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**DE-ESCALATION NELLA TERAPIA SISTEMICA
DEL CARCINOMA MAMMARIO:
QUALI EVIDENZE?
TERAPIA DELLE PAZIENTI
CON METASTASI OSSEE
CON BIFOSFONATI E DENOSUMAB**



ESMD
Designated Centers
of Integrated
Oncology and
Palliative Care



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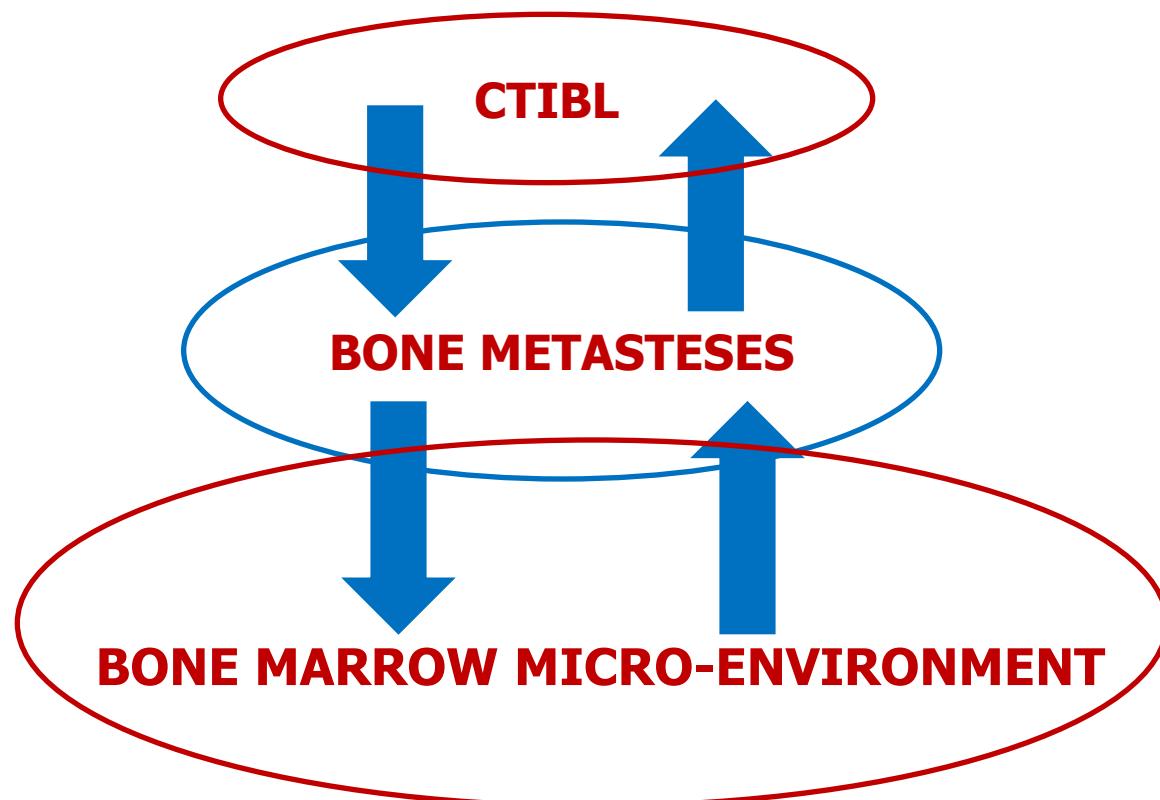
clinical practice guidelines

Annals of Oncology 00: 1–14, 2014
doi:10.1093/annonc/mdu103

Bone health in cancer patients: ESMO Clinical Practice Guidelines[†]

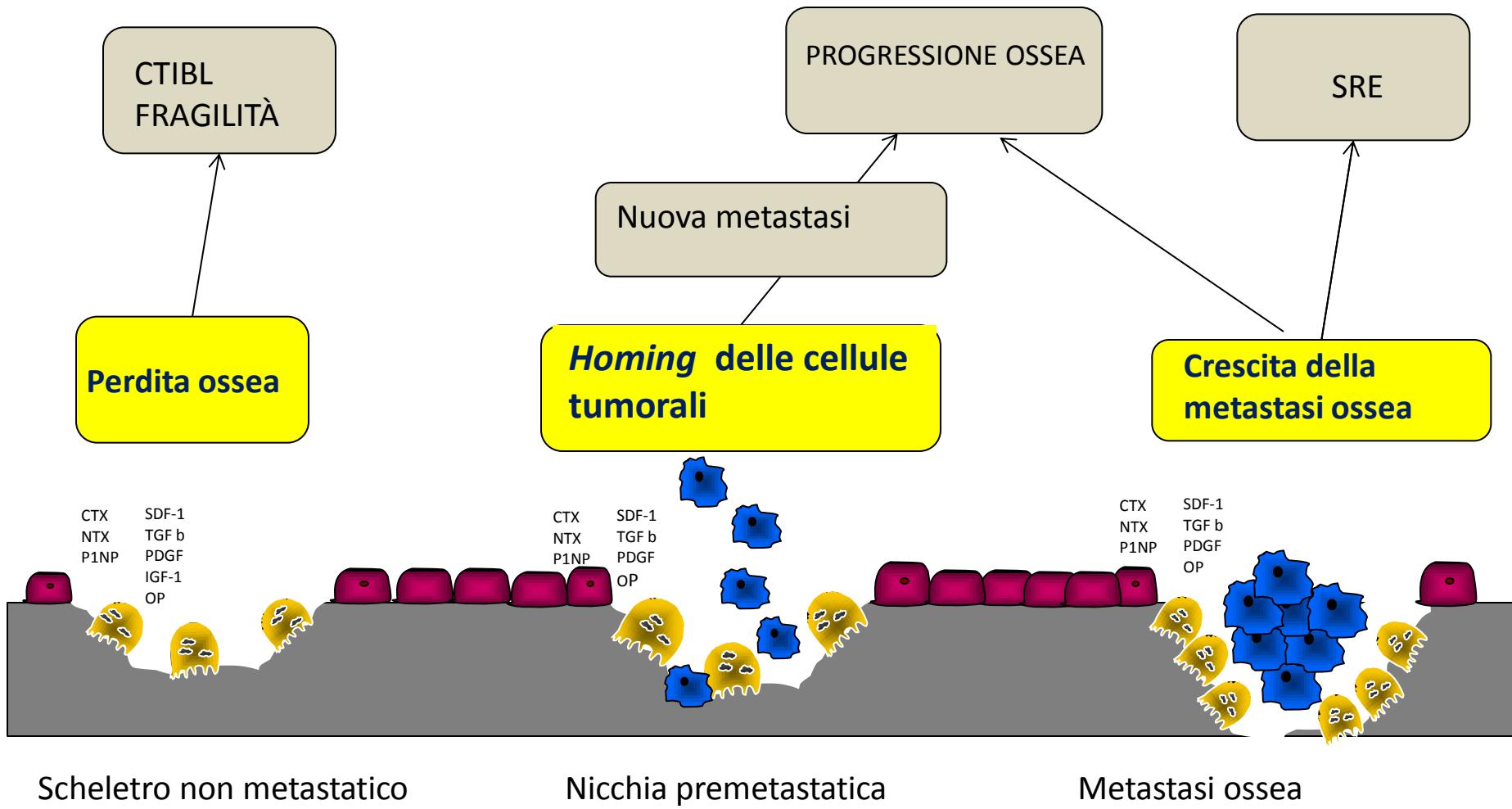
R. Coleman¹, J. J. Body², M. Aapro³, P. Hadji⁴ & J. Herrstedt⁵ on behalf of the ESMO Guidelines Working Group*

