Società Italiana di Osteoncologia

Novità sul trattamento medico delle metastasi ossee.

ONJ UPDATE 2018

OSTEONECROSI DELLE OSSA MASCELLARI (ONJ)
DA BIFOSFONATI E ALTRI FARMACI:
PREVENZIONE, DIAGNOSI, FARMACOVIGILANZA, TRATTAMENTO

5 Maggio 2018

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Medical Oncology Department

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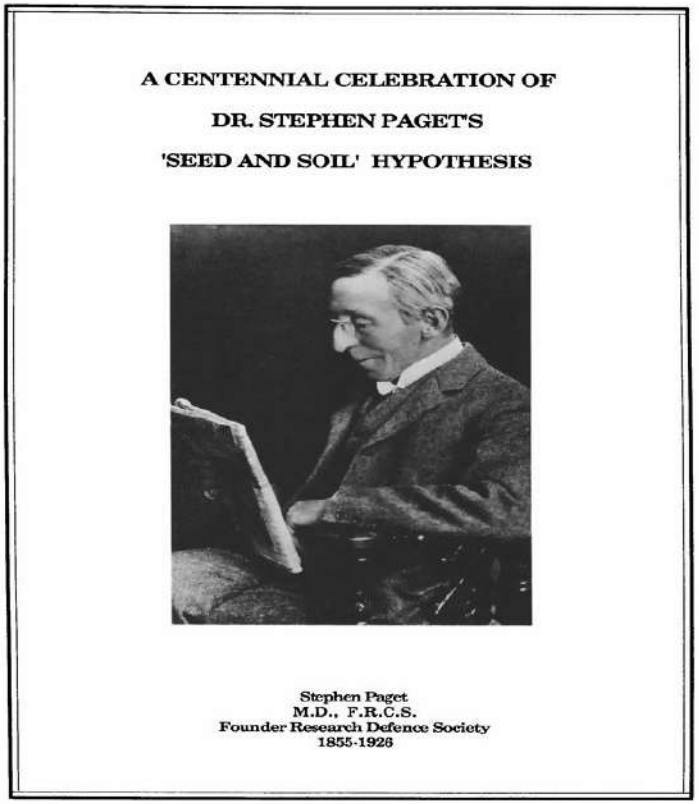
The question is:

Was "true revolution" in the cancer bone field?

The house believes:

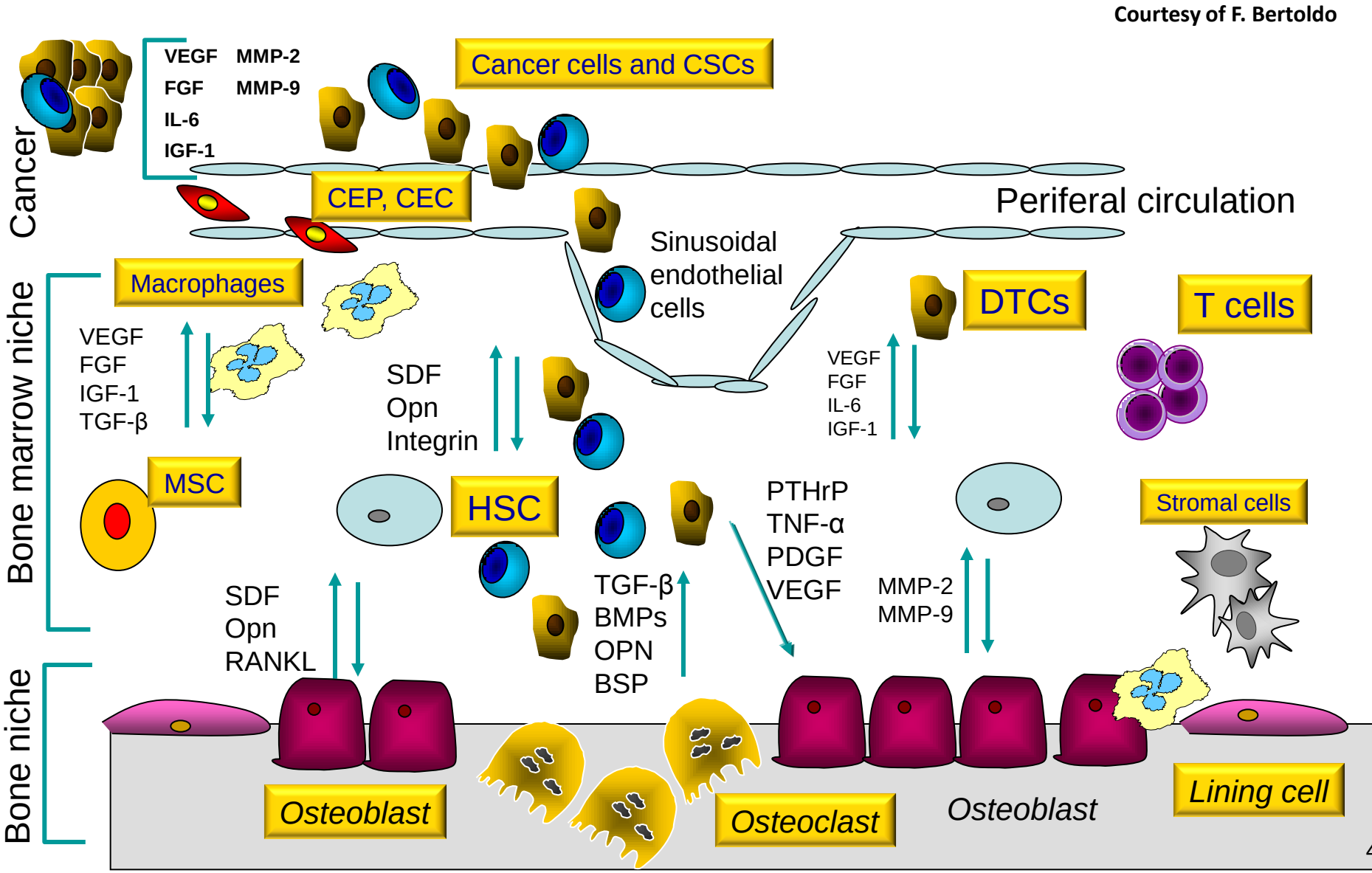
Yes, it was a "biological revolution"

From seed and soil “era”: where we were

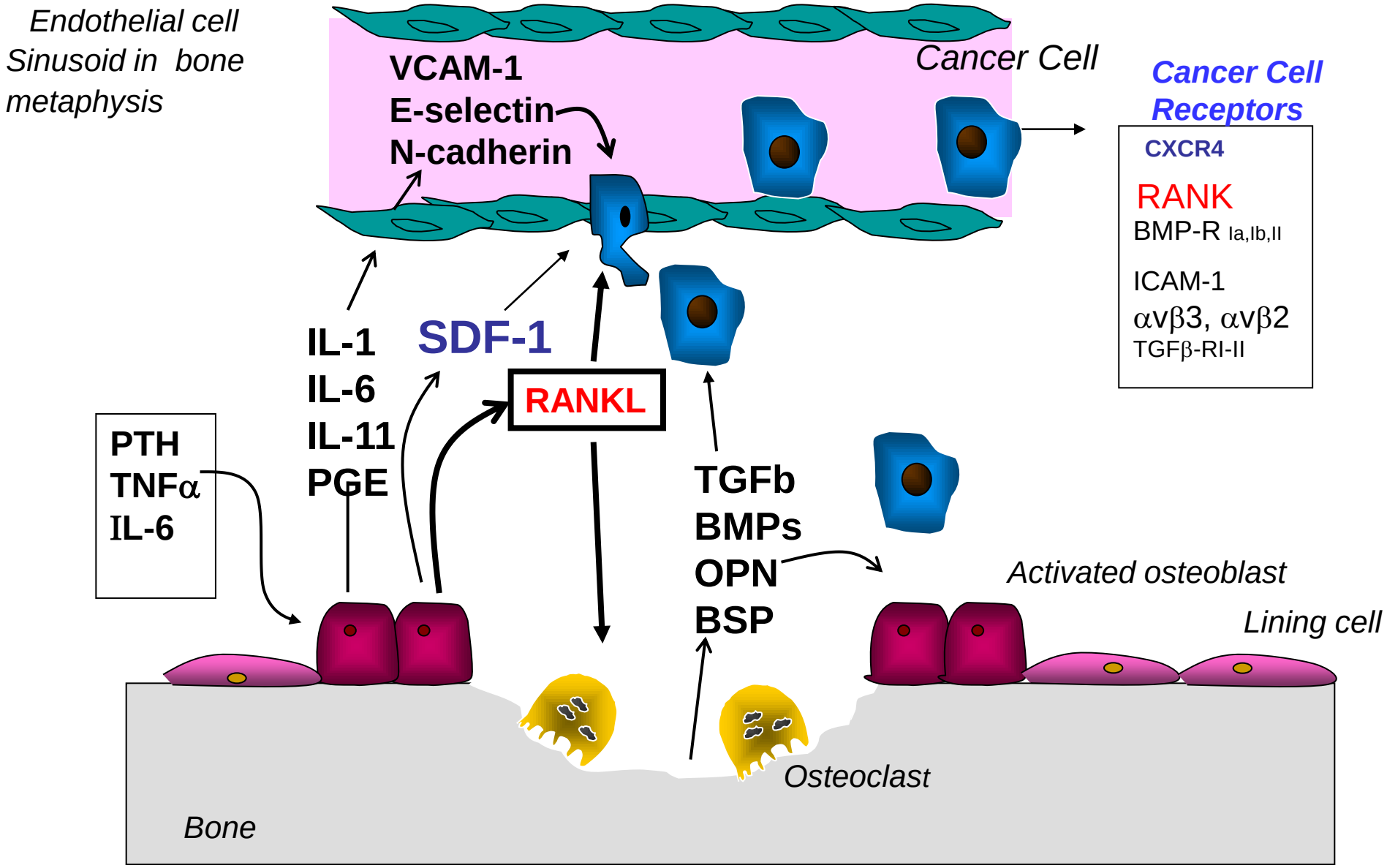


Where we are going to…..

The first question is: when the cancer cells arrive?

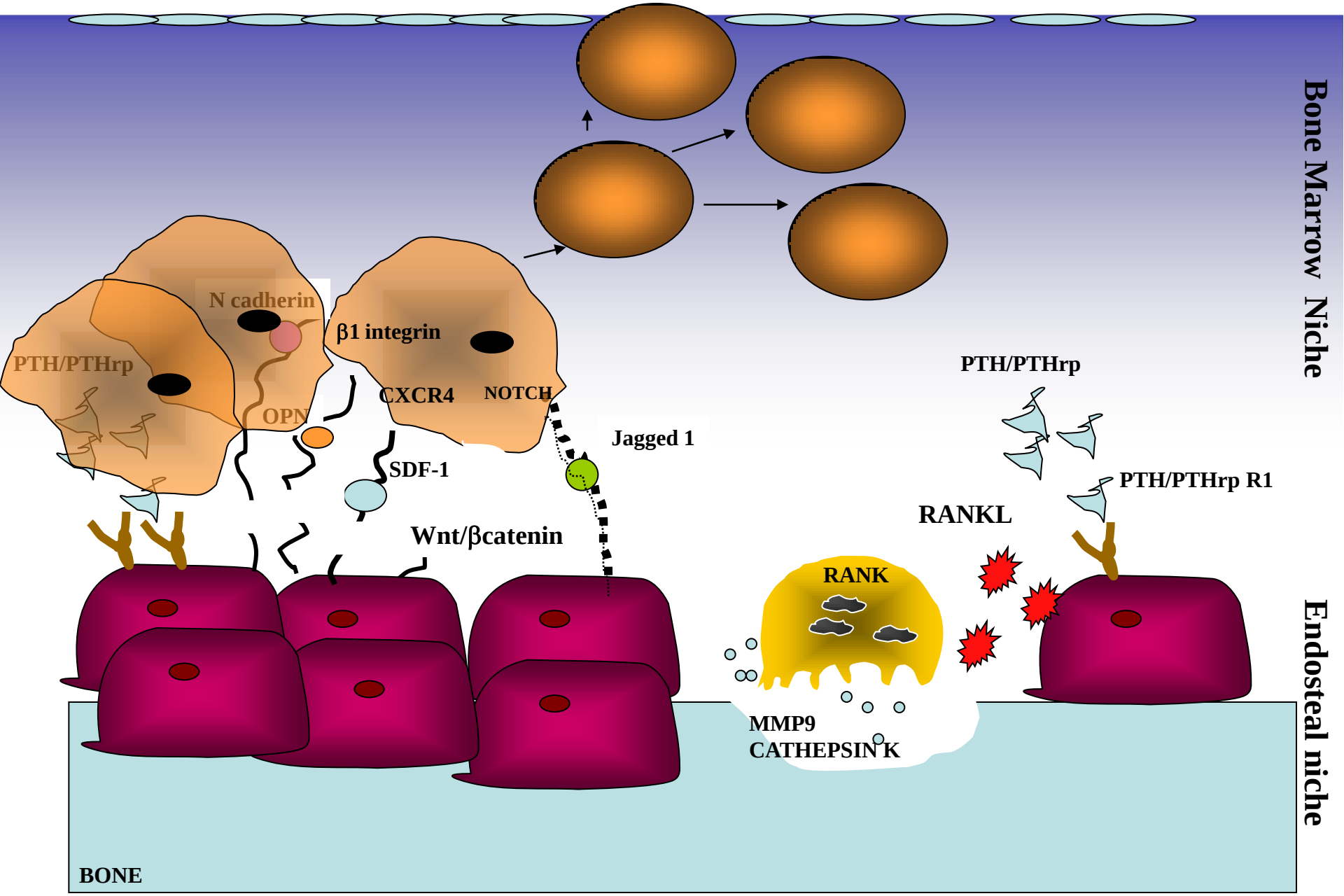


The second question is: how the cancer cells are attracted in the bone niche?



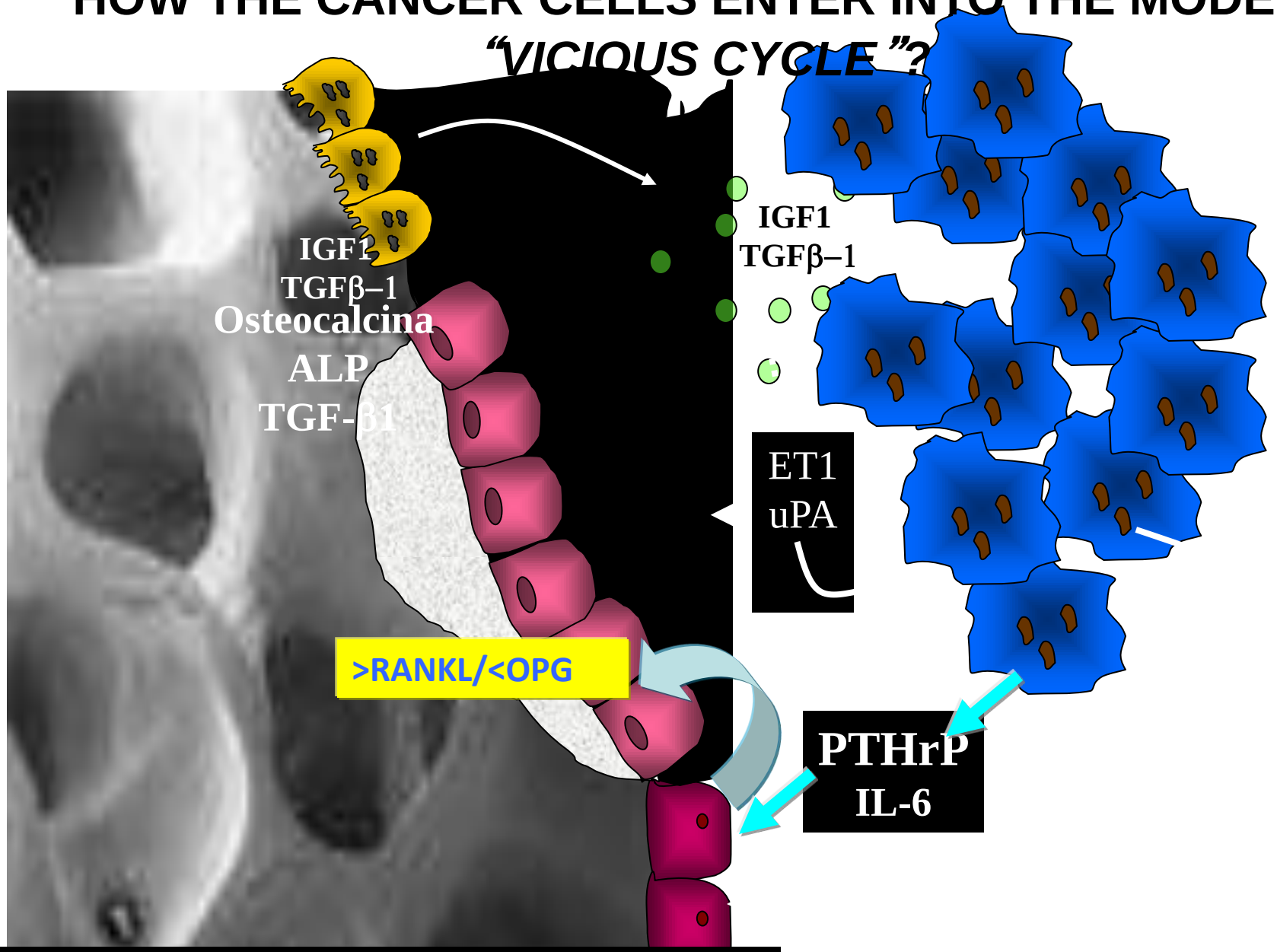
Bertoldo F, Santini D .Textbook of Osteoncology 2010

The third question is: how the cancer cells go away?



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

THE FOURTH QUESTION IS:
HOW THE CANCER CELLS ENTER INTO THE MODERN *"VICIOUS CYCLE"?*



Bertoldo F, Santini D Textbook of Osteoncology 2010

Was “true revolution” in the cancer bone field?

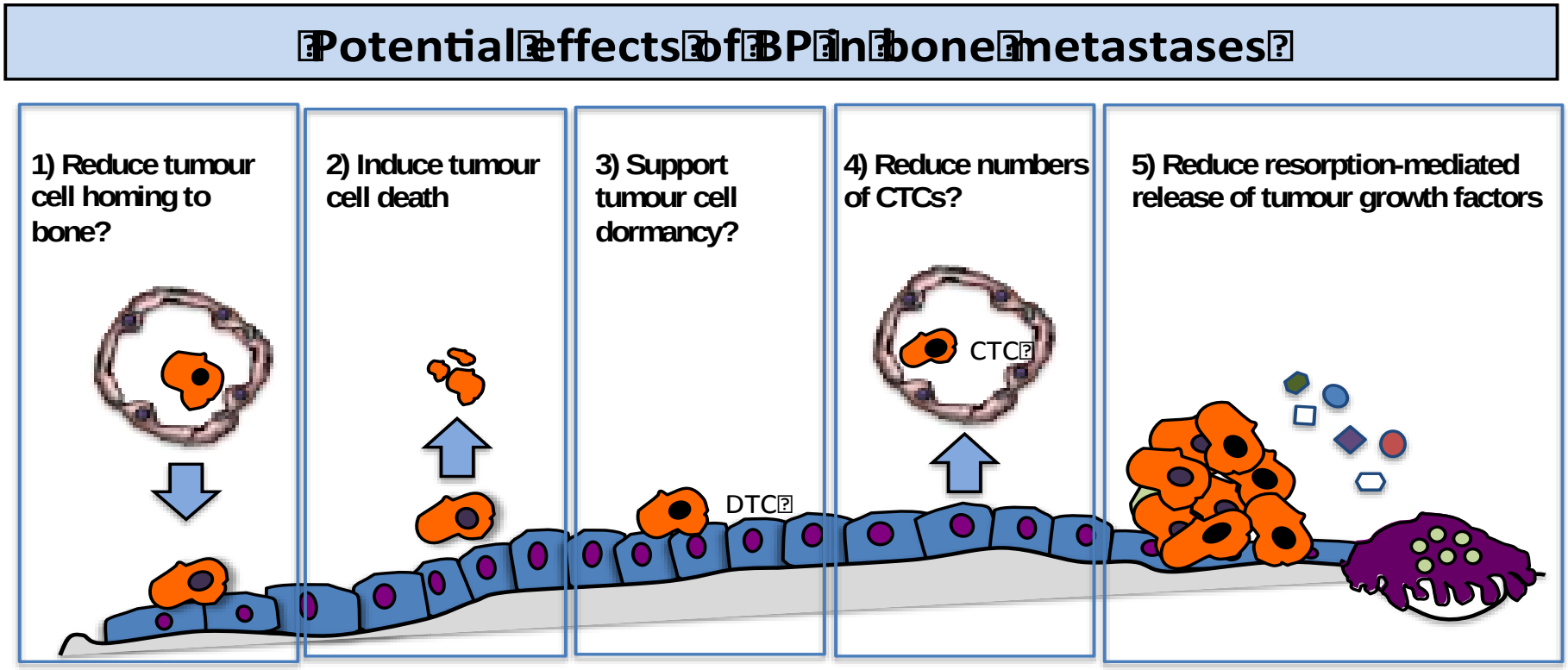
The house believes:

Yes, it was a “therapeutic revolution”

“Bone Health” and new drugs

- Bisphosonates (Zoledronic Acid)
- Anti RANKL MoAb (Denosumab)
- mTOR inhibitor
- Radiopharmaceutical (Radium-223)
- Endothelin A receptor antagonist (Zibotentan)
- Src inhibitors (Saracatinib, Dasatinib)
- Novel Antiandrogens (Abiraterone Acetate and Enzalutamide)
- Cabozantinib: MET/VEGFR-targeted agent

Bisphosphonates in preclinical animal models can modify the bone microenvironment



Other cell types in the bone/tumour microenvironment shown to be affected by BPs:

- **Osteoblasts:** Reduced by a single dose of Zol *in vivo* (54)
- **Macrophages:** Increased polarisation to M2 anti-tumour phenotype in mammary tumour, no evidence from bone metastasis models (58)
- **Immune cells:** Stimulation of immune cells by BPs affects tumour growth specifically in those tumours outside bone (59)

Courtesy by I. Holen, Sheffiled, UK

New

Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

THE LANCET

www.thelancet.com

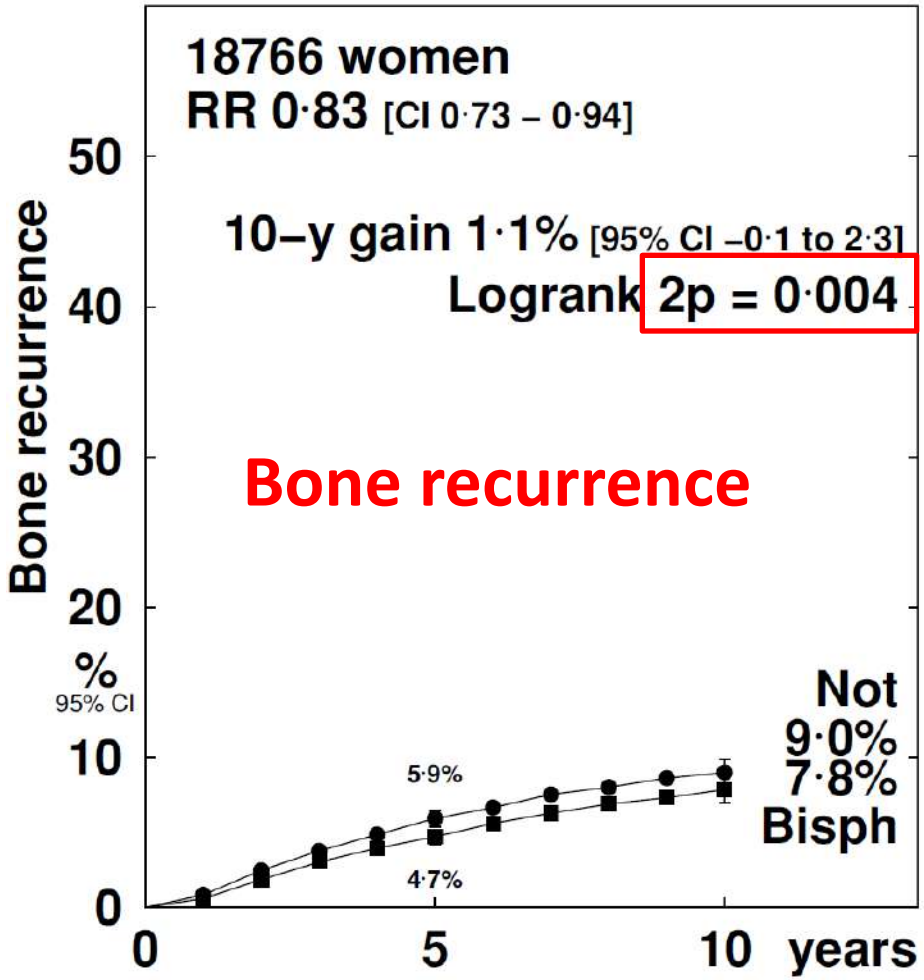
Published online July 24, 2015

http://dx.doi.org/10.1016/S0140-6736(15)60908-4

Data received: 18,766 women

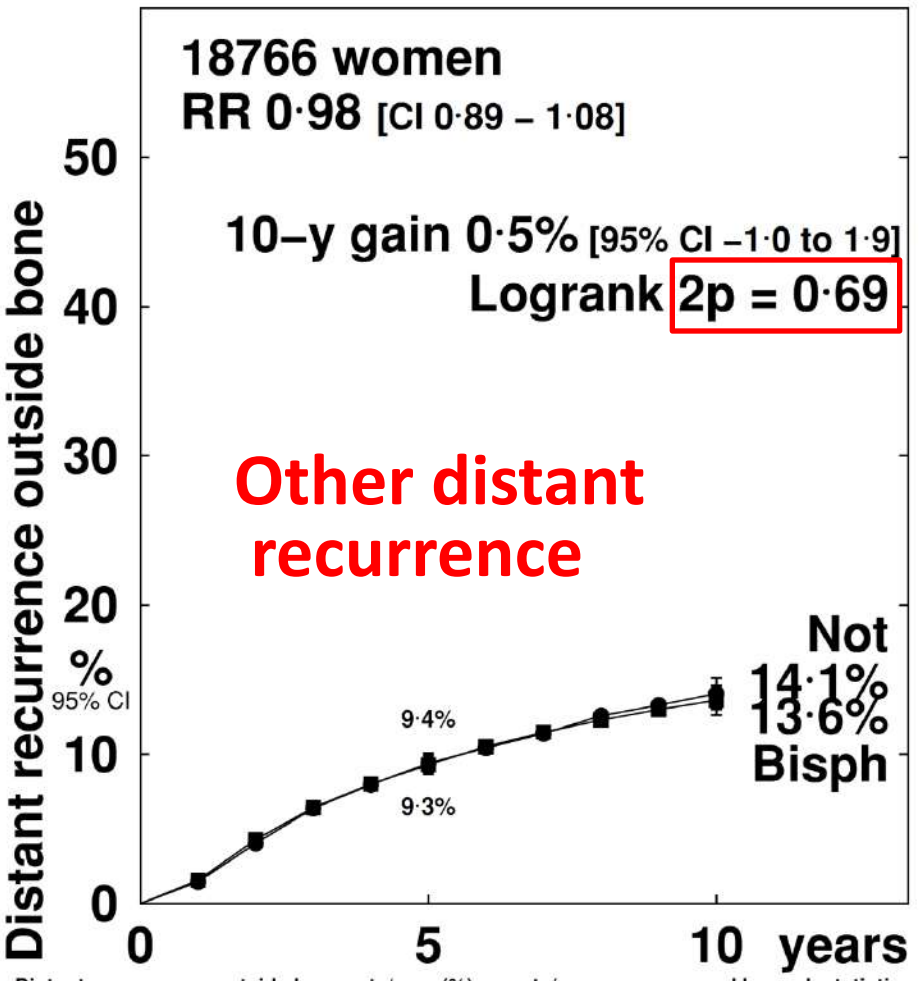
	Studies identified		Studies with data received			
	Trials	Patients	Trials	Patients	%	Years
<1 year clodronate	2	120	1	72	60	0·5
<1 year aminobisphosphonate	2	208	1	40	19	0·1
1 year aminobisphosphonate	7	1088	3	448	41	1·0
Subtotal: ≤1 year of treatment	**11**	**1416**	**5**	**560**	**40%**	**0·9**
2 years clodronate	4	3978	3	3912	98	2·0
3-5 years clodronate	1	1069	1	1069	100	3.0
2 years aminobisphosphonate	10	3654	8	3514	96	2·0
3-5 years aminobisphosphonate	12	11 910	9	9711	82	4·5
Subtotal: 2-5 yrs of treatment	**27**	**20 611**	**21**	**18 206**	**88%**	**3·5**
Any clodronate regimen	7	5167	5	5053	98	2·6
Any aminobisphosphonate‡	31	16 860	21	13 713	81	3·8
Total: All regimens	**38**	**22 027**	**26**	**18 766**	**85%**	**3·4**

