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Bone Health and Bone Metastases

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Disclosures

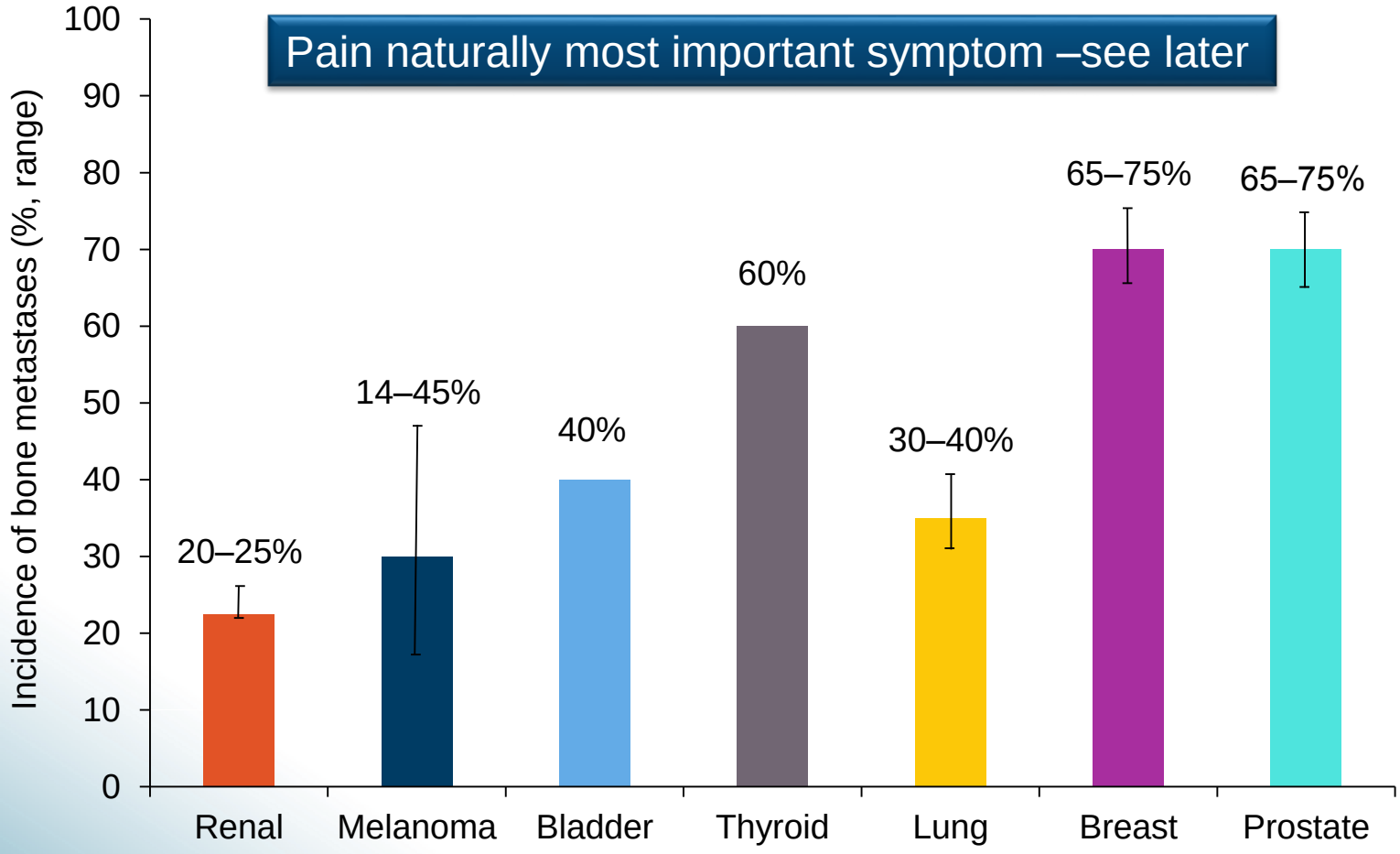
Lectures, Honoraria, Advisory Boards

- Astellas, BMS, Gelgene, Ipsen, Janssen, Medivation, Merck, Novartis, Pfizer, Roche/Genentech

Outline

- 1. Describe bony metastatic biology and address unmet questions
- 2. Describe comparisons between agents including benefit in metastatic setting and toxicity comparison
  - Describe recent adjuvant therapy data
  - Caucasian vs. Asian genome
- 3. Describe WHO list of essential medicines/QOL in advanced disease and ask whether bone directed therapy should be on the list
- Management of Bone Health

Bone metastases are common in patients with advanced solid tumours

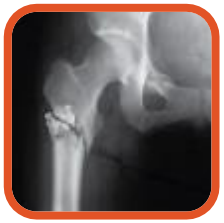


1. Coleman RE. Cancer Treat Rev 2001;27:165–76.

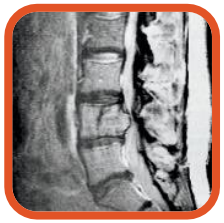
Bone metastases can have serious and debilitating consequences – SREs

- Skeletal-related events (SREs) are defined as:[1,2]

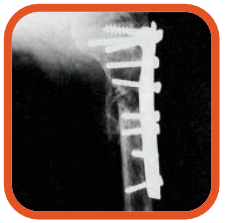
Radiation to bone



Pathological fracture



Spinal cord compression

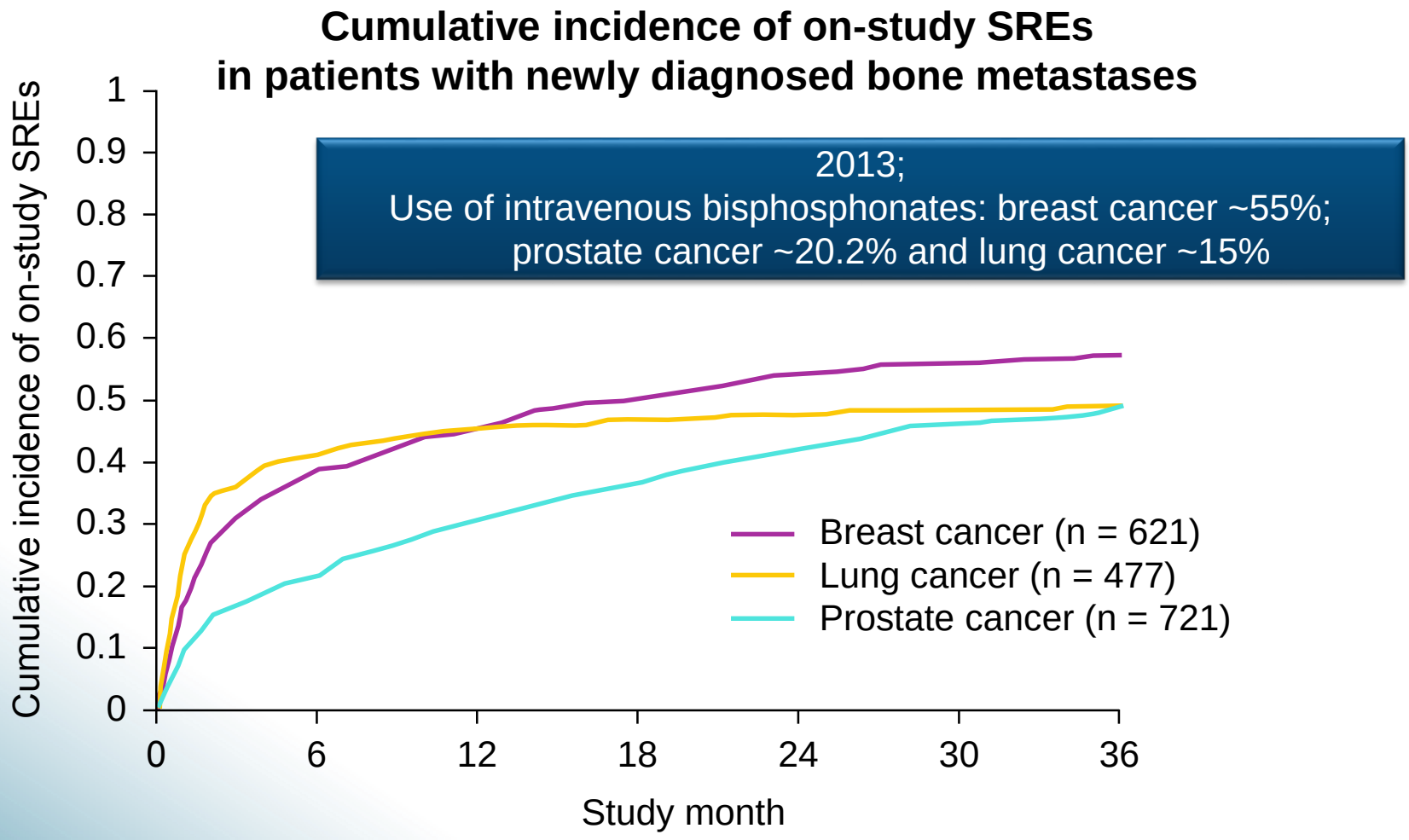


Surgery to bone

- Incidence untreated patients (placebo arm Kohno JCO 2005 vs next slide)
- A composite SRE endpoint is commonly used in clinical trials to evaluate the efficacy of bone-targeted agents[2]
  - Pathological fractures may be symptomatic or identified by imaging assessments
- Recently, **symptomatic** skeletal events (SSEs) has been used as an alternative study endpoint for skeletal complications[3,4]
  - Pathological fractures only included if clinically apparent (symptomatic)
- Hypercalcaemia of malignancy is an additional potential complication of bone metastases[5]

1. Saad F, et al. *J Natl Cancer Inst* 2004;96:879–82;
2.http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf (Accessed August 2014);
3. Sartor O, et al. *Lancet Oncol* 2014;15:738−46; 4. Smith MR, et al. *Ann Oncol* 2015;26:368–74. 5. Coleman RE, et al. *Clin Cancer Res* 2006;12:6243s−9s.

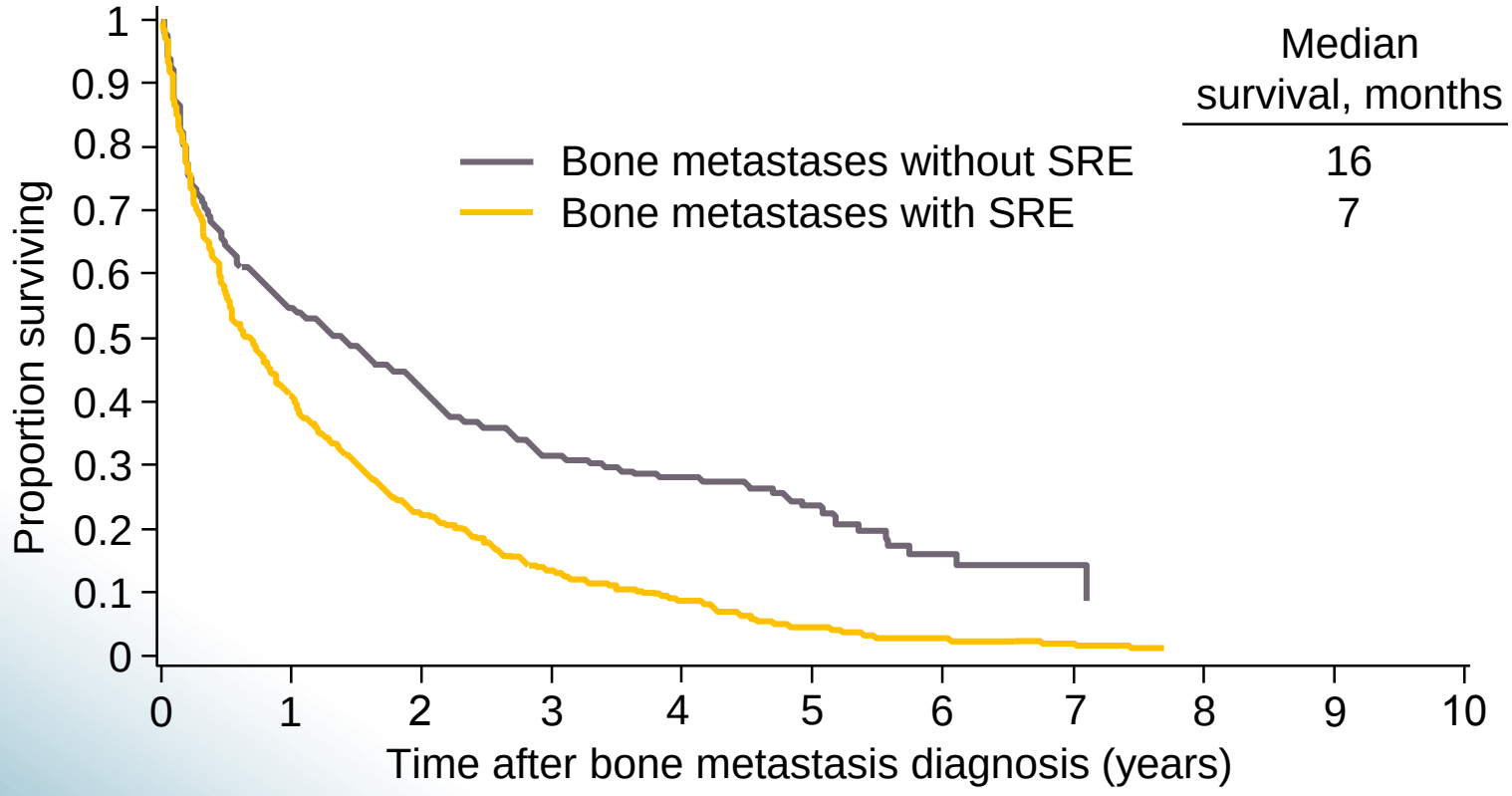
SREs are a common complication in patients with solid tumours and bone metastases



1. Oster G, et al. Support Care Cancer 2013;21:3279–86.

Patients with bone metastases and SREs have a poor prognosis vs those without SREs[1]