THERE ARE THREE AREAS OF CANCER MANAGEMENT THAT MAKE BONE HEALTH IN CANCER PATIENTS OF INCREASING CLINICAL IMPORTANCE



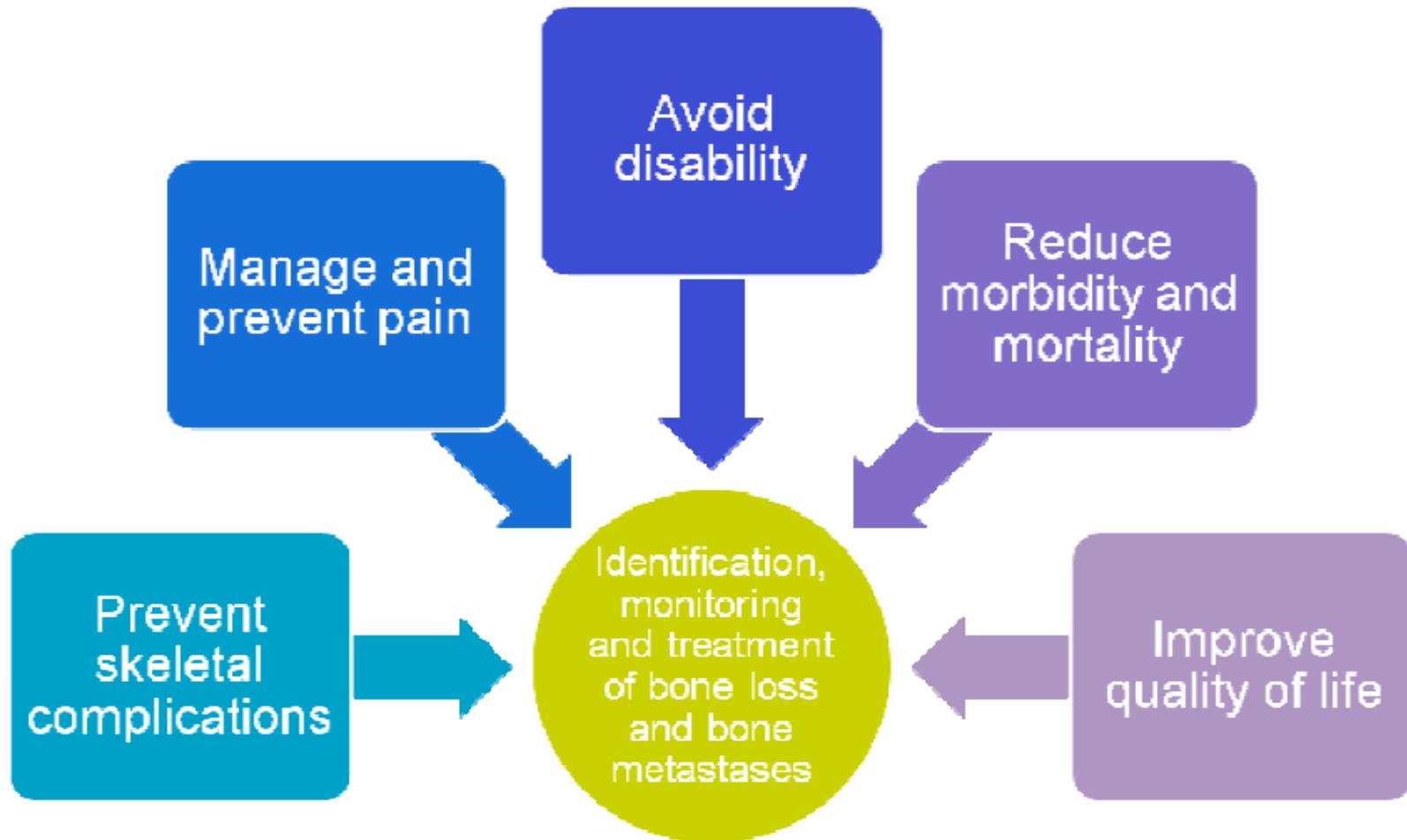
ELEVATO TURNOVER OSSEO

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



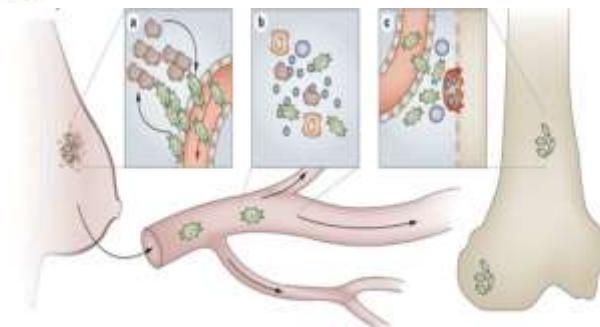
Courtesy by Bertoldo F

Why is awareness of bone health in cancer so important ?



BREAST CANCER AND BONE METASTASES

- Breast cancer is the most common cancer among women globally¹
 - Worldwide incidence in 2018 was 46.3 per 100,000 people
- Metastasis in breast cancer is characterized by a distinctive spread via regional lymph nodes to the lungs, liver, and bones²
 - ~73% of women with advanced breast cancer will develop bone metastases³
 - 5-10% of patients have metastases at breast cancer diagnosis⁴



1. GLOBOCAN 2018. Cancer today. Available at: <http://gco.iarc.fr/>. Accessed 06 11 19;

2. Muller A, Homey B, Soto H, et al. *Nature* 2001;410:50;

3. Coleman RE. *Clin Cancer Res* 2006;12:6243s-9s;

4. Cardoso F, Harbeck N, Fallowfield L, et al. *Ann Oncol* 2012;23(suppl_7):vii11-9.

SREs are ASSOCIATED with MORBIDITY



Pathologic Fracture

- Long bone fractures cause the most disability¹
- Vertebral collapse results in loss of height¹
- Rib fractures result in restrictive lung disease¹



Spinal Cord Compression

- Leads to considerable pain and disability²
- The outcome of decompressive surgery is improved if performed within 48 hours³



Radiation to Bone

- Major role in the treatment of bone metastases and related complications⁴
- Pain relief may only last 3-4 months⁴



Surgery to Bone

- Fixation of pathologic or impending fractures⁵
- 6-15% risk of peri-operative mortality⁵
- Median 2-14 months survival after surgery⁵

