Bone Modifying Agents nel carcinoma mammario metastatico: quando, perché e quanto a lungo

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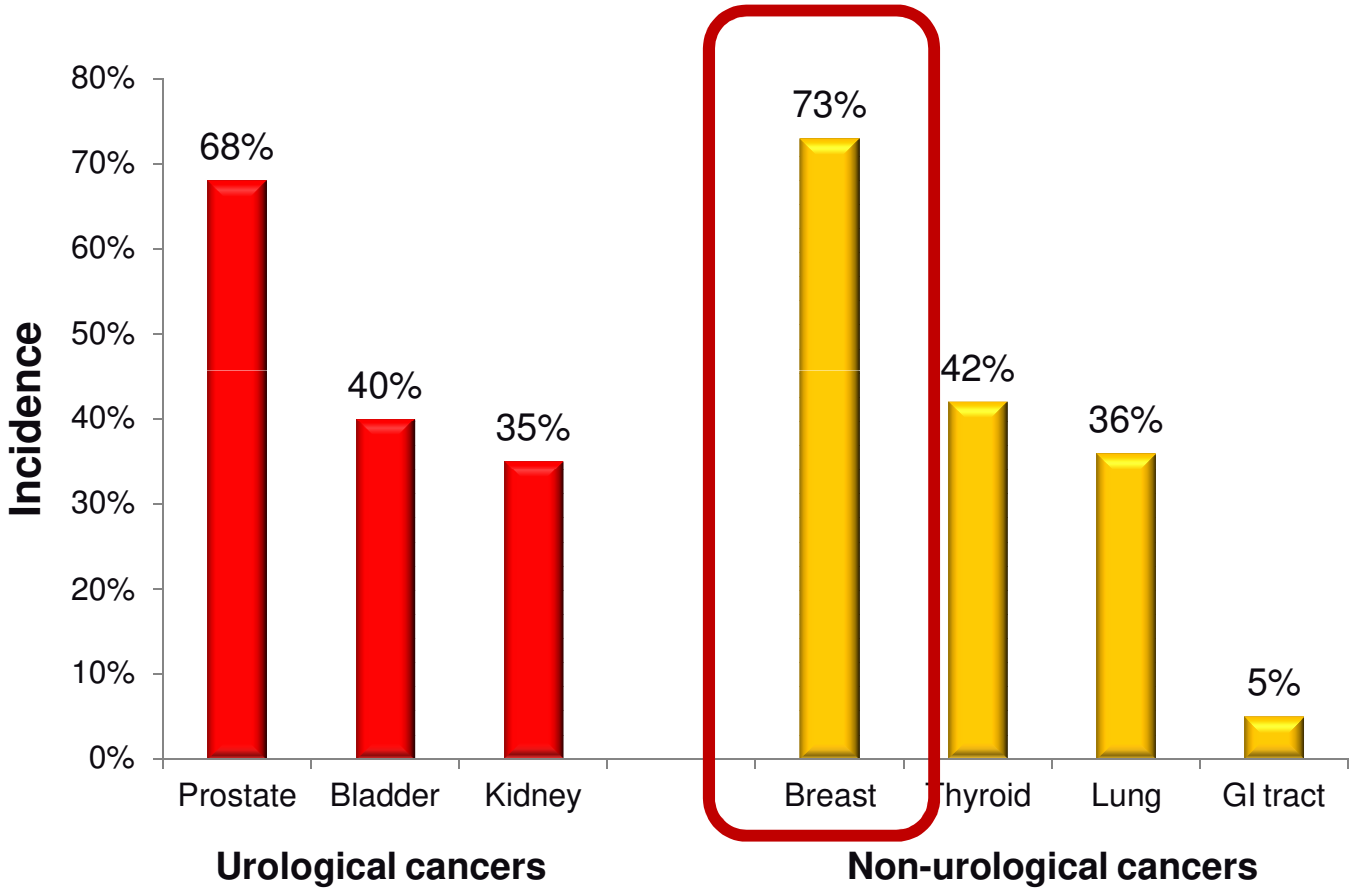
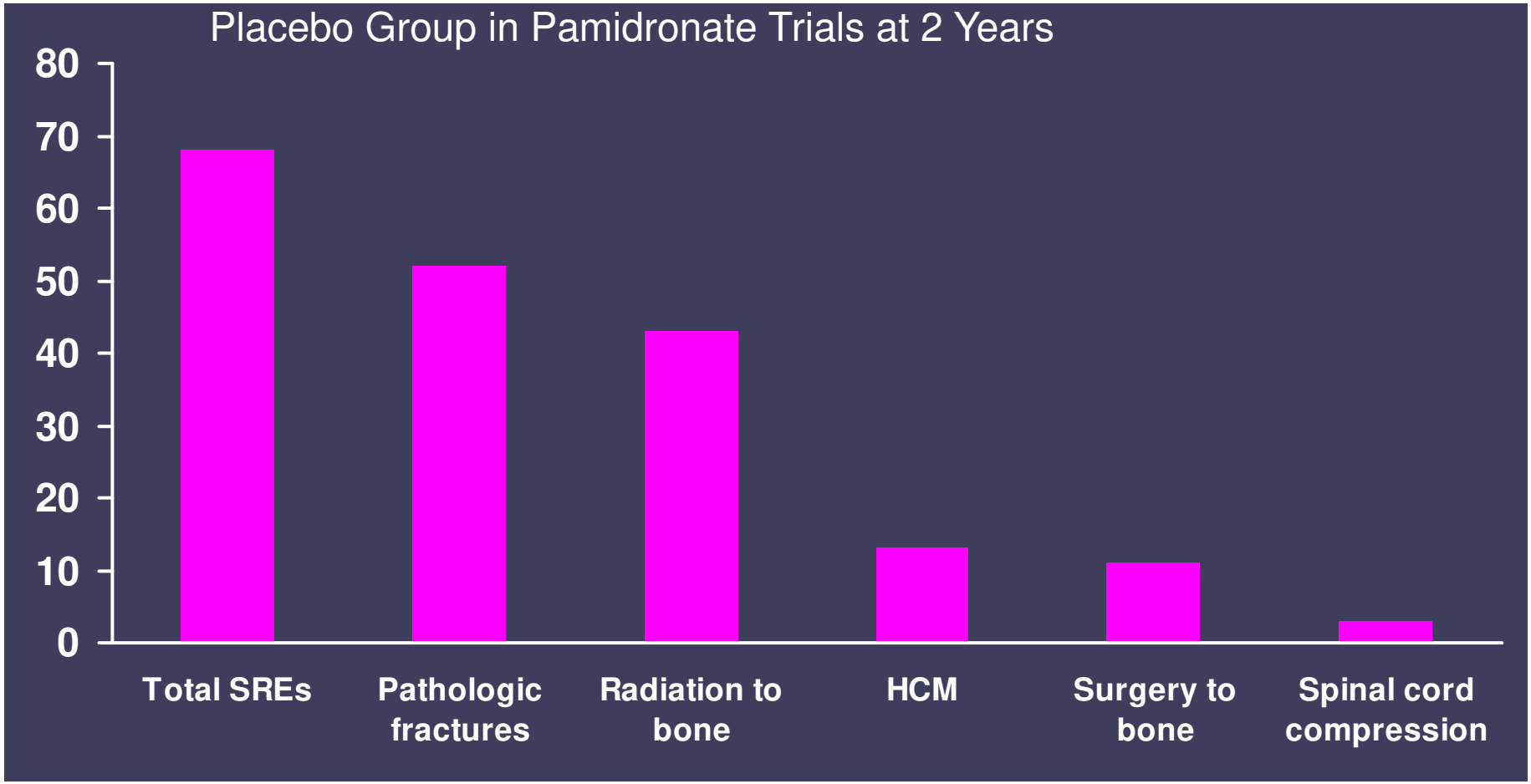
Incidence of bone metastases in cancer

Incidence of bone metastases highest in prostate and breast cancers



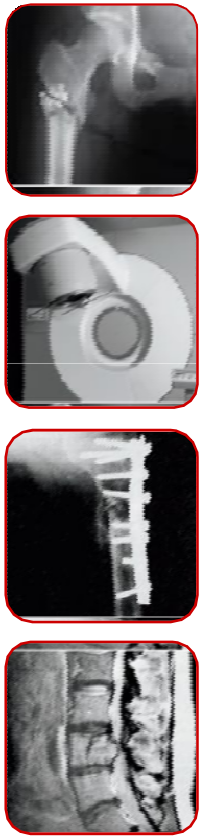
Coleman RE. *Clin Cancer Res* 2006;12:6243s–9s; Coleman RE. *Cancer Treat Rev* 2001;27:165–76; Scher HI, et al. *Clin Cancer Res* 2005;11:5223–32.

