TUMORI SOLIDI E METASTASI OSSEE: QUALI NOVITA' PER il 2015

Le Metastasi ossee da tumori solidi : patogenesi, incidenza e manifestazioni cliniche

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UNIVERSITA' DI VERONA

Elevato turnover osseo nei pazienti con PC

ELEVATO TURNOVER OSSEO
(eta' –livelli vit D – Terapia ormonale adiuvante- metastasi)

CTIBL
FRAGILITÀ

PROGRESSIONE
OSSEA

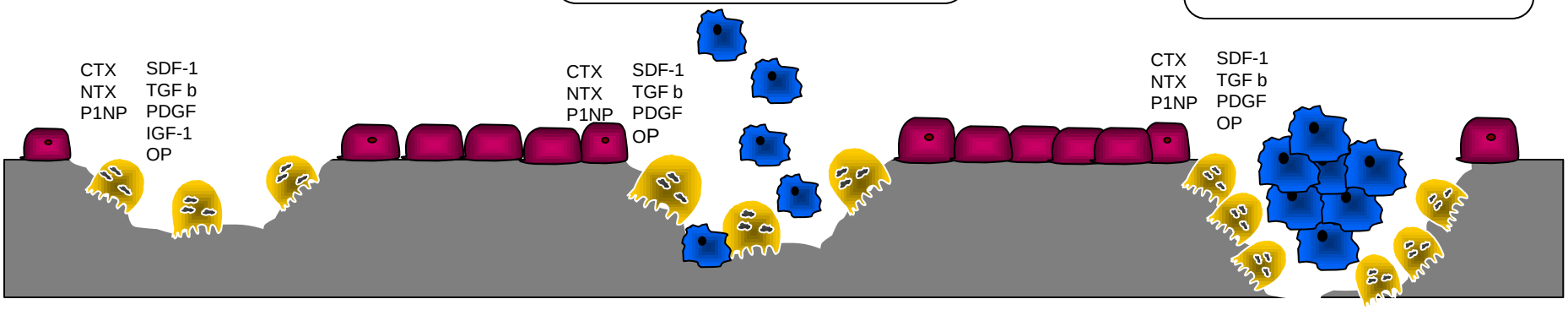
SRE

Nuova metastasi

Perdita ossea

Homing delle cellule tumorali

Crescita della metastasi ossea

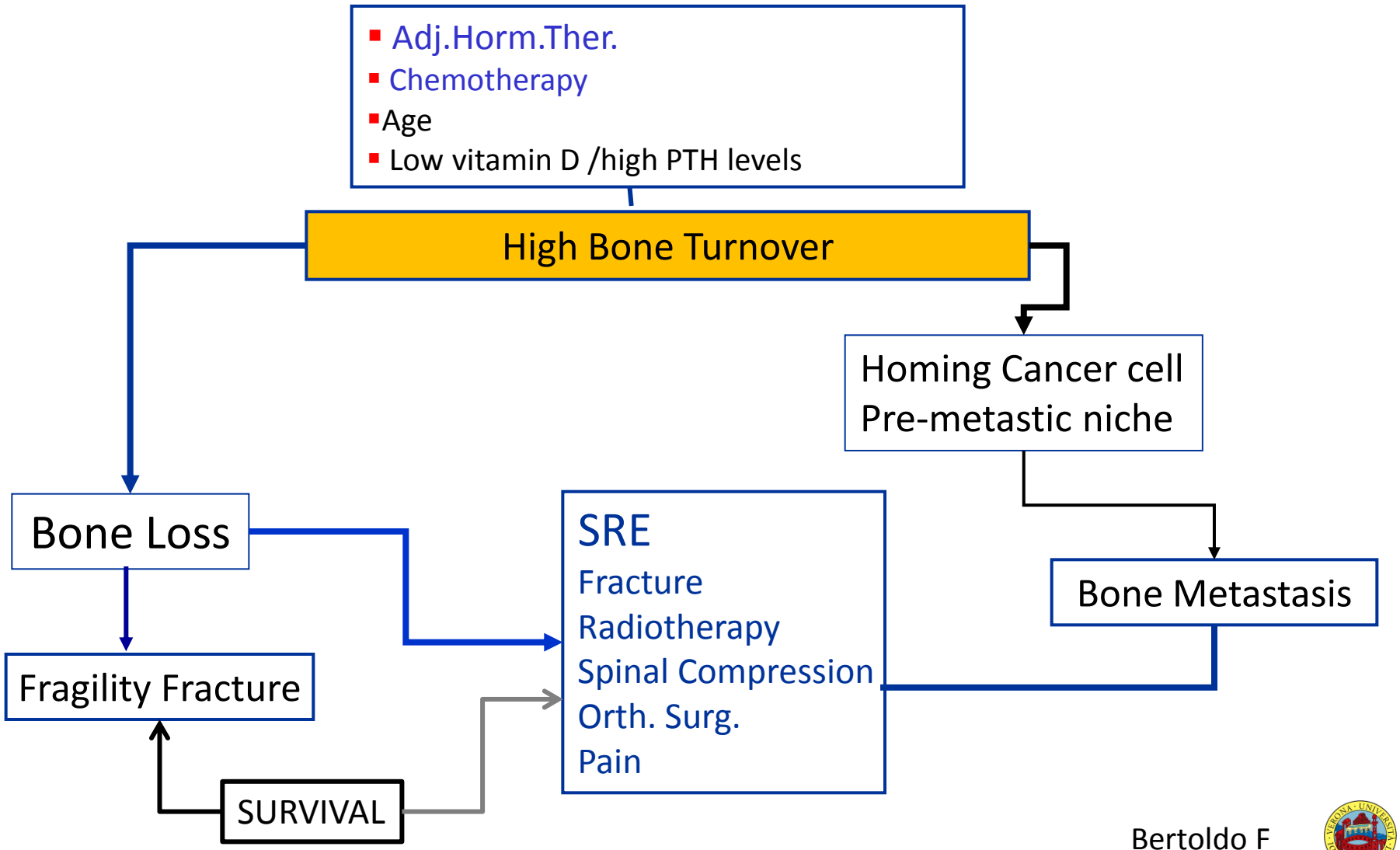


Scheletro non metastatico

Nicchia premetastatica

Metastasi ossea

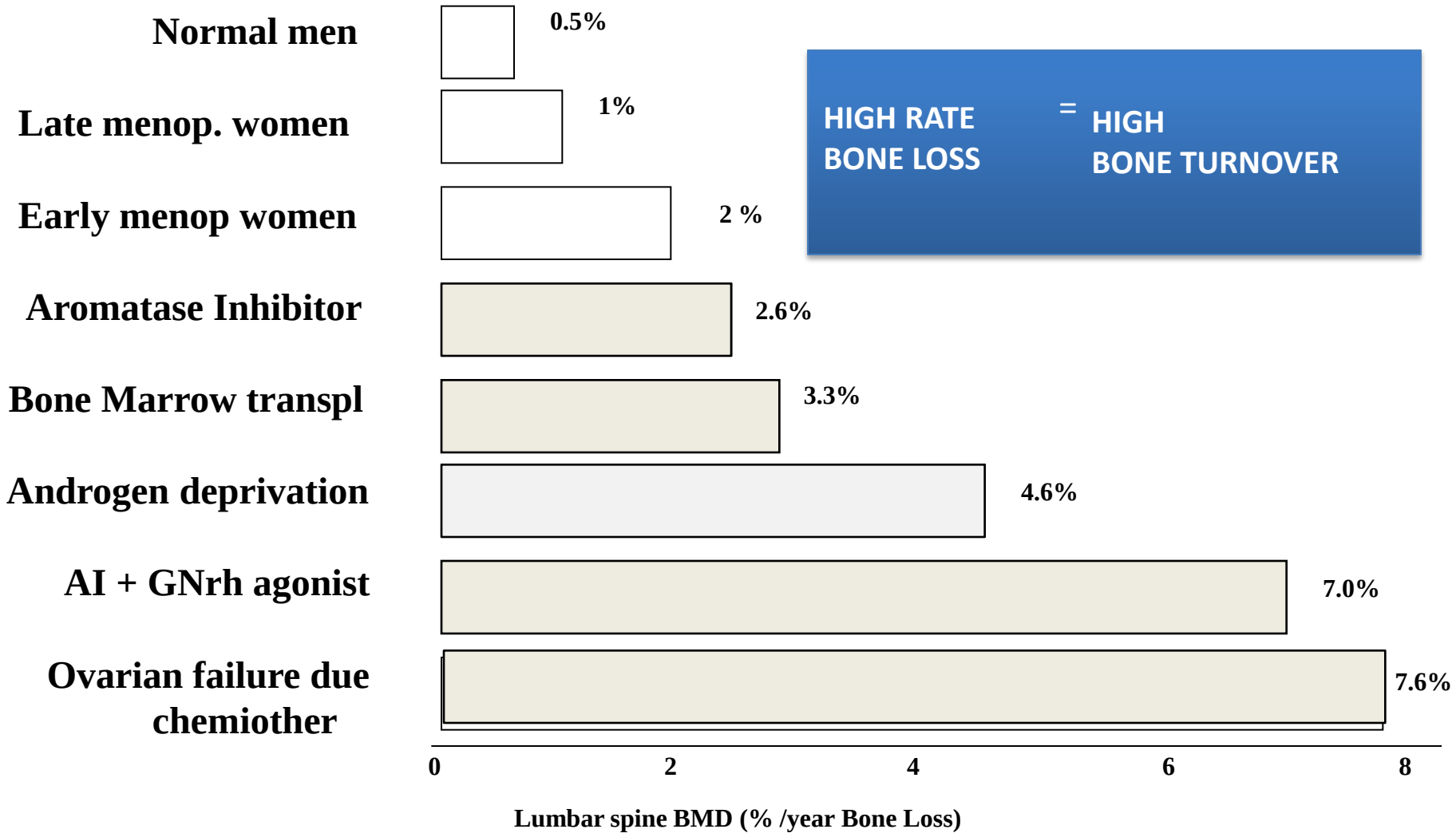
The “Bone Health” concept in Prostate Cancer Patients



Bertoldo F

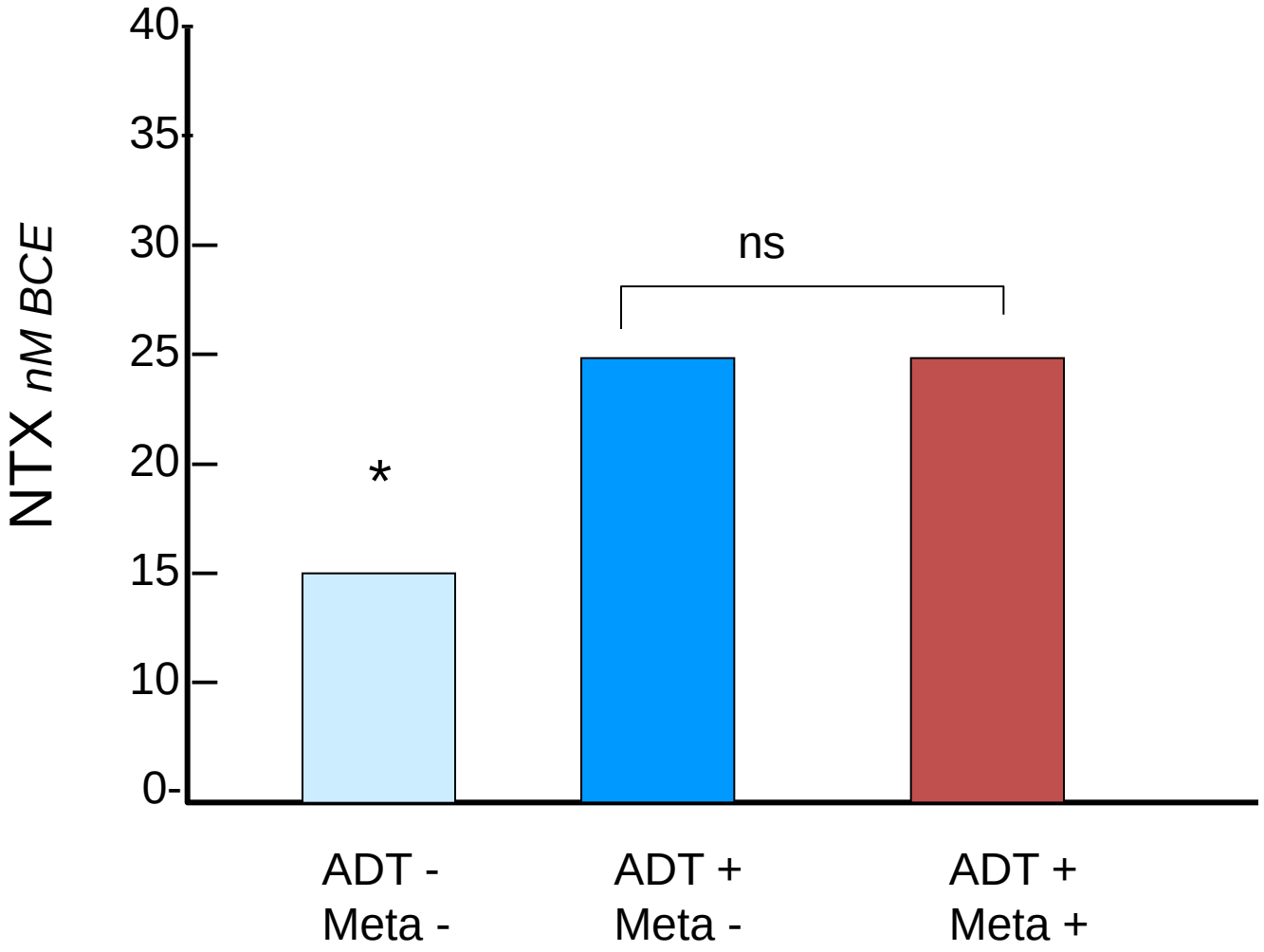
CANCER TREATMENT INDUCED BONE LOSS

Rate of BMD Loss



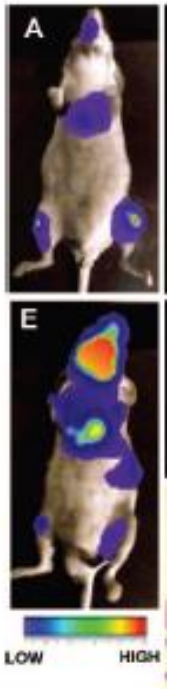
Brown SA, Guise TA Crit Rev Eukaryot Gene Expr 2009;19:47-60

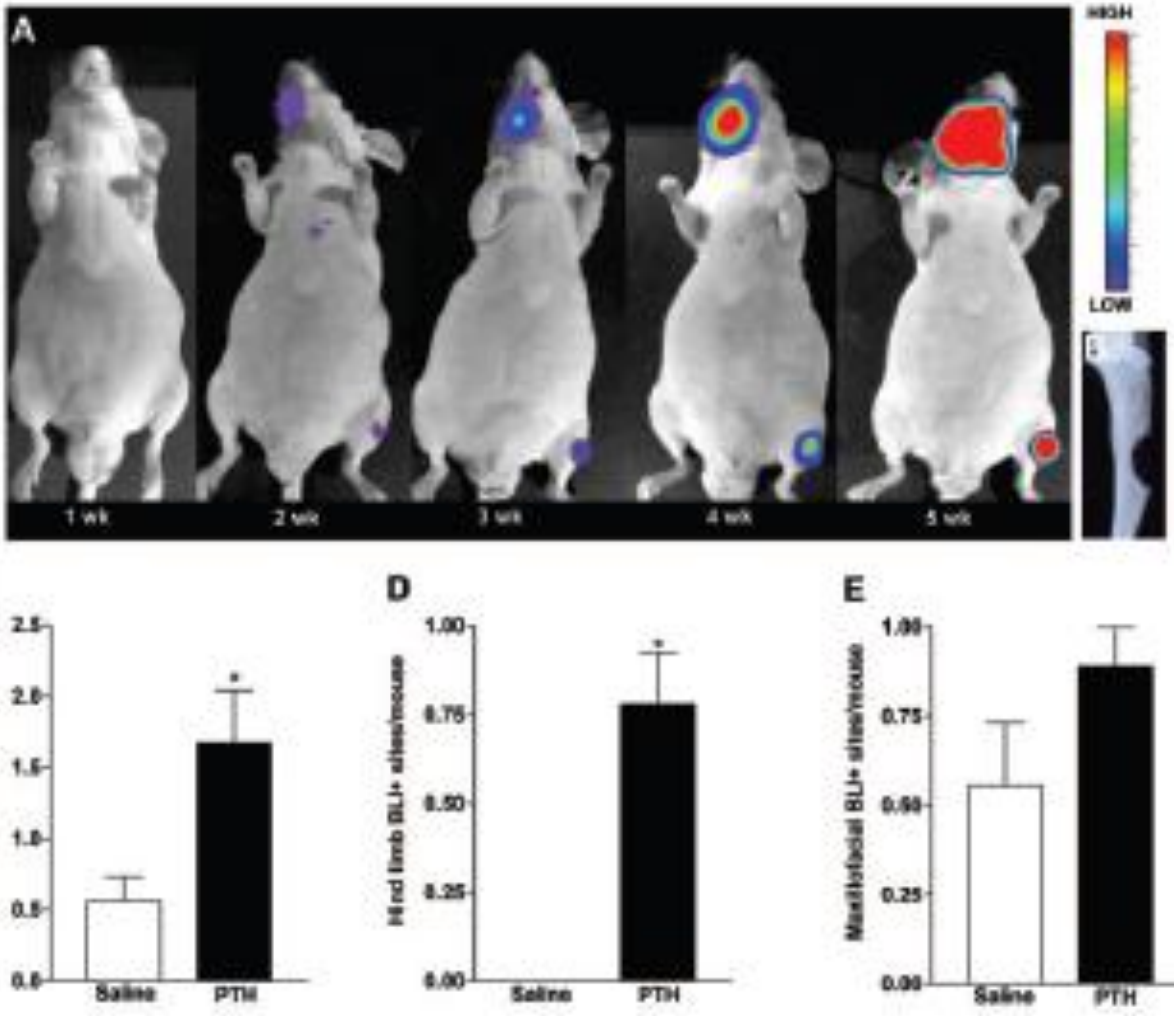
Contribution of Androgen Deprivation Therapy to Elevated Bone Turnover in Men with Metastatic Prostate Cancer



Michaelson MD et al *Clin Canc Res 2004*

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

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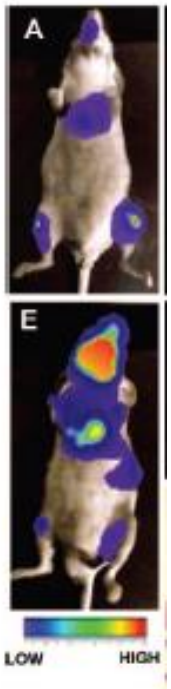
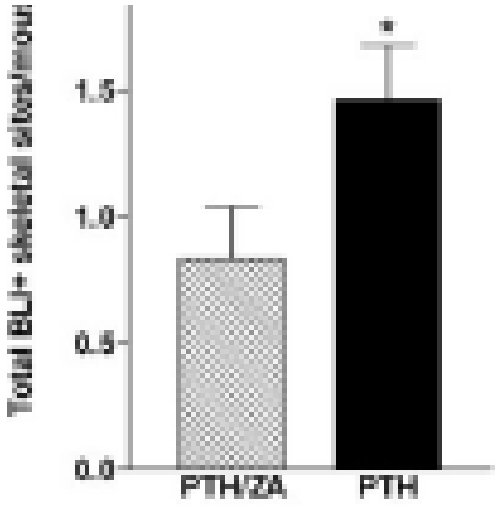
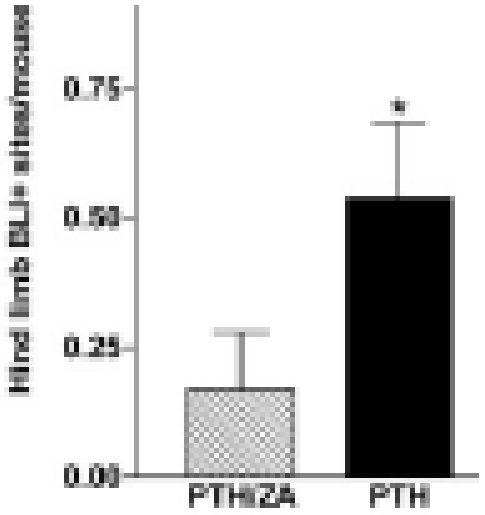
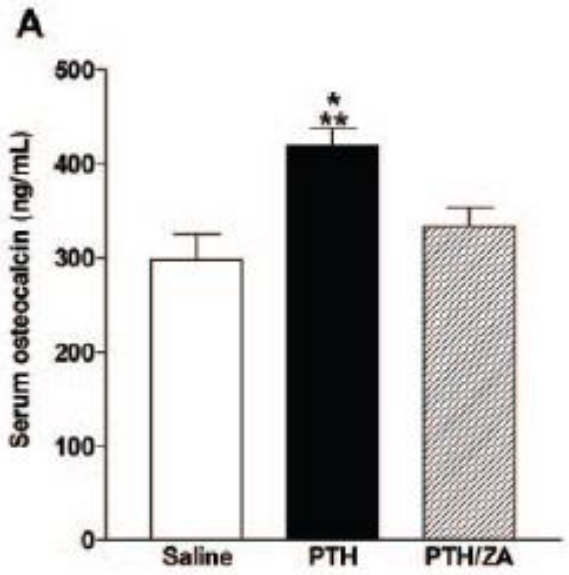
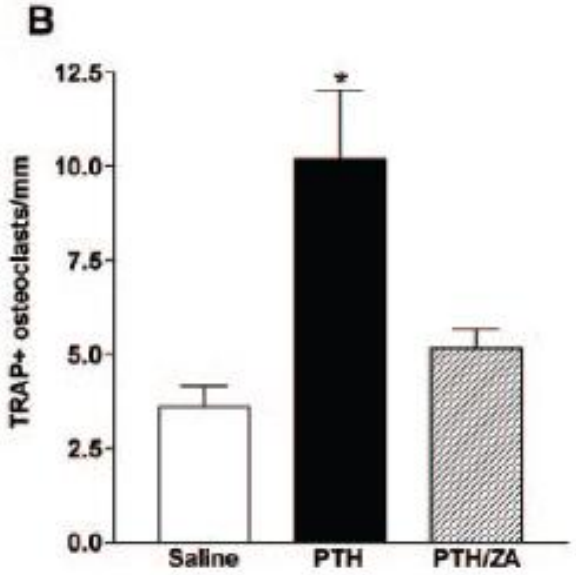


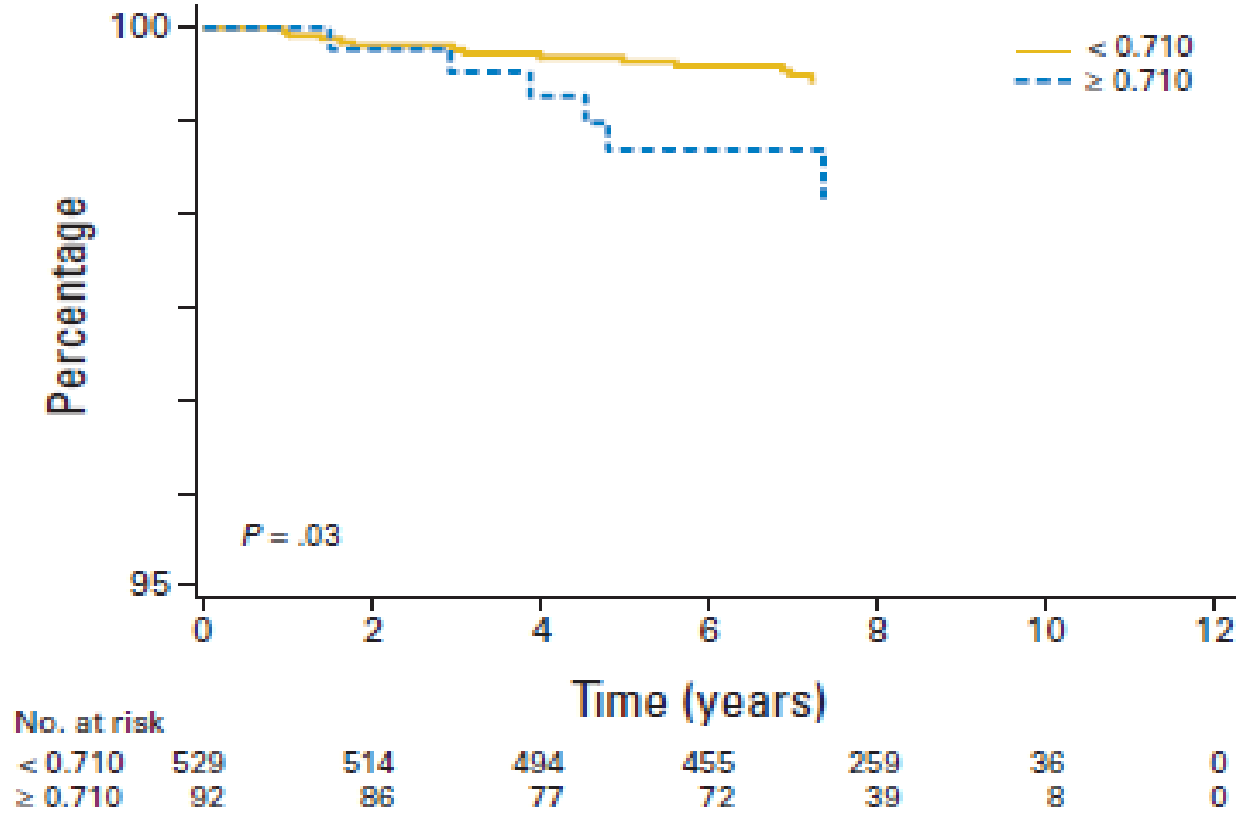








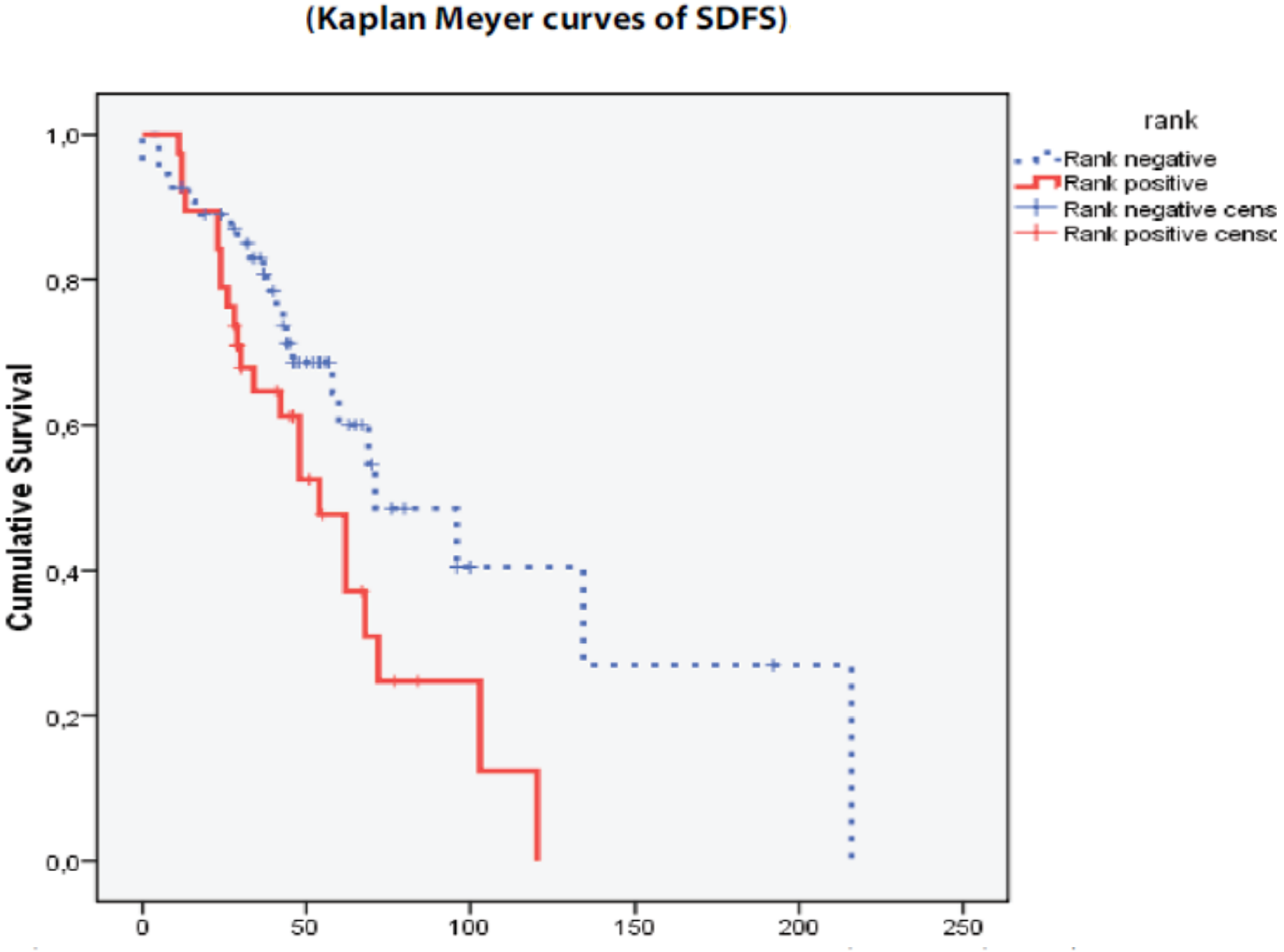
Elevated Bone Turnover Predicts for Bone Metastasis in Postmenopausal Breast Cancer: Results of NCIC CTG MA.14