Bisphosphonates reduce bone recurrences



Bone recurrence rate/year (%), events/woman–years and logrank statistics

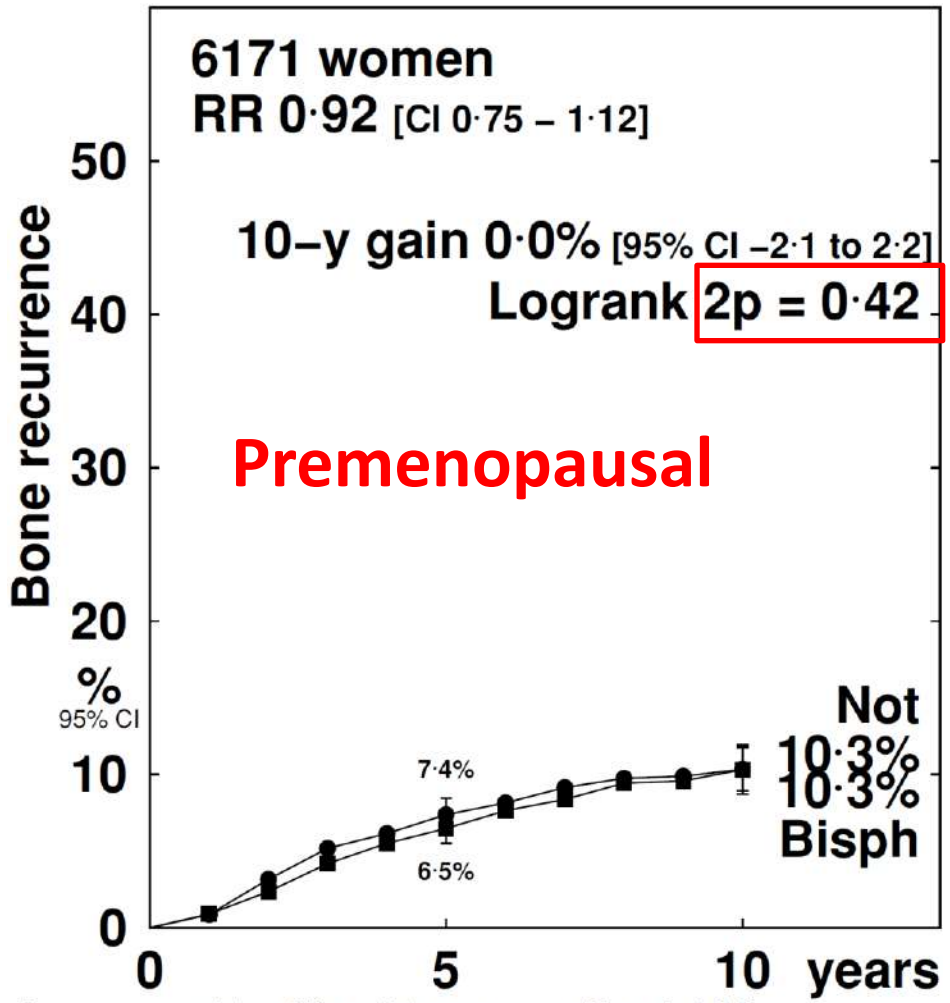
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	0·99 (391 / 39559)	0·76 (104 / 13746)	0·10 (2 / 1932)
Not	1·21 (441 / 36571)	0·71 (99 / 13931)	0·10 (2 / 1941)
Rate ratio, from (O–E) / V	0·79 [CI 0·66 – 0·92] –45·0 / 189·5	1·02 [CI 0·73 – 1·31] 0·8 / 46·8	0·61 [CI 0·08 – 2·25] –0·4 / 0·9



Distant recurrences outside bone rate/year (%), events/woman–years and logrank statistics

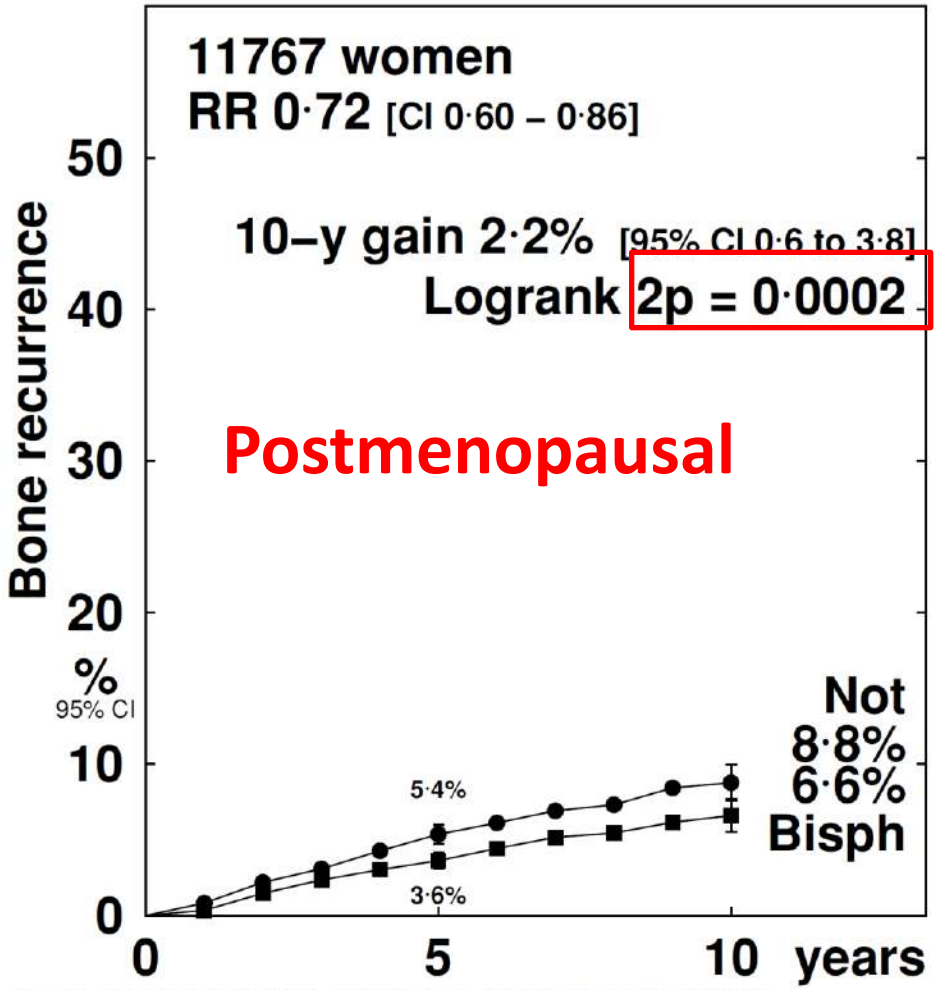
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	1·98 (782 / 39559)	1·08 (149 / 13746)	0·57 (11 / 1932)
Not	1·99 (729 / 36571)	1·11 (154 / 13931)	0·98 (19 / 1941)
Rate ratio, from (O–E) / V	0·99 [CI 0·89 – 1·10] –2·5 / 327·9	0·98 [CI 0·74 – 1·21] –1·5 / 68·7	0·45 [CI –0·15 – 1·05] –4·1 / 5·1

Benefits on bone recurrences appear to be confined to postmenopausal/ older women



Bone recurrence rate/year (%), events/woman–years and logrank statistics

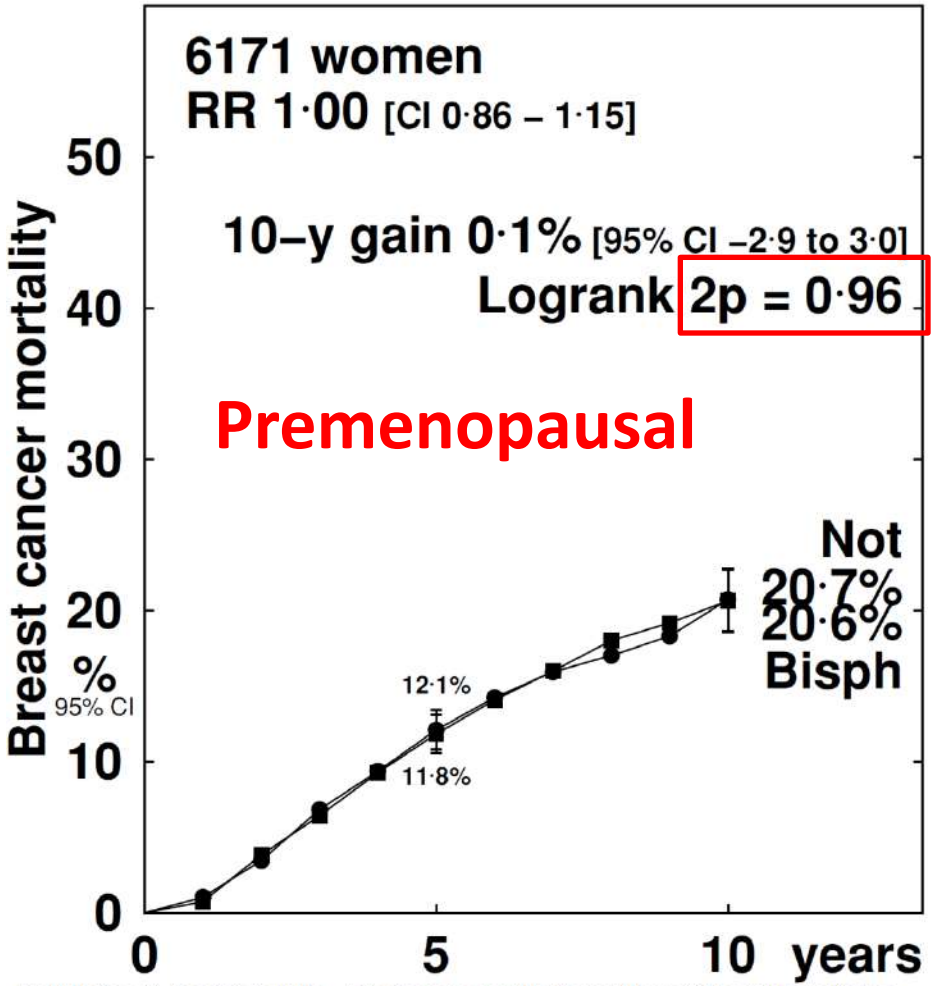
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	1·35 (169 / 12510)	1·00 (47 / 4710)	0·07 (1 / 1390)
Not	1·54 (175 / 11390)	0·69 (36 / 5196)	0·07 (1 / 1424)
Rate ratio, from (O–E) / V	0·86 [CI 0·66 – 1·07] –11·4 / 77·4	1·24 [CI 0·73 – 1·74] 3·9 / 18·5	0·37 [CI 0·02 – 2·33] –0·4 / 0·4



Bone recurrence rate/year (%), events/woman–years and logrank statistics

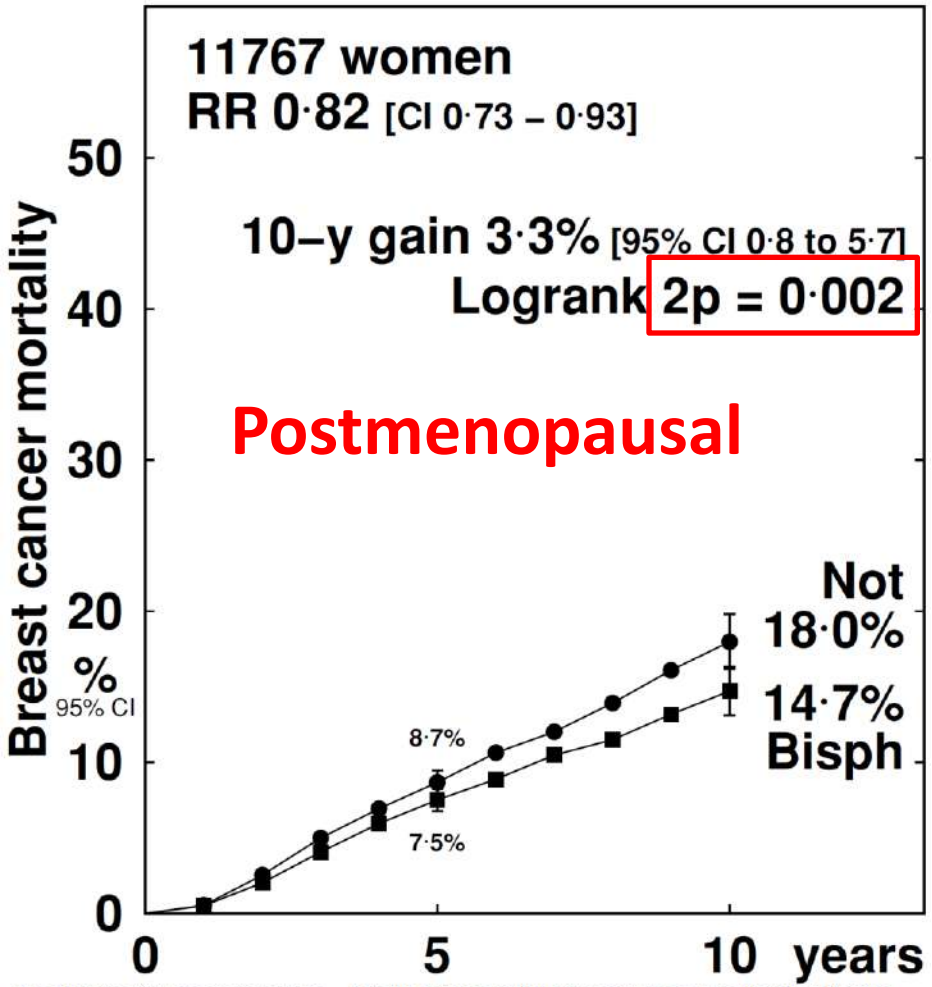
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	0·78 (197 / 25220)	0·67 (55 / 8157)	0·0(0/513)
Not	1·06 (251 / 23642)	0·76 (60 / 7870)	0·0(0/484)
Rate ratio, from (O–E) / V	0·68 [CI 0·52 – 0·84] –39·3 / 101·2	0·90 [CI 0·54 – 1·26] –2·8 / 26·8	

Among postmenopausal women, significant reductions in breast cancer mortality



Death rates (% / year: total rate – rate in women without recurrence) & logrank statistics

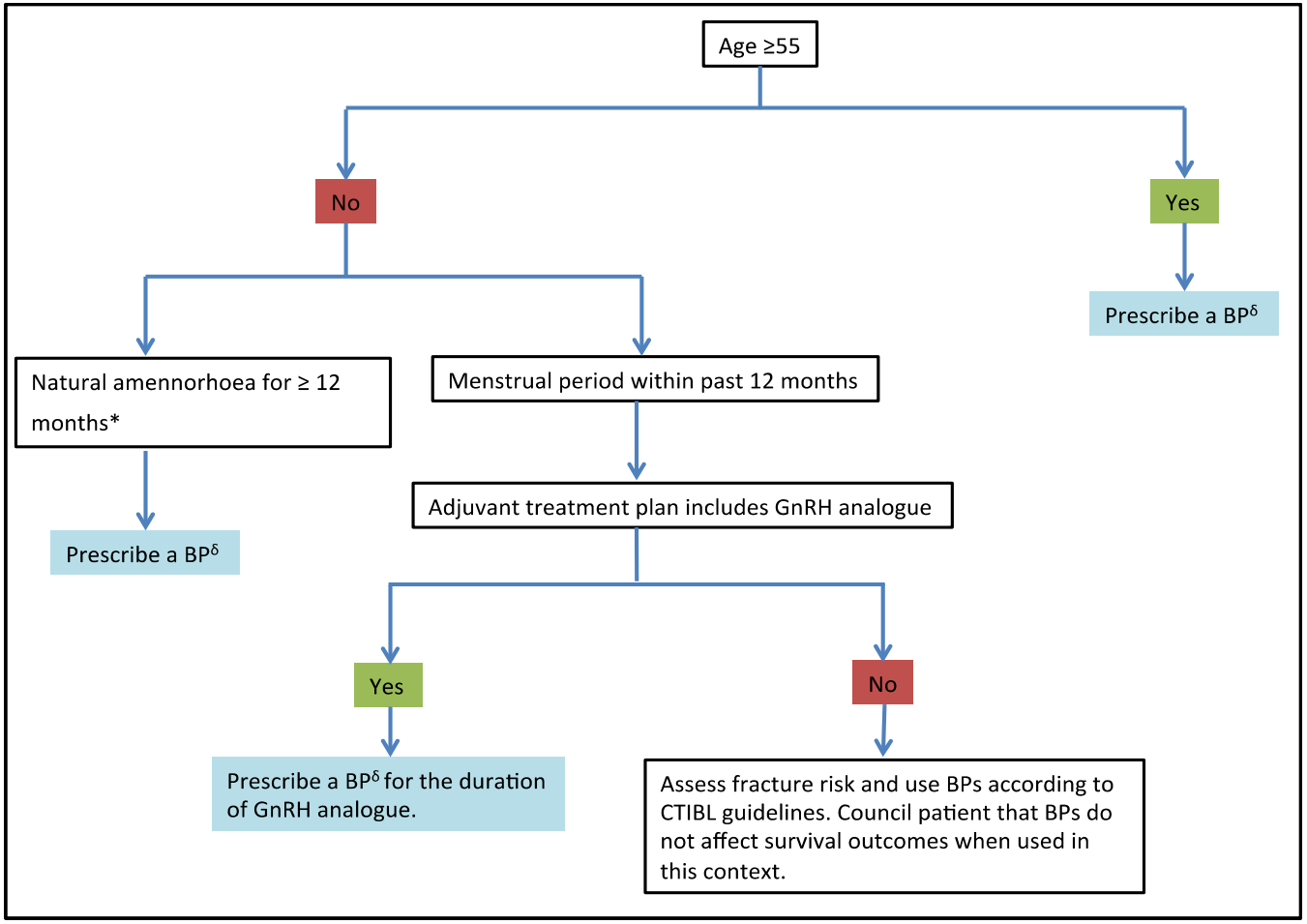
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisp	2·43 [CI 2·16 – 2·69]	2·26 [CI 1·84 – 2·67]	1·13 [CI 0·58 – 1·68]
Not	2·50 [CI 2·22 – 2·79]	2·03 [CI 1·65 – 2·40]	1·29 [CI 0·71 – 1·88]
Rate ratio, from (O–E) / V	0·97 [CI 0·81 – 1·14] –3·3 / 130·6	1·10 [CI 0·81 – 1·40] 5·0 / 50·0	0·71 [CI 0·34 – 1·50] –2·3 / 6·9



Death rates (% / year: total rate – rate in women without recurrence) & logrank statistics

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisp	1·56 [CI 1·41 – 1·72]	1·57 [CI 1·30 – 1·84]	1·30 [CI 0·34 – 2·26]
Not	1·74 [CI 1·58 – 1·91]	2·04 [CI 1·74 – 2·35]	2·73 [CI 1·30 – 4·16]
Rate ratio, from (O–E) / V	0·86 [CI 0·72 – 0·99] –27·1 / 174·9	0·76 [CI 0·55 – 0·97] –18·0 / 65·0	0·52 [CI 0·18 – 1·44] –2·4 / 3·6

Adjuvant bisphosphonates in early breast cancer: Consensus from a European Panel.



*If not clinically assessable i.e. hysterectomy/ IUD then ensure serum FSH is in postmenopausal range. Ensure patient is not receiving concurrent therapies that can affect the HPG axis.

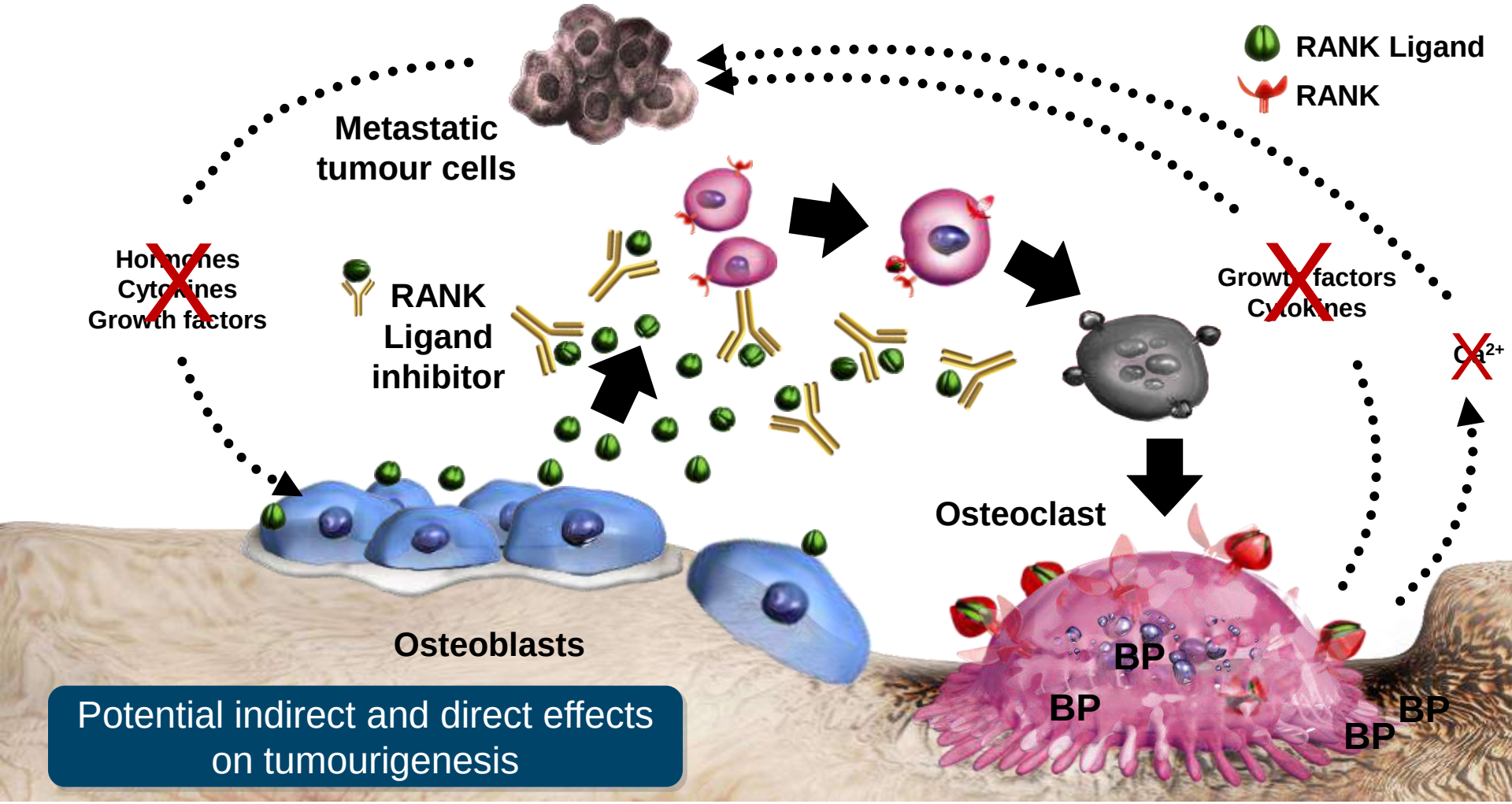
$^{\delta}$Include vitamin D 1000-2000IU and calcium 1000mg daily.

