferreira A **et al, BoneKey Rep 2015**

CORRELATIONS BETWEEN BONE TURNOVER AND CLINICAL OUTCOME IN PATIENTS WITH BONE METASTASES FROM SOLID TUMORS



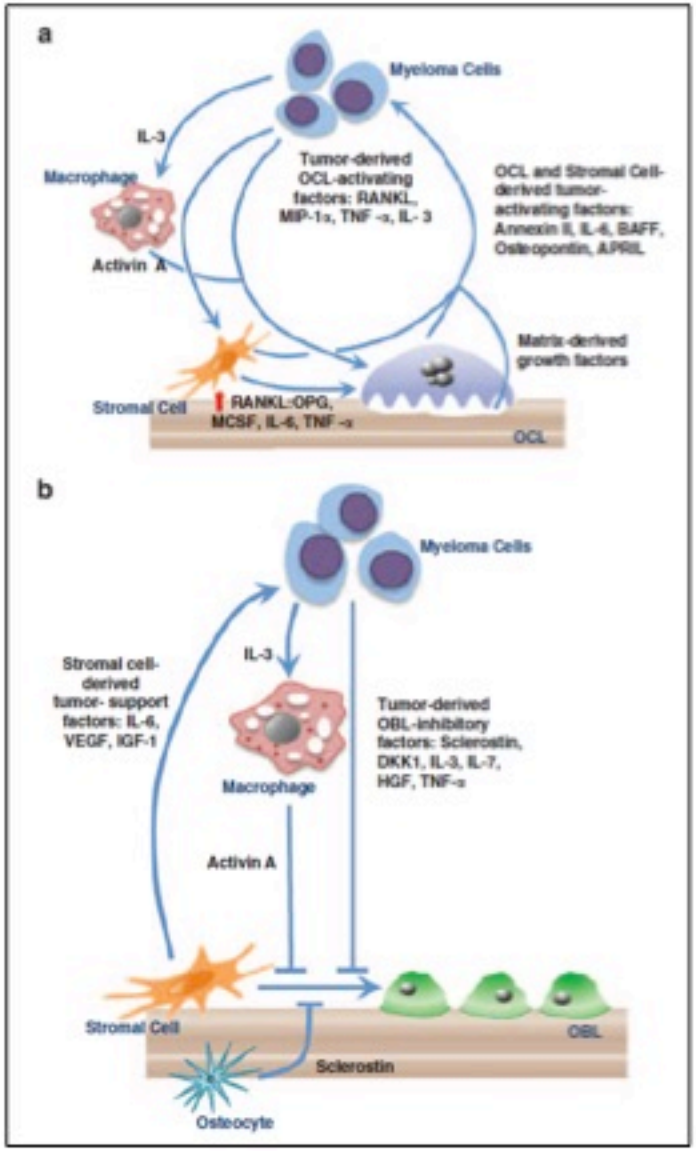
Coleman R et al, CritRevOnc 2011



PTHrP=parathyroid hormone-related peptide; BMP=bone morphogenetic peptide;
TGF-b=transforming growth factor b; IGF=insulin-like growth factors I and II;
FGF=fibroblast growth factor; VEGF=vascular endothelial growth factor;
ET1=endothelin1 PDGF=platelet-derived growth factor

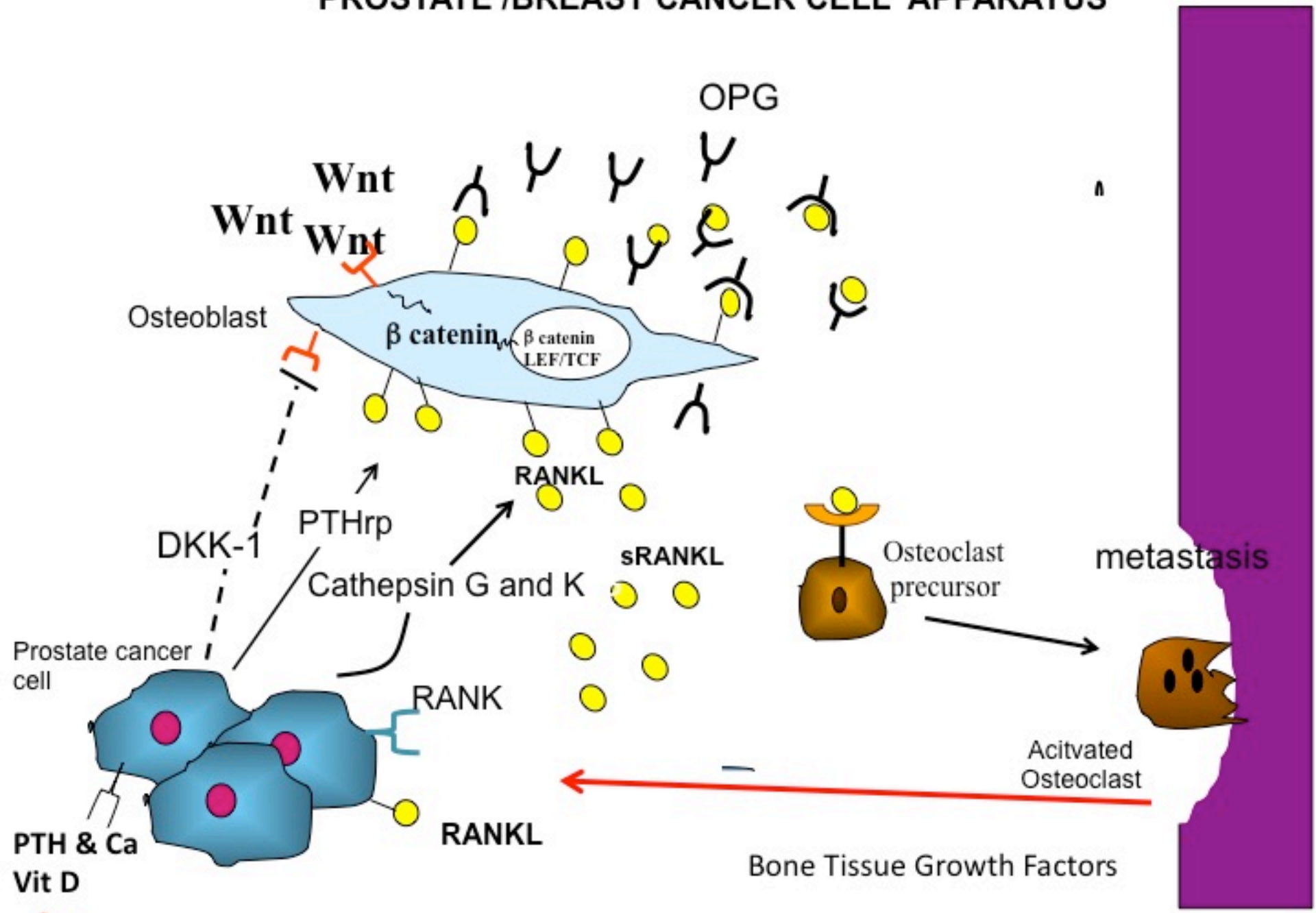
Adapted from Roodman D. Mechanism of Bone Metastasis. N Engl J Med 20[illegible]

Mechanisms of multiple myeloma bone disease



Galson DL et al, BoneKey Rep 2012

PROSTATE /BREAST CANCER CELL APPARATUS



Bertoldo F, Textbook of Osteoncology 2009-13

RANK/RANKL EXPRESSION IN CANCER CELLS

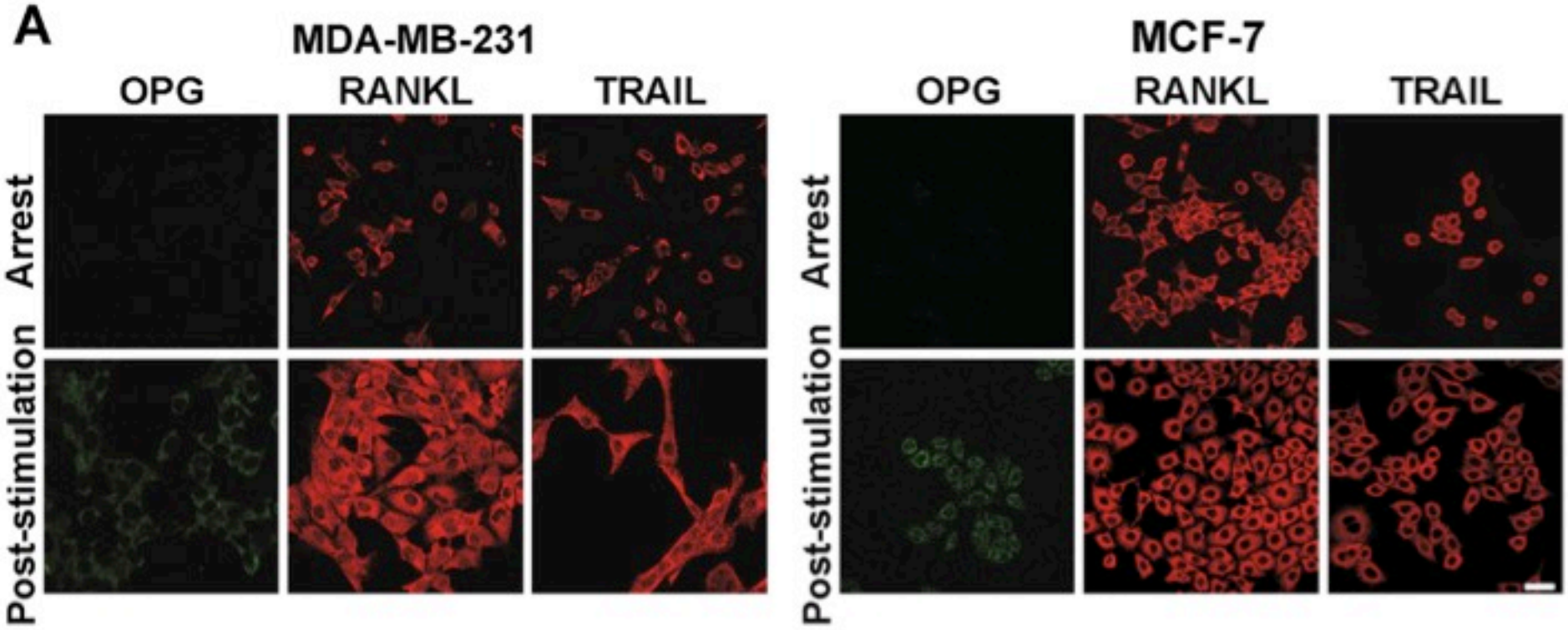
OSTEOPROTEGERIN AND RANK LIGAND EXPRESSION IN **PROSTATE CANCER**

Expression of osteoprotegerin, receptor activator of RANKL, tumor necrosis factor-related apoptosis-inducing ligand, SDF-1 and their receptors in **epithelial metastatic breast cancer cell lines**

Expression of RANK and RANKL in primary **human lung cancer** and human **lung cancer cell lines**

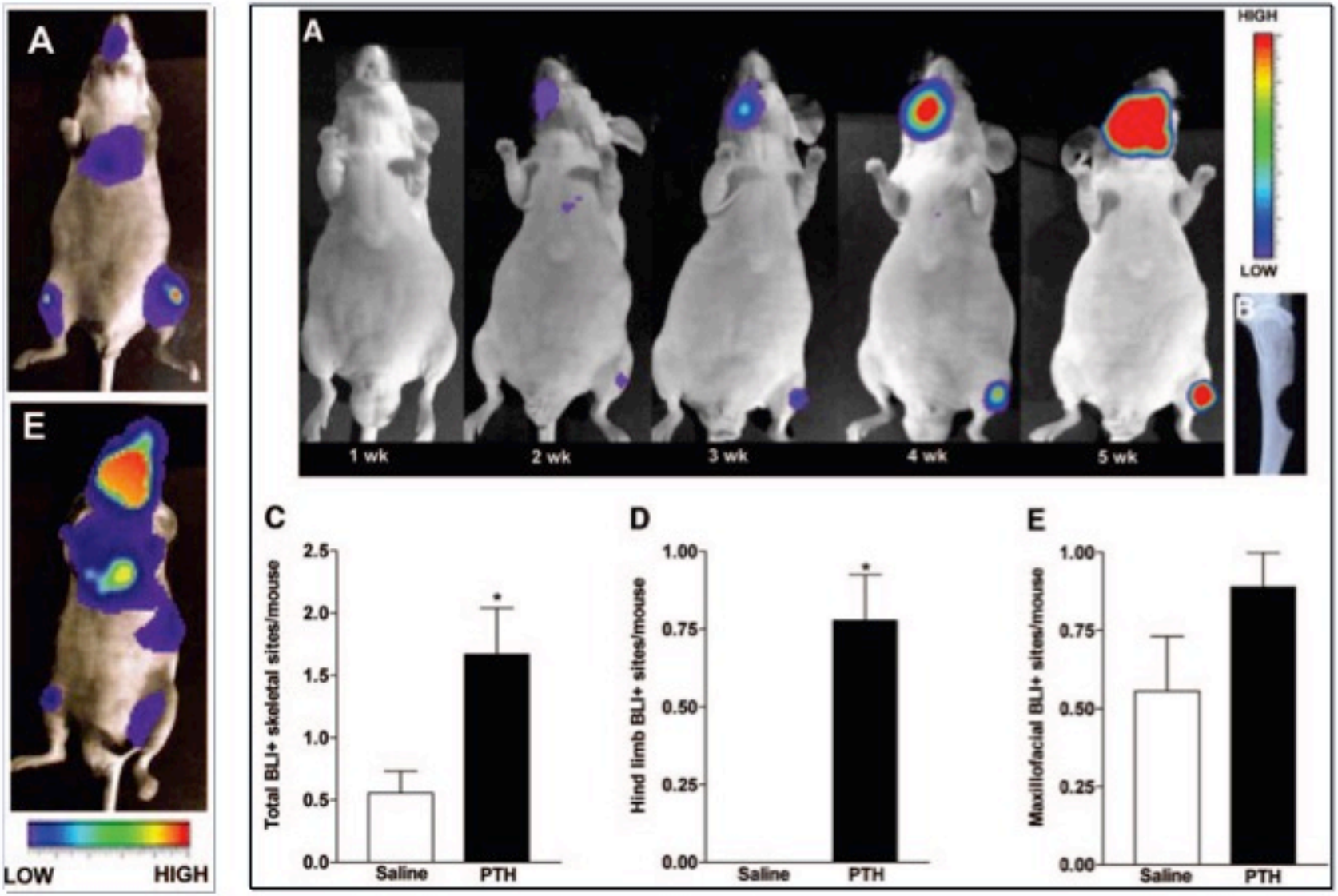
Brown JM et al Urology 2001; Labovsky V et al. Cancer Cell International 2012,

Expression of OPG, RANKL and TRAIL in both BC cell lines.



Labovsky *et al. Cancer Cell International* 2012, **12**:29

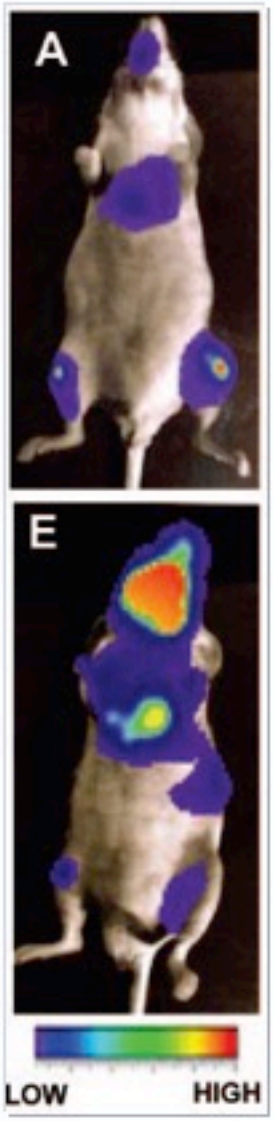
Bone Turnover Mediates Preferential Localization of Prostate Cancer in the Skeleton

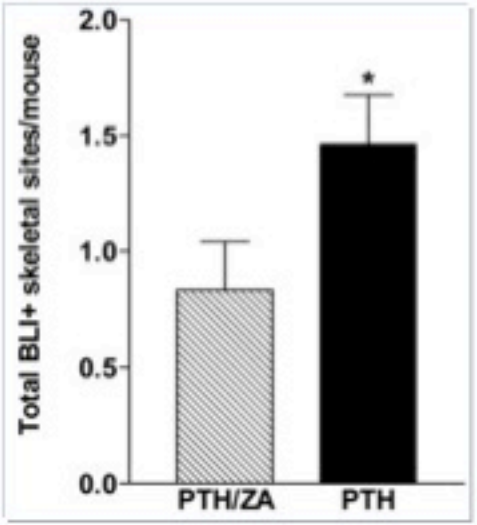


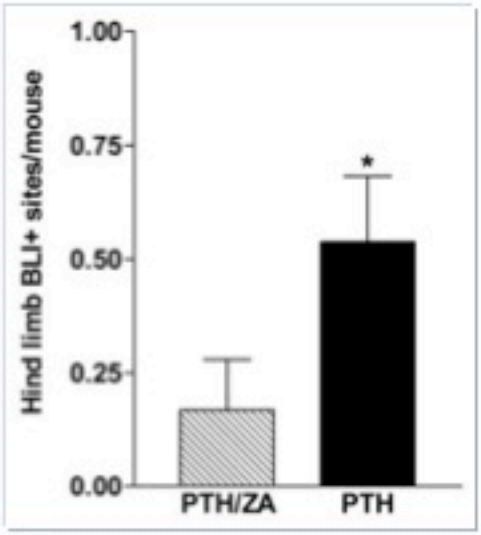
Schnieder A Endocrinology 2005

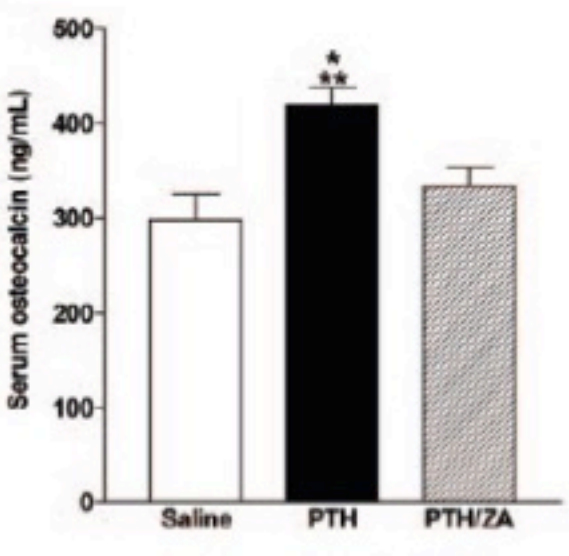
Bone Turnover Mediates Preferential Localization of Prostate Cancer in the Skeleton

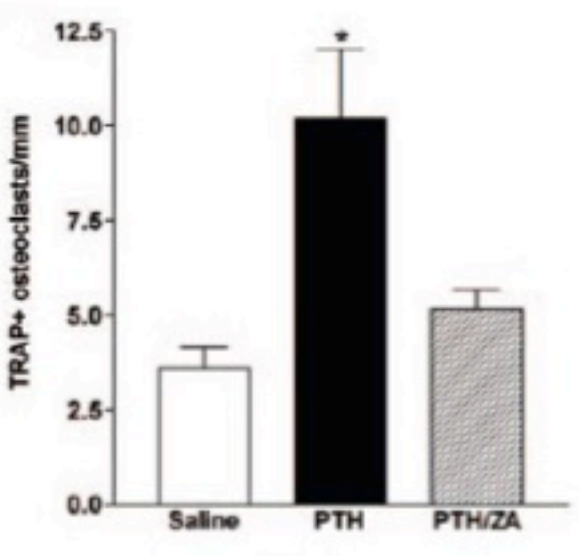
Schnieder A Endocrinology 2005



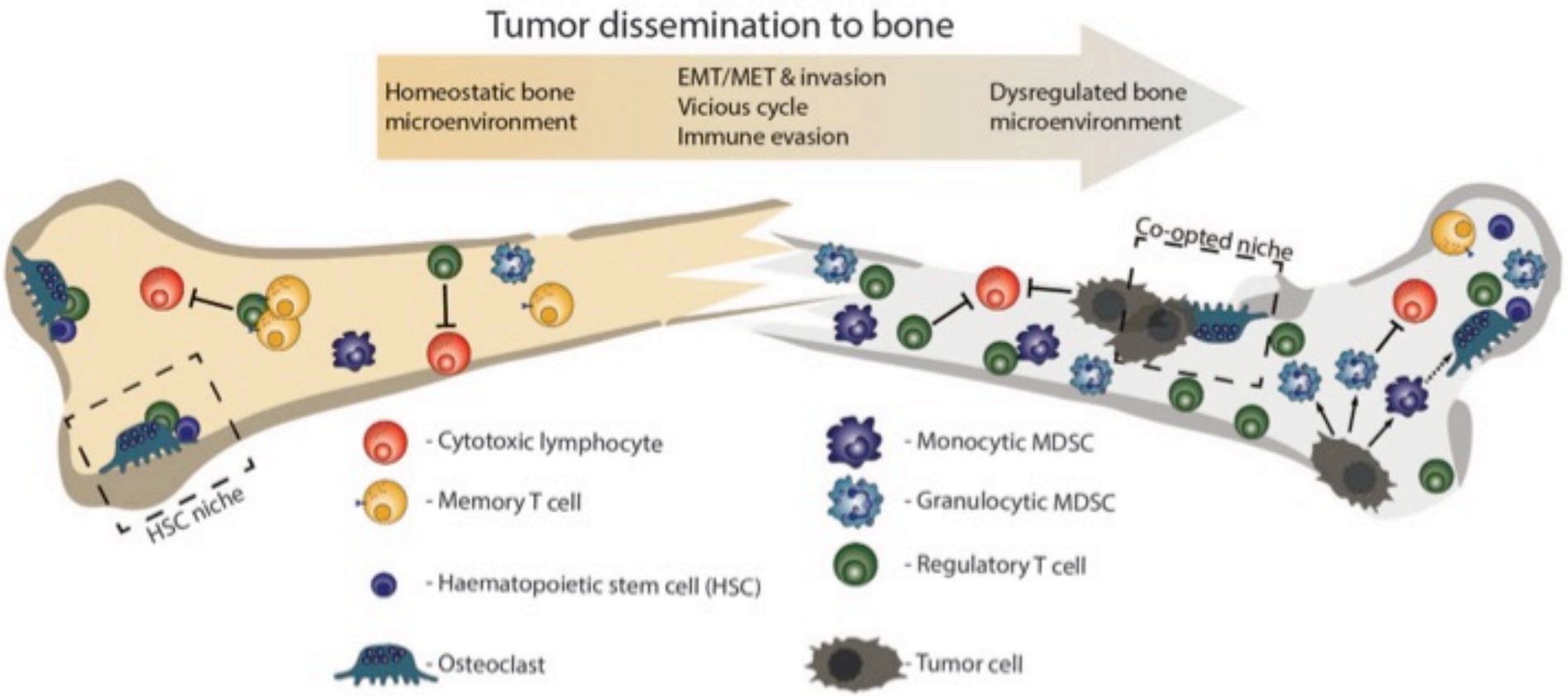






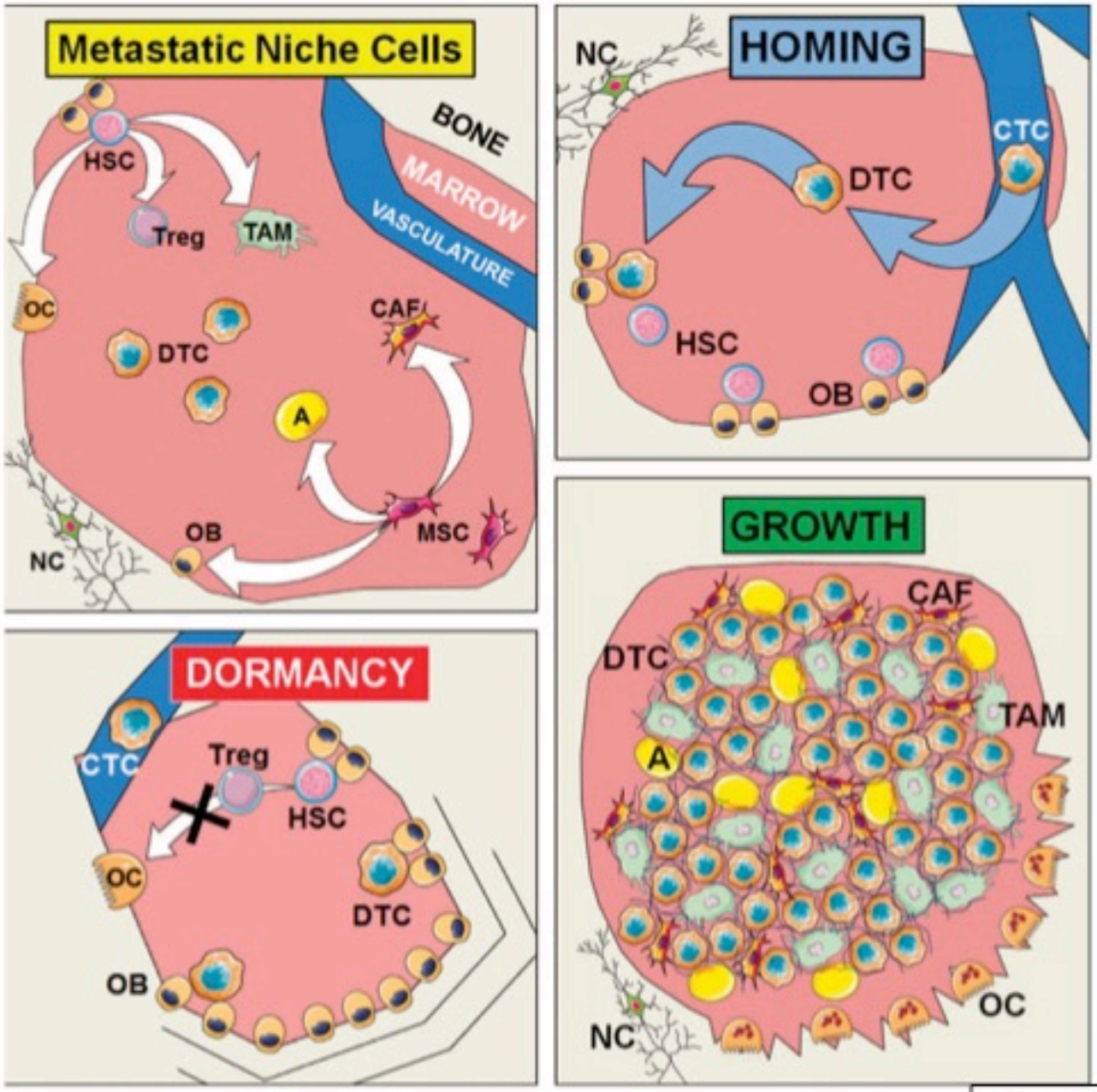


Bone specific immunity and its impact on metastasis



Baschuk N et al, BoneKey Rep 2015

Bone marrow as a metastatic niche for disseminated tumor cells from solid tumors



Shiozawa Y et al, BoneKey Rep 2015

Endothelial Mesenchimal Transition and MET

TGFβ, IGF1&2, PDGF, PTH(rP), VEGF, Wnt, ErbB/EGF, ILEI, **IL6,** SCF,HGF/SF, **Integrin αvβ3, MMPs, Cathepsin K, Hypoxia, Notch,** Mena^{INV}, microRNAs (miR21,200,205)...