Pretreatment serum CTX (>0.710,) preditcs bone only relaps

Lipton A *J Clin Oncol 2011*

RANK expression associates with accelerated bone metastasis in 93 breast cancer patients



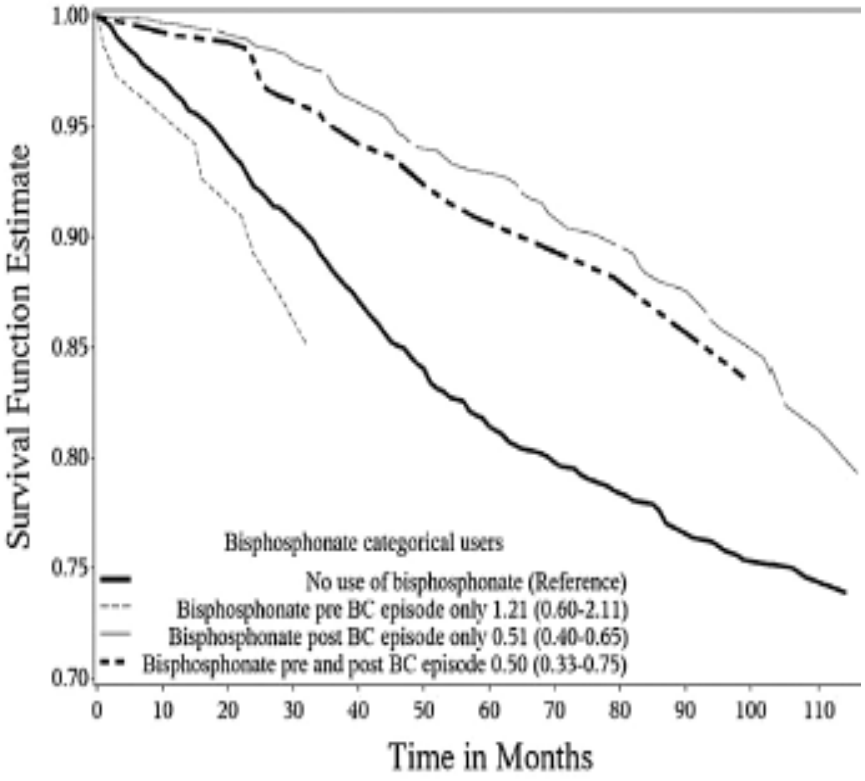
RANK negative patients showed a SDFS of 105.7 months (95% C.I: 73.9–124.4) compared with only 58.9 months (95% C.I: 34.7–68.5) in RANK positive patients. The difference is statistically significant ($P = 0.034$).

Santini D et al *PlosOne 2011*

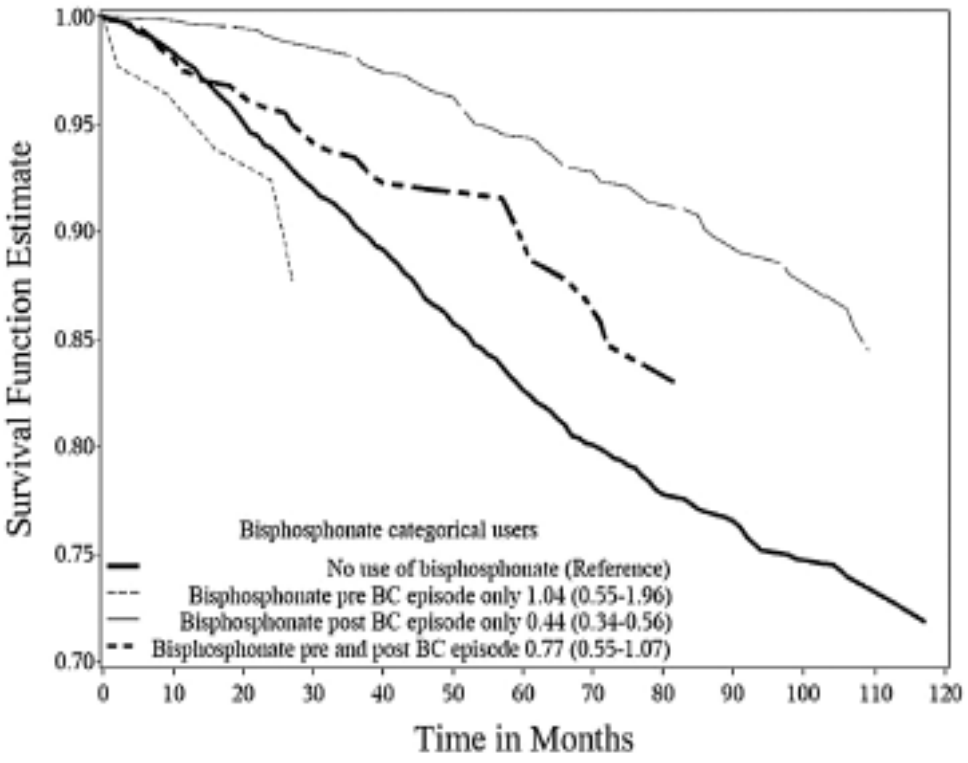
Effect of Oral Bisphosphonates for Osteoporosis on Development of Skeletal Metastases in Women With Breast Cancer: Results From a Pharmaco-Epidemiological Study

21.6664 BC pt 10 yr follow up

TIME TO BONE METASTASIS

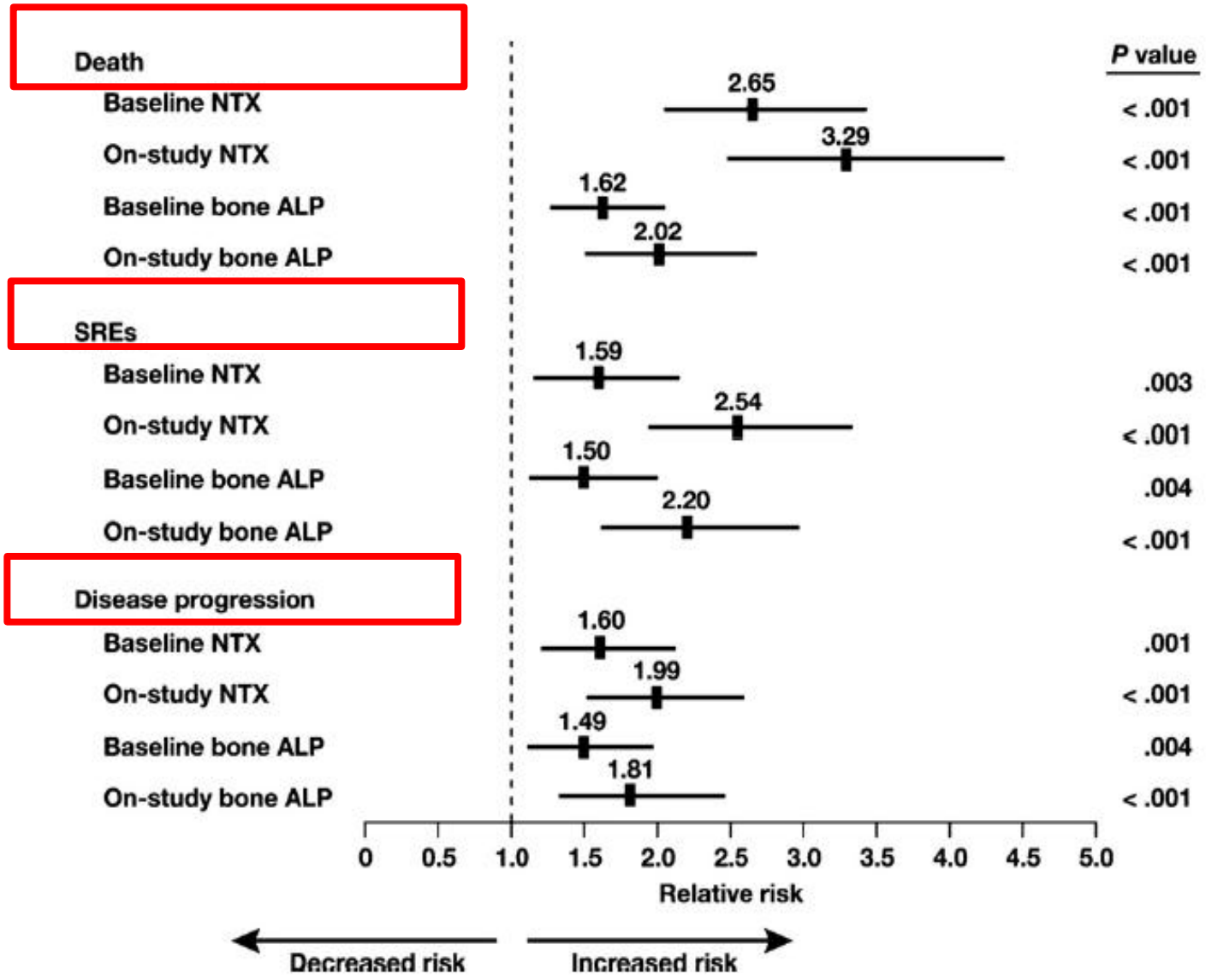


TIME TO CANCER SPECIFIC MORTALITY



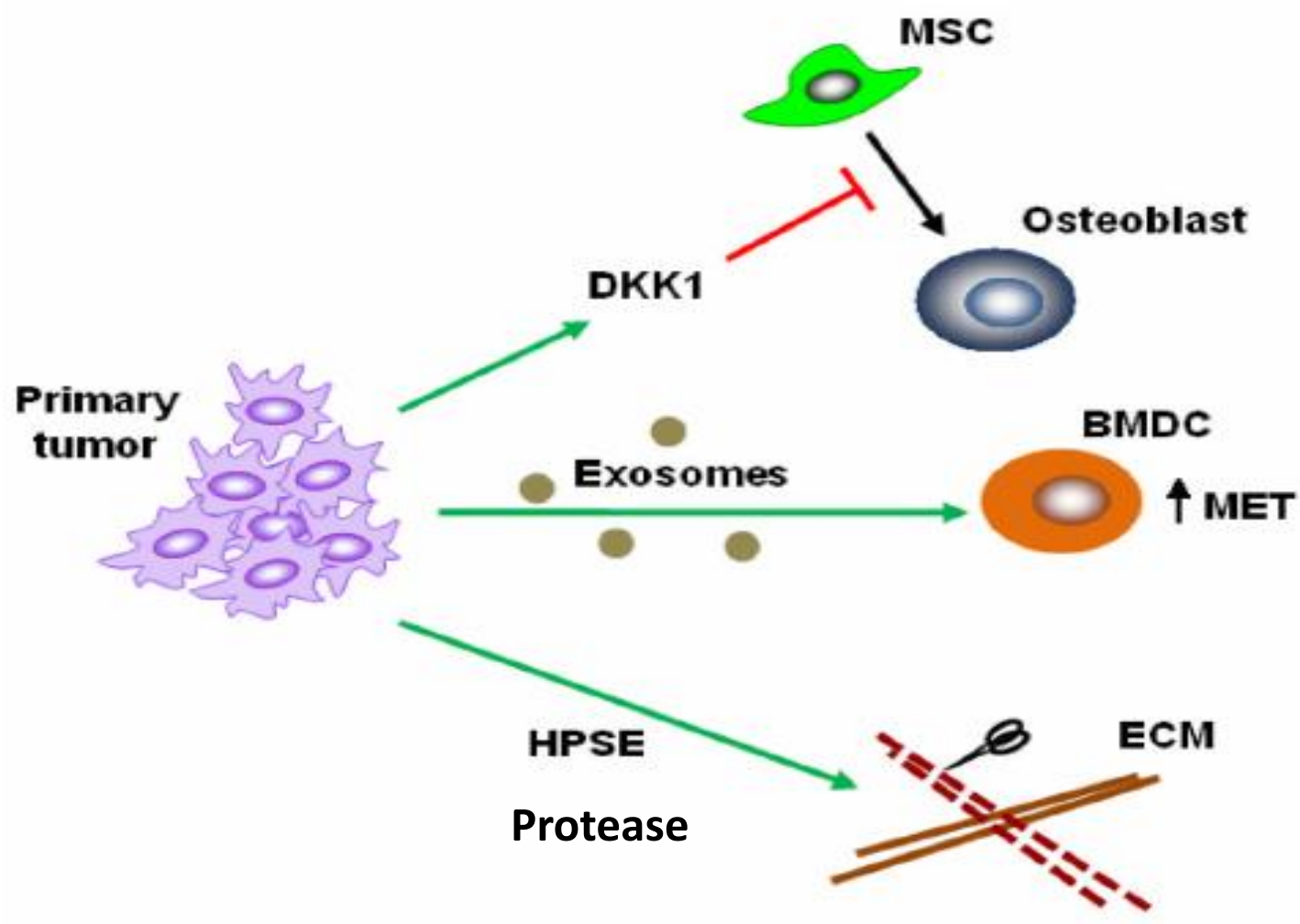
Kremer R et al *JNCI 2014*

CORRELATIONS BETWEEN BONE TURNOVER AND CLINICAL OUTCOME IN PATIENTS WITH BONE METASTASES FROM SOLID TUMORS (NO BPs)



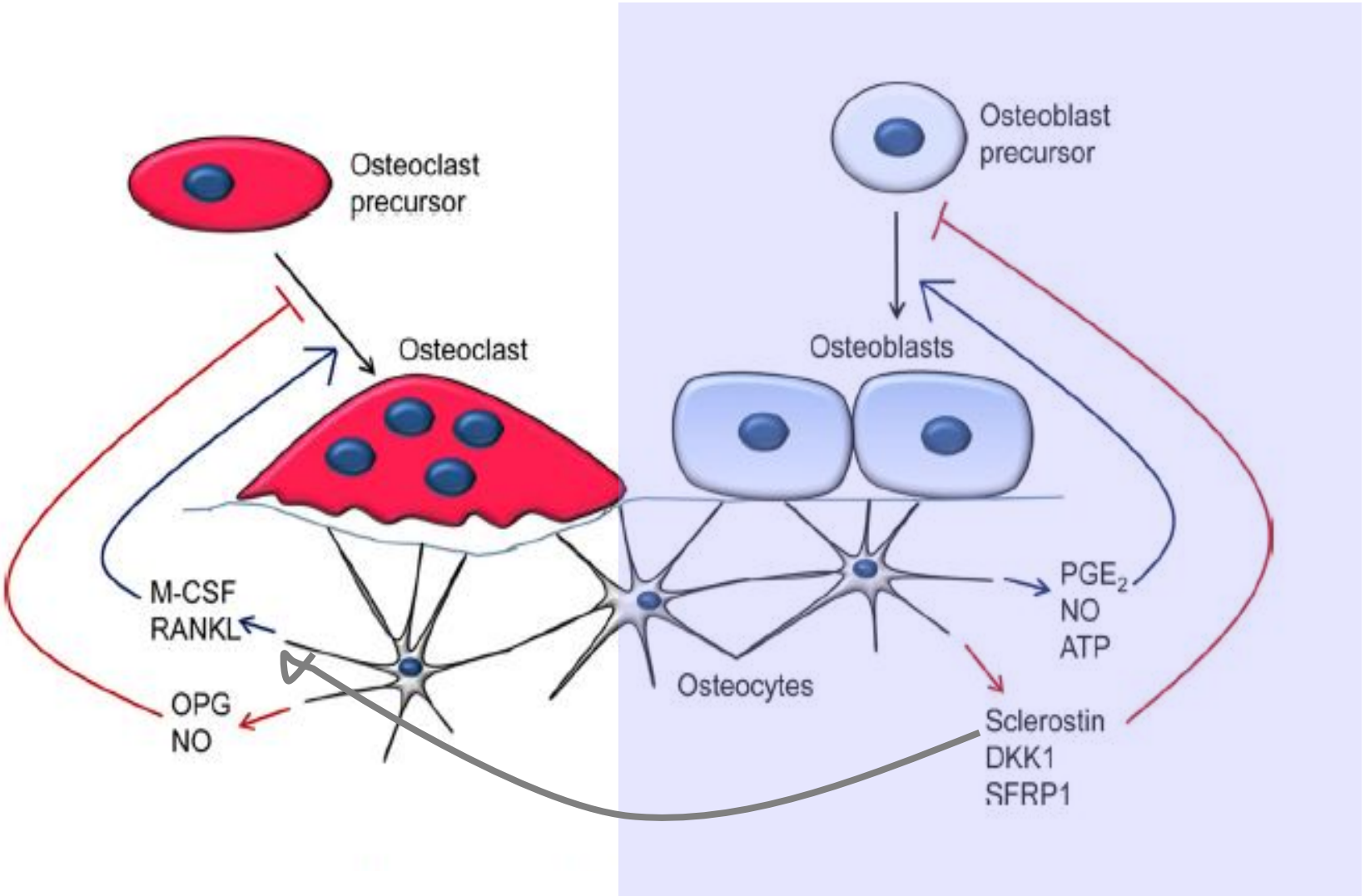
Robert Coleman [a,*] Critical Reviews in Oncology/Hematology xxx (2011) xxx–xxx

Targeting tumor-stromal interactions in bone metastasis



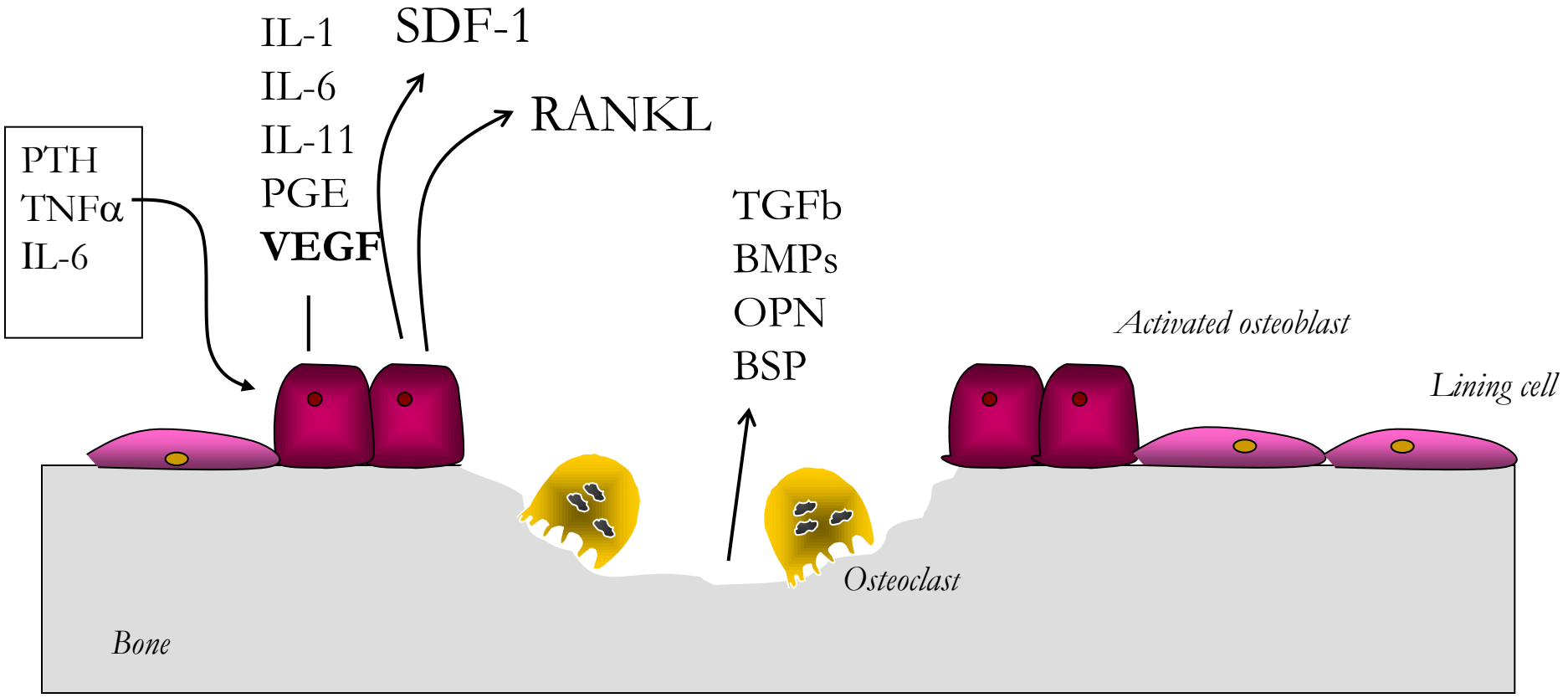
Esposito M. *Pharmacol Ther*. 2014 February ; 141(2): 222–233.

Osteocyte regulation of bone remodeling



Kowgawa M J Bone Miner Res 2013

Dallas SL et al. Endocr Rev, 2013

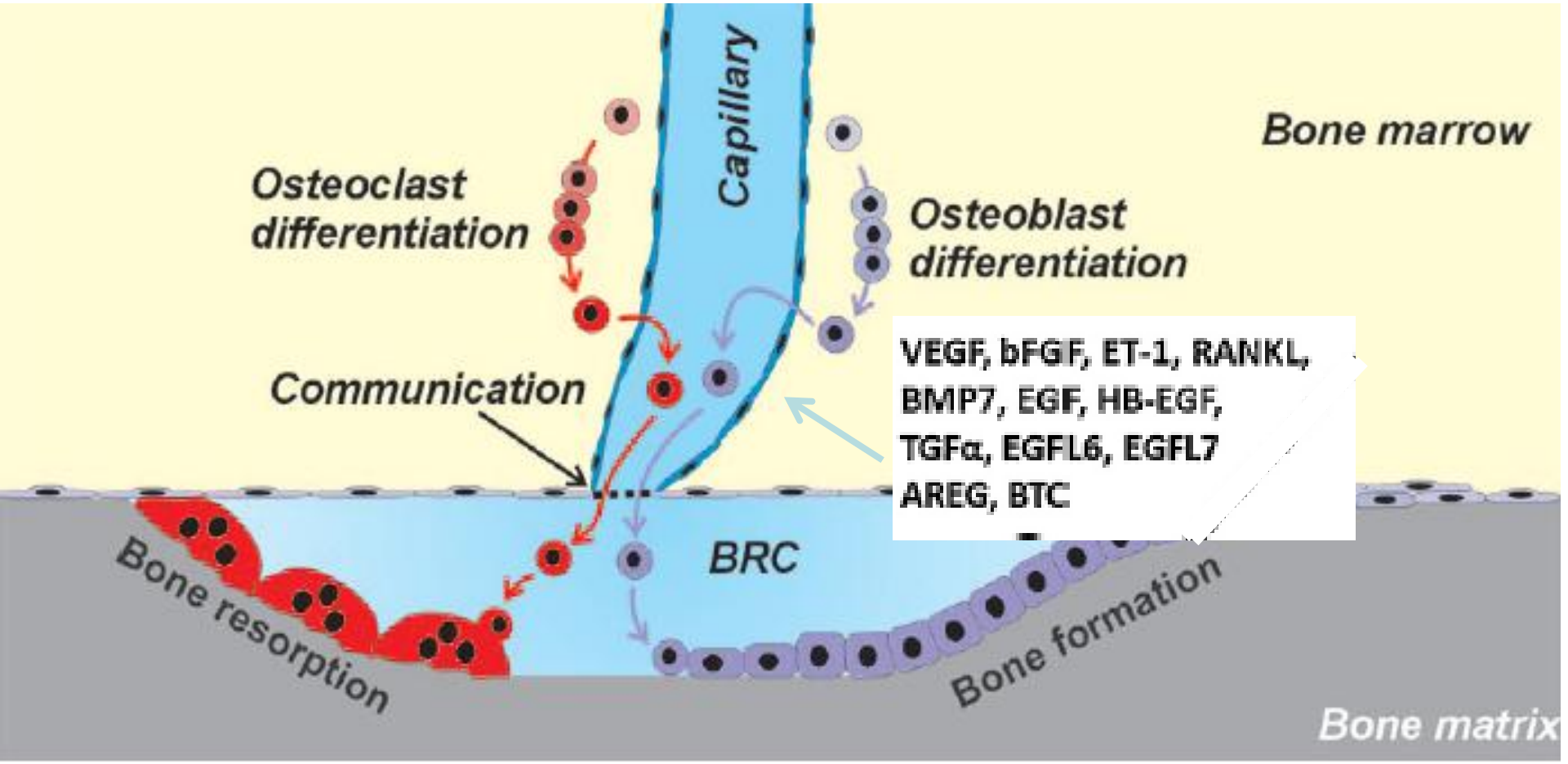


Bertoldo F, *Textbook of Osteoncology 2009*

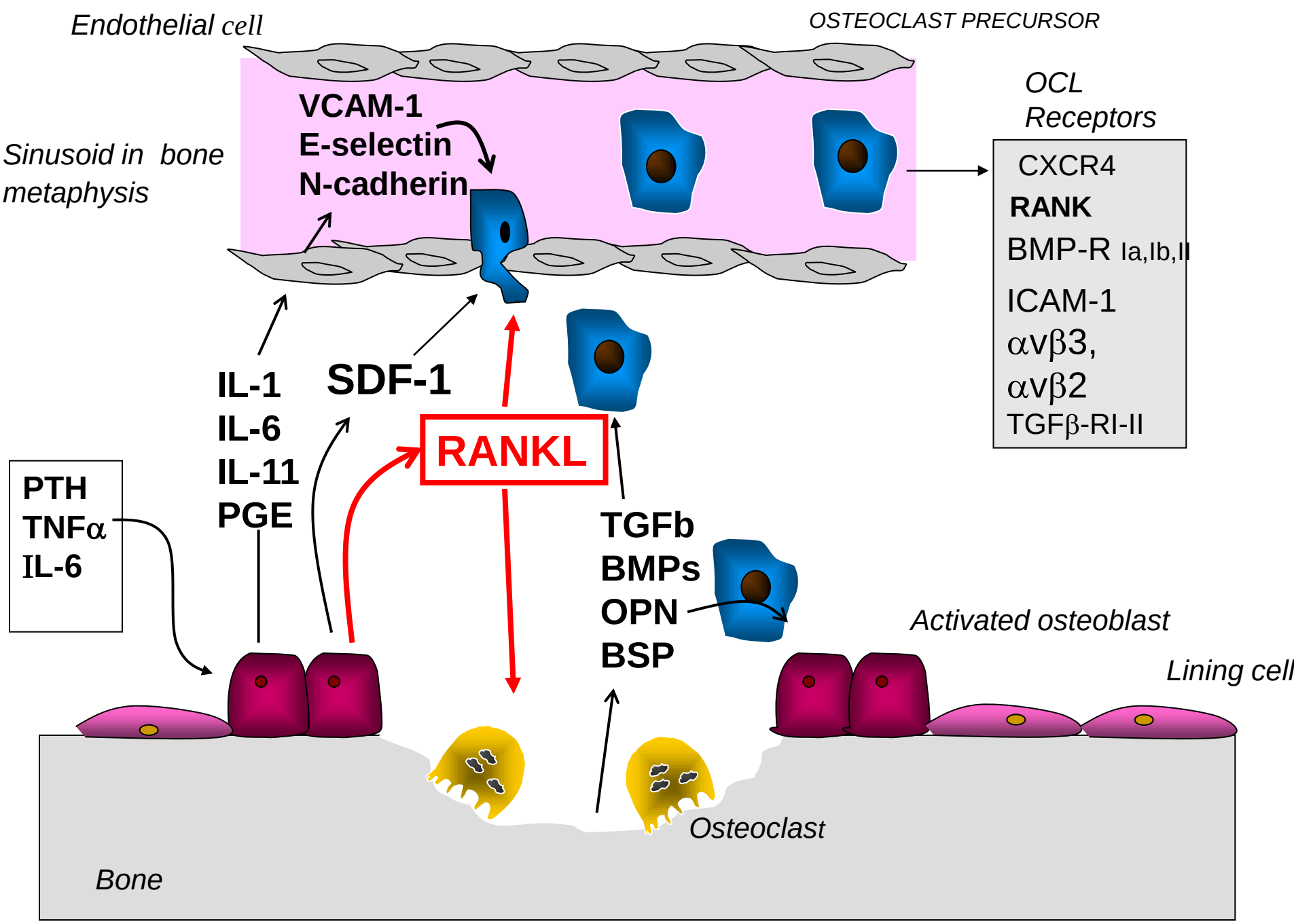
A Physical Mechanism for Coupling Bone Resorption and Formation in Adult Human Bone