P Hadji, RE Coleman, D. Santini Ann Onco 2015

“Bone Health” and new drugs

- Bisphosonates (Zoledronic Acid)
- Anti RANKL MoAb (Denosumab)
- mTOR inhibitor
- Radiopharmaceutical (Radium-223)
- Endothelin A receptor antagonist (Zibotentan)
- Src inhibitors (Saracatinib, Dasatinib)
- Novel Antiandrogens (Abiraterone Acetate and Enzalutamide)
- Cabozantinib: MET/VEGFR-targeted agent

Denosumab interrupt the ‘vicious cycle’ and change the bone microenvironment



Potential indirect and direct effects on tumourigenesis

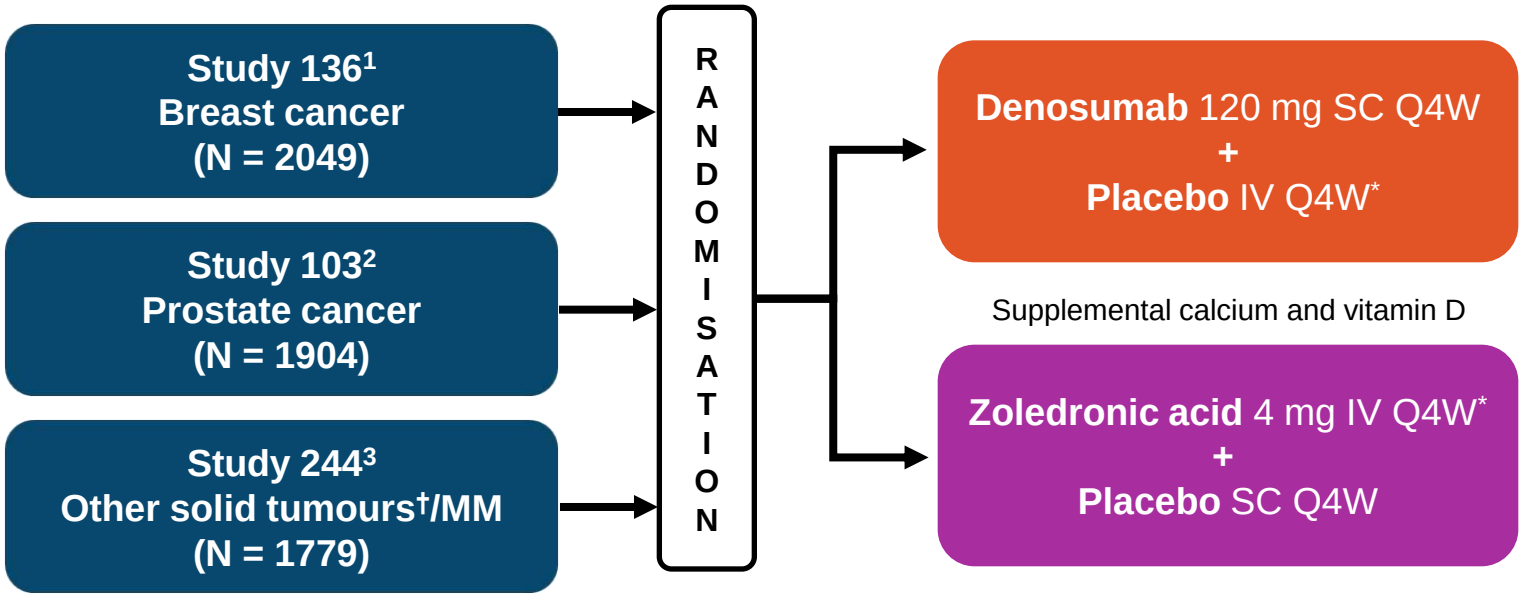
Adapted from Boyle WJ, et al. Nature 2003;423:337–42;
Roodman GD. N Engl J Med 2004;350:1655–64;
Roodman GD. Leukemia 2009;23:435–41.

BP, bisphosphonate.

Denosumab* Phase III SRE prevention trials

Three trials of identical design in patients with bone metastases from solid tumours or multiple myeloma

Lipton et al ASCO, 2014



- Primary endpoint: time to first on-study SRE
- Secondary endpoints: time to first and subsequent SREs, time to disease progression, overall survival, incidence of adverse events

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.

*IV product dose adjusted as per zoledronic acid product labelling.
†Excluding breast and prostate.
MM, multiple myeloma; Q4W, every 4 weeks; SC, subcutaneously.

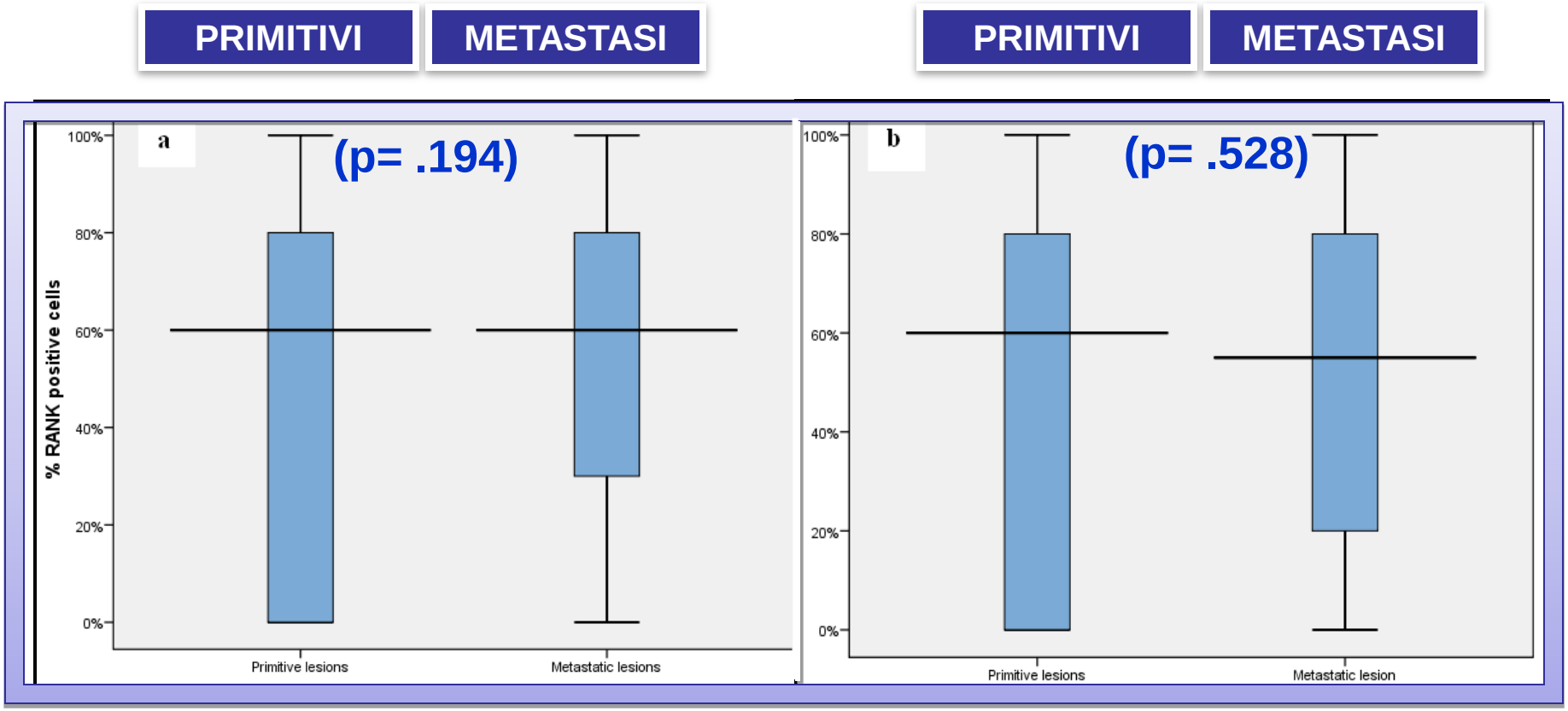
Subgroup analyses by baseline characteristics.

Denosumab significantly delayed patients' time to SREs compared to ZA regardless of patient's baseline status.

Benefit of denosumab vs ZA on time to first on-study SRE		
Baseline characteristic	**HR (95% CI)**	***P*-value**
Axial bone mets only (n=1,422)	0.83 (0.70,1.00)	0.046
Appendicular bone mets only (n=753)	0.78 (0.61,0.99)	0.042
Both axial & appendicular bone mets (n=1,695)	0.83 (0.71, 0.97)	0.022
≥2 bone mets (n=2,234)	0.81 (0.71,0.93)	0.003
<2 bone mets (n=3,489)	0.84 (0.74,0.94)	0.003
Visceral mets (n=2,341)	0.80 (0.69,0.93)	0.003
No visceral mets (n=3,382)	0.84 (0.75,0.94)	0.002
High uNTx (n=2,553)	0.86 (0.76,0.98)	0.028
Low uNTx (n=2,553)	0.75 (0.65, 0.86)	<0.001
ECOG 0 (n=2,312)	0.82 (0.71,0.94)	0.006
ECOG ≥1 (n=3,398)	0.84 (0.75,0.94)	0.002

Lipton et al ASCO, 2014

RANK is expressed in humans by cancer cells both at primary tumor and at bone metastases

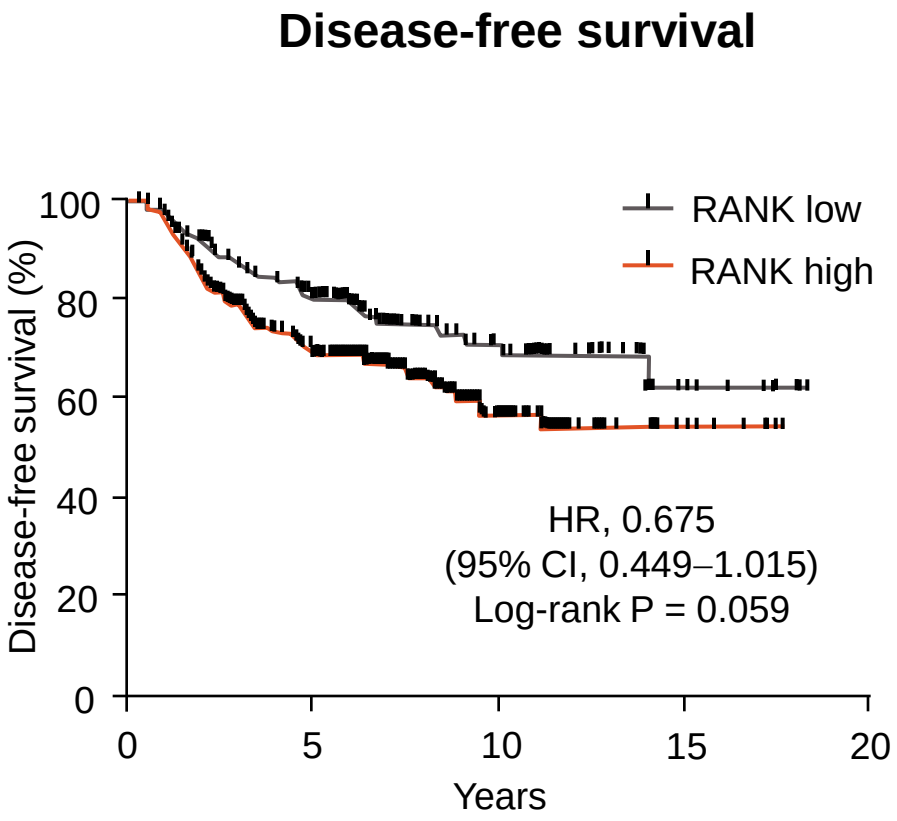


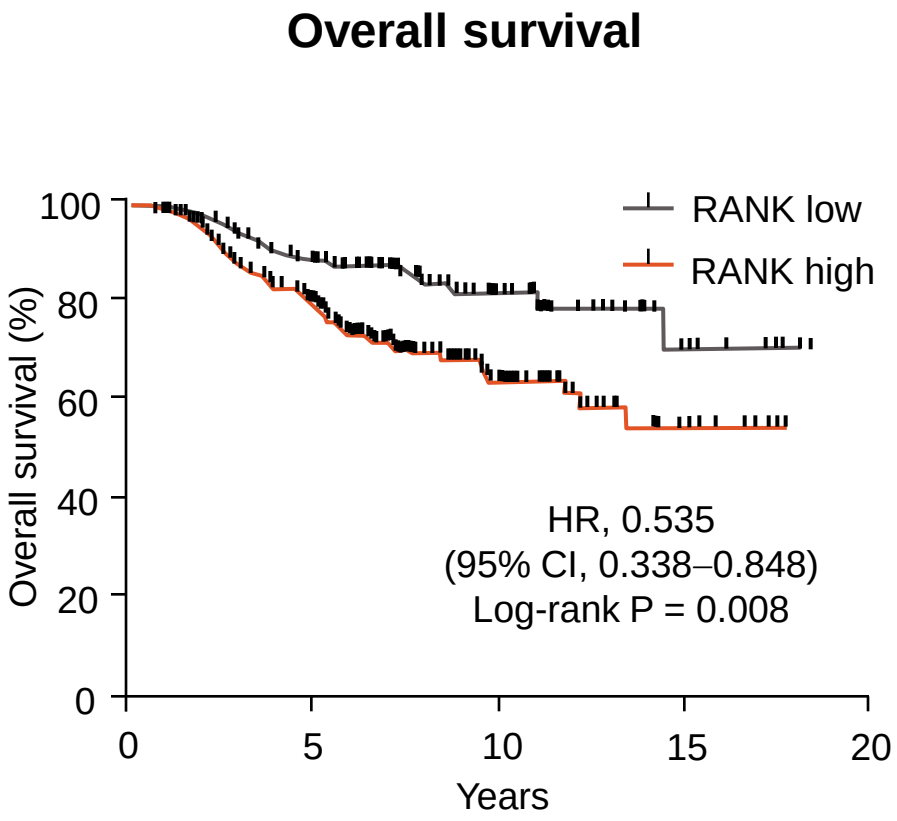
a. Relationships primary-bone metastases (all samples)

b. Relationships primary-bone metastases (in the same patients)

Santini D. et al. J Cell Phys, 2010

Low RANK expression was associated with better disease outcomes vs high RANK expression in human breast cancer patients

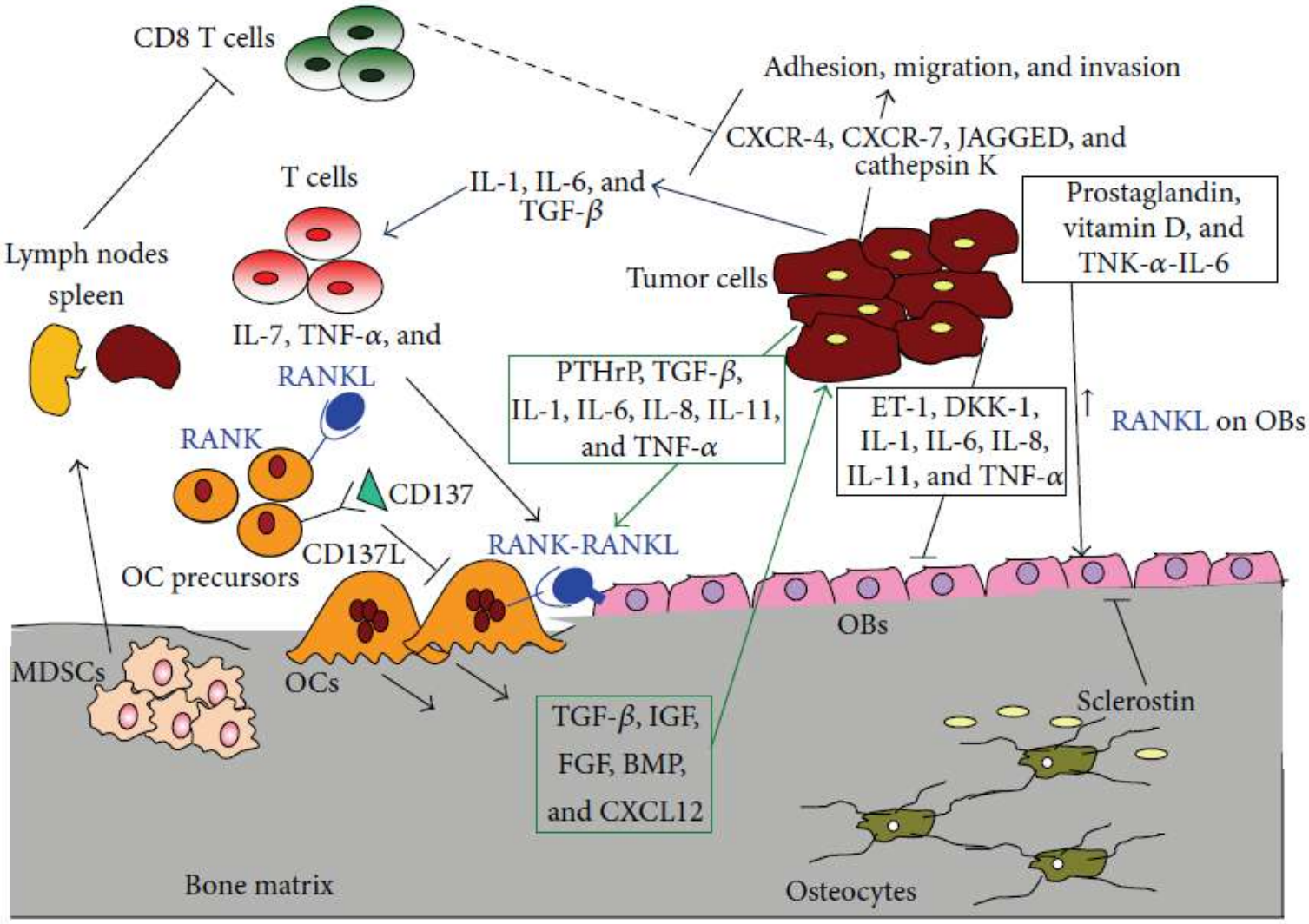




Santini D, et al. PLoS One 2011;6:e19234.

… for these reasons the preneoplastic niche and the vicious cycle can be disrupted targeting T-cell rank/rankl mediated functions

New

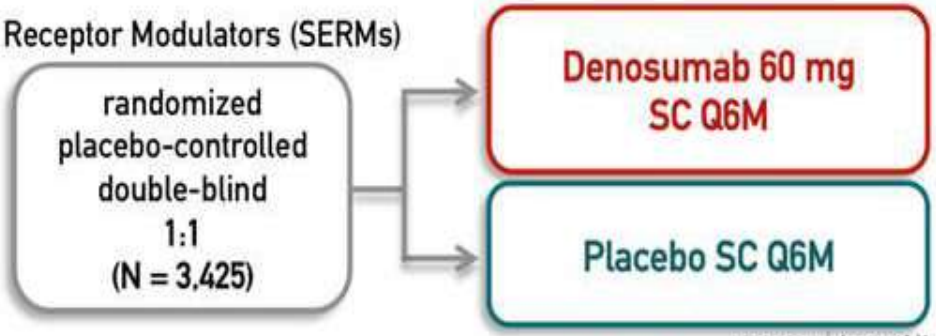


D'Amico L and Roato I, J of Immunology Research, 2015

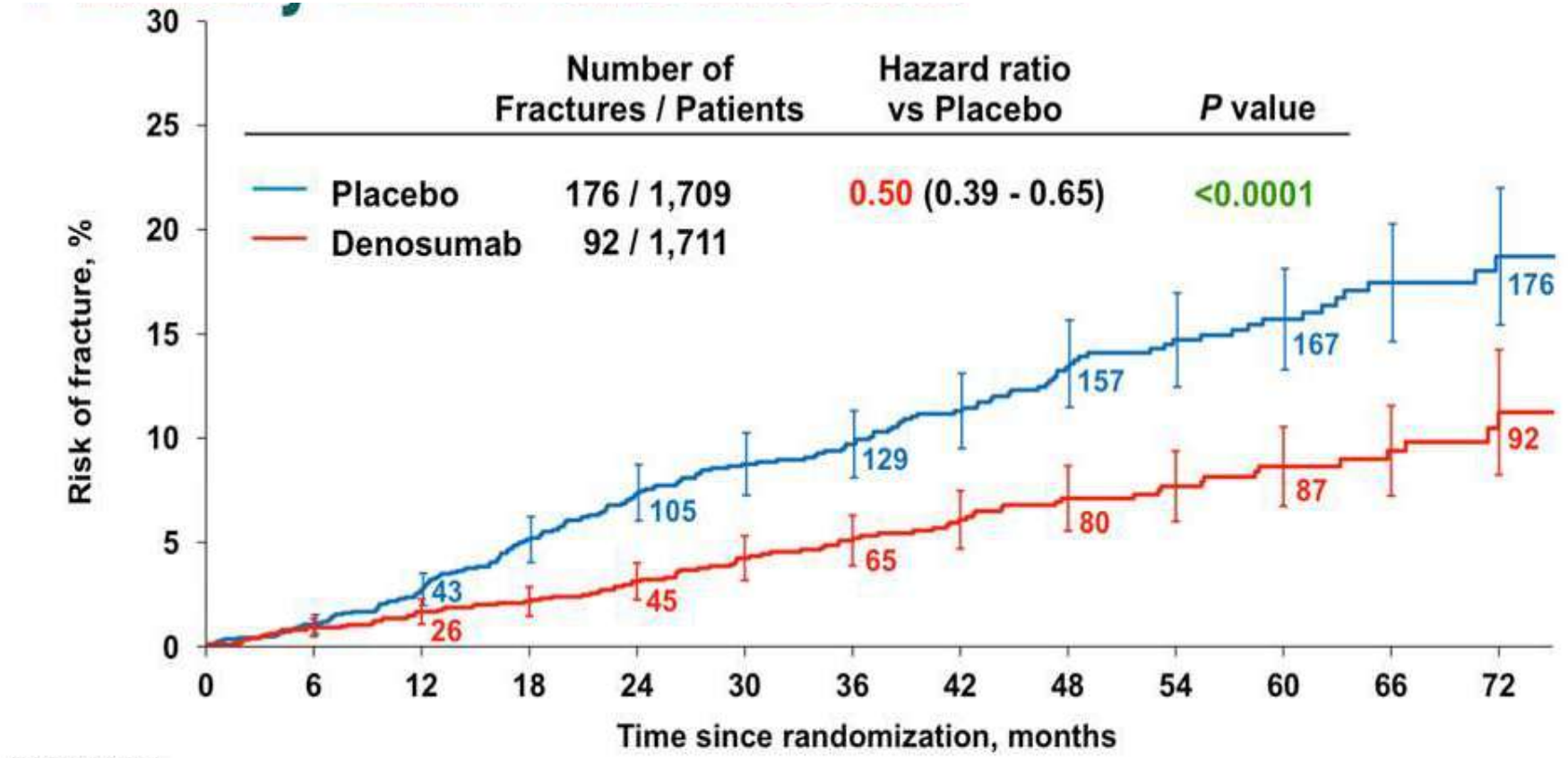
Trial Design ABCSG 18

New

- Prospective randomized placebo-controlled double-blind multicenter phase-3 trial
- Recruitment 2006 – 2013 (3,425 postmenopausal patients)
- Primary endpoint: Time to first clinical fracture
- Inclusion criteria:
  - Postmenopausal women with non-metastatic adenocarcinoma of the breast
  - ER+ and/ or PR+: adjuvant non-steroidal aromatase inhibitor therapy
- Exclusion criteria:
  - Prior or concurrent treatment with Selective Estrogen Receptor Modulators (SERMs)
  - Current or prior IV bisphosphonate administration
  - Recent use of oral bisphosphonates
  - Known history of:
    - Paget's disease
    - Cushing's disease
    - hyperprolactinemia
    - hypercalcaemia or hypocalcaemia
    - other active metabolic bone disease