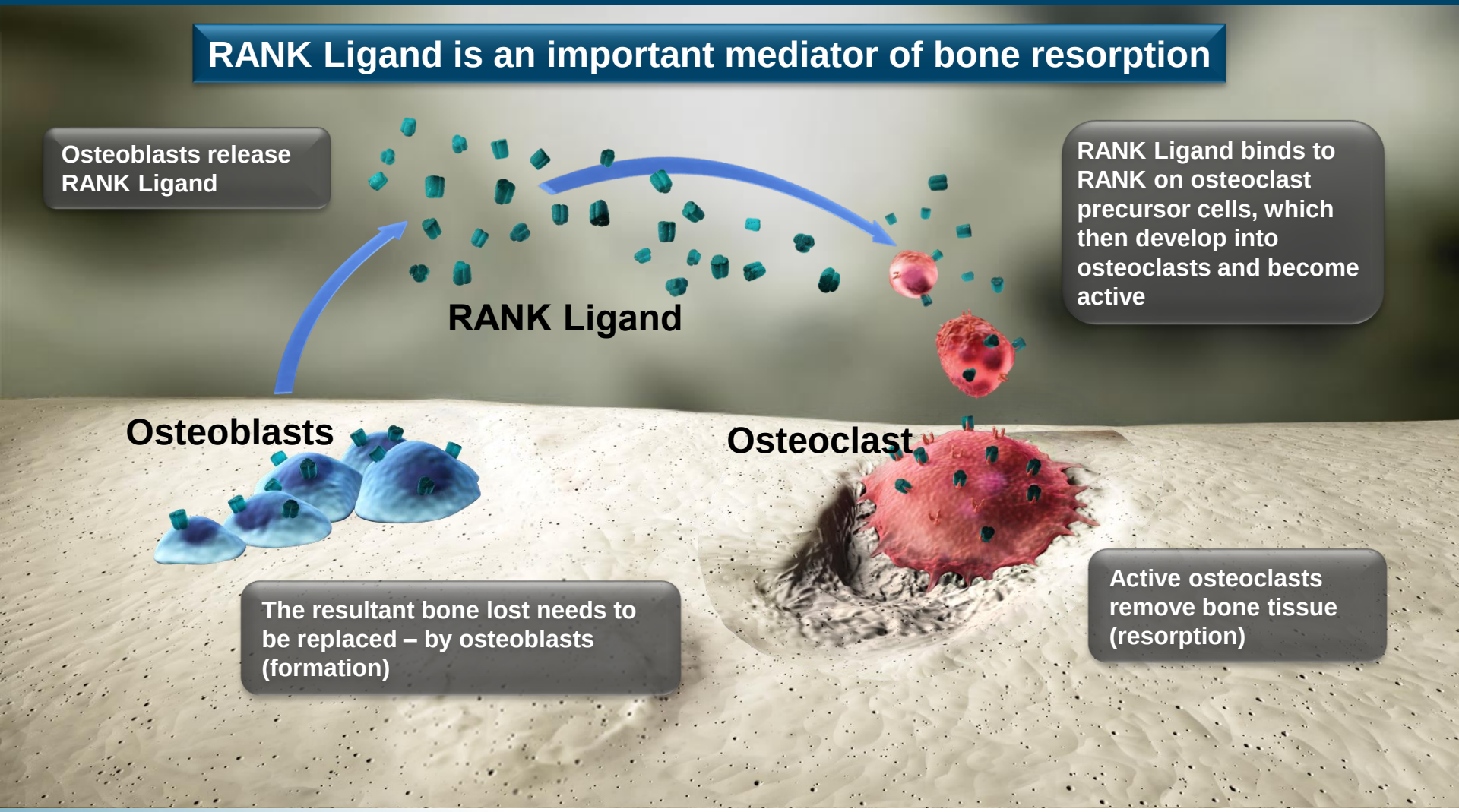
Survival curves for breast cancer patients with bone metastases (n = 2216) with and without SREs



1. Yong M, et al. Breast Cancer Res Treat 2011;129:495−503.

Data are from a population-based cohort study of 35,912 newly identified breast cancer patients conducted in Denmark (1999−2007)

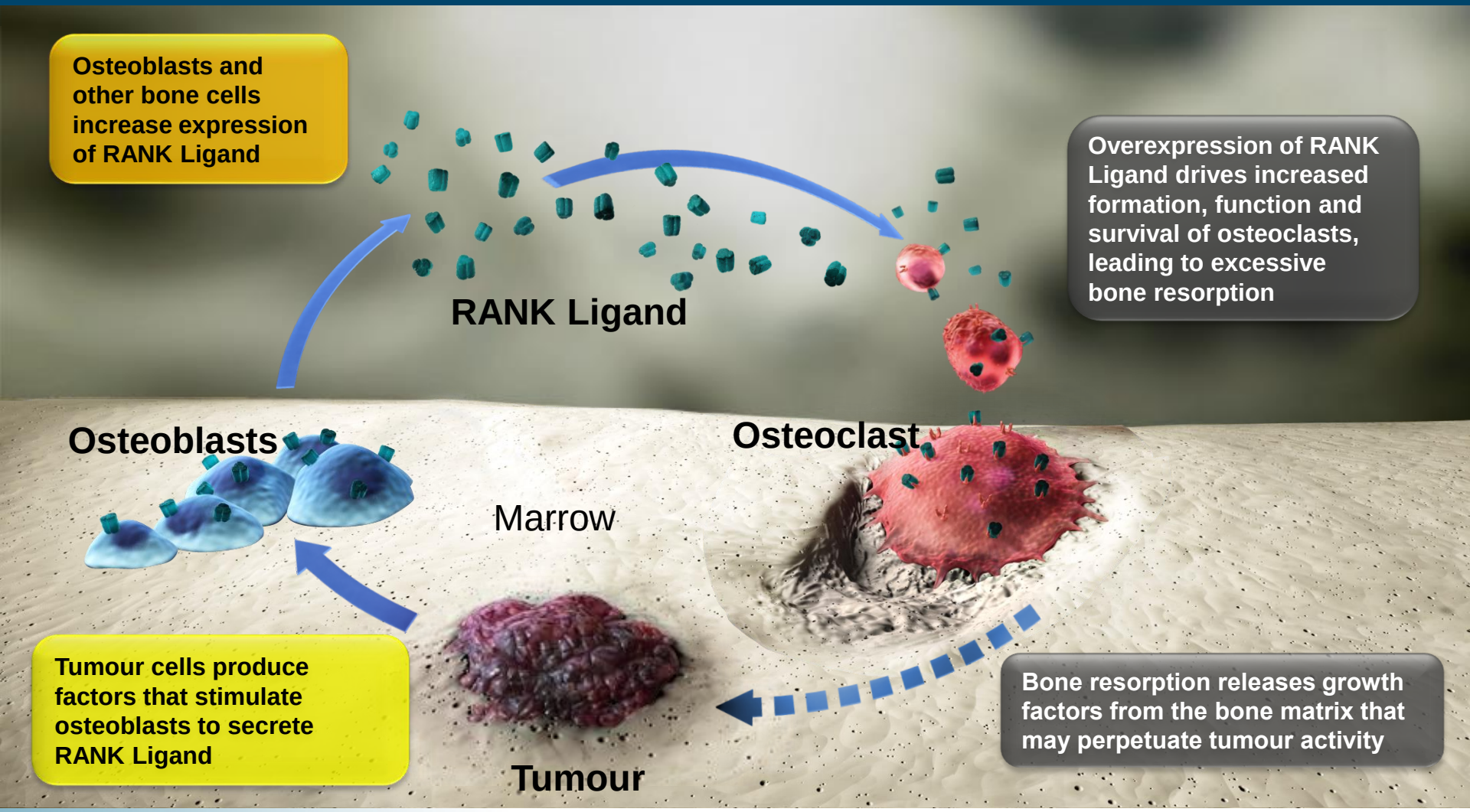
Normal bone remodelling is tightly regulated



Adapted from Boyle WJ et al. *Nature* 2003;423:337–42.

RANK, receptor activator of nuclear factor κ B

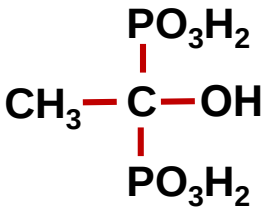
A vicious cycle of bone destruction may develop in the presence of tumour cells



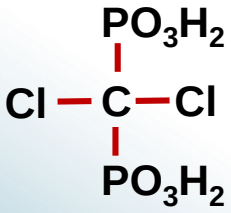
Adapted from Roodman GD. *N Engl J Med* 2004;350:1655–64 and Mundy GR. *Nat Rev Cancer* 2002;2:584–93.

Two classes of bisphosphonates

Non nitrogen-containing



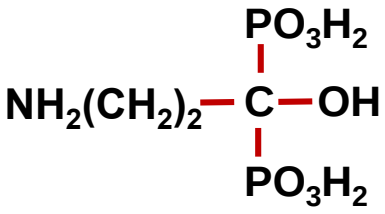
Etidronate



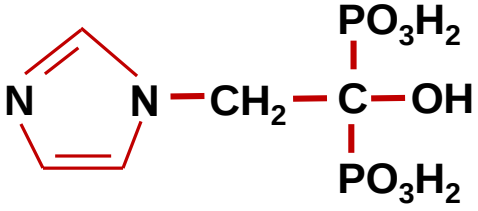
Clodronate

Nitrogen-containing

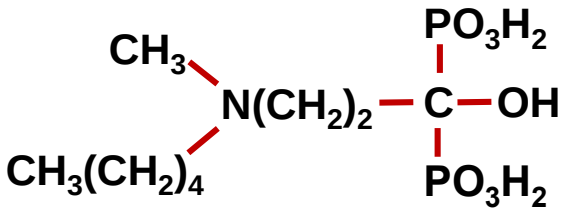
More potent inhibitors of bone resorption



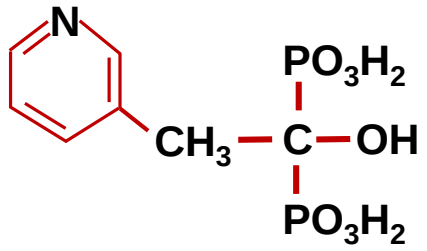
Pamidronate



Zoledronate



Ibandronate



Risedronate

Powles JCO 2002 & 2017

Bisphosphonates (CALGB 70604 [Alliance])

1. Zoledronic acid iv q 3-4 weeks reduced pain and the incidence of skeletal-related events, including clinical fracture, spinal cord compression, radiation to bone, and surgery to bone by 25% to 40%[1-3]

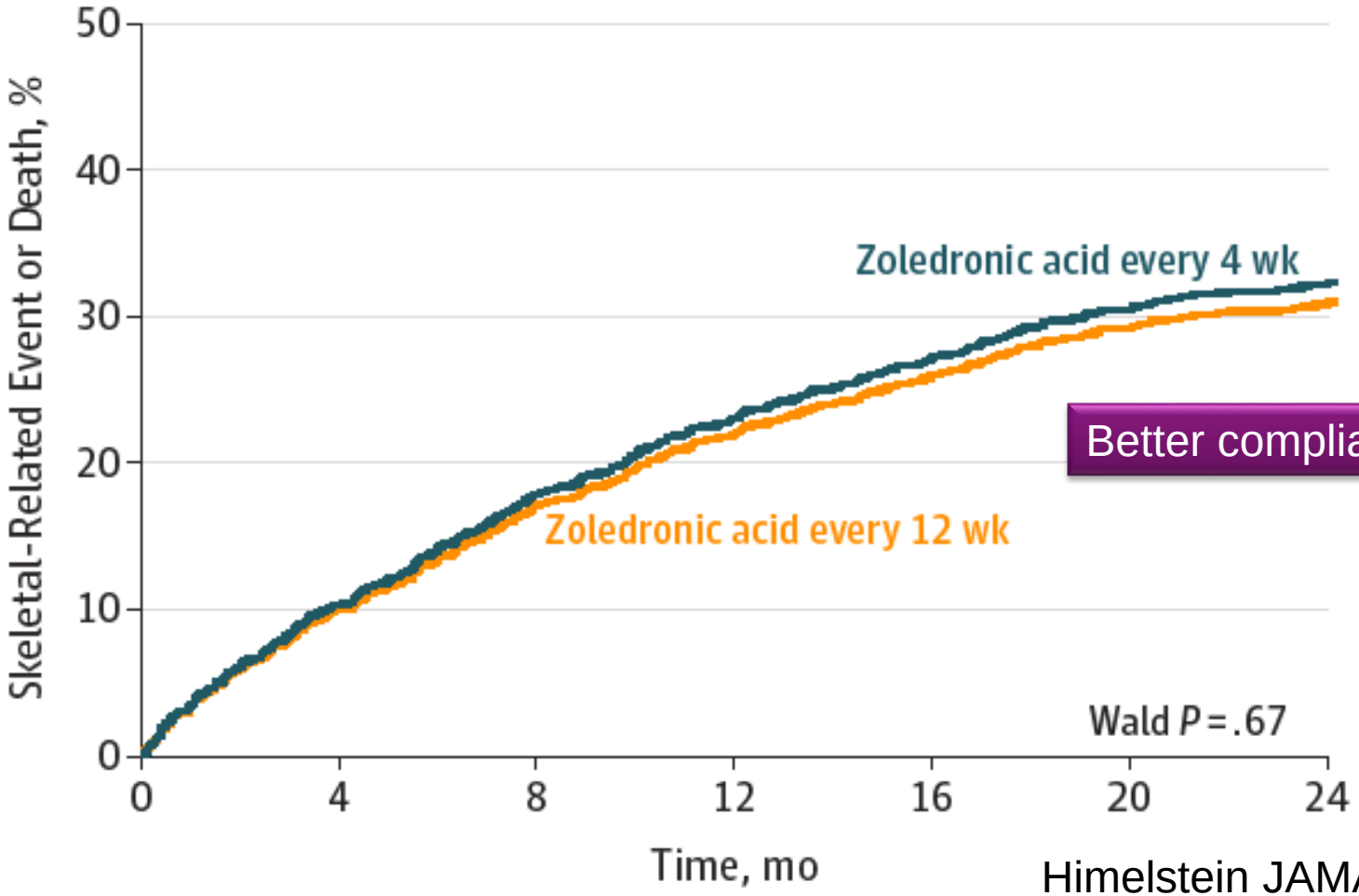
2. n = 1822, e = 795 open-label, non-inferiority clinical trial of patients with metastatic breast (47%), prostate cancers (38%), multiple myeloma (15%)
   – Primary outcome was the proportion of patients having at least 1 skeletal-related event within 2 years after randomization.

1.Kohno J Clin Oncol. 2005
2. Saad JNCI. 2002
3. Pavlakis CochraneDatabase Syst Rev. 2005

Himelstein JAMA 2016

Primary Objective (CALGB 70604 [Alliance])

Figure 2. Cause-Specific Cumulative Incidence of Skeletal-Related Events



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Secondary End Points

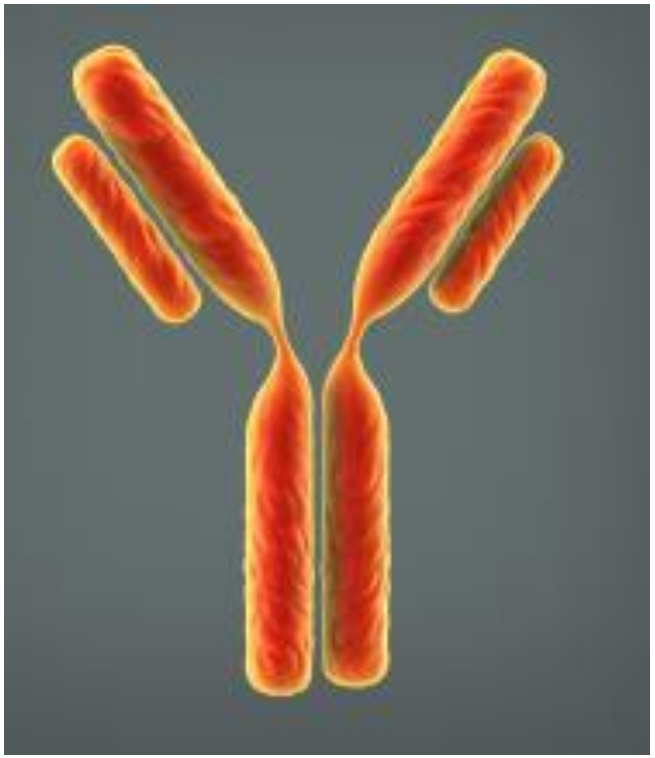
Table 3. Selected Secondary End Points

Secondary End Points	Zoledronic Acid Dose Group		Zoledronic Acid 4-wk Dose Group Minus 12-wk Dose Group (95% CI)	*P* Value
	Every 4 wk	Every 12 wk		
Brief Pain Inventory score[a]				
Worst pain	0.021	0.022	−0.001 (−0.022 to 0.021)	.96
Least pain	0.013	0.007	0.006 (−0.008 to 0.021)	.38
Average pain	0.011	0.008	0.003 (−0.014 to 0.02)	.75
Current pain	0.018	0.016	0.002 (−0.014 to 0.018)	.82
Composite pain	0.022	0.021	0.001 (−0.017 to 0.019)	.88
Relief from pain	0.016	0.009	0.007 (−0.018 to 0.032)	.59
Interference	0.019	0.023	−0.004 (−0.023 to 0.015)	.68
ECOG performance status[a]	0.025	0.024	0.001 (−0.005 to 0.008)	.64
Osteonecrosis of the jaw, No./total available for analysis (%)	18/911 (2.0)	9/911 (1.0)	1.0 (−0.2 to 2.2)	.08[b]
Kidney dysfunction				
Increased creatinine level, No./total available for analysis (%)[c]	10/852 (1.2)	4/837 (0.5)	0.7 (−0.3 to 1.7)	.10[b]
Increased creatinine level vs baseline level, No./total available for analysis (%)[d]	174/875 (19.9)	137/882 (15.5)	4.4 (0.7 to 8.0)	.02[b]
Skeletal morbidity rate, mean (median) [IQR][e]	0.4 (0) [0-0.5]	0.4 (0) [0-0.5]		
Total available for analysis	882	884		
Total person-years of follow-up	1397.5	1367.8		