Angiogenic factors in bone local environment

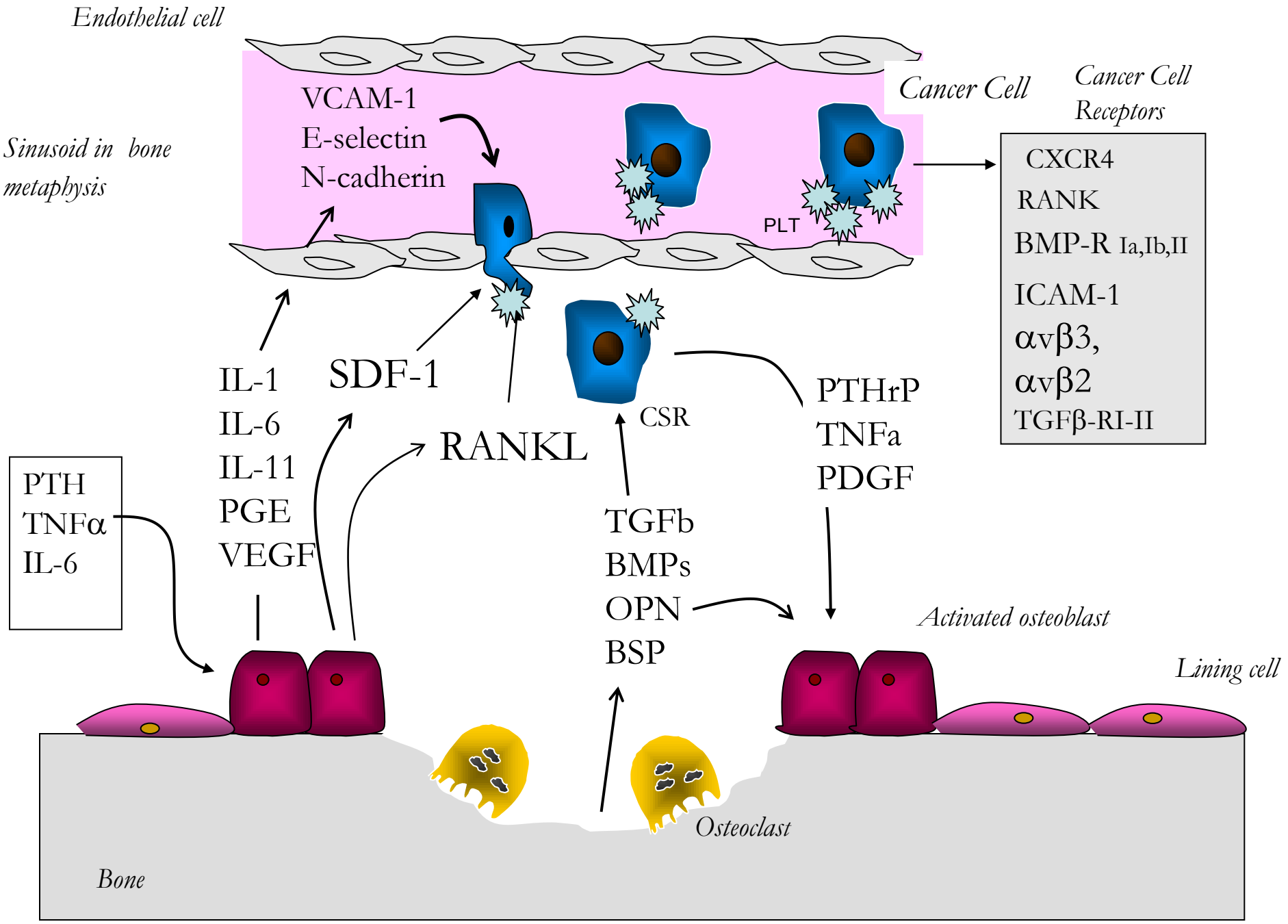
BRC= Bone Remodeling Compartment



Chim SM Cytokine & Growth Factor Reviews 24 (2013) 297–310 Andersen TL et al Am J Pathol 2009

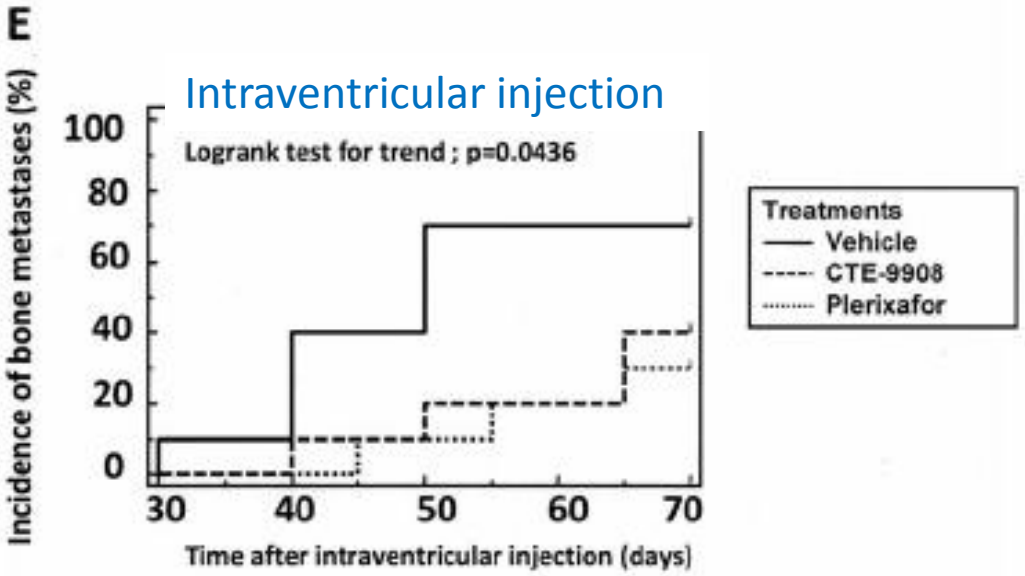


Bertoldo F, Santini D .Textbook of Osteoncology 2009

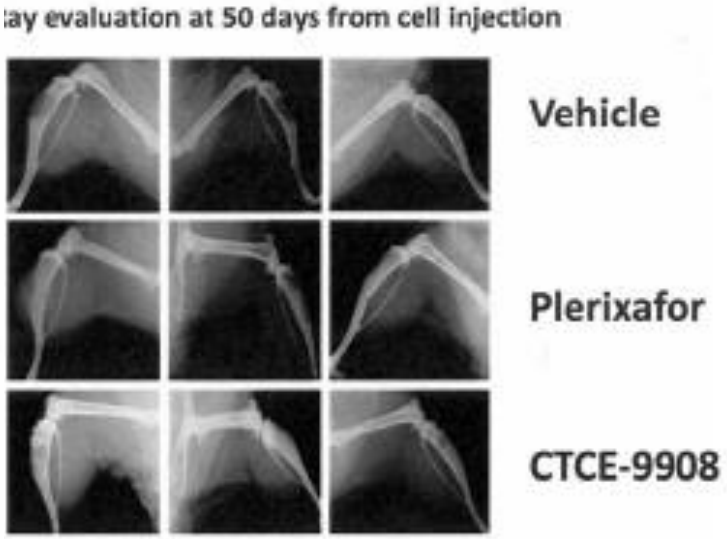


Bertoldo F, *Textbook of Osteoncology 2009*

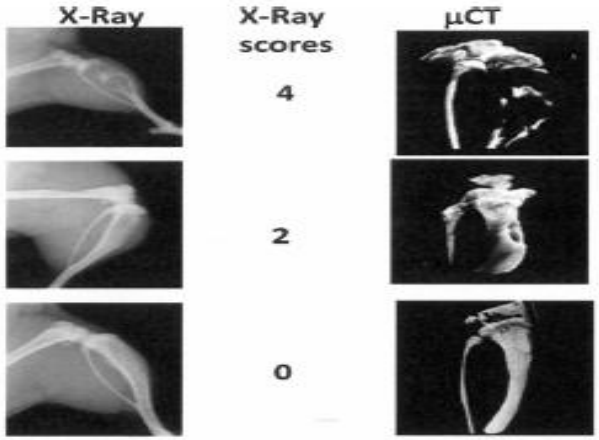
CXCR4 pharmacological Inhibition Reduces Bone Metastatic Burden



Intraventricular injection



Intratibial injection of PC3 cells

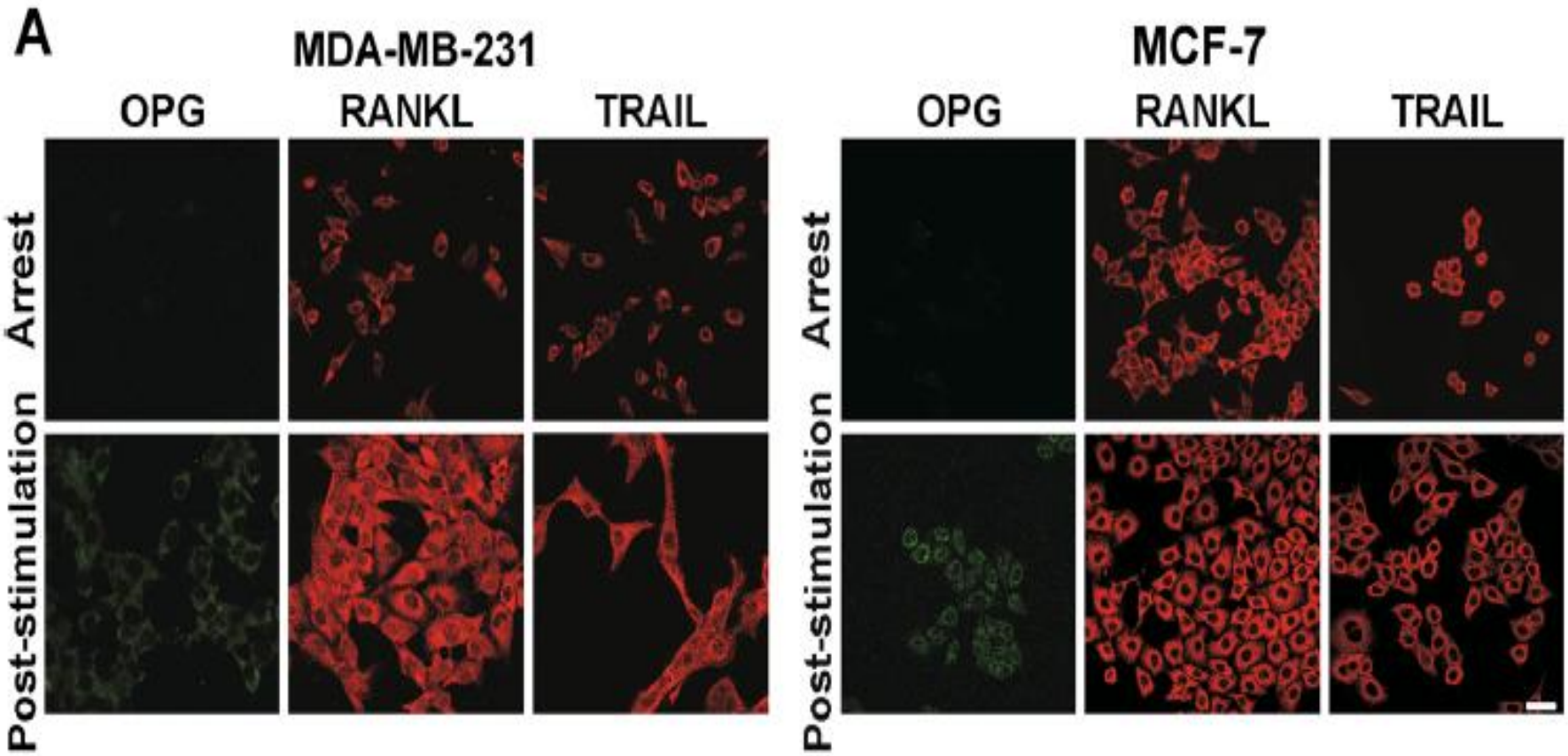


Tibiae with osteolytic lesions

X-Ray scores	≤ 2	≥ 3
Vehicle	2/10	8/10
plerixafor	7/10	3/10
CTCE-9908	5/10	5/10

The Prostate 75:1227–1246 (2015)

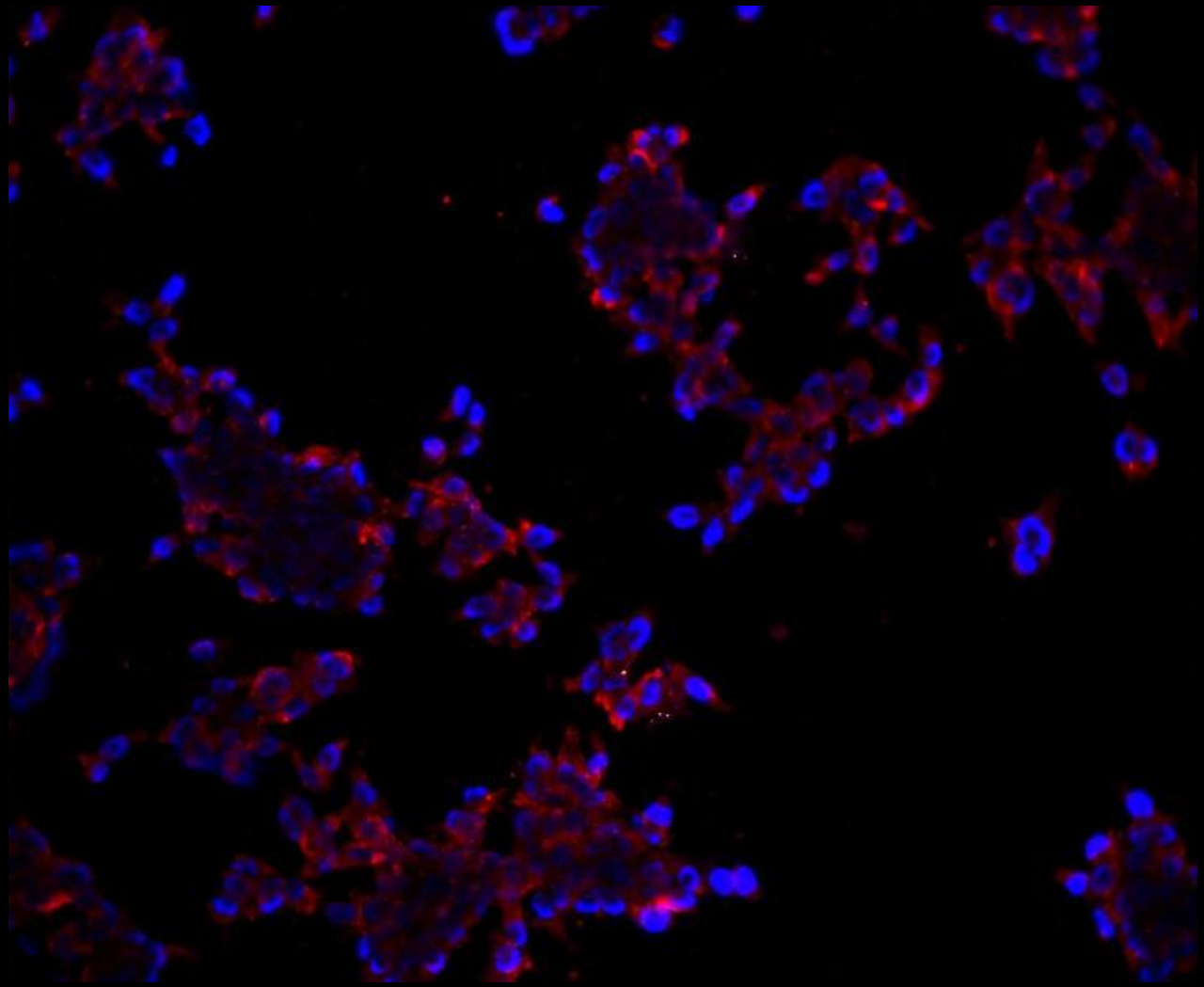
Expression of OPG, RANKL and TRAIL in both BC cell lines.



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

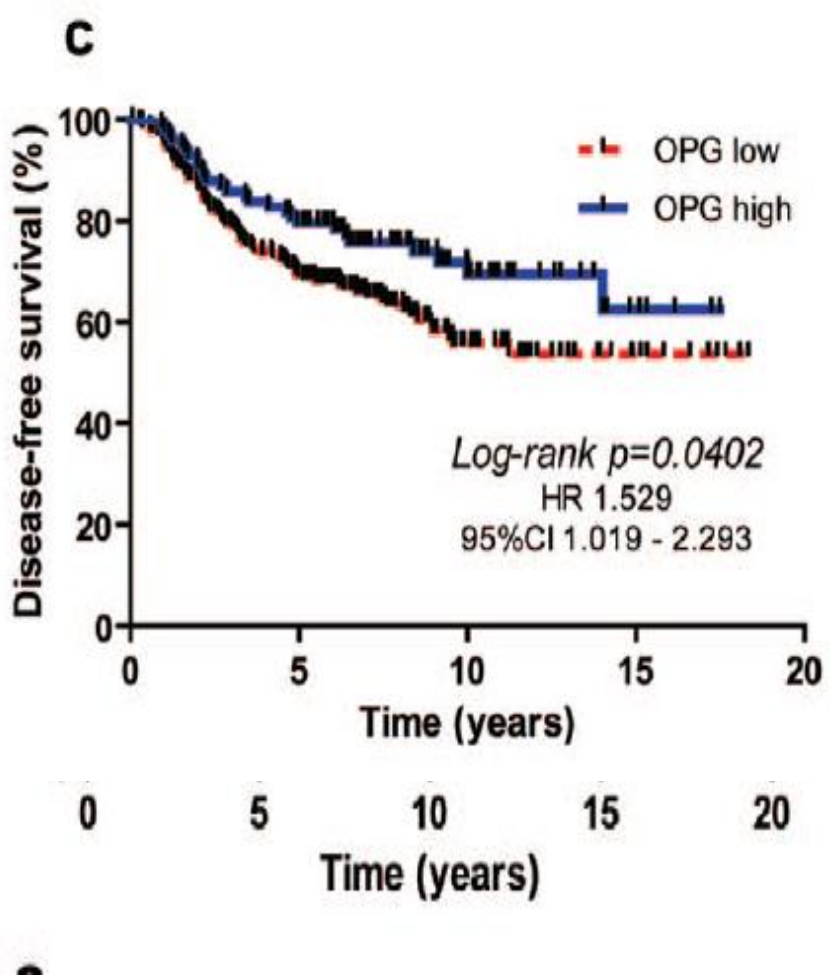
RANK IS EXPRESSED IN ANDROGEN-DEPENDENT PROSTATE CANCER CELL LINE LNCaP

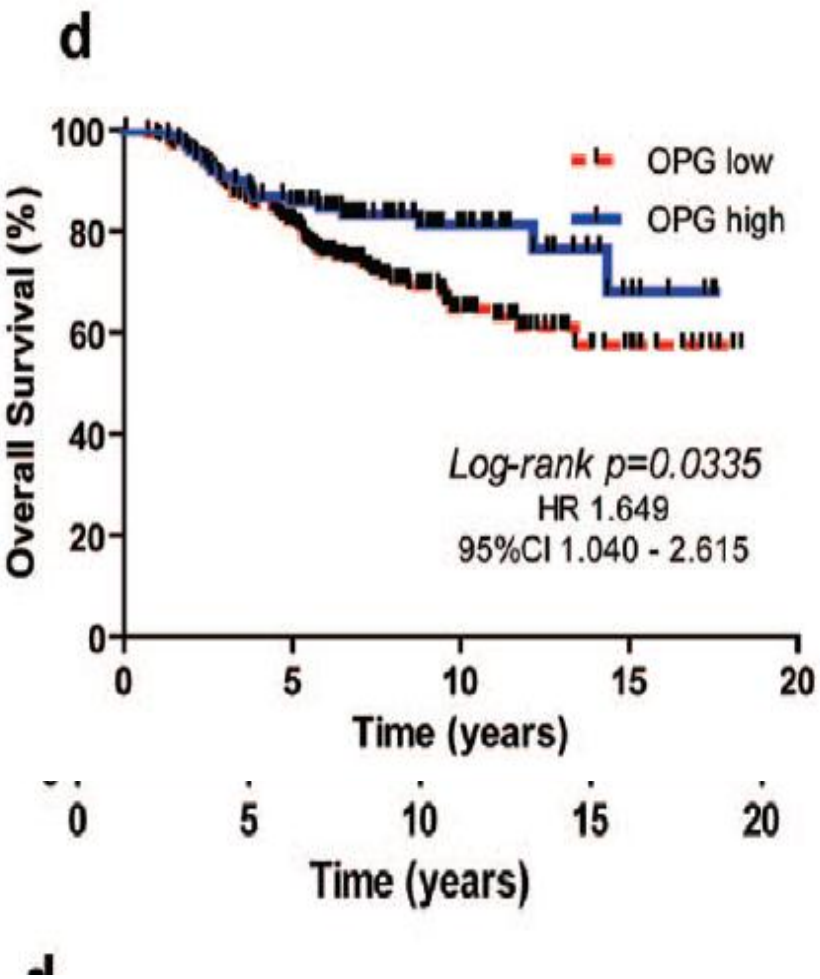
Immunofluorescence assays



Courtesy of Dott. M.Fioramonti

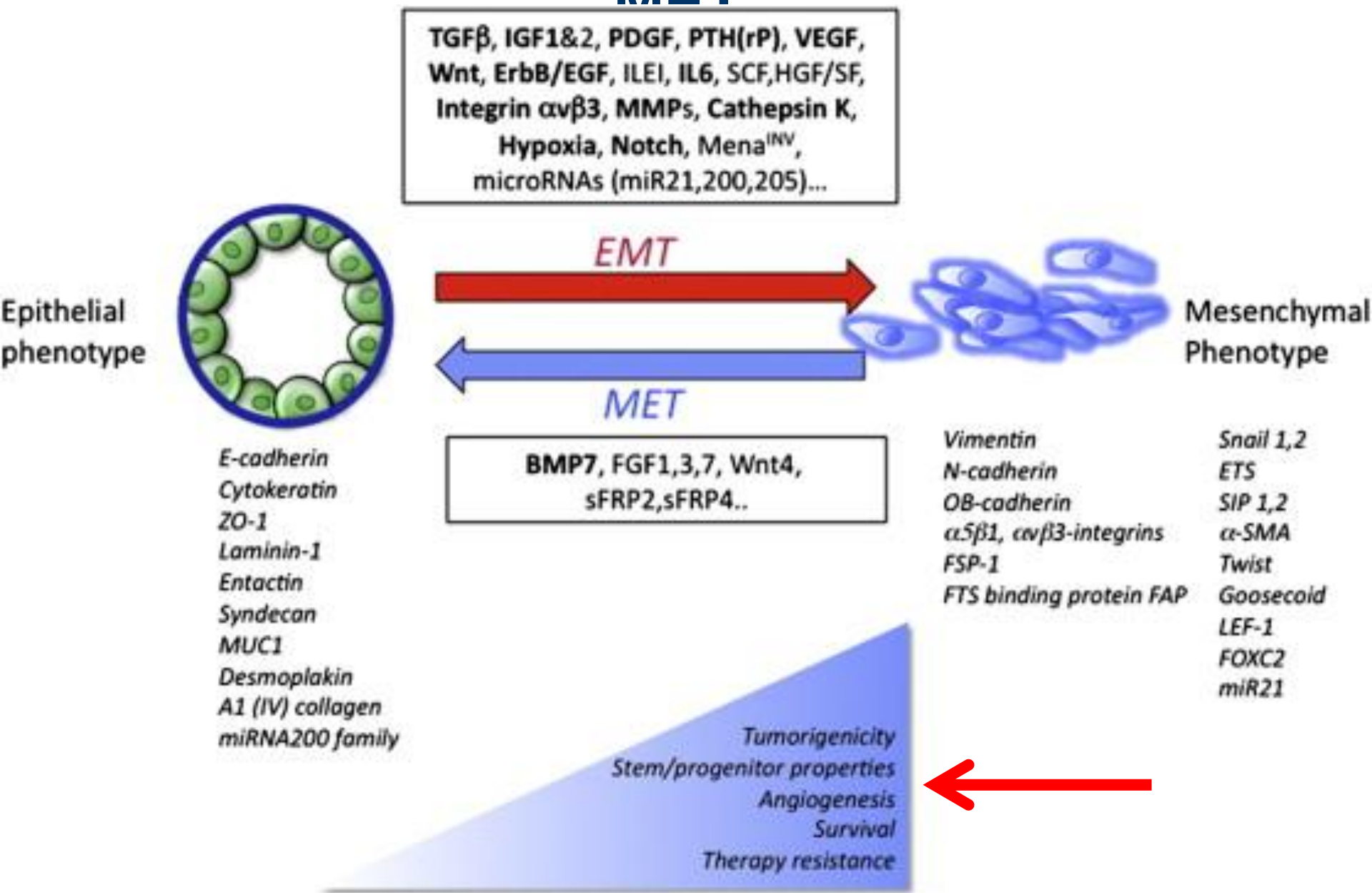
Receptor Activator of NF-kB (RANK) Expression in Primary Tumors Associates with Bone Metastasis Occurrence in Breast Cancer Patients