Epithelial phenotype

EMT

MET

Mesenchymal Phenotype

BMP7, FGF1,3,7, Wnt4, sFRP2,sFRP4..

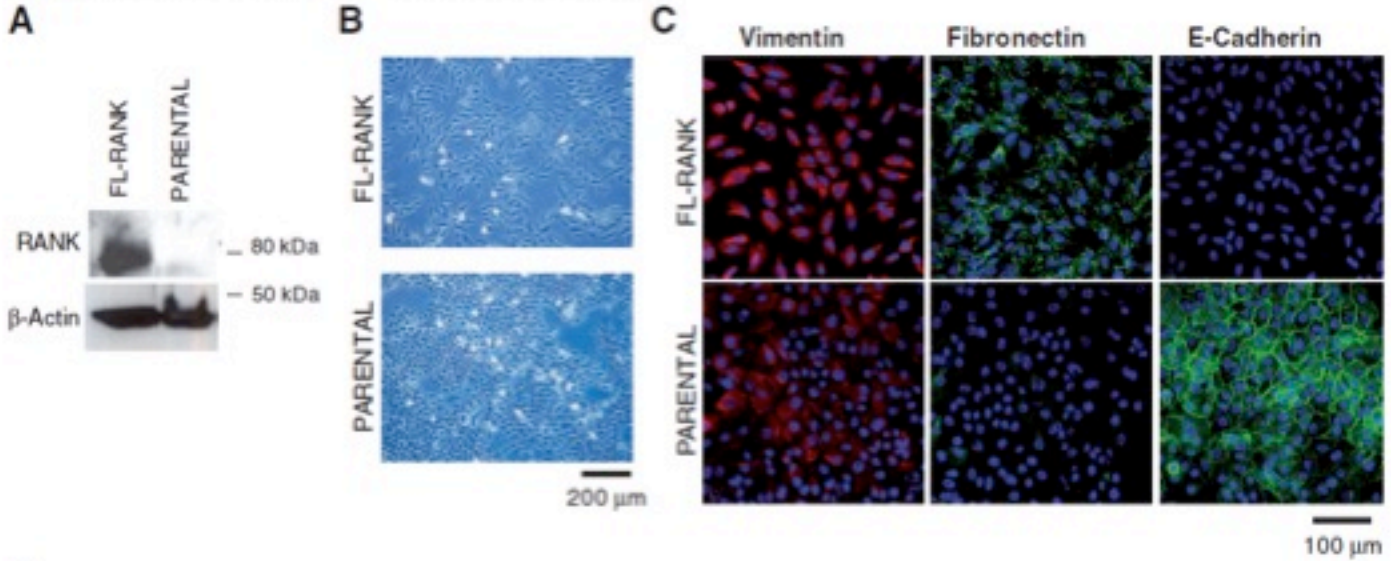
E-cadherin
Cytokeratin
ZO-1
Laminin-1
Entactin
Syndecan
MUC1
Desmoplakin
A1 (IV) collagen
miRNA200 family

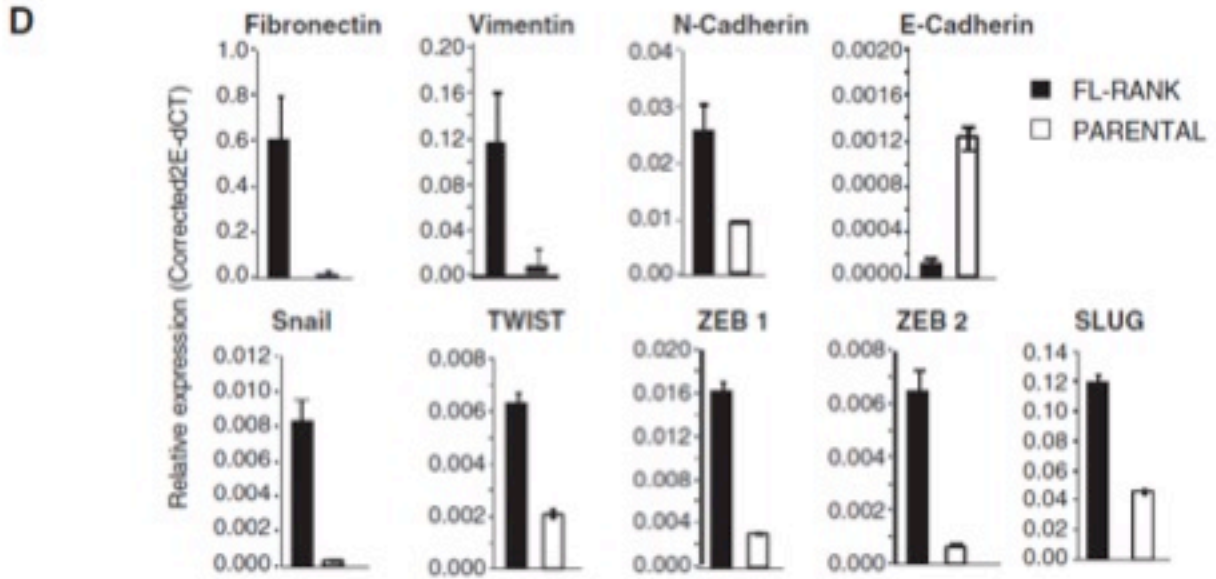
Vimentin
N-cadherin
OB-cadherin
α5β1, αvβ3-integrins
FSP-1
FTS binding protein FAP

Snail 1,2
ETS
SIP 1,2
α-SMA
Twist
Goosecoid
LEF-1
FOXC2
miR21

Tumorigenicity
Stem/progenitor properties
Angiogenesis
Survival
Therapy resistance

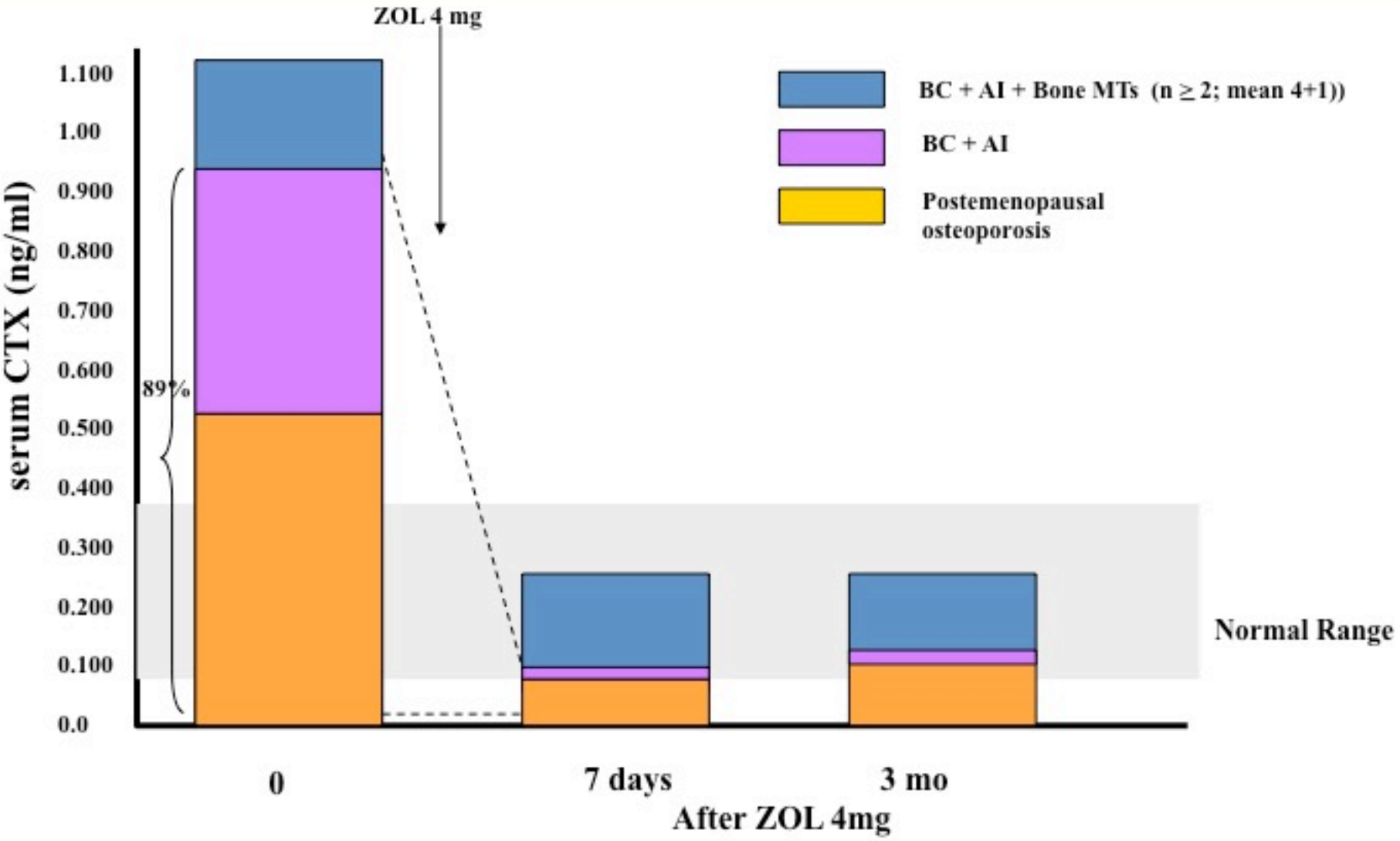
RANK Induces Epithelial–Mesenchymal Transition and Stemness in Human Mammary Epithelial Cells and Promotes Tumorigenesis and Metastasis





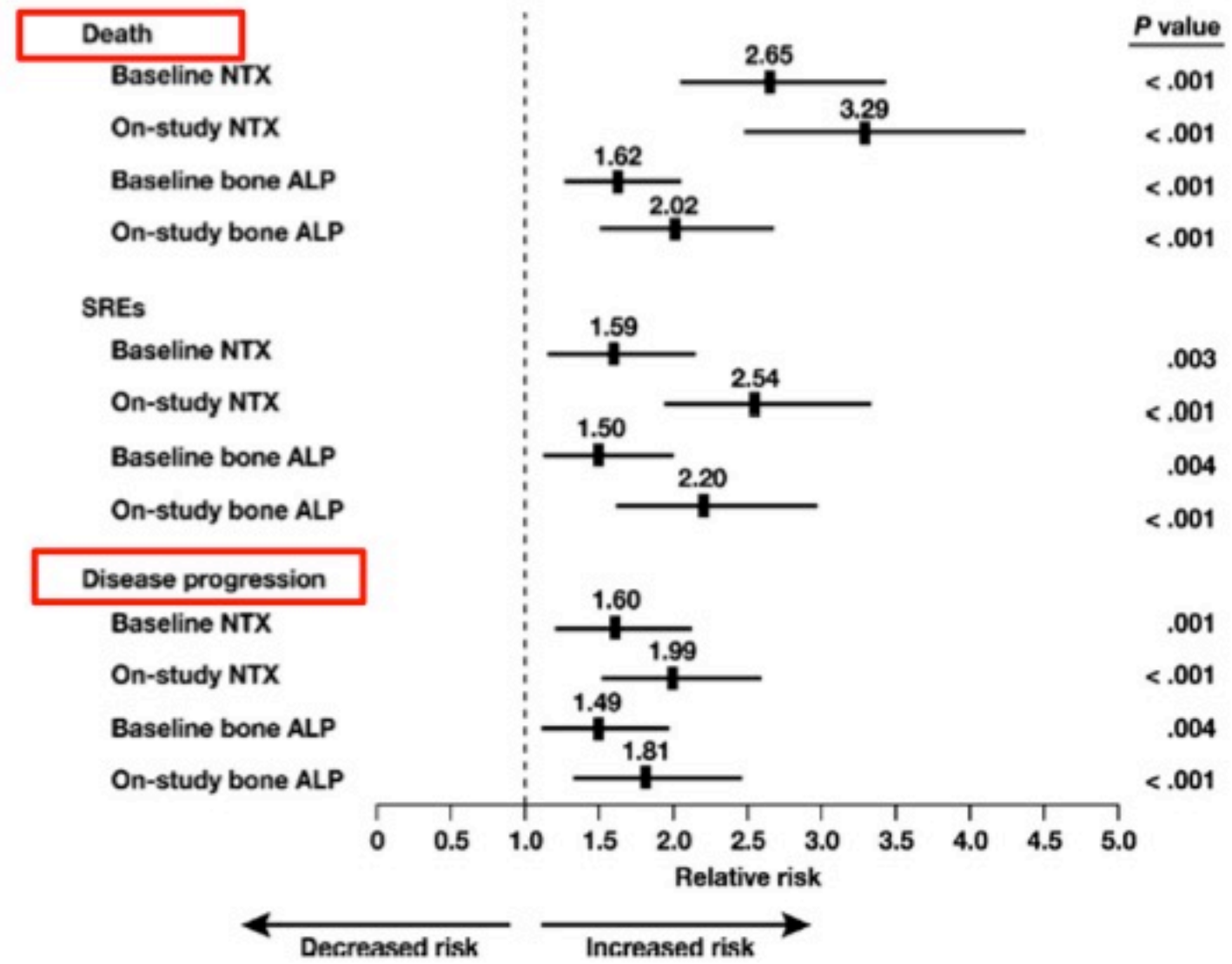
Palafox M et al., Cancer Res 2012

COMPOSITION OF SERUM CTX POOL IN BREAST CANCER WOMEN WITH BONE METASTASES



Bertoldo F et al *CABS 2010*

CORRELATIONS BETWEEN BONE TURNOVER AND CLINICAL OUTCOME IN PATIENTS WITH BONE METASTASES FROM SOLID TUMORS



Coleman R et al, CritRevOnc 2011

Elevato turnover osseo nei pazienti con BC & PC

ELEVATO TURNOVER OSSEO
(eta-vit D - ADT- metastasi)

CTIBL
FRAGILITÀ

PROGRESSIONE
OSSEA

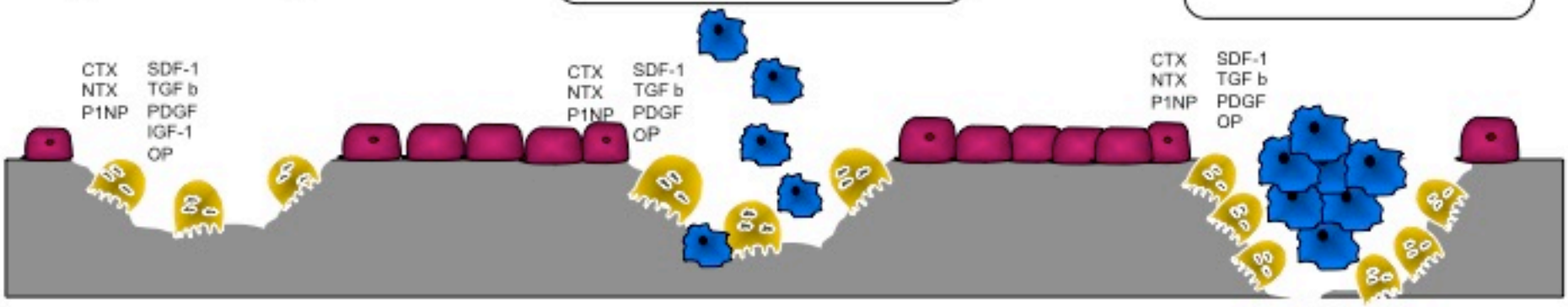
SRE

Prima /Nuova
metastasi

Perdita ossea

Homing delle cellule
tumorali

Crescita della
metastasi ossea



Scheletro non metastatico

Nicchia premetastatica

Metastasi ossea

Bertoldo F

Agenda

- Cancer treatment-induced bone loss
- Zoledronic ac/Denosumab therapy
- *Bone Modifying Agents and extraskeletal effects*
- Future competitors

Agenda

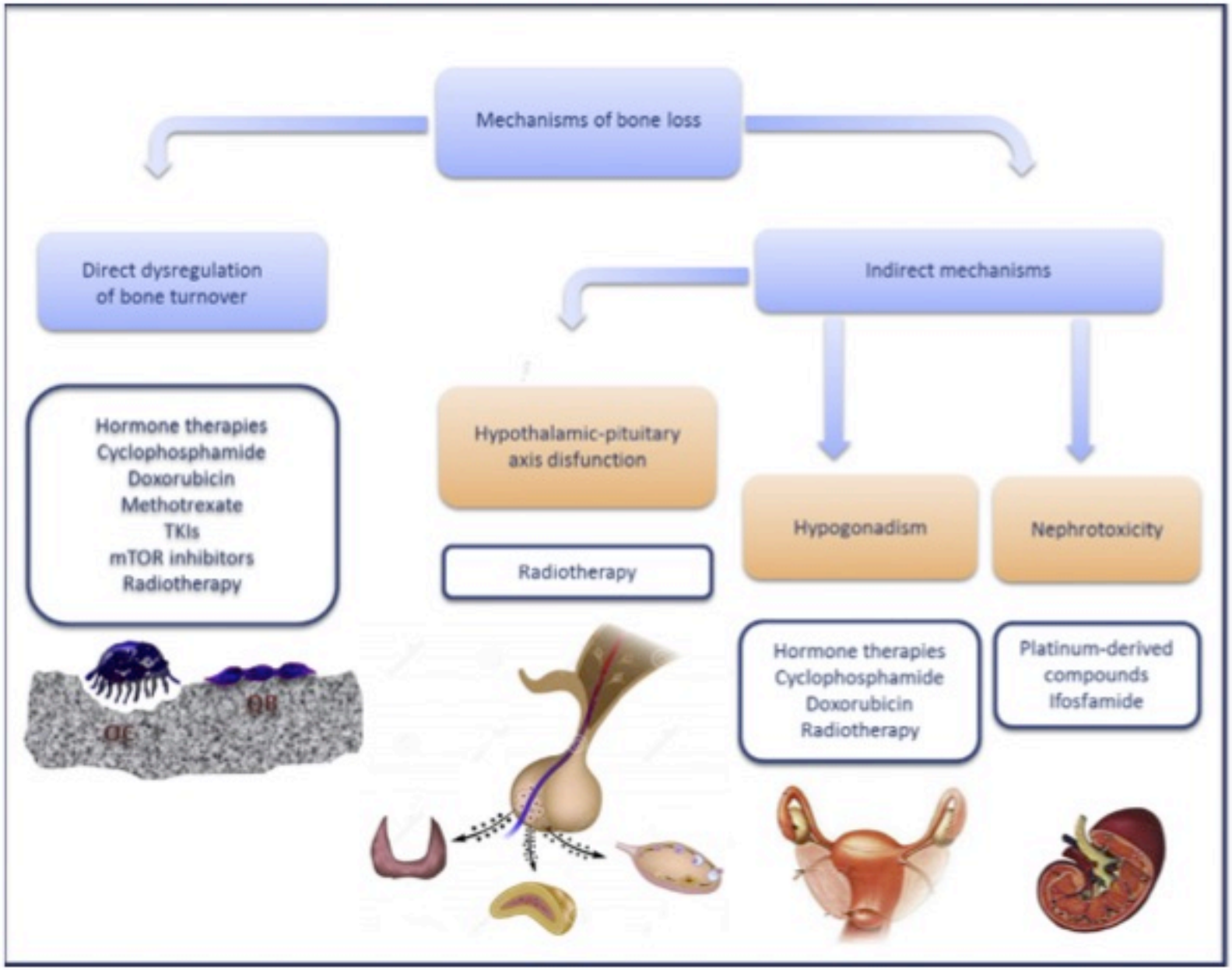
- **Cancer treatment-induced bone loss**
- Zoledronic ac/Denosumab therapy
- *Bone Modifying Agents and extraskeletal effects*
- Future competitors

Mechanisms of cancer treatment-induced bone loss

Drug	Mechanism of bone loss
Hormone therapies	Hypogonadism, ↓ OB proliferation, ↑ OB apoptosis
Platinum-derived compounds	Nephrotoxicity (hypomagnesemia)
Ifosfamide	Nephrotoxicity (oxidative stress)
Cyclophosphamide	Hypogonadism, ↓ bone formation and resorption
Doxorubicin	Hypogonadism, ↓ OB formation, ↑ OC formation and activation
Methotrexate	↓ OB proliferation, osteocyte apoptosis
TKIs	Bone-damaging effect: hypocalcemia and secondary hyperparathyroidism Bone-sparing effect: ↓ OC differentiation and activity, ↑ OB activation
Radiotherapy	Hypogonadism, ↓ GH, imbalanced activities of OBs and OCs