1. Coleman RE. *Cancer* 1997;80:1588-94;

2. Drudge-Coates L, Rajabu K. *Int J Palliat Nurs* 2008;4:110-6;

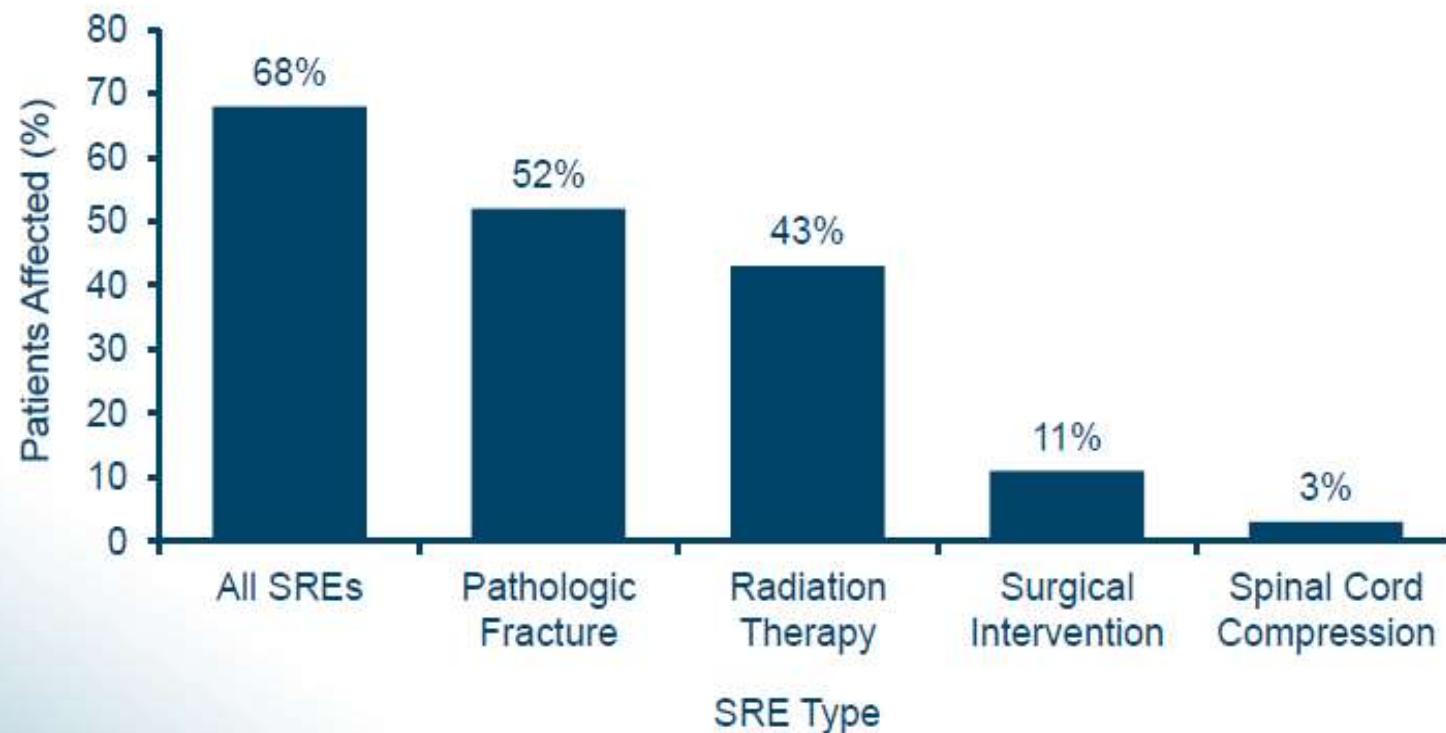
3. Furstenberg CH, Wiedenhöfer B, Gerner JF, et al. *J Bone Joint Surg Br* 2009;91:240-4;

4. Gralow JR, Biermann JS, Farooki A, et al. *J Natl Compr Canc Netw* 2009;7(suppl_3):S1-35;

5. Malviya A, Gerrard C. *Palliat Med* 2012;26:788-96.

SREs are COMMON in PATIENTS with Breast Cancer and BONE METASTASES

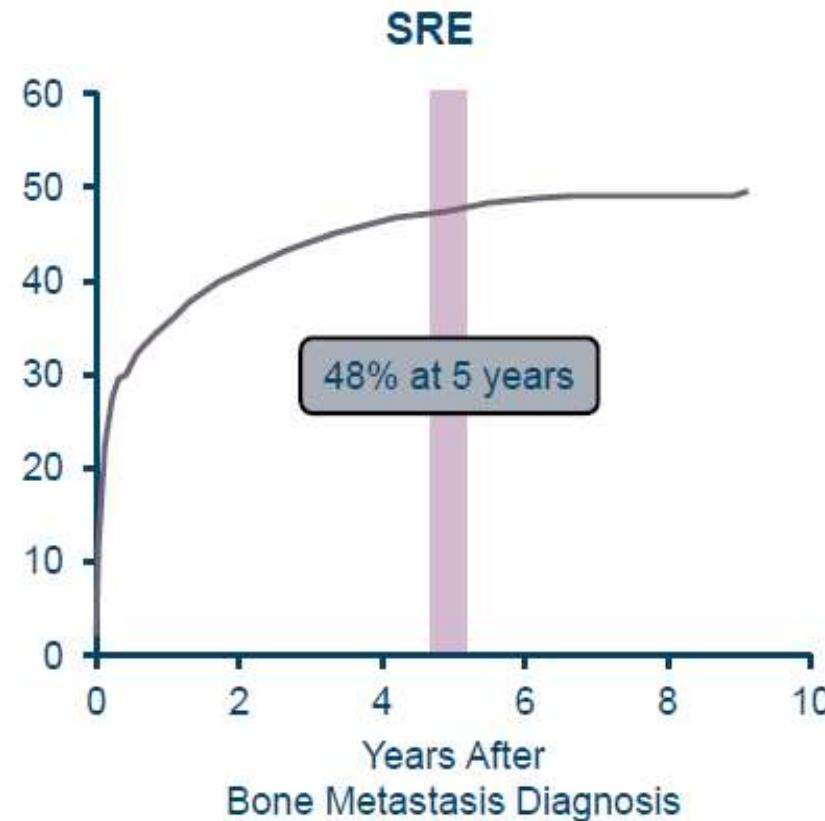
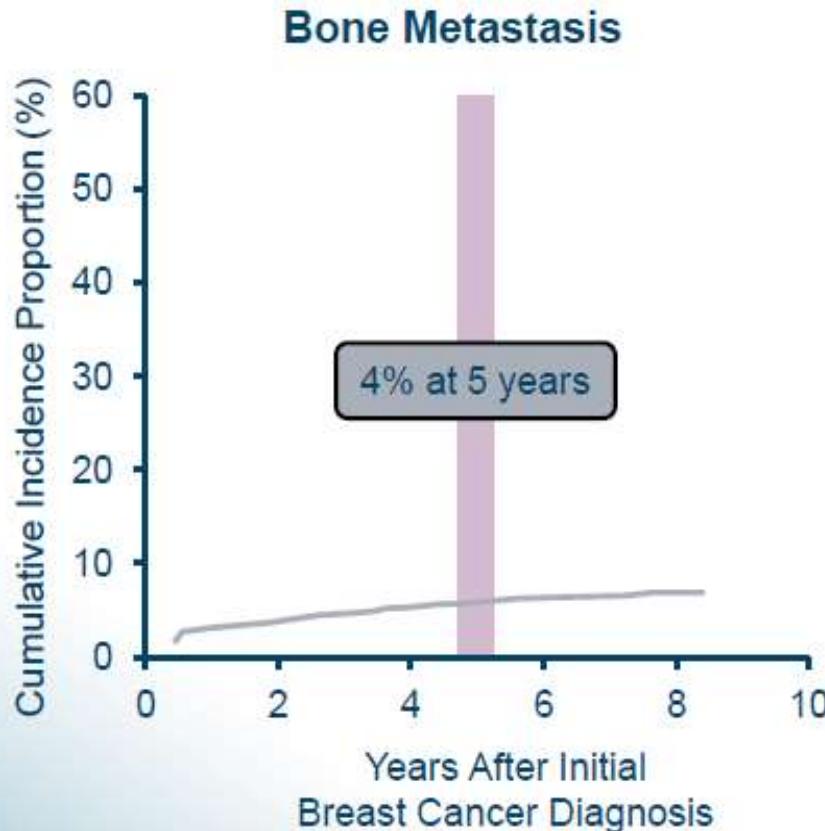
Proportion of Breast Cancer Patients with Bone Metastases Experiencing SREs in the Absence of Preventive Therapy (n=384)



Data taken from the placebo arm (n=384) of a randomized study (N=754) of women with Stage IV breast cancer and bone metastases.