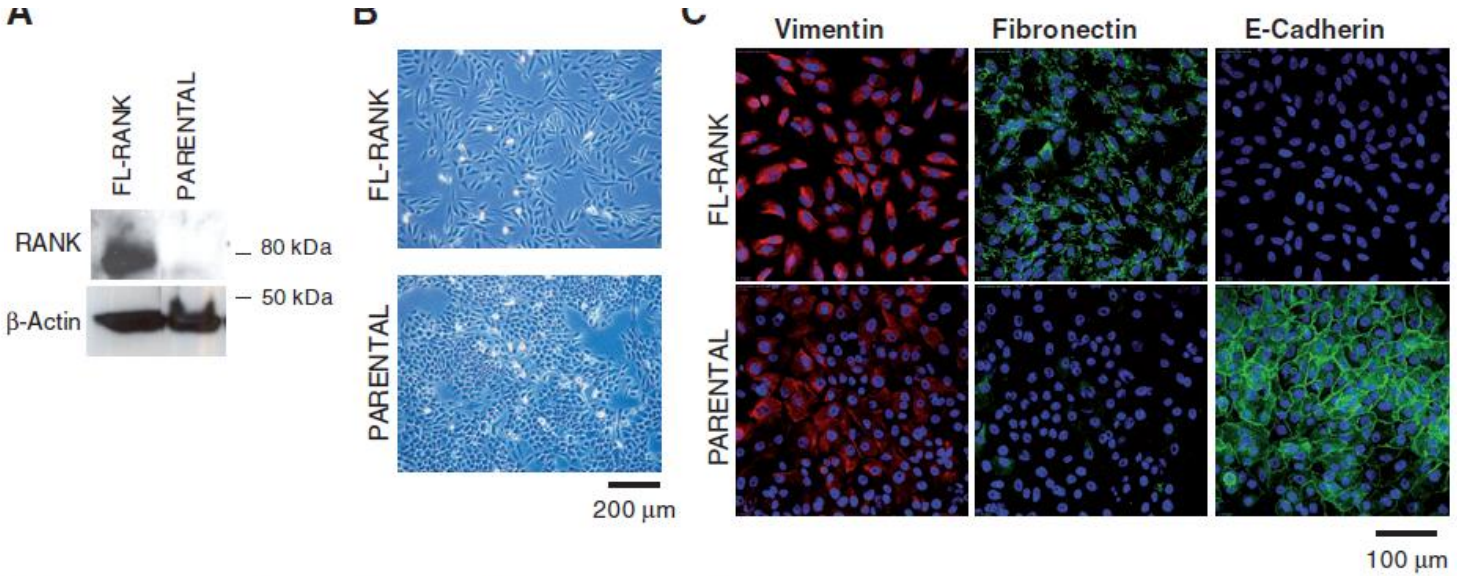


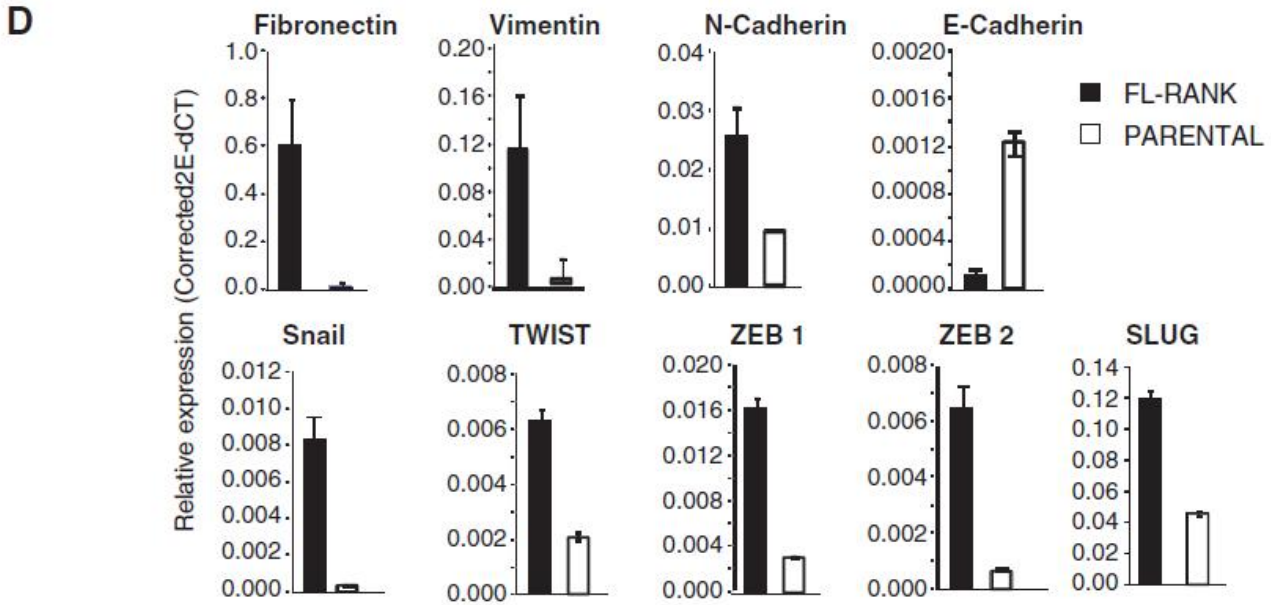
Santini D et al *PlosOne 2011*

Endothelial Mesenchimal Transition and MET



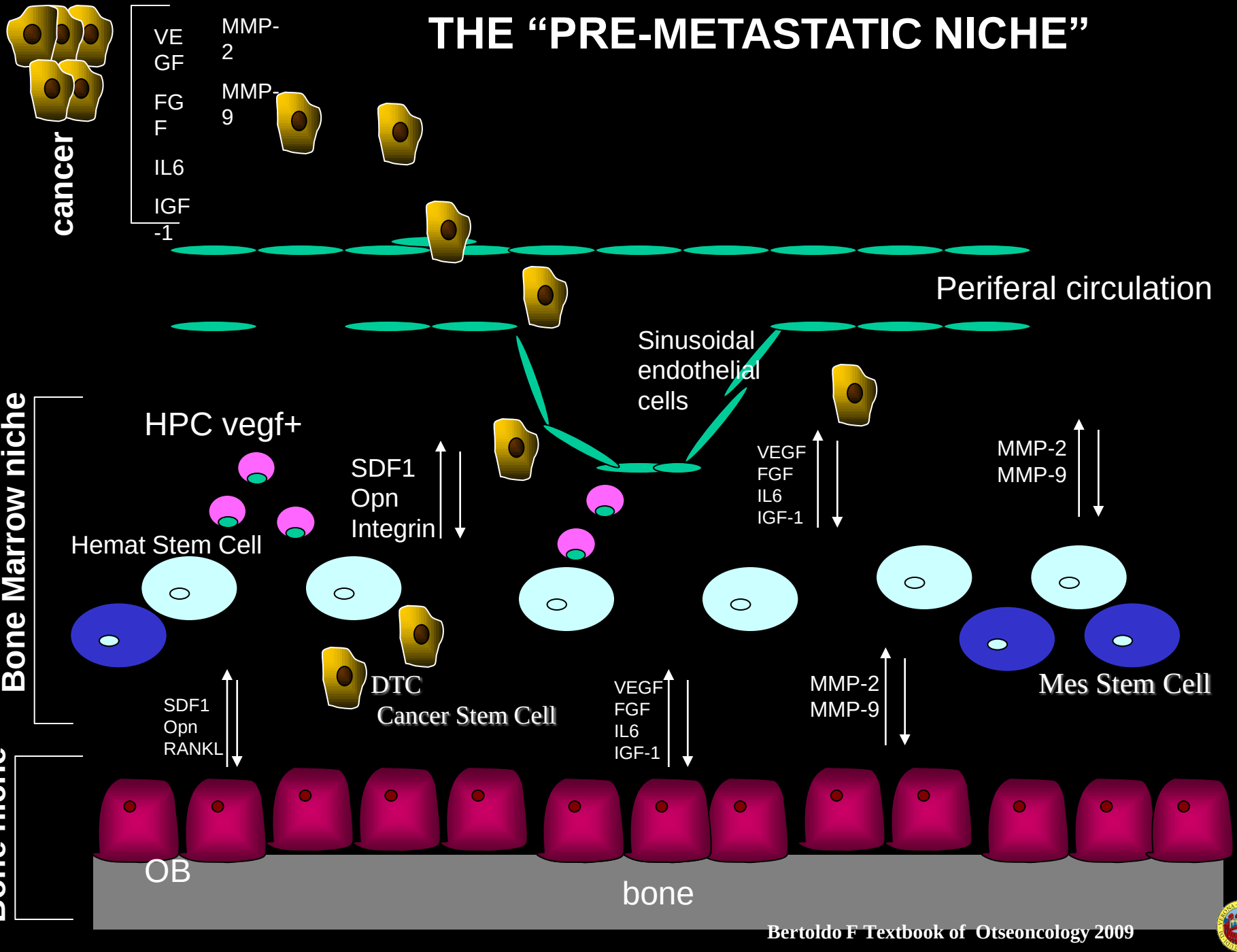
RANK Induces Epithelial–Mesenchymal Transition and Stemness in Human Mammary Epithelial Cells and Promotes Tumorigenesis and Metastasis





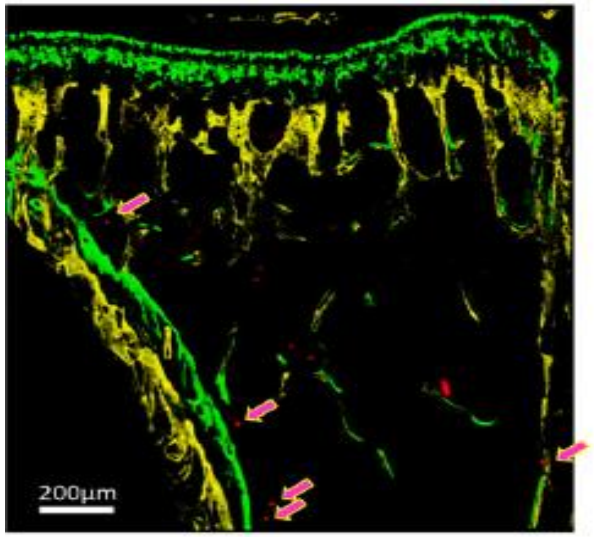
Plafox M et al. *Cancer Res* 2012;72:2879-2888.

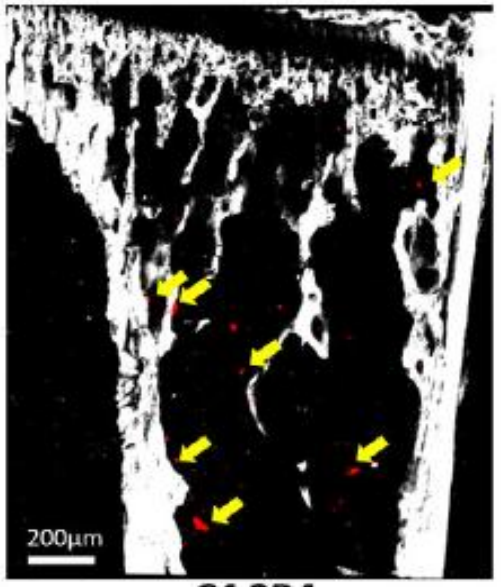
THE “PRE-METASTATIC NICHE”



Bertoldo F Textbook of Otseoncology 2009

Prostate Cancer Cells Preferentially Home to Osteoblast-rich Areas in the Early Stages of Bone Metastasis: Evidence From In Vivo Models





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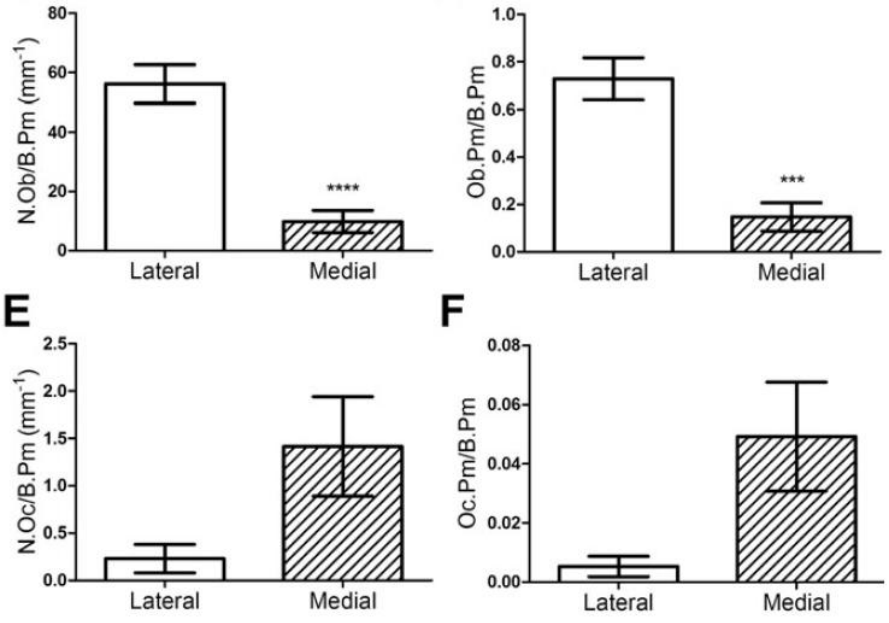
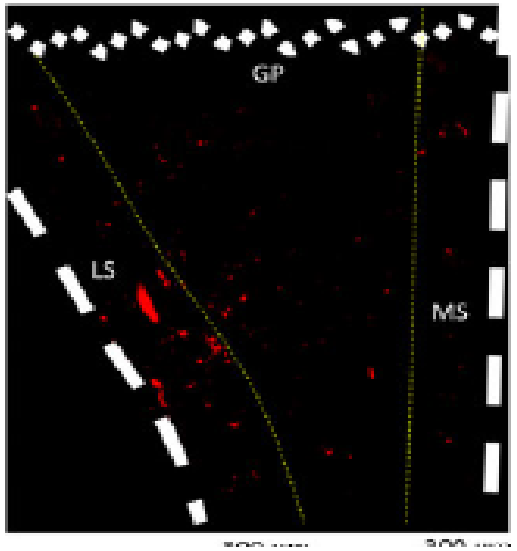


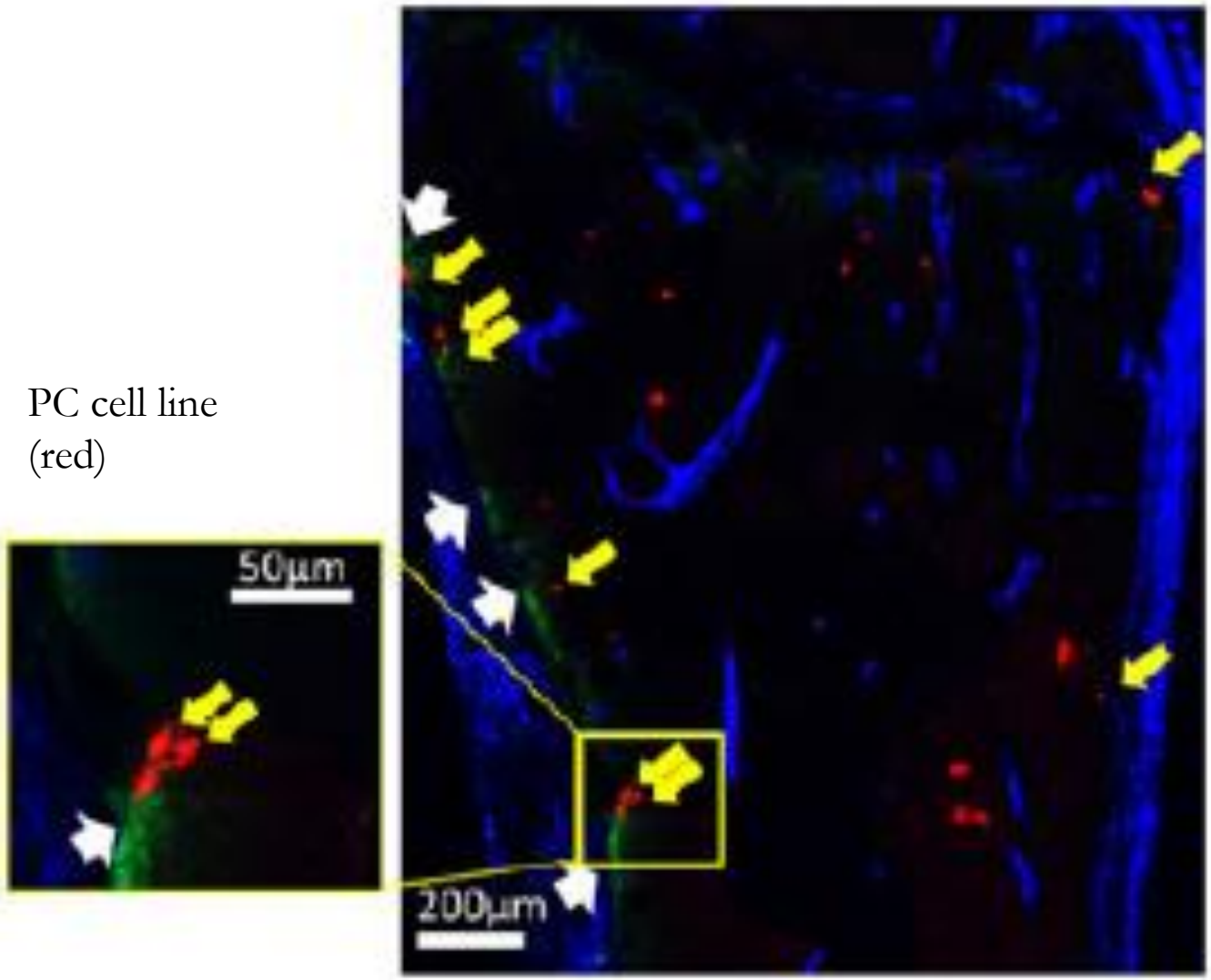


Wang N J Bone Miner Res 2015

SPATIAL DISTRIBUTION OF PROSTATE CANCER CELLS IN MOUSE BONE

PC cell line
(red)

Osteoblast
(green)



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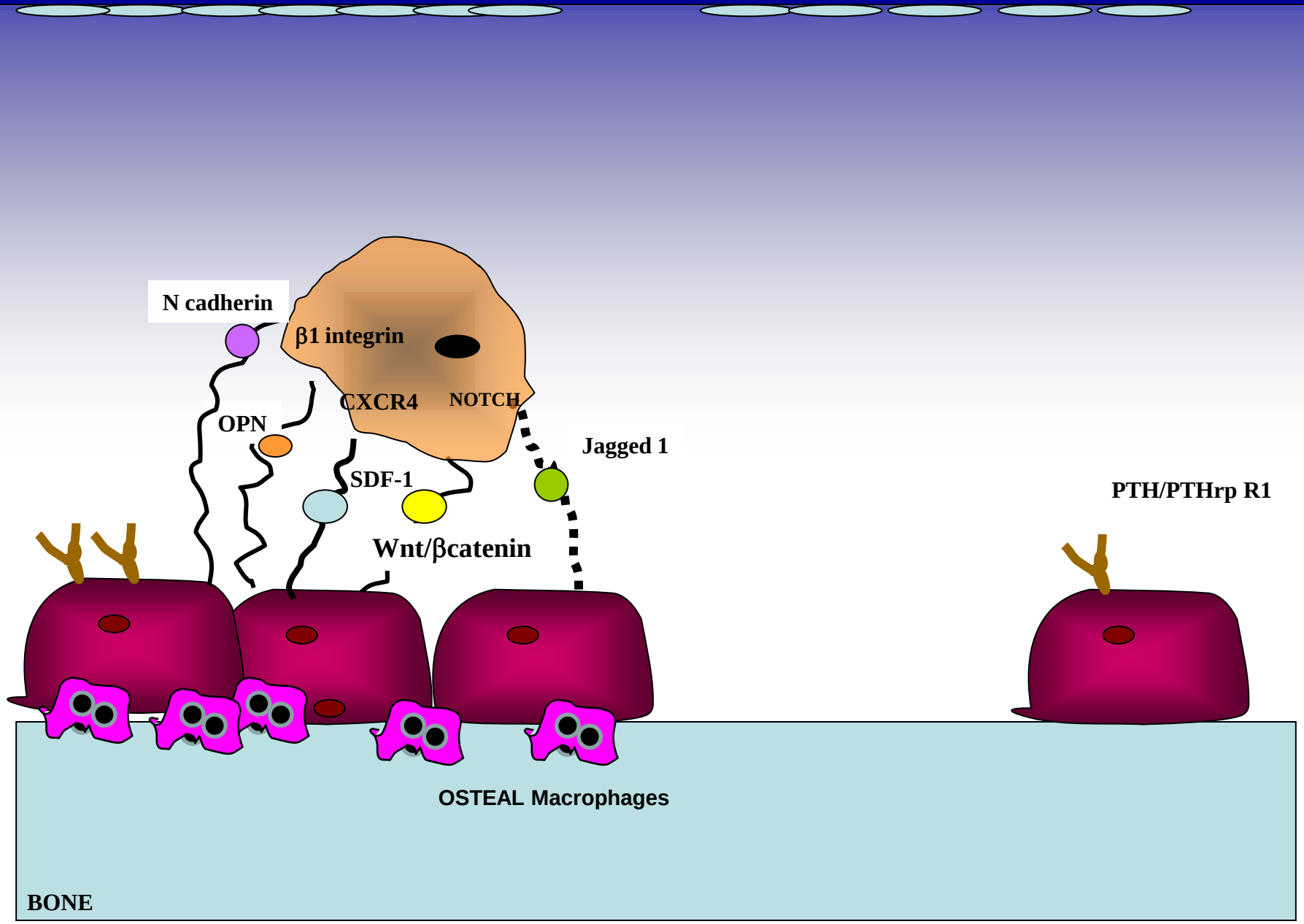
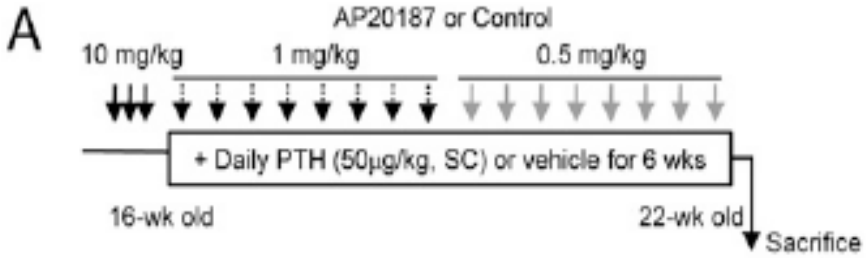
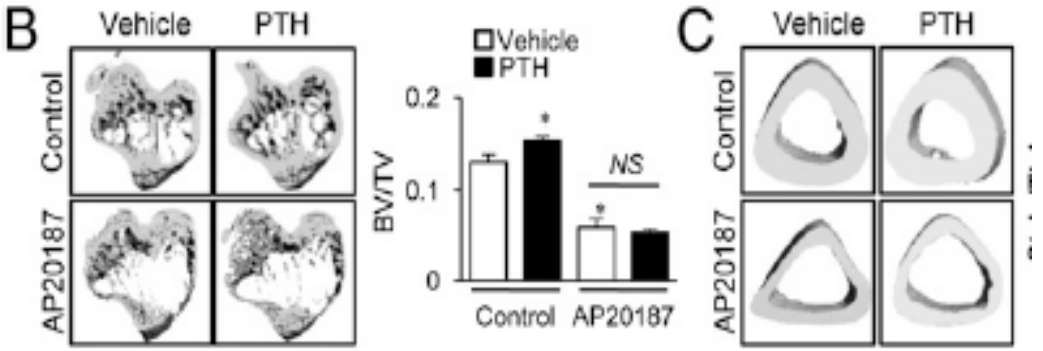
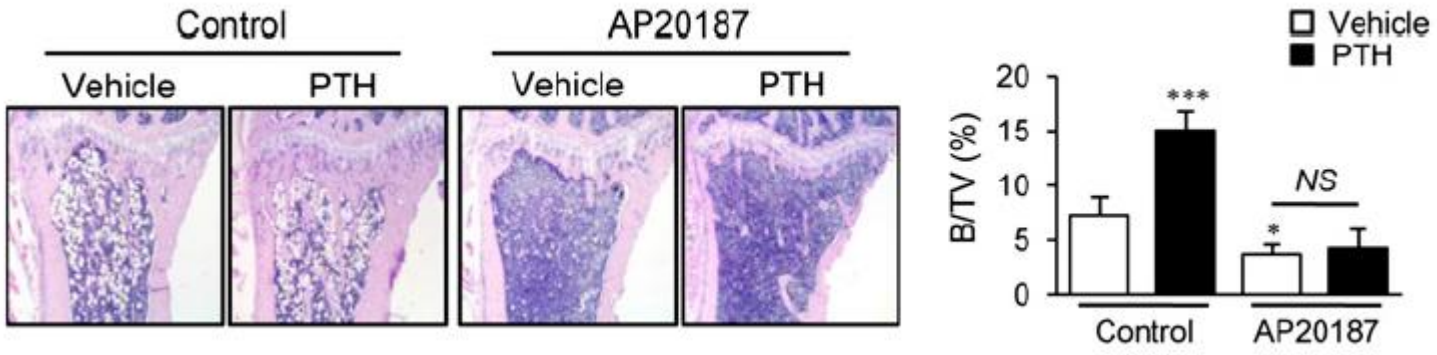


Ratajczak MZ Leukemia 2010; Kollet Ot Nature 2006; Calvi LM Ann NY Acad Sci 2006

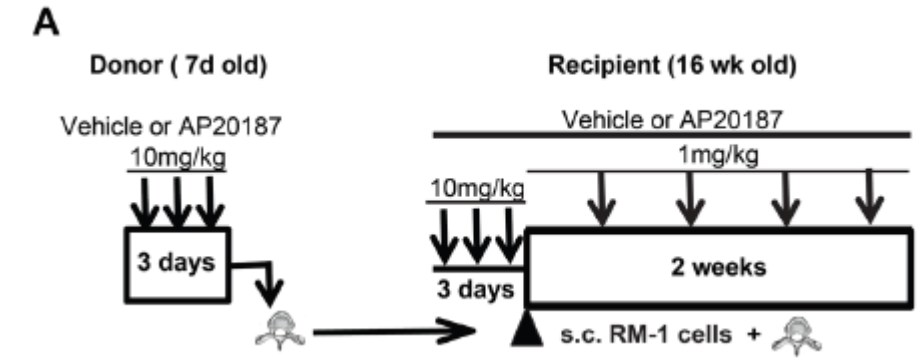
Osteal macrophages support physiologic skeletal remodeling and anabolic actions of parathyroid hormone in bone

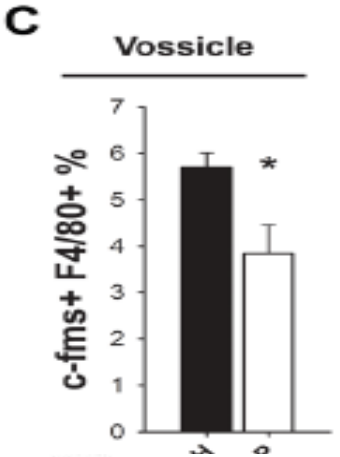


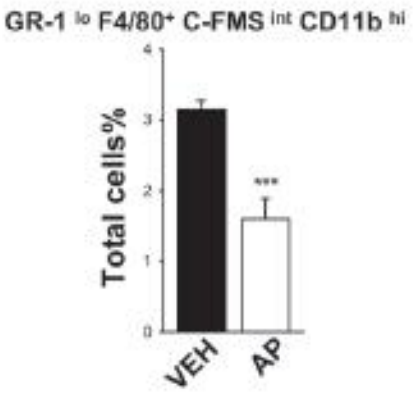


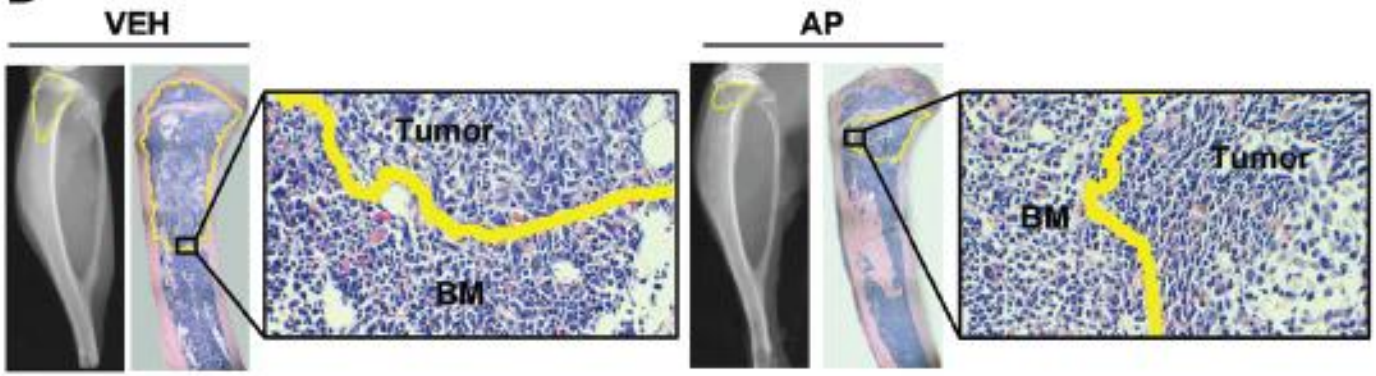


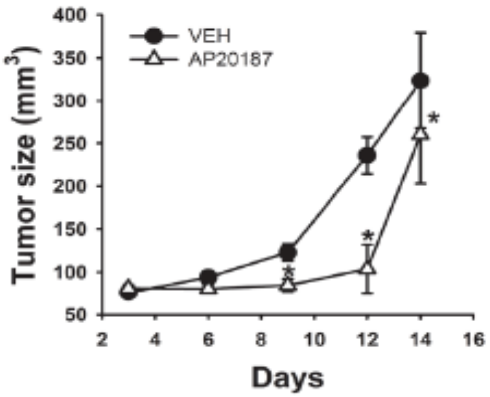
Bone marrow macrophages support prostate cancer growth in bone