Incidence of SRE in BC pts with bone MTS



Lipton et al. *Cancer*. 2000;88:1082.

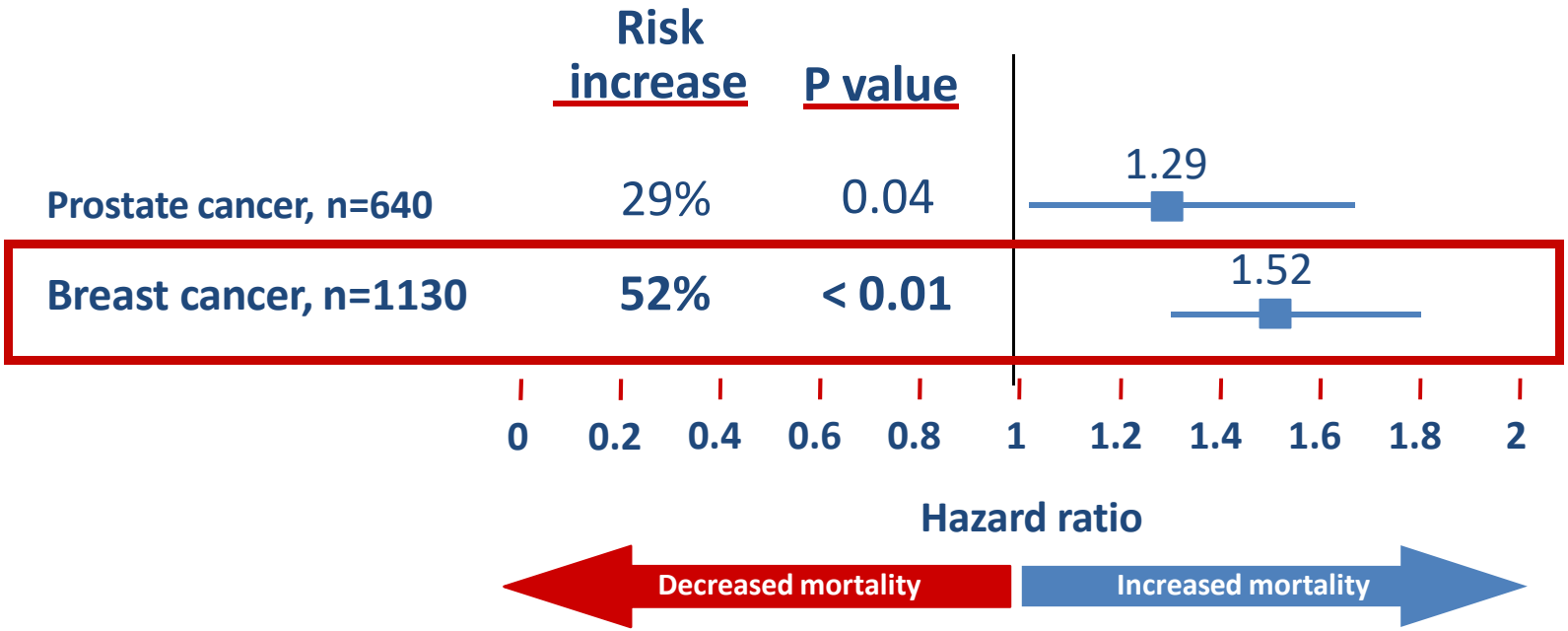
SREs create additional complications



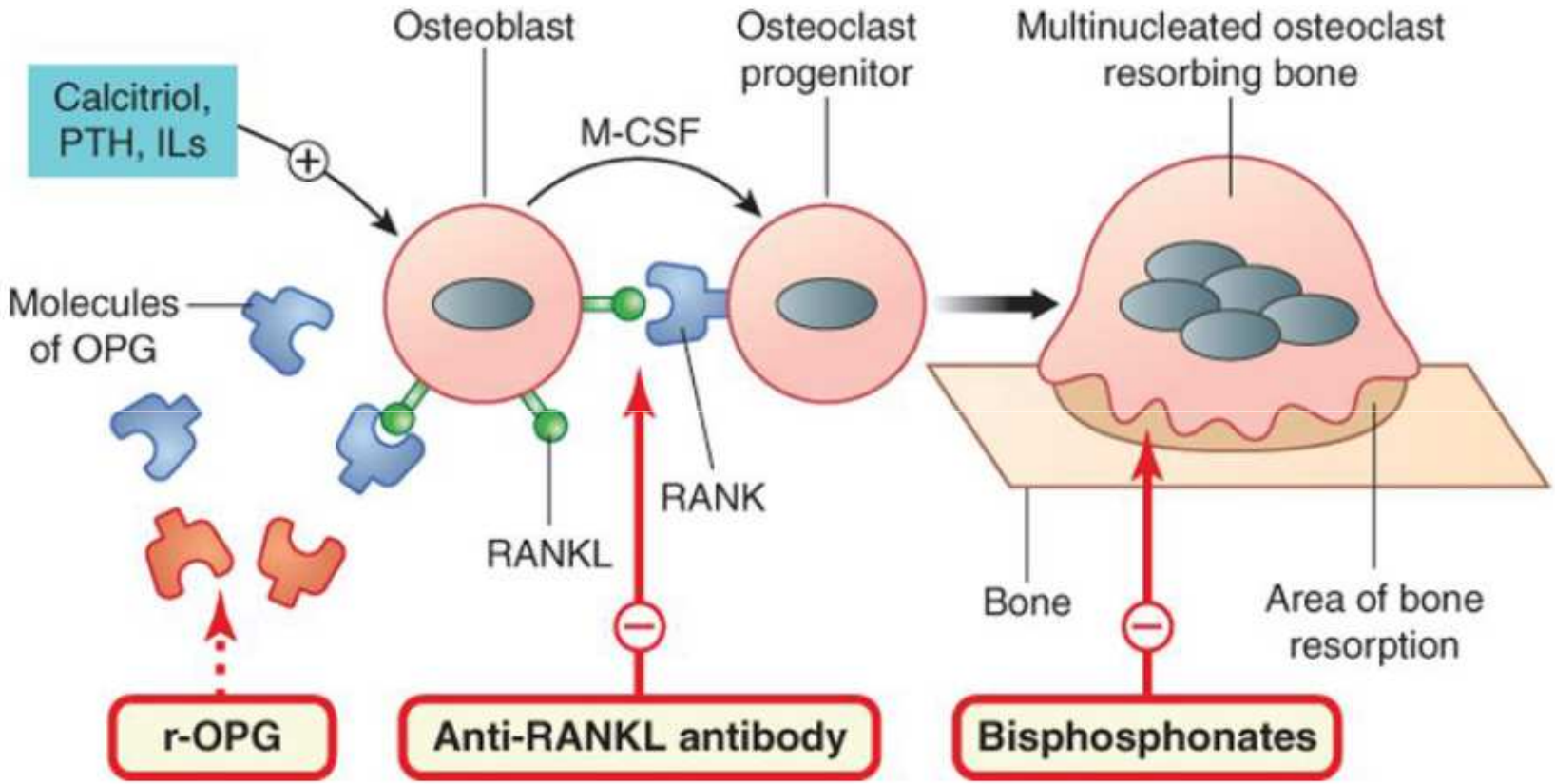
SRE	Potential complications
Pathological fracture	Extended healing time Reduced survival[1,2] Loss of mobility Need for care/nursing home residence (especially hip fracture)[3]
Radiation to bone	Potential for “pain flare” after therapy[4] Myelosuppression[5]
Surgery to bone	Hospital stay In-hospital mortality rate ≅8%[6] High rate of surgical complications[6,7] High failure rate; inability to restore function[6]
Spinal cord compression	Excruciating pain[7] Need for steroidal medications[7] Repeat visits for radiotherapy[8] Irreversible paraparesis or paraplegia[7] Loss of contincence[8]