Primary End Point Results

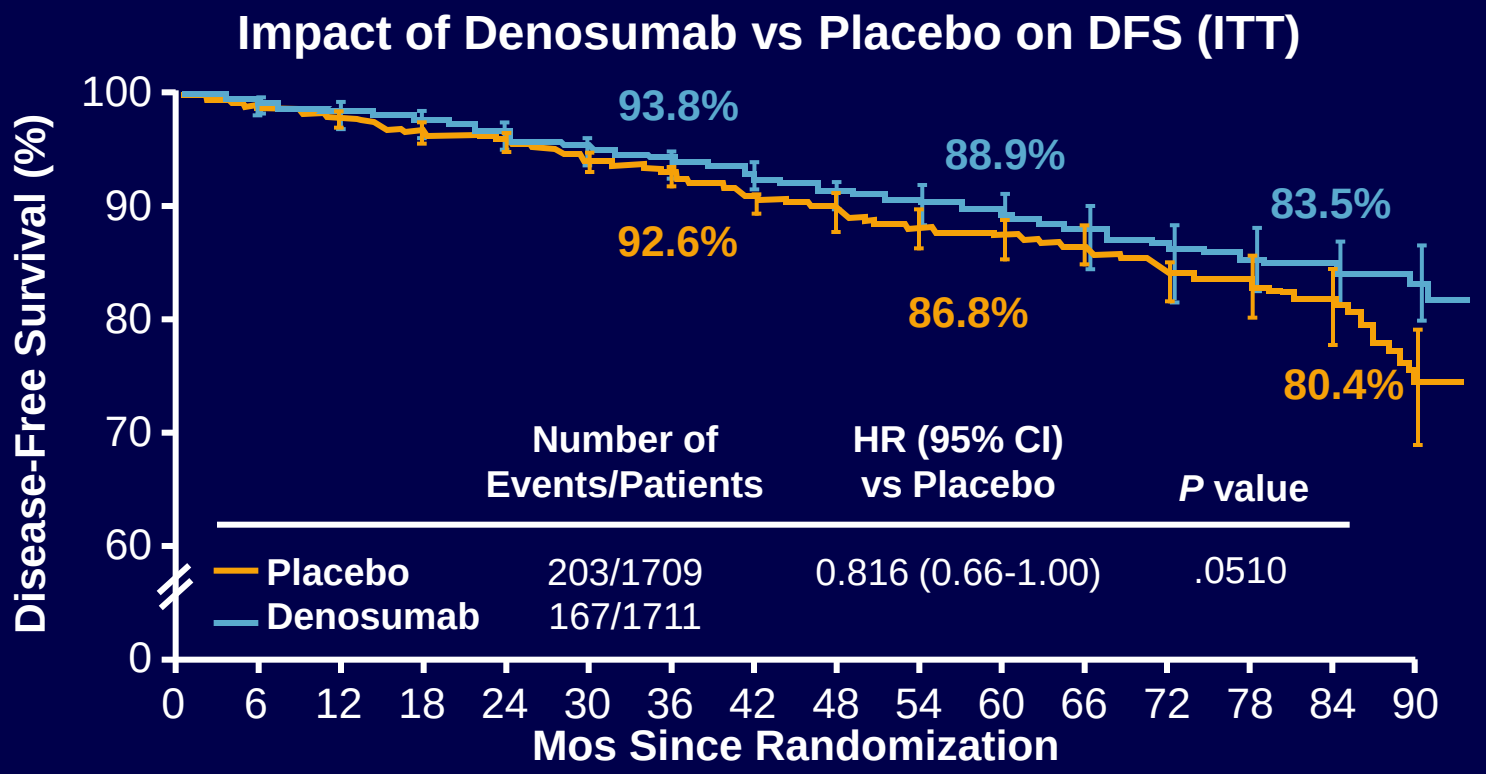


2015 ASCO Annual Meeting
Illumination&Innovation
transforming data into learning

….Waiting for outcome data

Presented By Michael Gnant at 2015 ASCO Annual Meeting

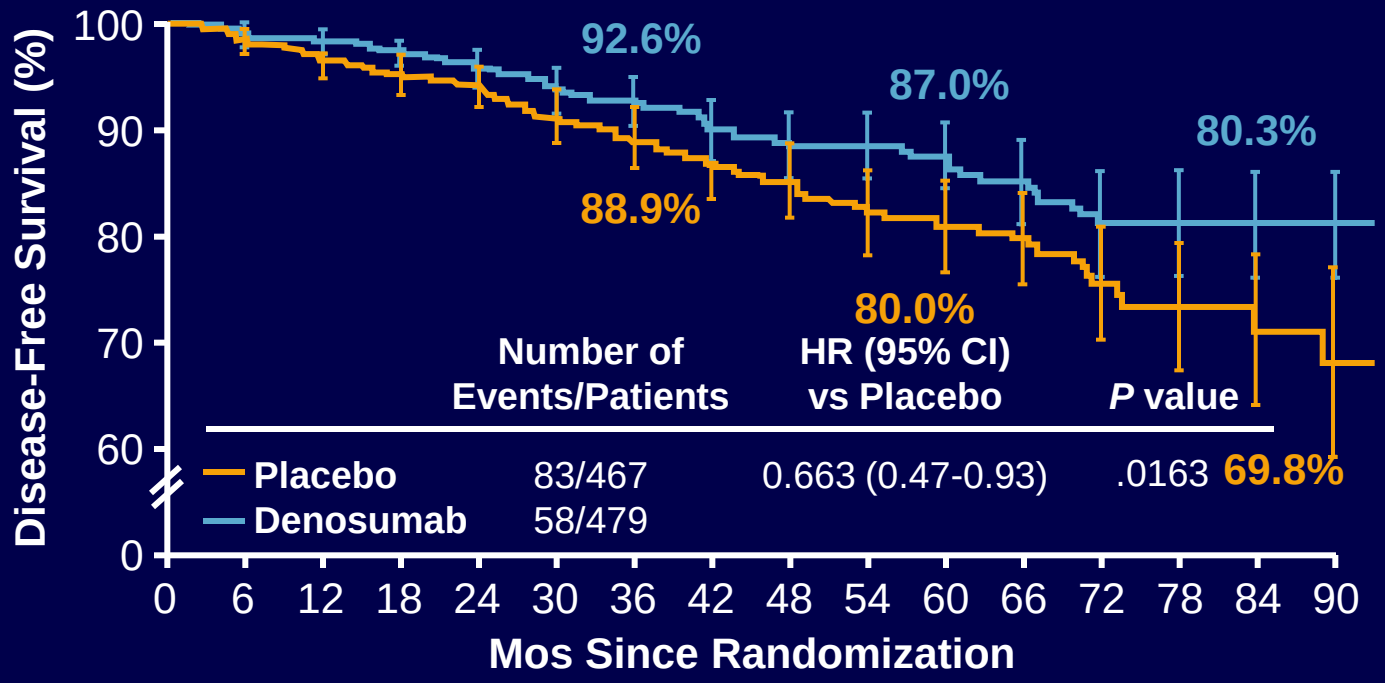
ABCSG-18: Disease-Free Survival



- ITT analysis consistent with sensitivity analysis in which pts switching to another bone-active treatment were censored
  - Hazard ratio, denosumab vs placebo: 0.807 (95% CI: 0.66-0.99; *P* = .0424)

Gnant M, et al. SABCS 2015. Abstract S2-02. Reproduced with permission.

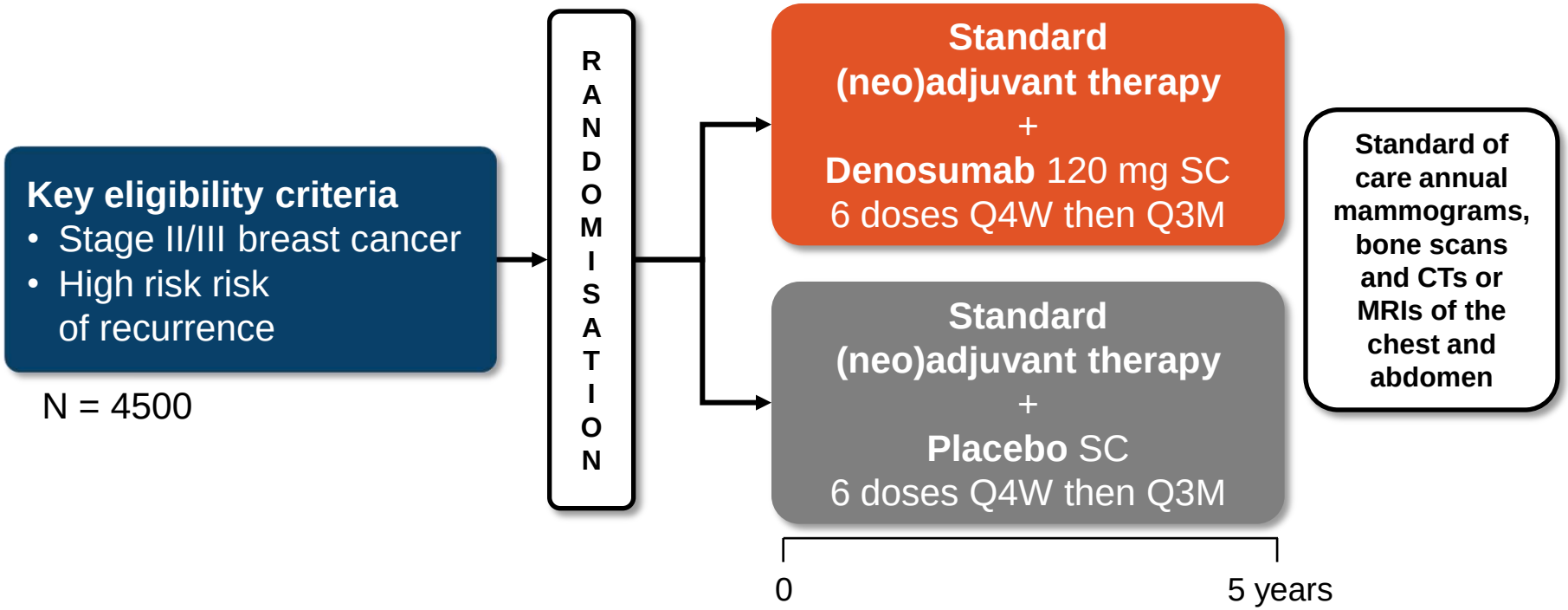
ABCSG-18: DFS by Tumor Size > 2 cm and Other Subgroups With Significant HR



Parameter	Significant HR
No AI prior to randomization	0.61
T-stage T2/T3/T4	0.66
Ductal invasive histology	0.79
ER+/PgR+ status	0.75

Gnant M, et al. SABCS 2015. Abstract S2-02. Reproduced with permission.

…Waiting for D-CARE: study design



- Primary endpoint: BMFS
- Secondary endpoints: DFS, overall survival, distant recurrence-free survival, safety, patient-reported outcomes (pain, health utilities)
- Exploratory: breast density, time to SREs, biomarkers

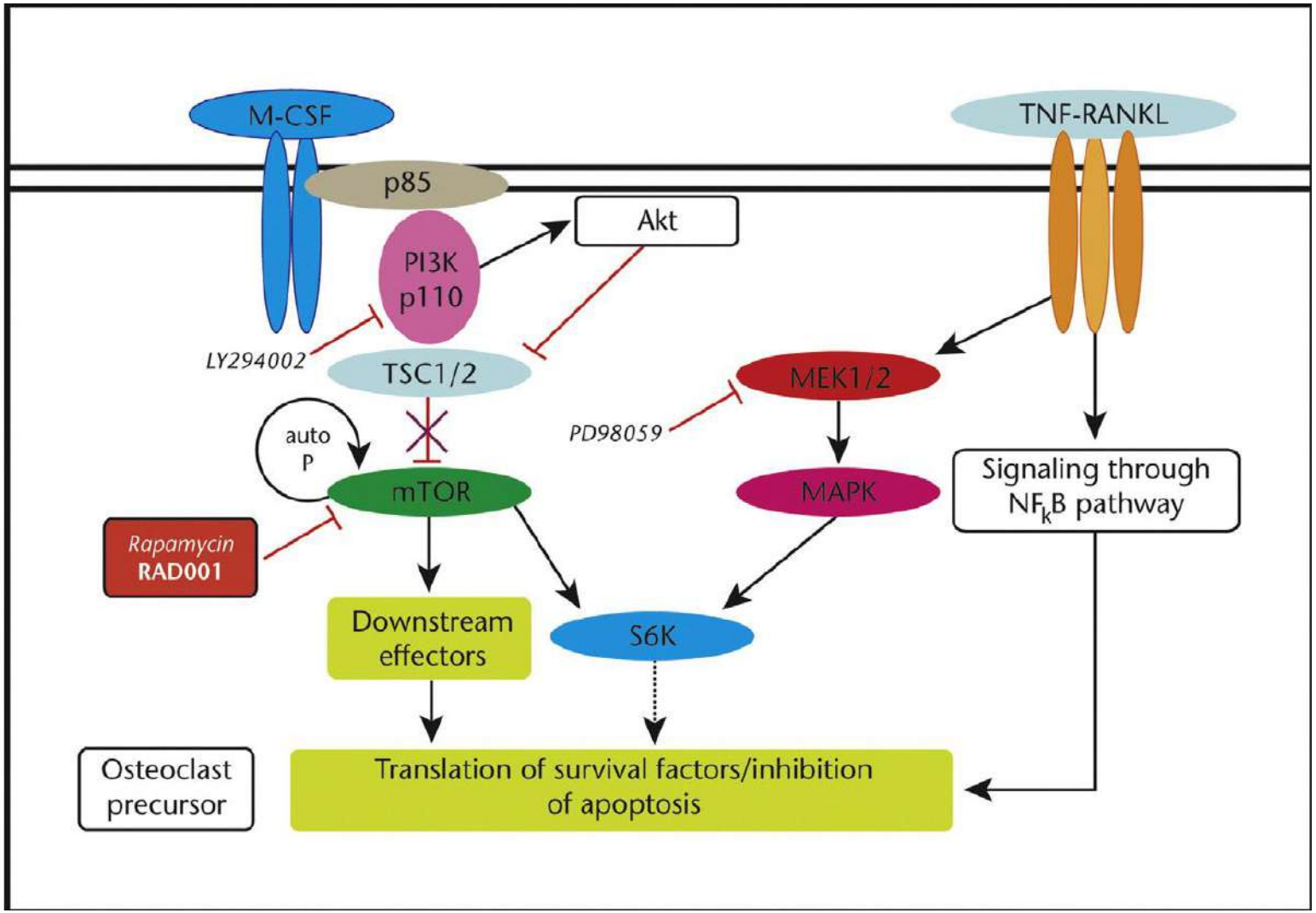
Denosumab (120 mg Q4W) is currently not approved for prevention of bone metastases. Denosumab is investigational in that setting
BMFS, bone metastasis-free survival.

Goss P, et al. ASCO 2013 (Abstract TPS662 and poster); NCT01077154.

“Bone Health” and new drugs

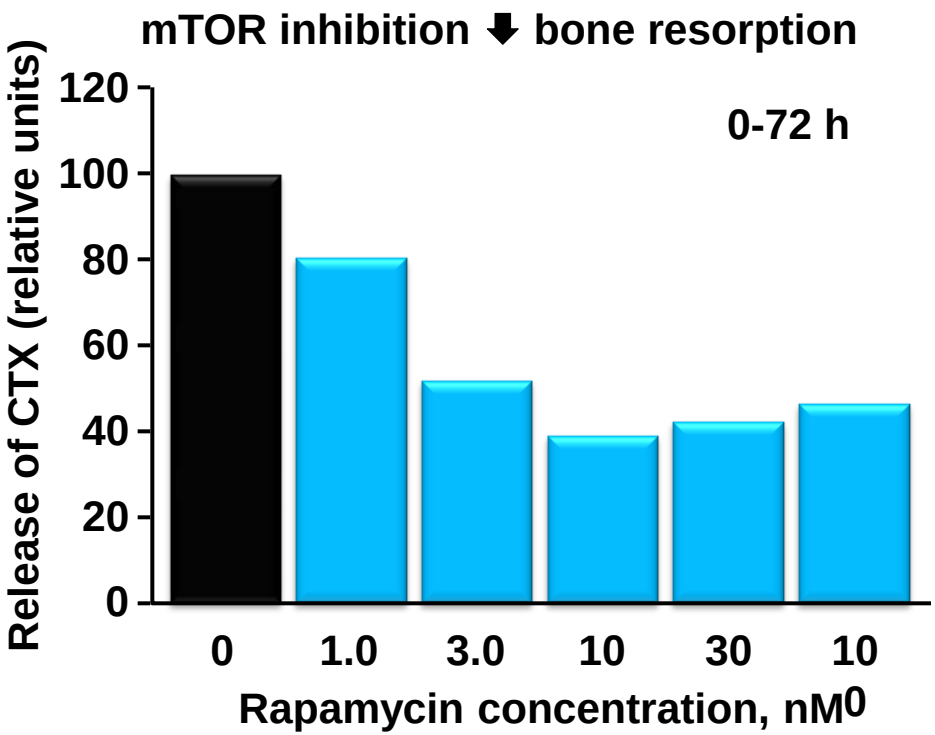
- Bisphosonates (Zoledronic Acid)
- Anti RANKL MoAb (Denosumab)
- mTOR inhibitor
- Radiopharmaceutical (Radium-223)
- Endothelin A receptor antagonist (Zibotentan)
- Src inhibitors (Saracatinib, Dasatinib)
- Novel Antiandrogens (Abiraterone Acetate and Enzalutamide)
- Cabozantinib: MET/VEGFR-targeted agent

M-CSF, TNF-alfa and RANK ligand promote osteoclast survival by signaling through mTOR/S6 kinase.

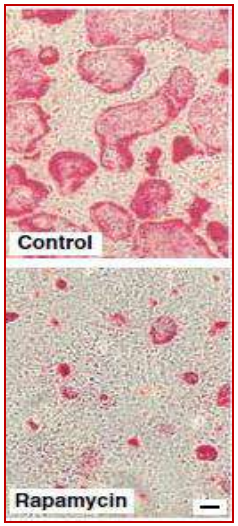


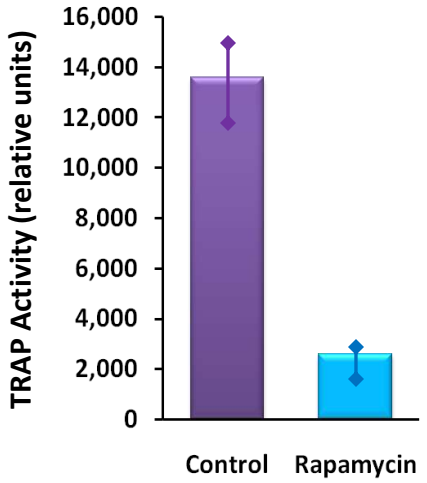
F. Bertoldo and D. Santini, BBA Reviews on Cancer, 2014

mTOR Inhibition ⬇ Bone Resorption, ⬇ Osteoclast Maturation, and ⬆ Osteoclast Apoptosis (Mouse Models)

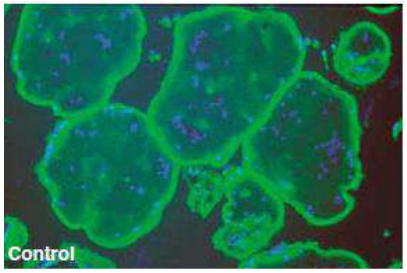


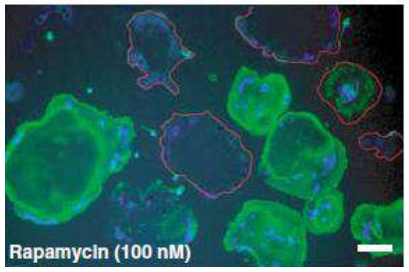
⬇ Formation and enzymatic activity of mature osteoclasts





⬆ Osteoclast apoptosis

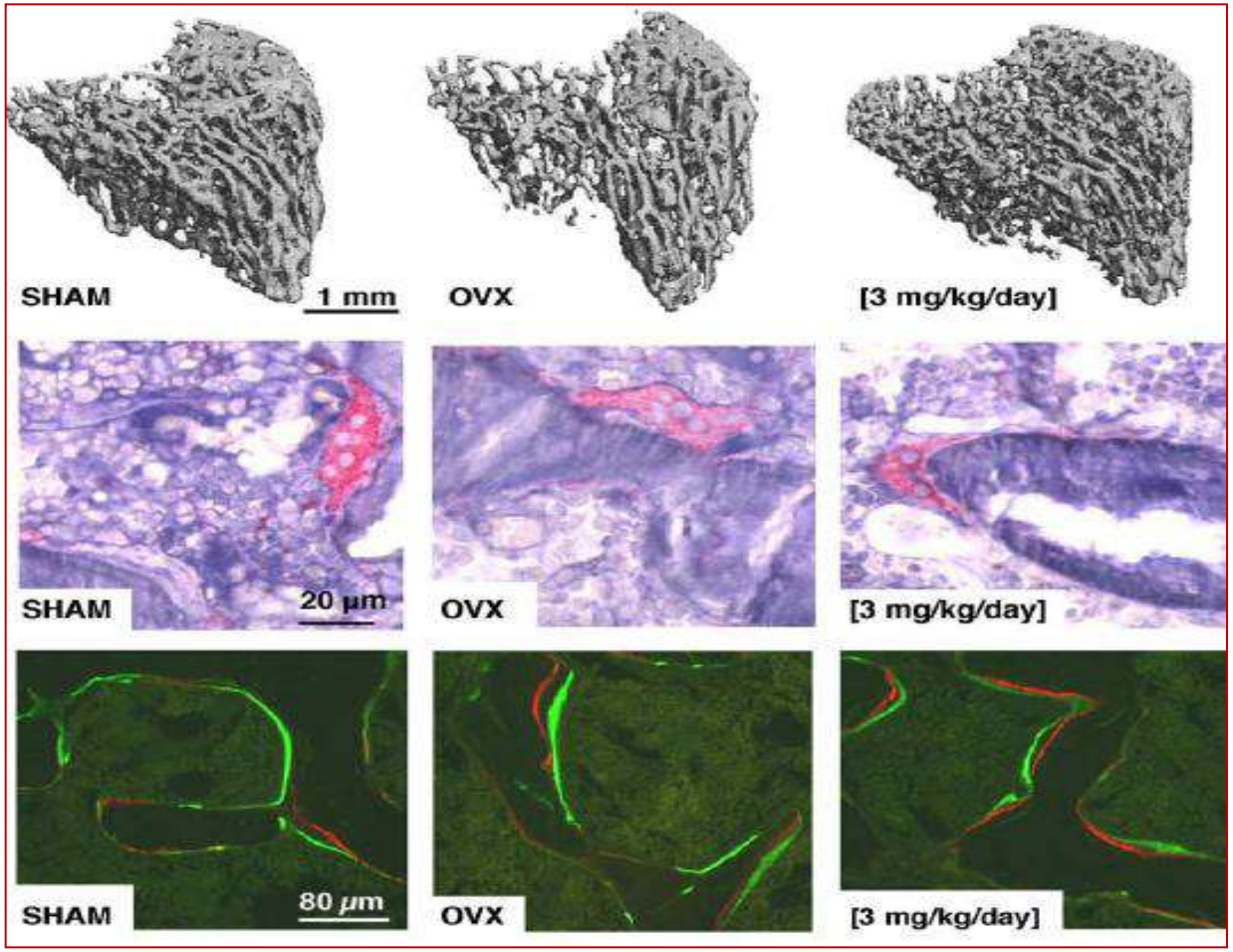




Abbreviations: CTX, C-telopeptide of type I collagen; h, hour; mTOR, mammalian target of rapamycin; TRAP, tartrate-resistant acid phosphatase.

Adapted/Reprinted from Glantschnig H, et al. *Cell Death Differ.* 2003;10(10):1165-1177.

Everolimus Treatment ⬇ Bone Loss Associated With Estrogen Deprivation (Rat Models)

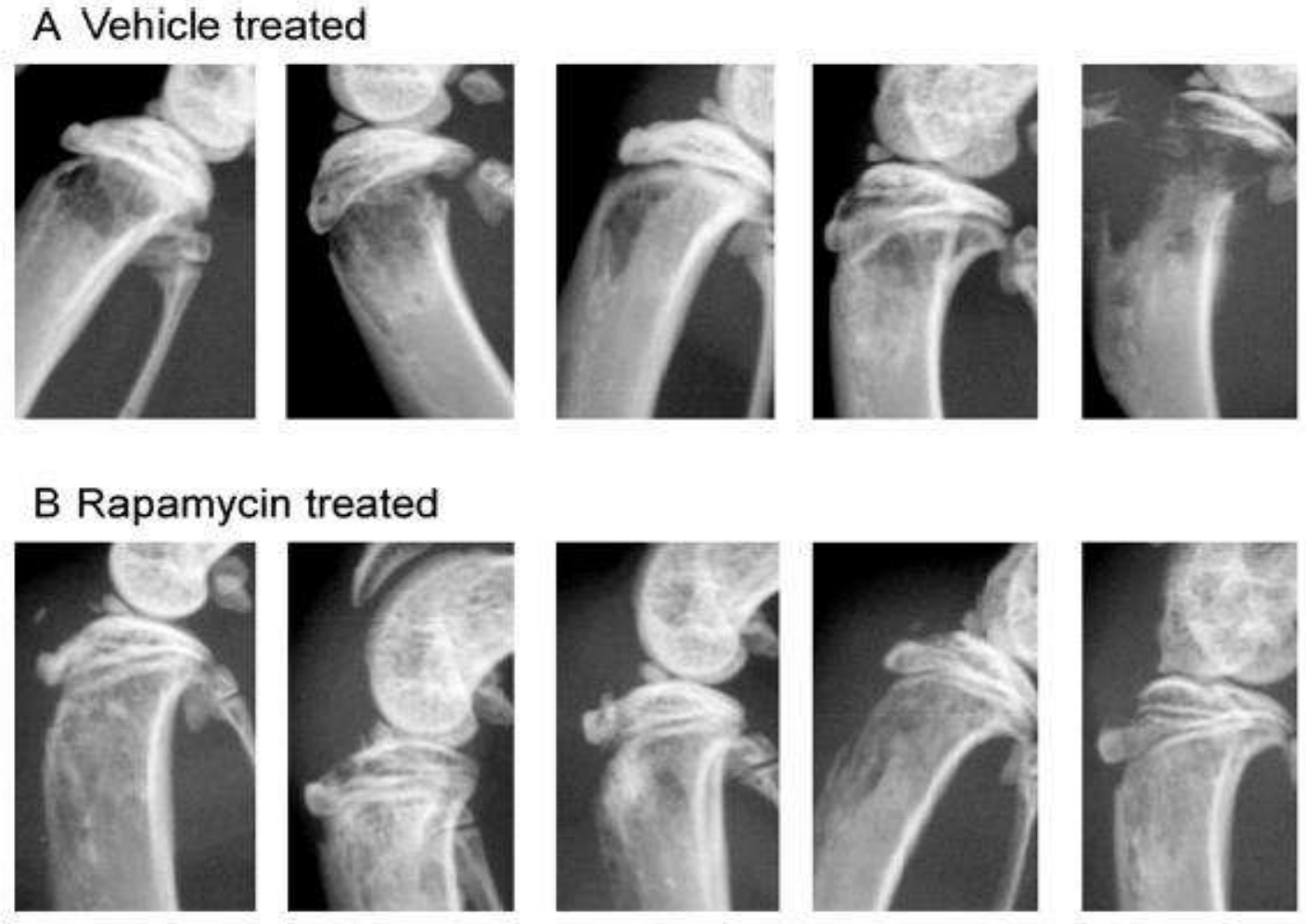


Control | **Estrogen-deprived** | **Estrogen-deprived + everolimus**

Abbreviation: OVX, ovariectomized.