Himelstein JAMA 2016

Denosumab inhibits RANK Ligand

- Denosumab is an **IgG_2** fully human mAb binds h-RANK Ligand with high affinity & specificity[1-3]
- By binding to RANK Ligand, denosumab prevents RANK Ligand from activating its receptor, RANK, on the surface of osteoclasts and their precursors, independent of bone surface[1,2]
  - Denosumab mimics the effects of OPG on RANK Ligand[2]
- Safety: In the phase 3 clinical trials, no neutralising antibodies were detected[3-5]

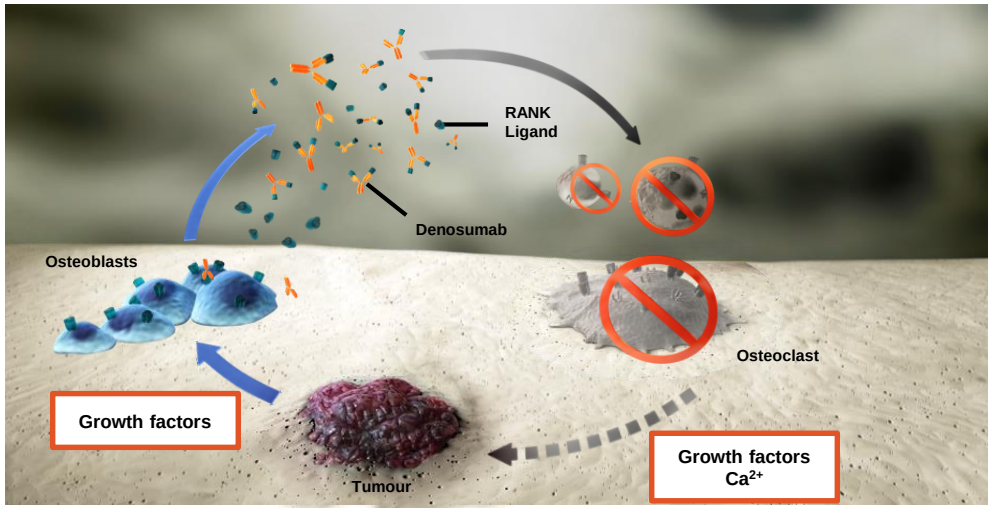


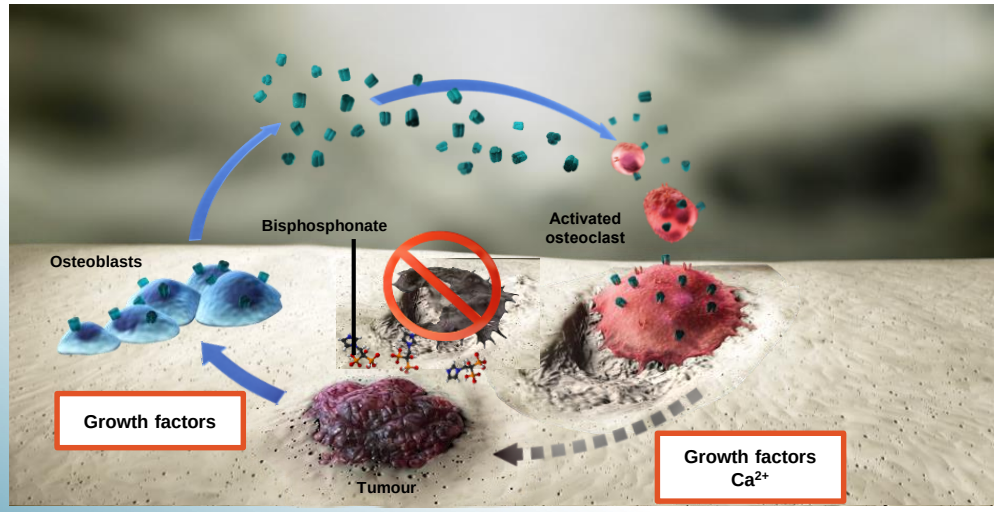
1. XGEVA® (denosumab) Approved Product Information, available at http://www.amgen.com.au/Xgeva.PI.
2. McClung MR, et al. *N Engl J Med* 2006;354:821–31.
3. Stopeck AT, et al. *J Clin Oncol* 2010;28:5132–9.
4. Fizazi K, et al. *Lancet* 2011;377:813–22.
5. Henry DH, et al. *J Clin Oncol* 2011;29:1125–32.

OPG = osteoprotegerin

RANK, receptor activator of nuclear factor kappa β

In metastatic bone disease, RANK-RANK Ligand signalling mediates a ‘vicious cycle’ of interaction between tumour cells and bone

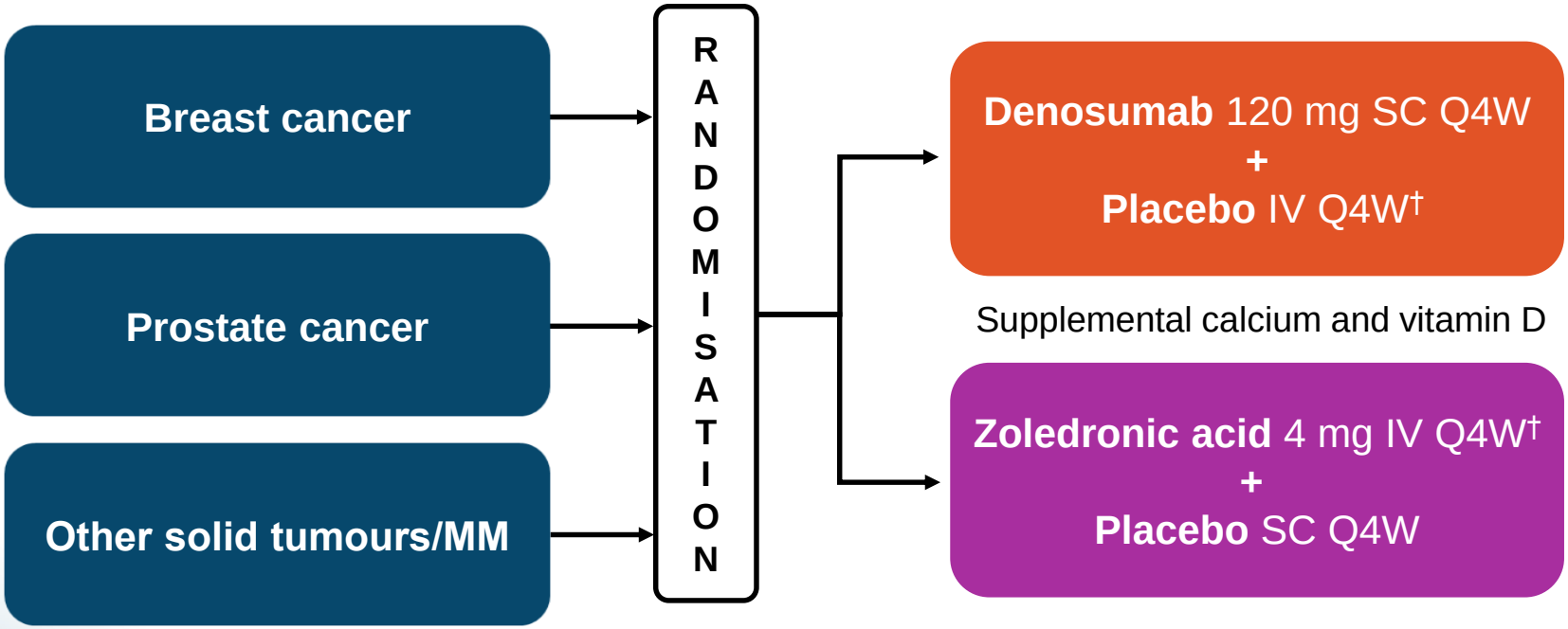




- Denosumab inhibits the **‘vicious cycle’** by binding to RANK Ligand to block osteoclast differentiation and activation[1–3]
- Bisphosphonates inhibit the vicious cycle by embedding in bone and inducing apoptosis of activated osteoclasts[4]

1. Roodman GD. *N Engl J Med* 2004;350:1655–64; 2. Mundy GR. *Nat Rev Cancer* 2002;2:584–93;
3. McClung MR, et al. *N Engl J Med* 2006;354:821–31; 4. Green JR. *Oncologist* 2004;9(Suppl 4):3–13.

Three pivotal Phase III trials of denosumab vs zoledronic acid in patients with bone metastases from advanced cancer

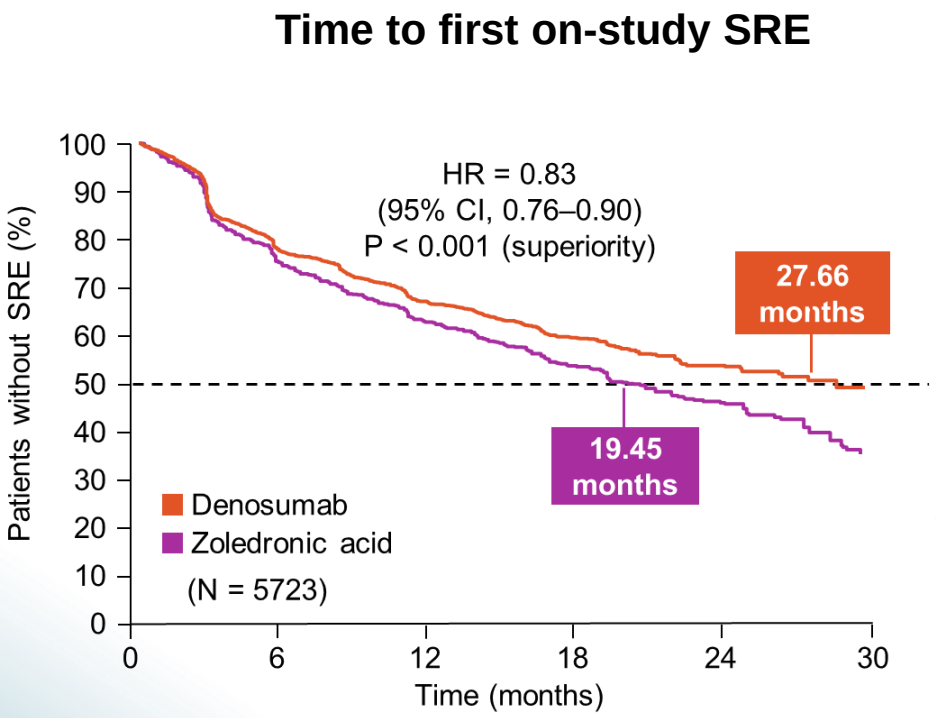


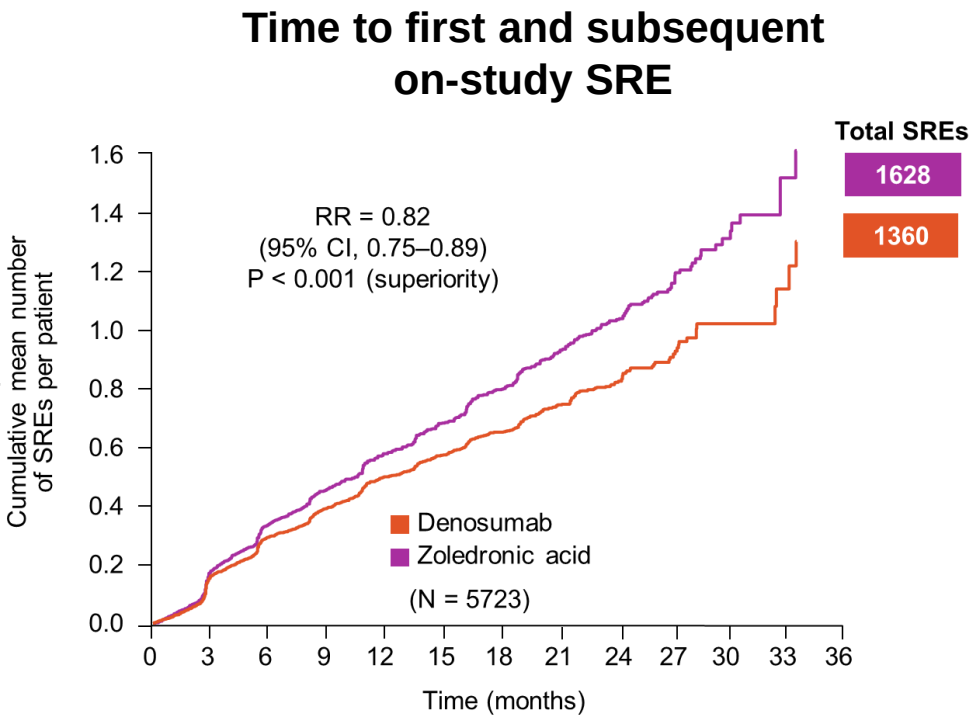
- Primary endpoint: time to first on-study SRE (non-inferiority)
- Secondary endpoints: time to first on-study SRE (superiority); time to first and subsequent on-study SRE; safety and tolerability

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; 4. Lipton A, et al. *Eur J Cancer* 2012;48:3082–92.

*Excluding breast and prostate.