Lipton A, Theriault RL, Hortobagyi GN, et al. *Cancer* 2000;88:1082-90.

Risk of SREs is High in Patients with Breast Cancer and Bone Metastases



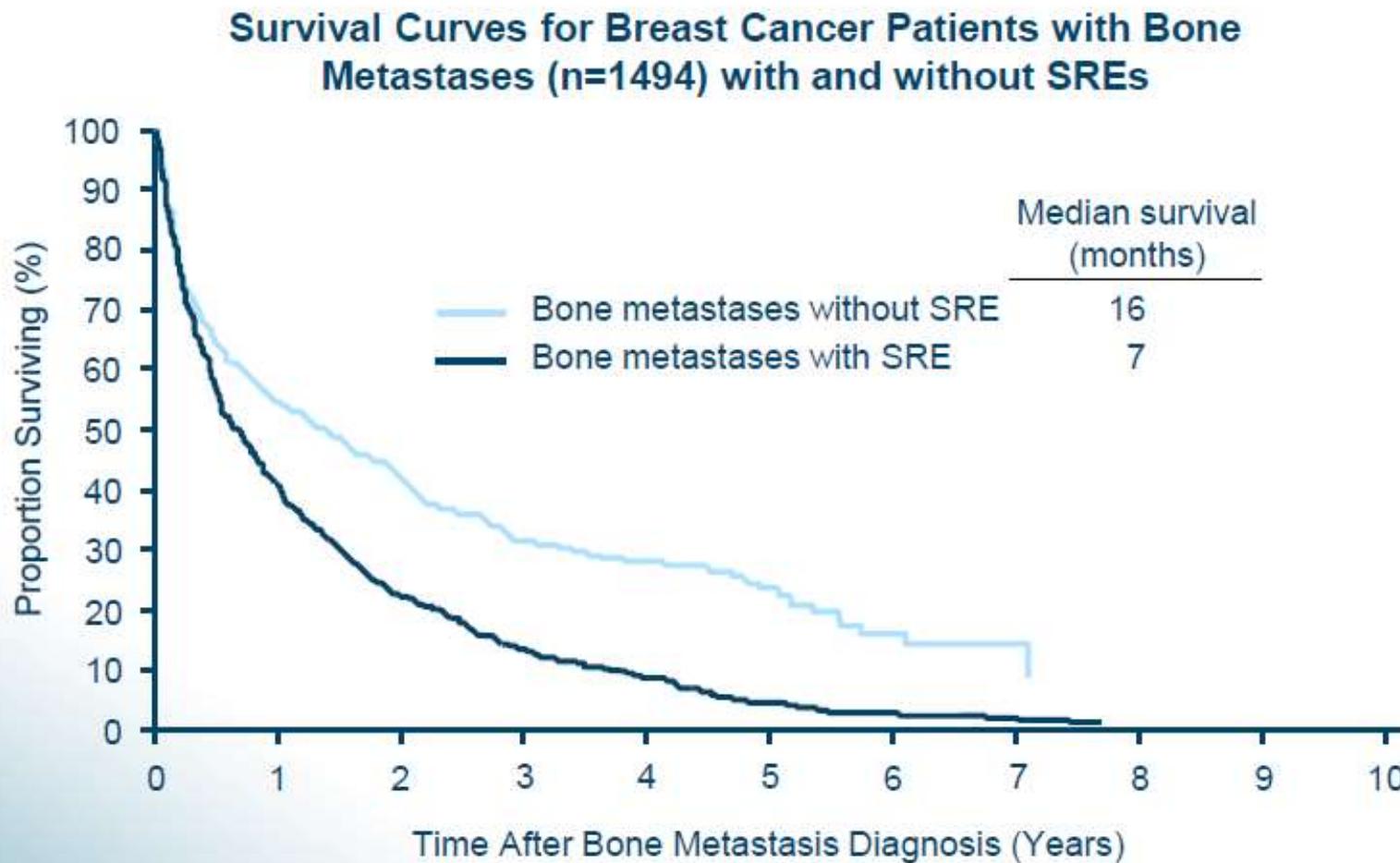
SRE risk rapidly increases after diagnosis of bone metastases in breast cancer patients

Data are based on analysis of the Denmark National Registry of Patients (NRP).

35,941 patients with breast cancer were identified January 1999–December 2007.

Yong M, Jensen A, Jacobsen J, et al. *Cancer Res* 2009;69(suppl_24): abstract 2051.

Breast Cancer Patients with Bone Metastases and SREs have a Worse Prognosis than those without SREs



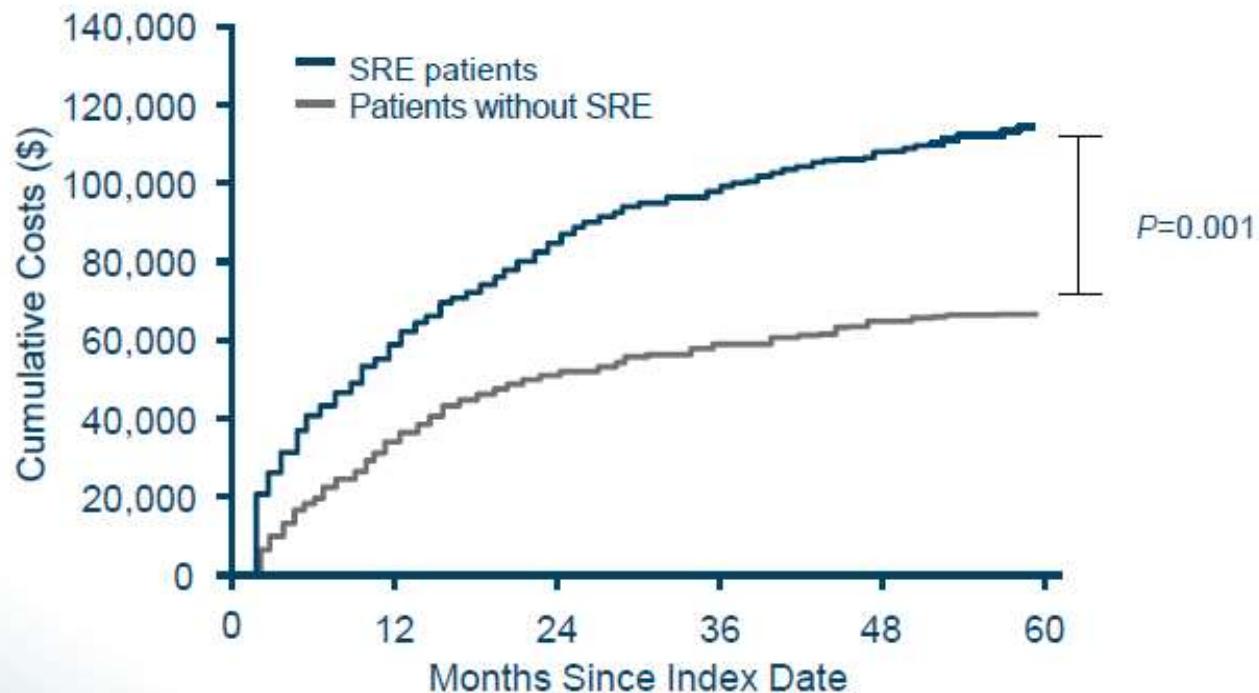
Data are based on analysis of the Denmark NRP.