1. Gainor BJ, et al. *Clin Orthopaed Rel Res* 1983;178:297–302; 2. Saad F. et al. *Cancer* 2007;110:1860–7; 3. Poor G, et al. *Osteoporos Int* 1995;5:419–26; 4. Loblaw DA, et al. *Supp Care Cancer* 2007;15:451–5; 5. Hellman D, et al. *J Palliat Med* 1998;1:277–83; 6. Katzer A, et al. *Arch Orthopaed Trauma Surg* 2002;122:251–8; 7. Loblaw DA, et al. *J Clin Oncol* 2005;23:2028–3; 8. Maranzano E, etal. *Tumori* 2003;89:469–75.

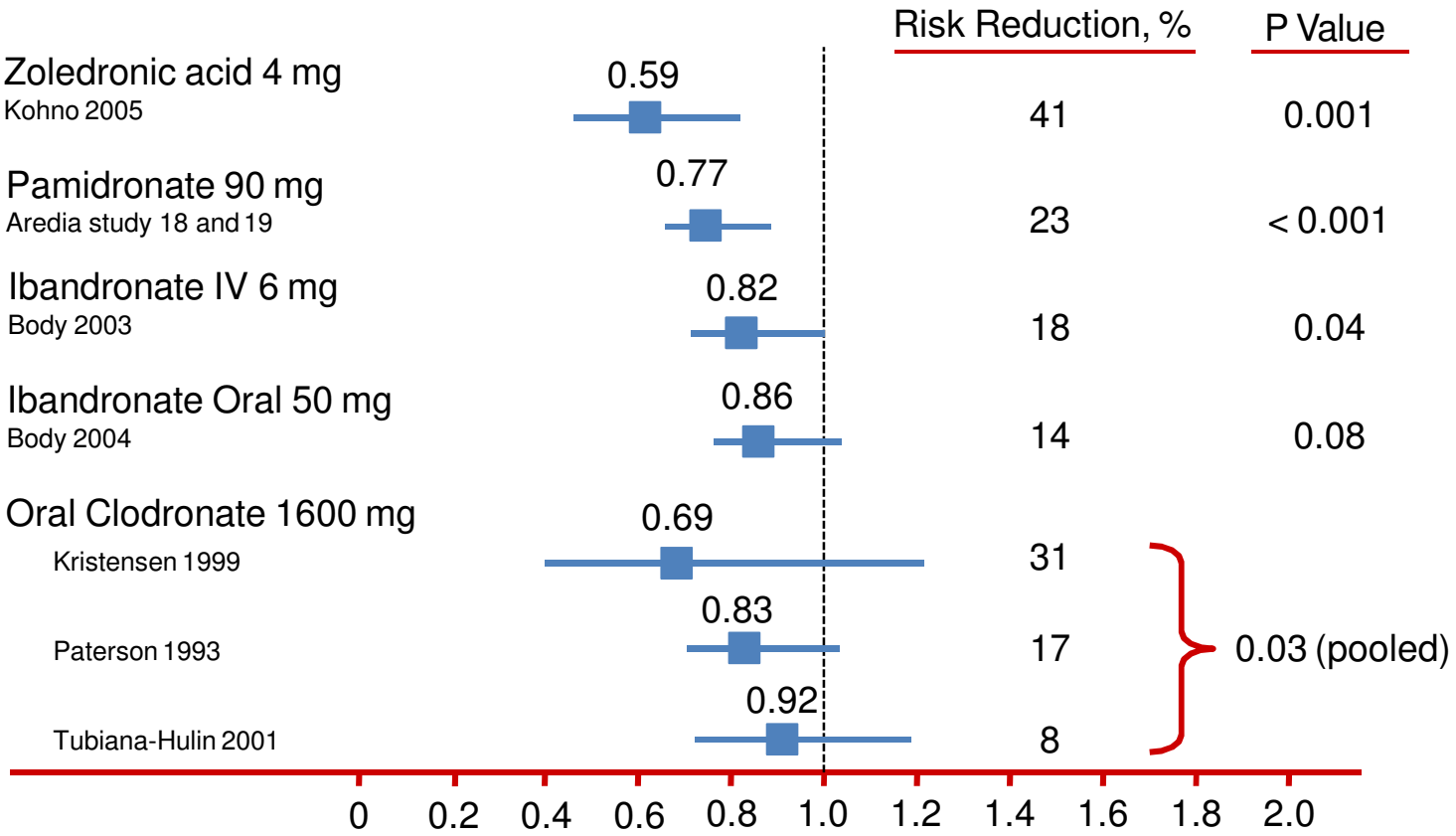
Pathologic fractures correlate with reduced survival in patients with malignant bone disease



Adapted from Saad F, et al. *Cancer* 2007;110:1860–7.



SRE risk reduction in breast cancer



Cochrane database comparing placebo-controlled trials in breast cancersetting.
Adapted from Pavlakis N, et al. *Cochrane Database Syst Rev*2005:CDC003474.

- Zoledronic acid is the most effective bisphosphonate for prevention of morbidity from metastatic bone disease (ESMO 2014)
- Evidence is insufficient to support the use of one BMA over another (ASCO2017)