Denosumab was superior to zoledronic acid for SRE prevention[1]





- Time to first on-study SRE reached almost 28 mo on denosumab
- Denosumab significantly reduced the total SREs vs. zoledronic acid

1. Lipton A, et al. Eur J Cancer 2012;48:3082–92.

Adverse events

Patient incidence, n (%)	Zoledronic acid (n = 2836)	Denosumab (n = 2841)
Adverse events (AEs), all grades	2745 (96.8)	2734 (96.2)
Most common AEs		
Nausea	895 (31.6)	876 (30.8)
Anaemia	859 (30.3)	771 (27.1)
Fatigue	766 (27.0)	769 (27.1)
Back pain	747 (26.3)	718 (25.3)
Decreased appetite	694 (24.5)	656 (23.1)
CTCAE grade 3, 4 or 5	2009 (70.8)	2000 (70.4)
AEs leading to study discontinuation	280 (9.9)	270 (9.5)

1. Lipton A, et al. *Eur J Cancer* 2012;48:3082–92.

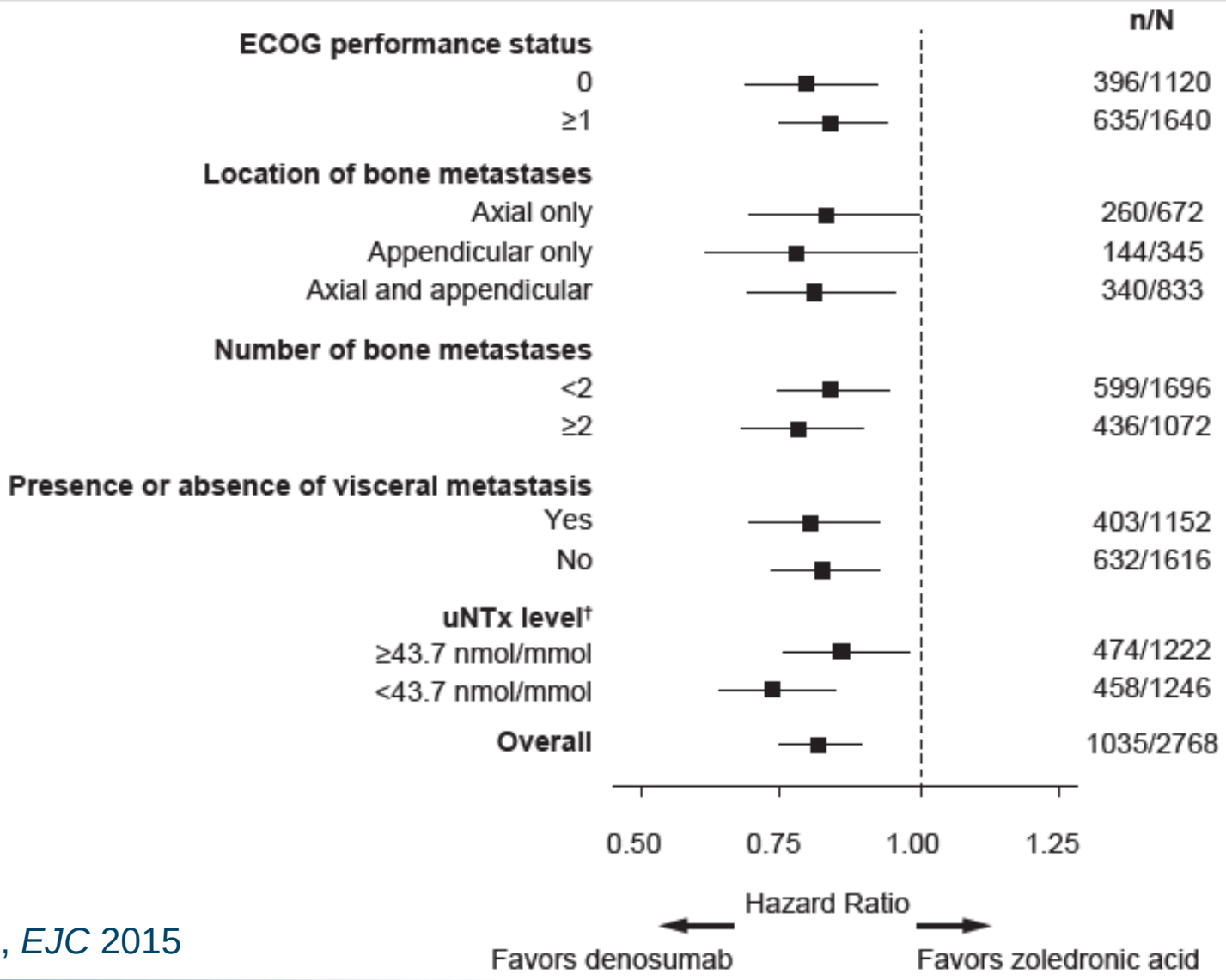
CTCAE, common terminology criteria for adverse events.

Safety results of interest

Patient incidence, n (%)	Zoledronic acid (n = 2836)	Denosumab (n = 2841)
Infectious AEs	1218 (42.9)	1233 (43.4)
Infectious serious AEs	**572 (20.2)**	**246 (8.7)**
Acute phase reactions (first 3 days)	**37 (1.3)**	**52 (1.8)**
Osteonecrosis of the jaw	**141 (5.0)**	**273 (9.6)**
Hypocalcaemia	141 (5.0)	273 (9.6)
New primary malignancy	18 (0.6)	28 (1.0)
AEs leading to study discontinuation	280 (9.9)	270 (9.5)

1. Lipton A, et al. *Eur J Cancer* 2012;48:3082–92.

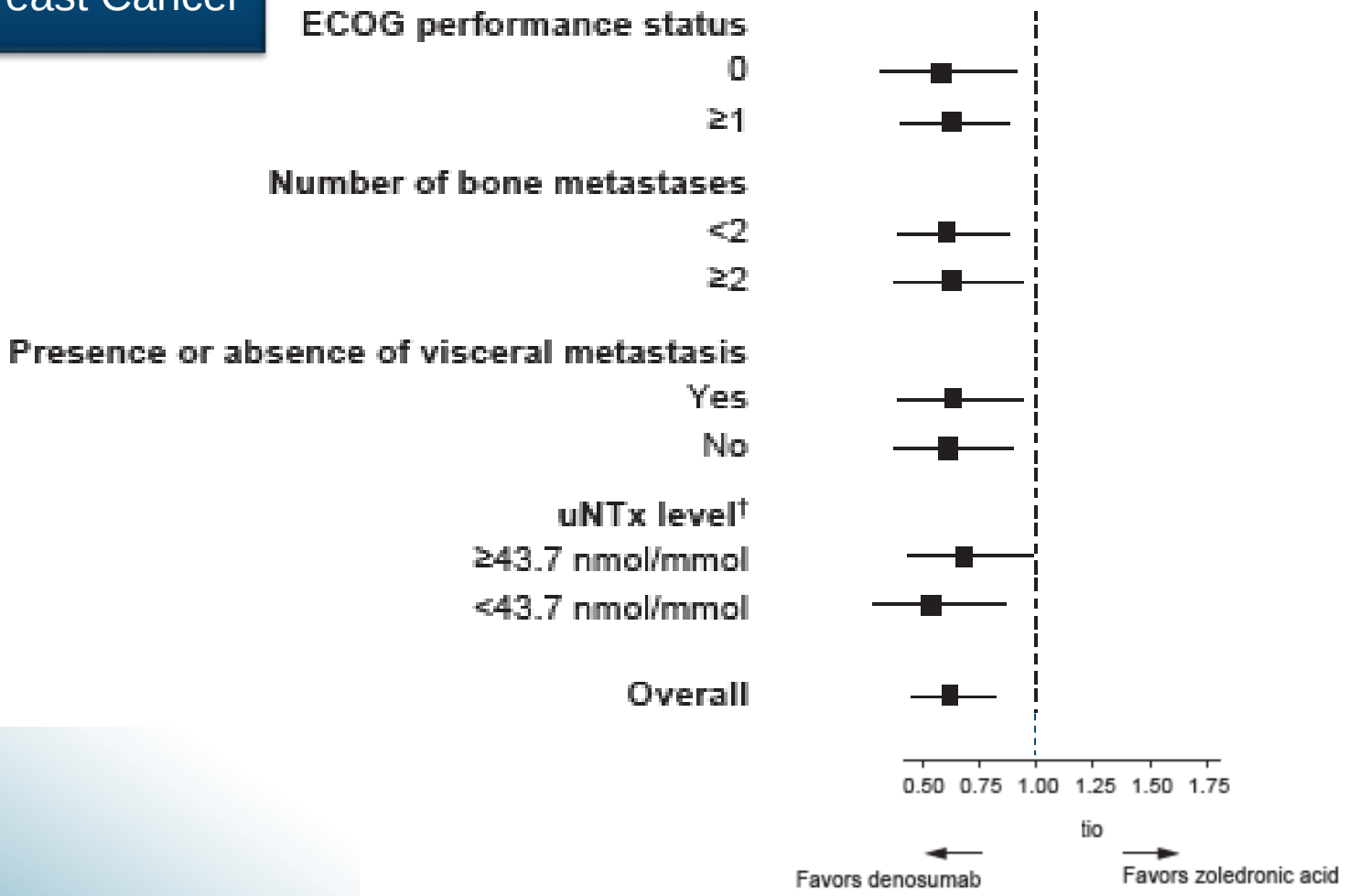
Characteristics



Lipton A, *EJC* 2015

First SRE – Baseline characteristics

Breast Cancer



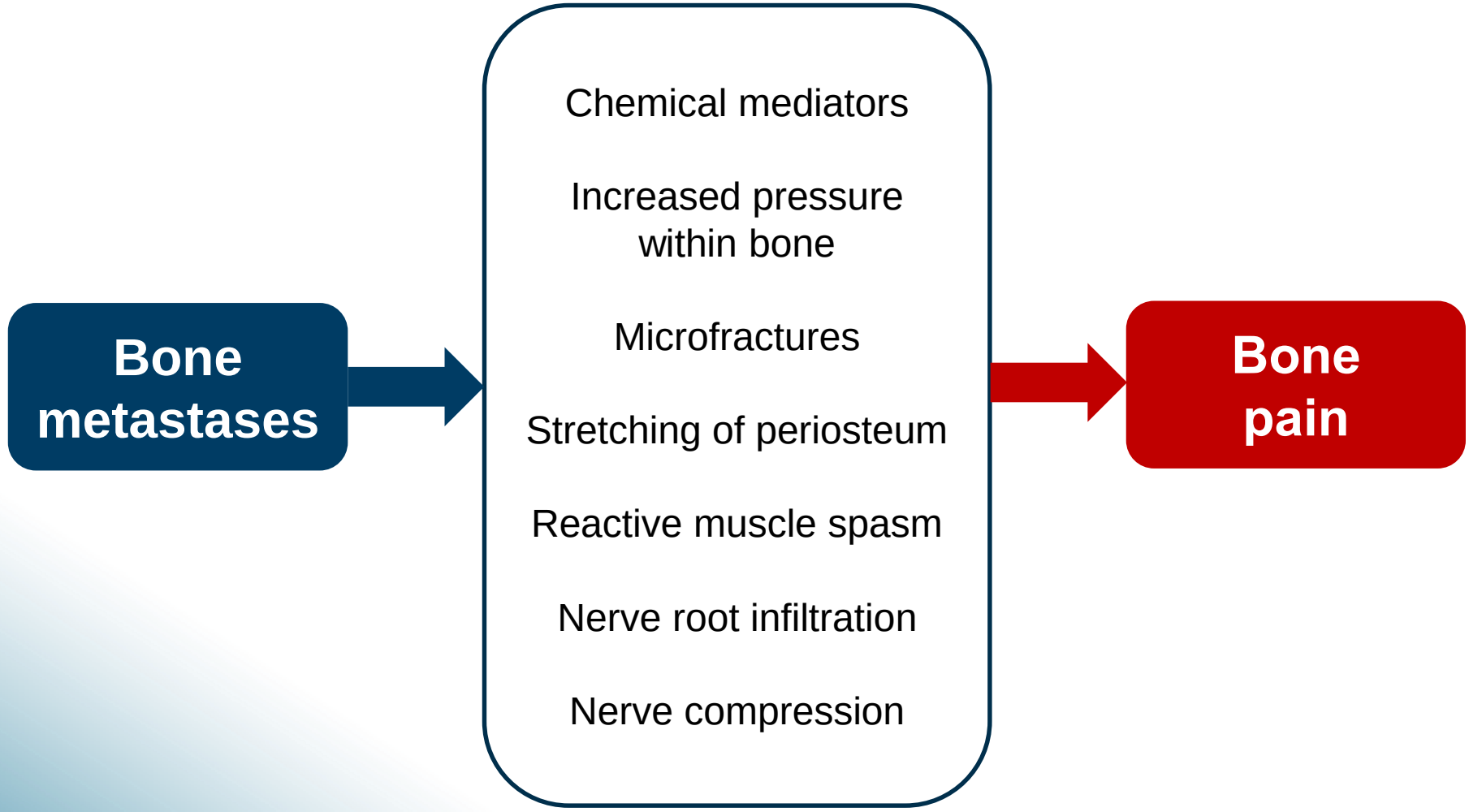
Lipton A, *EJC* 2015

Denosumab; q4 weeks vs. q 12 weeks

- A study comparing denosumab administered every 4 weeks vs every 12 weeks in patients with metastatic breast cancer and metastatic prostate cancer is currently under way in Switzerland with an expected completion date of 2022

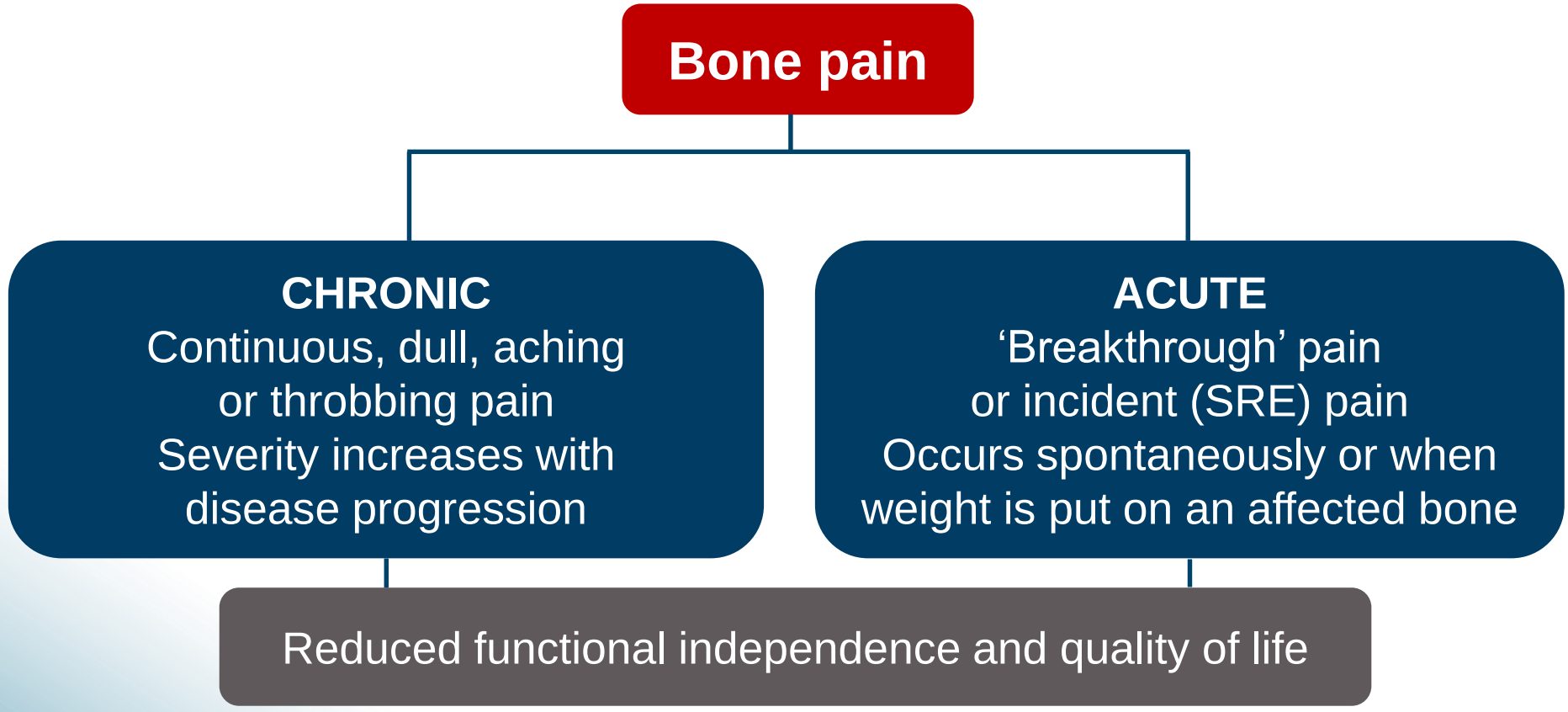
https://clinicaltrials.gov/ct2/show/NCT02051218?term=denosumab+metastatic&rank=2