35,912 newly diagnosed breast cancer patients were identified January 1999-December 2007.

Yong M, Jensen A, Jacobsen J, et al. *Breast Cancer Res Treat* 2011;129:495-503.

SREs Increase Medical Care Costs in Breast Cancer Patients

Estimated Cumulative Total Medical Care Costs by Month



Monthly costs*: Patients with SREs: \$3746; Patients without SREs: \$2318

*Mean monthly costs among patients remaining alive and not censored in each month of follow-up. Retrospective data from 617 breast cancer patients of whom 52% experienced an SRE. Data collected from claims July 1 1994 to June 30 2002. All costs were adjusted to 2002 price levels using the US Consumer Price Index for Medical Care.
Delea T, McKiernan J, Brandman J, et al. *J Support Oncol* 2006;4:341-7.



TREATMENT OPTIONS IN METASTATIC BONE DISEASE

SYSTEMIC THERAPY

LOCOREGIONAL THERAPY

- Radiation therapy
- Surgery
- Interventional procedures

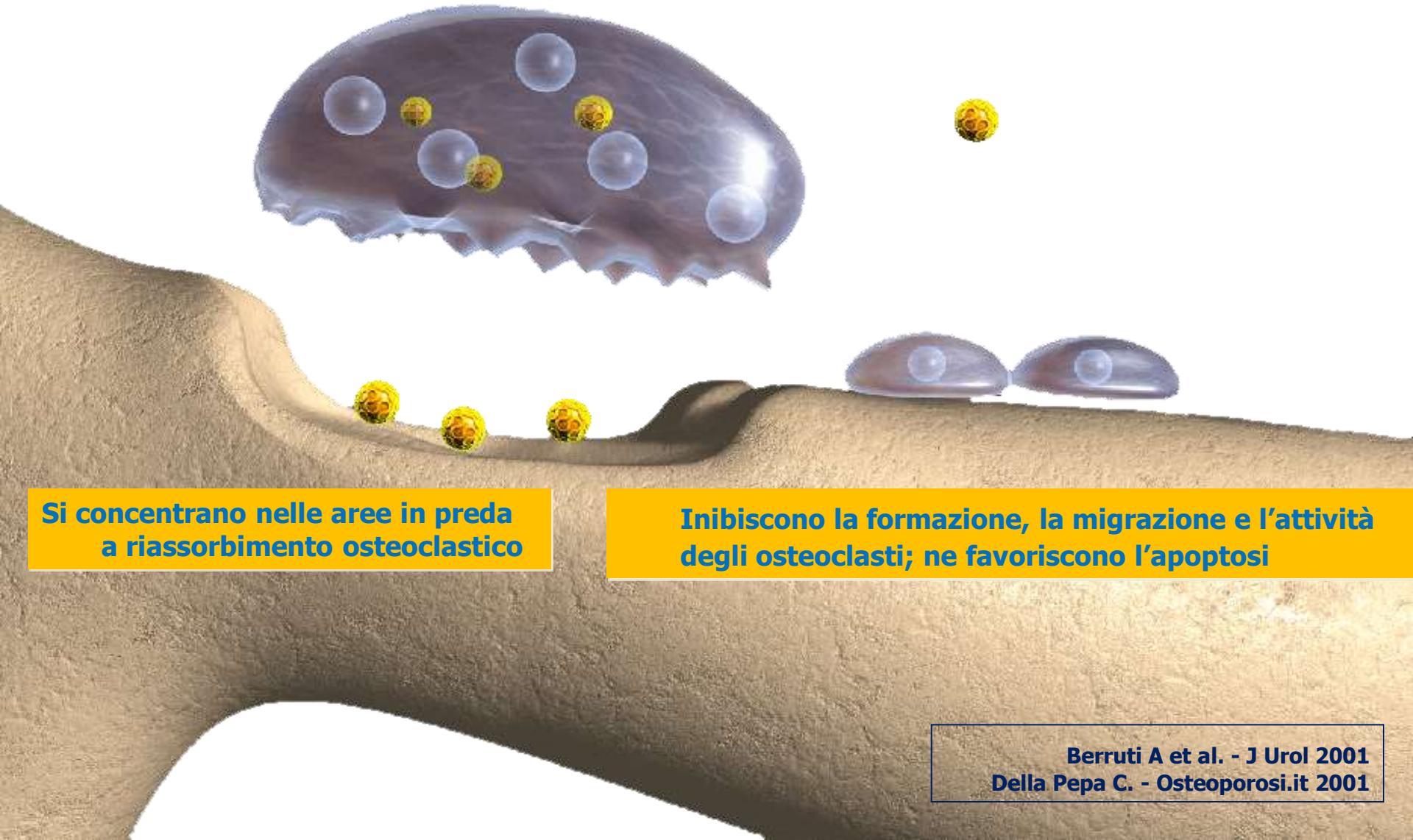
- Chemotherapy
- Hormone Therapy
- Target Therapy
- Radiometabolic Therapy
- **BISPHOSPHONATES**
- **DENOSUMAB**

Bone-modifying agents (BMAs)