Denosumab vs Zoledronic acid in patients with bone metastsases from BC

Calcium and Vit d supplementation recommended

N=2046
Advanced breast cancer and confirmed bone metastases, no previous BPS

Denosumab 120 mg sc and IV placebo q4wks

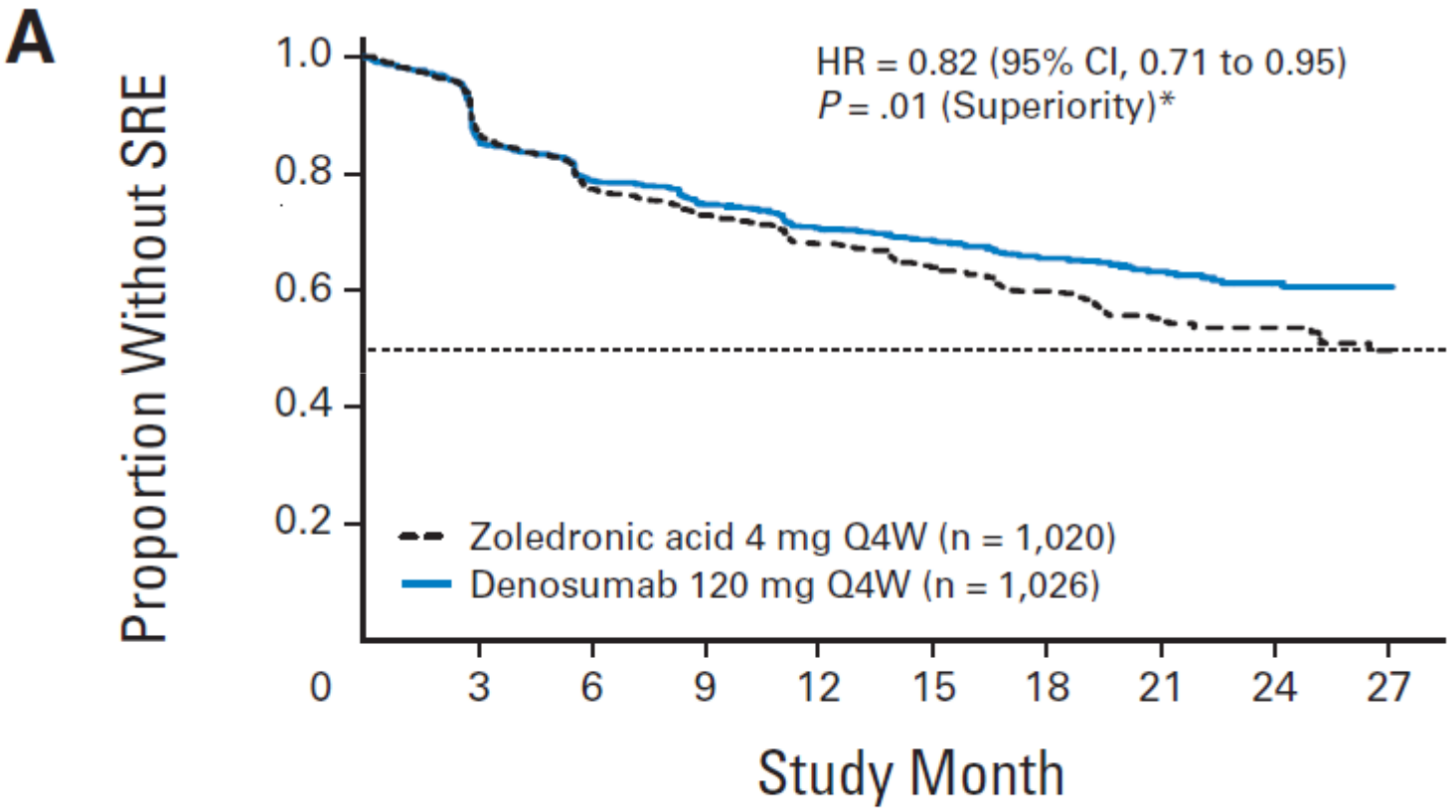
Zoledronic acid 4 mg iv and sc placebo q4wks

1° end-point: Time to first on-study SRE (non-inferiority)

2° endpoints: Time to first on-study SRE (superiority)
Time to first and subsequent on-study SRE (superiority)

Stopeck A. et al. JCO, 2010

Denosumab vs Zoledronic acid in patients with bone metastsases from BC



No. at risk										
Zoledronic acid	1,020	829	676	584	498	427	296	191	94	29
Denosumab	1,026	839	697	602	514	437	306	189	99	26

Stopeck A. et al. JCO, 2010

When to start

Evidence-based treatment guidelines recommend that treatment with bone-targeted therapy should start immediately following evidence of bone metastasis

- Patients with breast cancer who have evidence of bone metastases should be treated with BMAs (ASCO 2017)
- Bone-targeted therapy should be commenced at diagnosis of metastatic bone disease (ESMO 2014)

Treatment decisions should be individualized according to each patient's clinical presentation, comorbidities, PS, and optimal method of administration.

Treatment de-escalation

Three randomized clinical trials investigated zoledronic acid dosed every 4 weeks versus every 12 weeks

- **ZOOM**
- **OPTIMIZE-2**
- **CALGB (Alliance)**

Ongoing non-inferiority randomized clinical trials investigated denosumab every 4 weeks versus every 12 weeks

- **ReACT (NCT02721433)**
- **REDUSE (NCT02051218)**

Phase III ZOOM trial: ZA q 4 vs q 12 wks after 1 year standard treatment

N=425
Breast cancer and bone metastases who received zoledronic acid (9-12 doses) in past 15 months

Zoledronic acid 4 mg iv q 12 wks

Zoledronic acid 4 mg q 4 wks

Primary end-point: skeletal morbidity rate (#event/patient/year

Amadori D et al., Lancet Oncology 2013

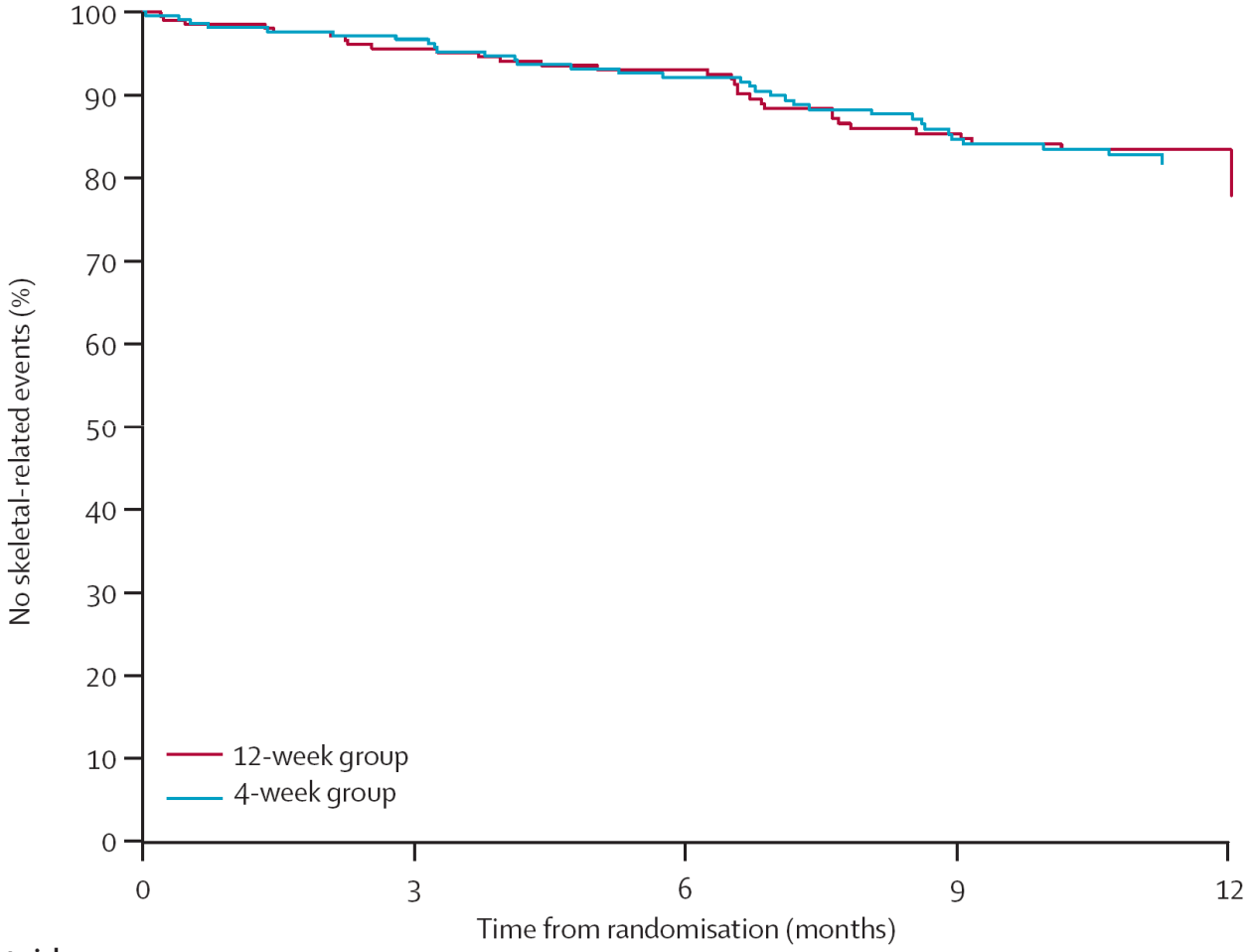
Phase III ZOOM trial: SMR and safety

Results	ZOL q4 weekly (n = 216)	ZOL q12 weekly (n = 209)
SMR (95% CI)	0.22 (0.14, 0.29)	0.26 (0.15, 0.37)