D'Oronzo S, Cancer Treatment Reviews 2015

Mechanisms of CTIBL



D'Oronzo S, Cancer Treatment Reviews 2015

Cancer treatment-induced bone loss

Entity of bone loss

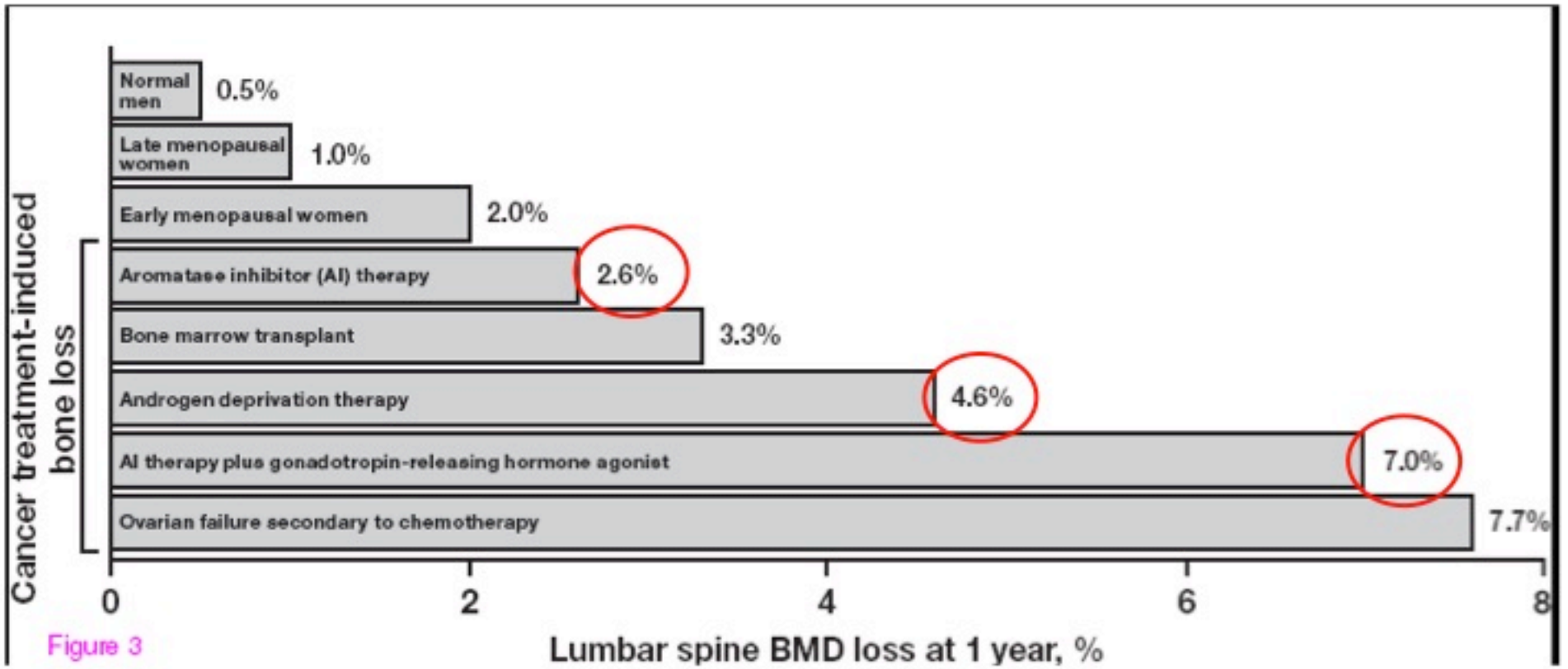
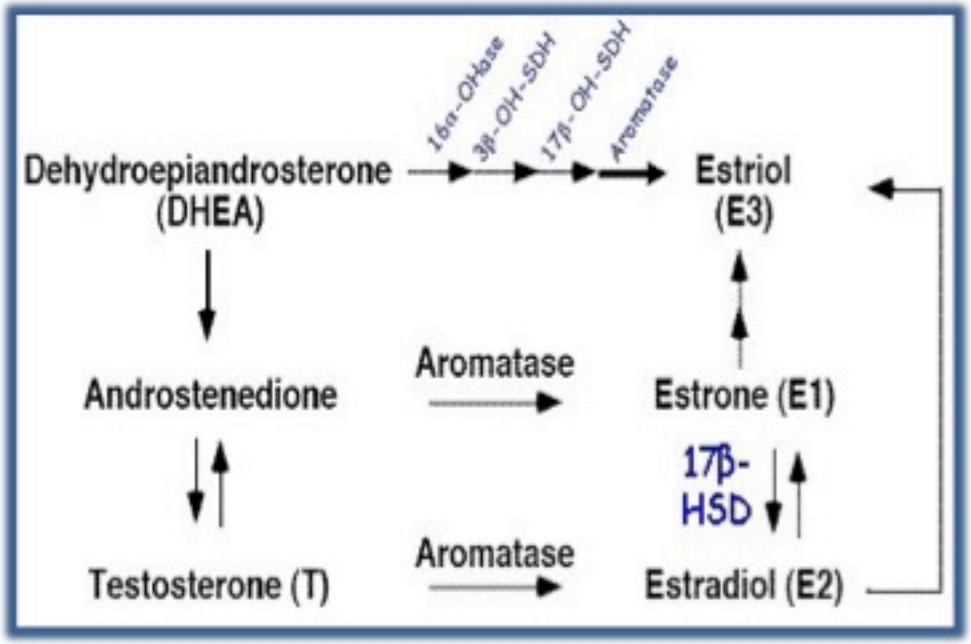
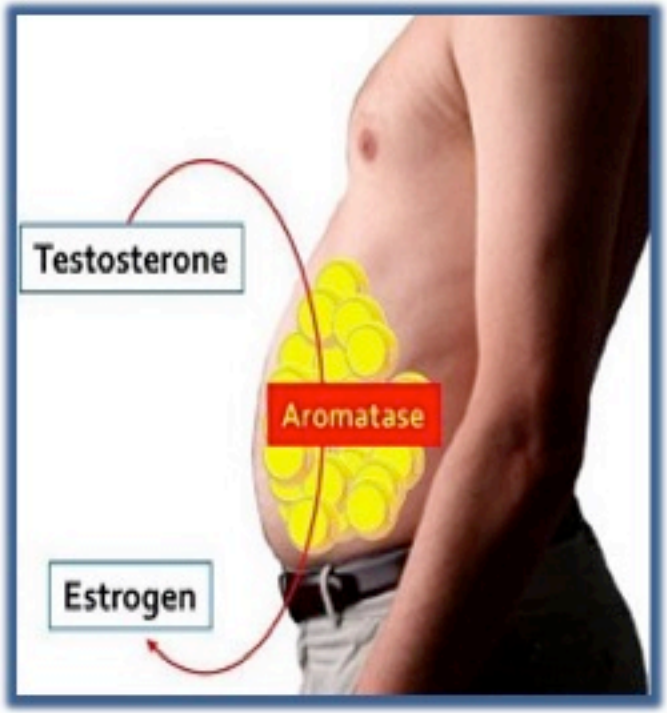


Figure 3

Body, BMC Cancer 2011





Aromatasi:

fisiologia

NON SOLO ovaio e surrene
MA ANCHE tessuto adiposo, muscolo, cervello, mammella, osso

Converte gli androgeni in estrogeni
(da androstenedione a estrone,
da testosterone a estradiolo)

Rappresenta la principale sorgente di E endogeni in post-M
(l'ovaio post-M sintetizza soprattutto androstenedione che viene trasformato dalla aromatasi dei tessuti periferici in estrone)

Inibitori della aromatasi

Bloccano il **98-99%** della produzione estrogenica

Effetto diverso a seconda dell'**età della paziente**:
donna più giovane, più alto livello di partenza di E2, maggiore il delta
di calo estrogenico, maggiore l'aumento del turn-over osseo

Steroidei (exemestane): irreversibili, tipo I, bloccano il sito di legame dell'aromatasi

Non steroidei (anastrozolo, letrozolo): reversibili, tipo II, bloccano il gruppo eme

Effetti collaterali: fratture, artro-mialgie, dislipidemia

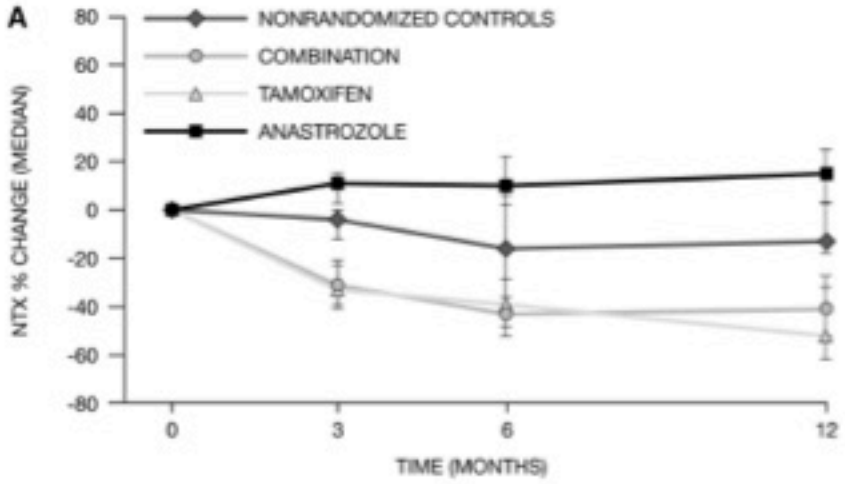
Clinical trials investigating aromatase inhibitor effects on bone turnover

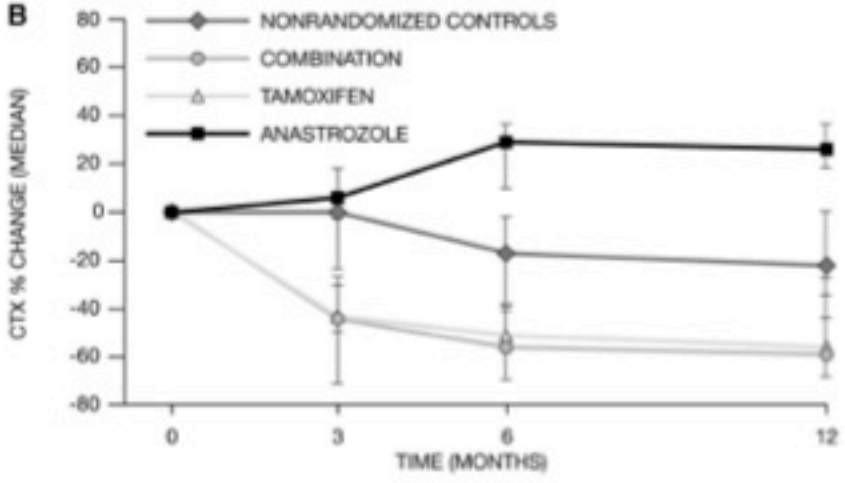
Clinical trial	Number of patients	Follow-up period (months)	Tested drug	Control	Fracture incidence
ATAC	9366	68	Anastrozole	Tamoxifen	11% vs 7.7%
ARNO/ABC SG8	3224	28	Anastrozole	Tamoxifen	2% vs 1%
BIG 1.98	4895	60.3	Letrozole	Tamoxifen	9.3% vs 6.5%
IES	4274	58	Exemestane	Tamoxifen	7% vs 5%
MA-17	5187	28.8	Letrozole	Placebo	3.6% vs 2.9%
MA-27	7576	49.2	Exemestane	Anastrozole	10% vs 9%
ABCSG18	3425	84	Denosumab + AI	Placebo + AI	11.1% vs 26.2%
ZO-FAST	1065	60	Letrozole + immediate ZA	Letrozole + delayed ZA	Statistically similar
AZURE	3360	84	Adjuvant treatment + ZA	Adjuvant treatment without ZA	6.2% vs 8.3%

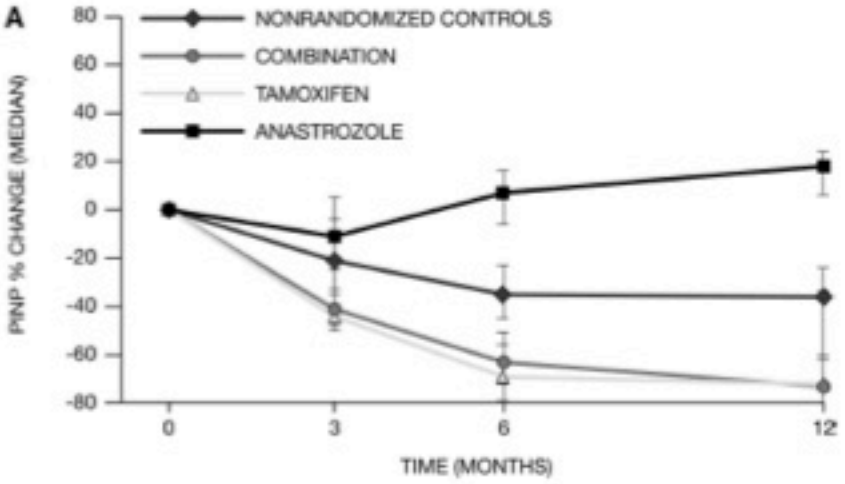
D'Oronzo S, Cancer Treatment Reviews 2015

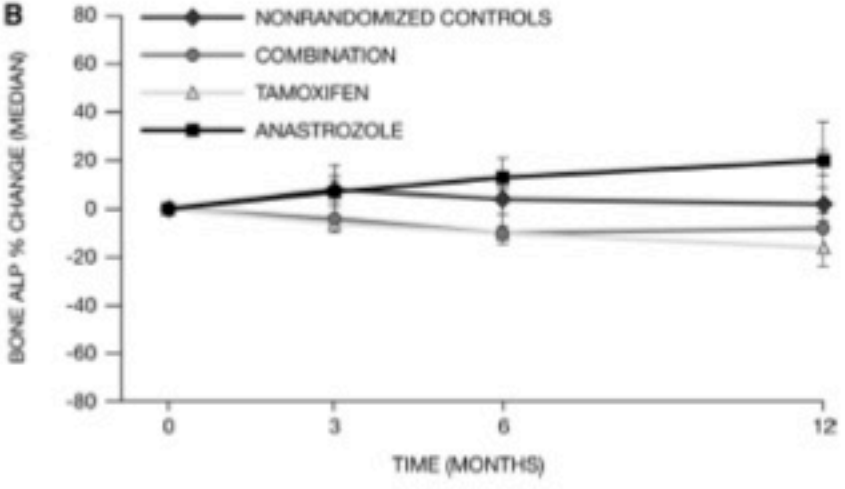
Skeletal effects of aromatase inhibitors

Markers of bone turnover





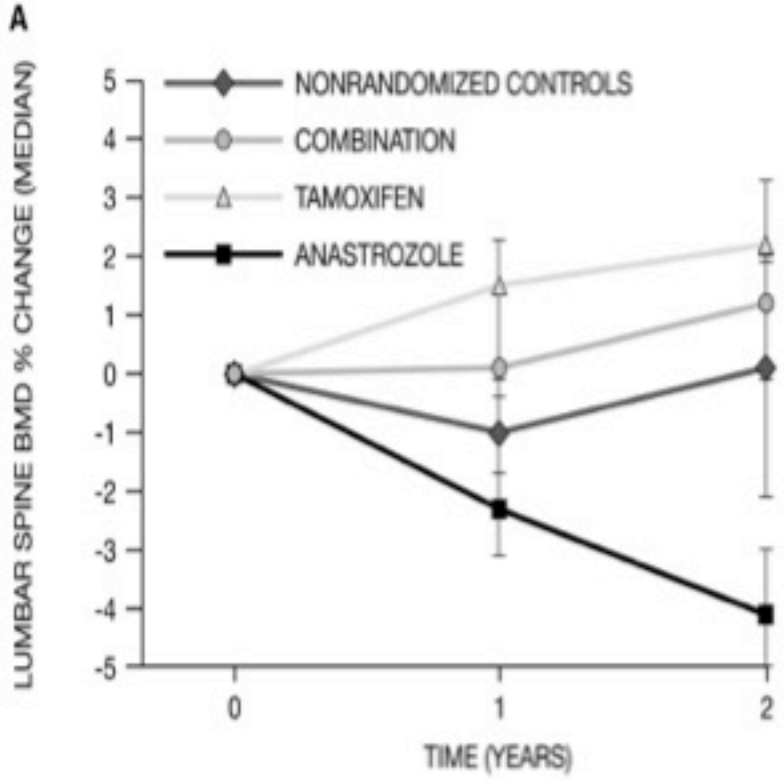


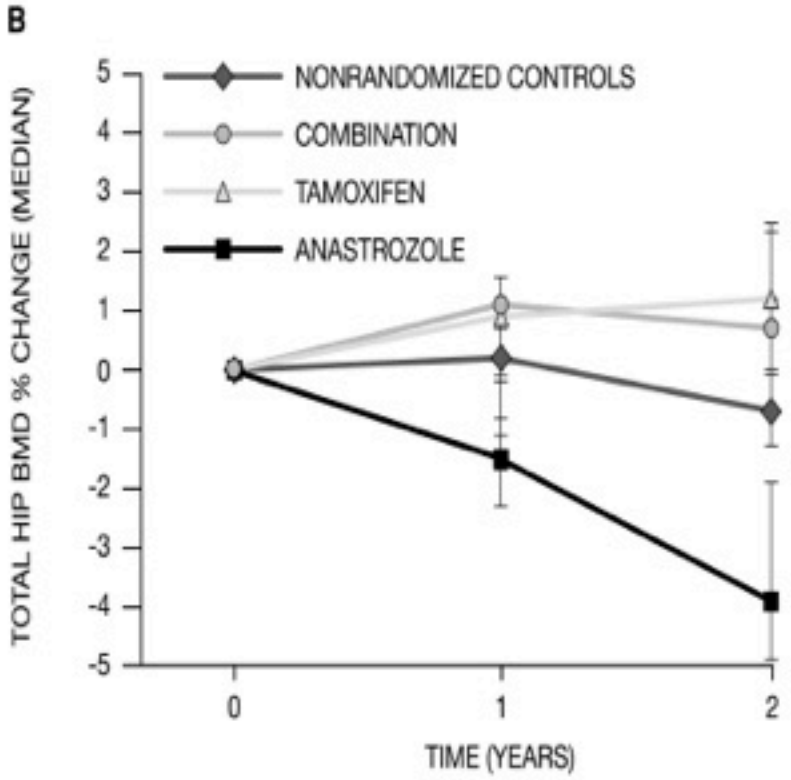


Eastell, JBMR 2006

Skeletal effects of aromatase inhibitors

BMD

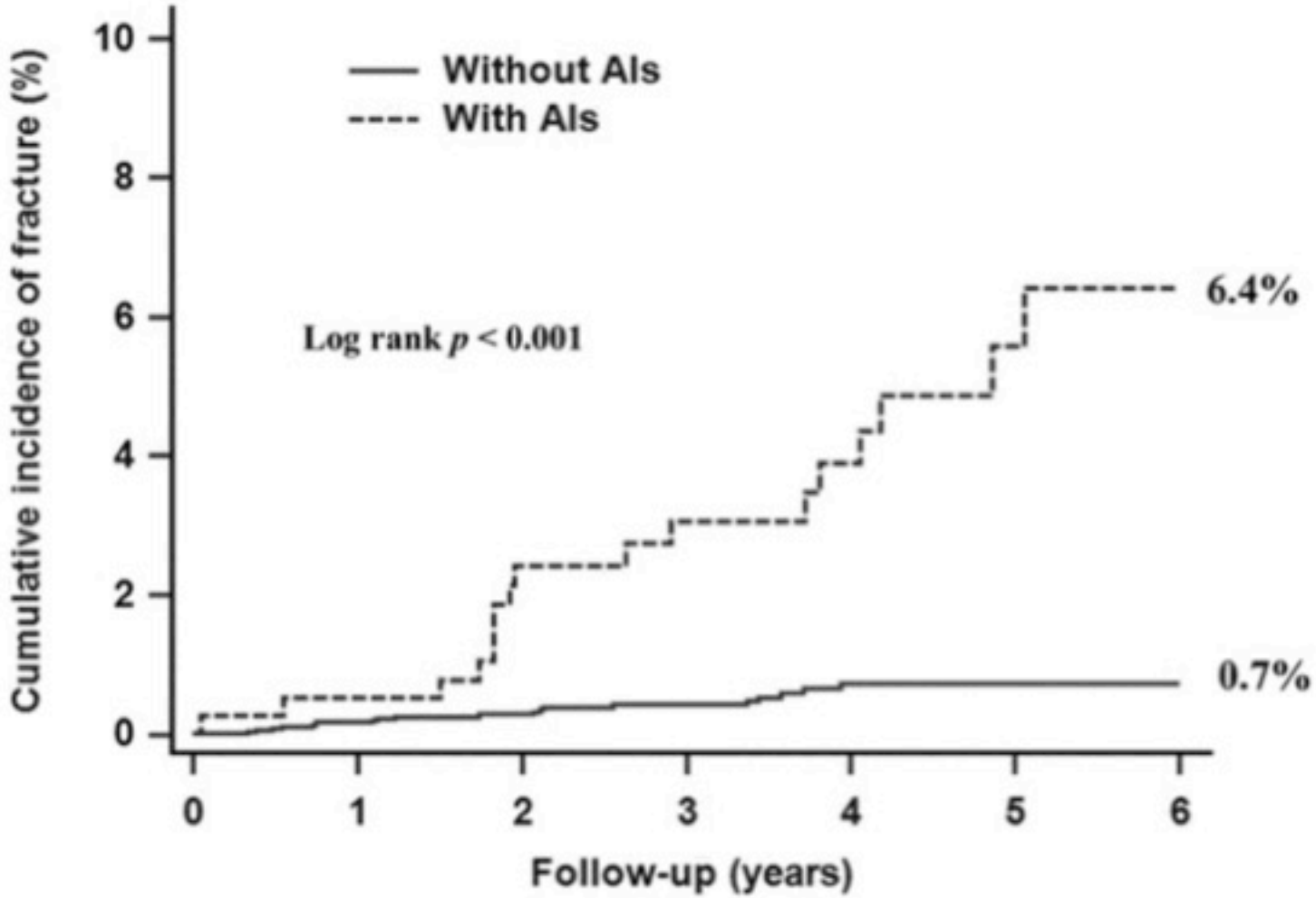




Eastell et al., J Bone Miner Res 2006

Skeletal effects of aromatase inhibitors

Fracture



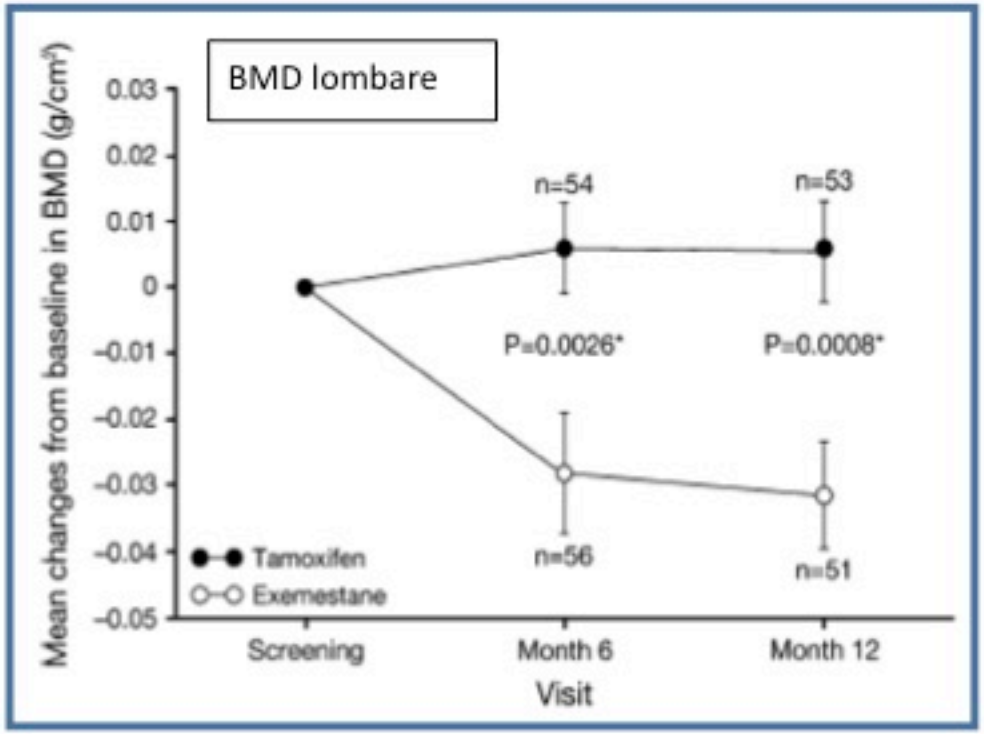
Chang et al., PLOSone 2015

original article

Annals of Oncology 20: 1489–1498, 2009
doi:10.1093/annonc/mdp033
Published online 27 May 2009

Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial

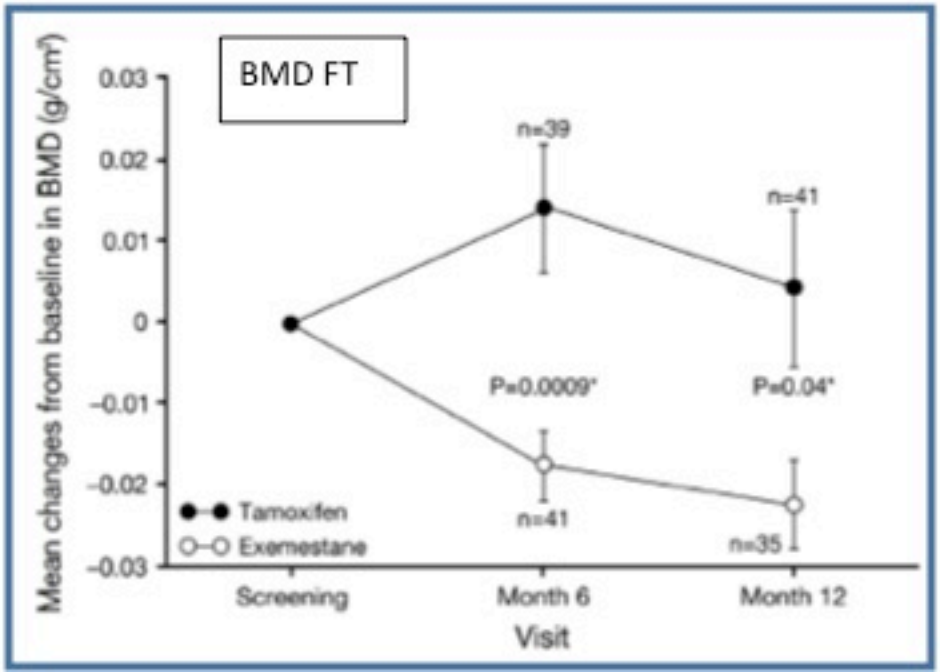
M. Rabaglio[1*], Z. Sun[2], K. N. Price[3], M. Castiglione-Gertsch[4], H. Hawle[4], B. Thürlimann[5], H. Mouridsen[6], M. Campone[7], J. F. Forbes[8], R. J. Paridaens[9], M. Colleoni[10], T. Pienkowski[11], J.-M. Nogaret[12], I. Láng[13], I. Smith[14], R. D. Gelber[15], A. Goldhirsch[16,17] & A. S. Coates[18] for the BIG 1-98 Collaborative and International Breast Cancer Study Groups