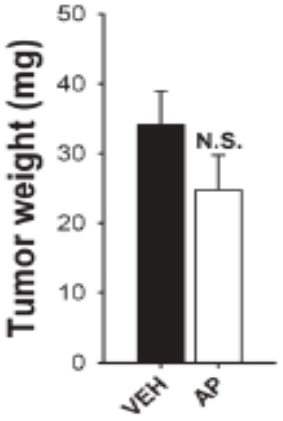






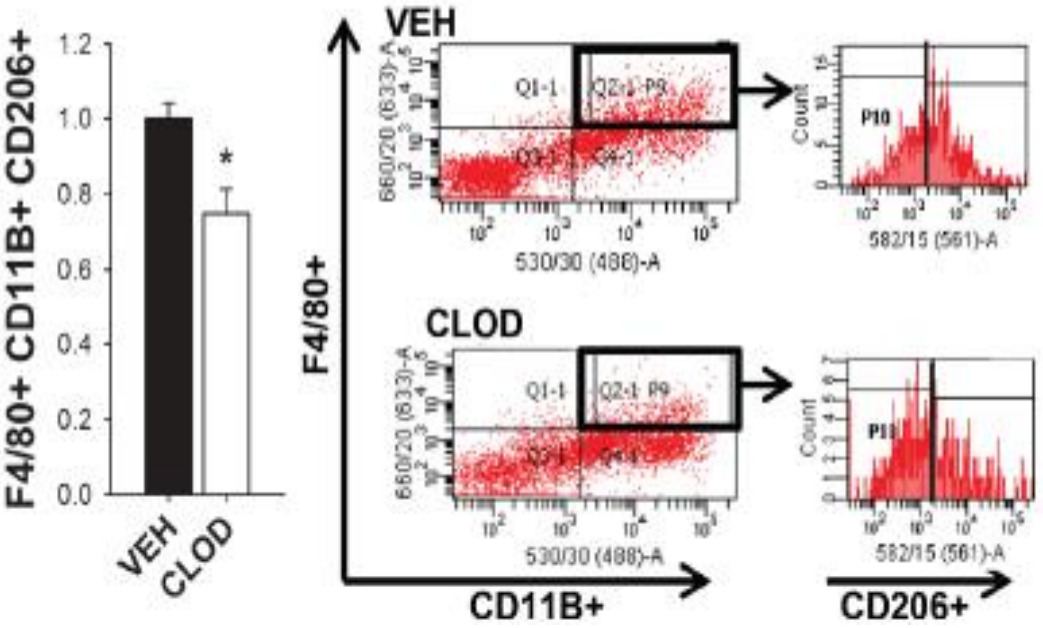


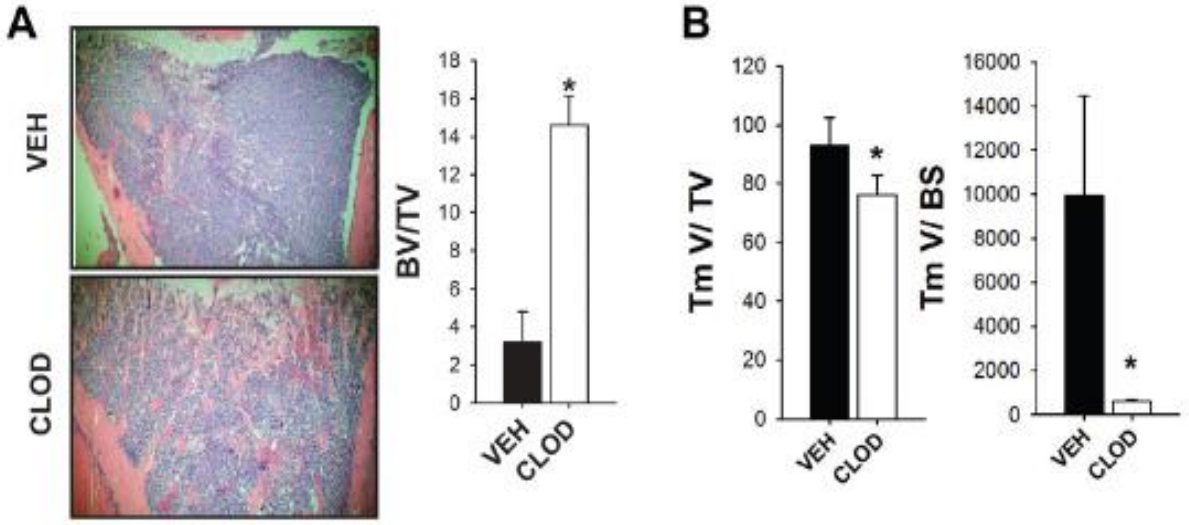




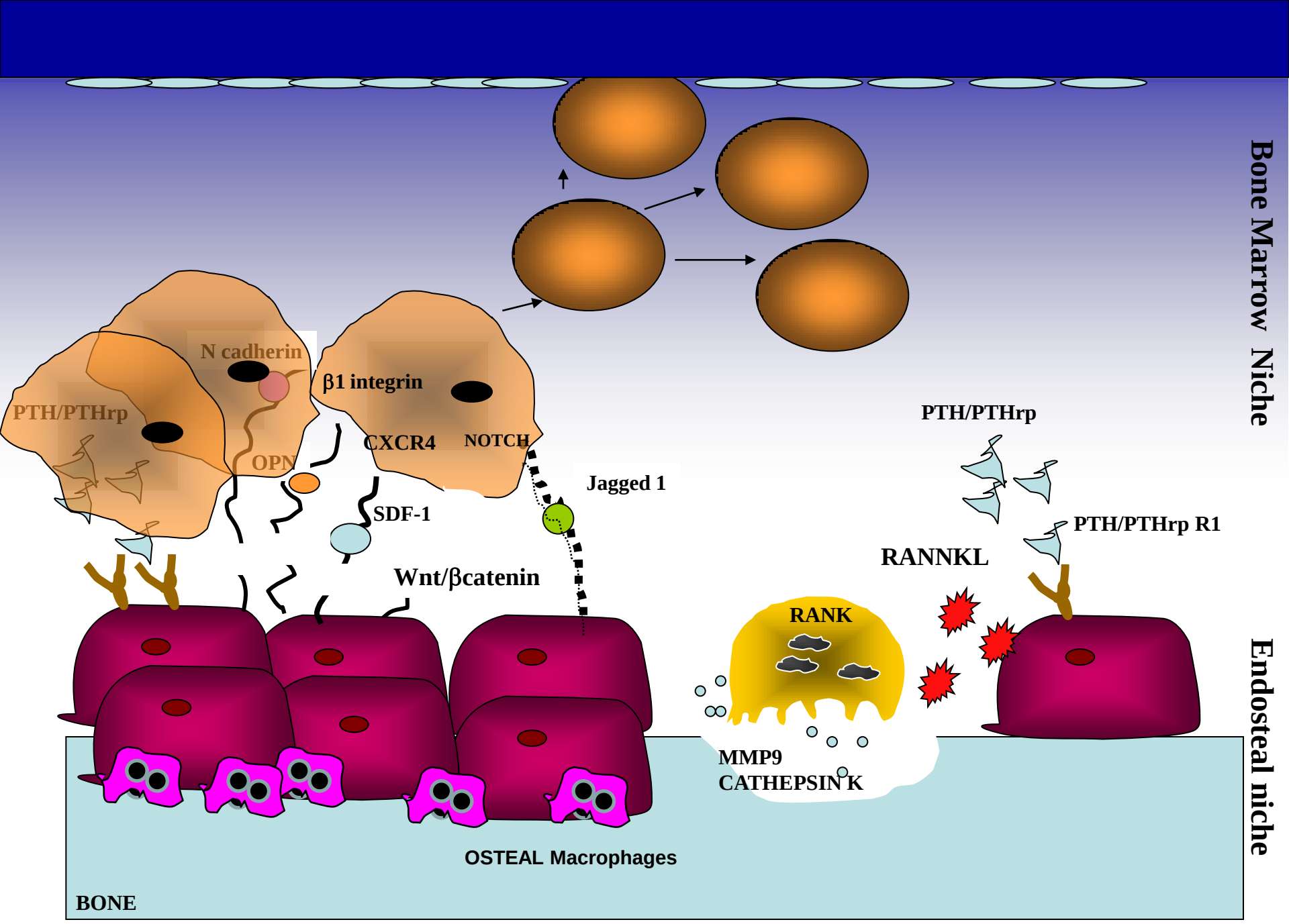
Soki FN et al Oncotarget 2015

Bone marrow macrophages support prostate cancer growth in bone



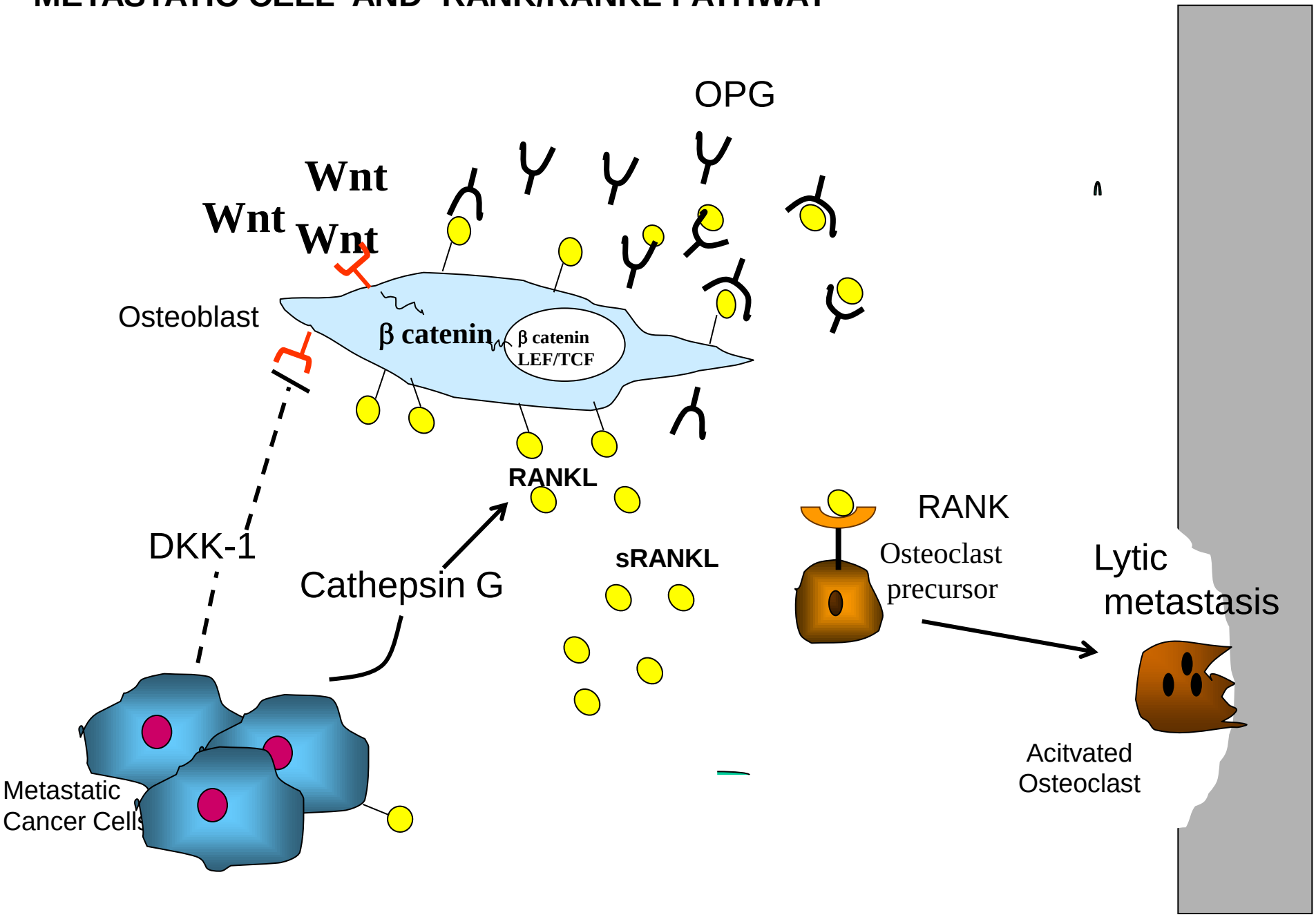


Soki FN et al Oncotarget 2015



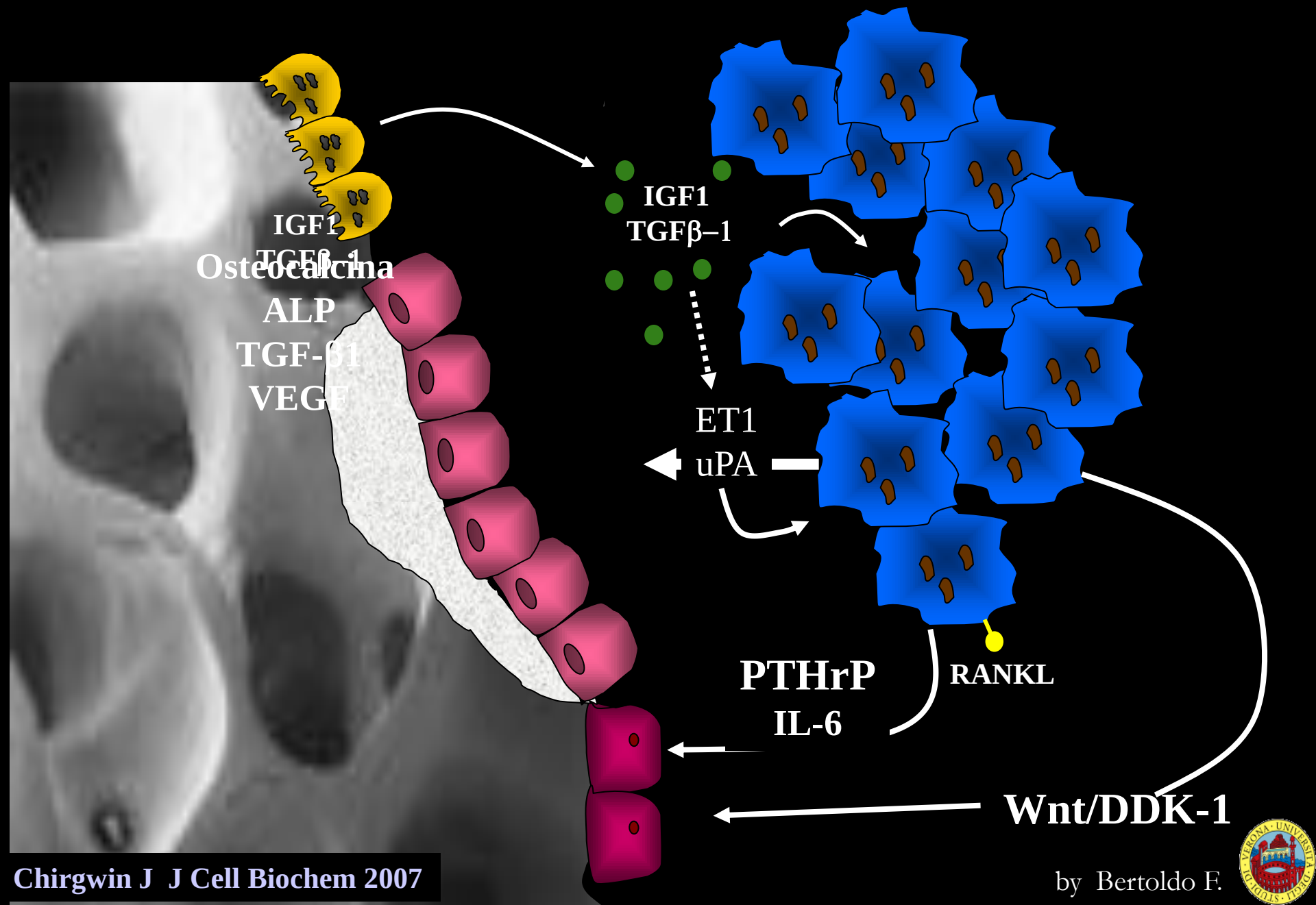
Ratajczak MZ Leukemia 2010; Kollet Ot Nature 2006; Calvi LM Ann NY Acad Sci 2006

METASTATIC CELL AND RANK/RANKL PATHWAY



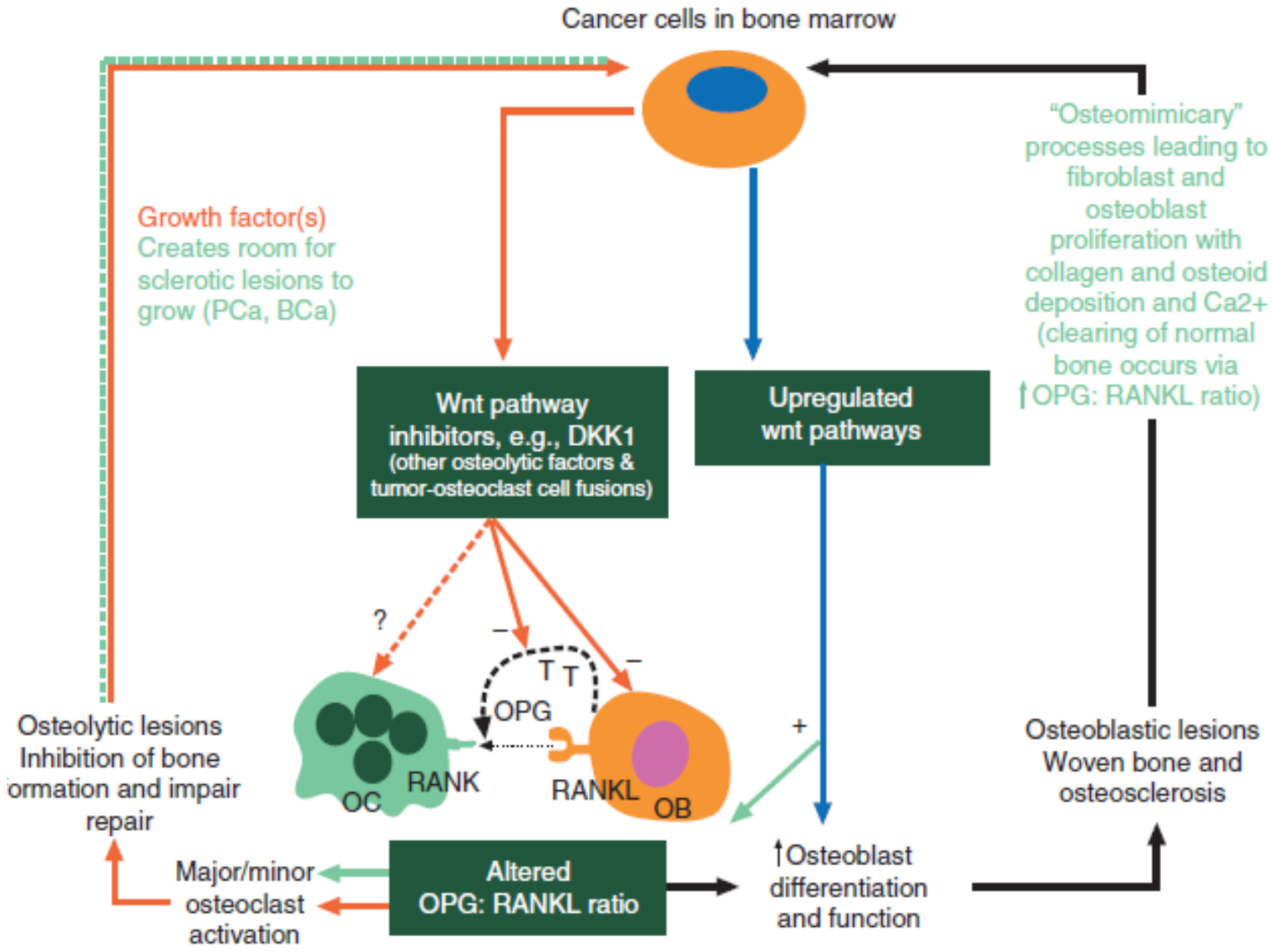
Frizzled/LRP5/6 receptor complex

Fisiopatologia della Metastasi Ossea



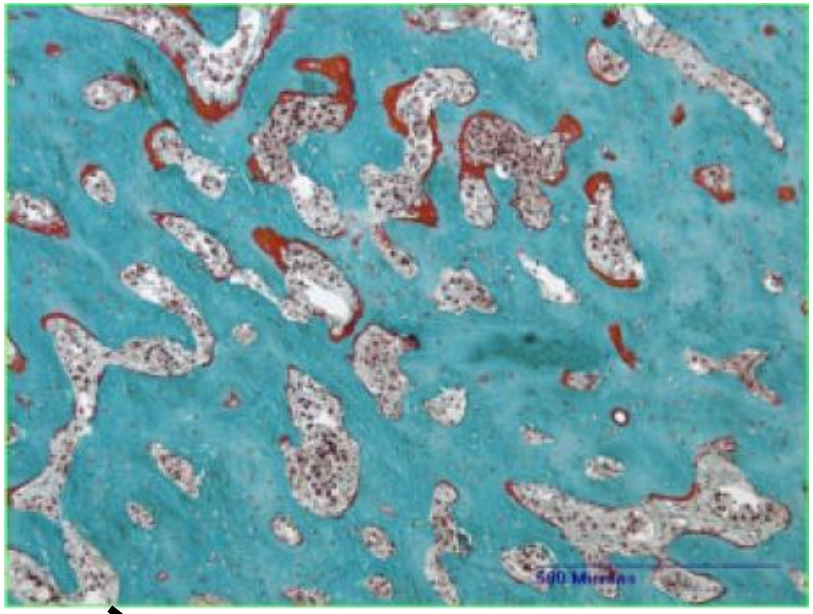
Chirgwin J J Cell Biochem 2007

by Bertoldo F.

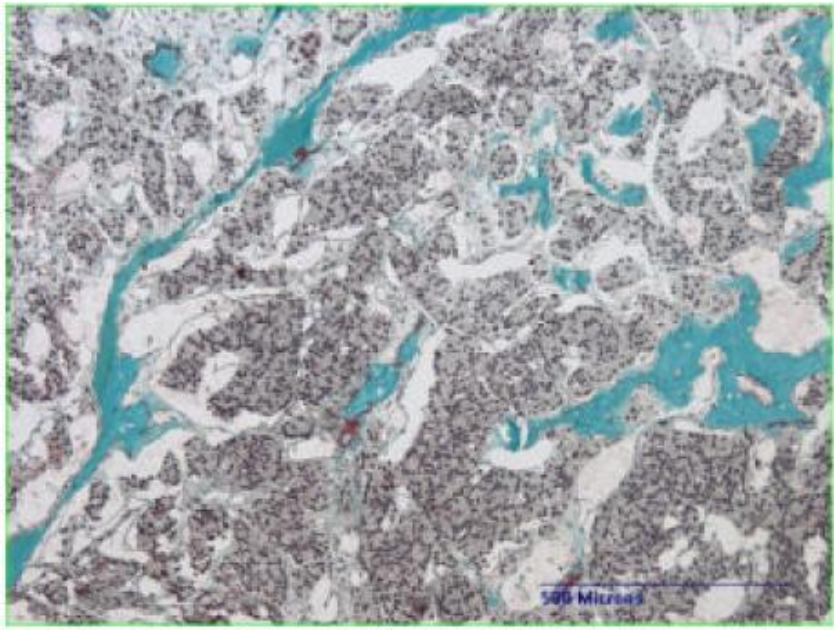


Annals of Oncology 26: 1048–1057, 2015
doi:10.1093/annonc/mdu558

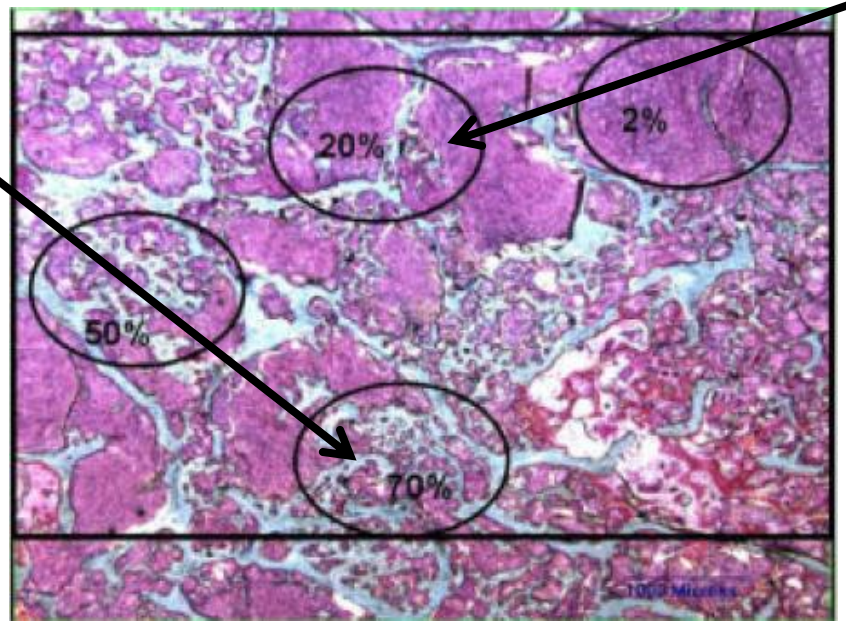
BONE METASTASIS IN PROSTATE CANCER
DIFFERENT PATTERNS IN THE SAME SUBJECT



Blastic Pattern



Lytic Patter



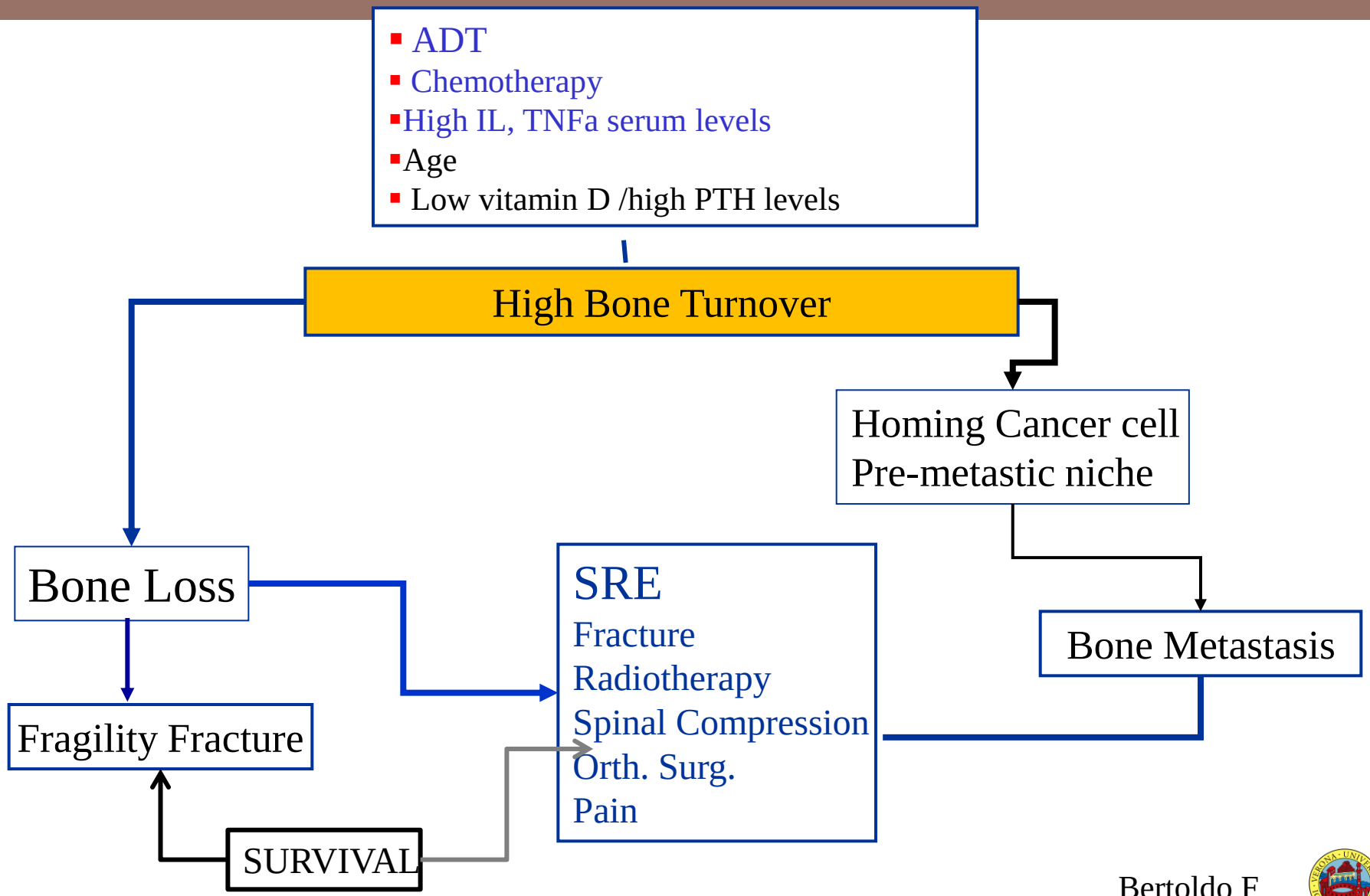
Mixed Pattern

Green = Bone
Red = Osteoid
Pink= Tumor Stroma

% Bone Volume

J Urol. 2008 September ; 180(3): 1154–1160.