- Non-inferiority of q12 vs q 4 weekly remains statistically significant"
- Safety:
  - Renal AEs similar in both arms
  - 7 cases of ONJ (1.65% overall)
    - q12 weekly: n = 4
    - q4 weekly: n = 3

Amadori D et al., Lancet Oncology 2013

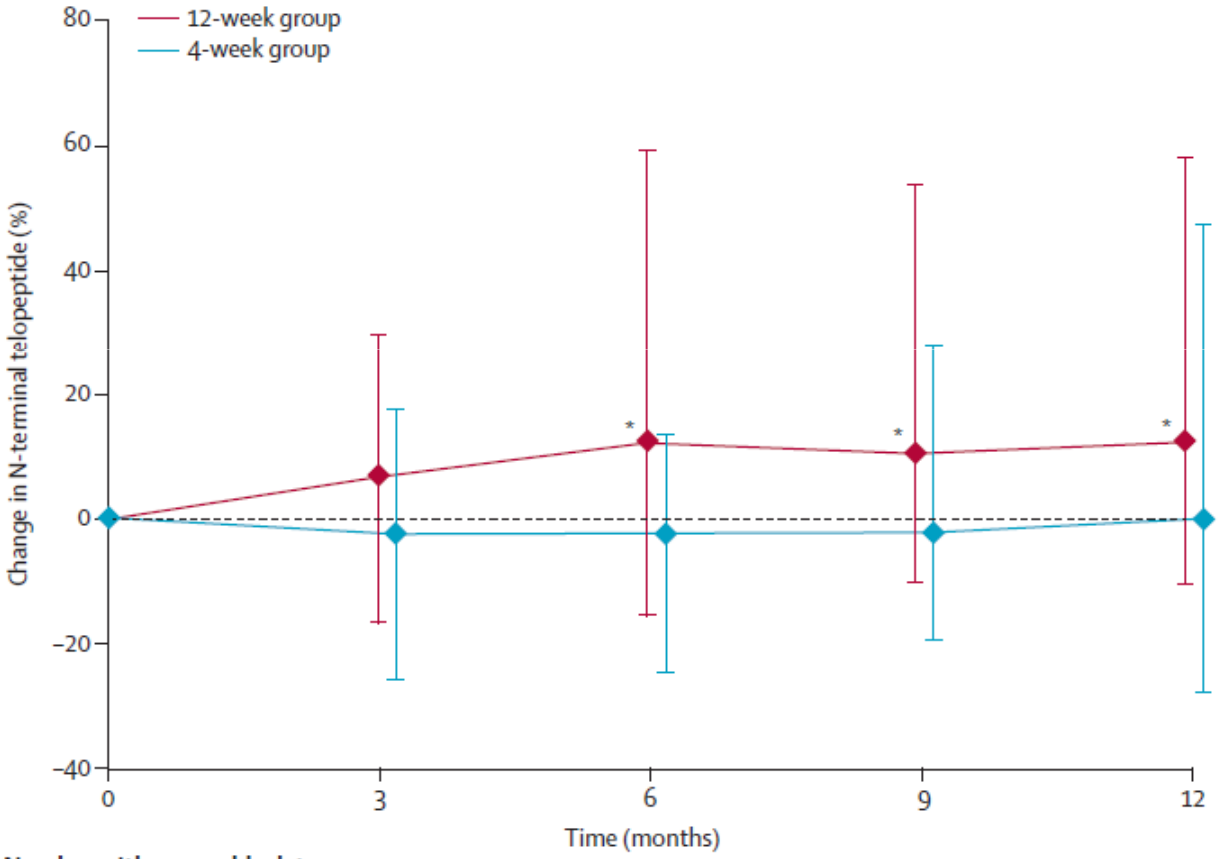
Phase III ZOOM trial: time to first on study SREs



Number at risk					
12-week group	209	193	163	137	15
4-week group	216	198	171	143	11

Amadori D et al., Lancet Oncology 2013

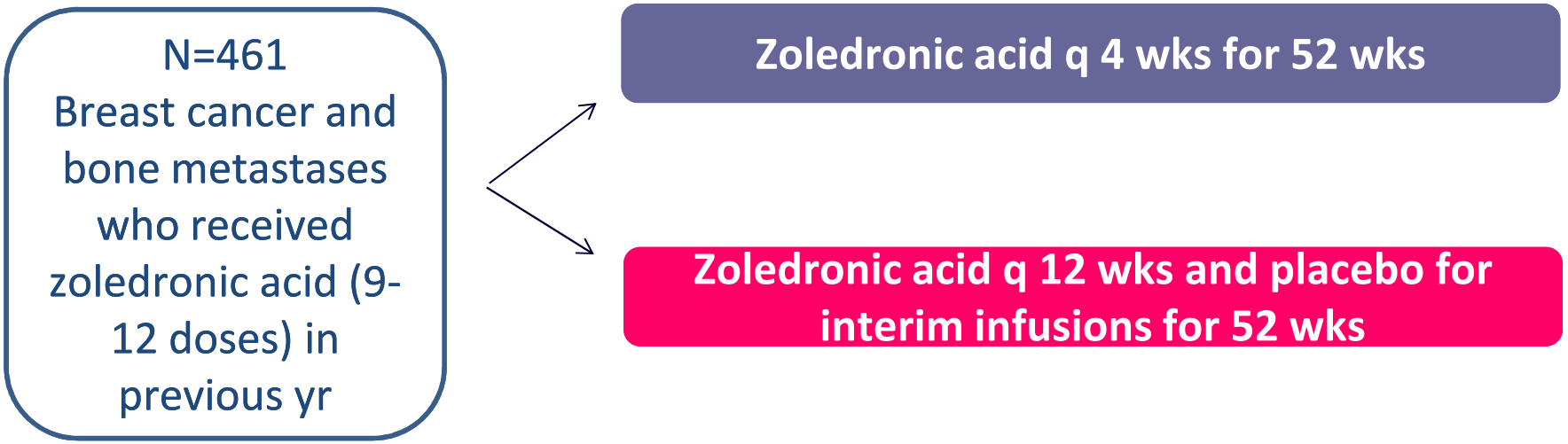
Phase III ZOOM trial: median change in N-terminal telopeptide concentration



Number with assessable data				
12-week group	85	79	71	68
4-week group	89	79	64	65