BMD lombare

TAM a 6 mesi : +0,5%
TAM a 12 mesi: stabile

IA a 6 mesi: -2,6%
IA a 12 mesi: ulteriore -0,2%

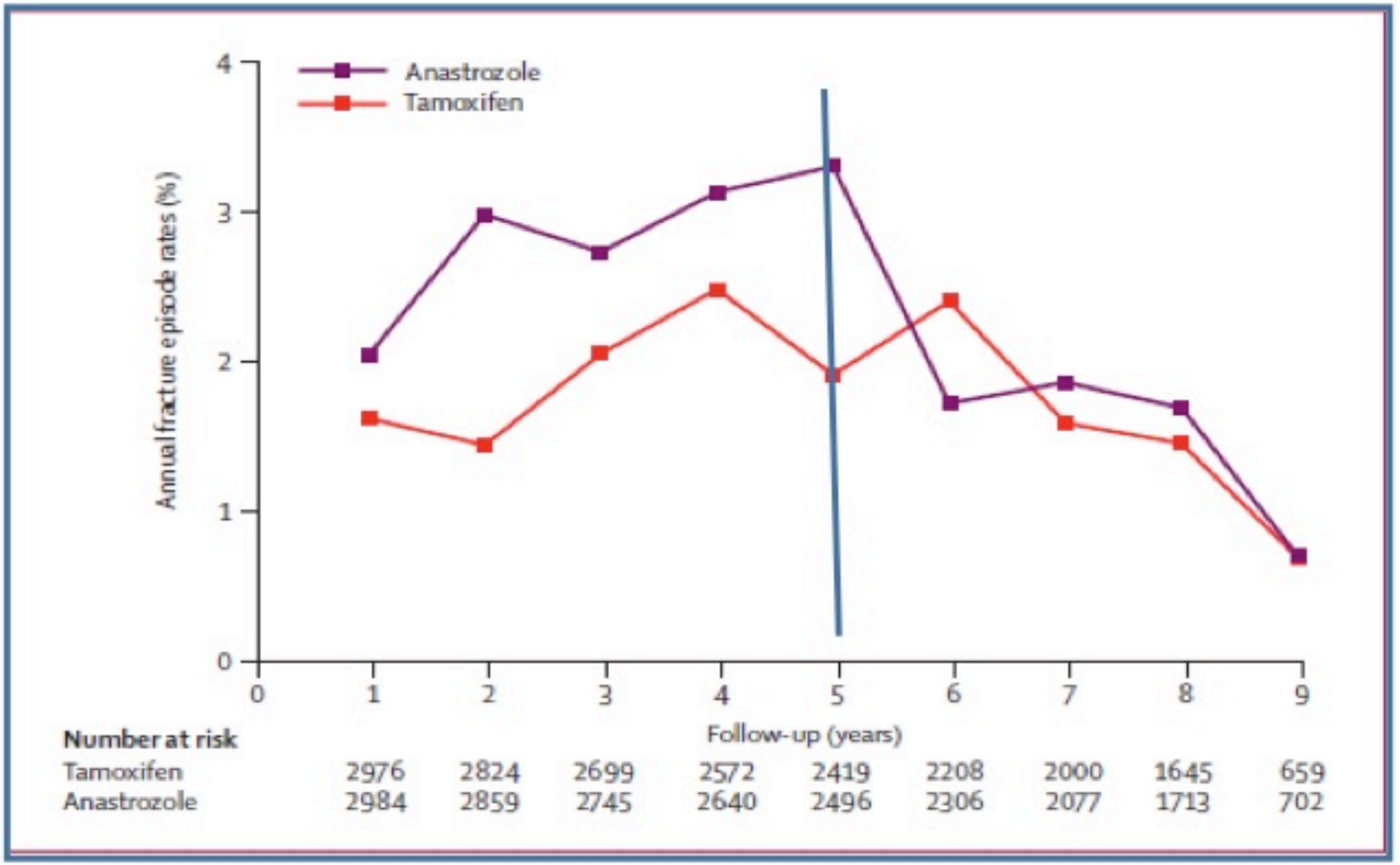


Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group*

Lancet Oncol 2008; 9: 45–53

Pazienti post-M con CA mammario
trattate con TAM per 5 anni vs anastrozolo per 5 anni



Fracture rate significativamente maggiore nel gruppo anastrozolo rispetto al gruppo TAM ma non differente off treatment (reversibilità alla sospensione del trattamento)

Blocco androgenico (ADT)

- **orchiectomia bilaterale**
- **analogo del GnRH** (leuprolide, goserelin, triptorelin)
  → blocco dell'asse gonadico
- **anti-androgeno** (flutamide, bicalutamide, nilutamide, ciproterone acetato)
  → antg del rec del testosterone
- **analogo del GnRH + anti-androgeno**: blocco androgenico completo

Ripresa funzionale asse gonadico alla sospensione
possibile, soprattutto: età < 65 anni, durata ADT < 24-30 mesi

Androgen-deprivation therapy (ADT) e BMD

ANALOGO DEL GnRH

- Calo del testosterone, DHT ed estradiolo
  - Calo della BMD

ANTI-ANDROGENO

- Aumento del testosterone ed estradiolo
  - Mantenimento/incremento della BMD

VOLUME 22 · NUMBER 13 · JULY 1 2004

JOURNAL OF CLINICAL ONCOLOGY

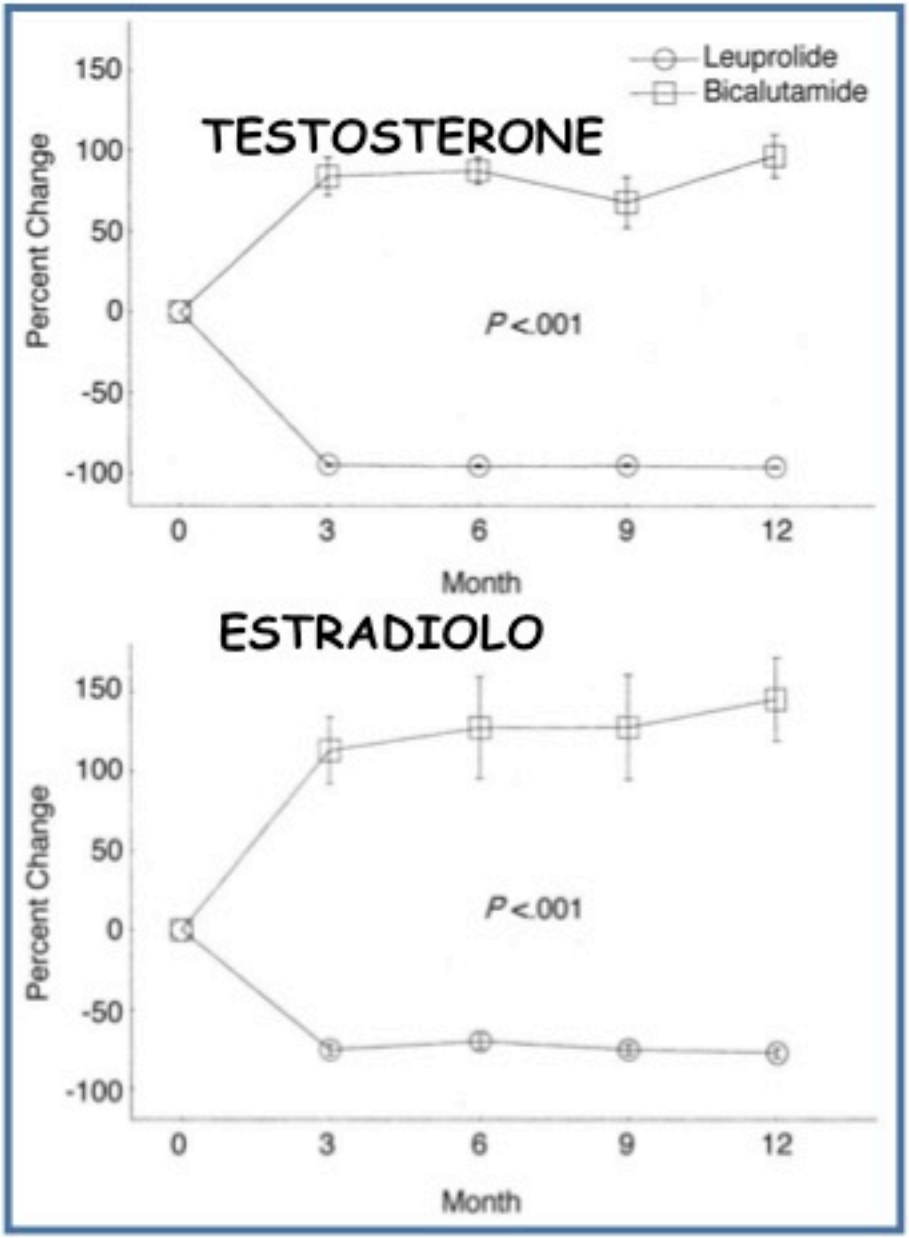
ORIGINAL REPORT

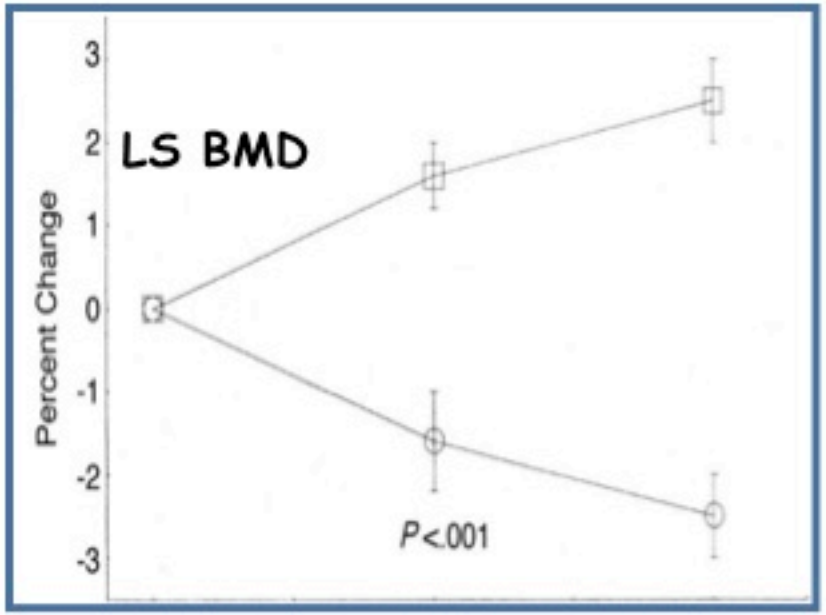
Bicalutamide Monotherapy Versus Leuprolide Monotherapy for Prostate Cancer: Effects on Bone Mineral Density and Body Composition

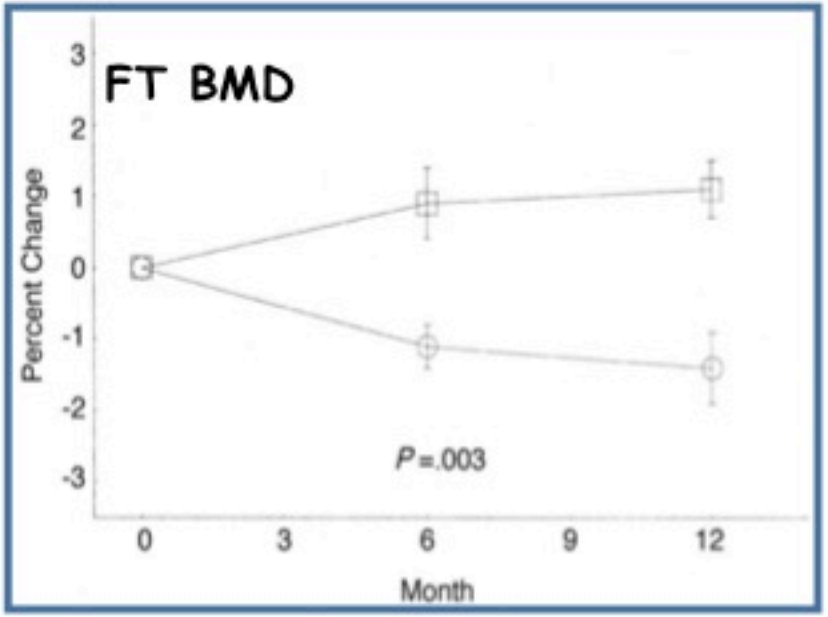
Matthew R. Smith, Melissa Goode, Anthony L. Zietman, Francis J. McGovern, Hang Lee, and Joel S. Finkelstein

52 maschi con CA prostata non metastatico trattati con leuprolide vs bicalutamide per 12 mesi

Effetto della bicalutamide vs GnRH agonista







N ENGL J MED 352;2 WWW.NEJM.ORG JANUARY 13, 2005

ORIGINAL ARTICLE

Risk of Fracture after Androgen Deprivation for Prostate Cancer

Vahakn B. Shahinian, M.D., Yong-Fang Kuo, Ph.D., Jean L. Freeman, Ph.D., and James S. Goodwin, M.D.

Studio retrospettivo di 50,613 maschi con CA prostata in ADT

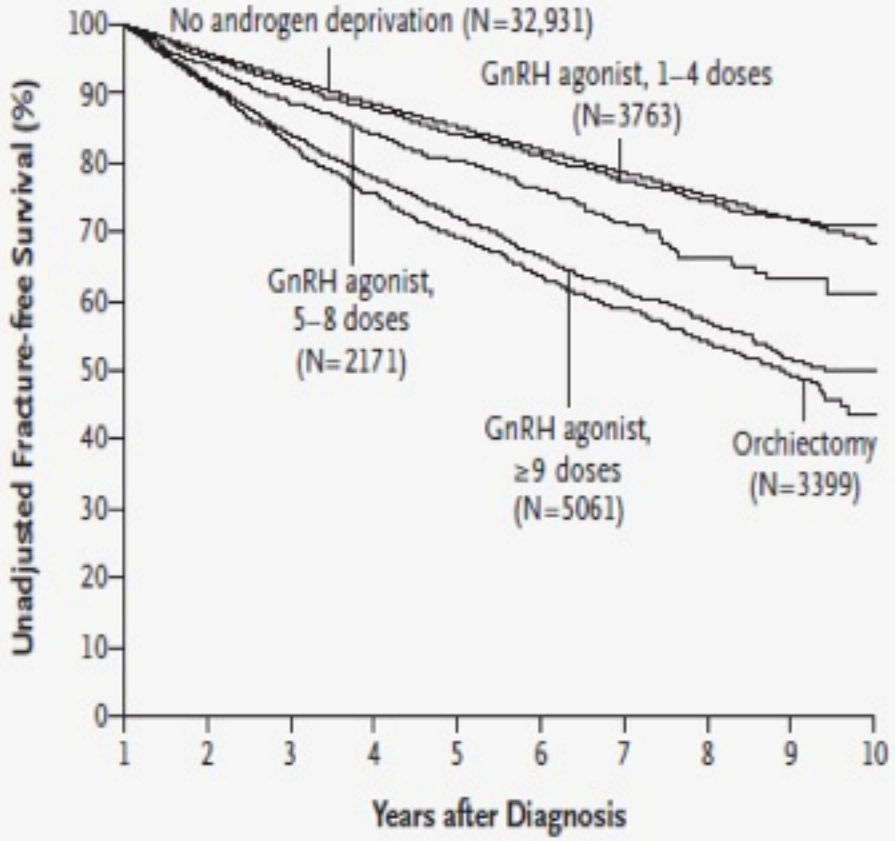


Figure 1. Unadjusted Fracture-free Survival among Patients with Prostate Cancer, According to Androgen-Deprivation Therapy.

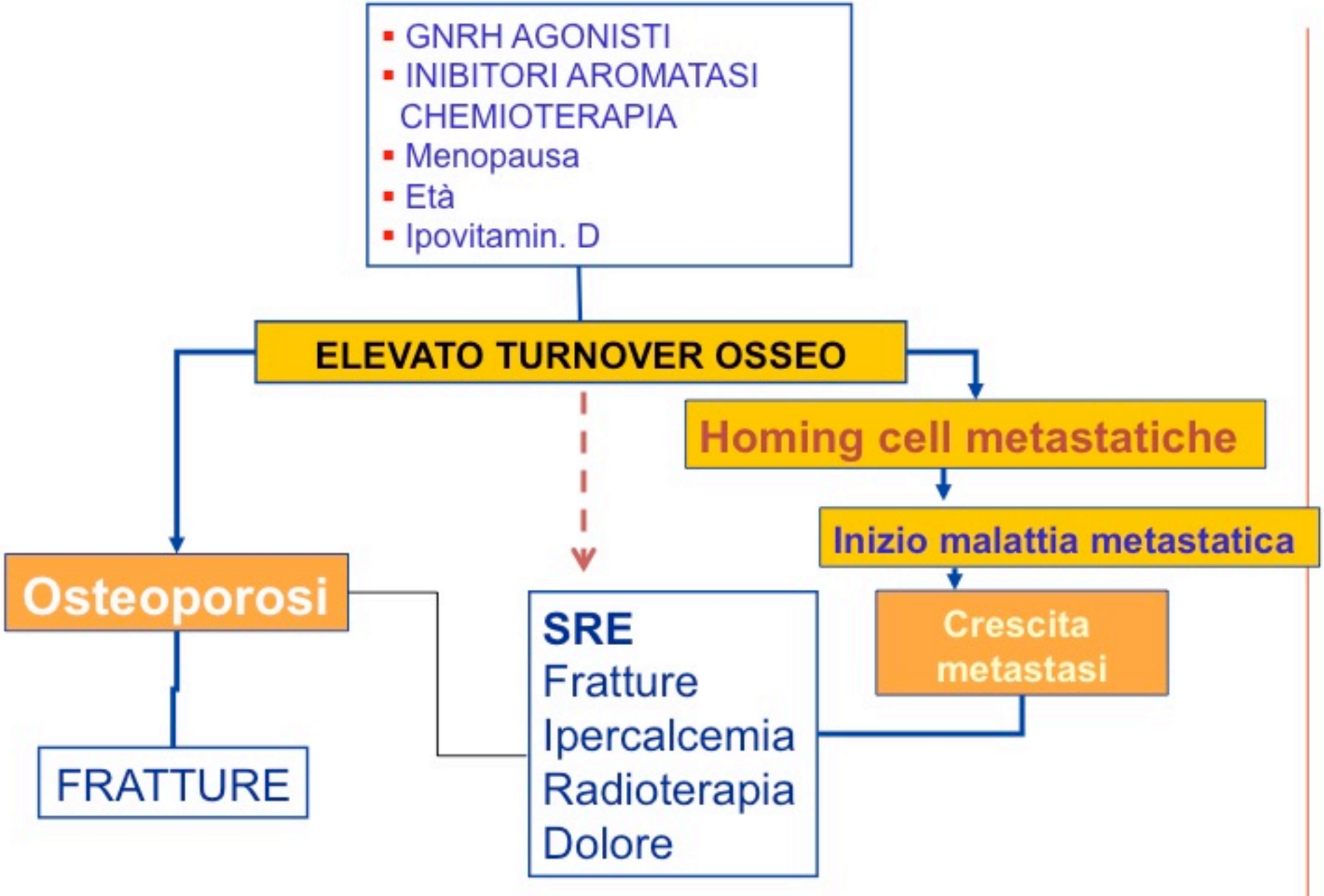
The survival curves start at 12 months after diagnosis, and androgen deprivation was initiated within 6 months after diagnosis. GnRH denotes gonadotropin-releasing hormone. The number of doses is the number administered within 12 months after diagnosis.

19,4% pz in ADT
hanno avuto una frattura vs
12,6% pz non in ADT

Associazione statisticamente significativa fra n° di dosi di GnRHa somministrate durante i 12 mesi dopo la diagnosi e rischio di frattura

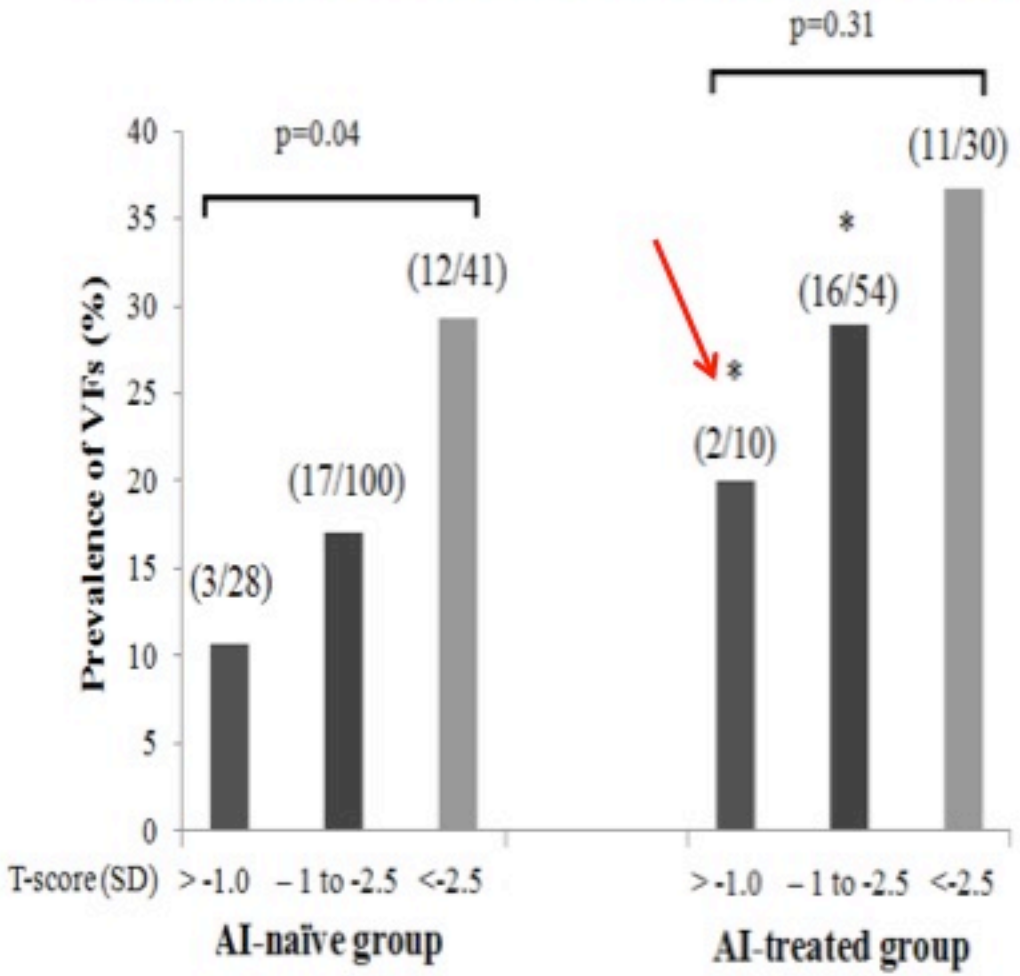
Agenda

- Cancer treatment-induced bone loss
- **Zoledronic ac/Denosumab therapy**
- *Bone Modifying Agents and extraskeletal effects*
- Future competitors


GNRH AGONISTI
INIBITORI AROMATASI
CHEMIOTERAPIA
Menopausa
Età
Ipovitamin. D
ELEVATO TURNOVER OSSEO
Homing cell metastatiche
Inizio malattia metastatica
Crescita metastasi
Osteoporosi
FRATTURE
SRE
Fratture
Ipercalcemia
Radioterapia
Dolore

Skeletal effects of aromatase inhibitors

High prevalence of fractures even in presence of normal BMD



Pedersini et al., Bone 2017

ADT-induced osteoporosis

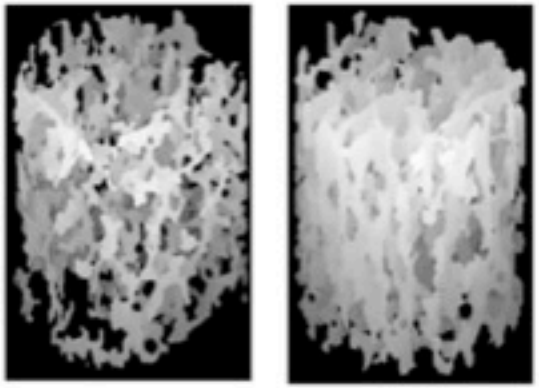
Vertebral fractures and BMD values

137 men ≥60 years with non metastatic prostate cancer on ADT for ≥6 months

37% of men without osteoporosis by DXA had VF identified

Patient A: Vertebral Fracture

Patient B: No Vertebral Fracture



Variable	Patient A	Patient B
Spine T-score (SD)	2.4	2.4
Total Hip T-score (SD)	-0.4	0.3
BV/TV (%)	12.82	17.16
Surface	6.16	8.68
Surface/curve	9.967	20.319
Erosion index	8.47	6.48