Bone metastases are the most common cause of pain in advanced cancer patients



1. Mercadante S. *Pain* 1997;69:1−18.

Bone pain reduces patient functional independence and quality of life



1. Sabino MA and Mantyh PW. *J Support Oncol* 2005;3:15−24; 2. Lipton A. *Support Cancer Ther* 2007;4:92−100.

The majority of patients with bone metastases report having pain

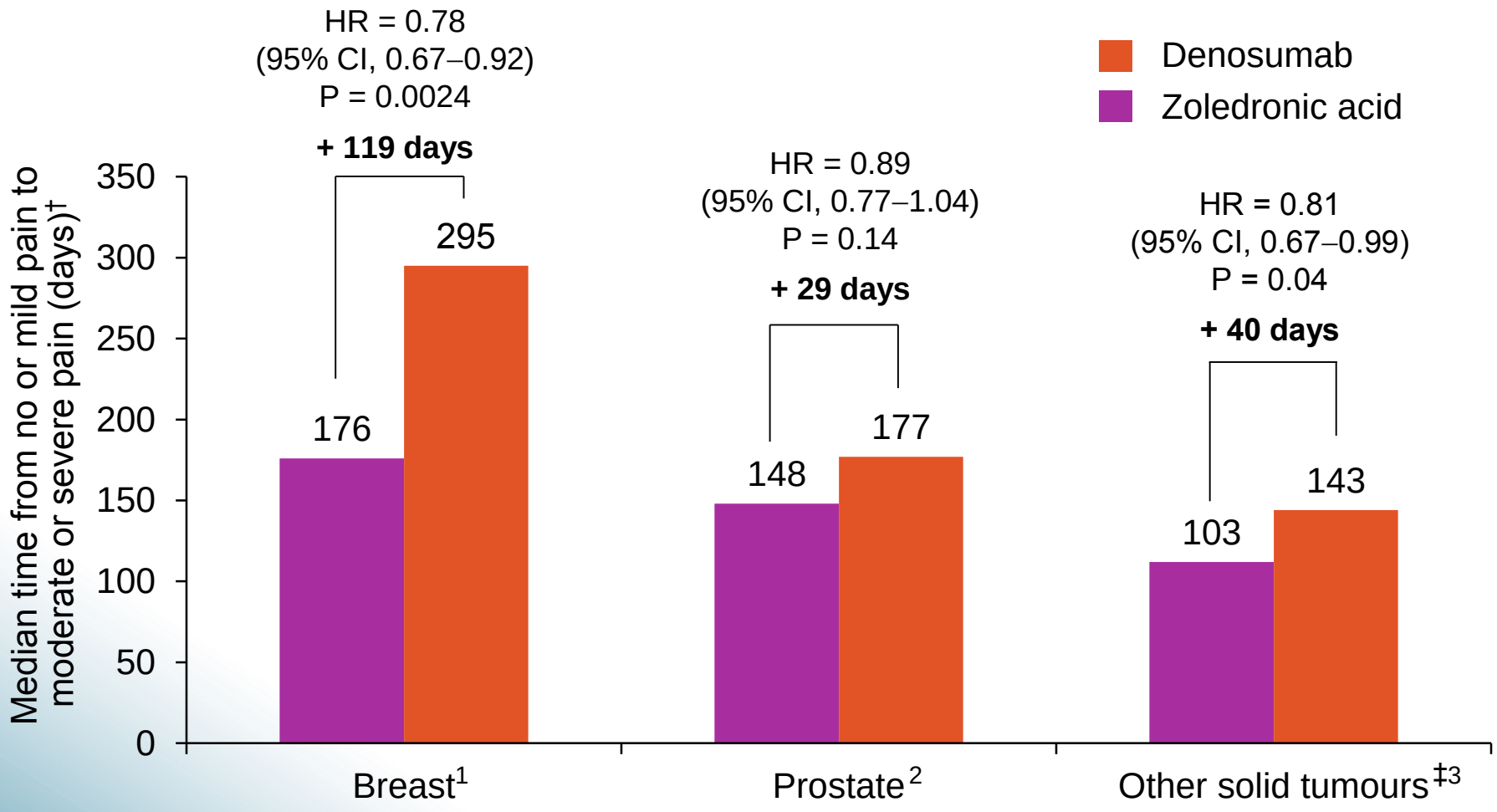
Characteristic[1]	Proportion of patients (%)† (N = 5544)
Pain status	
No pain	15.5
Mild pain	36.1
Moderate pain	21.9
Severe pain	26.5
Analgesic use	
No analgesic use	47.8
Opioid-based analgesic use	35.0

Typically bone pain is not adequately managed[2]

1. von Moos R, et al. *Support Care Cancer* 2013;21:3497–507;
2. Lipton A. *Support Cancer Ther* 2007;4:92−100.

†Data are pooled baseline data for patients in the three pivotal Phase III denosumab SRE prevention studies. Analysis excludes patients with multiple myeloma.

Pain worsening in patients on denosumab vs zoledronic acid by tumour type

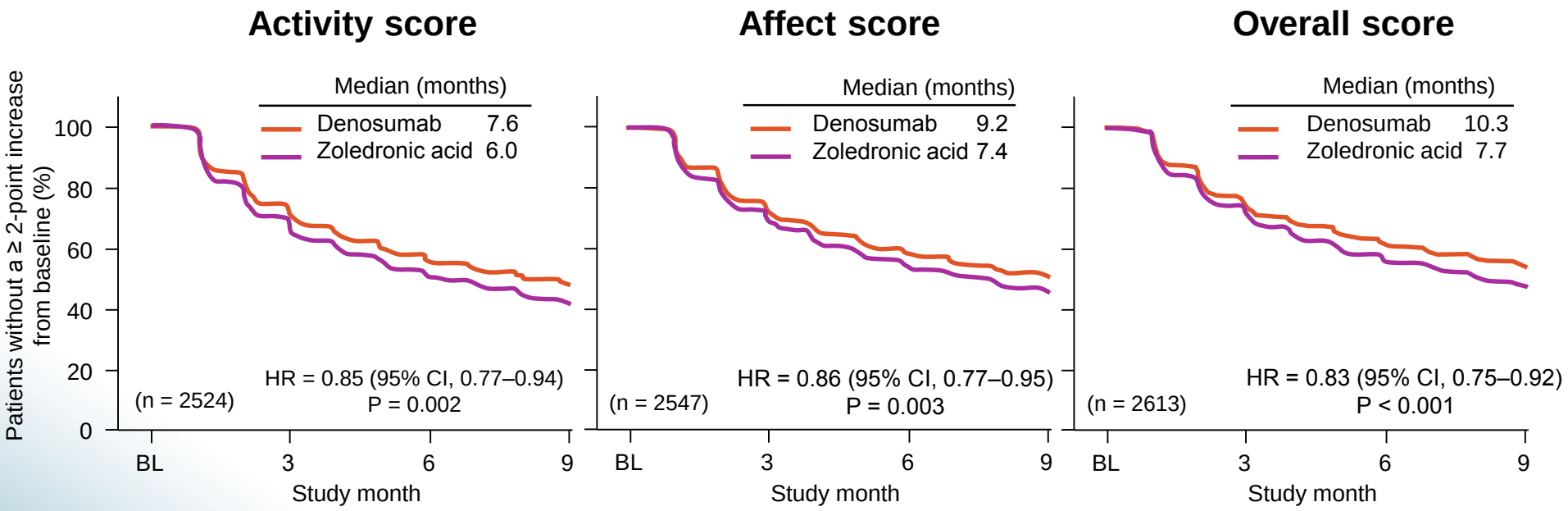


1. Cleeland CS, et al. *Cancer* 2013;119:832–8;
2. Brown JE, et al. EAU 2011:abstract 1091 (and poster);
3. Vadhan-Raj S, et al. *Ann Oncol* 2012;23:3045–51.

†Time to worst pain score > 4 points among patients with no or mild pain (0–4) at baseline. ‡Excluding breast and prostate. Data converted from months based on 1 month = 30.4 days.

Median time to increased pain interference was significantly longer with denosumab vs zoledronic acid for all 3 interference measures[1]

Time to clinically meaningful increase (ie ≥ 2-point increase) in pain interference among patients with no or mild pain at baseline



- General activity
- Walking ability
- Normal work

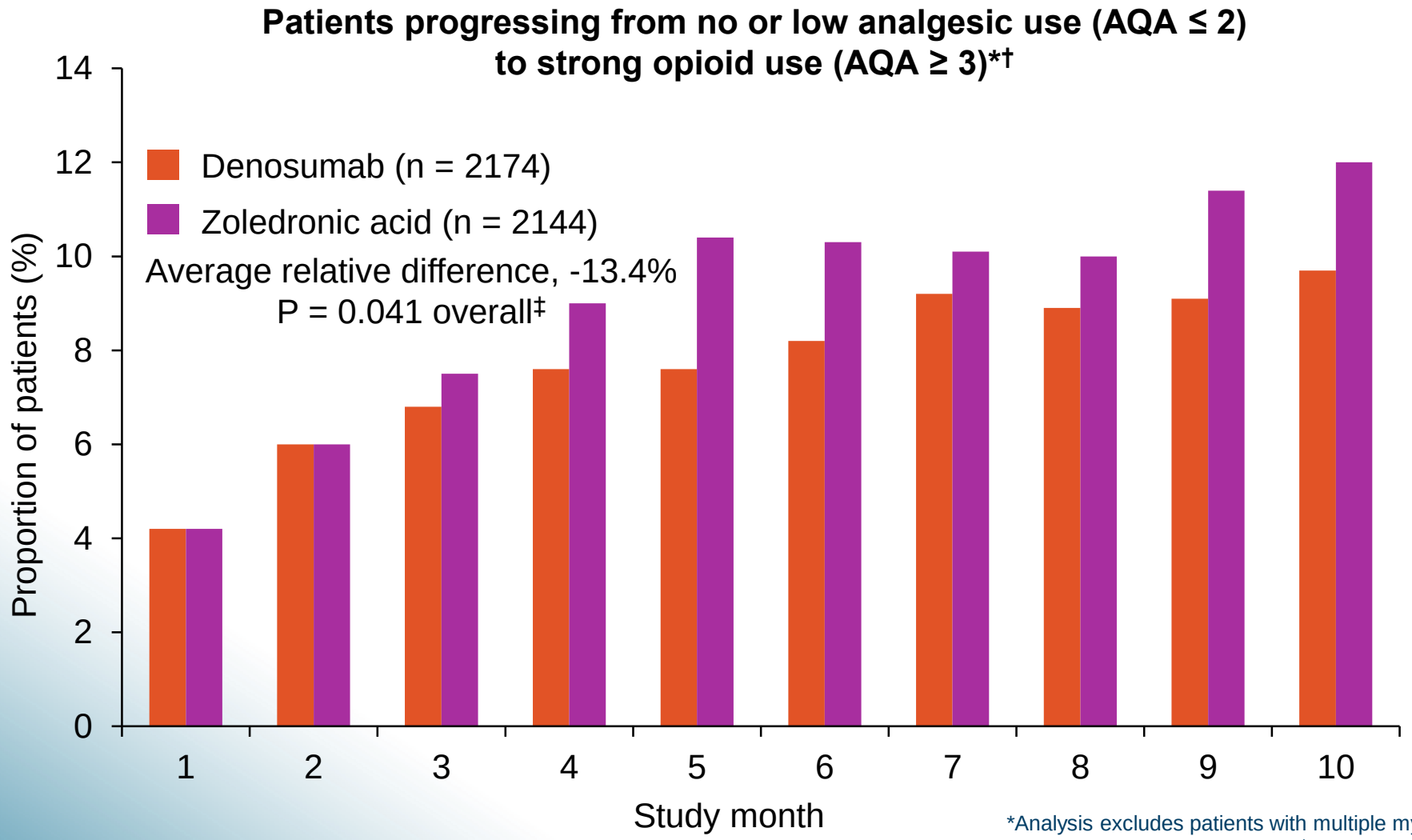
- Mood
- Relations with others
- Enjoyment of life

- Activity + affect + sleep

1. von Moos R, et al. *Support Care Cancer* 2013;21:3497–507.

BL, baseline; KM, Kaplan–Meier.

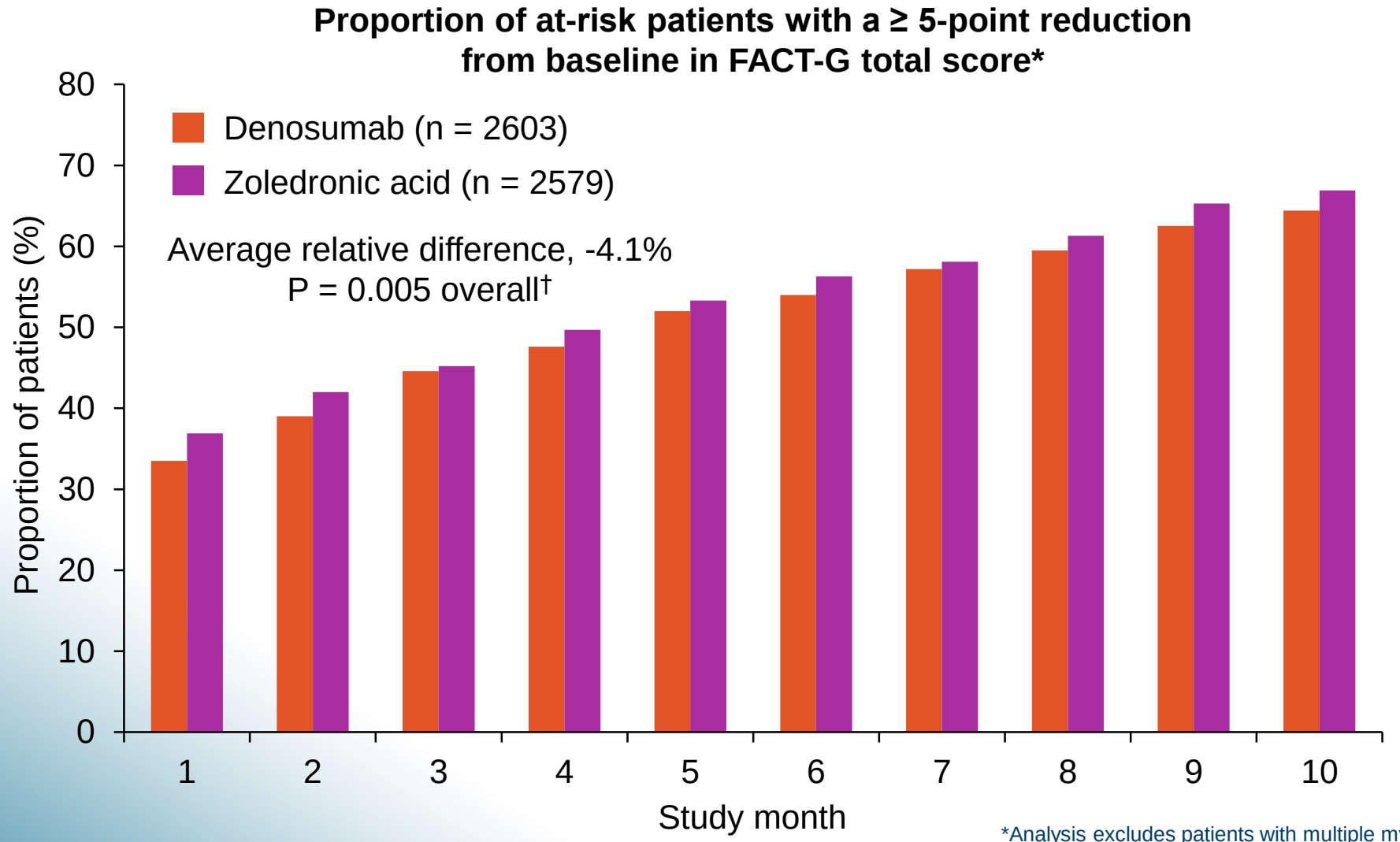
Fewer patients on denosumab progressed from no or low analgesic use to strong opioid use vs zoledronic acid[1]



*Analysis excludes patients with multiple myeloma.
†OME ≥ 75 mg/day;
‡Denosumab vs zoledronic acid by Generalised Estimating Equation.