Amadori D et al., Lancet Oncology 2013

OPTIMIZE-2 Phase III study

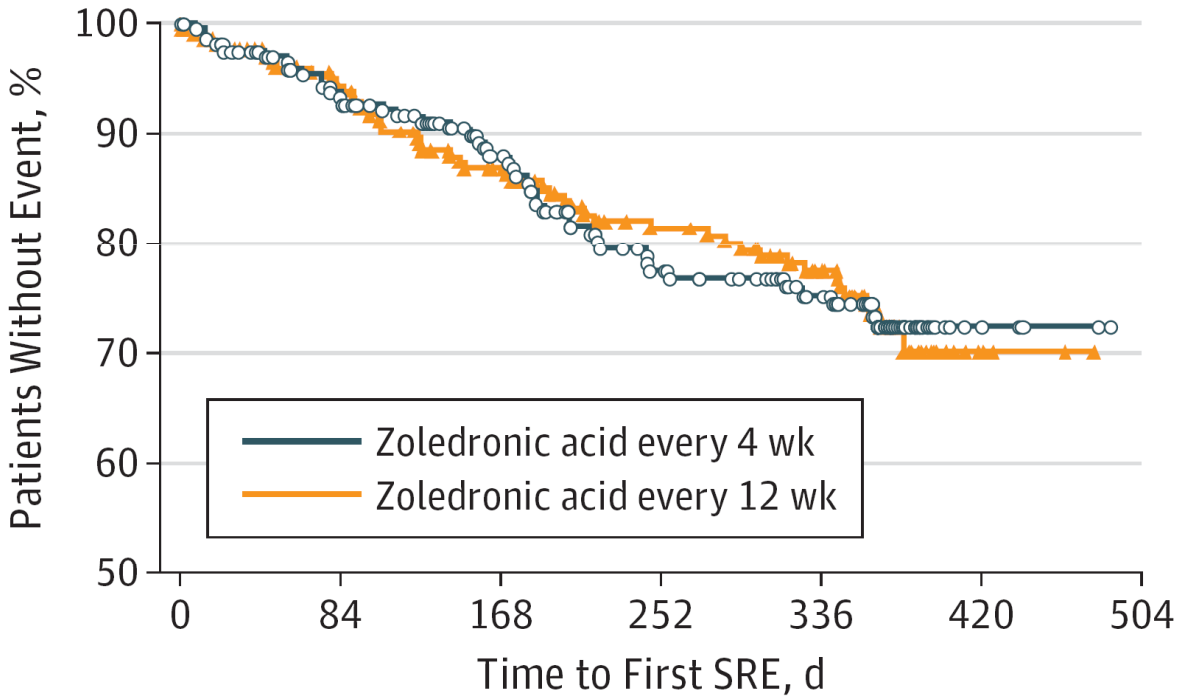


Primary end-point: time to first SRE

Hortobagyi G. et al., JAMA Oncology 2017

OPTIMIZE-2 Phase III study

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

Hortobagyi G. et al., JAMA Oncology 2017

CALGB 70604 Phase III trial

N= 1822
Patients with metastatic breast or prostate cancer or MM with bone involvement, no previous IV BPS

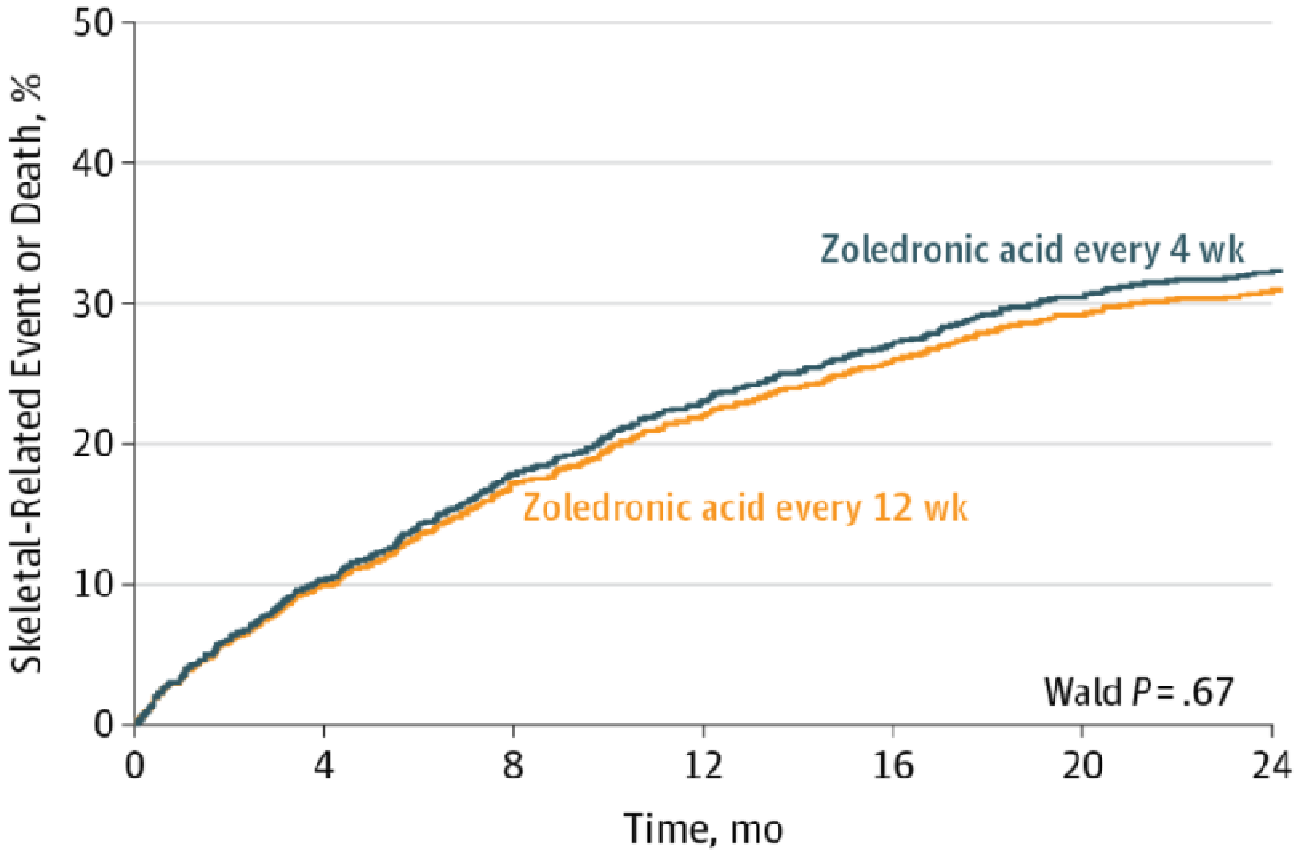
Zoledronic acid 4 mg iv q 4 wks

Zoledronic acid 4 mg q 12 wks

Primary end-point: proportion of patients with ≥ 1 SRE within 2 years of randomization