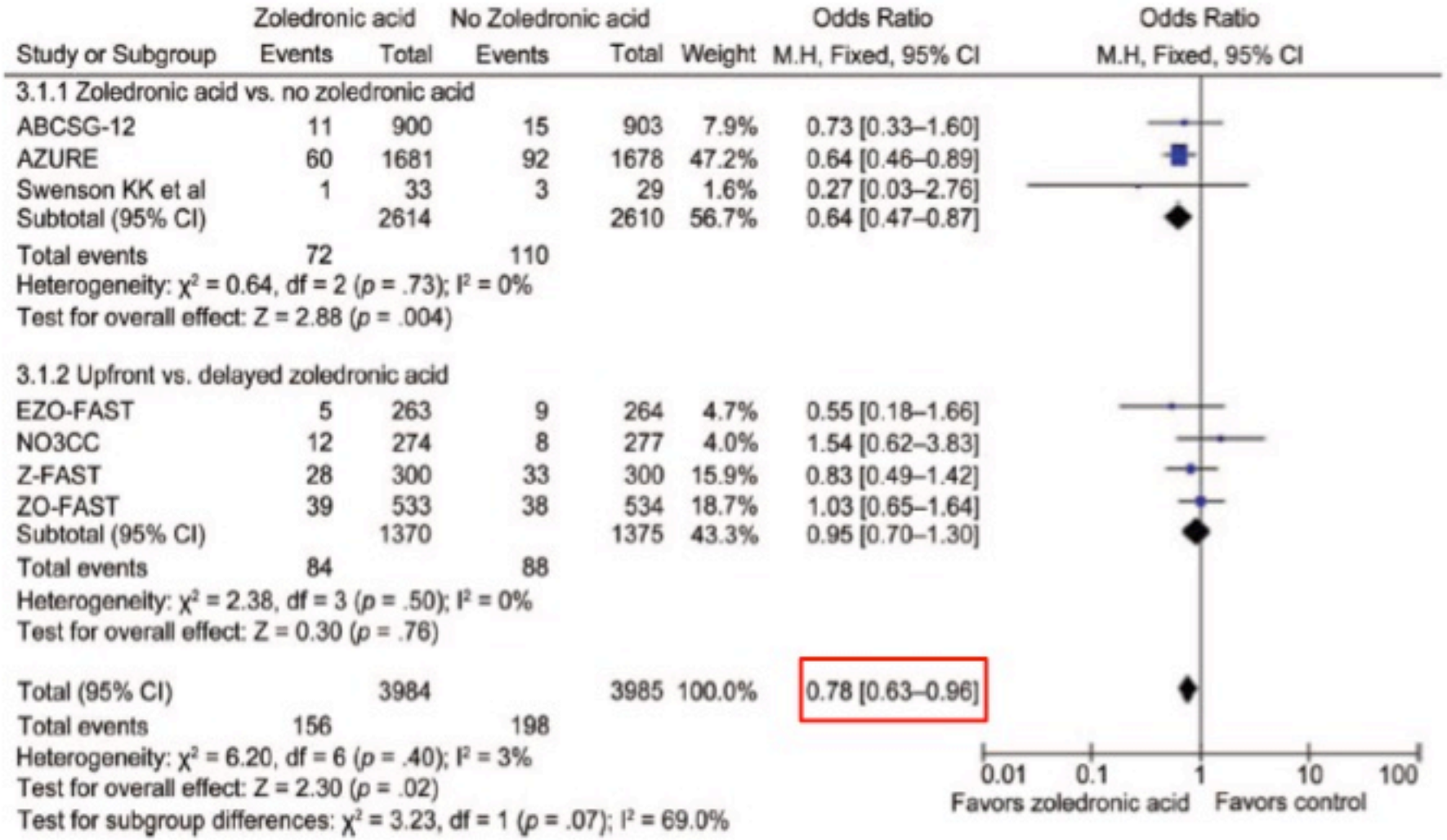
Greenspan et al., JBMR 2013

Adjuvant Therapy With Zoledronic Acid in Patients With Breast Cancer: A Systematic Review and Meta-Analysis

Study	Intervention	Zoledronic acid administration	Duration (yrs)	*n* of patients	Follow-up (mos)	*n* of recurrences	*n* of deaths
AZURE trial (2011) [20]	Zoledronic acid	4 mg every 4 wks × 6 ≥ every 3 mos × 8 ≥ every 6 mos × 5	5	1,681	59.3	377	243
	Observation			1,678	58.6	375	276
ABCSG-12 trial (2011) [21]	Zoledronic acid	4 mg every 6 mos	3	900	84	98	33
	Observation			903	84	132	49
ZO-FAST (2011) [22]	Upfront zoledronic acid	4 mg every 6 mos	5	532	54	34	26
	Delayed zoledronic acid			533	54	53	36
Z-FAST trial (2011) [23]	Upfront zoledronic acid	4 mg every 6 mos	5	300	61[a]	16	7
	Delayed zoledronic acid			300	61[a]	21	4
N03CC trial (2009) [24]	Upfront zoledronic acid	4 mg every 6 mos	5	274	24[a]	NR	NR
	Delayed zoledronic acid			277	24[a]		
EZO-FAST (2009) [25]	Upfront zoledronic acid	4 mg every 6 mos	5	263	36[a]	18	9
	Delayed zoledronic acid			264	36[a]	11	2
HOBOE trial (2011) [26]	Zoledronic acid	4 mg every 6 mos	5	154	NR	NR	NR
	Observation			305			
Takahashi et al. (2011) [27]	Upfront zoledronic acid	4 mg every 6 mos	5	97	12[a]	1	NR
	Delayed zoledronic acid			97	12[a]	0	
Aft et al. (2010) [28]	Zoledronic acid	4 mg every 3 wks	1	60	61.9	19	14
	Observation			59	61.9	18	13
KCSG-BR06–01 trial (2011) [12]	Zoledronic acid	4 mg every 6 mos	1	57	NR	NR	NR
	Observation			59			
Hershman et al. (2010) [13]	Zoledronic acid	4 mg every 3 mos	1	50	24[a]	NR	NR
	Placebo			53	24[a]		
Safra et al. (2011) [29]	Zoledronic acid	4 mg every 6 mos	2	47	41.4	NR	NR
	Observation			43	41.4		
ProBone trial (2011) [30]	Zoledronic acid	4 mg every 3 mos	2	40	NR	NR	NR
	Placebo			41			
Leal et al. (2010) [31]	Zoledronic acid	4 mg every 3 mos	1	36	96	5	5
	Observation			32	96	5	5
Swenson et al. (2010) [32]	Zoledronic acid	4 mg every 3 mos	15 mos	33	12[a]	NR	NR
	Physical activity			29	12[a]		

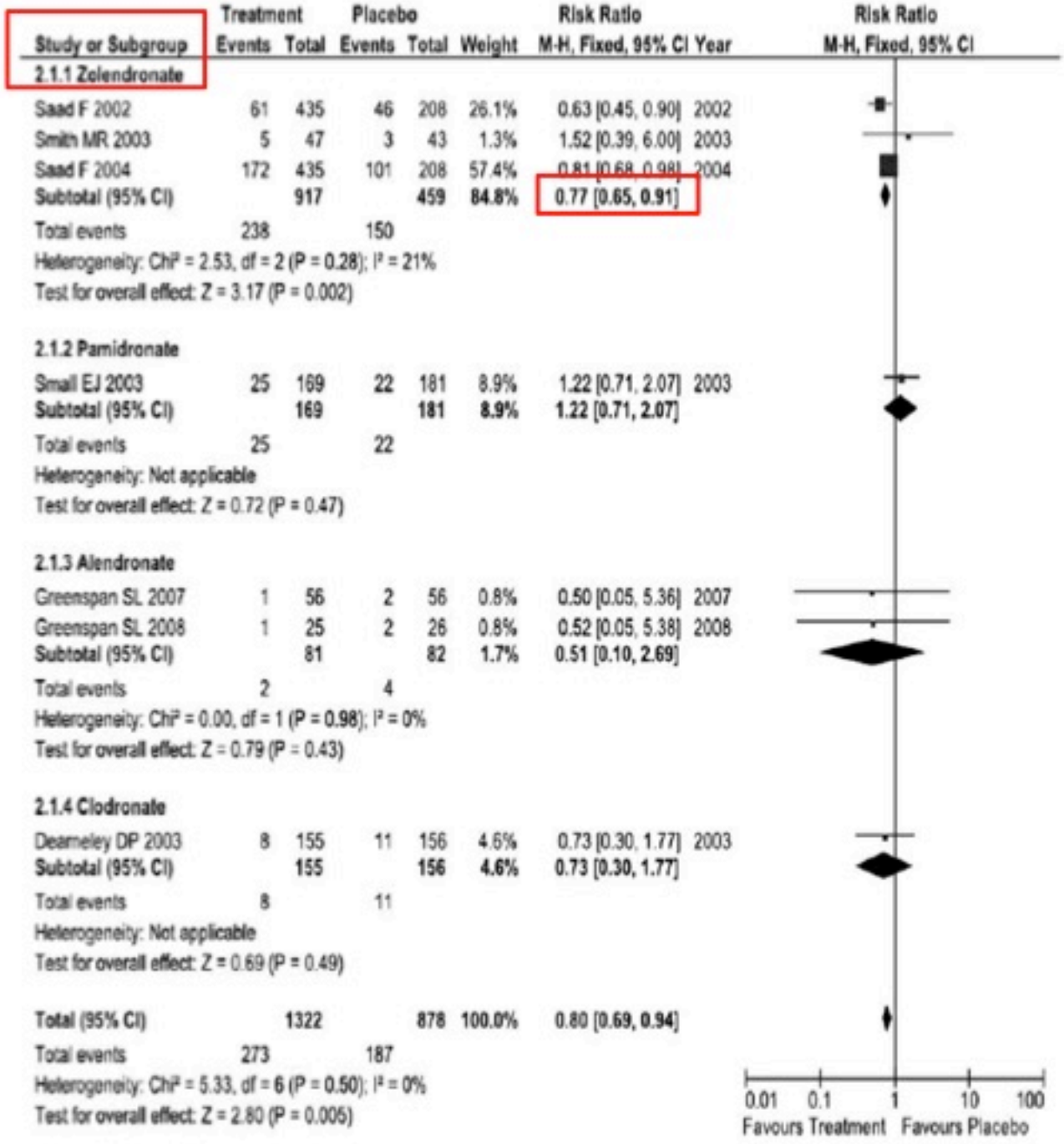
[a]Analysis when all patients reached this certain follow-up time.

FOREST PLOT FOR FRACTURE RATES



Study or Subgroup	Zoledronic acid Events	Total	No Zoledronic acid Events	Total	Weight	Odds Ratio M.H, Fixed, 95% CI
3.1.1 Zoledronic acid vs. no zoledronic acid						
ABCSG-12	11	900	15	903	7.9%	0.73 [0.33–1.60]
AZURE	60	1681	92	1678	47.2%	0.64 [0.46–0.89]
Swenson KK et al	1	33	3	29	1.6%	0.27 [0.03–2.76]
Subtotal (95% CI)		2614		2610	56.7%	0.64 [0.47–0.87]
Total events	72		110			
Heterogeneity: $\chi^2 = 0.64$, df = 2 ($p = .73$); $I^2 = 0\%$						
Test for overall effect: Z = 2.88 ($p = .004$)						
3.1.2 Upfront vs. delayed zoledronic acid						
EZO-FAST	5	263	9	264	4.7%	0.55 [0.18–1.66]
NO3CC	12	274	8	277	4.0%	1.54 [0.62–3.83]
Z-FAST	28	300	33	300	15.9%	0.83 [0.49–1.42]
ZO-FAST	39	533	38	534	18.7%	1.03 [0.65–1.64]
Subtotal (95% CI)		1370		1375	43.3%	0.95 [0.70–1.30]
Total events	84		88			
Heterogeneity: $\chi^2 = 2.38$, df = 3 ($p = .50$); $I^2 = 0\%$						
Test for overall effect: Z = 0.30 ($p = .76$)						
Total (95% CI)		3984		3985	100.0%	0.78 [0.63–0.96]
Total events	156		198			
Heterogeneity: $\chi^2 = 6.20$, df = 6 ($p = .40$); $I^2 = 3\%$						
Test for overall effect: Z = 2.30 ($p = .02$)						
Test for subgroup differences: $\chi^2 = 3.23$, df = 1 ($p = .07$); $I^2 = 69.0\%$						

The Oncologist 2013;18:353–361

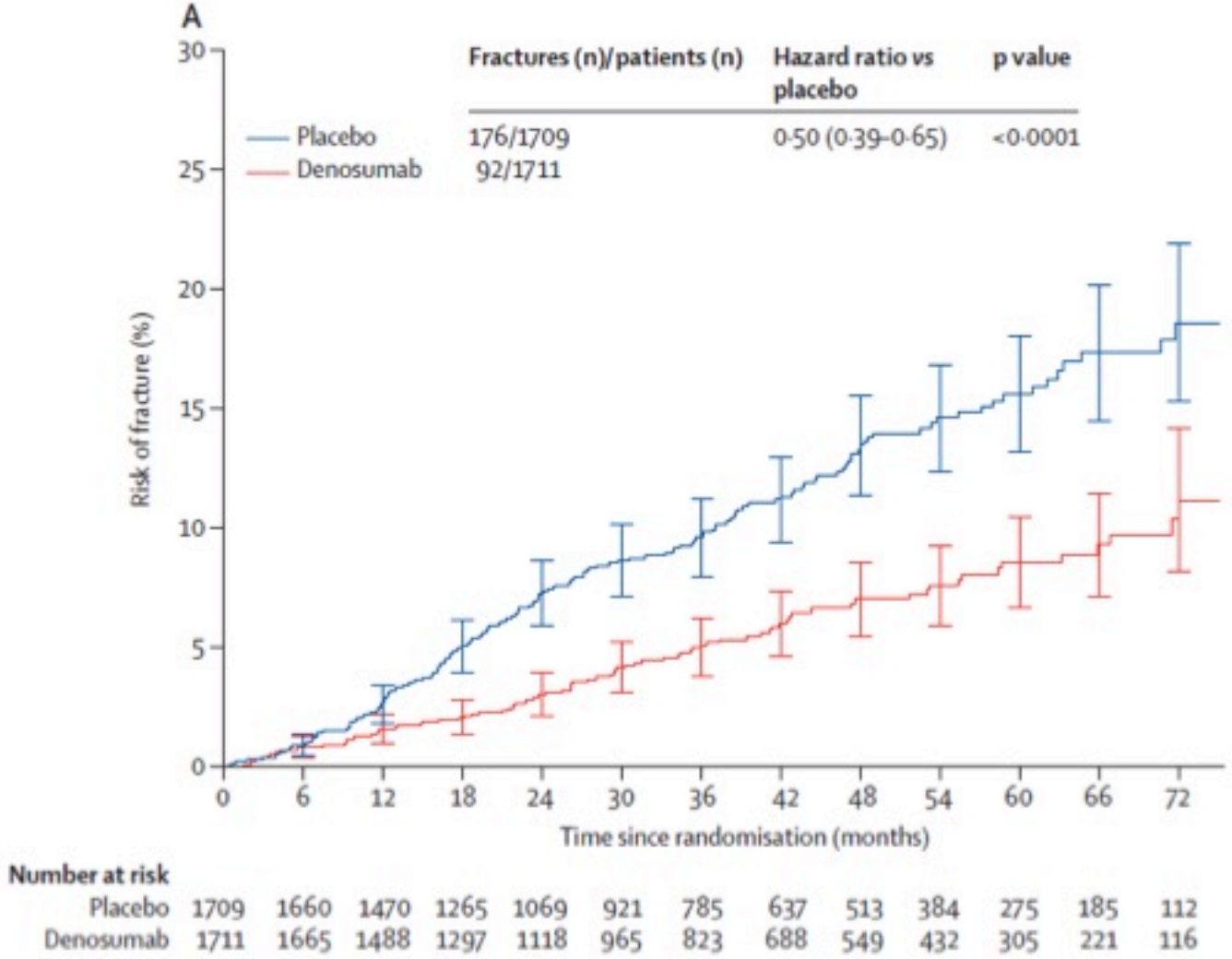


ADT-induced osteoporosis

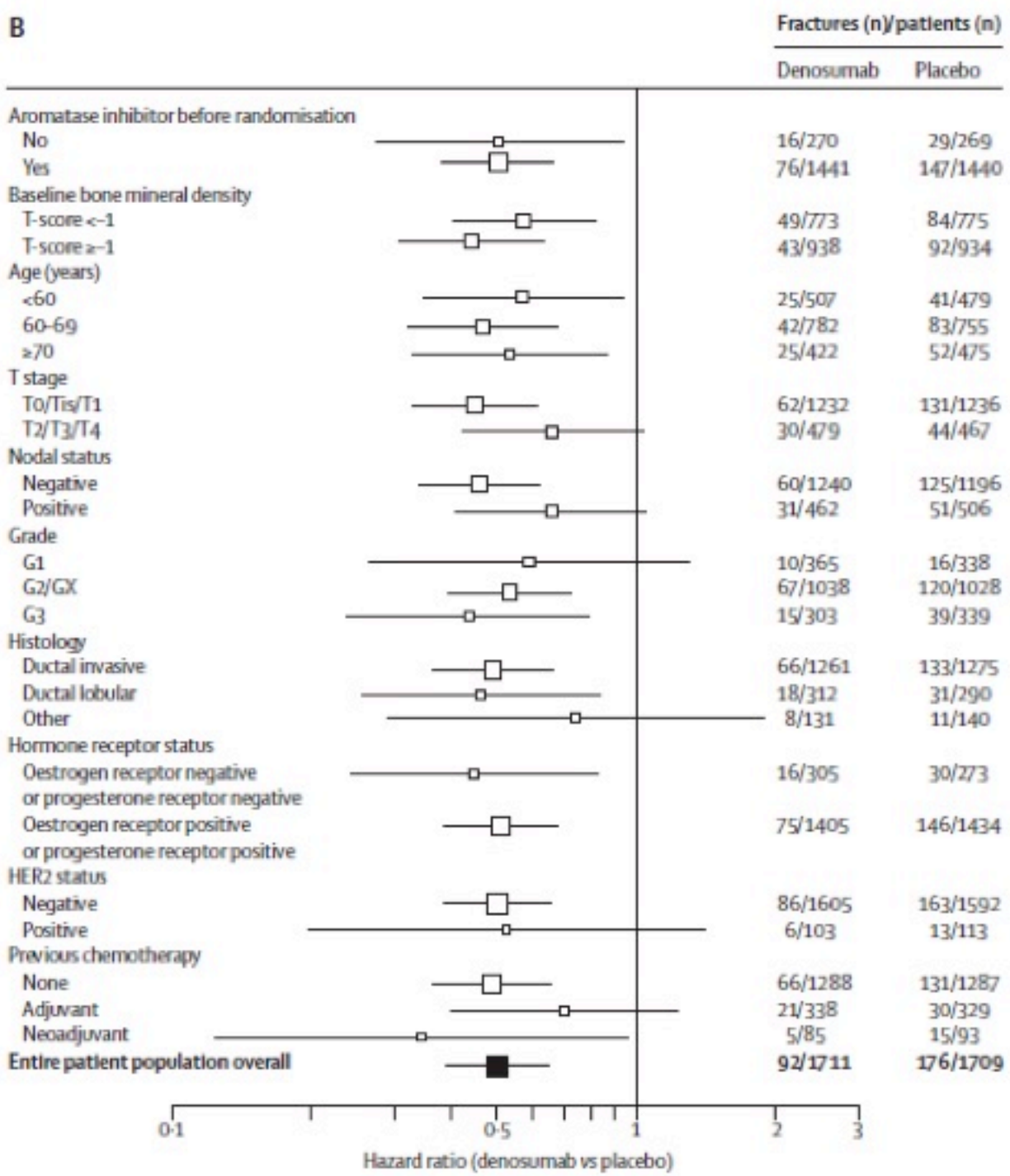
Effects of Bisphosphonates and fractures

Serpa Neto,
Prostate Cancer Prostatic Dis 2012

Adjuvant denosumab in **breast cancer** (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial



Gnant et al., Lancet 2015



Inibitori dell'aromatasi

Terapia con Denosumab

Gnant et al., Lancet 2015

ADT-induced osteoporosis

Effects of Denosumab/1

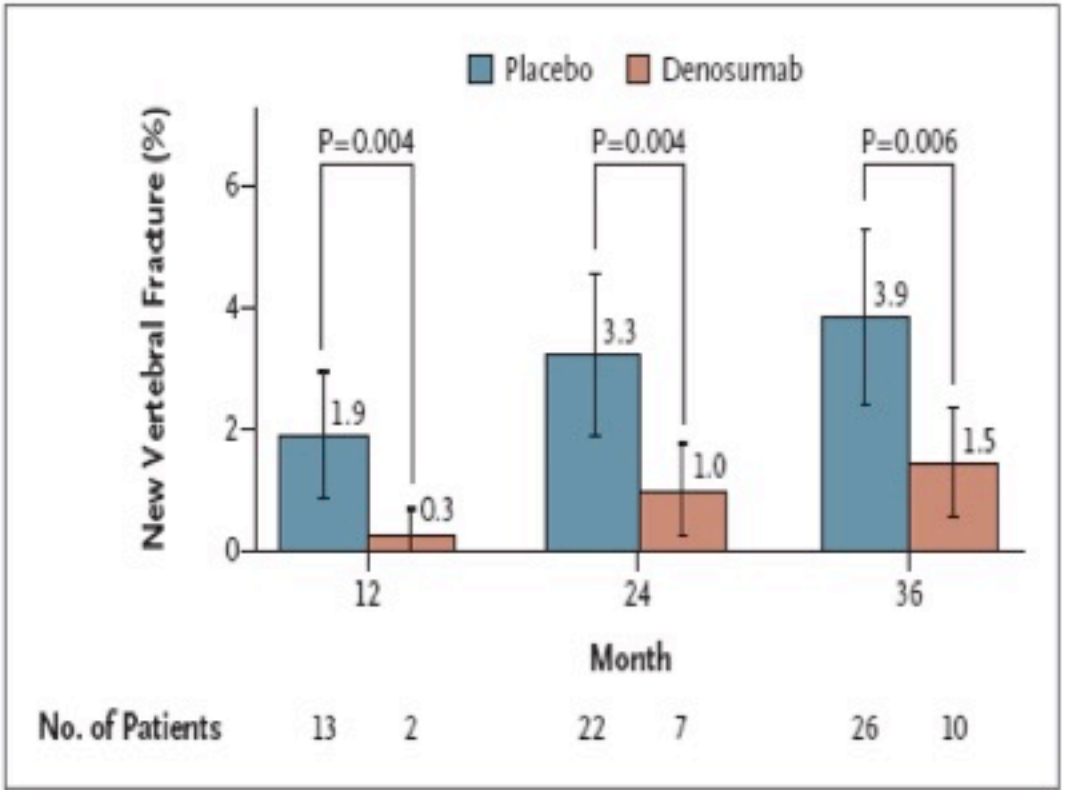


Figure 3. Cumulative Incidence of New Vertebral Fracture at 12, 24, and 36 Months, According to Study Group.

The relative risk for vertebral fracture among 679 patients in the denosumab group as compared with 673 patients in the placebo group was 0.15 at 12 months, 0.31 at 24 months, and 0.38 at 36 months.

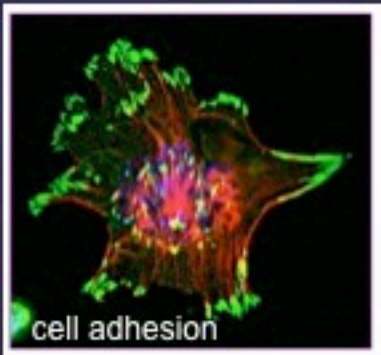
Smith et al., NEJM 2009

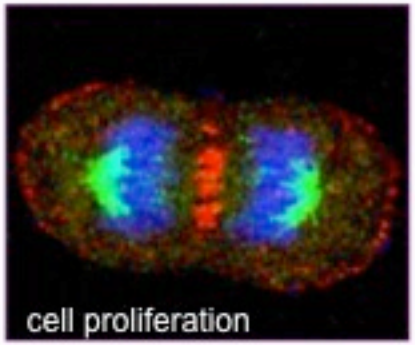
Agenda

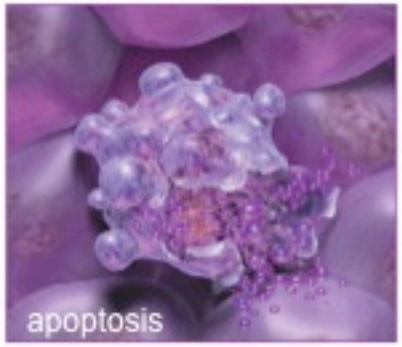
- Cancer treatment-induced bone loss
- Zoledronic ac/Denosumab therapy
- ***Bone Modifying Agents and extraskeletal effects***
- Future competitors

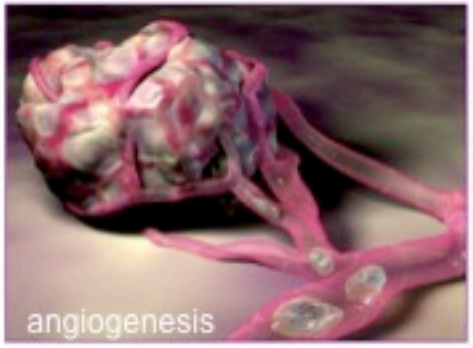
Preclinical antitumor profile of bisphosphonates

- Inhibition of cancer cell adhesion to extracellular matrix proteins
  (Pluijm *et al.*, J Clin Invest, 1996; Boissier, ... & Clézardin, Cancer Res, 1997; then others .....)
- Inhibition of cancer cell proliferation and induction of apoptosis
  (Shipman *et al.*, Br J Haematol, 1997; then others ....)
- Inhibition of cancer cell migration and invasion
  (Boissier, ... & Clézardin, Cancer Res, 2000; then others ....)
- Stimulation of the expansion of human γδT cells
  (Kunzmann *et al.*, Blood, 2000; then others ....)
- Inhibition of angiogenesis
  (Fournier, ... & Clézardin, Cancer Res, 2002; Wood *et al.*, JPET, 2002; then others ....)