1. von Moos R, et al. *Support Care Cancer* 2013;21:3497–507.

Fewer patients on denosumab experienced worsening in HRQoL vs zoledronic acid



*Analysis excludes patients with multiple myeloma

†Denosumab vs zoledronic acid by Generalised Estimating Equation

1. von Moos R, et al. *Support Care Cancer* 2013;21:3497–507.

Safety

- Higher risk hypocalcaemia with denosumab vs zolendronic acid (12.4% vs. 5.3%)(Body EJC 1990)
  - Not cumulative
- Zolendronic acid dose reduction
  - **recommended** in patients mild-to-moderate renal impairment.
  - **not** recommended for the prevention of SREs in patients with severe renal impairment
  - **cumulative** dose of zoledronic acid an independent predictor of renal impairment
- Rare toxicities
  - Encompass lots – so listen to patients

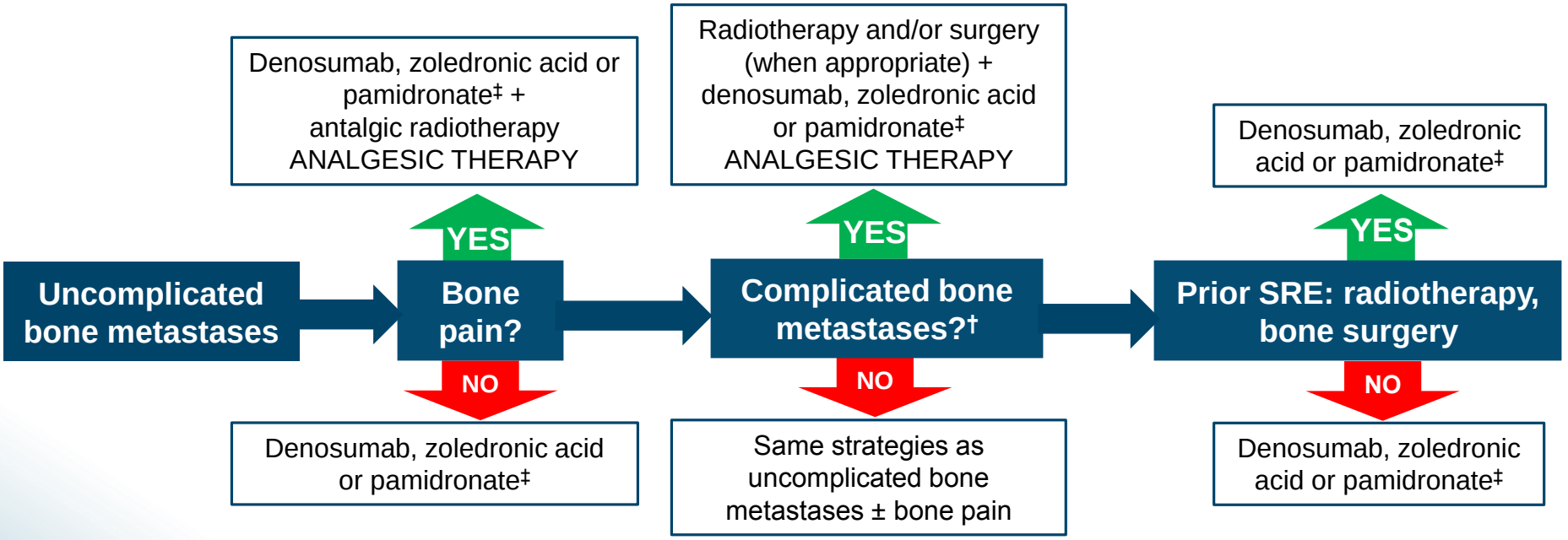
Osteonecrosis of Jaw

- ONJ ~1-2%, median time to onset 2.2 yrs
  - risk rises as treatment duration increases; avoid anti-angiogenesis agents
  - treatment delayed in unhealed, open, soft lesions in the mouth
  - preventative dentistry, recommended before treatment initiation

1. Maintain optimal oral hygiene
2. Administration of systemic antibiotics
3. Mouth rinses with chlorexidine
4. Chlorexidine mouth gel for local disinfection
5. Topical applied minocycline
6. Hyperbaric oxygen therapy
7. Oral irrigation with aqueous ozone
8. Treatment with teriparatide

Bone-targeted therapy ± radiotherapy is recommended in addition to analgesics in patients with bone pain[1]

2012 ESMO clinical practice guidelines on management of cancer pain



- Bone-targeted therapy is recommended, regardless of the presence of pain or prior SRE
  - These drugs delay both appearance and progression of pain, and both first and subsequent SREs

Adapted from Ripamonti CI, et al. *Ann Oncol* 2012;23(Suppl 7):vii139–54.

†Spinal cord compression or impending fracture;
‡Pamidronate only in breast cancer patients.

Bone-targeted therapy is recommended in patients with bone metastases whether they are symptomatic or not[1]

2014 ESMO clinical practice guidelines on bone health in cancer

Guidance on bone-targeted treatment (denosumab or zoledronic acid)	
Initiation	• Commence at diagnoses of metastatic bone disease – In all patients with breast cancer or CRPC, whether they are symptomatic or not – In selected patients with advanced lung cancer, renal cancer and other solid tumours if life expectancy > 3 months and considered at high risk of SREs
Continuation	• Continue indefinitely throughout the course of the disease – Ongoing treatment is recommended for patients with progression of underlying bone metastases, a recent SRE and/or elevated bone resorption markers†

†Results from clinical trials evaluating potential clinical applications of bone markers (e.g. helping to identify patients at high risk for bone metastasis or bone lesion progression) are awaited to identify the true value of bone markers in clinical practice.
CRPC, castration-resistant prostate cancer.

1. Coleman R, et al. Ann Oncol. 2014;25(Suppl 3):iii124-iii137.

ABC3 Bone Metastases

3rd ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3)

BONE METASTASES

A **bone modifying agent** (bisphosphonate, denosumab) should be routinely used in combination with other systemic therapy in patients with MBC and bone metastases.	1 A
Three-monthly zolendronic acid seems to be not inferior to standard monthly schedule.	1 B
Supplementation of calcium and vitamin D3 is mandatory, unless contraindications exist.	1 C

ASCO/CCO Focused Guideline Update on Role of Bone-Modifying Agents in Metastatic Breast Cancer

Recommendation Updated for 2017 Guideline

- As recommended in the 2011 version of the ASCO bone-modifying agent guideline, patients with breast cancer who have evidence of bone metastases should be treated with bone-modifying agents. One bone-modifying agent is not recommended over another. If patients are treated with zoledronic acid at 4 mg IV administered over no less than 15 minutes, dosing options are every 12 weeks or every 3 to 4 weeks [Type = evidence based, benefits outweigh harms; evidence quality = high; strength of recommendation = strong].

Recommendation Updated for 2017 Guideline

- The analgesic effects of bone-modifying agents (denosumab, pamidronate, or zoledronic acid) are modest, and they should not be used alone for bone pain. The panel recommends that the current standard of care for supportive care and pain management be applied. This can include analgesia, adjunct therapies, radiotherapy, surgery, systemic anticancer therapy, and referral to supportive care and pain management. Evidence of a clinically meaningful benefit is insufficient to support the use of one bone-modifying agent over another. Further research is needed on this clinical question [Type = evidence based, benefits outweigh harms; evidence quality = low; strength of recommendation = weak].

Recommendations Unchanged From 2011 Guideline Update

- Bone-modifying agents are recommended for patients with metastatic breast cancer with evidence of bone destruction. One bone-modifying agent is not recommended over another.
- The mechanism of action, as well as the potential benefits and harms, should be taken into account when considering long-term use of bone-modifying agents.
- In patients with creatinine clearance > 60 mL/min, no change in dosage, infusion time, or interval is required; creatinine level should be monitored with each IV bisphosphonate dose.
- In patients with creatinine clearance < 30 mL/min or on dialysis who may be treated with denosumab, close monitoring for hypocalcemia is recommended.
- All patients should have a dental examination and preventive dentistry before using a bone-modifying agent.

Van Poznak
JCO 2017

Adjuvant Bisphosphonates in Early Breast Cancer

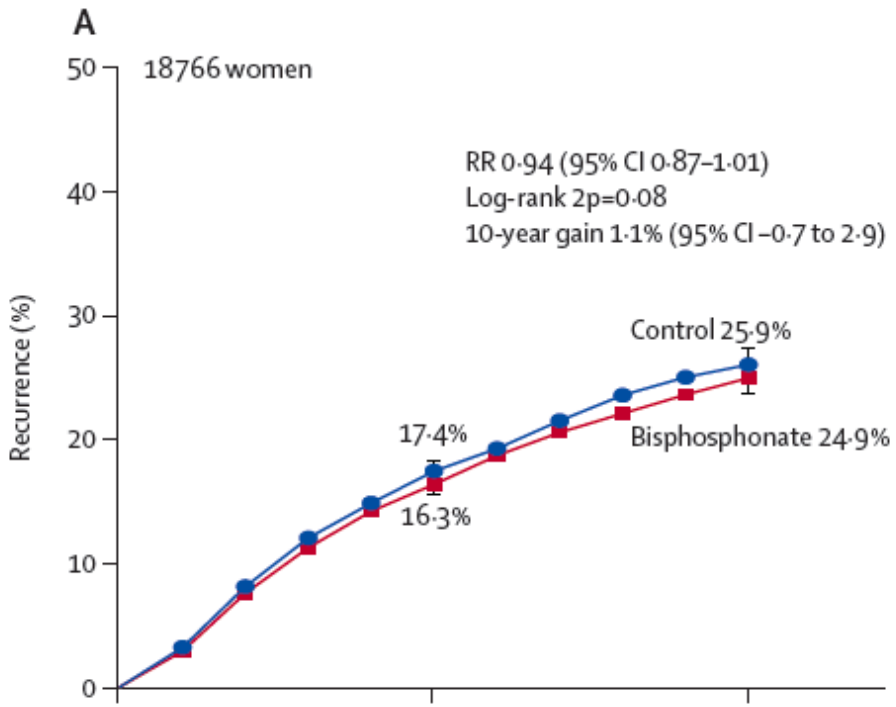
15 Years of Adjuvant Bisphosphonate Trial Data

- Clodronate
  - Diel et al (GABG; n=302) - *NEJM* 1998
  - Saarto et al (Finnish; n=299) - *JCO* 2001
  - Powles et al (RMH; n=1089) - *JCO* 2002
  - Paterson et al (NSABP-B34; n=3323) - *Lancet Oncol* 2012
- Zoledronic acid
  - Gnant et al (ABCSG-12; n=1803) - *NEJM* 2009
  - Coleman et al (AZURE; n=3360) - *NEJM* 2011
  - Coleman et (ZO-FAST; n=1065) - *Ann Oncol* 2013

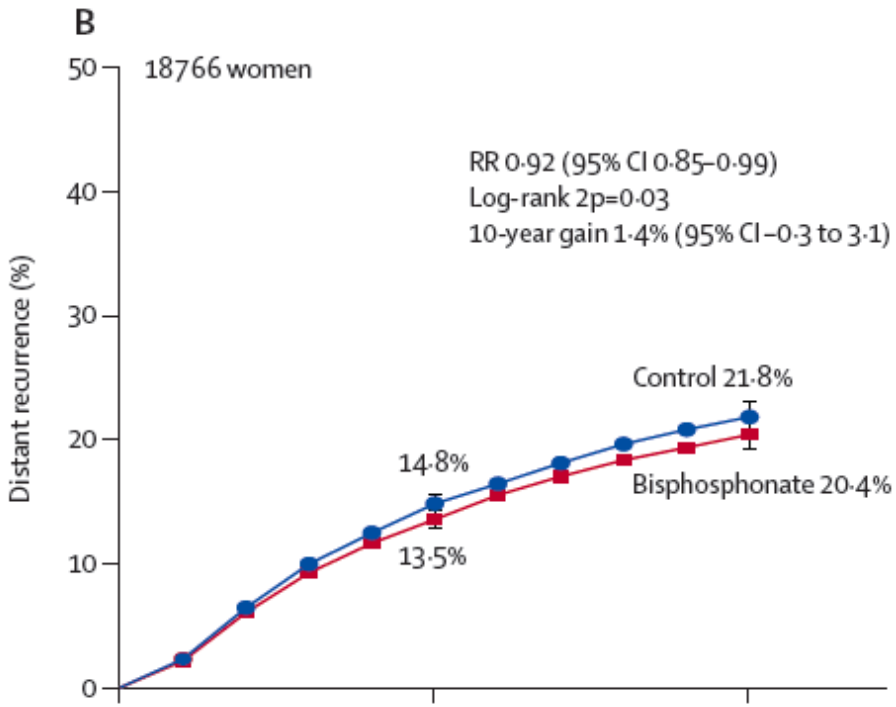
Improved outcomes on ITT analysis No improved outcomes on ITT analysi