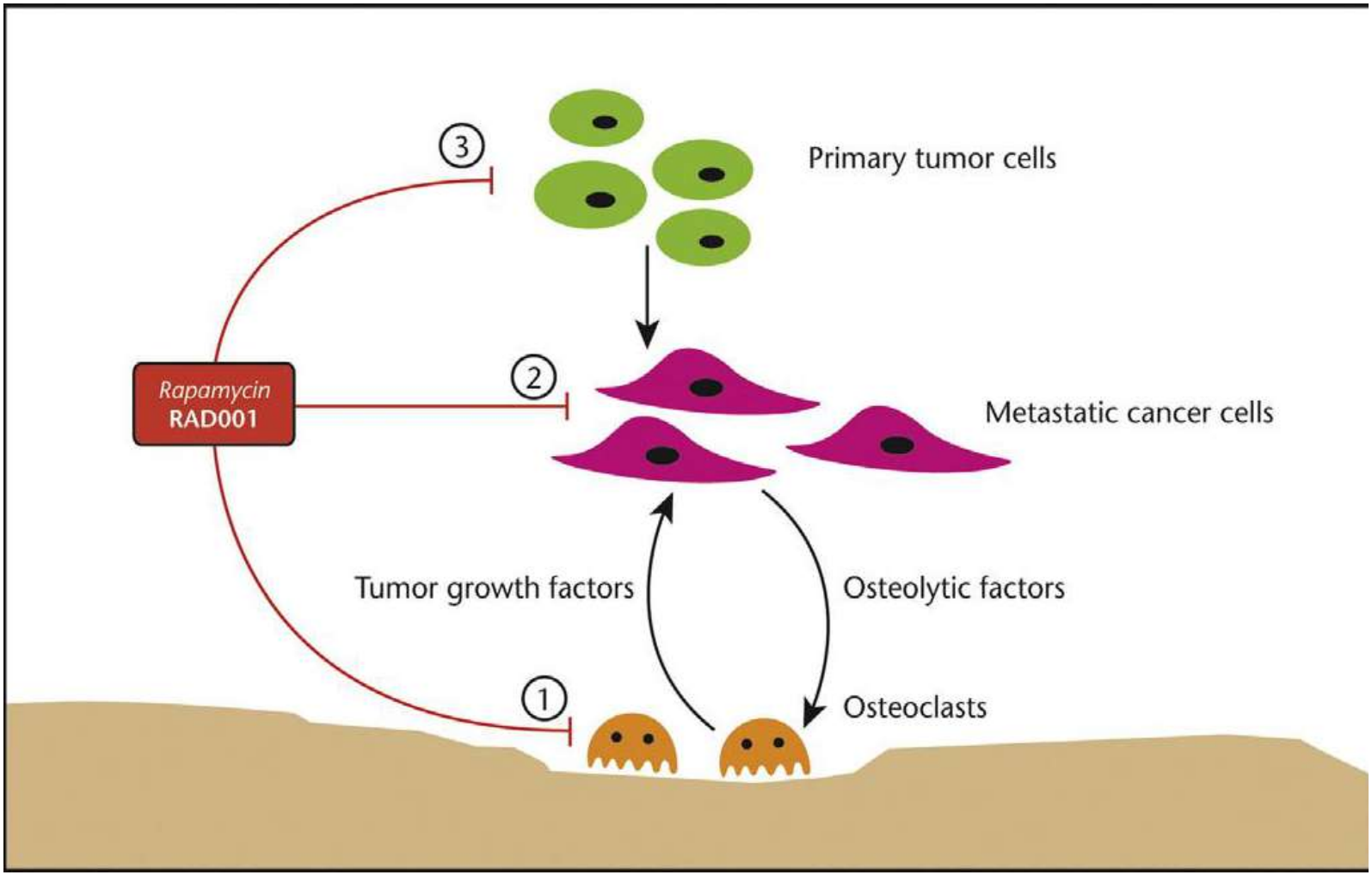
Adapted from Kneissel M, et al. *Bone.* 2004;35(5):1144-1156.

Rapamycin decreased osteolysis associated with experimental bone metastasis in a mouse mammary carcinoma



Hussein O et al. Cancer Letters, 2011

mTOR inhibition and bone microenvironment



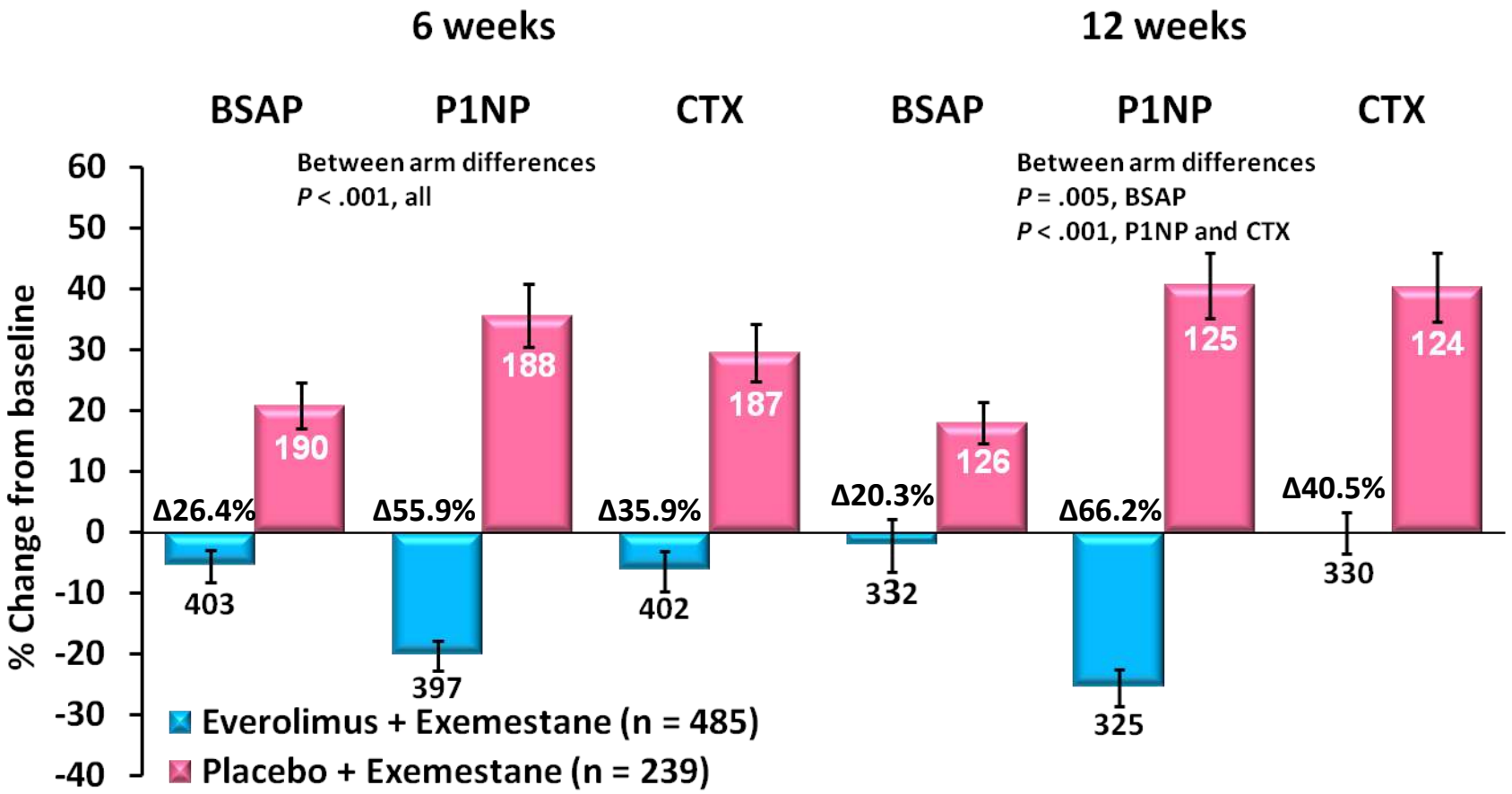
F. Bertoldo and D. Santini, BBA Reviews on Cancer, 2014

Effect of Everolimus on Bone Marker Levels and Progressive Disease in Bone in BOLERO-2

Michael Gnant, Jose Baselga, Hope S. Rugo, Shinzaburo Noguchi, Howard A. Burris, Martine Piccart, Gabriel N. Hortobagyi, Janice Eakle, Hirofumi Mukai, Hiroji Iwata, Matthias Geberth, Lowell L. Hart, Peyman Hadji, Mona El-Hashimy, Shantha Rao, Tetiana Taran, Tarek Sahmoud, David Lebwohl, Mario Campone, Kathleen I. Pritchard

Gnant M, et al. *JNCI*. 2013 February 19 Epub, doi: 10.1093/jnci/djt026.

EVE ⬇ Bone Turnover Marker Levels at 6 and 12 Weeks (Overall Population)

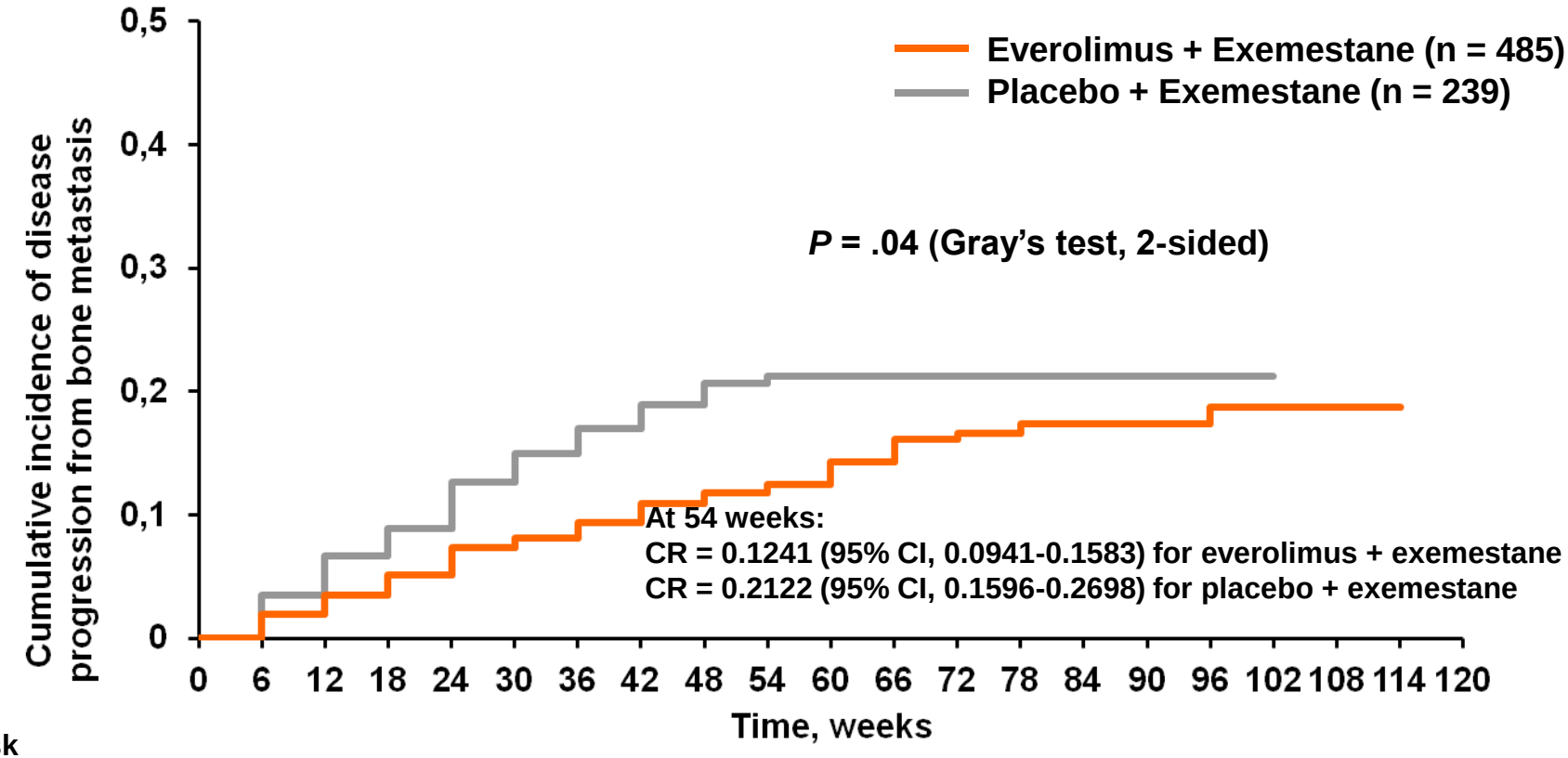


Data from full analysis set.
Proportions of patients with bone metastases or bisphosphonate use reflect the status at study entry among patients with baseline bone marker assessments.

Abbreviations: BSAP, bone-specific alkaline phosphatase; CTX, C-terminal cross-linking telopeptide of type I collagen; P1NP, amino-terminal propeptide of type I collagen.

Gnant M, et al. *JNCI*. 2013 February 19 Epub, doi: 10.1093/jnci/djt026.

EVE ⬇ Disease Progression in Bone: Overall Population (N = 724)



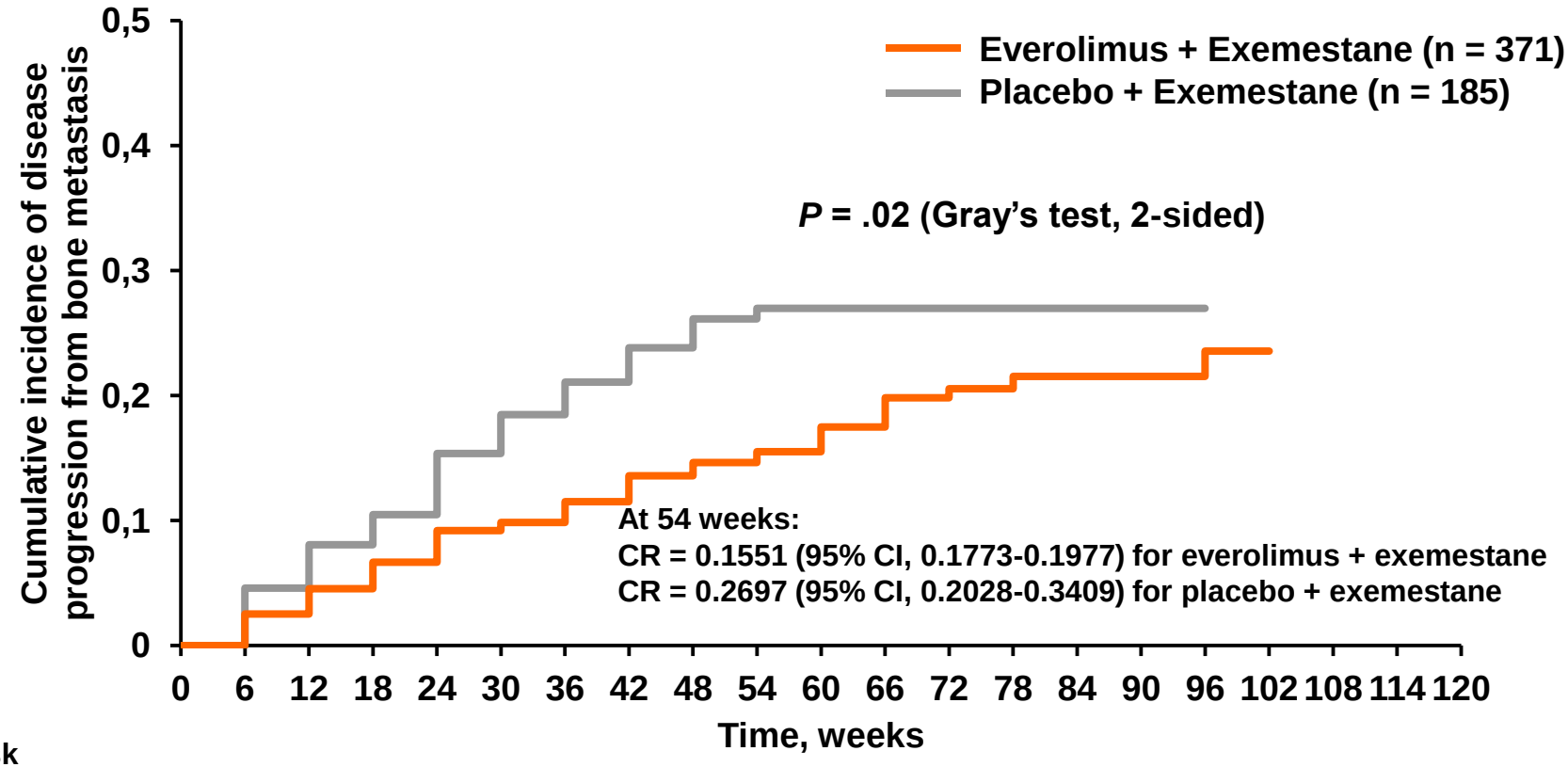
Patients at risk																				
Everolimus + Exemestane	485	436	366	304	257	221	185	158	124	91	66	50	35	24	22	13	10	8	2	1	0
Placebo + Exemestane	239	190	132	96	67	50	39	30	21	15	10	8	5	3	1	1	1	0	0	0	0

Cumulative incidence of disease progression was determined using the competing risk method; exploratory *P* = .036 by Gray's test.

Abbreviations: CI, confidence interval; CR, competing risk estimate.

Gnant M, et al. *JNCI*. 2013 February 19 Epub, doi: 10.1093/jnci/djt026.

EVE ⬇ Disease Progression in Bone: Patients With Bone Metastases at Baseline (n = 556)



Patients at risk

Everolimus + Exemestane	371	327	278	230	200	172	144	122	95	69	50	45	25	15	13	8	6	5	0	0	0
Placebo + Exemestane	185	135	91	69	47	36	26	20	13	10	5	3	3	2	1	1	1	0	0	0	0

Cumulative incidence of disease progression was determined using the competing risk method; exploratory *P* = .0165 by Gray's test.

Abbreviations: CI, confidence interval; CR, competing risk estimate.

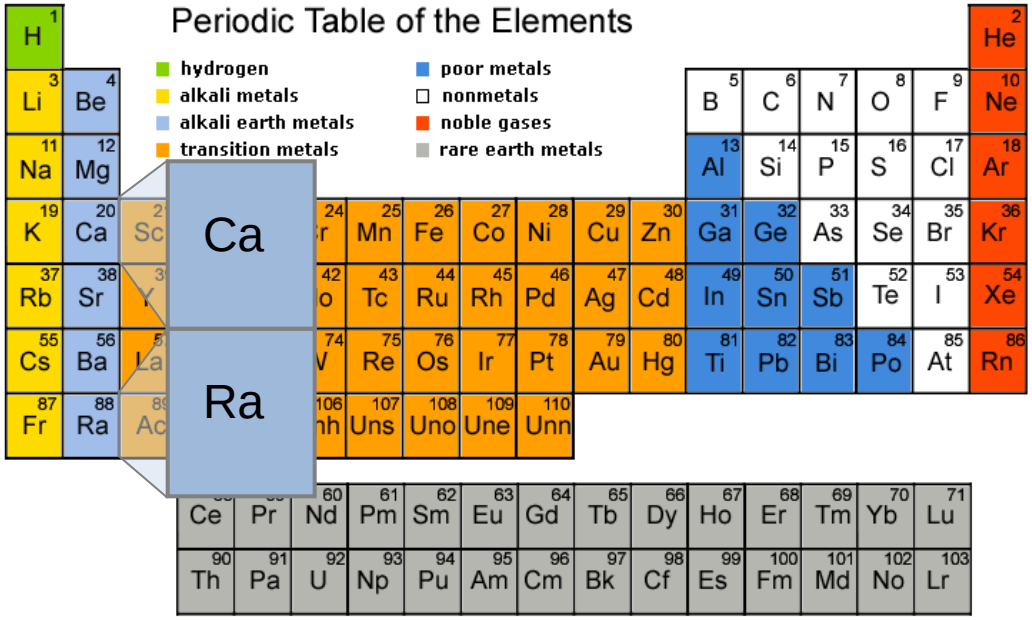
Gnant M, et al. *JNCI*. 2013 February 19 Epub, doi: 10.1093/jnci/djt026.

“Bone Health” and new drugs

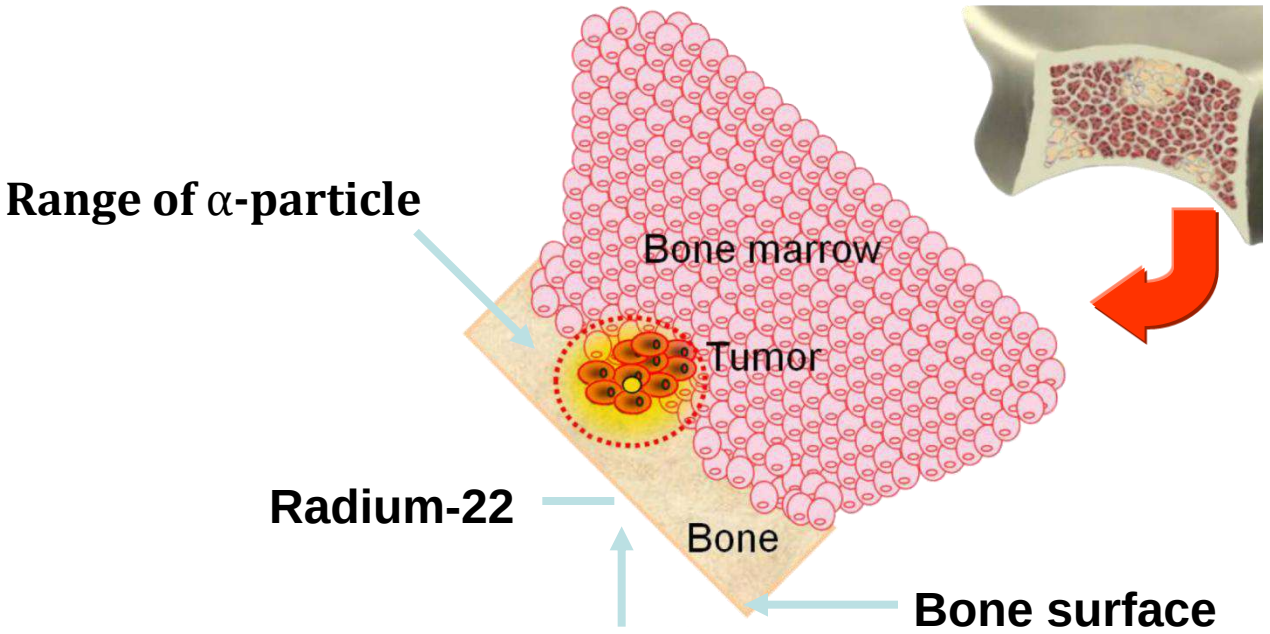
- Bisphosonates (Zoledronic Acid)
- Anti RANKL MoAb (Denosumab)
- mTOR inhibitor
- Radiopharmaceutical (Radium-223)
- Endothelin A receptor antagonist (Zibotentan)
- Src inhibitors (Saracatinib, Dasatinib)
- Novel Antiandrogens (Abiraterone Acetate and Enzalutamide)
- Cabozantinib: MET/VEGFR-targeted agent

Radium-223 Targets Bone Metastases

- Radium-223 functions as a calcium mimic
- Targets sites of new bone growth within and around bone metastases
- Excreted by the small intestine



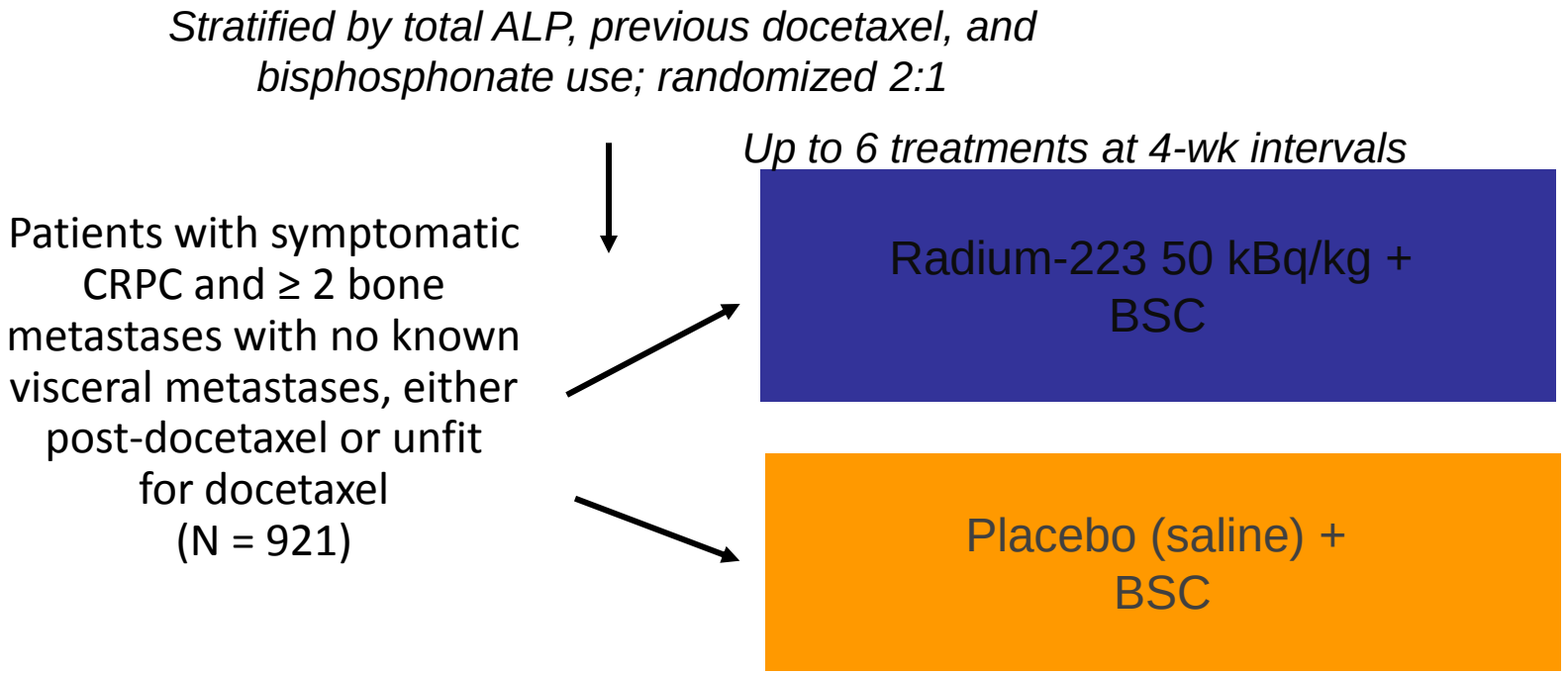
Radium-223 Targets Bone Metastases



- α-particles cause double-strand DNA breaks in nearby tumour cells
  - Limited penetration of α emitters (~ 2-10 cell diameters) results in highly localized killing of tumor cells with minimal collateral damage to normal tissue in surrounding area

Parker C, et al. 2012 ASCO GU Cancers Symposium. Abstract 8. Perez CA, et al. Principles and practice of radiation oncology. 5th ed. 2007.