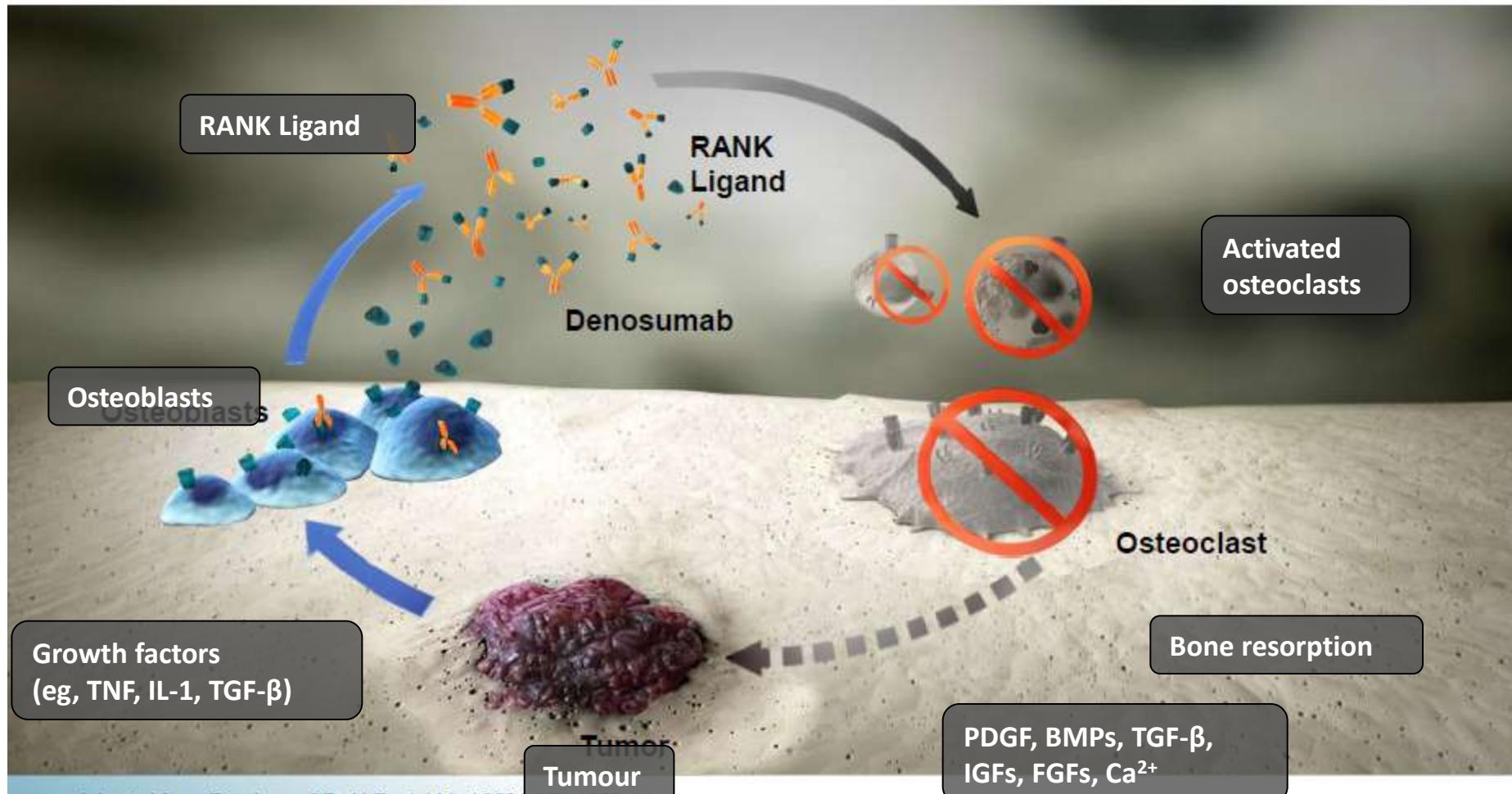
| Non-nitrogen-containing bisphosphonates | Nitrogen-containing bisphosphonates | RANKL inhibitor |
|--|--|--|
| clodronate , etidronate | zoledronate, pamidronate, ibandronate | Denosumab |
| metabolized to cytotoxic compounds by osteoclasts | Inhibit farnesyl pyrophosphate synthase (FPPS) | Neutralize Circulating RANKL |
| <ul style="list-style-type: none"> • accumulation of cytotoxic ATP analogs • induce osteoclast apoptosis | <ul style="list-style-type: none"> • mevalonate pathway of cholesterol biosynthesis • protein prenylation | Inhibit osteoclast formation, function, and survival |
| <p>Etidronate: <chem>CC(O)C(=O)N(CCl)C(Cl)Cl</chem></p> <p>Clodronate: <chem>CC(=O)N(CCl)C(Cl)Cl</chem></p> <p>Tiludronate: <chem>CC(=O)N(Cc1ccccc1)C(Cl)Cl</chem></p> | <p>Alendronate: <chem>CC(=O)N(Cc1ccccc1)C(C(=O)N(C)c2ccccc2)C(Cl)Cl</chem></p> <p>Risedronate: <chem>CC(=O)N(Cc1ccccc1)C(C(=O)N(C)c2ccccc2)C(O)C(Cl)Cl</chem></p> <p>Ibandronate: <chem>CC(=O)N(Cc1ccccc1)C(C(=O)N(C)c2ccccc2)C(O)C(O)C(Cl)Cl</chem></p> <p>Pamidronate: <chem>CC(=O)N(Cc1ccccc1)C(C(=O)N(C)c2ccccc2)C(O)C(O)C(O)C(Cl)Cl</chem></p> <p>Zoledronate: <chem>CC(=O)N(Cc1ccccc1)C(C(=O)N(C)c2ccccc2)C(O)C(O)C(O)C(O)C(Cl)Cl</chem></p> | <p>R 2 position: potency for inhibition of bone resorption</p> <p>R 1 position: affinity to bone (bone hook)</p> |
| 1 | 10 | 10 |
| 500 | 2000 | 1000 |
| 100 | 10000 | |

American Society of Clinical Oncology Guideline on the Role of Bisphosphonates in Breast Cancer

By Bruce E. Hillner, James N. Ingle, James R. Berenson, Nora A. Janjan, Kathy S. Albain, Allan Lipton, Gary Yee,
J. Sybil Biermann, Rowan T. Chlebowski, and David G. Pfister
for the American Society of Clinical Oncology Bisphosphonates Expert Panel*



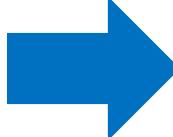
Denosumab Binds to RANK Ligand to Break the Vicious Cycle of Bone Destruction and Tumor Growth in Metastatic Bone Disease



Adapted from Roodman GD. *N Engl J Med* 2004;350:1655-64,
Mundy GR. *Nat Rev Cancer* 2002;2:584-93;
McClung MR, Lewiecki EM, Cohen SB, et al. *N Engl J Med* 2006;354:821-31.

AMGEN®

Background

 **Bisphosphonates are the standard of care for bone metastases**

Hillner BE, et al. *J Clin Oncol* 2003;21:4042-4057

- **Bisphosphonates can prevent CTIBL in breast cancer**
 - ABCSG-12, Z/ZO-FAST, ARIBON, SABRE, IBIS-II, etc.
- **Bisphosphonates preclinically demonstrate anticancer activity**
 - Inhibit cancer cell proliferation, adhesion, and invasion; inhibit angiogenesis
 - Synergy with cytotoxic chemotherapy; induce cancer cell apoptosis
 - Activate anticancer immune responses (eg, γ δ T cells)
 - Modify the bone marrow microenvironment

Gnant M, et al. *Lancet Oncol* 2008;9:840-849

Brufsky AM, et al. *Clin Breast Cancer* 2009;9:77-85

Lester JE, et al. *Clin Cancer Res* 2008;14:6336-6342

Van Poznak C, et al. *J Clin Oncol* 2010;28:967-975

- **Adjuvant zoledronic acid improved outcomes in early breast cancer**
 - ABCSG-12, Z/ZO-FAST

Gnant M, et al. *N Engl J Med* 2009;360:679-691

Eidtmann H, et al. *Ann Oncol*. 2010 May 5. [Epub ahead of print]

- **Bisphosphonates reduce breast cancer risk in healthy women**
 - WHI, BCINIS, Wisconsin

Newcomb P, et al. *British Journal of Cancer* (2010) 102, 799 – 802

Rennert G, et al. *SABCS 2009*. Abstract 27

Chlebowski R, et al. *SABCS 2009*. Abstract 21

- **Bisphosphonates improve survival in various tumor entities**
 - Lung cancer, bladder cancer, and multiple myeloma

Zarogoulidis K, et al. *Int J Cancer*. 2009;125(7):1705-1709.