Adjuvant Bisphosphonates; EBCTCG

All Recurrences



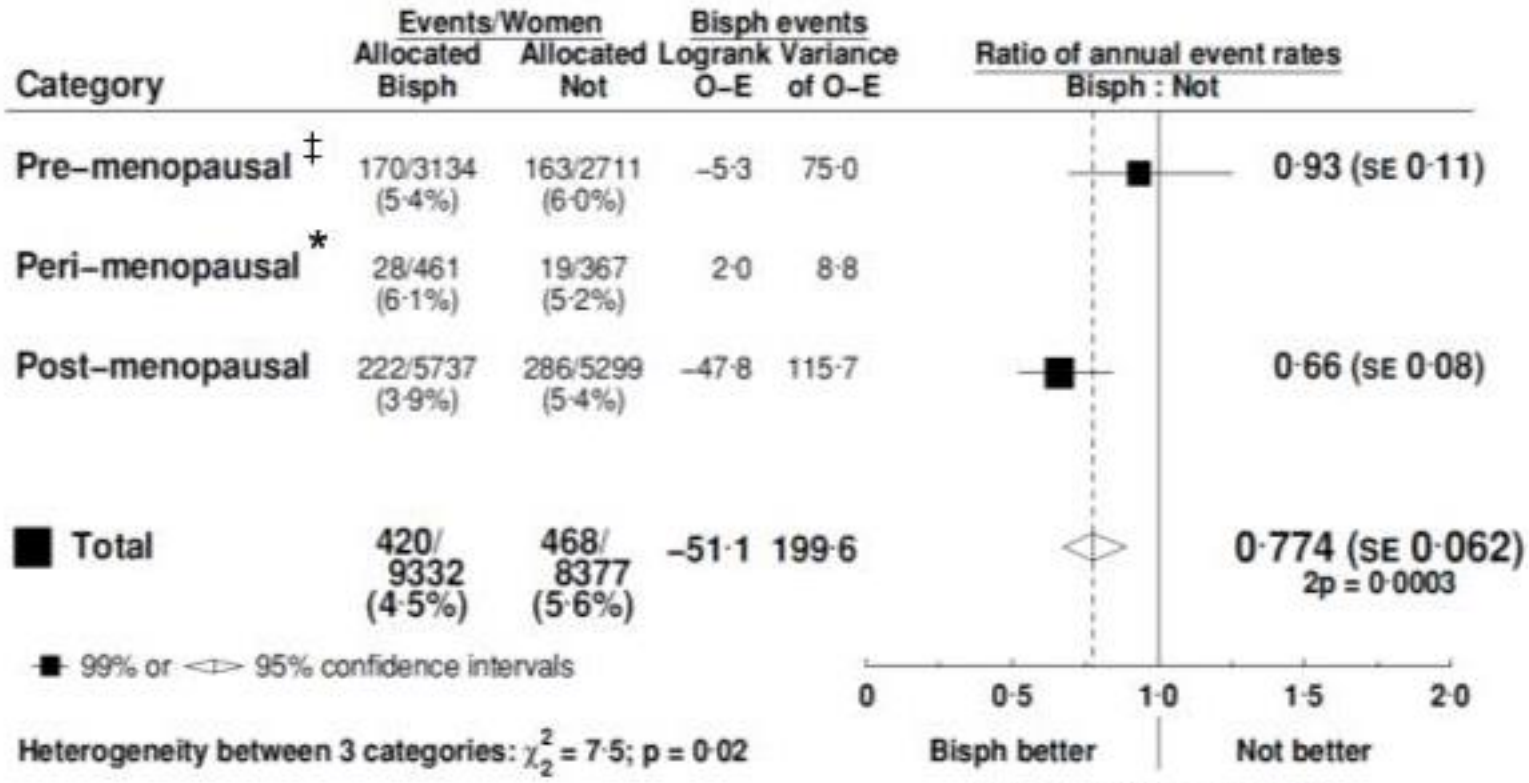
Distant Recurrences



Coleman Lancet 2015

Adjuvant Bisphosphonates; EBCTCG

Bone Recurrence By Menopausal Status



‡ includes women aged < 45 if unknown

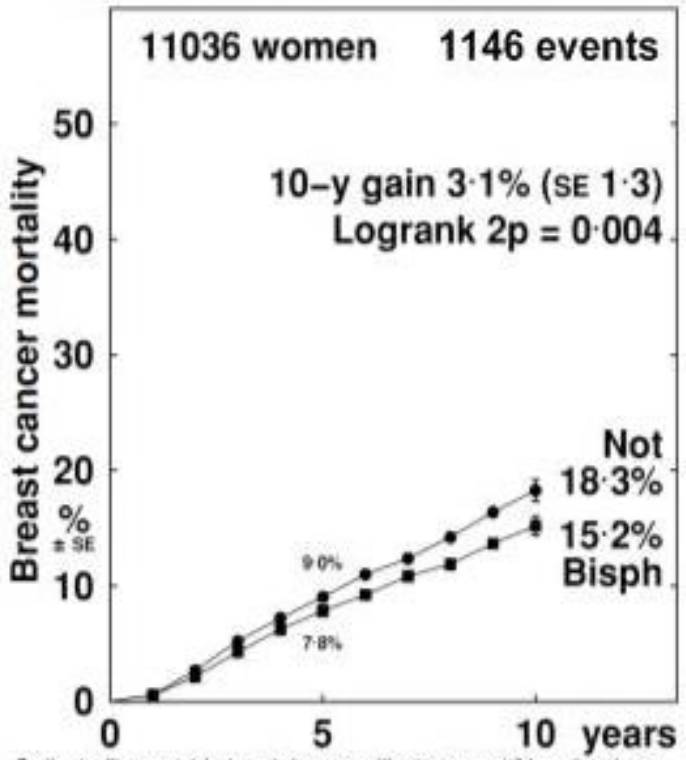
* Includes women aged 45-55 if menopausal status unknown

Significantly Reduced Bone Recurrence in Postmenopausal Women

Adjuvant Bisphosphonates; EBCTCG

Mortality In Post-menopausal Women

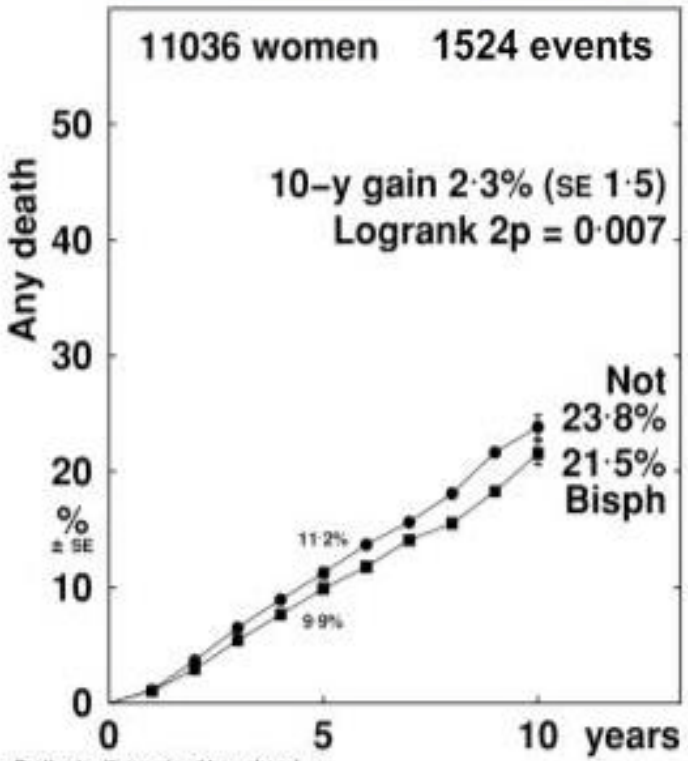
Breast cancer mortality



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

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	1·64 ss 0·08	1·60 ss 0·14	1·30 ss 0·49
Not	1·83 ss 0·09	2·04 ss 0·16	2·73 ss 0·73
Rate ratio, from (O–E) / V	0·86 ss 0·07 −20·4 / 173·1	0·78 ss 0·11 −16·3 / 65·0	0·52 ss 0·30 −2·4 / 3·6

All cause mortality



Death rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	2·07 (510 / 24627)	2·40 (201 / 8380)	3·71 (20 / 539)
Not	2·32 (534 / 23006)	2·66 (236 / 8189)	4·48 (23 / 513)
Rate ratio, from (O–E) / V	0·87 ss 0·06 −31·3 / 224·4	0·84 ss 0·09 −17·2 / 95·6	0·94 ss 0·34 −0·5 / 8·0

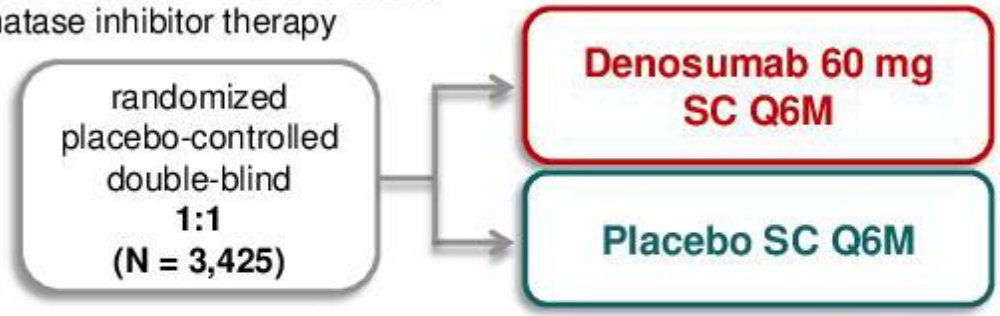
Adjuvant Bisphosphonates; EBCTCG

Conclusions

- Adjuvant bisphosphonates reduce bone metastases and improve survival in post-menopausal women.
  - 34% reduction in risk of bone recurrence (p=0.00001).
  - 17% reduction in risk of breast cancer death (p=0.004).
  - No significant reduction in first distant recurrence outside bone
  - Risk reductions similar irrespective of ER, node status, use/non use of chemotherapy.
  - Benefits similar for aminobisphosphonates and clodronate.
- No effects apparent on disease outcomes in pre-menopausal women.
- No significant effects on non breast cancer deaths, contralateral breast cancer or loco-regional recurrence.

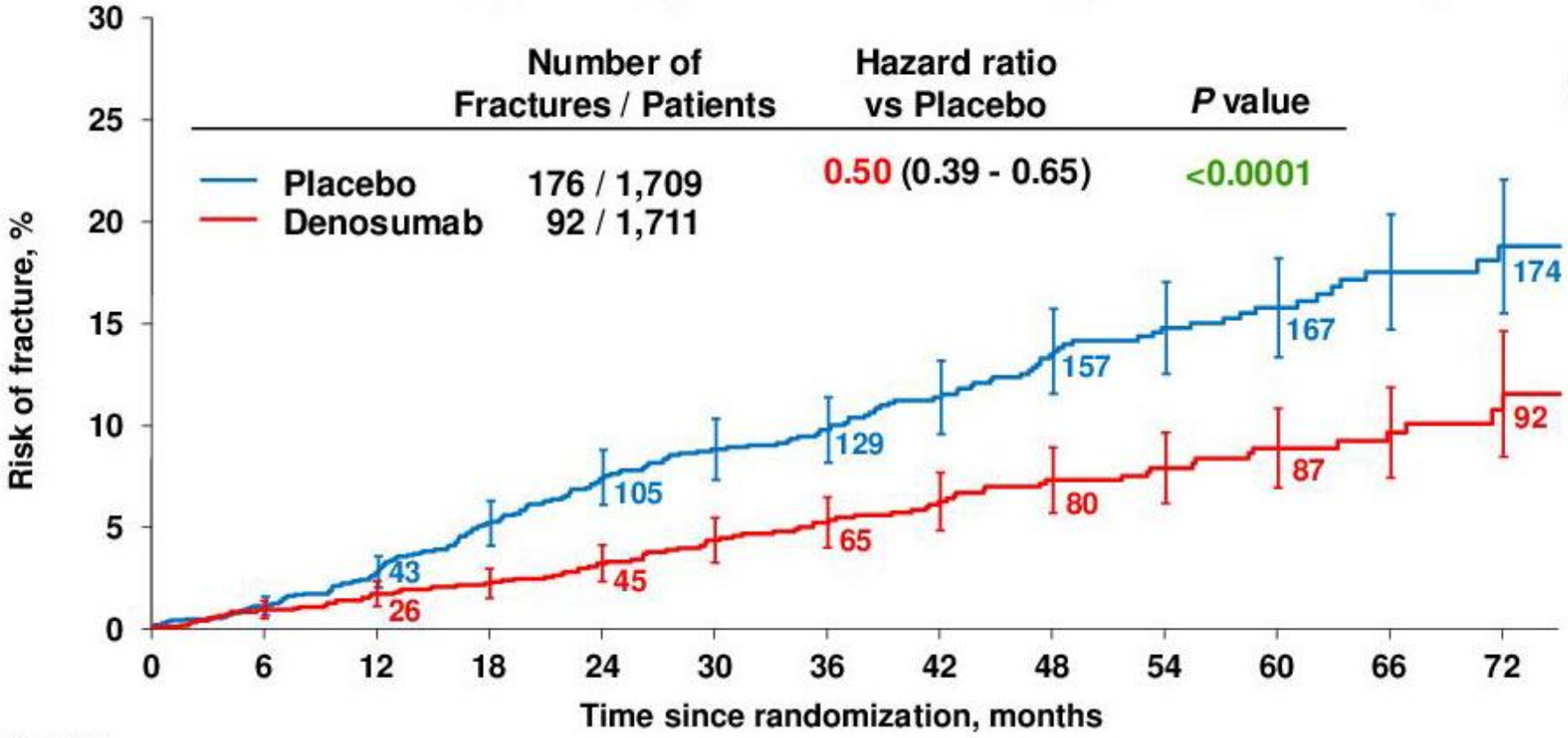
Trial Design ABCSG-18

- Prospective randomized placebo-controlled double-blind multicenter phase-3 trial
- Recruitment 2006 – 2013 (3,425 postmenopausal patients)
- Primary endpoint: Time to first clinical fracture (reached March 2014)
- Secondary endpoints:
  - Fracture related secondary endpoints (Primary Analysis March 2015)
  - **Disease outcome related endpoints**
    - **DFS – time driven analysis of disease free survival**
    - **OS, BMFS (will be analyzed at EoS)**
- 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 SERMs
  - Current or prior IV bisphosphonate administration
  - Known history of:
    - Paget's disease
    - Cushing's disease
    - hyperprolactinemia
    - hypercalcaemia or hypocalcaemia
    - other active metabolic bone disease

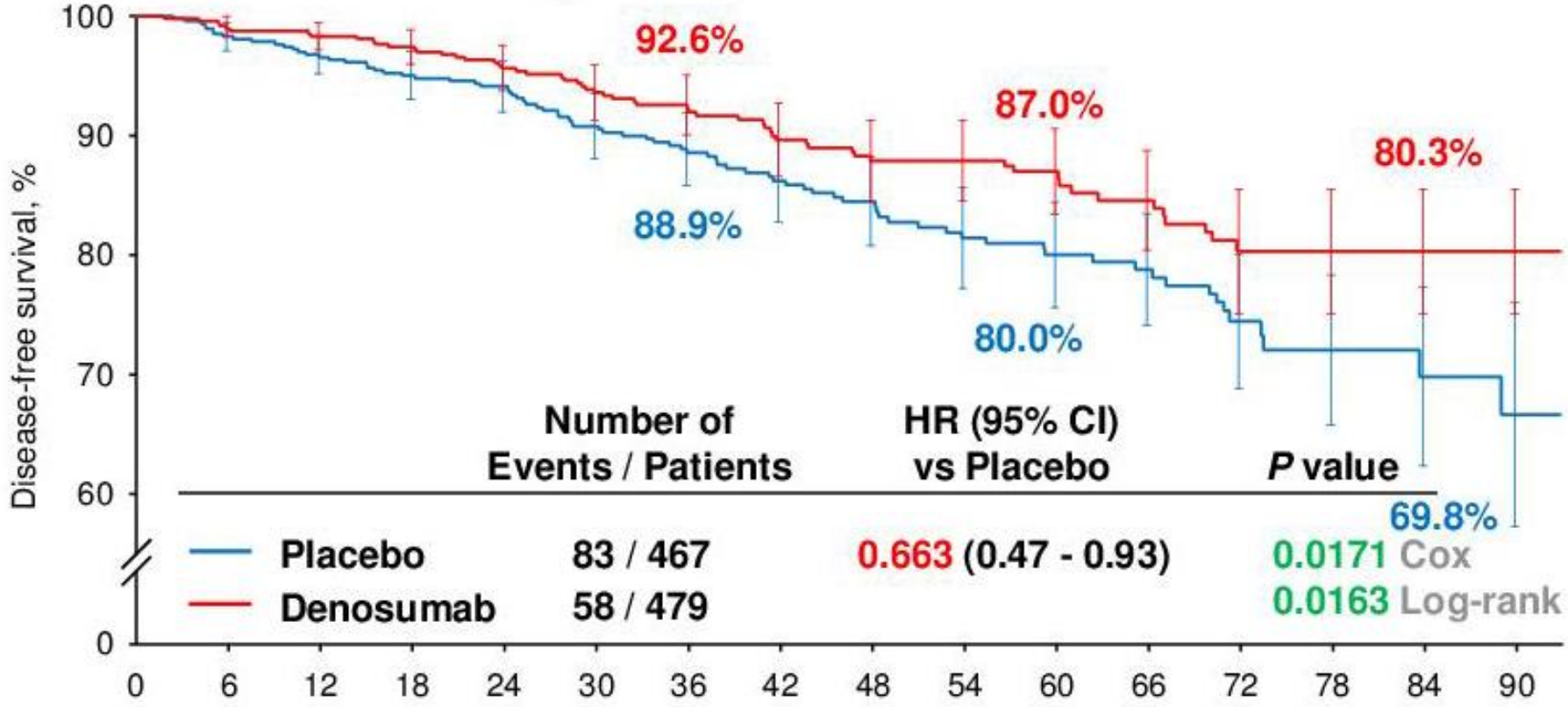


Gnant et al, Lancet 2015; 386: 433-43

ABCSG-18 Primary Endpoint Results (ASCO 2015)