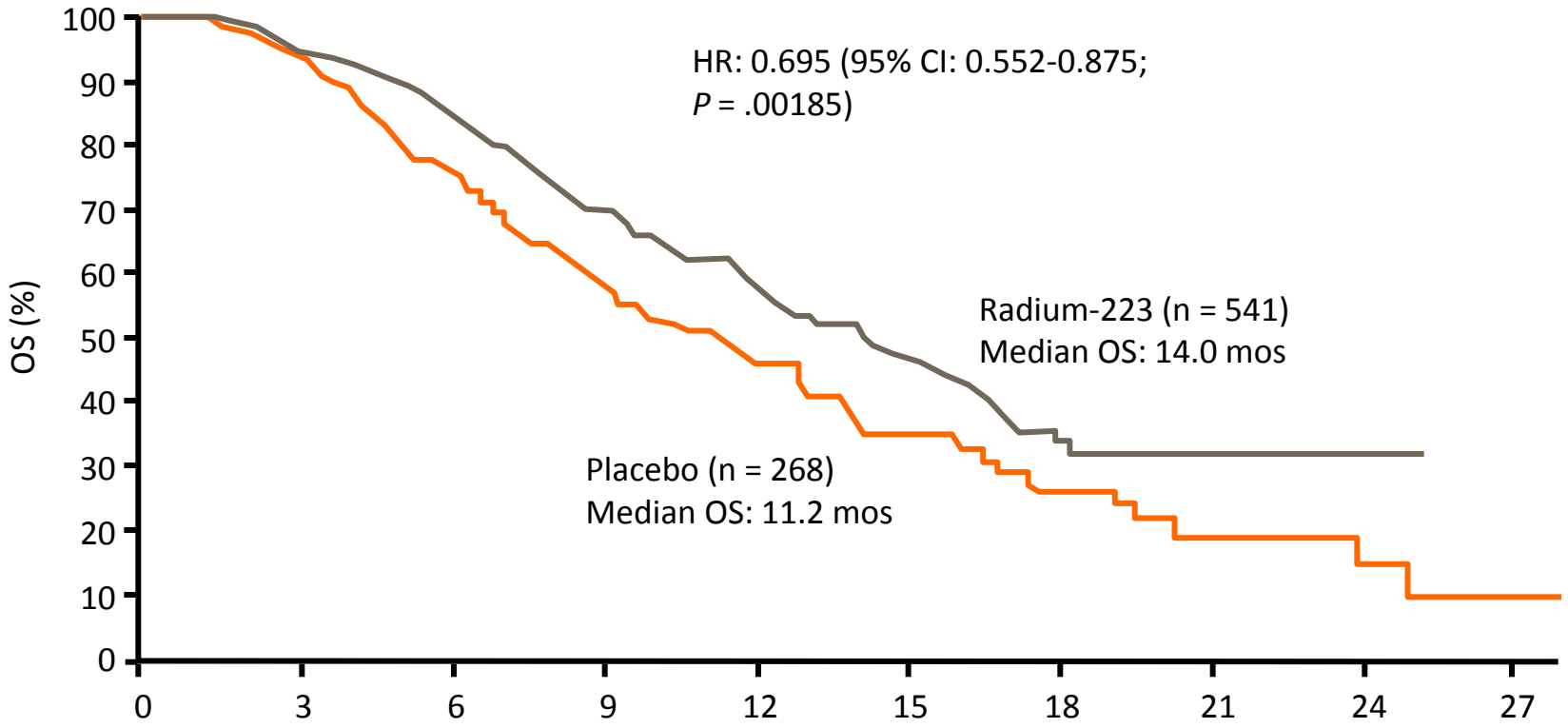
ALSYMPCA: Phase III Trial of Radium-223 in Symptomatic Prostate Cancer



- Primary endpoint: OS
- Secondary endpoints: time to first SRE, time to total ALP progression, total ALP response, ALP normalization, time to PSA progression, safety, QoL

Parker C, et al. ASCO GU 2012. Abstract 8.

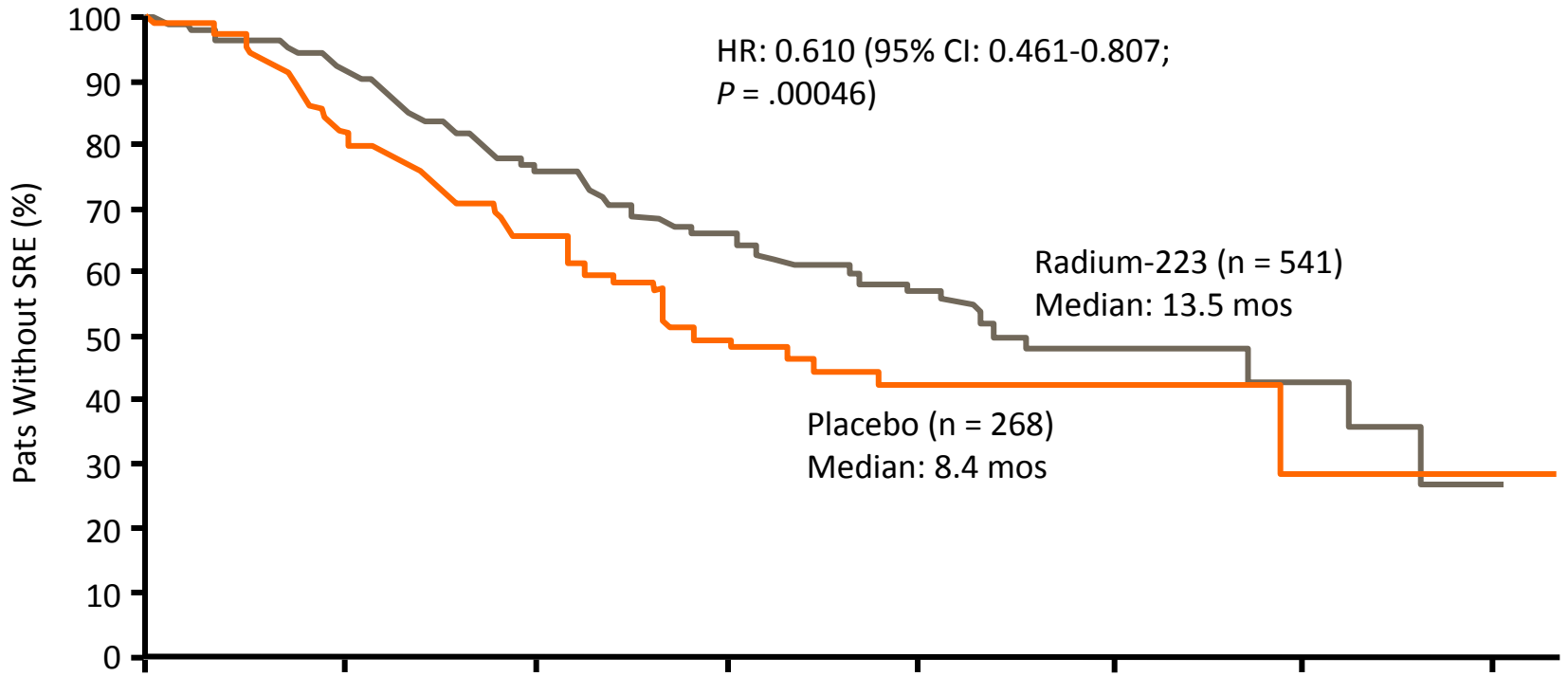
ALSYMPCA: Overall Survival



Pts at Risk, n										
Radium-223	541	450	330	213	120	72	30	15	3	0
Placebo	268	218	147	89	49	28	15	7	3	0

Parker C, et al. 2012 ASCO GU Cancers Symposium. Abstract 8.

ALSYMPCA: Time to First SRE



Pts at Risk, n								
Radium-223	541	379	214	111	51	22	6	0
Placebo	268	159	74	30	15	7	2	0

Sartor O, et al. ASCO GU 2012. Abstract 9.

“Bone Health” and new drugs

- Bisphosonates (Zoledronic Acid)
- Anti RANKL MoAb (Denosumab)
- mTOR inhibitor
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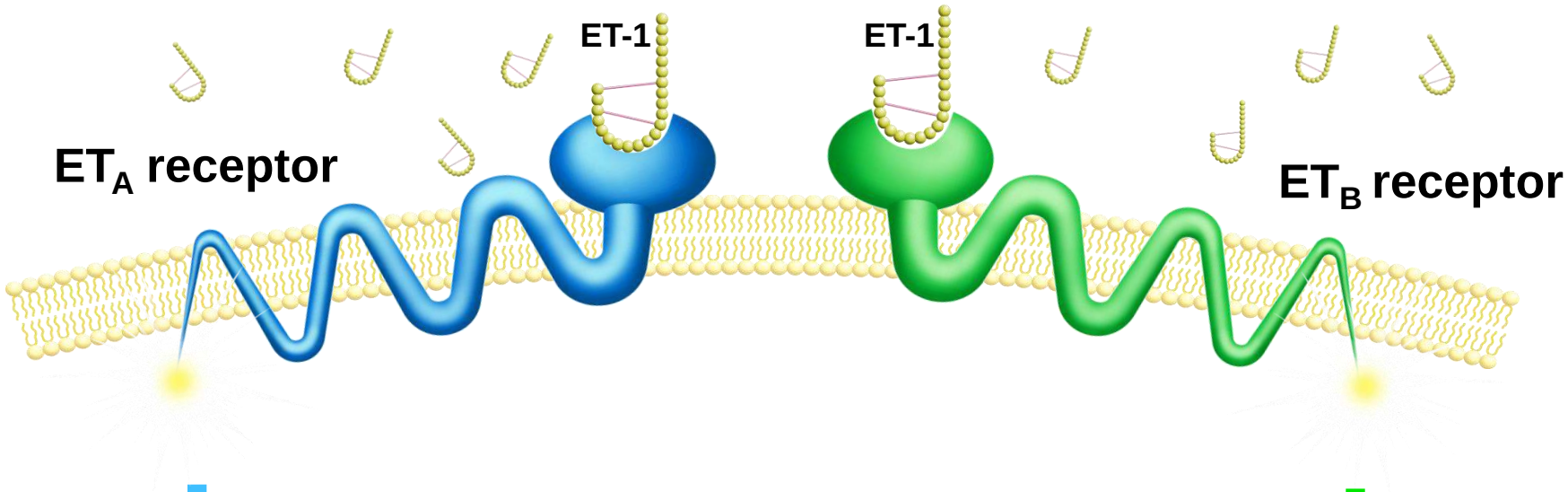
- Endothelin A receptor antagonist (Zibotentan)
- Src inhibitors (Saracatinib, Dasatinib)
- Novel Antiandrogens (Abiraterone Acetate and Enzalutamide)
- Cabozantinib: MET/VEGFR-targeted agent

ET-1: direct effects on tumour cells

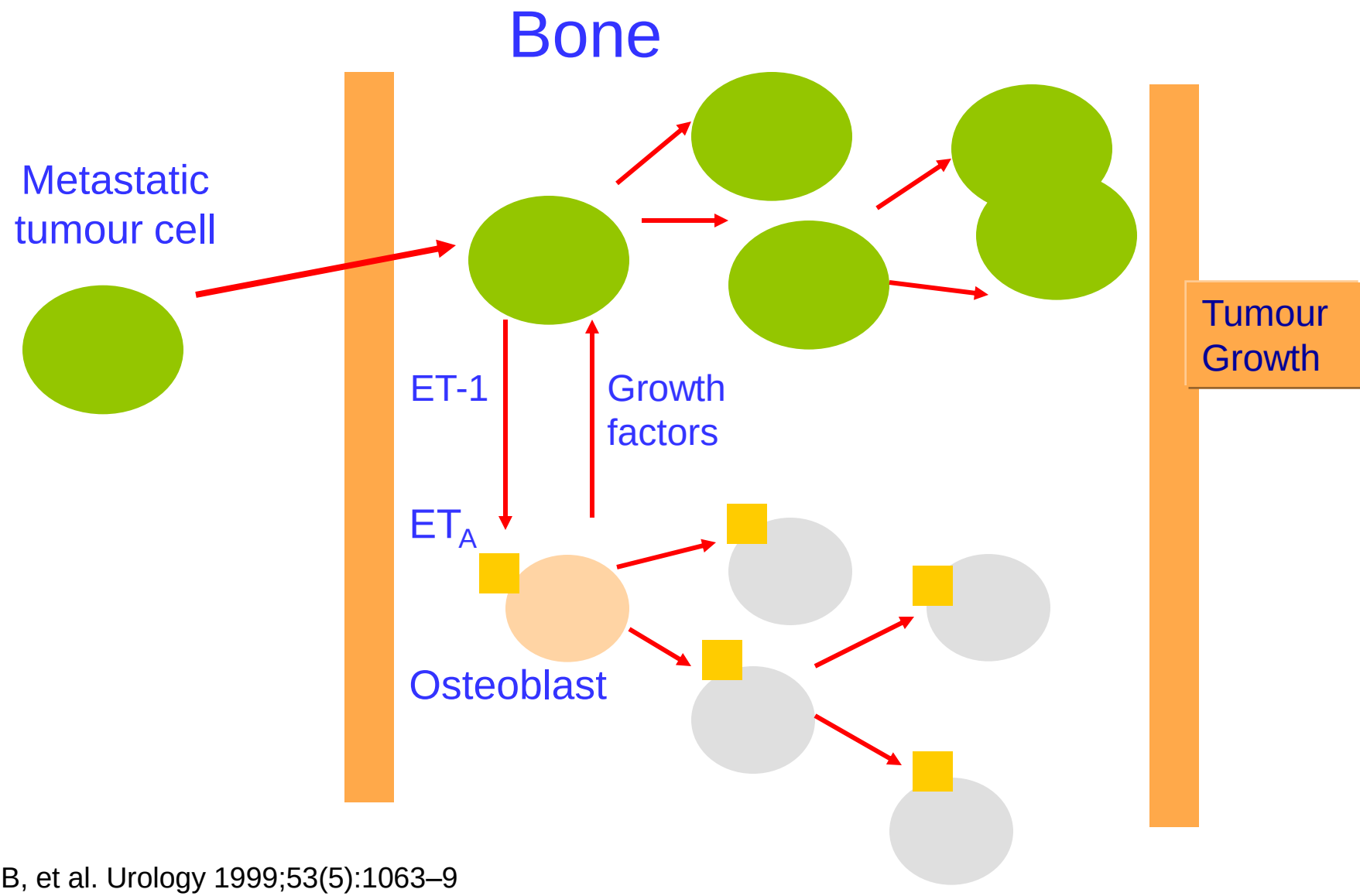


- Proliferation
- Inhibition of apoptosis
- Angiogenesis
- Migration, invasion and metastasis
- Bone ‘vicious cycle’

- Apoptosis
- Clearance

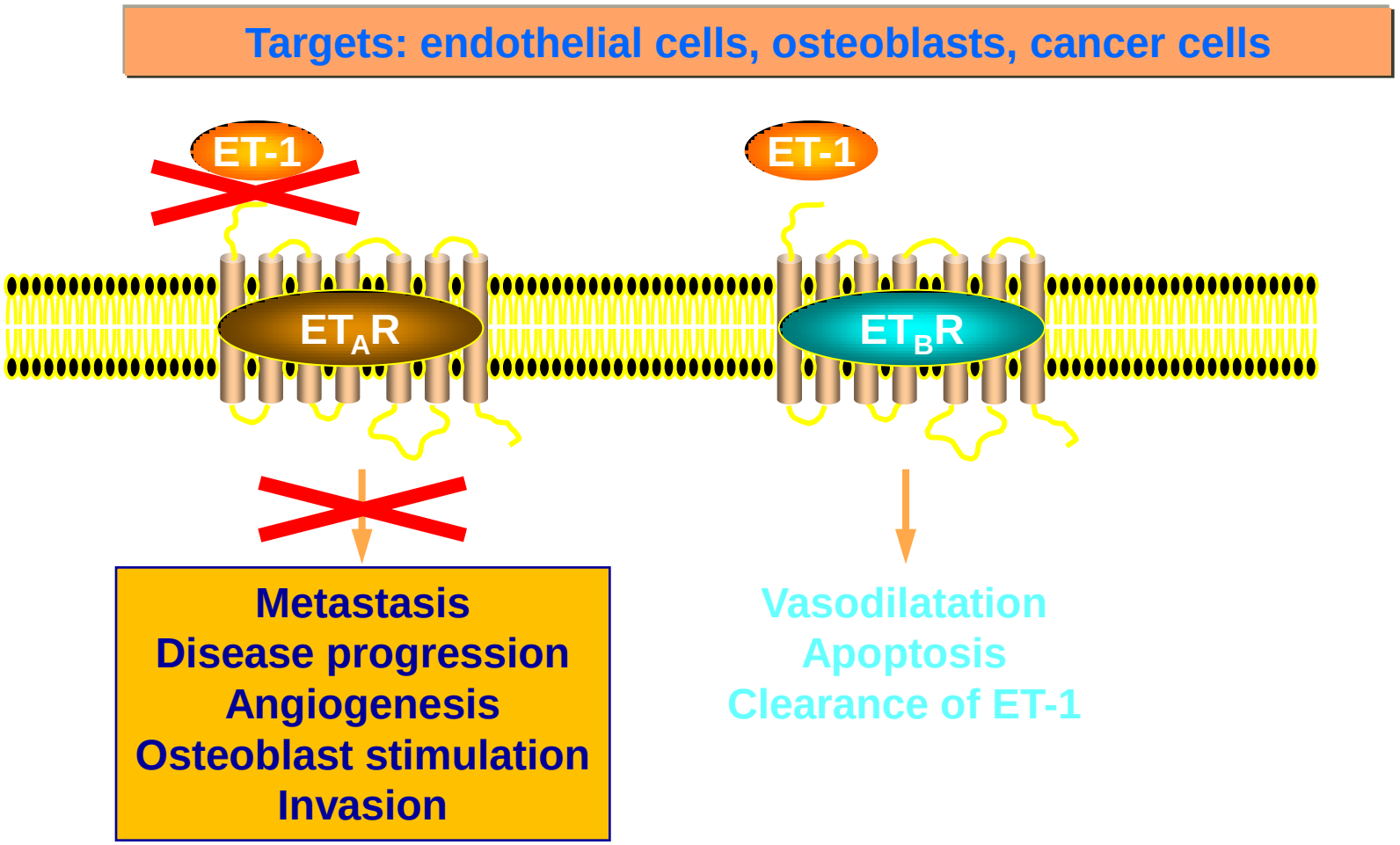
Nelson JB, et al. Nat Med 1995;1(9):944–9;
Okazawa M, et al. J Biol Chem 1998;273(20):12584–92;
Del Bufalo D, et al. Mol Pharmacol 2002;61(3):524–32

ET-1: a role in bone metastasis



Nelson JB, et al. Urology 1999;53(5):1063–9

ZD4054 (Zibotentan)– a specific-ET_AR antagonist



ZD4054 specifically blocks ET_AR, with no detectable activity at ET_BR

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

ENTHUSE (Endothelin A receptor Antagonist Use)

The Phase III Clinical Trials to Evaluate a … Endothelin A Receptor Antagonist (ZD4054) in Hor… sistant Prostate Cancer

PRIMARY E… SURVIVAL

FAILED

ENTHUSE … 5)
ZD4054 vs placebo

ENTHUSE M1 (14)
ZD4054 vs placebo

ENTHUSE M1C (33)
ZD4054 + docetaxel vs docetaxel + placebo

Asymptomatic or mildly symptomatic metastases for whom chemotherapy not yet appropriate

Metastatic patients for whom docetaxel is appropriate

“Bone Health” and new drugs

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- Anti RANKL MoAb (Denosumab)
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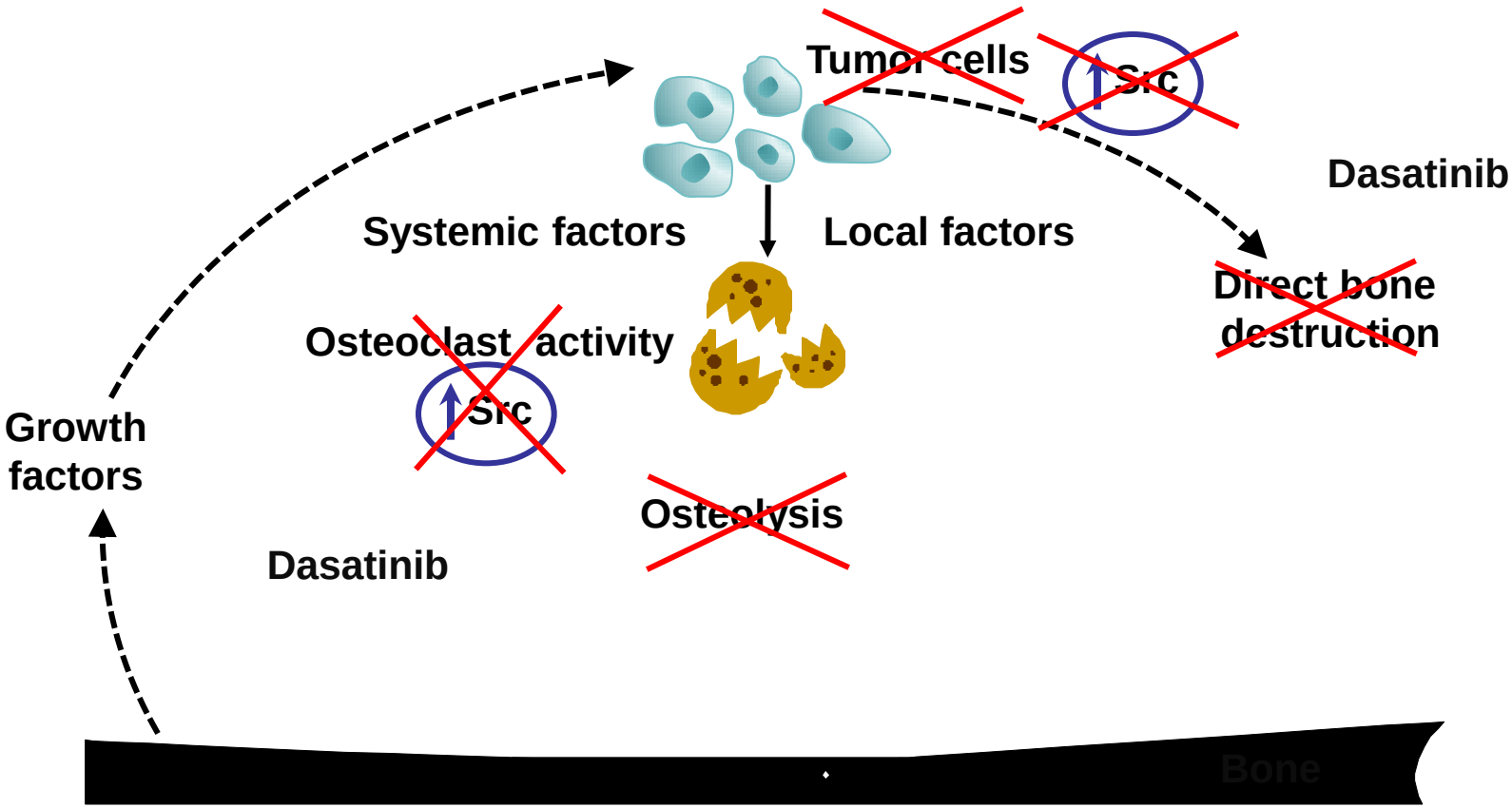
- Src inhibitors (Saracatinib, Dasatinib)
- Novel Antiandrogens (Abiraterone Acetate and Enzalutamide)
- Cabozantinib: MET/VEGFR-targeted agent

Evidence for a Role of Src in Bone Metabolism and Metastatic Bone Disease

- Src kinase is a non-receptor tyrosine kinase, highly expressed in normal osteoclasts[1,2]
- Src plays an essential role in RANKL-mediated osteoclast activation[3] and osteoblast inhibition[4]
- Src knockout mice are osteopetrotic[5]
- Src may be critical for tumor cell survival in bone microenvironment[6]

DASATINIB in PC: Inhibition of Tumor Cells and Osteoclast Activity Through Src



Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READ… randomised, double-blind phase III …

FAILED

Patients with chemotherapy-naive, metastatic, castration-resistant prostate cancer, (N = 1522)

Doc… mg/m2) 3w +
…isone 5 mg bid
+
Placebo

Docetaxel (75 mg/m2) 3w +
oral prednisone 5 mg bid
+
Dasatinib
(100 mg orally bid)

Median overall … 21·5 months in the dasatinib group and 21·2 months in the placebo group

The addition of dasati…b to docetaxel did not improve overall survival for chemotherapy-naive men with metastatic castration-resistant prostate cancer. This study does not support the combination of dasatinib