The “Bone Health” concept in Cancer Patients



Bertoldo F

Eventi correlati all'apparato scheletrico (SRE)

Eventi correlati all'apparato scheletrico – skeletal-related events (SRE):[1,2]

radioterapia all'osso

fratture patologiche

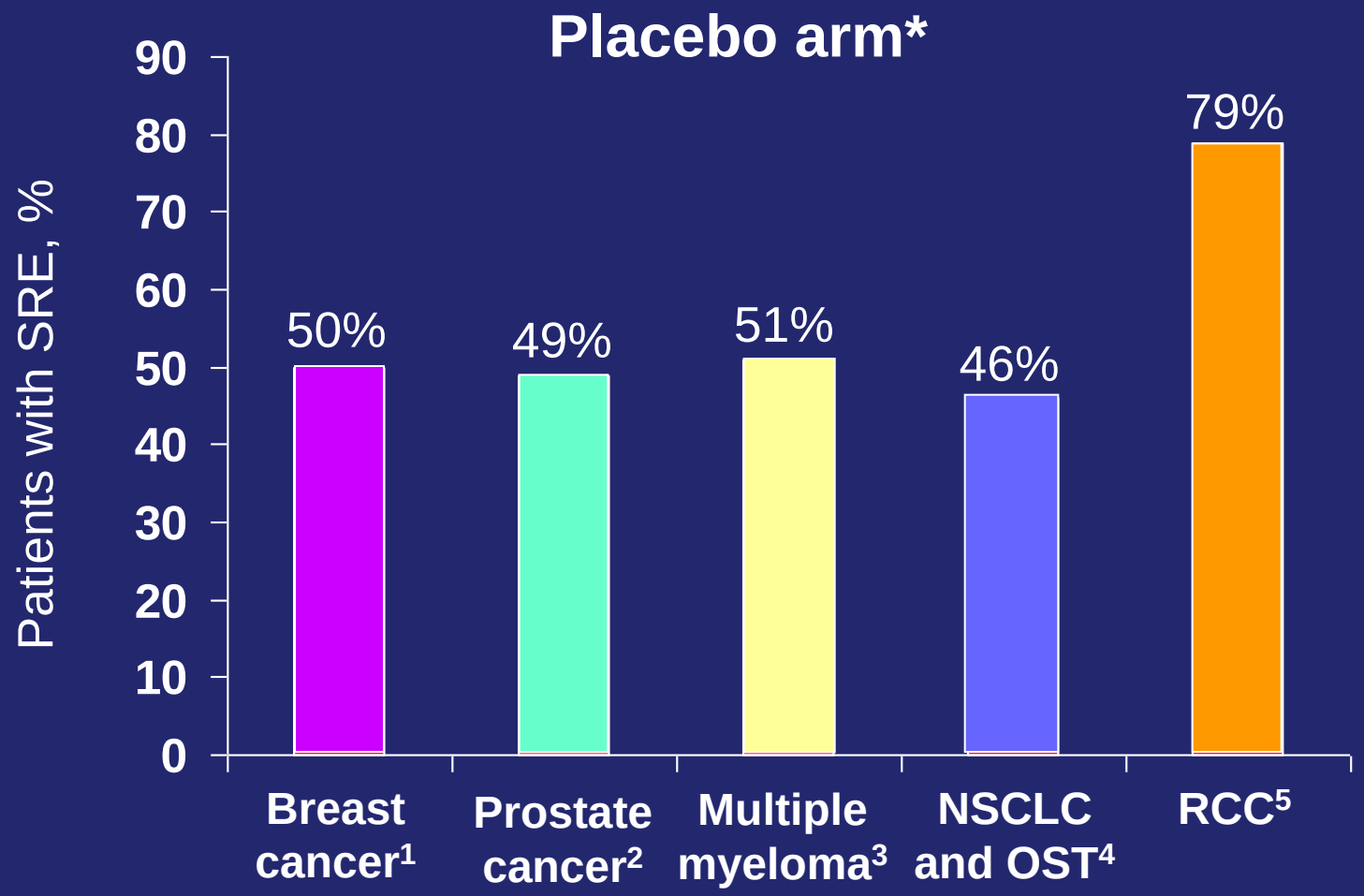
compressione del midollo spinale

interventi chirurgici all'osso

PAIN ? HYPERCALCEMIA?

1. Saad F, et al. J Natl Cancer Inst 2004;96:879–82;
2. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf (Accessed 2 March 2011).

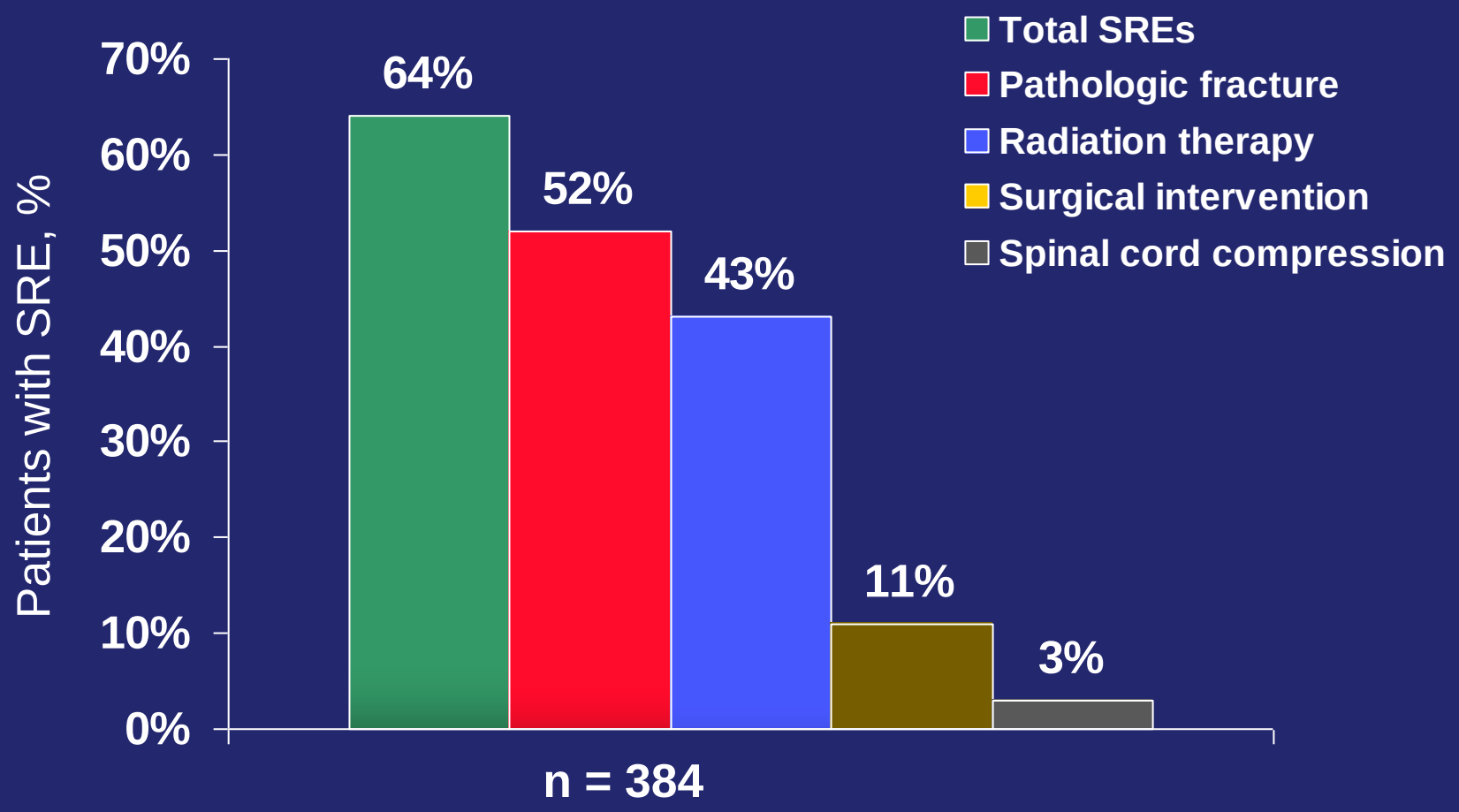
Skeletal-Related Events Are Prevalent in the Absence of Bisphosphonate Therapy



NSCLC = Non-small cell lung cancer; OST = Other solid tumors; RCC = Renal cell carcinoma.
*Placebo arm from zoledronic acid and pamidronate clinical trials.

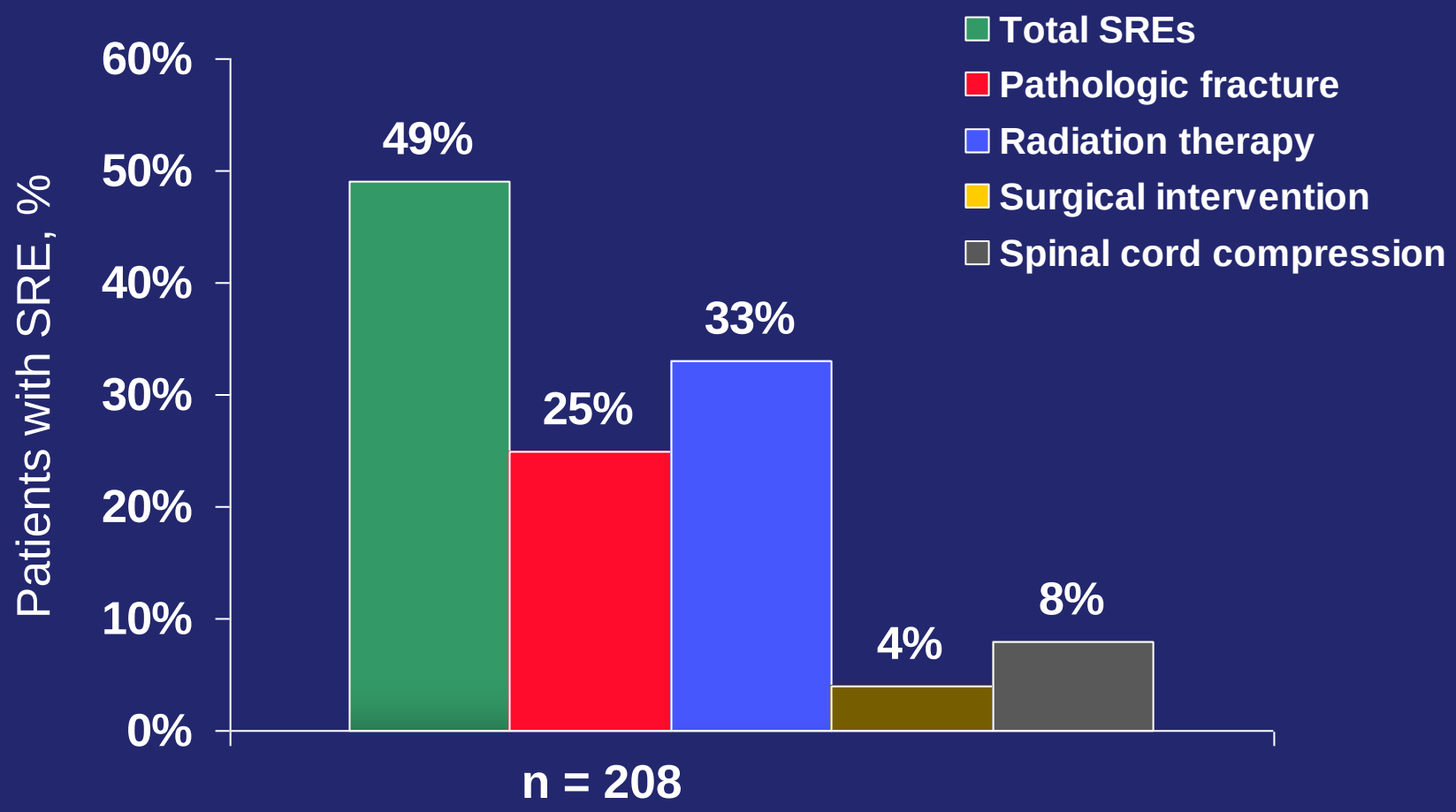
1. Kohno N, et al. *J Clin Oncol*. 2005;23:3314-3321; 2. Saad F, et al. *J Natl Cancer Inst.* 2004;96:879-882; 3. Berenson JR, et al. *J Clin Oncol*. 1998;16:593-602; 4. Rosen LS, et al. *Cancer*. 2004;100:2613-2621; 5. Mulders PF. Presented at: EAU 2007.

Clinical Trials Indicate Skeletal-Related Events Are a Serious Threat To Breast Cancer Patients*



SRE = Skeletal-related event.
*24-month data from placebo arm of randomized study.
Data from Lipton A, et al. *Cancer*. 2000;88:1082-1090.

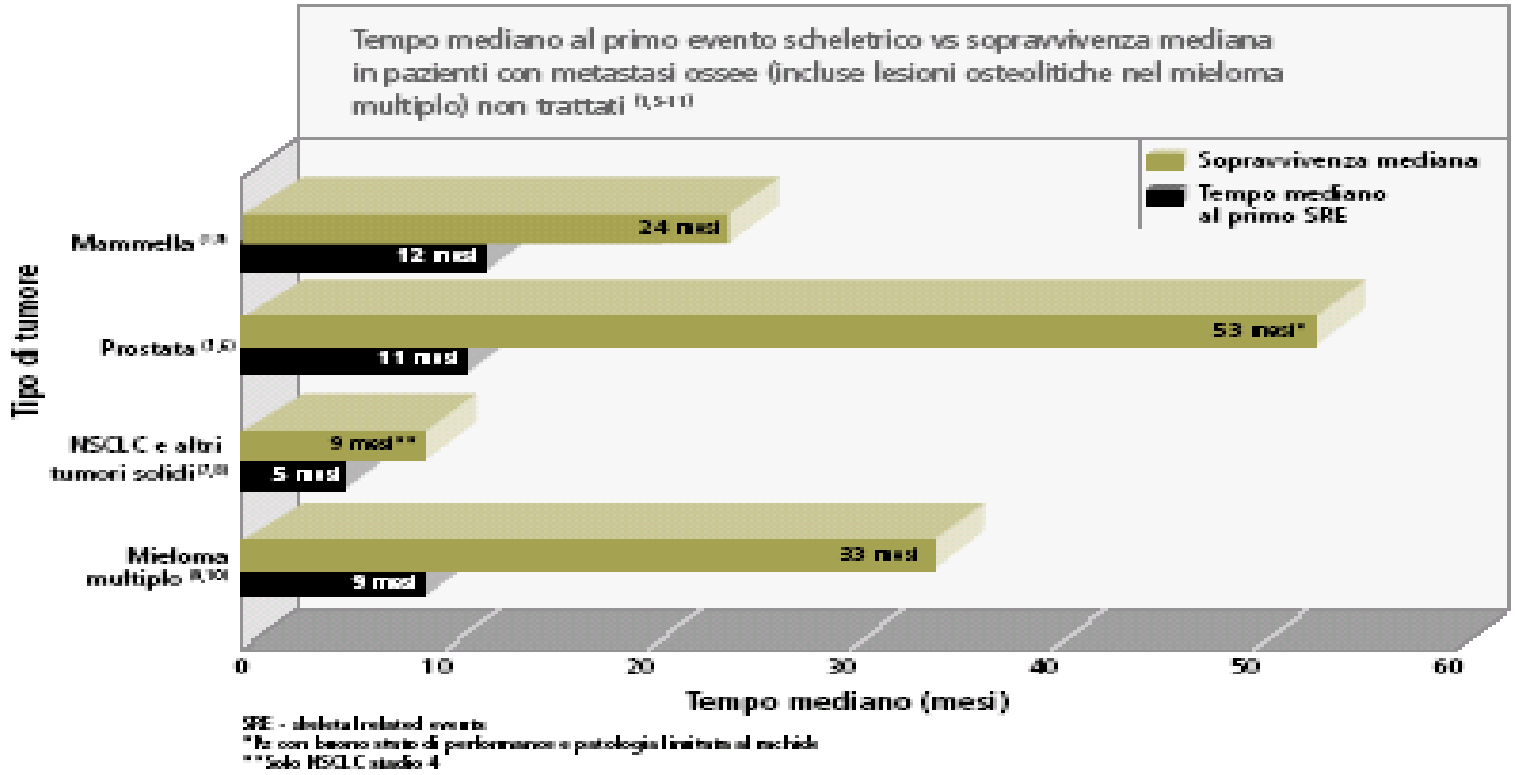
Clinical Trials Indicate Skeletal-Related Events (SREs) Are Serious Threats to Prostate Cancer Patients*



*24-month data from placebo arm of randomized study.
Saad F, et al. Presented at: AUA 2003. Abstract 1472.

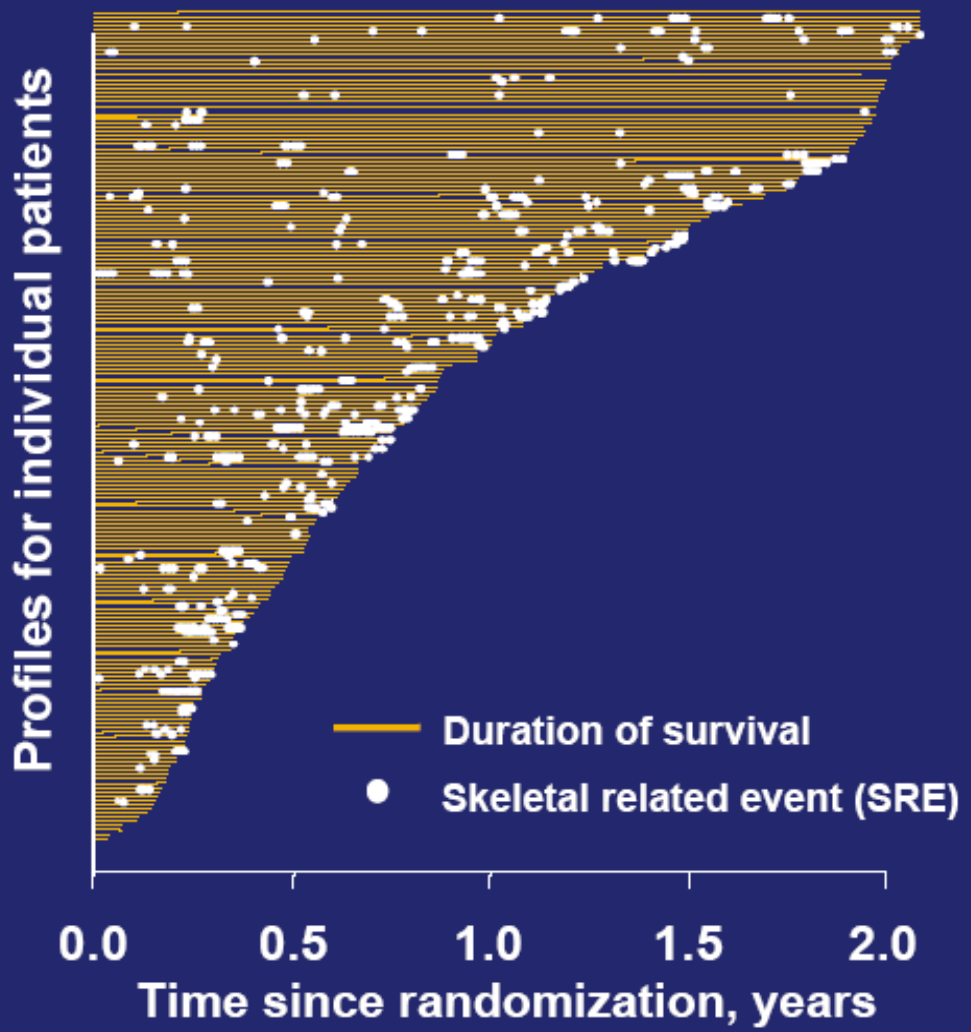
Tempo mediano alla comparsa del primo SRE: *generalmente inferiore a 12 mesi*

In pazienti non trattati, **il primo evento scheletrico si manifesta già nel primo anno** dalla diagnosi di metastasi ossee[1,5-11]



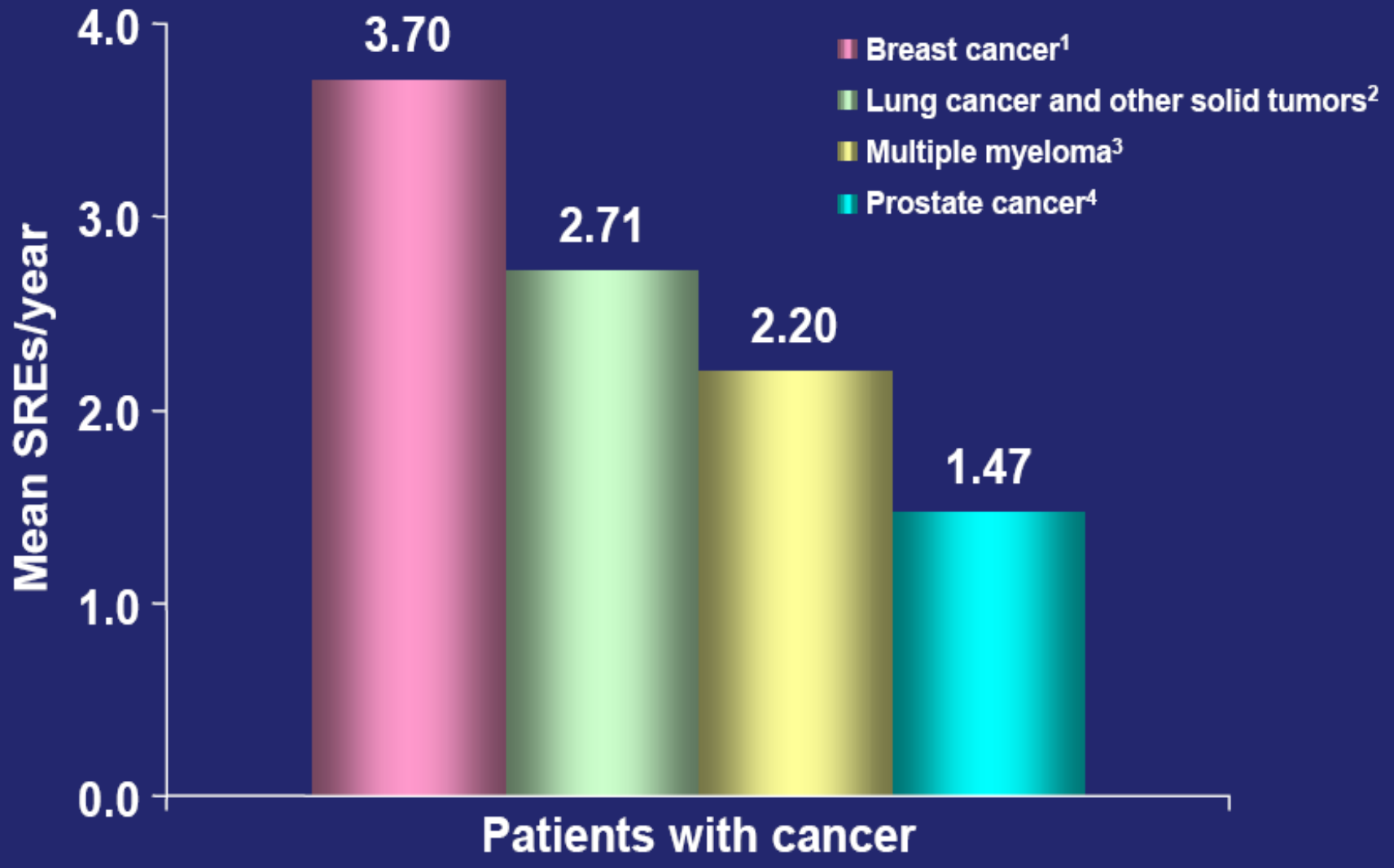
Patients Experience Multiple Skeletal Complications before Death

- Patients at long-term risk of developing SREs
- Risk increases as disease progresses
- Risk increases twofold after first SRE
- Clustering of events



Data from Hortobagyi GN, et al. *J Clin Oncol*. 1998;16:2038-2044.
Reproduced with permission from Major PP, et al. *Am J Clin Oncol*. 2002;25(suppl 1):S10-S18.