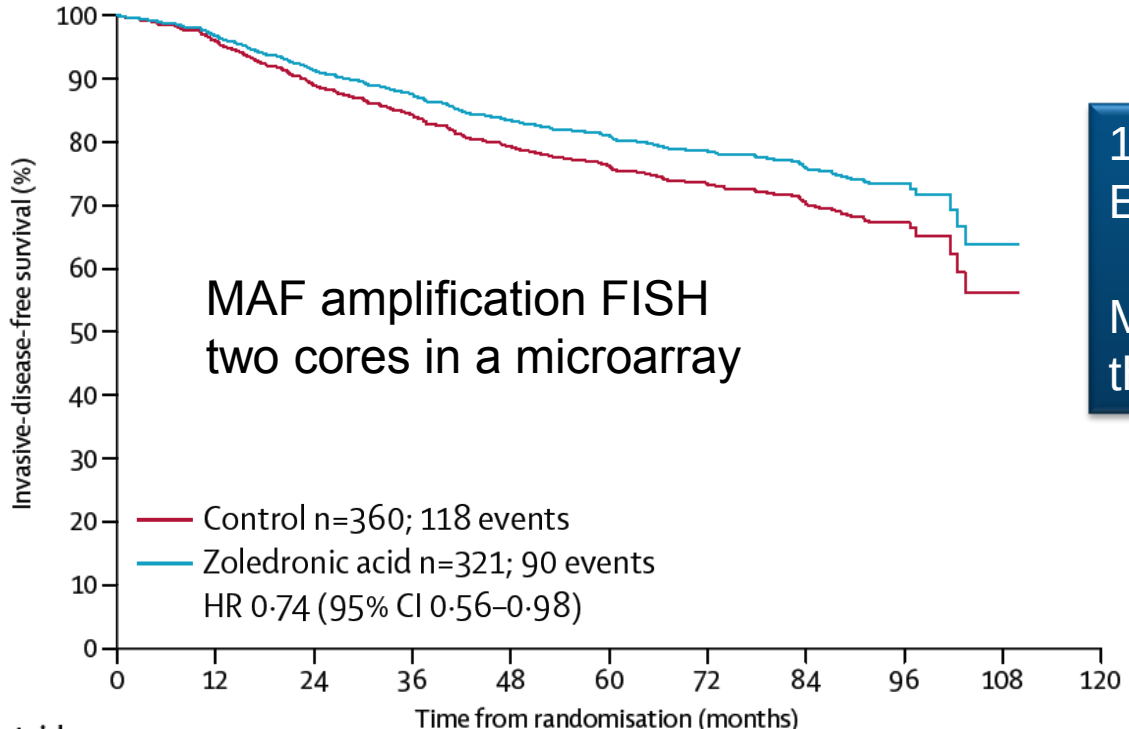
ABCSG 18- Subgroup Tumor Size >2 cm



AZURE; *MAF* a bone metastasis marker

Randomly assigned (1:1), n=865 had sufficient tissue

- Standard adjuvant systemic therapy alone (control group)
- or with zoledronic acid every 3–4 weeks for six doses, then every 3–6 months until the end of5 years.



16q23 copy number gain
Encodes MAF transcription factor

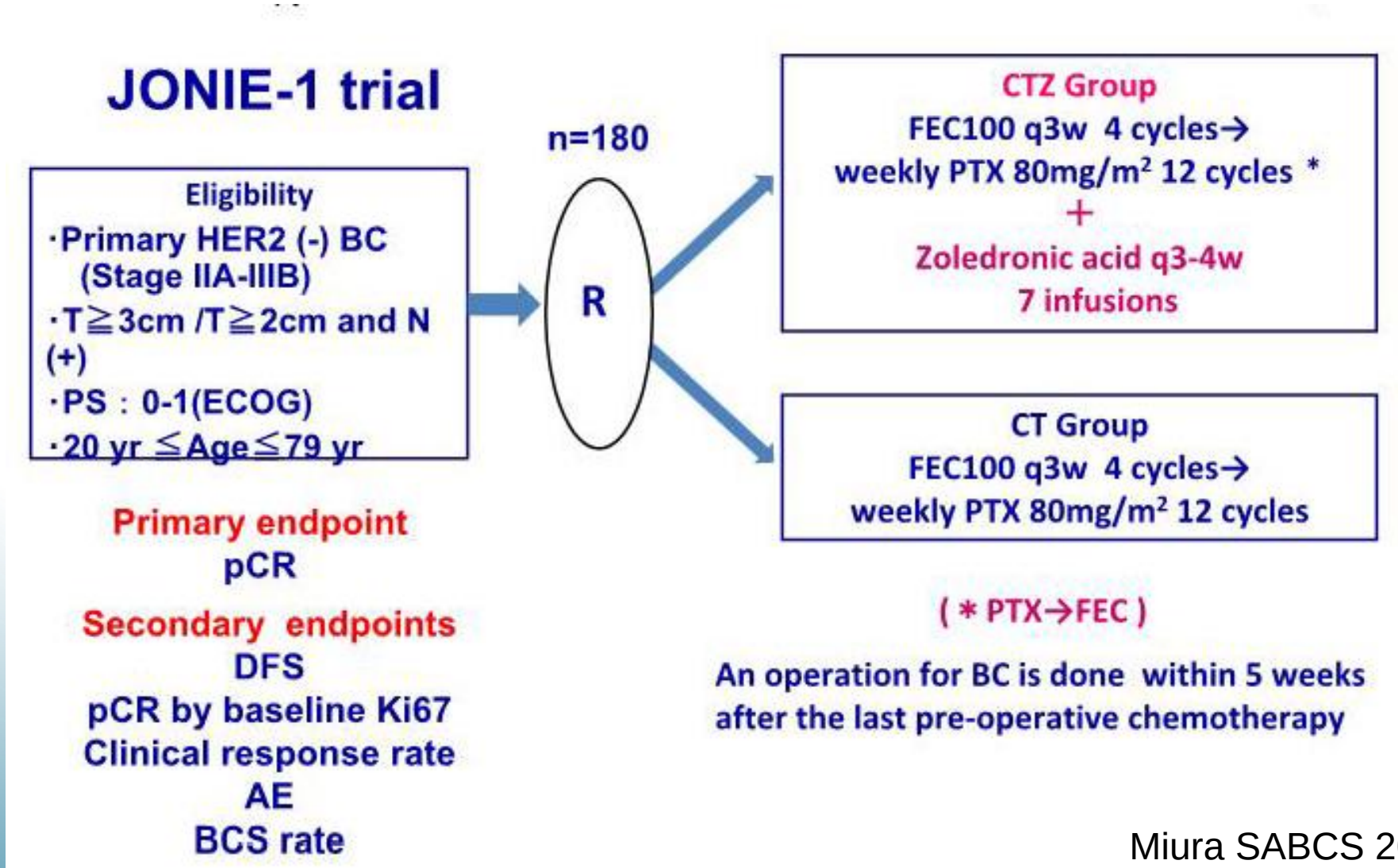
Mediates bone cancer metastases through control of PTHrP

Coleman Lancet Oncol 2017

Adjuvant Guidelines

- St Gallen International Expert Consensus Conference 2017, strongly recommended the use of bisphosphonates for the adjuvant treatment of postmenopausal women with breast cancer (Coates Annals)
- ESMO 2016 guidelines (Hadji ESMO 2016)
  - Bisphosphonates; routine clinical practice for the prevention of CTIBL all patients with a T-score < -2.0 or ≥ fracture risk factors
  - Adj bisphosphonates for the prevention in all women ≥ 55 years
  - For younger, adj bisphosphonates recommended if amennorheic > 12 mo, and /or on OFS
    - Duration of low-dose bisphosphonate treatment for premenopausal women should not exceed that of ovarian suppression (3-5 years) unless indicated in patients with low BMD

Neoadjuvant Therapy



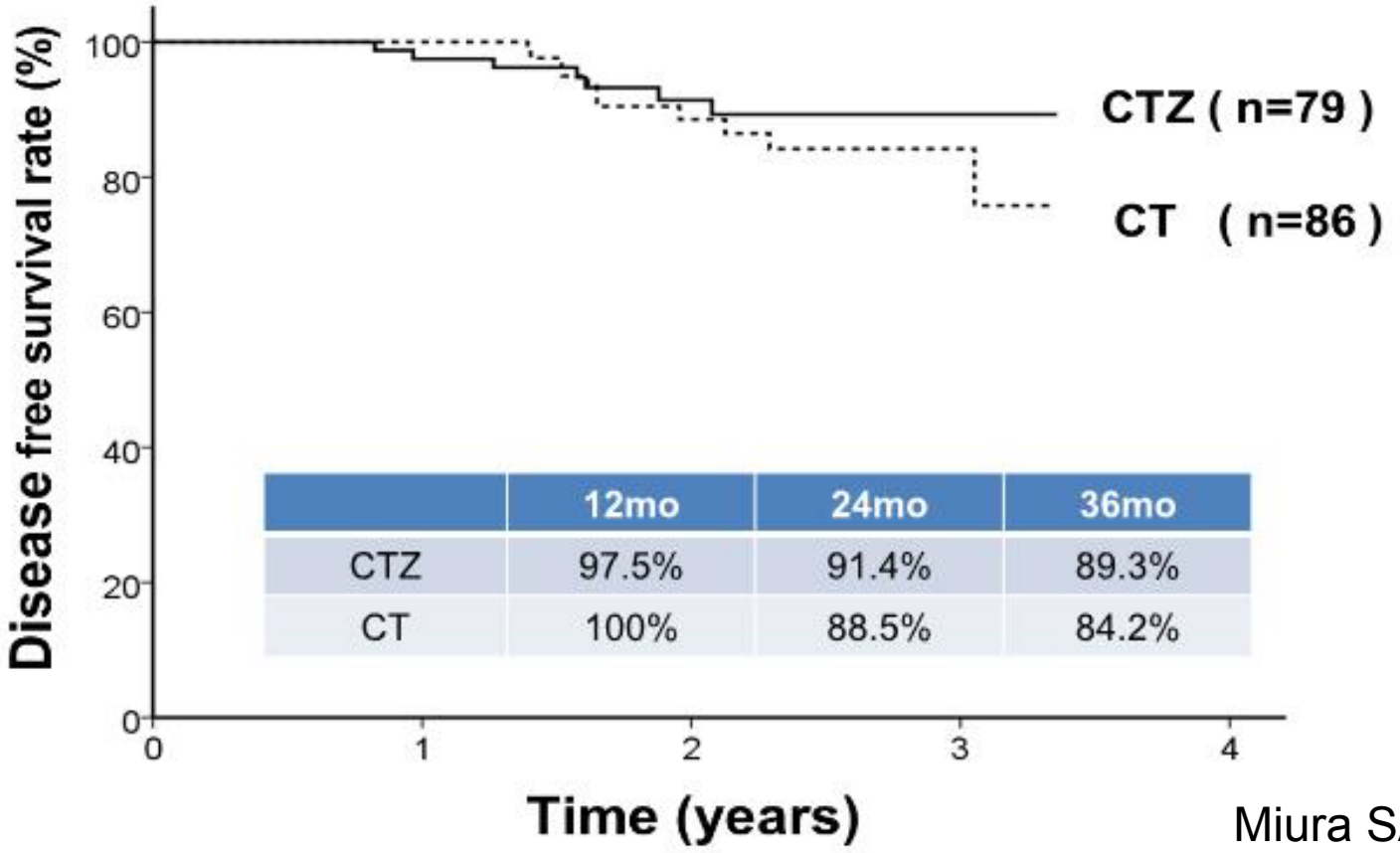
Miura SABCS 2014

Neoadjuvant Therapy

San Antonio Breast Cancer Symposium

- Cancer Therapy and Research Center at UT Health Science Center – December 10-14, 2013

Disease-free survival



	12mo	24mo	36mo
CTZ	97.5%	91.4%	89.3%
CT	100%	88.5%	84.2%

Miura SABCS 2014

Bone Health

Bone mineral loss in breast cancer

- The mean age at breast cancer diagnosis is 62 years
- Perimenopausal or postmenopausal women,
  - may already have experienced some osteopenic or osteoporotic bone loss
  - Onset of menopause, declining E2 levels lead to a gradual decrease in bone mineral density (BMD) over time, with the potential for the development of postmenopausal osteoporosis
  - Significant & rapid decrease in BMD may be exacerbated by the bone-destabilizing effects of aromatase inhibitors (twice normal pop'n), and some chemotherapies (60% rendered menopausal).
    - Cancer treatment-induced bone loss (CTIBL)
    - ATAC anastrozole: median BMD loss from baseline of 6.1% at the lumbar spine and 7.2% from the total hip after 5 years

- Reductions in BMD increase the risk of pathologic fracture; the 3-year risk of vertebral fracture is almost fivefold greater in women with newly diagnosed breast cancer than in women in the general population
- Even in women with normal BMD, the risk of fracture in patients with breast cancer is high.
- Placebo arm of ABCSG-18 incidence of pathologic fracture was 10% in individuals with normal BMD and 11% in those with low BMD.

Prophylactic Therapy

- Denosumab 60 mg sc q 6 mo
  - Ellis BCRT 2009
  - ABCSG-18; relative increases in BMD at the lumbar spine, total hip and femoral neck compared with placebo ($p < 0.0001$)
- Zoledronic Acid 4 mg q 6mo
  - Z-FAST total hip BMD (+8.9% with upfront treatment; +6.7% with delayed treatment)
  - NC03CC (Alliance); +0.58%

Individual Therapy

- Patients should be assessed for baseline fracture risk, and that BMD should be measured.
- Lifestyle changes, such as
  - increasing the amount of weight-bearing exercise
  - Stopping smoking
  - Dietary measures ensuring
    - adequate calcium intake (1000 mg/day) and vitamin D supplementation (total intake: 1000-2000 units/day)
- Early breast cancer at risk CTIBL
  - OFS; Aromatase Inhibition, chemotherapy
  - Prophylactic bisphosphonate/denosumab therapy

Coleman ESMO 2014

Prophylaxis French Cohort

- 64,438 postmenopausal women participating in the French E3N cohort;
- 2,407 first primary breast cancer cases were identified.
- The HR of breast cancer associated with exposure to BPs was 0.98 (95% CI, 0.85 to 1.12)

Table 3. HRs for Different Types of Breast Cancer Associated With Exposure to BPs (ever *v* never; E3N Cohort, 2004 to 2011)

Breast Cancer Characteristic (No. women included)	Never Exposed to BPs		Ever Exposed to BPs		
	No. Cases	HR* (95% CI)	No. Cases	HR* (95% CI)	*P*
All breast cancers (n = 64,438)	2,099	1 (reference)	308	0.98 (0.85 to 1.12)	.76
According to ER status (n = 63,950†)					
ER+	1,429	1 (reference)	199	0.95 (0.80 to 1.12)	.52
ER−	255	1 (reference)	36	0.98 (0.65 to 1.46)	.90
$P_{homogeneity}$					.89
According to invasive or in situ status (n = 64,250‡)					
Invasive	1,700	1 (reference)	245	0.97 (0.83 to 1.14)	.72
In situ	242	1 (reference)	32	0.87 (0.57 to 1.33)	.52
$P_{homogeneity}$					.64

Fournier JCO 2017