Himelstein A. et al., JAMA 2017

CALGB 70604 Phase III trial



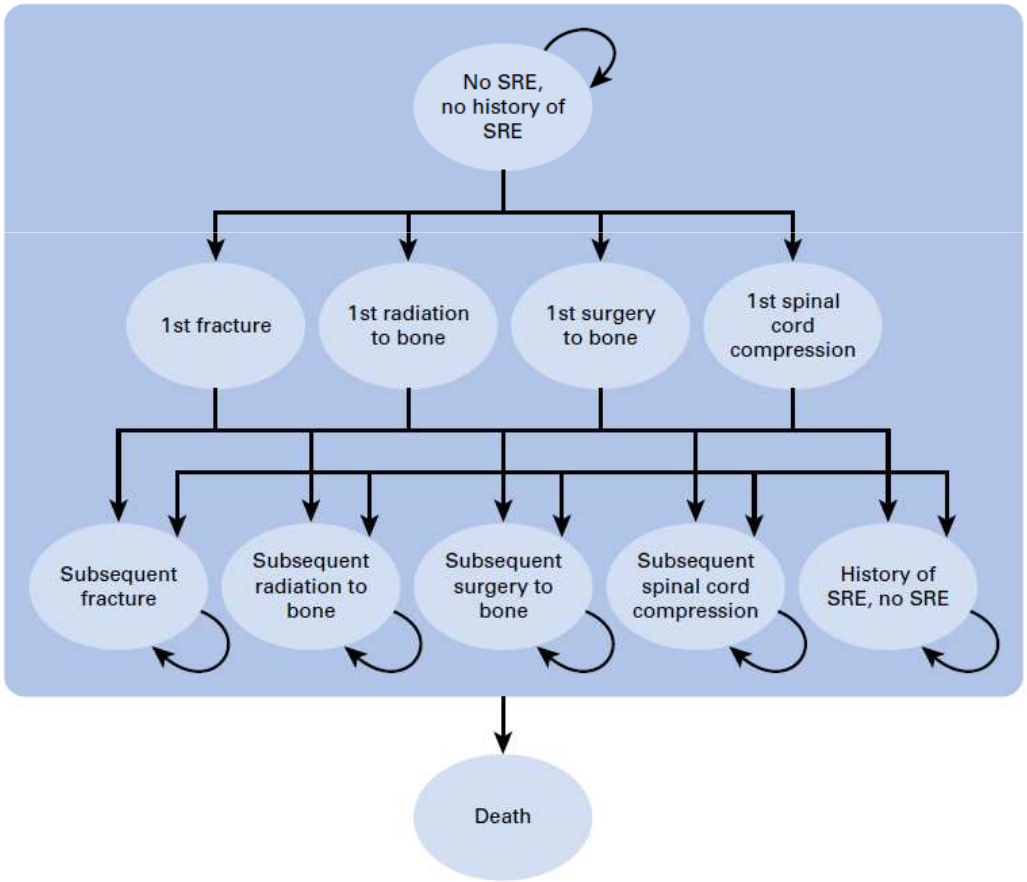
No. at risk							
Every 4 wk	911	882	703	586	467	367	245
Every 12 wk	911	884	726	576	484	392	244

Himelstein A. et al., JAMA 2017

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Cost-Effectiveness Analysis of Monthly Zoledronic Acid, Zoledronic Acid Every 3 Months, and Monthly Denosumab in Women With Breast Cancer and Skeletal Metastases: CALGB 70604 (Alliance)

Charles L. Shapiro, James P. Moriarty, Stacie Dusetzina, Andrew L. Himelstein, Jared C. Foster, Stephen S. Grubbs, Paul J. Novotny, and Bijan J. Borah



Markov model to calculate the costs per SRE avoided for the three treatments

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Table 2. Base-Case Results

Treatment Strategy*	Mean Costs (US$)	Mean SREs	QALY Year 1	QALY Year 2	Cost per SRE Avoided: Monthly ZA Reference	Cost per SRE Avoided: ZA Every 3 Months Reference
Monthly ZA	9,290	0.23	0.90	0.91	Reference	Dominated
Denosumab	57,200	0.8	0.88	0.90	Dominated	Dominated
ZA every 3 months	5,667	0.22	0.91	0.91	Dominant	Reference

Abbreviations: QALY, quality-adjusted life-year; SREs, skeletal-related events; ZA, zoledronic acid.
*The mean costs of a treatment strategy include the drug costs, administration costs, and costs of SREs.

The mean costs of the denosumab treatment strategy are nine-fold higher than generic ZA every 3 months.

Quality-adjusted life-years were virtually identical in all the three treatment arms; hence, the optimal treatment would be ZA every 3 months because it was the least costly treatment.

The sensitivity analyses showed that relative to ZA every 3 months, the incremental costs per mean SRE avoided for denosumab ranged from $162,918 to $347,655.

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

J Clin Oncol 35. © 2017 by American Society of Clinical Oncology

Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology–Cancer Care Ontario Focused Guideline Update

Catherine Van Poznak, Mark R. Somerfield, William E. Barlow, J. Sybil Biermann, Linda D. Bosserman, Mark J. Clemons, Sukhbinder K. Dhesy-Thind, Melissa S. Dillmon, Andrea Eisen, Elizabeth S. Frank, Reshma Jagsi, Rachel Jimenez, Richard L. Theriault, Theodore A. Vandenberg, Gary C. Yee, and Beverly Moy

Recommendation updated for 2017 guideline. As recommended in the 2011 version of the ASCO BMAs guideline, patients with breast cancer who have evidence of bone metastases should be treated with BMAs. One BMA is not recommended over another. If patients are treated with zoledronic acid, 4 mg intravenously administered over no less than 15 minutes, dosing options are every12 weeks or every 3 to 4 weeks (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Table 4. Estimated Prices for BMAs in the United States

Agent, Route	Dose	Schedule	Price Per Dose (USD)	Total Price Per 1-Year Treatment Cycle (USD)
Bisphosphonates				
Pamidronate, intravenous	90 mg	Delivered over no less than 2 hours every 3 or 4 weeks	$30.67*	Every 4 weeks price: $398.71 ($30.67 × 13)
Zoledronic acid, intravenous	4 mg	Delivered over no less than 15 minutes every 12 weeks or every 34 weeks	$53.64†	Every 12 weeks price: $214.56 ($53.64 × 4) Every 4 weeks price: $697.37 ($53.64 × 13)
Monoclonal antibodies				
Denosumab, subcutaneous injection	120 mg	Every 4 weeks	$1,995.48‡	Every 4 weeks price: $25,941.24 ($1,995.48 × 13)

Linee Guida
Trattamento delle metastasi ossee
Edizione 2017

La nuova schedula di acido zoledronico ogni 3 mesi dopo 9-12 somministrazioni della schedula mensile nel tumore della mammella potrebbe rappresentare oggi una opzione terapeutica. Tuttavia tale schedula non è approvata dagli enti regolatori

La nuova schedula di acido zoledronico ogni 3 mesi upfront nei tumori della mammella, prostata e MM […….] potrebbe rappresentare oggi una alternativa terapeutica alla schedula mensile in casi selezionati di pazienti che non possono assumere la formulazione mensile. Tuttavia tale schedula non è approvata dagli enti regolatori

BMAs: how long?

- Patients with metastatic cancer are living longer and with improved quality of life
- Bone metastases and the risk of SREs continue throughout the trajectory of metastatic breast cancer
- Optimal treatment duration should be considered in view of toxicity, costs, and expected benefits

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Symptom Management and Supportive Care

Renal Safety and Efficacy of i.v. Bisphosphonates in Patients with Skeletal Metastases Treated for up to 10 Years

VALENTINA GUARNERI,[a] SARA DONATI,[b] MASSIMILIANO NICOLINI,[a]
SIMONA GIOVANNELLI,[a] ROBERTO D'AMICO,[a] PIER FRANCO CONTE[a]

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Key Words. Bone metastases • Bisphosphonates • Renal safety • Jaw osteonecrosis