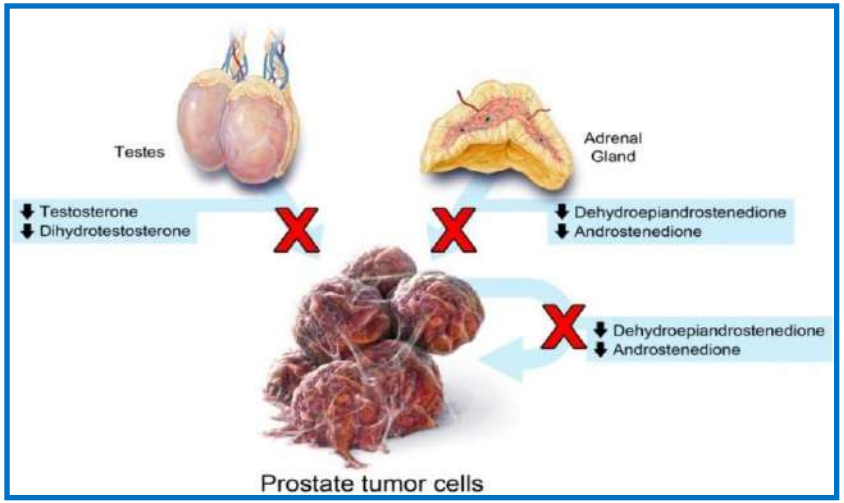
“Bone Health” and new drugs

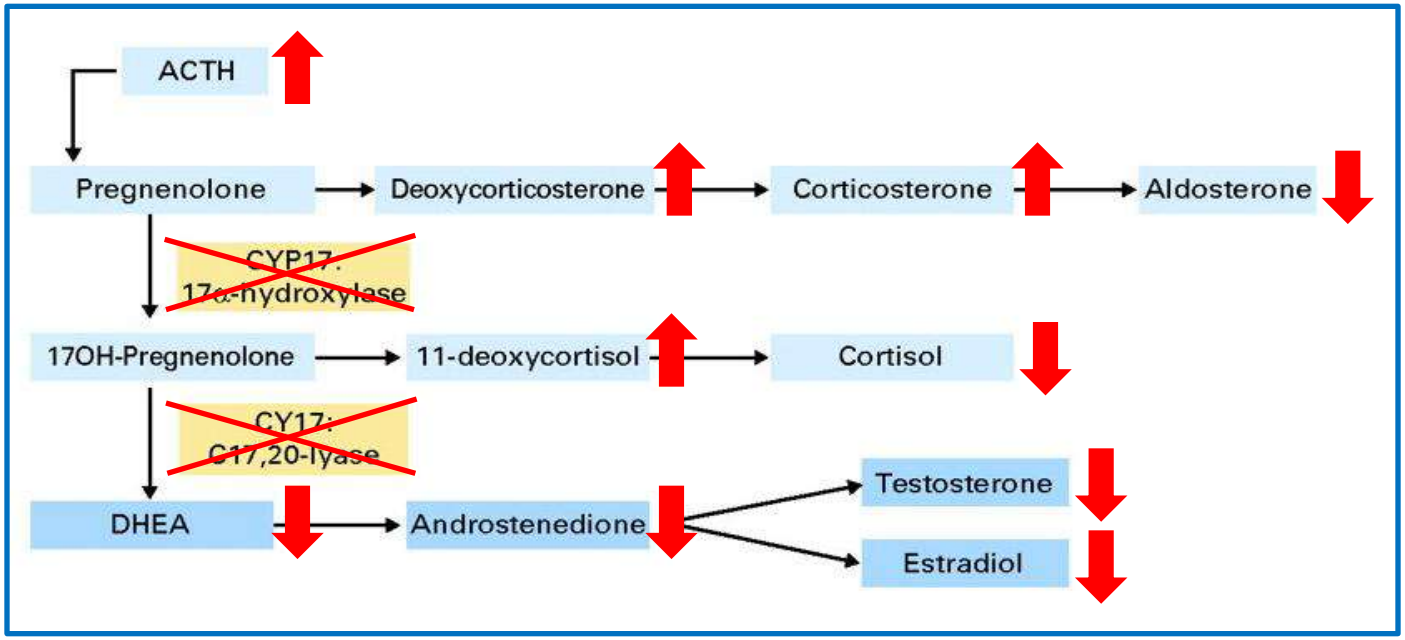
- Bisphosonates (Zoledronic Acid)
- Anti RANKL MoAb (Denosumab)
- mTOR inhibitor
- Radiopharmaceutical (Radium-223)
- Endothelin A receptor antagonist (Zibotentan)
- Src inhibitors (Saracatinib, Dasatinib)
- Novel Antiandrogens (Abiraterone Acetate and Enzalutamide)
- Cabozantinib: MET/VEGFR-targeted agent

Abiraterone Inhibits Androgen Biosynthesis Through CYP17: 17α-Hydroxylase/17,20-lyase

Abiraterone inhibits biosynthesis of androgen produced at 3 critical sites:

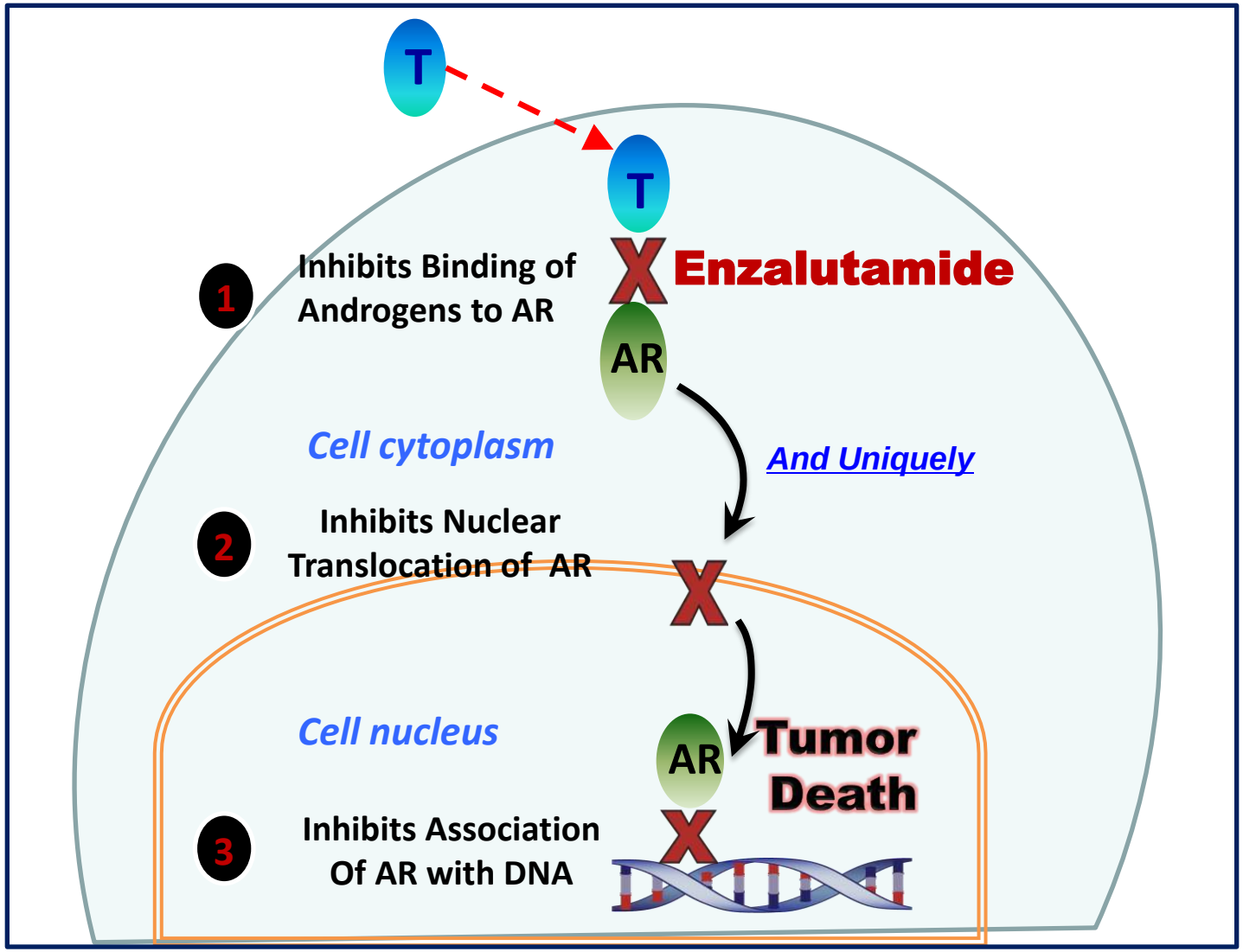
- Testes
- Adrenal Gland
- Prostate Tumor Cell





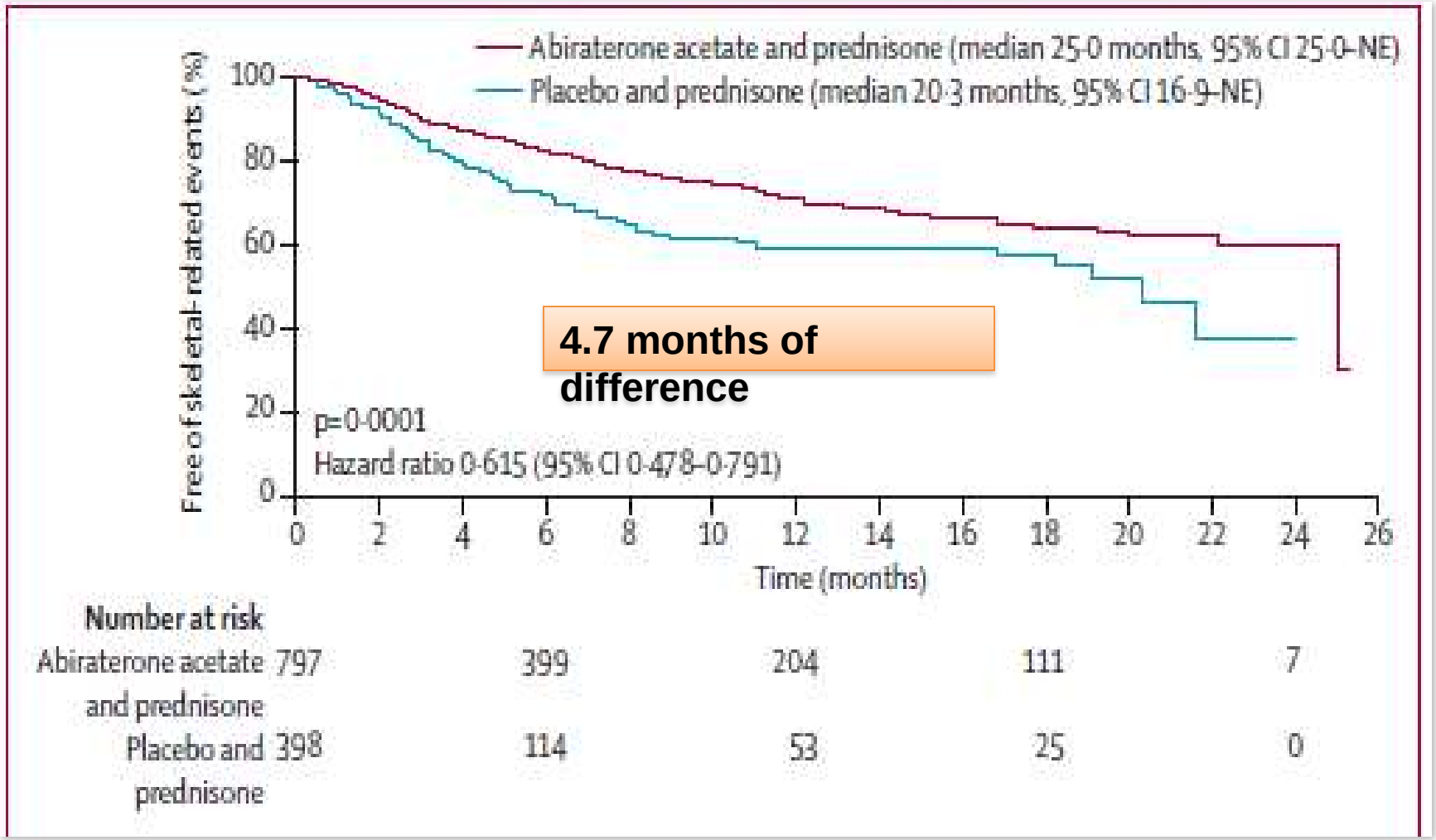
Modified from Attard G. et al. J Clin Oncol 2008

Enzalutamide impacts multiple steps in AR signaling pathway



Modified from Tran et al. Science 2009

Abiraterone post-docetaxel does delay SREs



Logothetis et al. Lancet Oncology, 2012

Enzalutamide pre-docetaxel does delay SREs

Enzalutamide Reduced Risk of First Skeletal-Related Event*

Patients at Risk

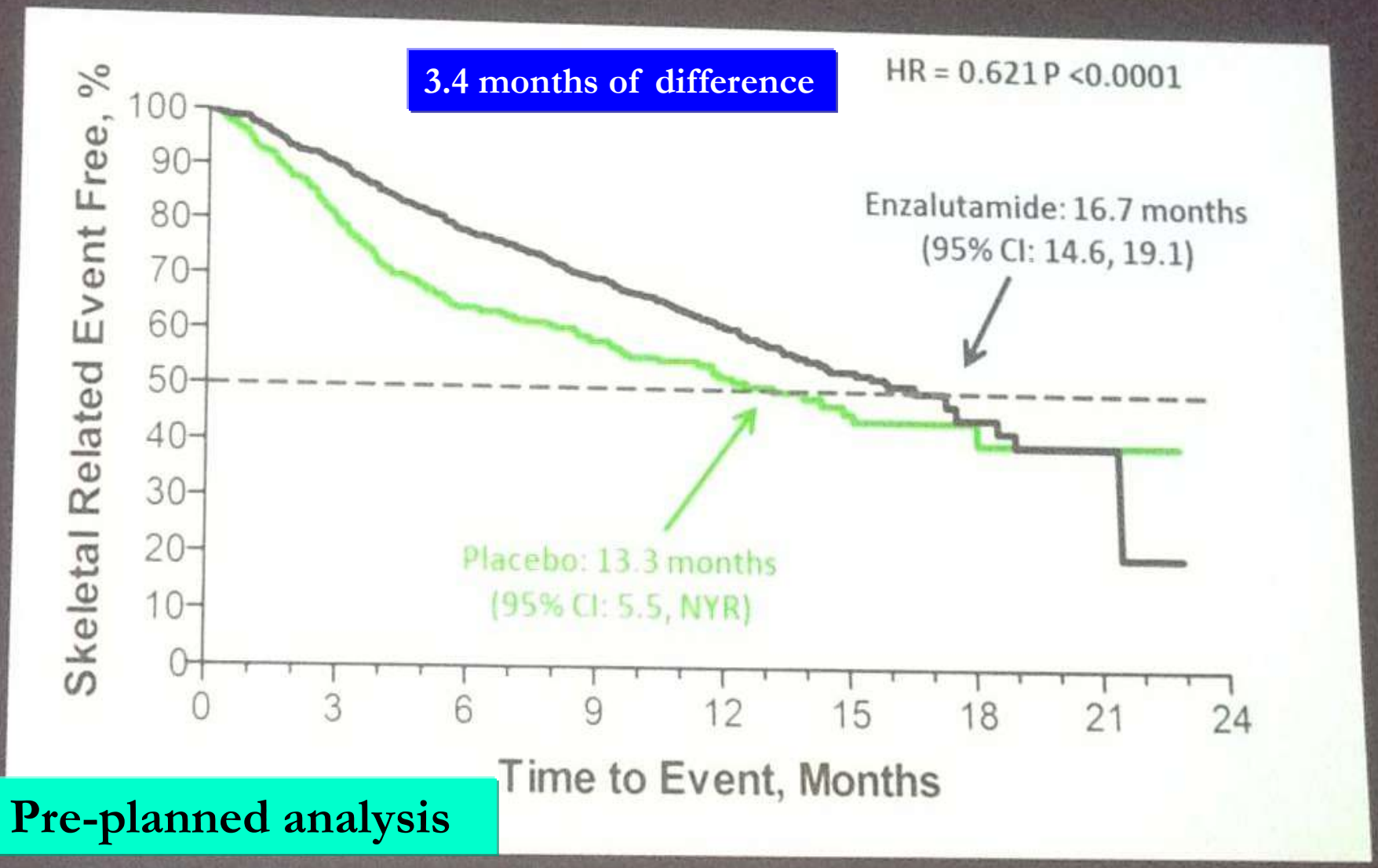
Enzalutamide	872	843	797	732	674	605	447	286	183	90	24	1	0
Placebo	845	750	644	585	520	463	319	198	118	59	18	0	0

*Included radiation therapy or surgery to bone for prostate cancer, pathological bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain from prostate cancer. †12 month landmark for percentage of patients SRE-free

Beer TM et al. N Engl J Med. 2014

Presented By Andrew Armstrong at 2014 ASCO Annual Meeting

Enzalutamide post-docetaxel does delay SREs



Pre-planned analysis

Enzalutamide	800	676	548	379	209	87	19	2	0
Placebo	399	278	196	128	68	33			

JS De Bono, ASCO, 2012

Linee Guida - AIOM Carcinoma prostatico con metastasi ossee

Le nuove molecole: abiraterone e enzalutamide

L'abiraterone e l'enzalutamide sono capaci, nei pazienti affetti da tumore della prostata metastatico allo scheletro in fase di resistenza alla castrazione, di ritardare la comparsa degli SRE e la progressione scheletrica
Livello di evidenza: 1+

“Bone Health” and new drugs

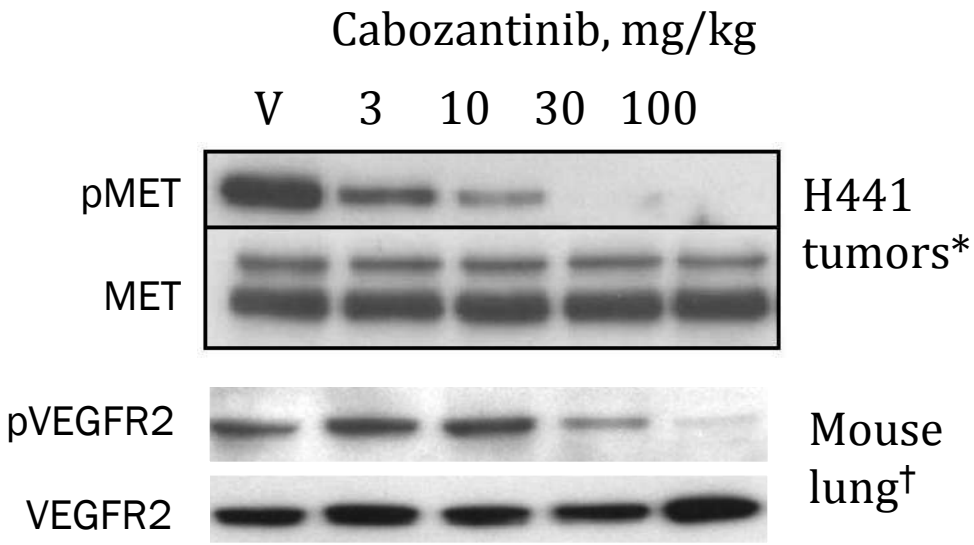
- Bisphosonates (Zoledronic Acid)
- Anti RANKL MoAb (Denosumab)
- mTOR inhibitor
- Radiopharmaceutical (Radium-223)
- Endothelin A receptor antagonist (Zibotentan)
- Src inhibitors (Saracatinib, Dasatinib)
- Novel Antiandrogens (Abiraterone Acetate and Enzalutamide)
- Cabozantinib: MET/VEGFR-targeted agent

Cabozantinib (XL184): Target Profile

Kinase	IC_{50}, nM
MET	1.8
VEGFR2	0.035
RET	5.2
KIT	4.6
AXL	7.0
TIE2	14
FLT3	14
S/T Ks (47)	>200

ATP competitive, reversible

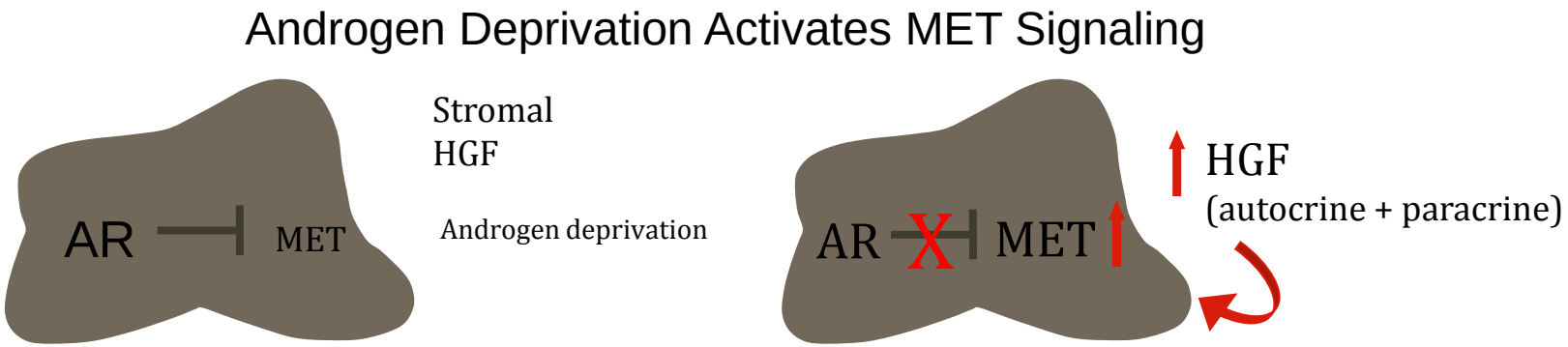
RTK	Cellular IC_{50}, nM, Autophosphorylation
MET	8
VEGFR2	4

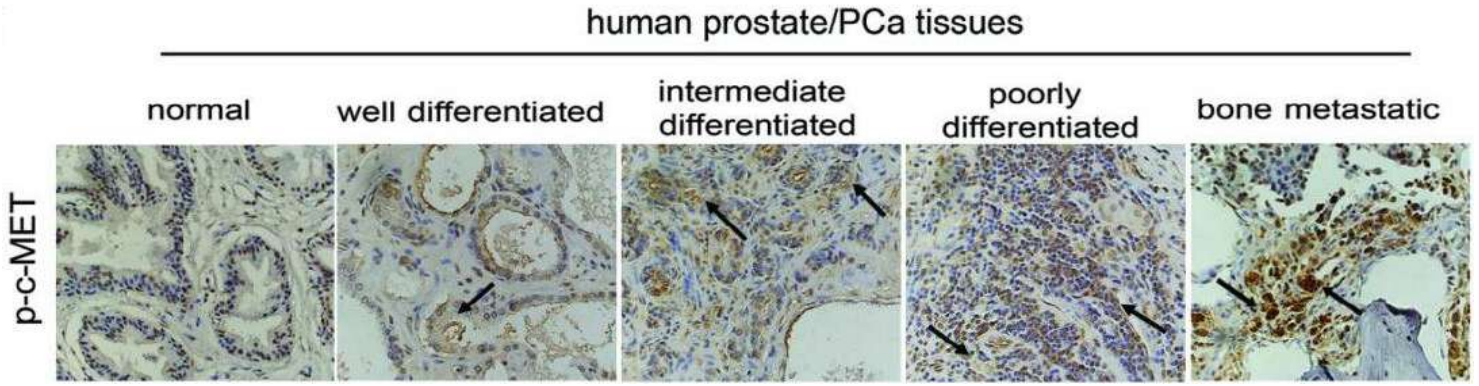


*No growth factor stimulation.
†VEGF-A administered 30 min prior to harvest.

Data courtesy of Ron Weitzman and Dana Aftab.

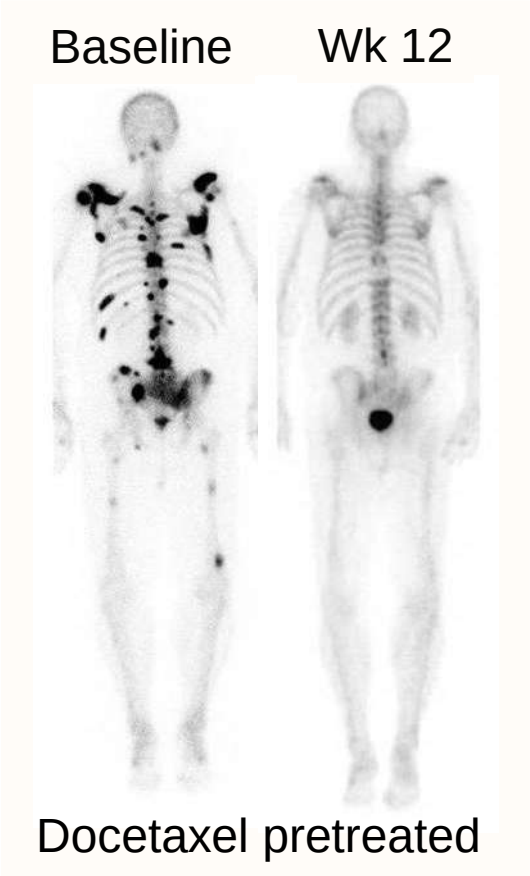
ROLE OF MET IN PROSTATE CANCER AND BONE METASTASES



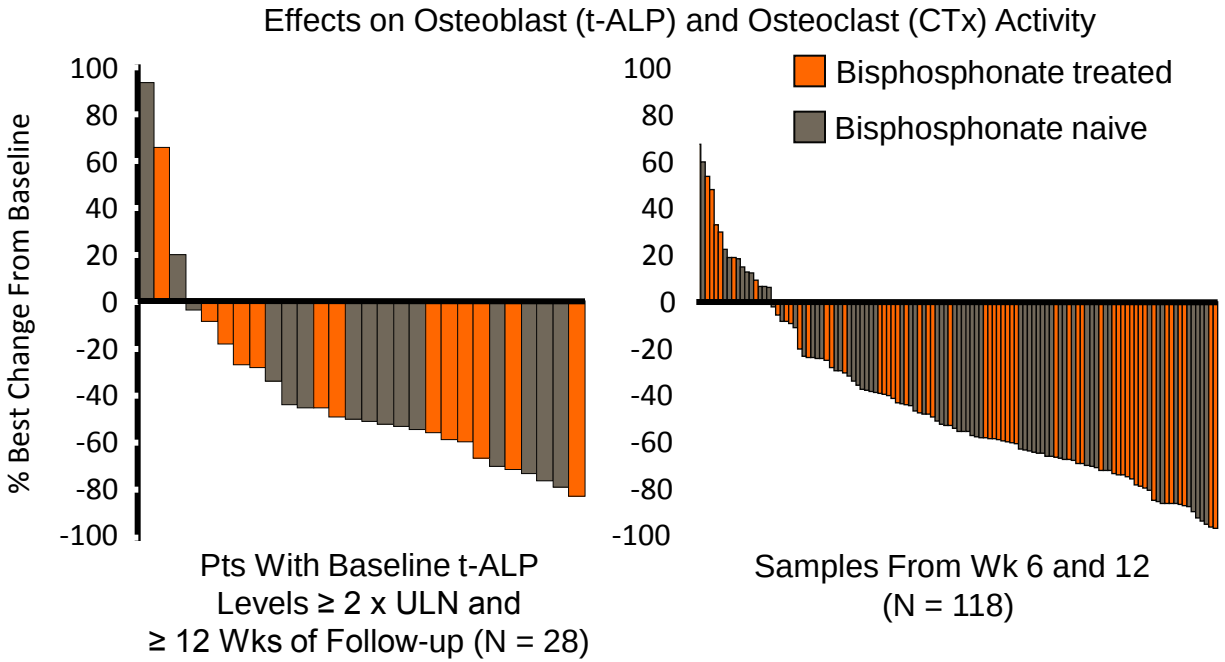


Zhang S, et al. Mol Cancer. 2010;9:9.