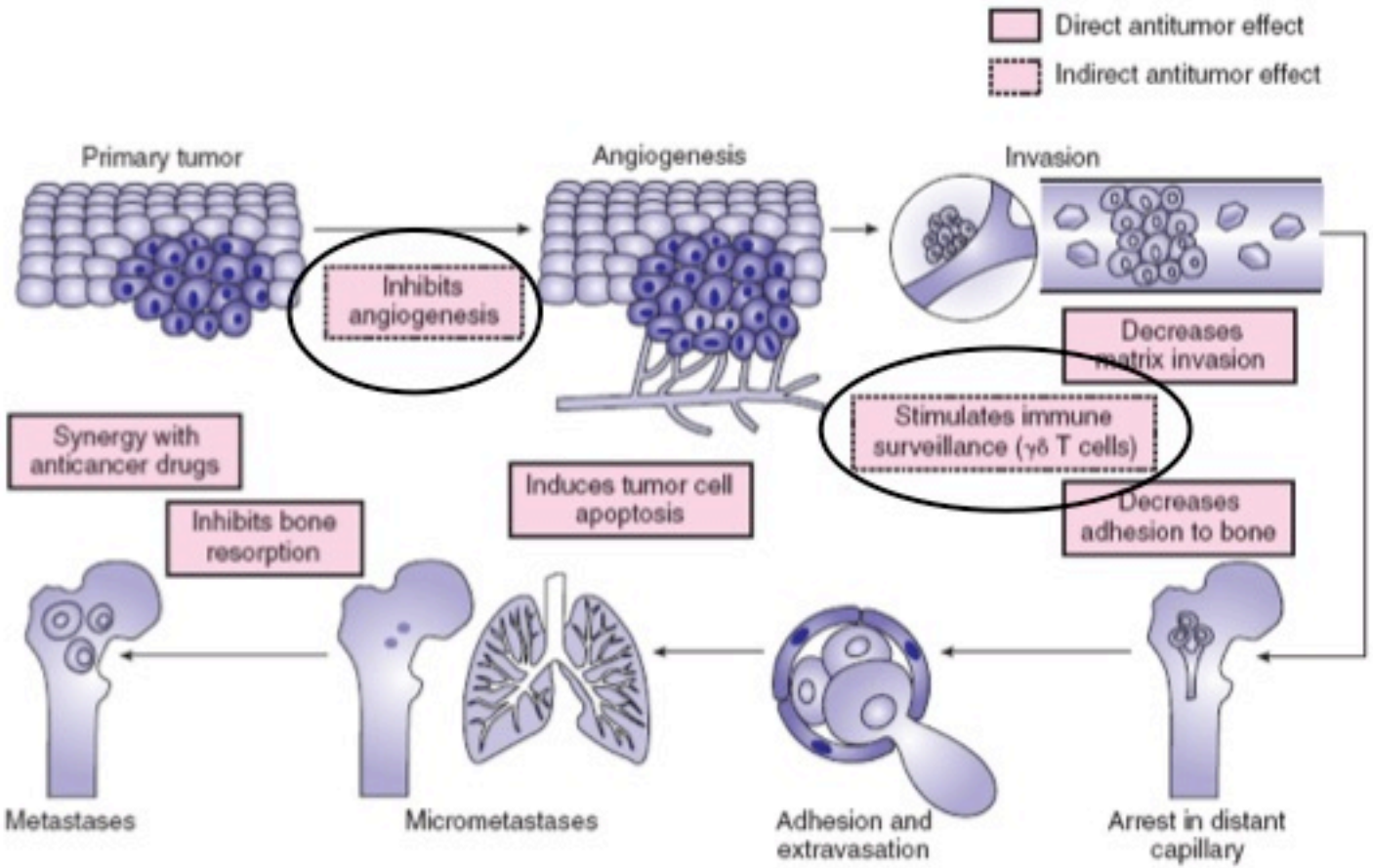








Effetti extra-scheletrici dei bisfosfonati



Gnant et al., Ther Adv Med Oncol 2009

Effects of bisphosphonates on the preclinical cancer course

	ALEN	CLO	IBAN	PAM	ZOL
A. Apoptosis and inhibition of tumour growth (breast cancer only)					
Fromigue et al.[69]			✓+	✓	✓+
Senaratne et al.[70]			✓	✓	✓+
Jagdev et al.[71]					✓
Senaratne et al.[72,73]					✓
Monkkonen et al.[74]		✓			✓+
Verdijk et al[75]	✓	✓	✓	✓	✓+
B. Antiangiogenic activity					
Fournier et al.[76]		✓	✓		✓+
Wood et al.[77]				✓	✓+
Bezzi et al.[78]		✓			✓+
C. Inhibition of adherence and invasion					
Muller et al.[79]	✓				
Montague et al.[80]				✓	✓+

Abbreviations: ALEN, alendronate; CLO, clodronate; IBAN, ibandronate; PAM, pamidronate; ZOL, zoledronic acid.

✓ = Activity reported.

✓+ = Activity more potent than others tested in the study.

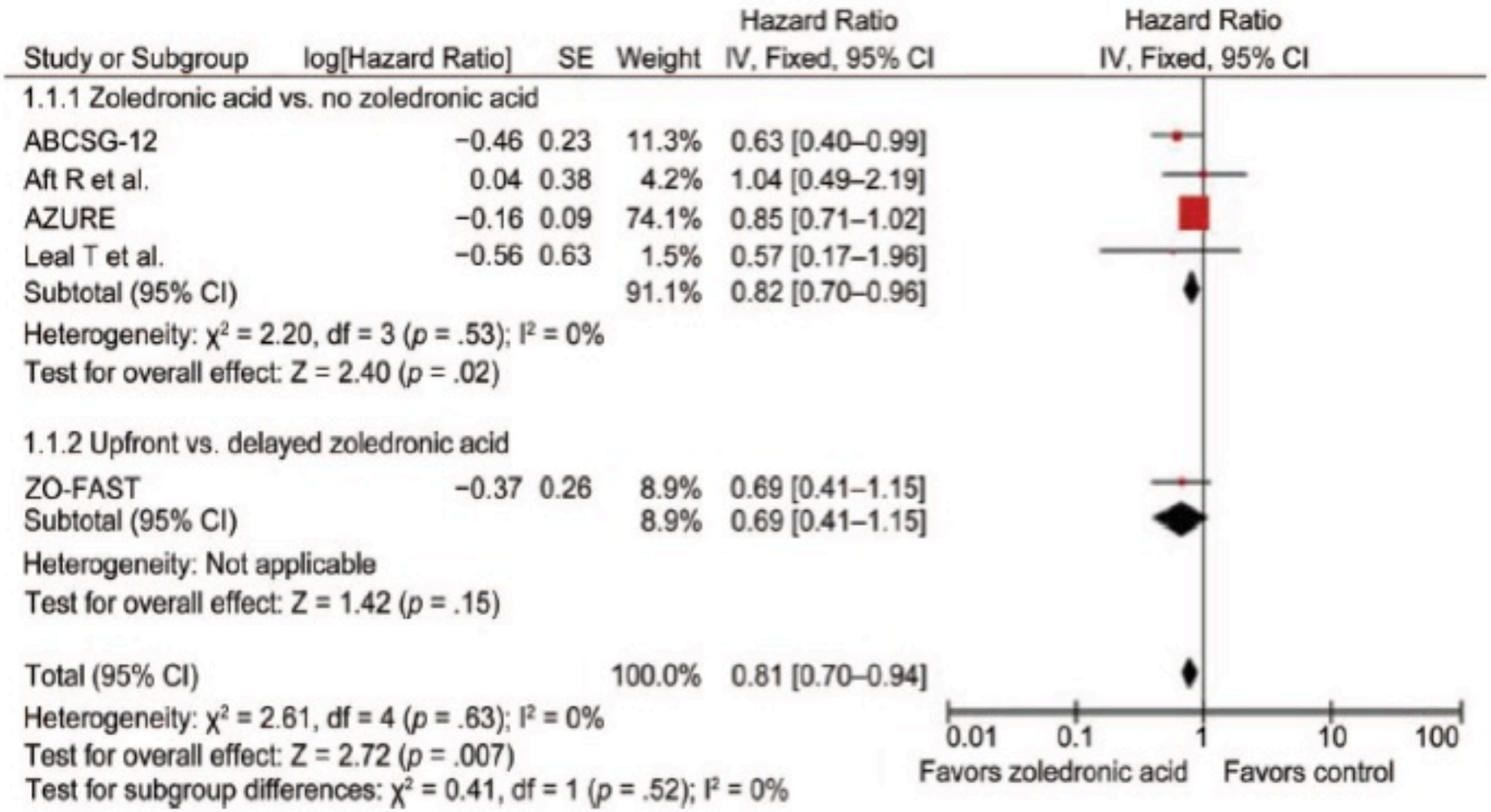
Bundred N, Canc Treat Rev 2012

Adjuvant Therapy With Zoledronic Acid in Patients With Breast Cancer: A Systematic Review and Meta-Analysis

Study	Intervention	Zoledronic acid administration	Duration (yrs)	*n* of patients	Follow-up (mos)	*n* of recurrences	*n* of deaths
AZURE trial (2011) [20]	Zoledronic acid	4 mg every 4 wks × 6 ≥ every 3 mos × 8 ≥ every 6 mos × 5	5	1,681	59.3	377	243
	Observation			1,678	58.6	375	276
ABCSG-12 trial (2011) [21]	Zoledronic acid	4 mg every 6 mos	3	900	84	98	33
	Observation			903	84	132	49
ZO-FAST (2011) [22]	Upfront zoledronic acid	4 mg every 6 mos	5	532	54	34	26
	Delayed zoledronic acid			533	54	53	36
Z-FAST trial (2011) [23]	Upfront zoledronic acid	4 mg every 6 mos	5	300	61[a]	16	7
	Delayed zoledronic acid			300	61[a]	21	4
N03CC trial (2009) [24]	Upfront zoledronic acid	4 mg every 6 mos	5	274	24[a]	NR	NR
	Delayed zoledronic acid			277	24[a]		
EZO-FAST (2009) [25]	Upfront zoledronic acid	4 mg every 6 mos	5	263	36[a]	18	9
	Delayed zoledronic acid			264	36[a]	11	2
HOBOE trial (2011) [26]	Zoledronic acid	4 mg every 6 mos	5	154	NR	NR	NR
	Observation			305			
Takahashi et al. (2011) [27]	Upfront zoledronic acid	4 mg every 6 mos	5	97	12[a]	1	NR
	Delayed zoledronic acid			97	12[a]	0	
Aft et al. (2010) [28]	Zoledronic acid	4 mg every 3 wks	1	60	61.9	19	14
	Observation			59	61.9	18	13
KCSG-BR06–01 trial (2011) [12]	Zoledronic acid	4 mg every 6 mos	1	57	NR	NR	NR
	Observation			59			
Hershman et al. (2010) [13]	Zoledronic acid	4 mg every 3 mos	1	50	24[a]	NR	NR
	Placebo			53	24[a]		
Safra et al. (2011) [29]	Zoledronic acid	4 mg every 6 mos	2	47	41.4	NR	NR
	Observation			43	41.4		
ProBone trial (2011) [30]	Zoledronic acid	4 mg every 3 mos	2	40	NR	NR	NR
	Placebo			41			
Leal et al. (2010) [31]	Zoledronic acid	4 mg every 3 mos	1	36	96	5	5
	Observation			32	96	5	5
Swenson et al. (2010) [32]	Zoledronic acid	4 mg every 3 mos	15 mos	33	12[a]	NR	NR
	Physical activity			29	12[a]		

[a]Analysis when all patients reached this certain follow-up time.

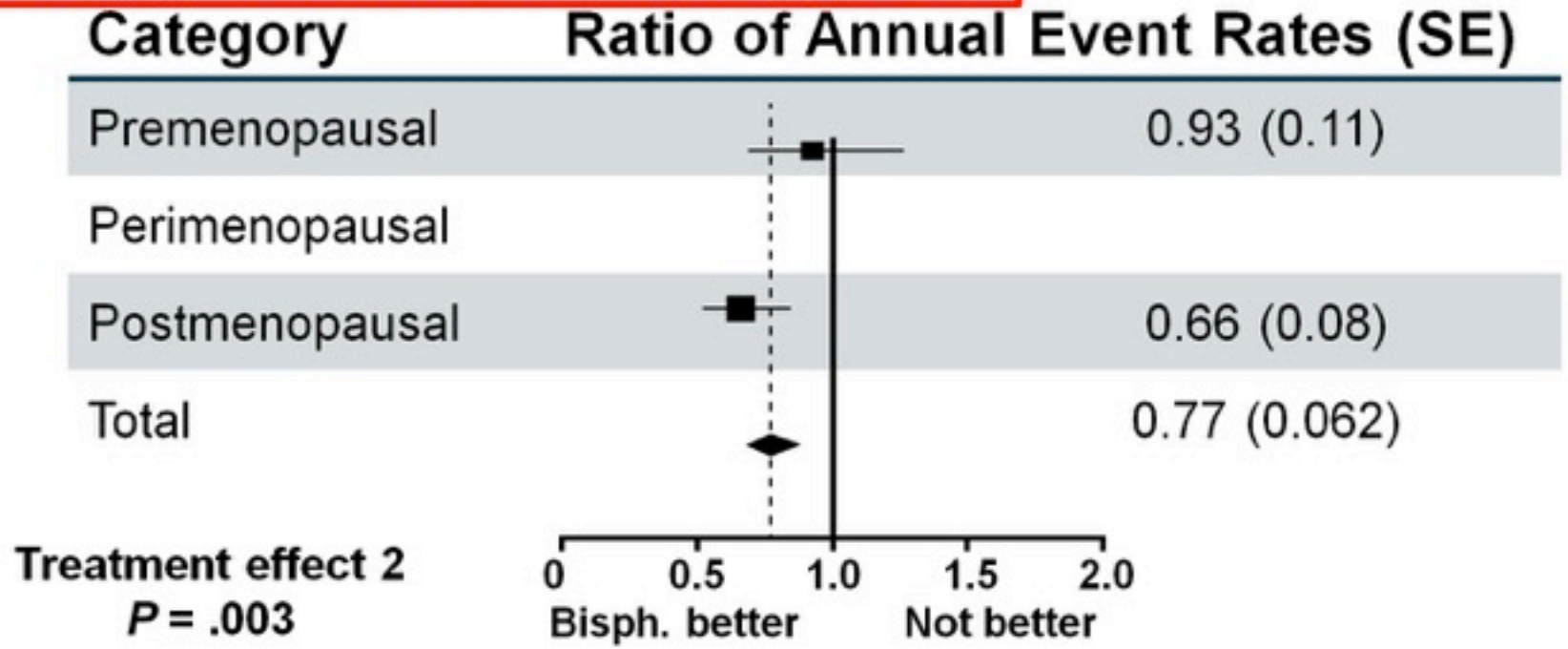
OVERALL SURVIVAL OUTCOME



The Oncologist 2013;18:353–361

Meta-analysis of Bisphosphonate Treatment to Prevent BC Recurrence

Bone Metastasis Recurrence

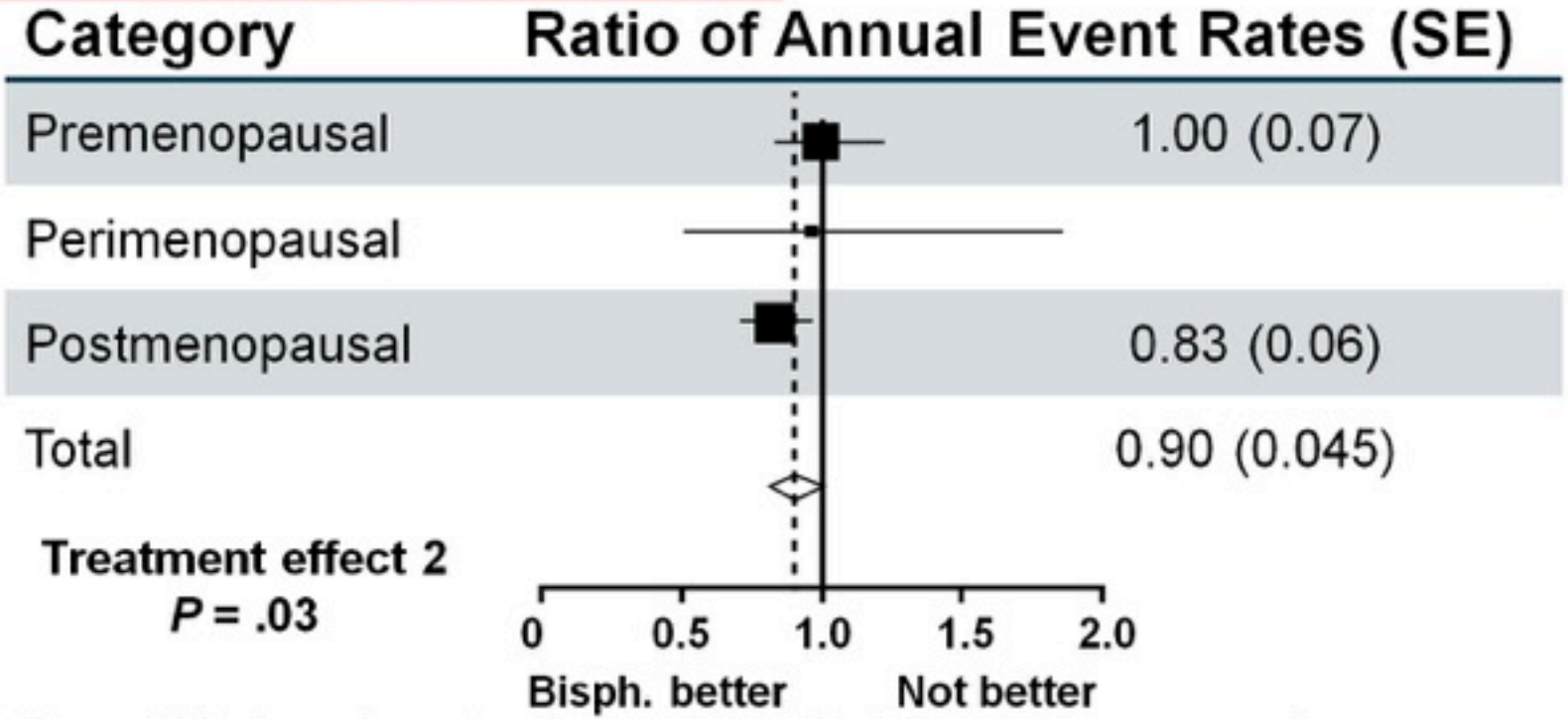


- Adjuvant bisphosphonates reduce bone metastases in postmenopausal women
  - 34% reduction in risk of bone recurrence at 10 y (6.9% vs 8.4%, *P* = .001)
  - No significant reduction in first distant recurrence outside of bone
  - Risk reductions similar, irrespective of ER status, node status, use/non-use of chemotherapy
  - Benefits similar for aminobisphosphonates and clodronate

Coleman R, et al. SABCS 2013. Abstract S4-07. Republished with permission.[26]

Meta-analysis of Bisphosphonate Treatment to Prevent BC Recurrence

Breast Cancer Mortality

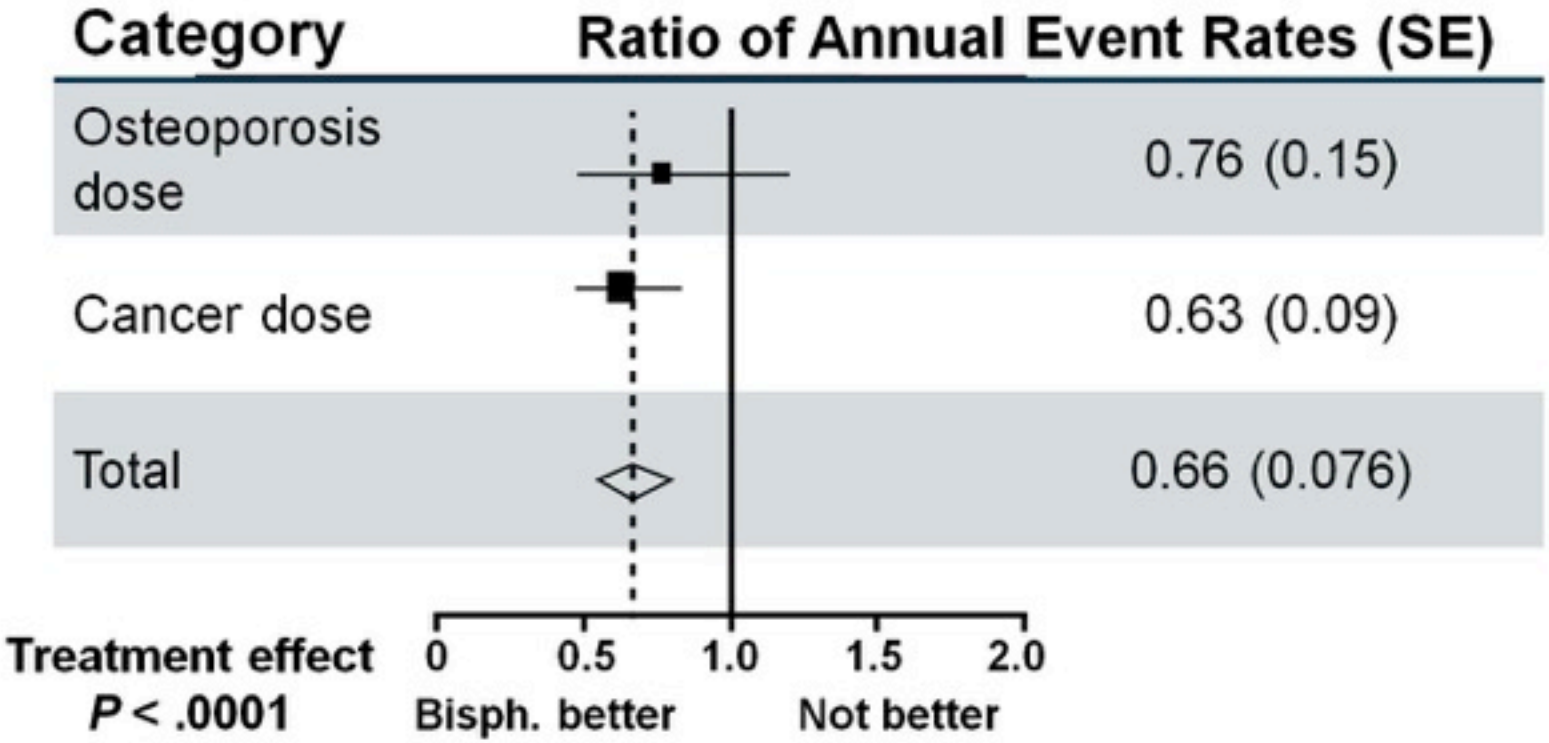


- Adjuvant bisphosphonates improve survival in postmenopausal women
  - 17% reduction in risk of breast cancer death at 10 y (15.2% vs 18.3%, *P* = .004)
  - Risk reductions similar irrespective of ER status, node status, use/non-use of chemotherapy
  - Benefits similar for aminobisphosphonates and clodronate

Coleman R, et al. SABCS 2013. Abstract S4-07. Republished with permission.[26]

Meta-analysis of Bisphosphonate Treatment to Prevent BC Recurrence

Bisphosphonate Schedule vs Annual Event Rate



Treatment effects stronger with higher dose of bisphosphonates

Coleman R, et al. SABCS 2013. Abstract S4-07. Republished with permission.[26]

RAZIONALE ANTI-NEOPLASTICO

- Il sistema RANK/RANKL è coinvolto in molteplici passaggi della malattia neoplastica, non solo nella metastasi ossea

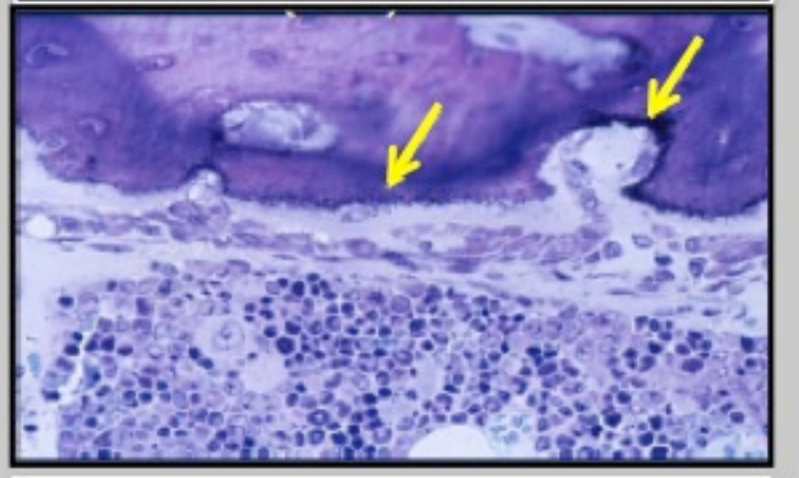
- Denosumab è in grado di "contattare" tutte le possibili fonti di RANKL :