Zaghoul MS, et al. *Int J Clin Oncol*. 2010 Apr 1. Epub ahead of print.

Avilés A, et al. *Med Oncol*. 2007;24(2):227-230.

Morgan G, et al. *J Clin Oncol*. 2010;28:7s. (suppl; abstract 8021).

- **AZURE overall shows no difference**
 - Significant Overall Survival and Relapse-Free Survival Benefits in postmenopausal subgroup

Coleman, R, et al. *SABCS 2010*

RUOLO DEI BISFOSFONATI NEL CARCINOMA DELLA MAMMELLA CON METASTASI OSSEE

- Prevenire SRE
- Ridurre l'incidenza di nuovi SRE
- Prolungare il tempo di insorgenza del primo e dei successivi SRE

Una metanalisi ha analizzato il ruolo dei bisfosfonati:

- 9 studi (2806 pazienti) che confrontavano l'efficacia dei bisfosfonati vs placebo
- **Bisfosfonati riducono del 15% il rischio di insorgenza di SRE.**

| Bifosfonato | Studio | RR per CS (CI 95%) | RRR per CS (%) | %Tempo di comparsa CS (no. giorni vs placebo) |
|--------------------------------------|---|--------------------|----------------|---|
| Ac zoledronico | Kohono et al (10) | 0.59 (0.42,0,82) | 41% | 110 % (NR vs 52) |
| Pamidronato | Hortobagyi et al (5) Theriault et al (6) | 0.77 (0.69-0.87) | 33 % | 39 % (21.0 vs 15.1) |
| Ibandronato ev | Body et al. (7) | 0.80 (0.67-0.96) | 20 % | 53 % (11.8 vs 7.7) |
| Ibandronato os | Body et al (8) | 0.86 ((0.73-0.02) | 14 % | 39 % (90.3 vs 64.9) |
| Clodronato | Kristensen (3) | 0.69 (040-1.20) | 31 % | |
| Clodronato | Paterson et al (9) | 0..83 (0.68-1.02) | 17 % | 2% (9.9 vs 4.9) |
| Clodronato | Tubiana -Hullin et al (4) | 0.92 (0.92-1.19) | 8 % | 36% (8.7 vs 6.4) |
| Metanalisi di tutti gli studi | | 0. 85 (0.77-0.94) | 15% | |

Cochrane database comparing placebo-controlled trials in breast cancer setting

IV, intravenous; mBC, metastatic breast cancer; PAM, pamidronate; SRE, skeletal-related event; ZOL, zoledronic acid.

Adapted from Pavlakis N, et al. Cochrane Database Syst Rev. 2005;CDC003474.

BIFOSFONATI NEL CARCINOMA DELLA MAMMELLA E METASTASI OSSEE

| BISFOSFONATI | Classe | Via* | Dose | Frequenza |
|----------------|---------------------|------|--------|---------------|
| Clodronato | Non N-BP | OS | 800 mg | 2 cp/die |
| | | I.V. | 900mg | 3-4 settimane |
| Pamidronato | N-BP 2° generazione | I.V. | 90 mg | 3-4 settimane |
| Ibandronato | N-BP 2° generazione | OS | 50 mg | 1cp/die |
| | | I.V | 6 mg | 3-4 settimane |
| Ac zoledronico | N-BP 3° generazione | I.V | 4 mg | 3-4 settimane |

* La somministrazione per os dei BP necessita, per un adeguato assorbimento, che vengano assunti al mattino a digiuno solo con acqua e venga rispettato il digiuno per circa un'ora in stazione eretta. La somministrazione endovenosa per clodronato e pamidronato richiede un tempo di infusione di 2 ore. Per ac zoledronico ed ibandronato infusione per 15 minuti.

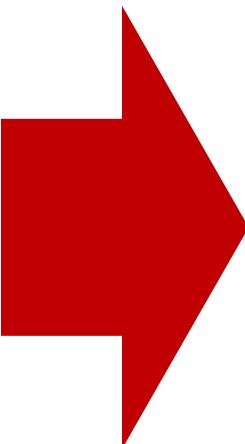


Pavlakis N , Schmidt RL et al « Bisphonates for breast cancer. Cochrane database of Systematic review 2005»
Ross JR et al « Systematic review of role of bisphonates on skeletal morbidity in metastatic cancer». BMJ 2003
Wong et al « Bisphonates and other bone agents for breast cancer» Cochrane Database Syst Rev 2012

| Qualità dell'evidenza SIGN | Raccomandazione clinica | Forza della raccomandazione clinica |
|----------------------------|--|-------------------------------------|
| MOLTO BASSA | <p>La terapia target all'osso dovrebbe essere iniziata al momento dell'evidenza <u>radiologica</u> di metastasi ossee in assenza di sintomi.</p> <hr/> | <p>Positiva forte</p> |

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

| Qualità dell'evidenza SIGN | Raccomandazione clinica | Forza della raccomandazione clinica |
|----------------------------|---|-------------------------------------|
| MOLTO BASSA | Si raccomanda di monitorare la funzionalità renale durante il trattamento con BP per via endovenosa. | Positiva forte |
| MOLTO BASSA | Nei pazienti con funzionalità renale compromessa si consiglia di iniziare il trattamento con acido zoledronico con adeguate riduzioni della dose (mai con una creatinina clearance sotto i 30 mL/min). | Positiva forte |
| MOLTO BASSA | Nel caso sia necessario interrompere la terapia con acido zoledronico a causa di insufficienza renale severa, il trattamento può essere ripreso quando i livelli di creatininemia rientrano entro una variazione di non più del 10% dei valori normali. | Positiva forte |
| MOLTO BASSA | In corso di trattamento con BP per via endovenosa è necessario monitorare i pazienti per segni e sintomi di sbilancio degli elettroliti. | Positiva forte |
| MOLTO BASSA | In corso di terapia con denosumab vanno monitorati i livelli di calcemia basale e dopo le prime infusioni | Positiva forte |
| BASSA | In corso di terapia con bisfosfonati e soprattutto con denosumab i pazienti dovrebbero ricevere una supplementazione giornaliera di vit. D e di calcio. Mediamente la dose di mantenimento in corso di terapia con inibitori del riassorbimento osseo è tra 1000-4000 UI /die | Positiva forte |