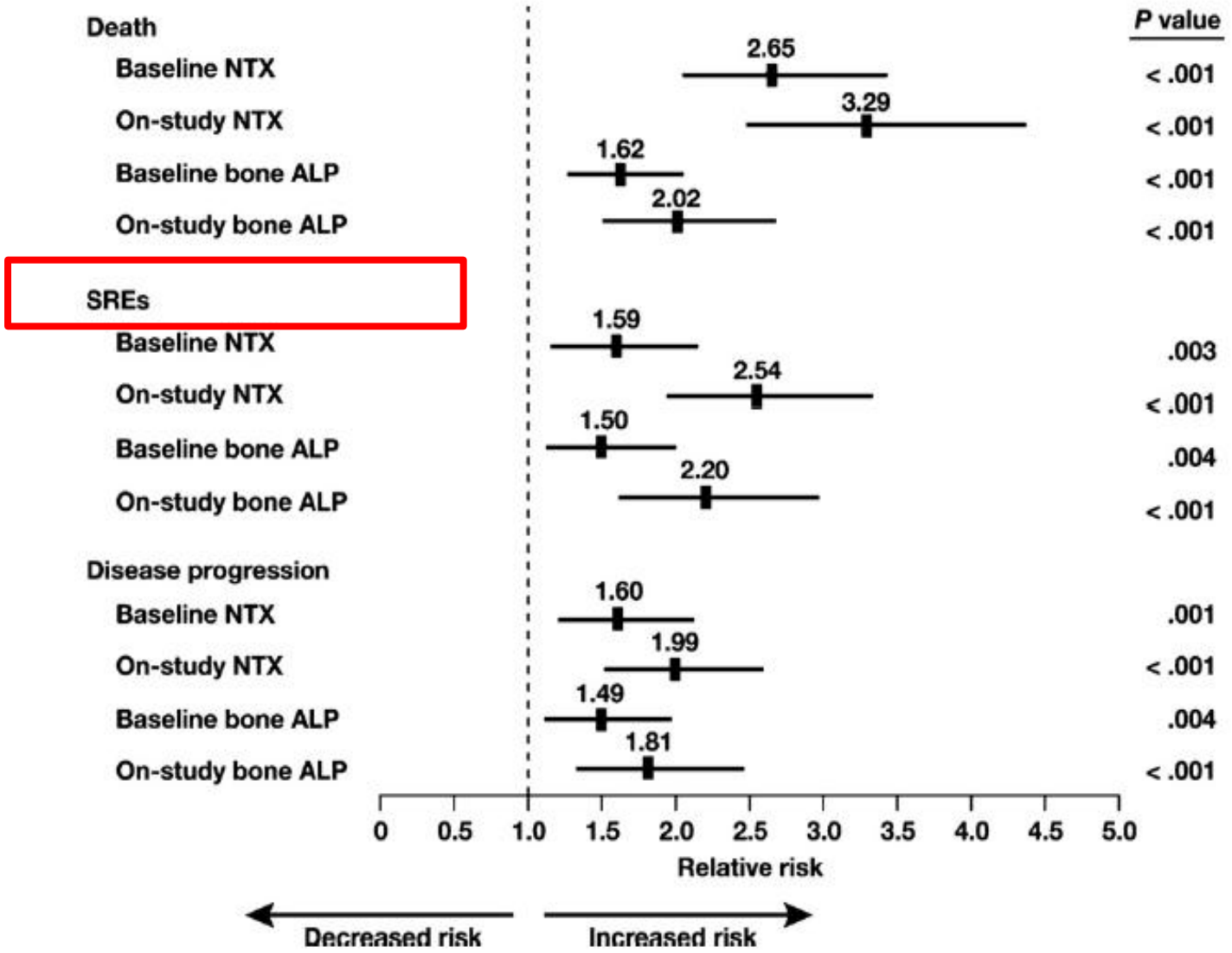
Patients Can Experience Multiple SREs/Year



Data are from placebo-control arms of bisphosphonate trials.

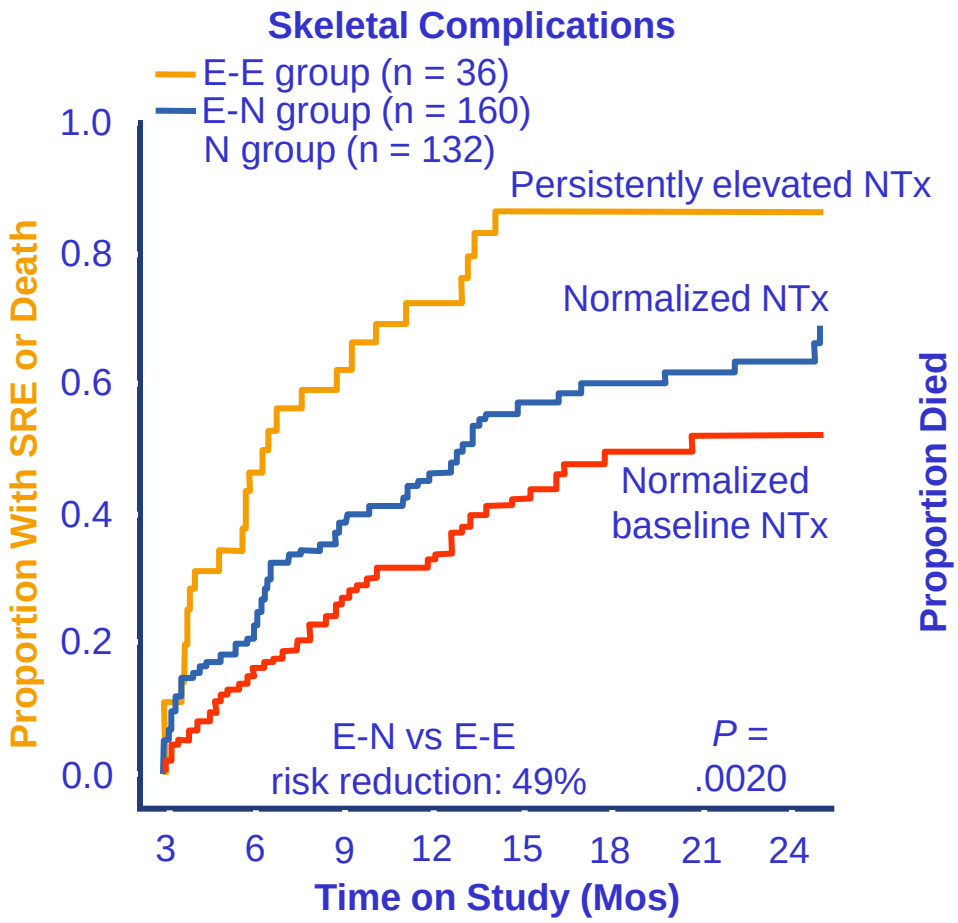
1. Lipton A, et al. *Cancer*. 2000;88:1082-1090; 2. Rosen LS, et al. *Cancer*. 2004;100:2613-2621;
3. Berenson JR, et al. *J Clin Oncol*. 1998;16:593-602; 4. Saad F, et al. *J Natl Cancer Inst*. 2004;96:879-882.

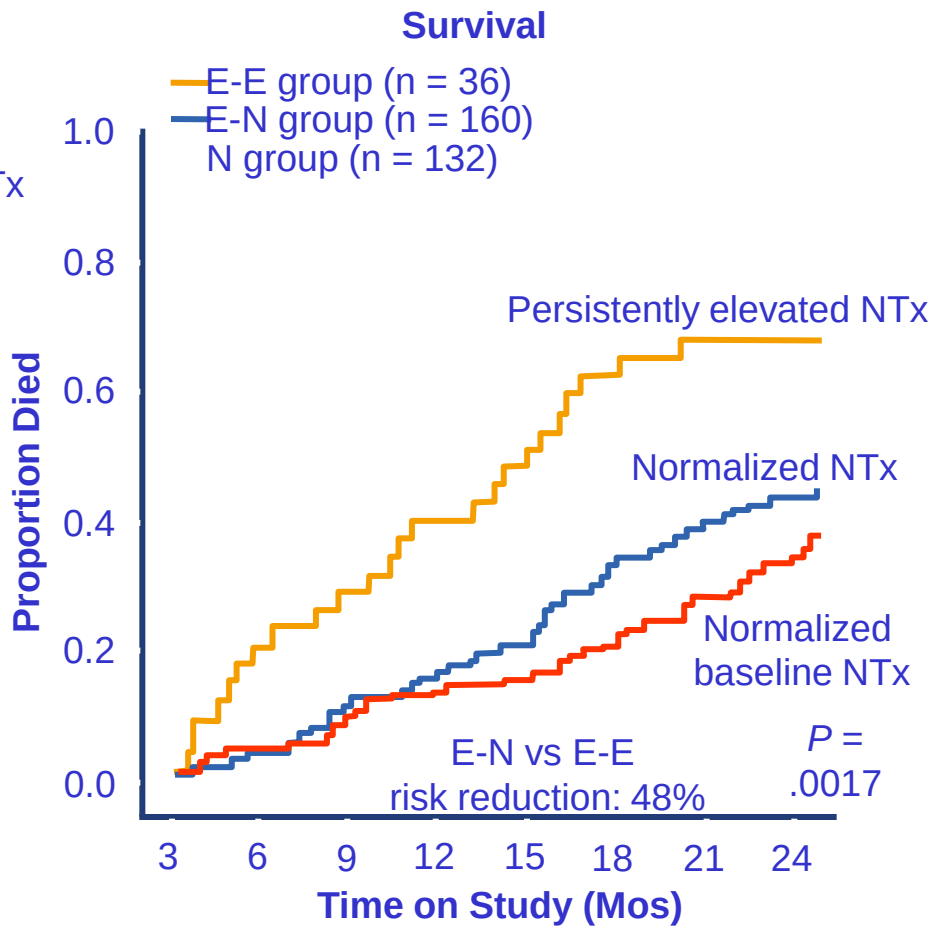
CORRELATIONS BETWEEN BONE TURNOVER AND CLINICAL OUTCOME IN PATIENTS WITH BONE METASTASES FROM SOLID TUMORS (NO BPs)



Robert Coleman [a,*] Critical Reviews in Oncology/Hematology xxx (2011) xxx–xxx

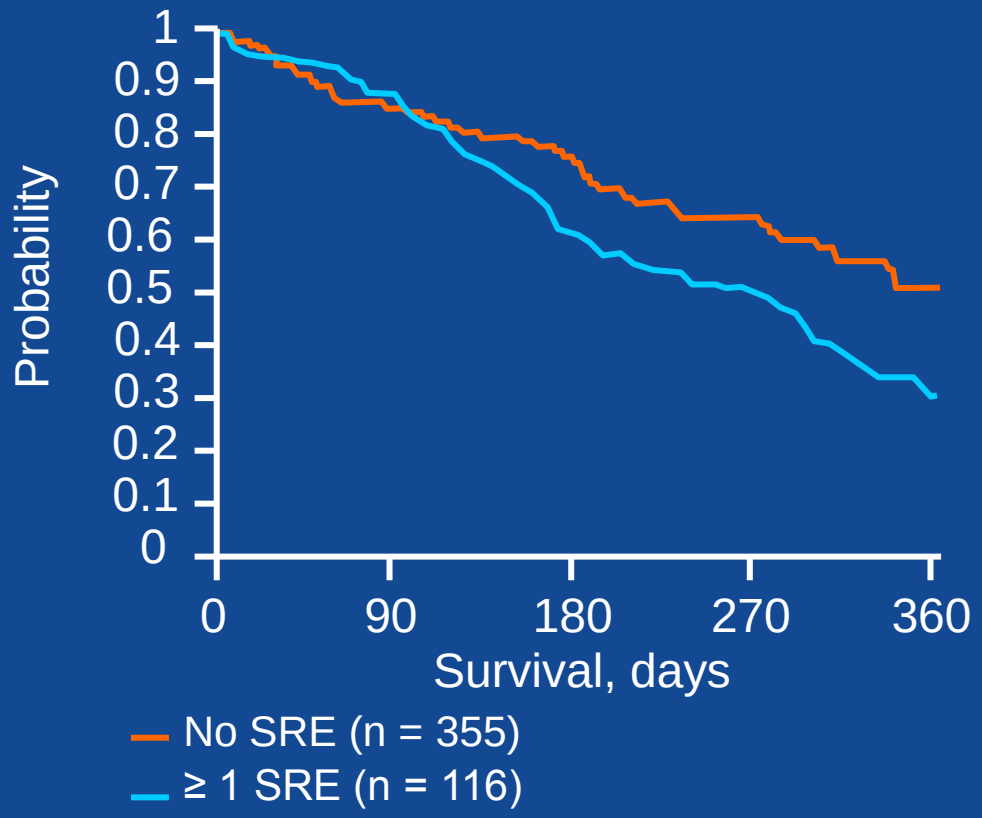
Biochemical Response Correlates With Improved Outcome





Lipton A, et al. Oncologist. 2007;12:1035-1043..

SREs Are Associated With Lower Survival in Prostate Cancer



360 Days' Survival

- No SRE: 49.7%
- ≥1 SRE: 28.2%
- *P* = .02

Median Survival Times

- No SRE: 338 days (95% CI = 189, 460)
- ≥ 1 SRE: 248 days (95% CI = 181, 296)

Abbreviation: CI, confidence interval; SRE, skeletal-related event.

Reprinted from DePuy V, et al. *Support Care Cancer*. 2007;15(7):869-876.

Patients With Bone Metastases May Suffer Potentially Lethal Skeletal-Related Events

SRE	Potential complication
Pathologic fracture	• Extended healing time[1] • Surgical fixation or prosthetic replacement[2] • 58.6% higher mortality rate associated with fracture[3]
Pain requiring radiation to bone	• Negative impact on quality of life[4] • Narcotics
Surgery to bone	• Hospital stay • Increased mortality[2]
Spinal cord compression	• Excruciating pain[5] • Irreversible paraparesis or paraplegia[6] • Chronic narcotics for analgesia[6]
Hypercalcemia of malignancy	• Heart failure • Coma • Death

1. Gainor BJ, et al. *Clin Orthop Relat Res*. 1983;178:297-302. 2. Jacofsky DJ, et al. *J Orthop Trauma.* 2004;18:459-469.
3. Hei YJ, et al. Presented at: SABCS 2005. Abstract 6036; 4. Smith JA Jr, et al. *Urology*. 1999;54(suppl):8-14.
5. Coleman RE. *Cancer*. 1997;80:1588-1594; 6. Abrahm JL. *J Support Oncol.* 2004;2:377-388.

SKELETAL RELATED EVENT CRITICISMS

1. SRE is used in RCT but **not in clinical practice**

2. **Preplanned** control (radiographs)

3. **Symptomatic vs asymptomatic** events, i.e fractures

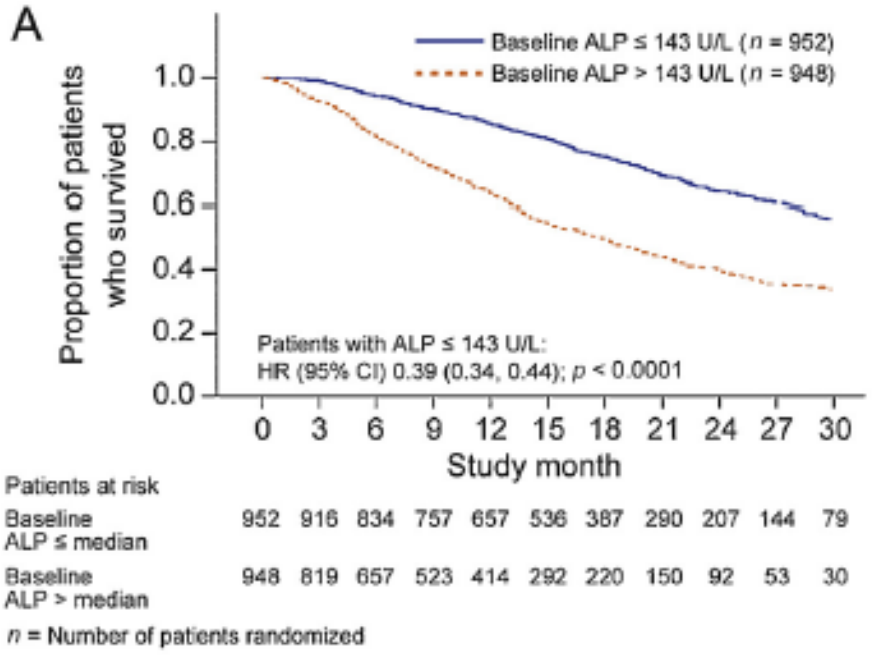
4. SRE are **composite** end points .Different clinical weight of component

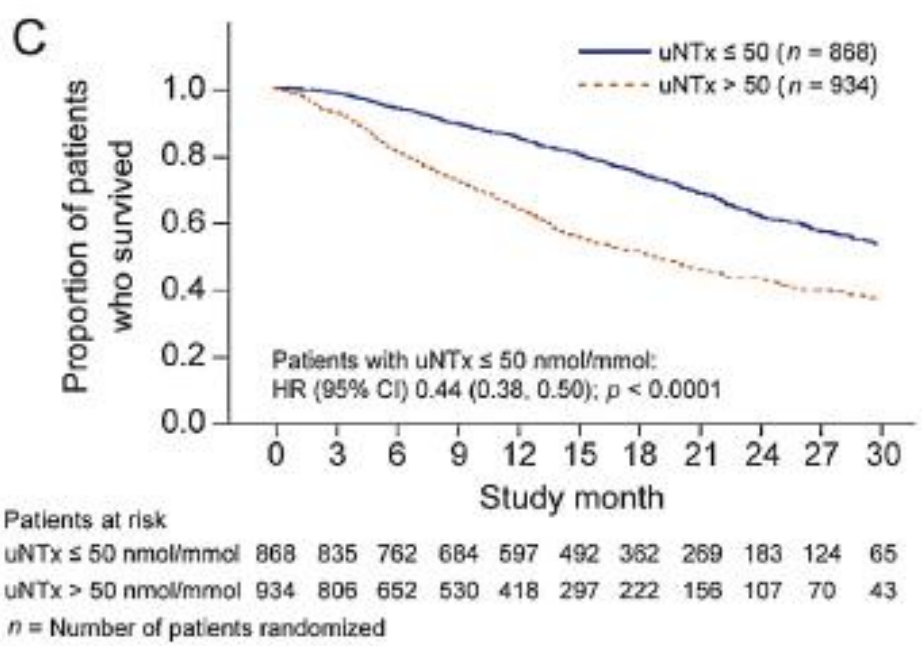
5. **Include** complications of BMT and **therapeutic or preventive measure** (orthopedic surgery or radiation)

6. No direct measure of factors that are **important to patients** (pain or mobility)

SRE >>>>> SSE (Symptomatic Skeletal Events)

Bone-related Parameters are the Main Prognostic Factors for Overall Survival in Men with Bone Metastases from Castration-resistant Prostate Cancer

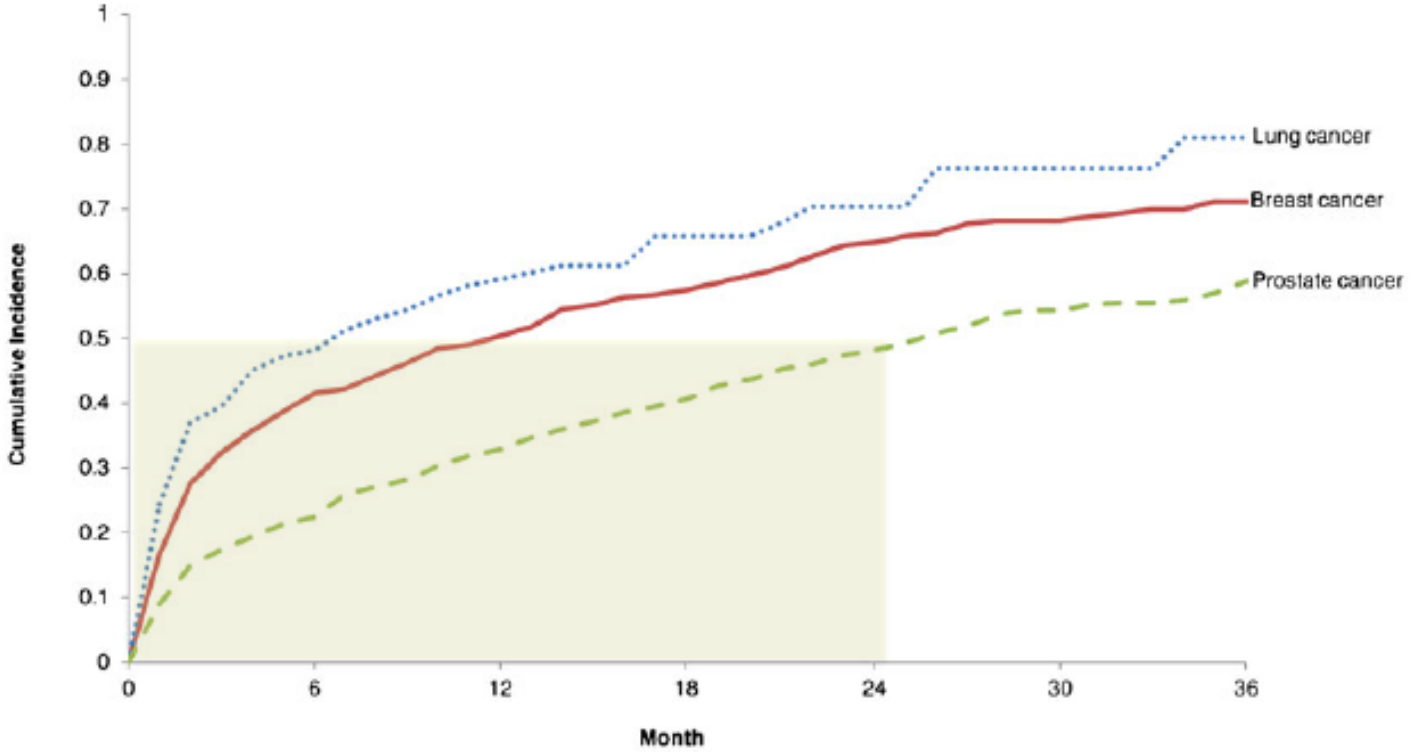




Fizizi et al Eur Urol 2015

Natural history of skeletal-related events in patients with breast, lung, or prostate cancer and metastases to bone: a 15-year study in two large US health systems

(**SSE CUMULATIVE INCIDENCE**)



No. at Risk							
Breast cancer	621	280	186	122	80	57	46
Lung cancer	477	111	46	20	10	7	3
Prostate cancer	721	466	347	257	193	148	118

Oster G et al

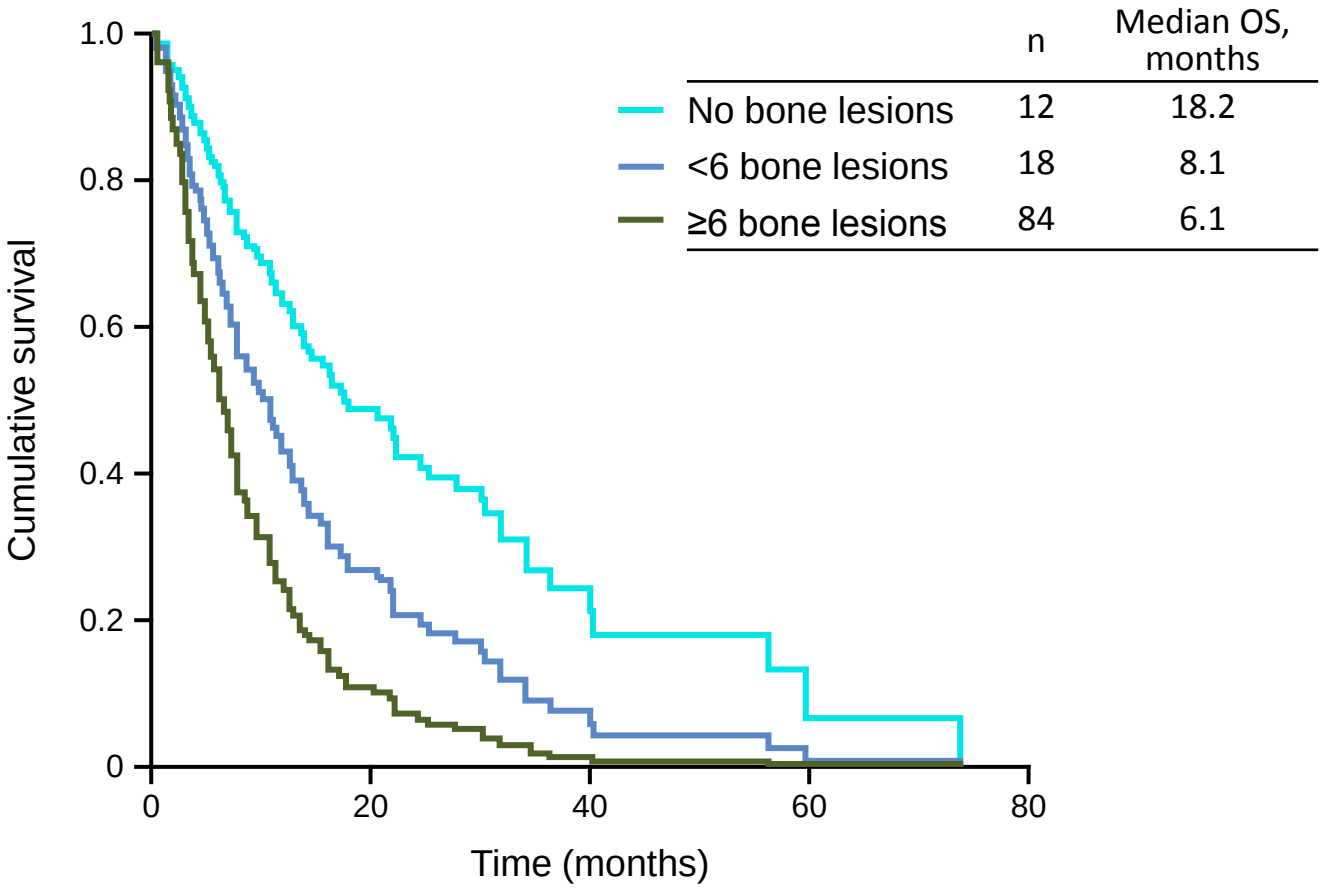
Support Care Cancer (2013) 21:3279–3286

TIME TO EVENT BY TYPE OF SRE (SSE) IN PC PATIENTs STAGE IV (2000-2007)

Variable	N[a]	Mean	SD	Median	Minimum	Maximum
Time to SRE (in days)[b]						
Any SRE	1,131	379	527	146	(30)	2,928
Spinal cord compression only	591	335	502	93	(30)	2,928
Pathological fracture only	157	345	464	152	(22)	2,423
Bone surgery only	184	603	651	417	(14)	2,854
Pathological fracture with concurrent surgery[e]	149	305	414	124	(3)	2,152
Spinal cord compression with concurrent surgery[f]	50	403	600	90	(3)	2,820
Time to death from incident SRE (in days)[c]						
Any SRE	975	329	438	149	1	2,863
Spinal cord compression only	520	302	432	122	1	2,863
Pathological fracture only	139	311	470	107	2	2,732
Bone surgery only	145	342	349	225	1	1,485
Pathological fracture with concurrent surgery[e]	131	382	458	180	1	2,652
Spinal cord compression with concurrent surgery[f]	40	517	563	309	44	2,274