CABOZANTINIB
DEMONSTRATES SIGNIFICANT BONE EFFECTS



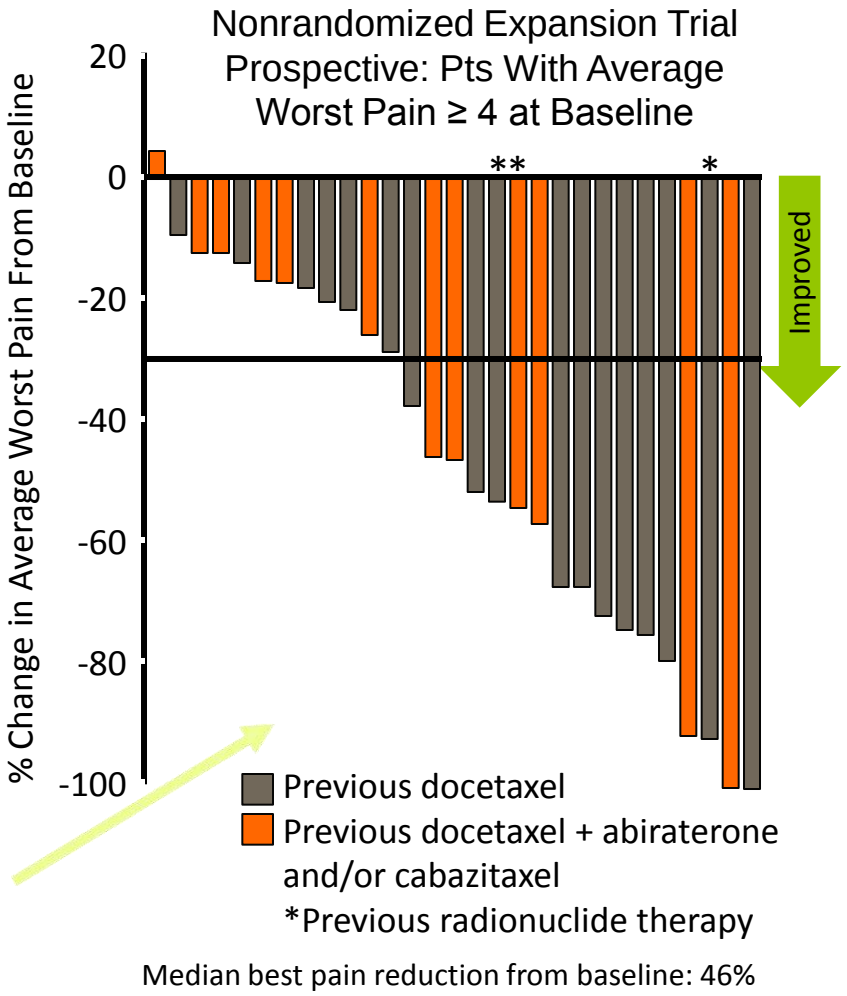
Bone Scan Evaluable (N = 108)	n (%)
Complete resolution	21 (19)
Partial resolution	61 (56)
Stable	23 (21)
Progressive disease	3 (3)



Hussain M, et al. ASCO 2011. Abstract 4516.

CABOZANTINIB:
EFFECTS ON BONE PAIN AND NARCOTIC USE

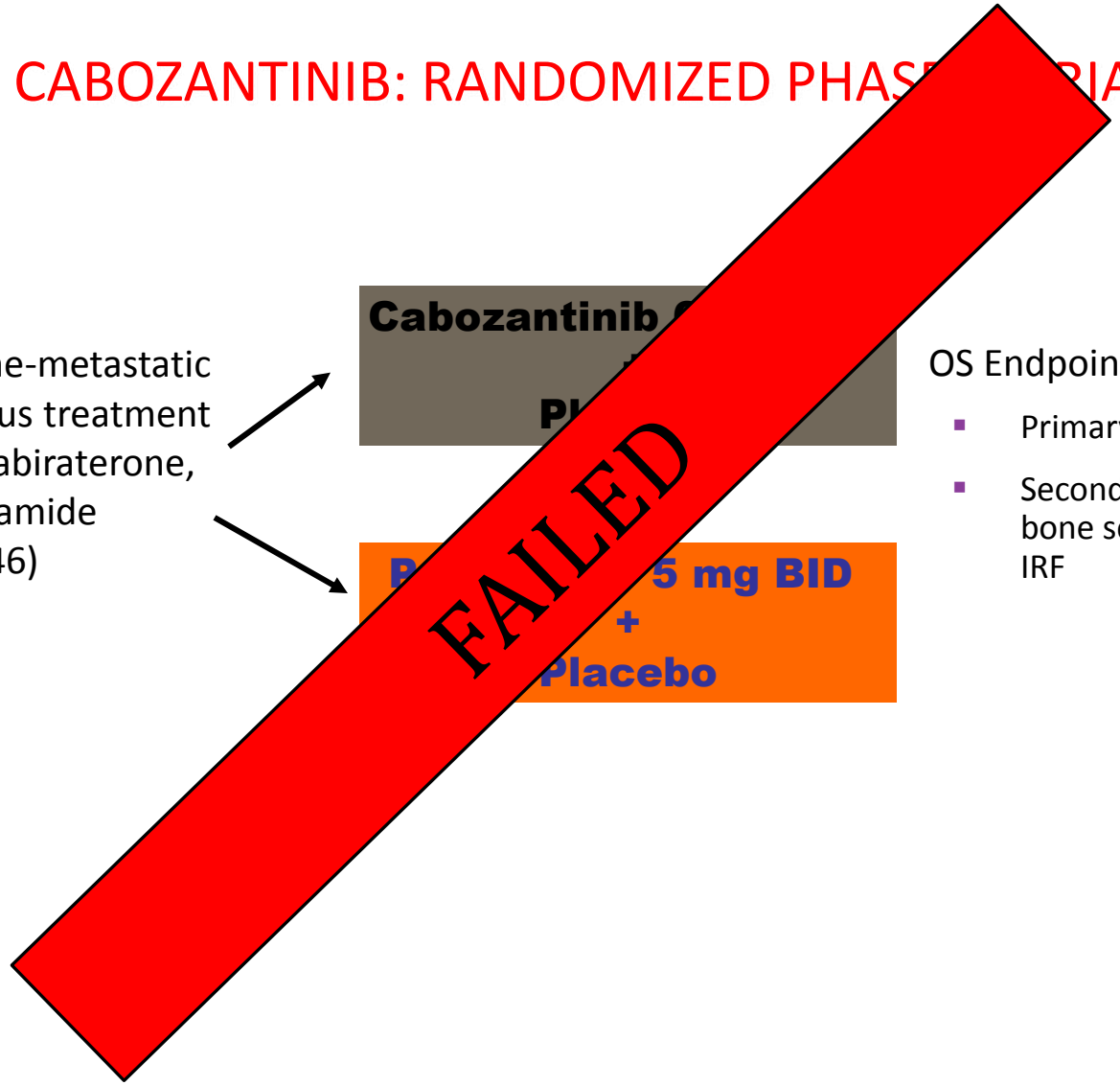
Randomized Discontinuation Trial; Post Hoc Investigator Survey	n (%)
Bone metastases and bone pain at baseline (n = 83): pain improvement at Wk 6 or 12	56 (67)
Narcotics for bone pain at baseline (n = 67): pain improvement at Wk 6 or 12	47 (70)
Evaluable for narcotics change (n = 55): decrease or discontinuation of narcotics	31 (56)



7/27 (26%) patients discontinued narcotics entirely

Hussain M, et al. ASCO 2011. Abstract 4516. Basch EM, et al. 2011 AACR-NCI-EORTC Abstract B57.

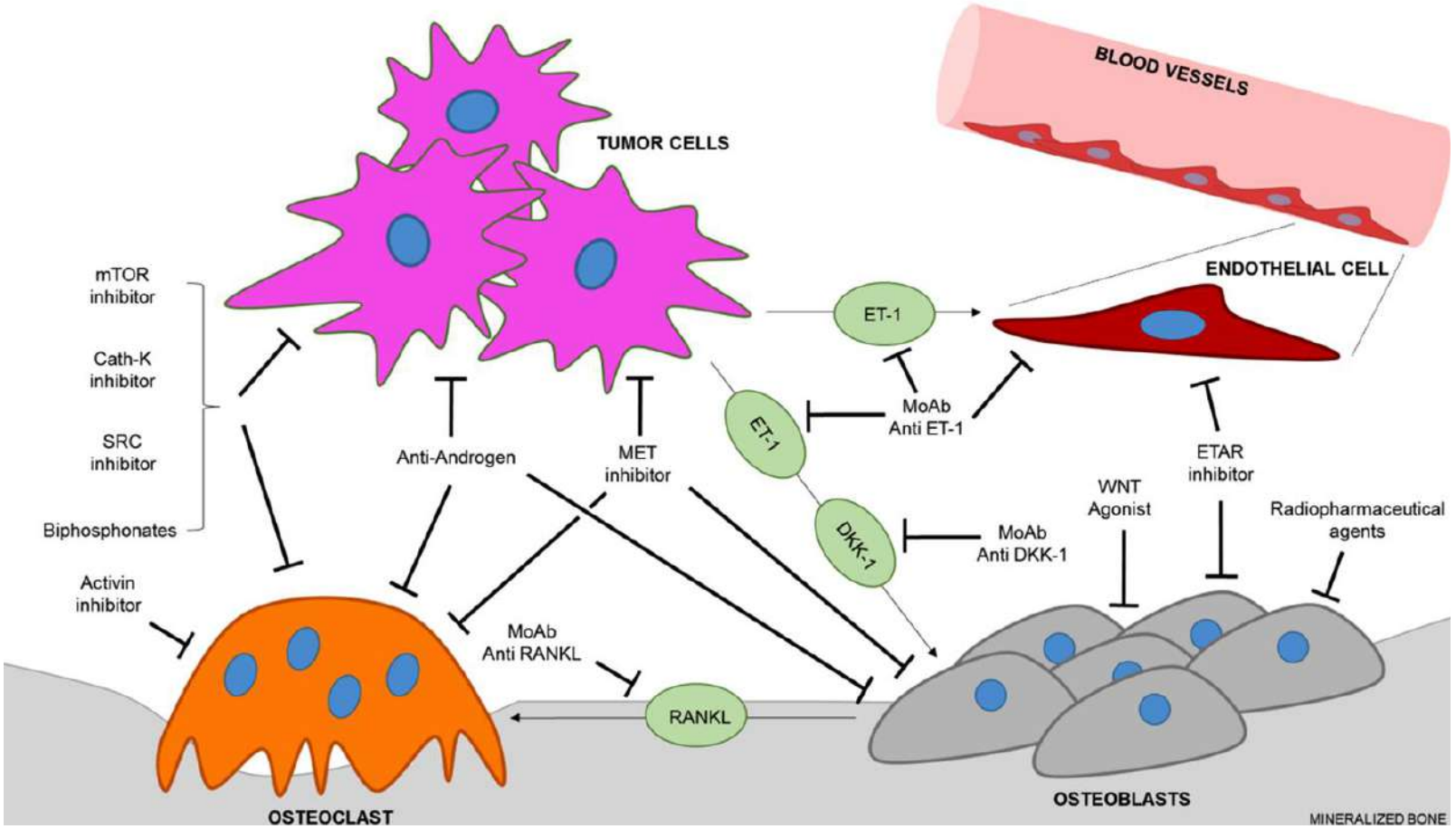
CABOZANTINIB: RANDOMIZED PHAS RIALS



OS Endpoint Trial[2]

- Primary endpoint: OS
- Secondary endpoints: bone scan response by IRF

Which are the future molecular targets in bone metastases treatment?.



Pantano F and Santini D, EOED, 2015

Thank you

Società Italiana
di Osteoncologia

Alessandria 5 Maggio 2018

Zoledronato trimestrale e denosumab nel trattamento delle metastasi ossee

Vittorio Fusco
ASO Alessandria

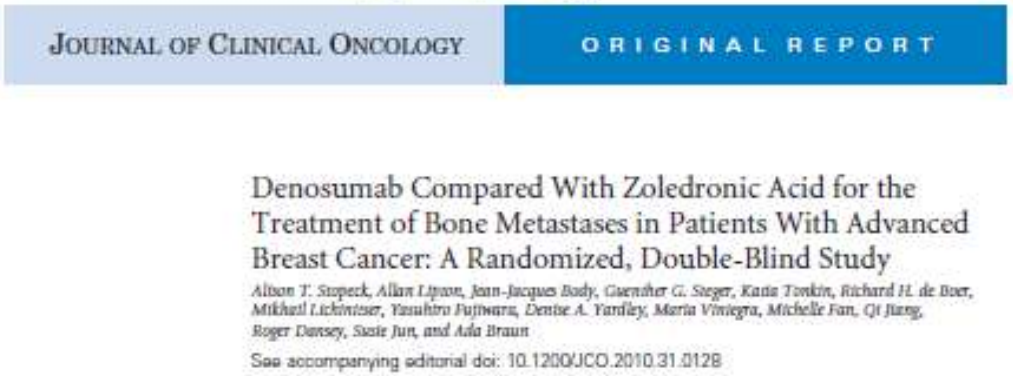
- Perché usiamo gli antiresorptive drugs (pamidronato, zoledronato, ibandronato, denosumab) nella malattia metastatica all'osso?

- Perché li usiamo così (mensilmente) ?

- Per quanto tempo?

- Cosa possiamo cambiare?

ZOLEDRONATO *vs* DENOSUMAB: 3 TRIALS


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study

Alison T. Stopeck, Allan Lipton, Jean-Jacques Body, Guenther G. Steger, Kasia Tonkin, Richard H. de Boer, Mikhail Lichinitser, Yasuhiro Fujiwara, Denise A. Yardley, Maria Viniegra, Michelle Fan, Qi Jiang, Roger Dansey, Susie Jun, and Ada Braun

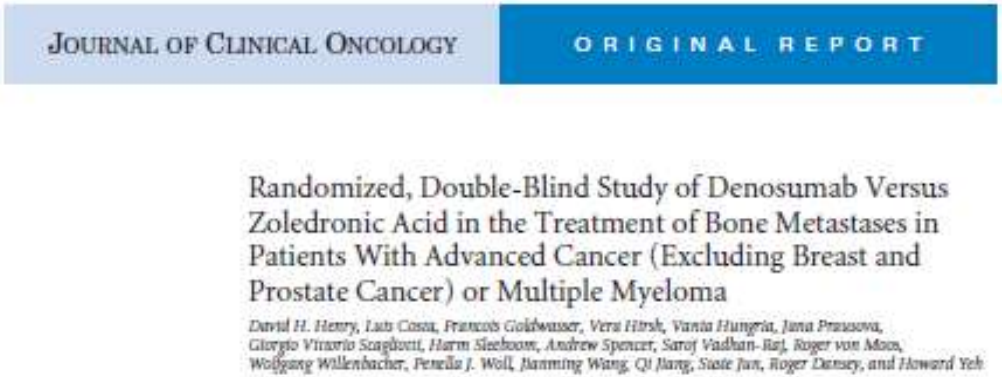
See accompanying editorial doi: 10.1200/JCO.2010.31.0128

Stopeck, JCO 2010
2046 pts
First on-study SRE: HR 0.82
(26.4 months *vs* not reached)


Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study

Karim Fizazi, Michael Carducci, Matthew Smith, Ronaldo Damião, Janet Brown, Lawrence Karsh, Piotr Milecki, Neal Shore, Michael Rader, Huei Wang, Qi Jiang, Sylvia Tadros, Roger Dansey, Carsten Goessl

Fizazi, Lancet 2011
1904 pts
First on-study SRE: HR 0.82
(17.1 *vs* 20.7 months)


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

David H. Henry, Luis Costa, Francois Goldwasser, Vera Hirsh, Vania Hungria, Jana Prausova, Giorgio Vittorio Scagliotti, Harm Sleeboom, Andrew Spencer, Saroj Vadhan-Raj, Roger von Moos, Wolfgang Willenbacher, Penella J. Woll, Jianming Wang, Qi Jiang, Susie Jun, Roger Dansey, and Howard Yeh

Henry, JCO 2011
1776 pts
First on-study SRE: HR 0.8 (non inferiority)
(16.3 *vs* 20.6 months)

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	L'uso dei bisfosfonati ibandronato, pamidronato e zoledronato è raccomandato in donne con carcinoma della mammella e metastasi ossee in quanto è in grado di ridurre il numero di eventi scheletrici e ritardarne significativamente la comparsa.	**Positiva forte**

Qualità Globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	Nelle pazienti affetta da carcinoma mammario con metastasi ossee alla prima diagnosi il trattamento con denosumab può essere utilizzato **La valutazione complessiva della qualità delle evidenze ad oggi disponibili circa "l'efficacia di denosumab in pazienti affetta da carcinoma mammario con metastasi ossee alla prima diagnosi", la valutazione del rapporto tra i benefici ed i danni correlati e la formulazione della raccomandazione relativa al quesito posto, sono state analizzate secondo metodologia GRADE (vedere capitolo 12).*	**Positiva debole**

Take home message: I bisfosfonati sono efficaci nel ridurre le complicanze scheletriche, nel ritardare il tempo di comparsa delle complicanze scheletriche e nel ridurre il dolore osseo in pazienti con metastasi ossee secondarie a carcinoma mammario. Il Denosumab è una valida alternativa all'uso dei bisfosfonati per quanto riguarda la prevenzione delle complicanze scheletriche. **Il Denosumab è superiore all'acido zoledronico in termini di ritardo della comparsa del primo e dei successivi SRE.**

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	L'uso dei bisfosfonati e di Denosumab è raccomandato in pazienti con metastasi ossee da carcinoma prostatico resistente alla castrazione, in quanto in grado di ritardare la comparsa di eventi scheletrici.	**Positiva forte**

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
B	Bisfosfonati e Denosumab possono trovare impiego per il controllo del dolore in pazienti con metastasi ossee da carcinoma prostatico resistente alla castrazione, ma non possono sostituire i farmaci analgesici.	**Positiva debole**

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
B	Il denosumab potrebbe essere impiegato nel paziente con metastasi ossee da carcinoma prostatico ormono-sensibile.	**Positiva debole**

Take home message: I bisfosfonati (ac. zoledronico) sono efficaci nel ridurre e ritardare le complicanze scheletriche di pazienti con metastasi ossee da carcinoma prostatico refrattario alla castrazione e possono essere efficaci nel controllare parzialmente il dolore osseo. Il Denosumab è una valida alternativa all'uso dei bisfosfonati per quanto riguarda la prevenzione delle complicanze scheletriche nel paziente con malattia refrattaria alla castrazione

JAMA 2017 : due studi

Research

JAMA Oncology | Original Investigation

Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in Women With Breast Cancer Metastatic to Bone
The OPTIMIZE-2 Randomized Clinical Trial

Gabriel N. Hortobagyi, MD; Catherine Van Poznak, MD; W. Graydon Harker, MD; William J. Gradishar, MD; Helen Chew, MD; Shaker R. Dakhil, MD; Barbara B. Haley, MD; Nicholas Sauter, MD; Ramon Mohanlal, MD; Ming Zheng, PhD; Allan Lipton, MD

Research

JAMA | Original Investigation

Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases
A Randomized Clinical Trial

Andrew L. Himelstein, MD; Jared C. Foster, PhD; James L. Khatcheressian, MD; John D. Roberts, MD; Drew K. Seisler, BS; Paul J. Novotny, MS; Rui Qin, PhD; Ronald S. Go, MD; Stephen S. Grubbs, MD; Tracey O'Connor, MD; Mario R. Velasco Jr, MD; Douglas Weckstein, MD; Ann O'Mara, PhD, RN, MPH; Charles L. Loprinzi, MD; Charles L. Shapiro, MD

Breast

Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial

Dino Amadori, Massimo Aglietta, Barbara Alessi, Lorenzo Gianni, Toni Ibrahim, Gabriella Farina, Fernando Gaion, Francesco Bertoldo, Daniele Santini, Roberta Rondena, Paola Bogani, Carla I Ripamonti

ZOOM (Amadori Lancet Oncol 2013)

425 pts
in 62 centres
in Italy
2006-2009

Pretrattati
per 12-15 mesi

Research

JAMA Oncology | Original Investigation

Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in Women With Breast Cancer Metastatic to Bone
The OPTIMIZE-2 Randomized Clinical Trial

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OPTIMIZE-2 (Horthobagyi, JAMA 2017)

416 pts
in 102 centres
in USA
2006-2013

Pretrattati
per 12-15 mesi

Breast

OPTIMIZE-2
(Horthobagyi, JAMA 2017)

416 pts
in 102 centres
in USA
2006-2013

Pretrattati
per 12-15 mesi

Research

JAMA Oncology | Original Investigation

Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in Women With Breast Cancer Metastatic to Bone
The OPTIMIZE-2 Randomized Clinical Trial

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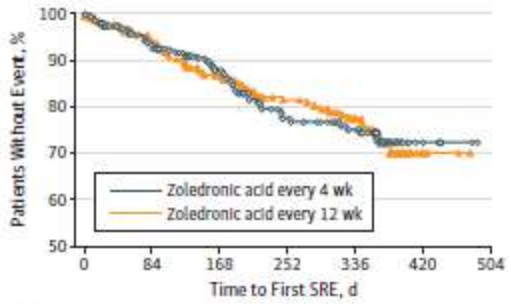
Figure 2. Kaplan-Meier Curve for Time From Randomization to First Skeletal-Related Event (SRE)



No. at risk: No. of events

Every 4 wk regimen	200:0	174:13	142:22	112:38	92:41	4:44	0:44
Every 12 wk regimen	203:0	180:11	154:25	128:34	109:40	3:47	0:47

Forza :
-placebo (NB : Zoom era open-label)

Limiti :
-Cambio sample size in corso di studio (sulla base di ZOOM …)
-Assenza di dati a più lungo termine

Research

JAMA | Original Investigation

Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases
A Randomized Clinical Trial

Andrew L. Himelstein, MD; Jared C. Foster, PhD; James L. Khatcheressian, MD; John D. Roberts, MD; Drew K. Seisler, BS; Paul J. Novotny, MS; Rui Qin, PhD; Ronald S. Go, MD; Stephen S. Grubbs, MD; Tracey O'Connor, MD; Mario R. Velasco Jr, MD; Douglas Weckstein, MD; Ann O'Mara, PhD, RN, MPH; Charles L. Loprinzi, MD; Charles L. Shapiro, MD

INTERVENTIONS Patients were randomized to receive zoledronic acid administered intravenously every 4 weeks (n = 911) vs every 12 weeks (n = 911) for 2 years.

MAIN OUTCOMES AND MEASURES The primary end point was the proportion of patients having at least 1 skeletal-related event (defined as clinical fracture, spinal cord compression, radiation to bone, or surgery involving bone) within 2 years after randomization and a between-group absolute difference of 7% as the noninferiority margin. Secondary end points included the proportion of patients with at least 1 skeletal-related event by disease type, pain as assessed by the Brief Pain Inventory (range, 0-10; higher scores indicate worse pain), Eastern Cooperative Oncology Group performance status (range, 0-4; higher scores indicate worse disability), incidence of osteonecrosis of the jaw, kidney dysfunction, skeletal morbidity rate (mean number of skeletal-related events per year), and, in a subset of 553 patients, suppression of bone turnover (assessed by C-terminal telopeptide levels).

RESULTS Among 1822 patients who were randomized (median age, 65 years; 980 [53.8%] women; 855 with breast cancer, 689 with prostate cancer, and 278 with multiple myeloma), 795 completed the study at 2 years. A total of 260 patients (29.5%) in the zoledronic acid every 4-week dosing group and 253 patients (28.6%) in the every 12-week dosing group experienced at least 1 skeletal-related event within 2 years of randomization (risk difference of −0.3% [1-sided 95% CI, −4% to ∞]; $P < .001$ for noninferiority). The proportions of skeletal-related events did not differ significantly between the every 4-week dosing group vs the every 12-week dosing group for patients with breast cancer, prostate cancer, or multiple myeloma. Pain scores, performance status scores, incidence of jaw osteonecrosis, and kidney dysfunction did not differ significantly between the treatment groups. Skeletal morbidity rates were numerically identical in both groups, but bone turnover was greater (C-terminal telopeptide levels were higher) among patients who received zoledronic acid every 12 weeks.

CONCLUSIONS AND RELEVANCE Among patients with bone metastases due to breast cancer, prostate cancer, or multiple myeloma, the use of zoledronic acid every 12 weeks compared with the standard dosing interval of every 4 weeks did not result in an increased risk of skeletal events over 2 years. This longer interval may be an acceptable treatment option.

Himelstein et al, JAMA 2017
CALGB 70604 [Alliance]

1822 patients enrolled
between May 2009
and April 2012

855 breast cancer
689 prostate cancer
279 myeloma

A total of 260 patients (29.5%) in the zoledronic acid every 4-week dosing group and 253 patients (28.6%) in the every 12-week dosing group experienced at least 1 skeletal-related event within 2 years of randomization (risk difference of −0.3%[1-sided 95%CI, −4%to]; $P < .001$ for noninferiority).

The proportions of skeletal-related events did not differ significantly between the every 4-week dosing group vs the every 12-week dosing group for patients with breast cancer, prostate cancer, or multiple myeloma.

LG AIOM 2017 non si pronunciano su zoledronato trimestrale

Proposta in discussione all'interno della Rete Oncologica Piemonte – VdA (*working in progress*)

Cosa usare	Categorie	Pazienti
ZOLEDRONATO TRIMESTRALE	"BASSO" RISCHIO Di SRE	-Breast ER+ indolente -Prostate not aggressive - ??? -???
ZOLEDRONATO MENSILE (1-2 aa) →Trimestrale ?	RISCHIO INTERMEDIO	-Breast (most) -Prostate "aggressive" -???
DENOSUMAB (1-2 aa) →??	ALTO RISCHIO	-Breast "aggressive" -??? -???