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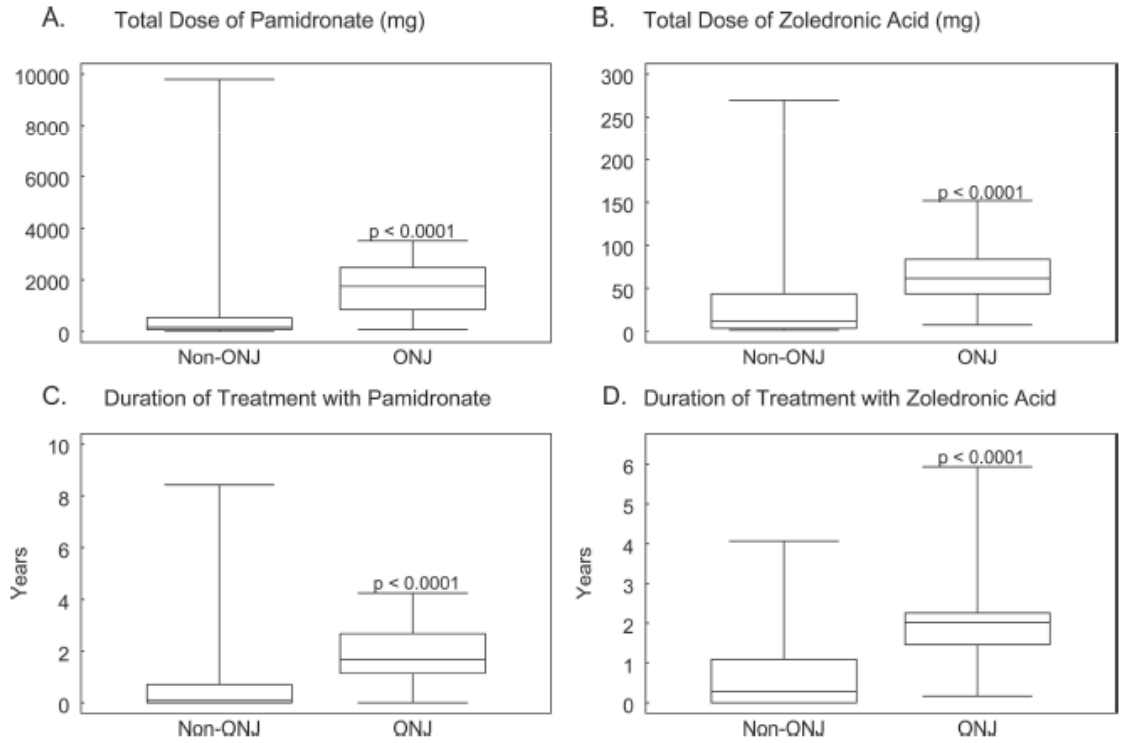
Volume 23, Number 6, 2008
Published online on February 4, 2008; doi: 10.1359/JBMR.080205

Frequency and Risk Factors Associated With Osteonecrosis of the Jaw in Cancer Patients Treated With Intravenous Bisphosphonates

Ana O Hoff,[1] Béla B Toth,[2] Kadri Altundag,[3] Marcella M Johnson,[4] Carla L Warneke,[4] Mimi Hu,[1] Ajay Nooka,[1] Gilbert Sayegh,[1] Valentina Guarneri,[3] Kimberly Desrouleaux,[1] Jeffrey Cui,[1] Andrea Adamus,[5] Robert F Gagel,[1] and Gabriel N Hortobagyi[3]

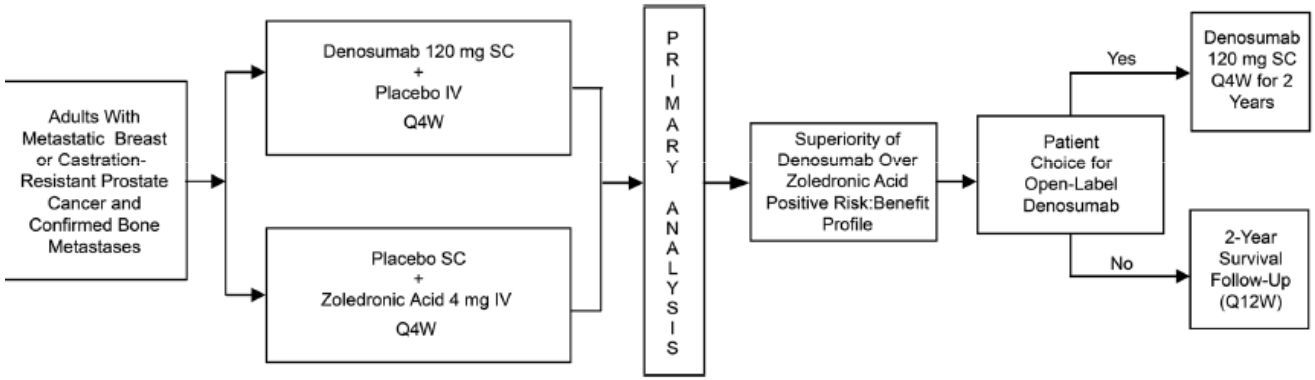


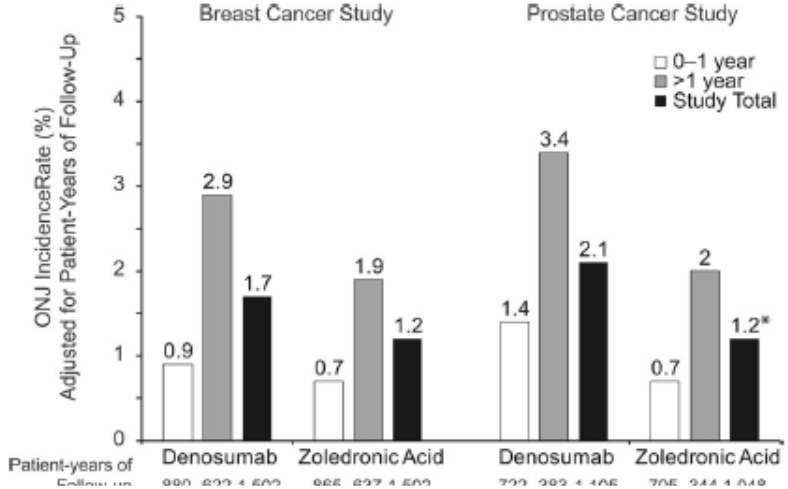
Support Care Cancer (2016) 24:447–455
DOI 10.1007/s00520-015-2904-5

ORIGINAL ARTICLE

Safety of long-term denosumab therapy: results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer

Alison T. Stopeck[1] · Karim Fizazi[2] · Jean-Jacques Body[3] · Janet E. Brown[4,5] · Michael Carducci[6] · Ingo Diel[7] · Yasuhiro Fujiwara[8] · Miguel Martín[9] · Alexander Paterson[10] · Katia Tonkin[11] · Neal Shore[12] · Paul Sieber[13] · Frank Kueppers[14] · Lawrence Karsh[15] · Denise Yardley[16] · Huei Wang[17] · Tapan Maniar[17] · Jorge Arellano[17] · Ada Braun[17]





Optimal duration of BMAs therapy

The necessary duration of BMAs therapy remains unclear

- *Reconsider bisphosponate therapy at 2 yrs: continued bisphosphonate treatment should be considered in pts with active cancer (NCCN 2009)*
- *Once initiated, bone –modifying agents should be continued until evidence of substantial decline in performance score (ASCO 2011, ASCO 2017)*
- *Bone-targeted therapy for metastatic bone disease should continue indefinitely and throughout the course of the disease (ESMO 2014)*

Associazione Italiana di Oncologia Medica

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Edizione 2017

In considerazione delle evidenze citate, in assenza di dati specifici e sufficienti ad individuare un periodo di trattamento ottimale, la durata attualmente consigliata per la terapia target all'osso, è di almeno 2 anni sospendendo il trattamento in caso di peggioramento del Performance Status. Il proseguimento del trattamento oltre il limite dei due anni, è comunque consigliato (soprattutto in caso di terapia con denosumab), tenendo conto dei rischi di sviluppo di eventi scheletrici, della tollerabilità e delle condizioni cliniche generali del paziente [6,10,31,43].

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
MOLTO BASSA	La durata consigliata in fase metastatica per la terapia target all'osso è di almeno 2 anni.	**Positiva debole**