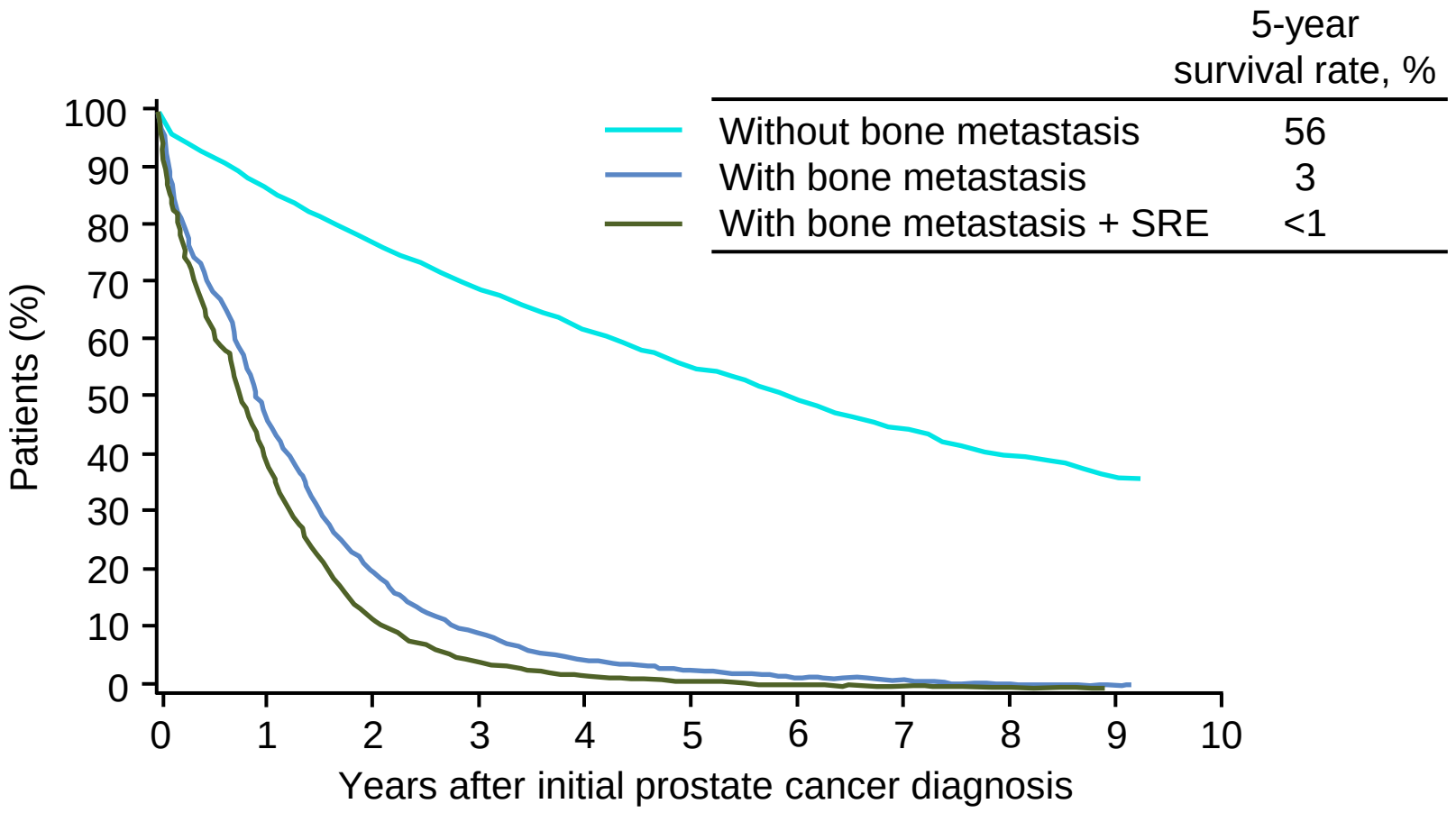
PharmacoEconomics (2014) 32:173–191

L’estensione delle lesioni ossee è associata ad aumento della mortalità



Pezaro C, et al. Eur Urol 2014;65:270–3

SREs sono associati ad incremento della mortalità



N=23 087 with median follow-up of 2.2 years (Danish National Patient Registry)
SRE, skeletal-related event
Nørgaard M et al. J Urol 2010;184:162-7

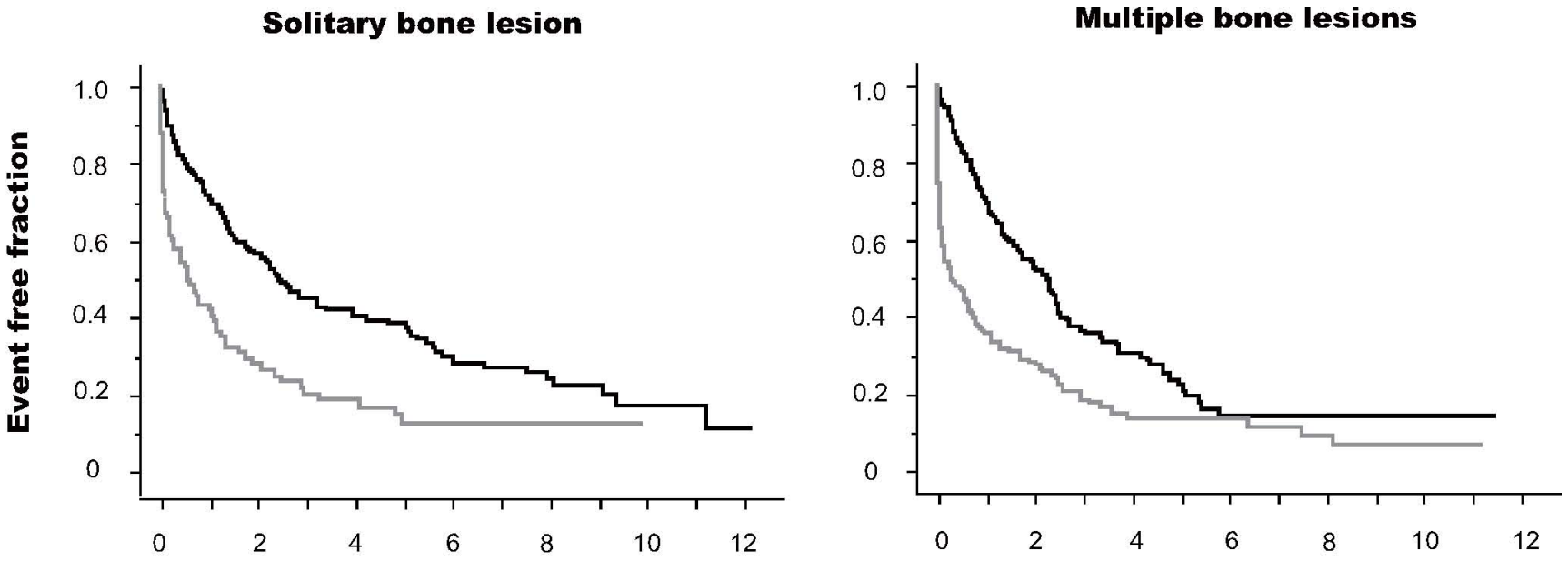
Mortality following bone metastasis and skeletal-related events among women with breast cancer: a population-based analysis of U.S. Medicare beneficiaries, 1999–2006

Table 3 Adjusted hazard ratio (HR)[a] for death in relation to bone metastasis and skeletal-related events (SRE) among women with breast cancer, by stage at diagnosis: SEER-Medicare, July 1, 1999–December 31, 2006

		Bone metastasis		
		No	Yes, without SRE	Yes, with SRE
Deaths		19,644	2,590	2,372
In situ	HR	1.0 (referent)	8.5	16.9
	(95% CI)		(6.4–11.3)	(13.2–21.5)
Localized	HR	1.0 (referent)	7.9	11.6
	(95% CI)		(7.3–8.7)	(10.7–12.7)
Regional	HR	1.0 (referent)	6.9	10.0
	(95% CI)		(6.4–7.5)	(9.2–10.8)
Distant	HR	1.0 (referent)	1.9	2.3
	(95% CI)		(1.8–2.1)	(2.1–2.4)
Unstaged	HR	1.0 (referent)	2.8	4.4
	(95% CI)		(2.4–3.3)	(3.5–5.5)

Sathiakumar N et al Breast Cancer Res Treat (2012) 131:231–238

Post-operative breast cancer patients diagnosed with skeletal metastasis **without bone pain** had fewer skeletal-related events than those with bone pain



Koizumi et al. BMC Cancer 2010, 10:423

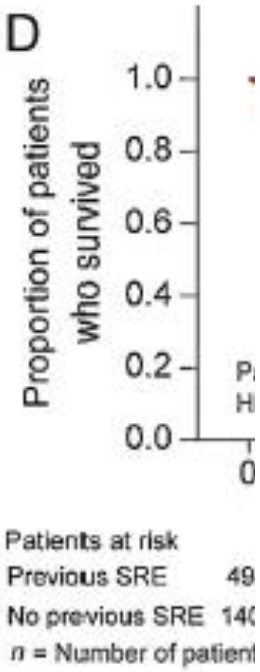
Table 3 – Multivariate analysis of baseline prognostic variables for overall survival

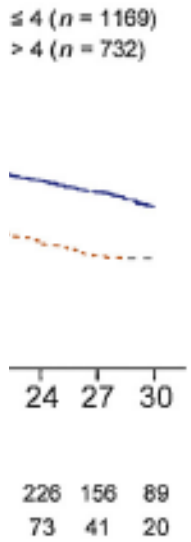
Variable	Hazard ratio (95% CI)	*p* value
PSA <10 ng/ml	0.486 (0.381, 0.619)	<0.0001
No previous SRE	0.748 (0.643, 0.871)	0.0002
Pain absent or mild (BPI-SF score ≤4)	0.648 (0.563, 0.745)	<0.0001
ALP ≤ median	0.664 (0.559, 0.789)	<0.0001
BSAP <146 µg/l	0.683 (0.568, 0.822)	<0.0001
Corrected uNTX ≤50 nmol/mmol	0.755 (0.640, 0.889)	<0.0008
Hemoglobin > median	0.614 (0.532, 0.709)	<0.0001
No visceral metastases	0.733 (0.621, 0.864)	0.0002
ECOG score ≤1	0.755 (0.599, 0.950)	0.0167
Age in years	1.012[a] (1.003, 1.021)	0.0081
Time from initial diagnosis to bone metastases diagnosis (mo)	0.997 (0.995, 0.998)	<0.0001
Time from diagnosis of bone metastases to randomization (mo)	0.990[b] (0.986, 0.995)	<0.0001

ALP = alkaline phosphatase; BPI—SF = Brief Pain Inventory—Short Form; BSAP = bone-specific alkaline phosphatase; CI = confidence interval; ECOG = Eastern Co-operative Oncology Group; uNTx = urinary N-telopeptide.

[a] Reflects the change in the hazard for any increase of 1 yr.

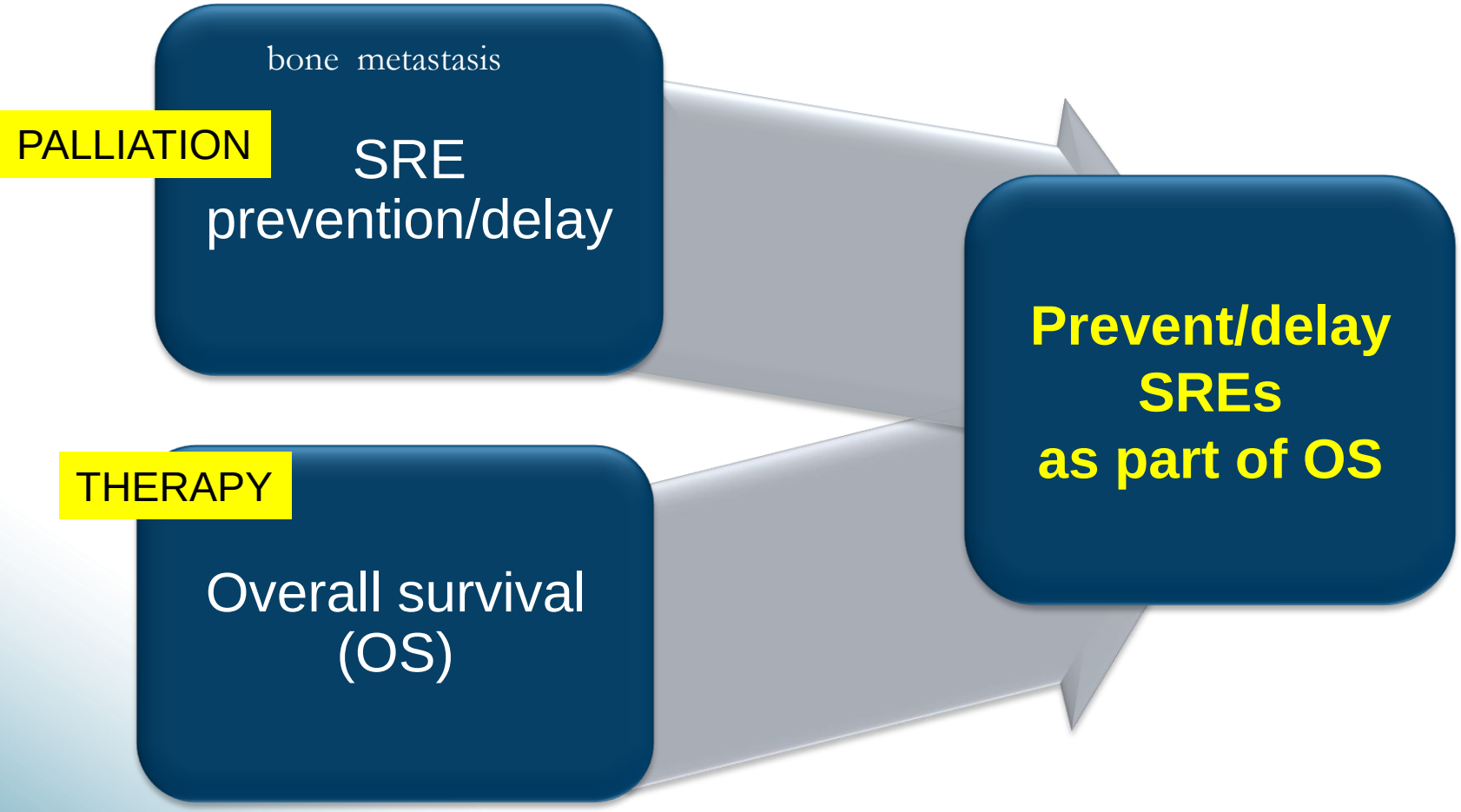
[b] Reflects the change in the hazard for any increase of 1 mo.



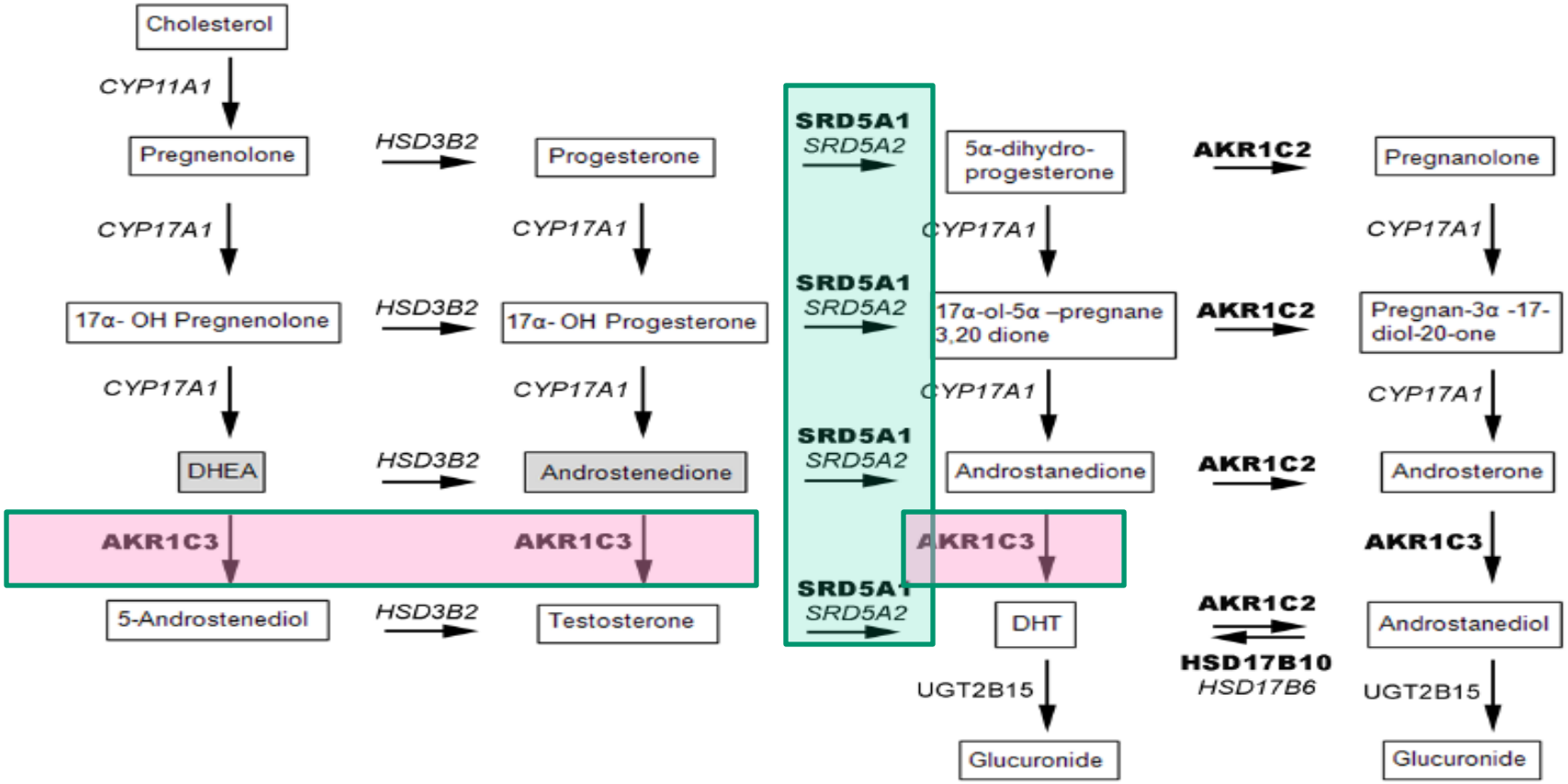


Fizizi et al Eur Urol 2

Treatment goals in cancer patients



Characterization of Prostate Cancer Bone Metastases According to Expression Levels of Steroidogenic Enzymes and Androgen Receptor Splice Variants



Jernberg E et al PLOS/one 2014

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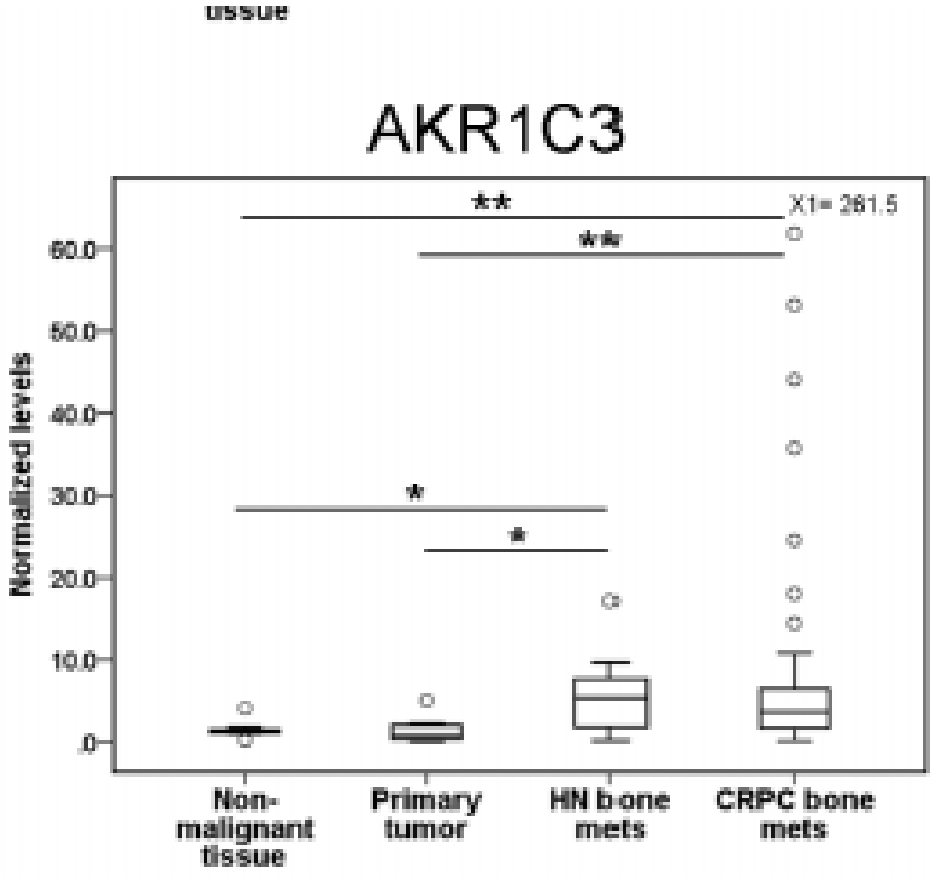
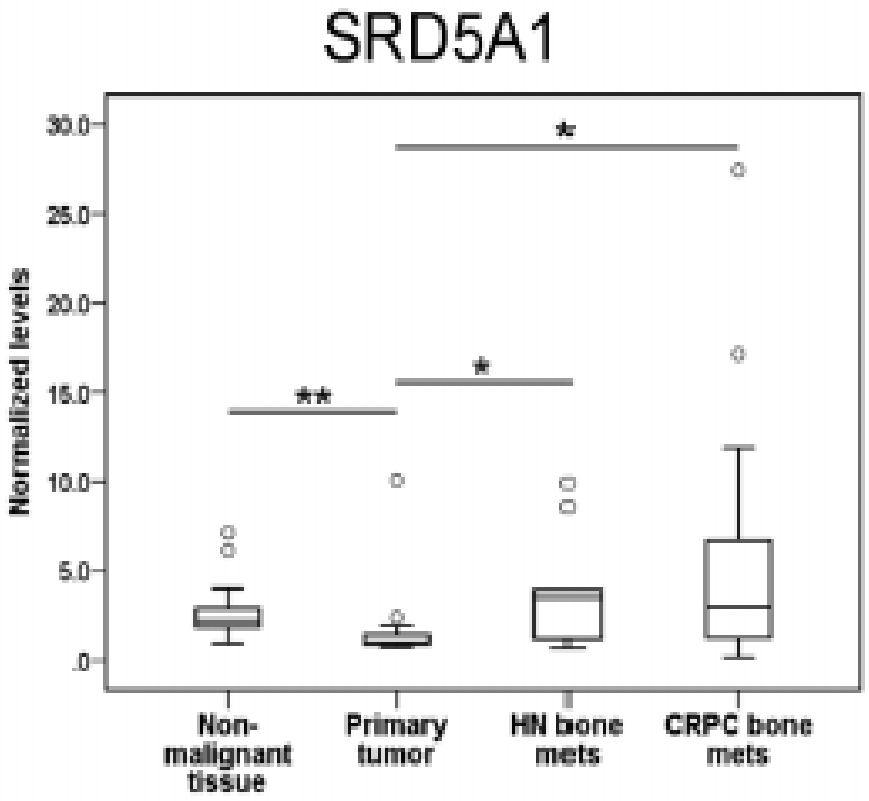
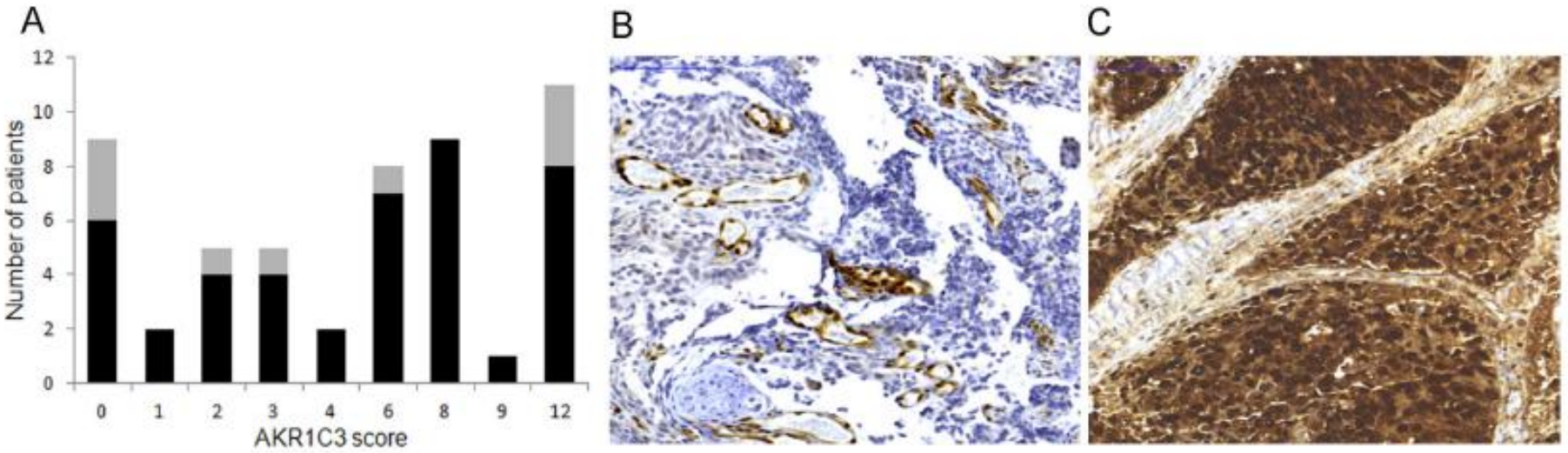




Jernberg E et al PLOS/one 2014

Characterization of Prostate Cancer Bone Metastases According to Expression Levels of Steroidogenic Enzymes and Androgen Receptor Splice Variants

Immunohistochemical staining of AKR1C3 in bone metastases.



Jernberg E et al PLOS/one 2014

Characterization of Prostate Cancer Bone Metastases According to Expression Levels of Steroidogenic Enzymes and Androgen Receptor Splice Variants

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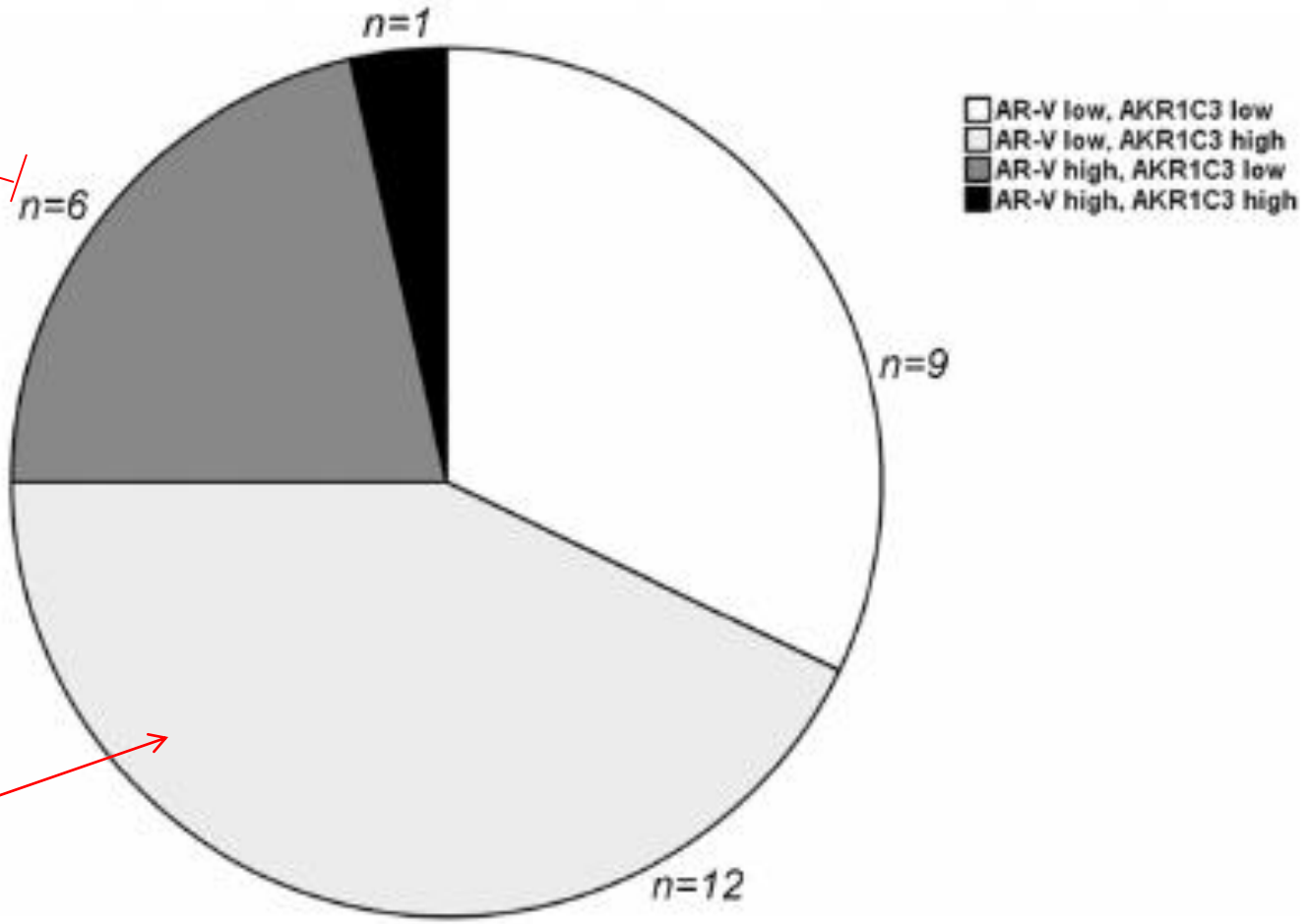

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Jernberg E et al PLOS/one 2014