- OSTEOBLASTI
- OSTEOCITI
- CELLULE NEOPLASTICHE TUMORE PRIMITIVO
- CELLULE METASTATICHE
- LINFOCITI T

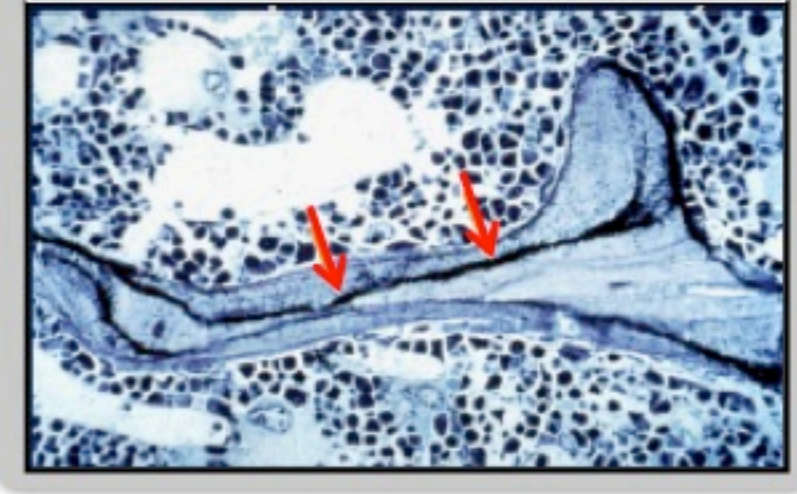
- Anche in distretti scheletrici poco raggiungibili dai BPs e in sedi non scheletriche

Distribuzione di denosumab e bisfosfonati

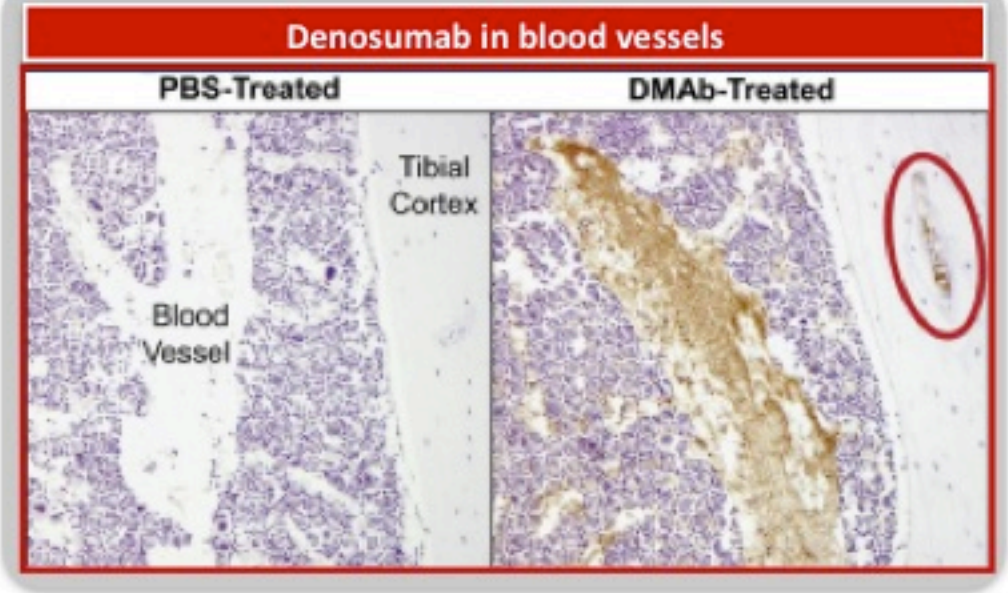
Alendrontae (ALN) on bone surfaces at 24 h



ALN deep within bone at 7 days

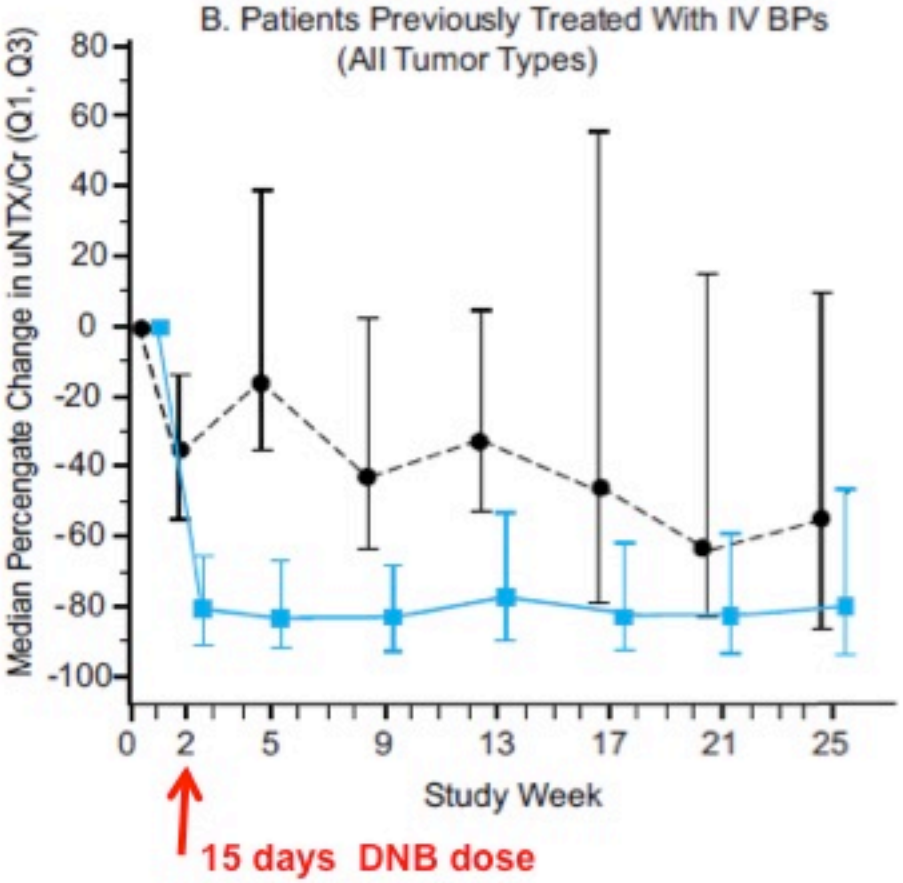


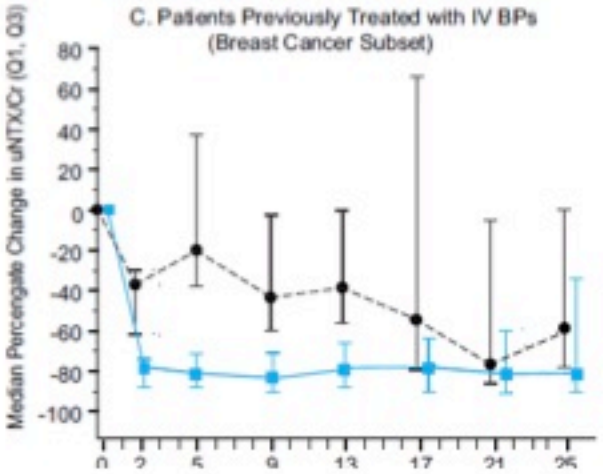
Denosumab in blood vessels

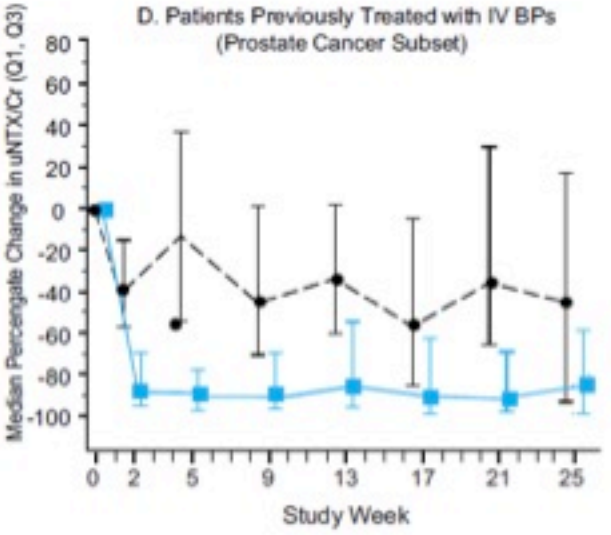


Masarachia P et al, Bone 1996; 19: 281-290
Kostenuik PJ et al, JBMR 2009; 24: 182-95

Effetto di denosumab in pazienti con metastasi ossee e precedente trattamento con BP



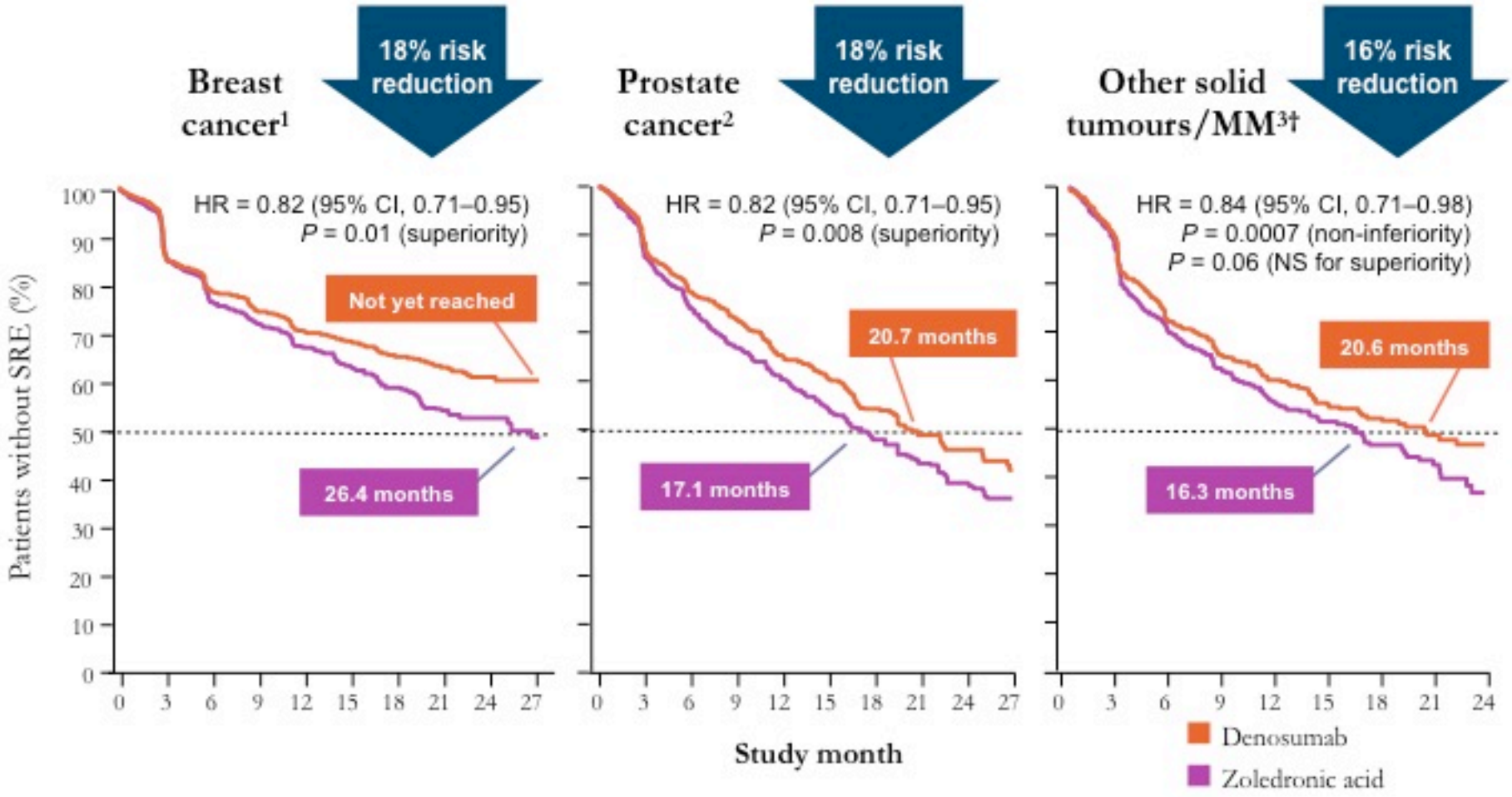




Body JJ, J Bone Miner Res 2010

La riduzione del rischio di sviluppare il primo evento scheletrico è a favore di denosumab in maniera consistente in tutti i tumor type

Efficacia nella prevenzione del primo evento scheletrico e successivi nella maggioranza di istotipi tumorali



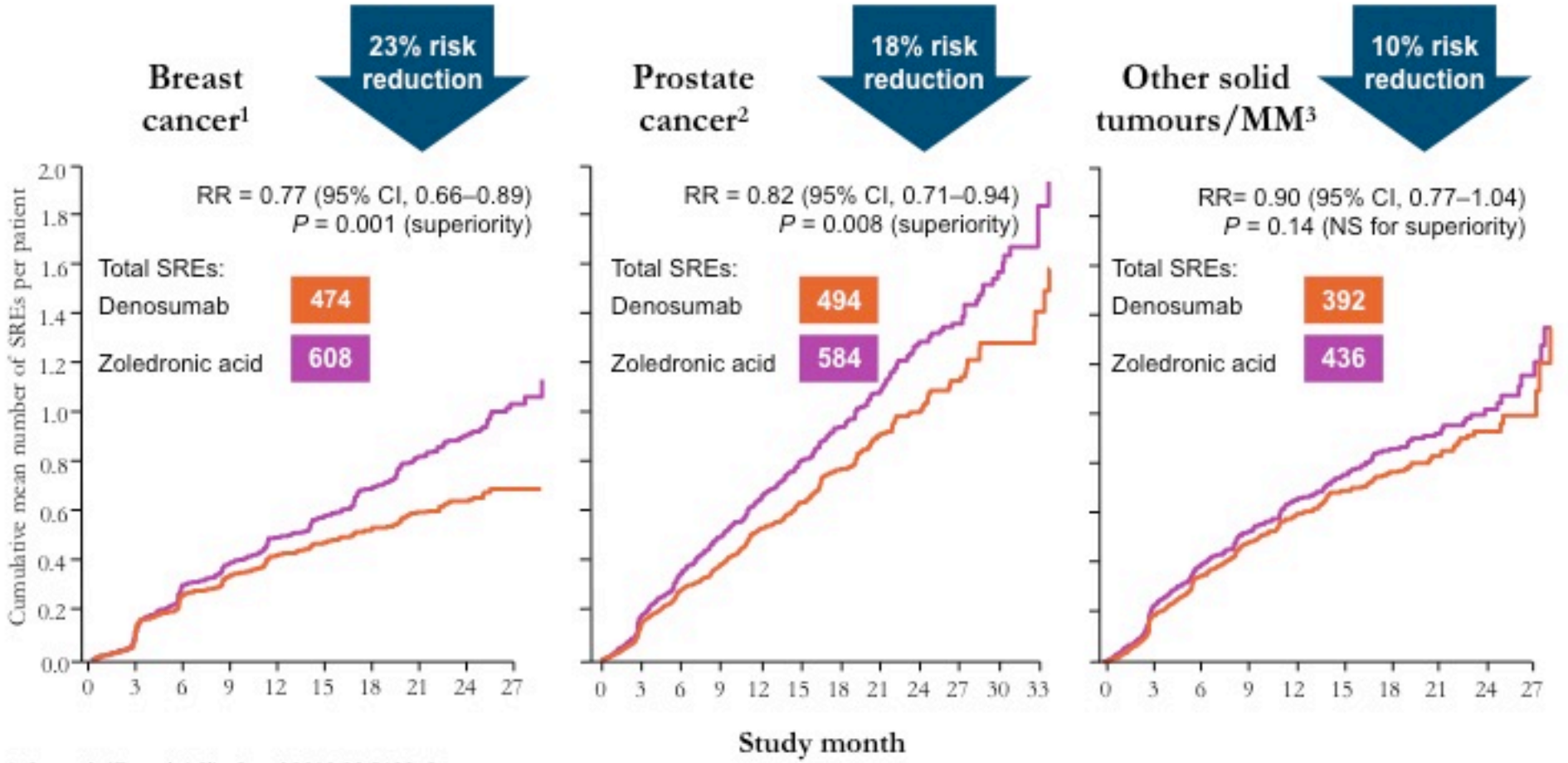
1. Stopeck AT, et al. J Clin Oncol 2010;28:5132–9;
2. Fizazi K, et al. Lancet 2011;377:813–22;
3. Henry DH, et al. J Clin Oncol 2011;29:1125-32.

†Excluding breast and prostate. All data from primary analyses.
MM, multiple myeloma; NS, non-significant.

La riduzione del rischio di sviluppare il primo evento e successivi è a favore di denosumab in maniera consistente in tutti i tumor type

Efficacia nella prevenzione del primo evento scheletrico e successivi nella maggioranza di istotipi tumorali

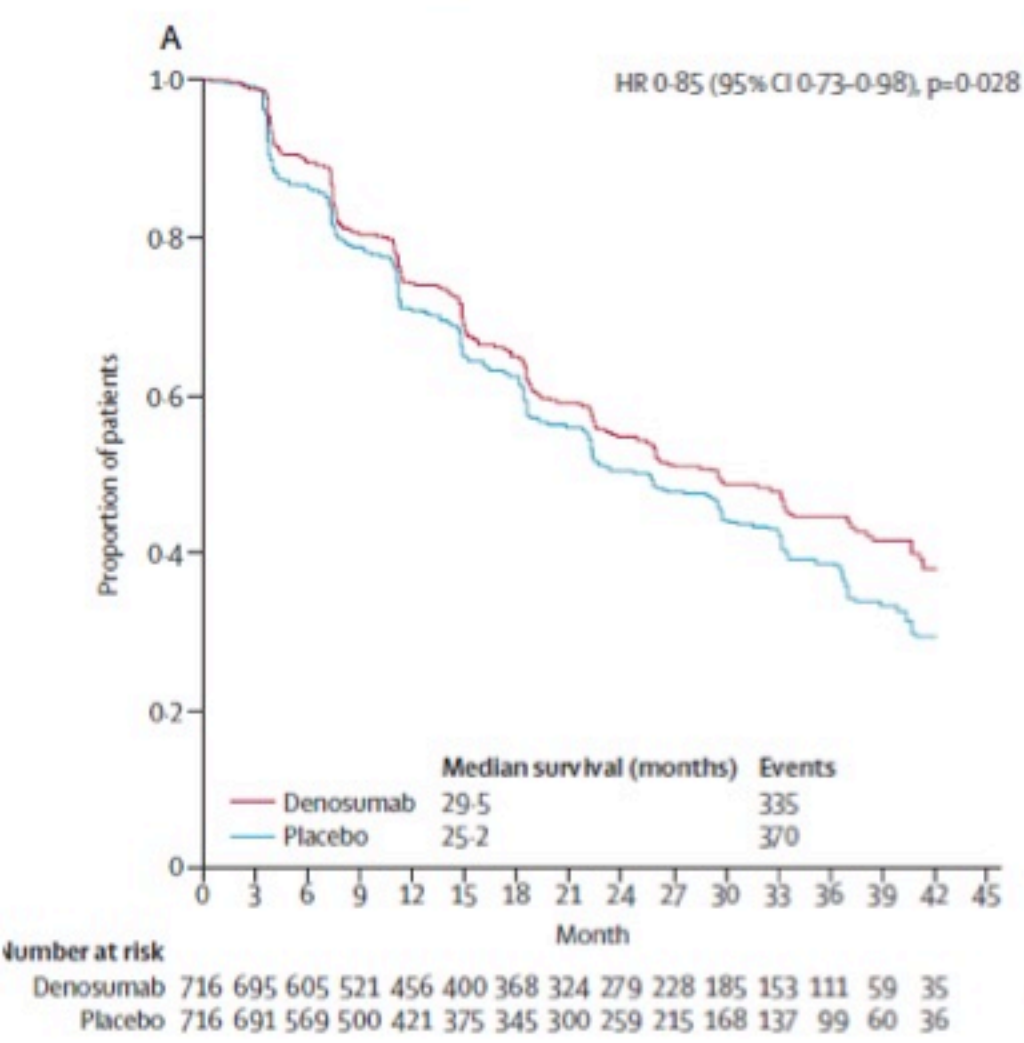
Time to first and subsequent SREs



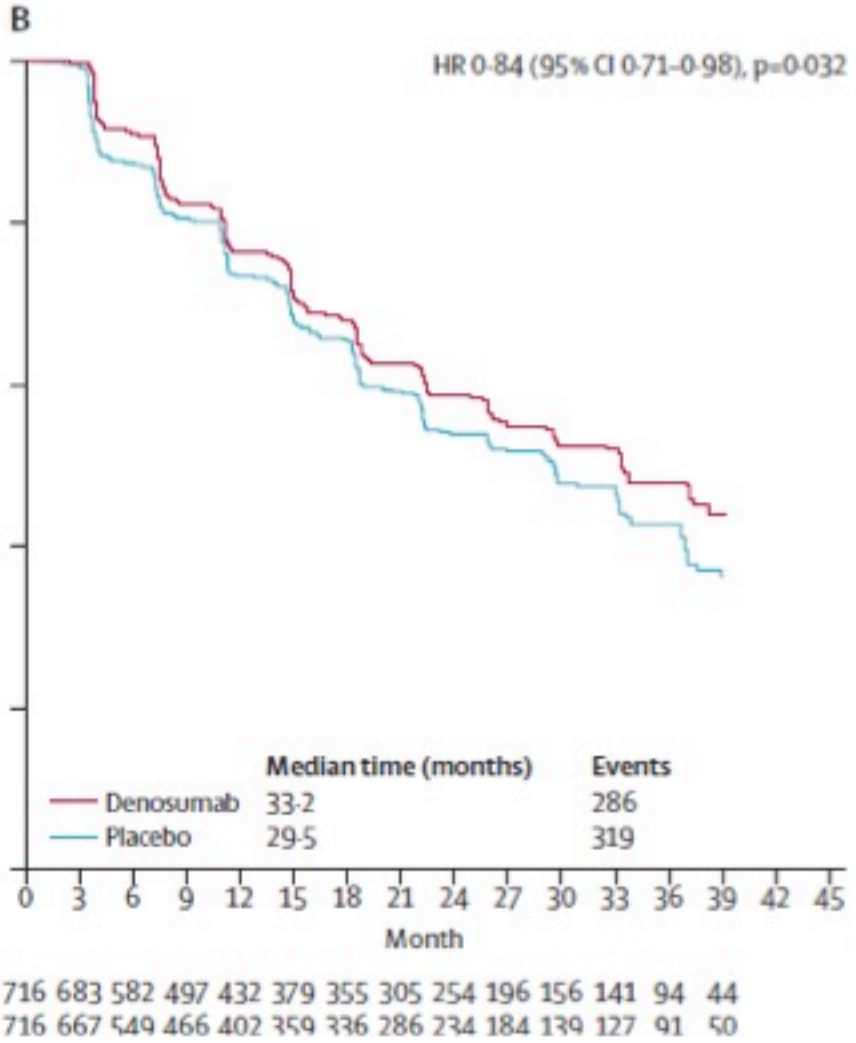
1. Stopeck AT, et al. J Clin Oncol 2010;28:5132–9;
2. Fizazi K, et al. Lancet 2011;377:813–22;
3. Henry DH, et al. J Clin Oncol 2011;29:1125-32.

All data from primary analyses.
RR, rate ratio.

Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial



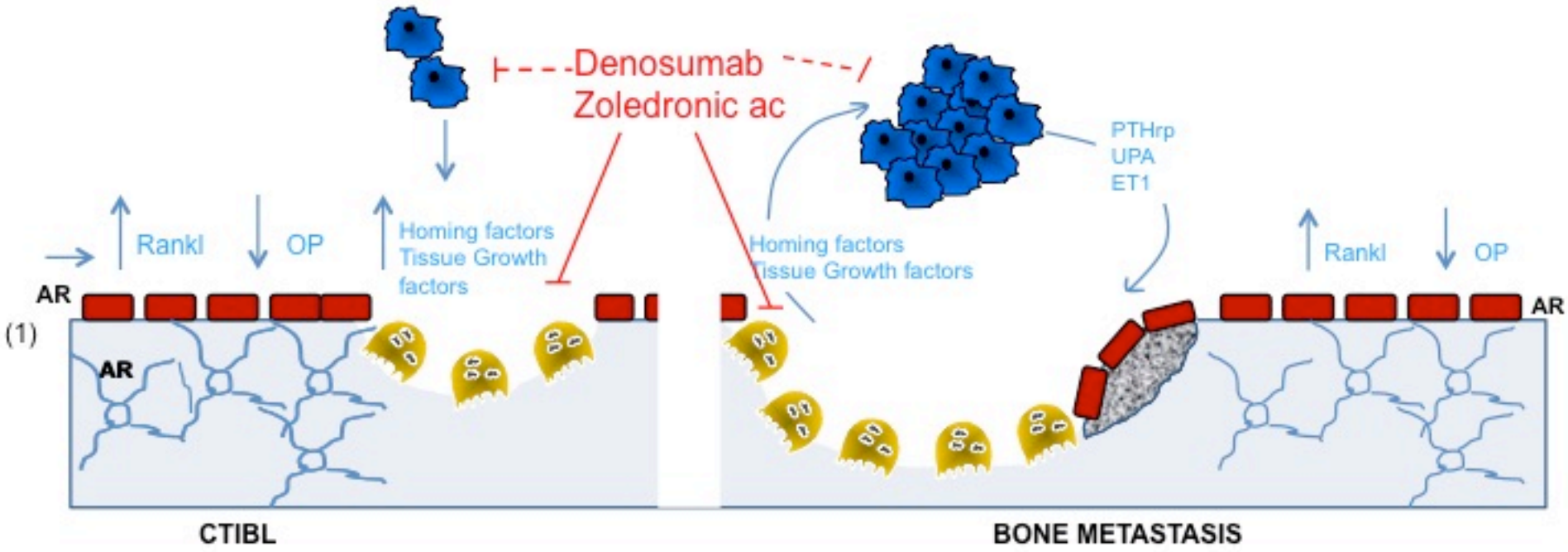
Bone metastasis free survival



Time to first metastasis

Smith MR et al lancet 2011

Two Compartment Model :
Bone Target Therapy vs Tumor Target Therapy



(1) Monolagas S et al, Nature Rev Endocrinol 2013 2; (2) Scher HI, et al. N Engl J Med 2012; (3) Fizazi K, et al. Lancet Oncology 2012;
(4) Smith DC et al J Clin Oncol 2013; (5) Parker C, et al. N Engl J Med 2013.

Denosumab for treatment of bone metastases secondary to solid tumours: Systematic review and network meta-analysis

Breast cancer NMA results.

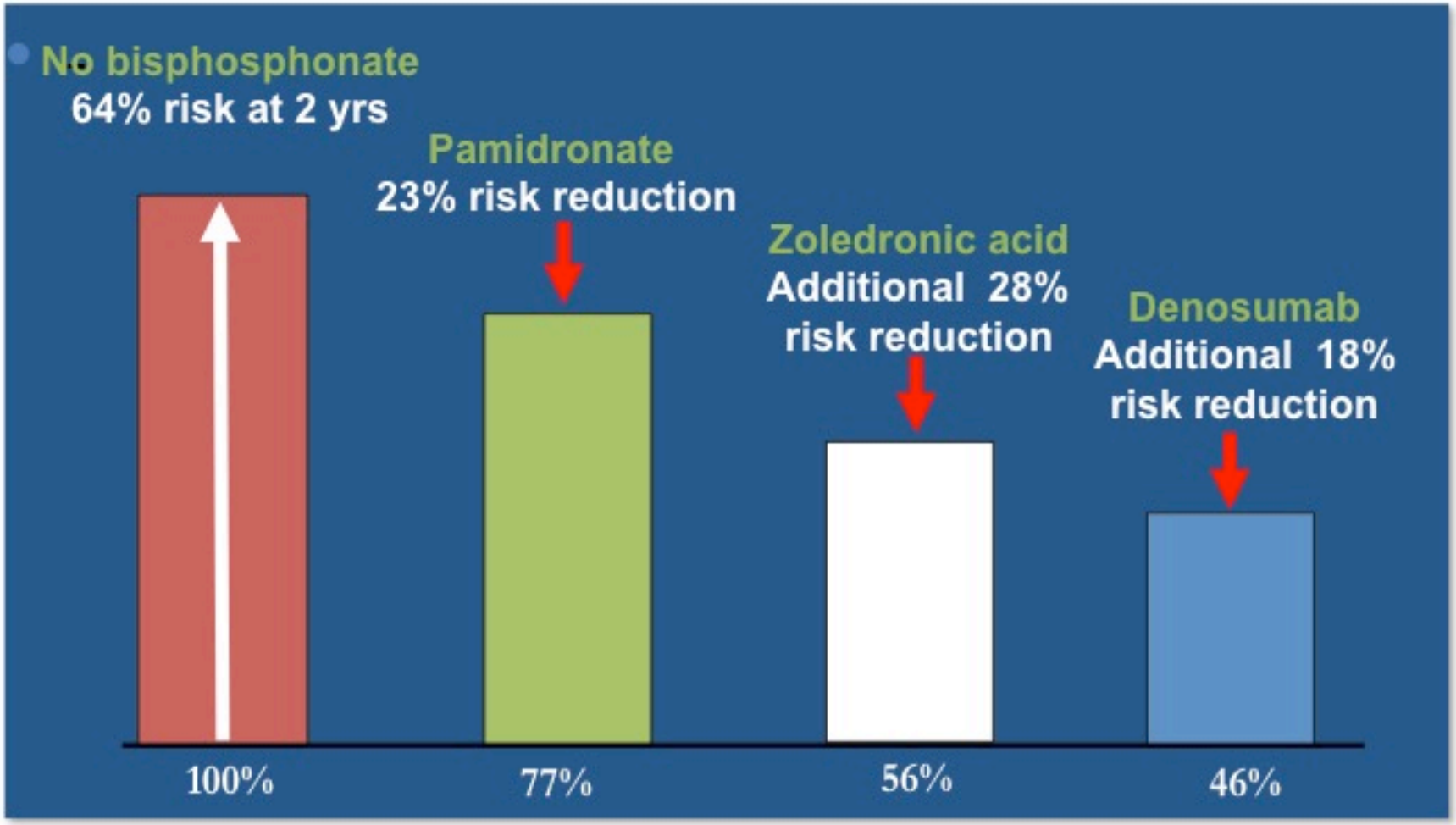
Comparison	TTF SRE hazard ratio (95% CI)	TTF + S risk ratio (95% CI)	SMR rate ratio (95% CI)
Denosumab versus zoledronic acid	0.82 (0.71–0.95)	0.77 (0.66–0.89)	0.90 (0.67–1.09)
Denosumab versus pamidronate	0.73 (0.56–0.94)	0.62 (0.48–0.80)	0.73 (0.41–1.06)
Denosumab versus placebo	0.46 (0.29–0.72)	0.45 (0.28–0.72)	0.47 (0.25–0.67)
Zoledronic acid versus placebo	0.56 (0.36–0.86)	0.59 (0.37–0.91)	0.52 (0.32–0.70)

CI, confidence interval; TTF SRE, time to first skeletal related event; TTF + S SRE, time to first and subsequent skeletal related events; SMR, skeletal morbidity rate.

Ford JA, European Journal of Cancer, 2013

Skeletal Complication Risk

Incremental Benefits in Breast Cancer (Time To First SRE)



Ford JA, European Journal of Cancer, 2013

Denosumab for treatment of bone metastases secondary to solid tumours: Systematic review and network meta-analysis

Prostate cancer NMA results.

	TTF SRE hazard ratio (95%CI)	TTF + S risk ratio (95% CI)	SMR rate ratio (95% CI)
Denosumab versus zoledronic acid	0.82 (0.71–0.95)	0.82 (0.71–0.94)	0.95 (0.46–1.47)
Denosumab versus placebo	0.56 (0.40–0.77)	0.53 (0.39–0.72)	0.52 (0.07–0.82)
Zoledronic acid versus placebo	0.68 (0.50–0.91)	0.64 (0.48–0.85)	0.54 (0.11–0.83)

CI, confidence interval; TTF SRE, time to first skeletal related event; TTF + S SRE, time to first and subsequent skeletal related event; SMR, skeletal morbidity rate.

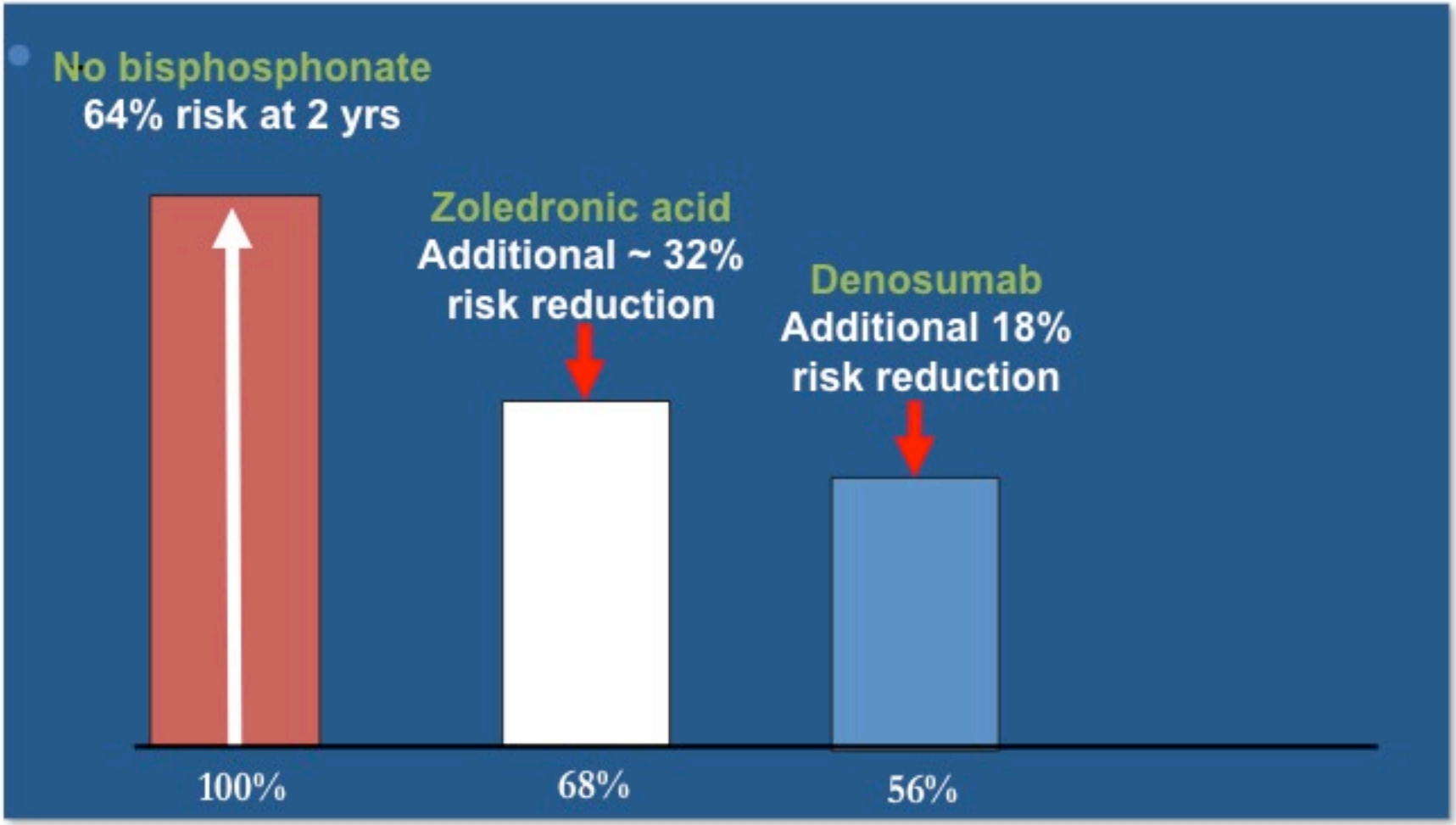
Other solid tumours and non-small cell lung cancer NMA results.

	Other solid tumours		NSCLC	
	TTF SRE hazard ratio (95%CI)	TTF + S SRE risk ratio (95%CI)	TTF SRE hazard ratio (95%CI)	TTF + S SRE RR (95%CI)
Denosumab versus zoledronic acid	0.79 (0.62–0.99)	0.83 (0.67–1.03)	0.84 (0.64–1.10)	0.87 (0.68–1.12)
Denosumab versus placebo	0.30 (0.11–0.82)	0.61 (0.39–0.97)	0.68 (0.45–1.03)	0.63 (0.42–0.97)
Zoledronic acid versus placebo	0.37 (0.14–1.01)	0.74 (0.49–1.10)	0.81 (0.59–1.11)	0.73 (0.52–1.02)

Ford JA, European Journal of Cancer, 2013

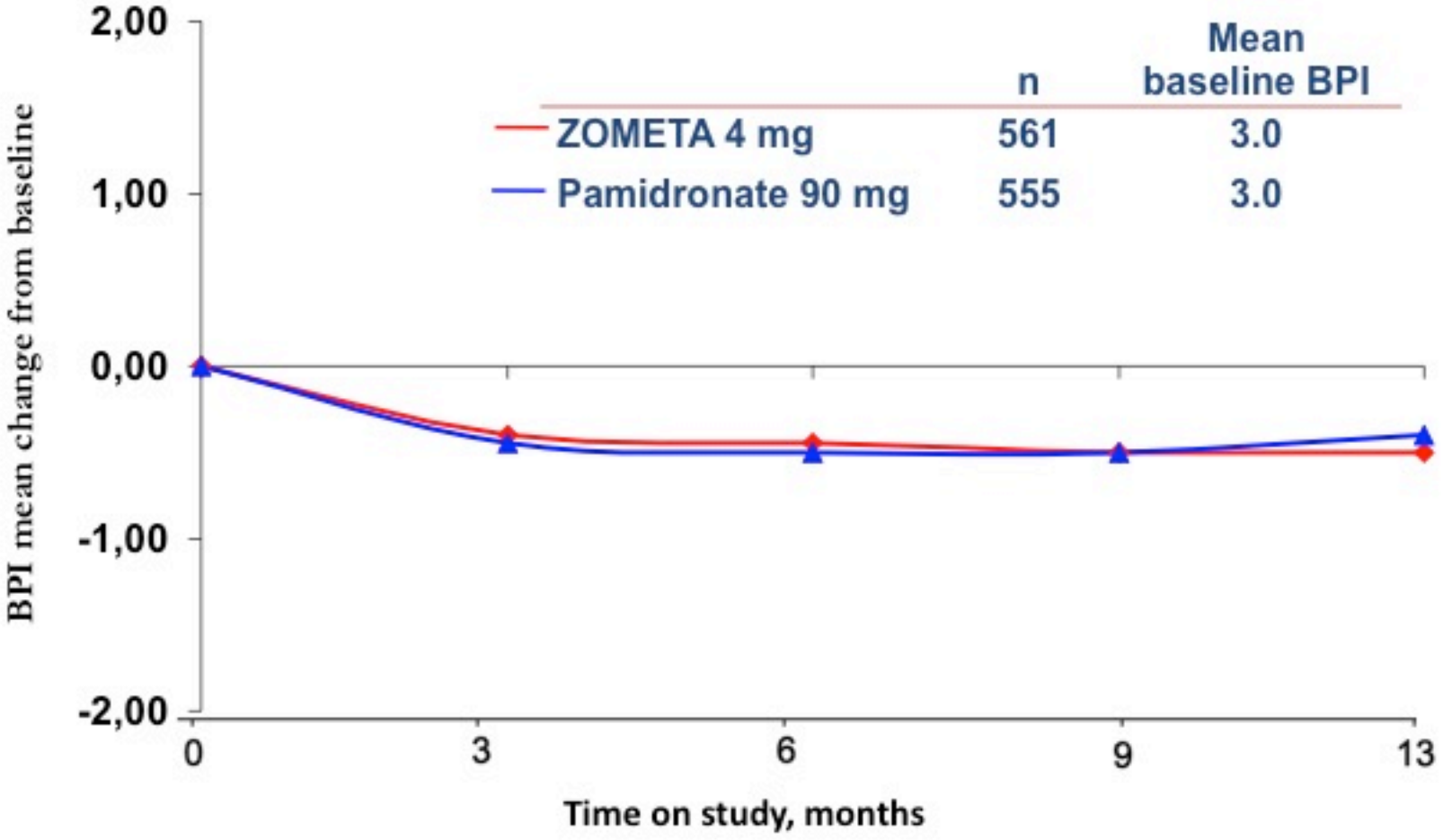
Skeletal Complication Risk

Incremental Benefits in Prostate Cancer (Time To First SRE)



Ford JA, European Journal of Cancer, 2013

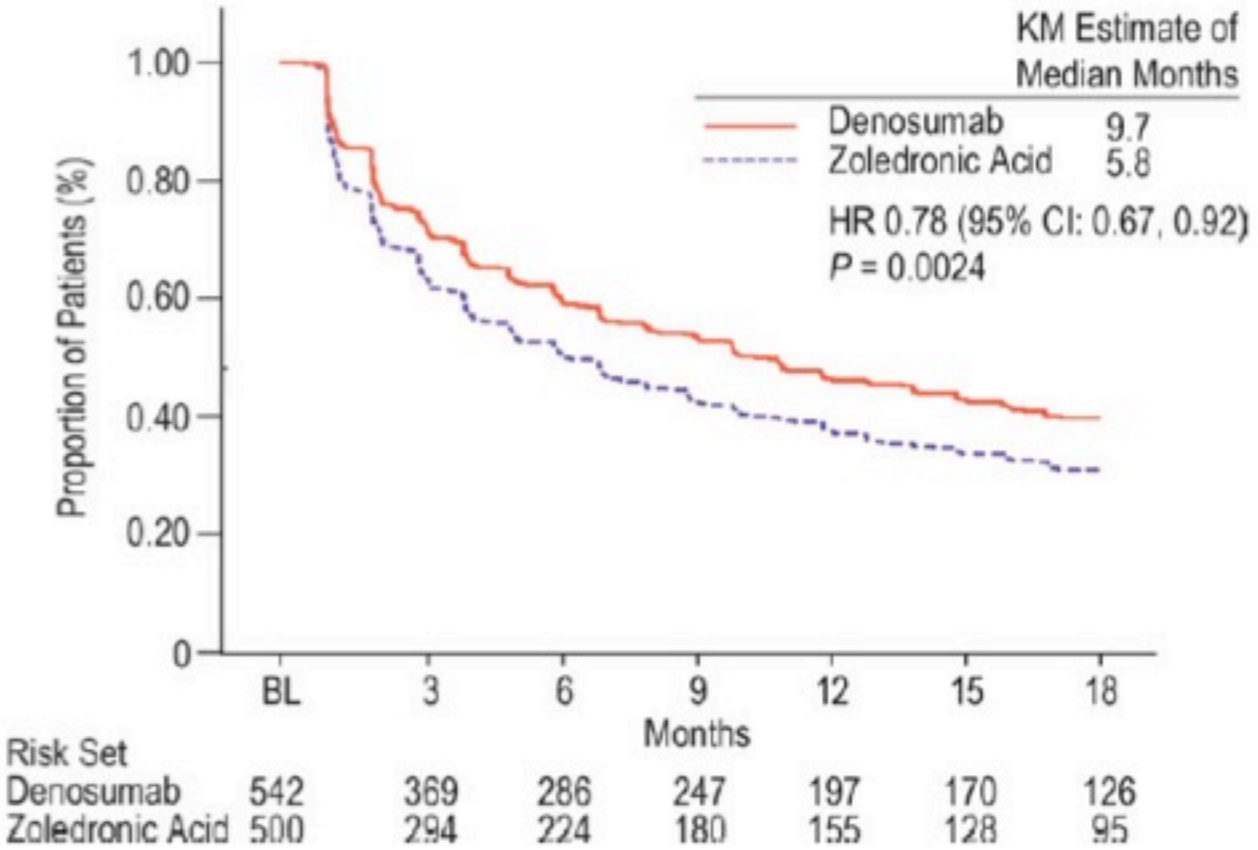
ZOMETA Reduces Bone Pain Similar to Pamidronate in Breast Cancer and Multiple Myeloma Patients



Adapted from Rosen L, et al. *Cancer J*. 2001;7:377-387.

Denosumab è più efficace di acido zoledronico nel ritardare il peggioramento del dolore (BC)

Patients progressing to moderate or severe pain (> 4 points) among patients with no or mild pain (0-4) at baseline



Cleeland CS et al. Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer. 2013 Feb 15;119(4):832-8.

Prevenzione/terapia
chi,come e per quanto tempo?

Linee guida AIOM 2017

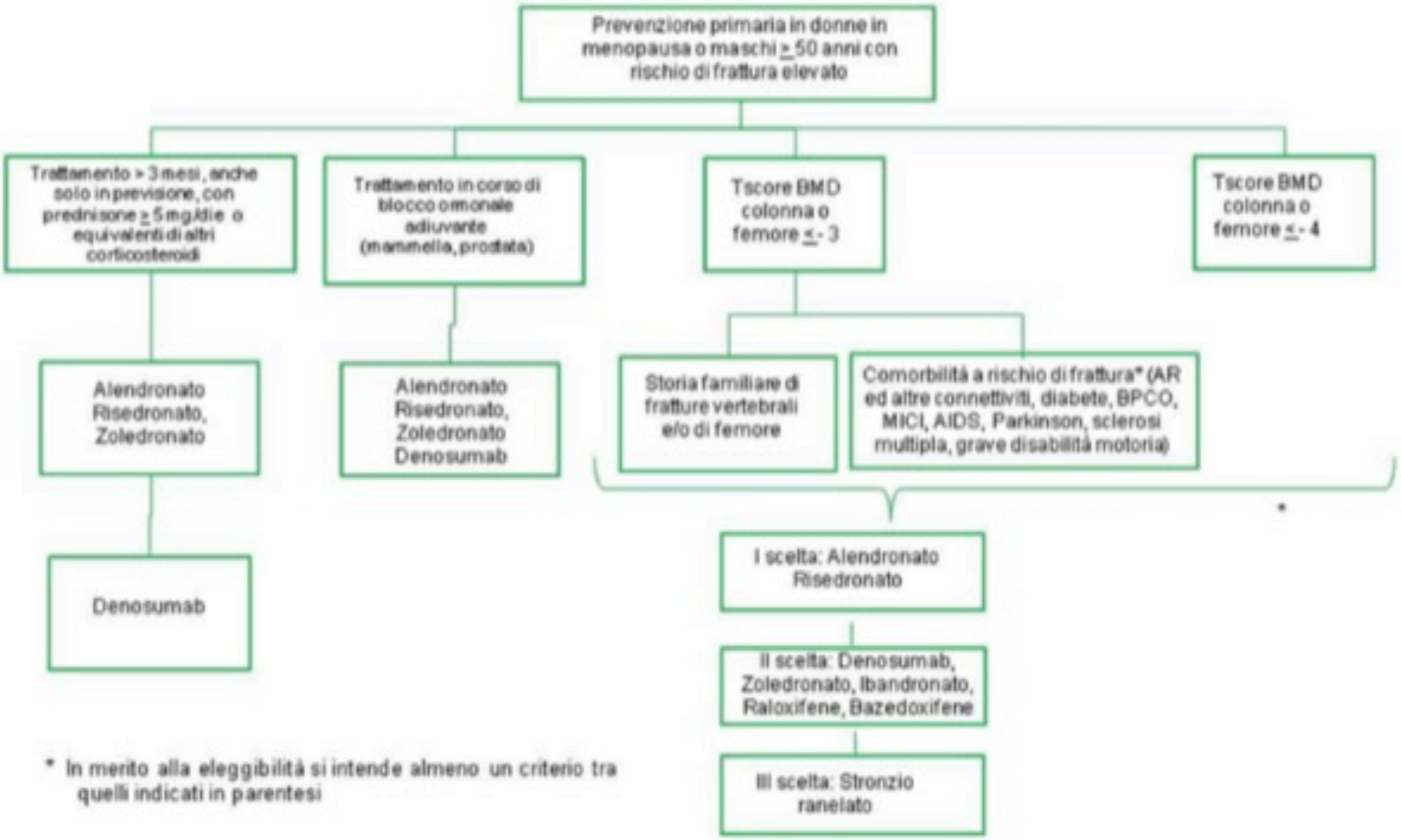
Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	Per le pazienti (pre e post-menopausa) in terapia ormonale adiuvante e per le pazienti con menopausa secondaria a chemioterapia andrebbe iniziata subito la terapia con inibitori del riassorbimento osseo (prevenzione primaria)	Positiva Forte

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	I bisfosfonati (in particolare l'ac zoledronico 4 mg/6 mesi) e Il denosumab 60 mg/ogni 6 mesi prevengono la perdita di BMD nella donna con tumore della mammella in pre e post-menopausa in terapia ormonale adiuvante e nel maschio con cr della prostata in blocco androgenico	Positiva Forte

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	Il denosumab 60 mg/ogni 6 mesi previene tutte le fratture da fragilità nella donna con tumore della mammella in postmenopausa in terapia con inibitori della aromatasi e le fratture vertebrali nel maschio con cancro della prostata in blocco androgenico	Positiva Forte

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
Bassa	Per i pazienti in terapia ormonale adiuvante pazienti la terapia con farmaci antiriassorbitivi andrebbe protratta per tutta la durata delle terapia ormonale adiuvante	Positiva Forte

Algoritmo per la l'applicazione in PREVENZIONE PRIMARIA della nota AIFA 79 (rimborsabilità farmaci per la prevenzione e la terapia dell'osteoporosi



* In merito alla eleggibilità si intende almeno un criterio tra quelli indicati in parentesi

GRAZIE PER L'ATTENZIONE