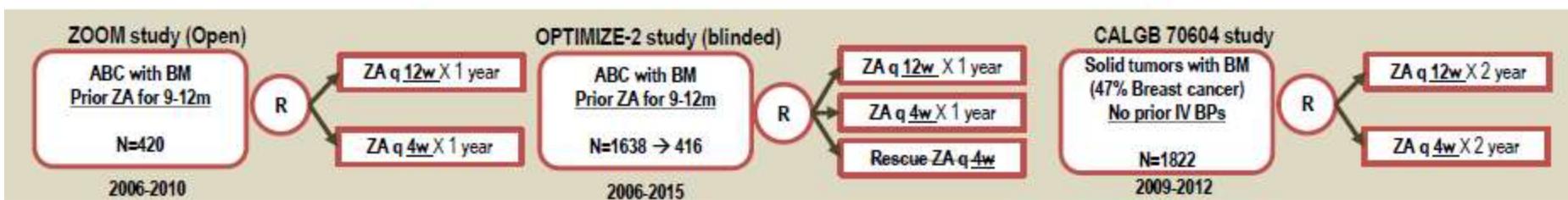




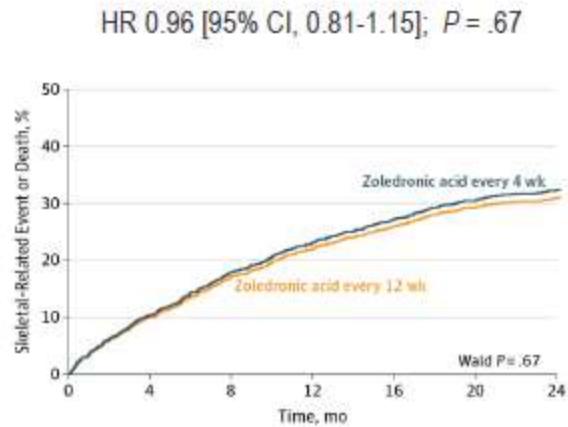
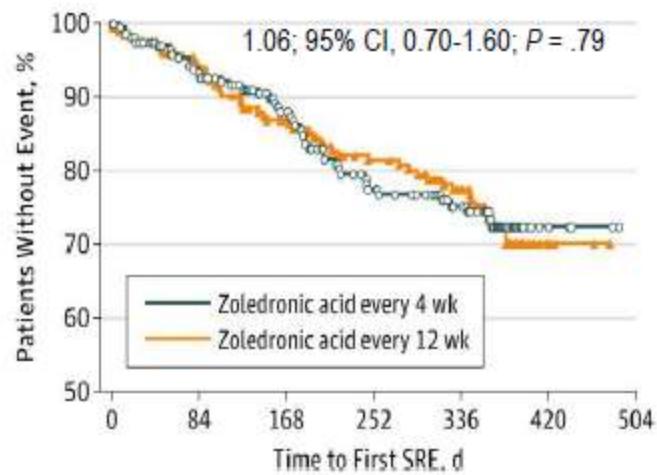
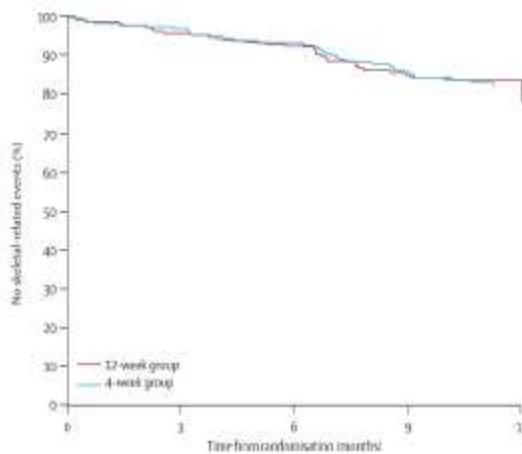
ESISTE UNA DOSE E UNA SCHEDULA OTTIMALE DA UTILIZZARE NELLA MALATTIA METASTATICA ?



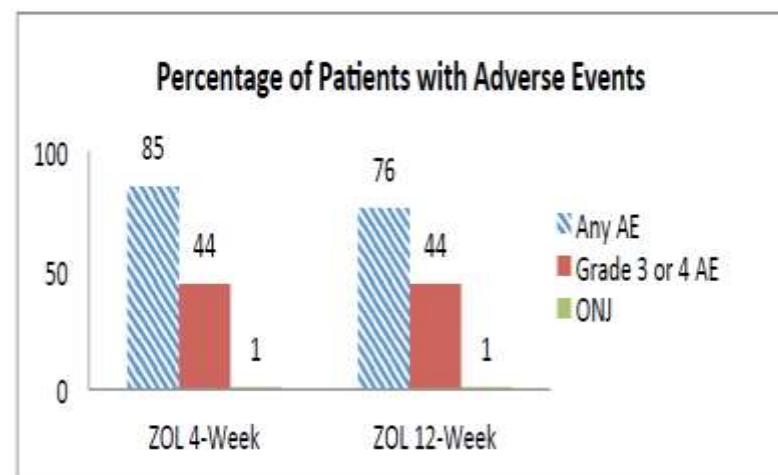
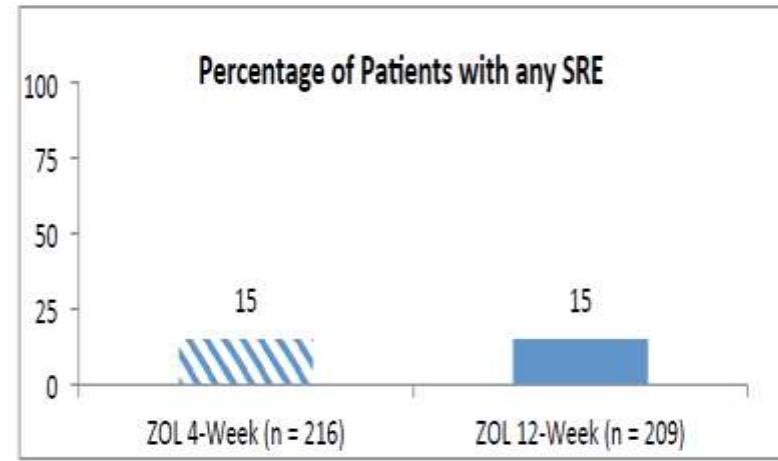
Optimal interval of ZA: 3-monthly vs. monthly



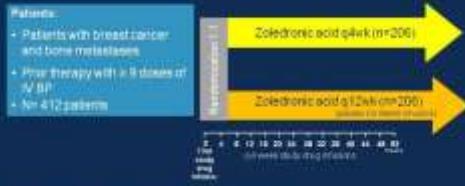
| | ZOOM | | OPTIMIZE-2 | | CALGB 70604 | |
|----------|------------------|------------------|-----------------|---------|-----------------|---------|
| | <u>ZA q 12w</u> | ZA q 4w | <u>ZA q 12w</u> | ZA q 4w | <u>ZA q 12w</u> | ZA q 4w |
| N | 209 | 216 | 203 | 200 | 911 | 911 |
| Mean SMR | 0.26 (0.15-0.37) | 0.22 (0.14-0.29) | 0.58 | 0.46 | 0.4 | 0.4 |
| SRE | 15% | 15% | 23.2% | 22.0% | 29 % | 30 % |



| ZOOM | |
|---------------------|------------------------------------|
| Patient population | Breast cancer |
| Study design | Randomized, open-label |
| Medication | Zoledronic acid |
| Dose | 4mg q 4 weeks vs 4mg q 12 weeks |
| Length of follow-up | 1 year |
| Result | Non-inferior |



Final OPTIMIZE-2 study design



Presented By Gabriel Hortobagyi at 2014 ASCO Annual Meeting

OPTIMIZE-2

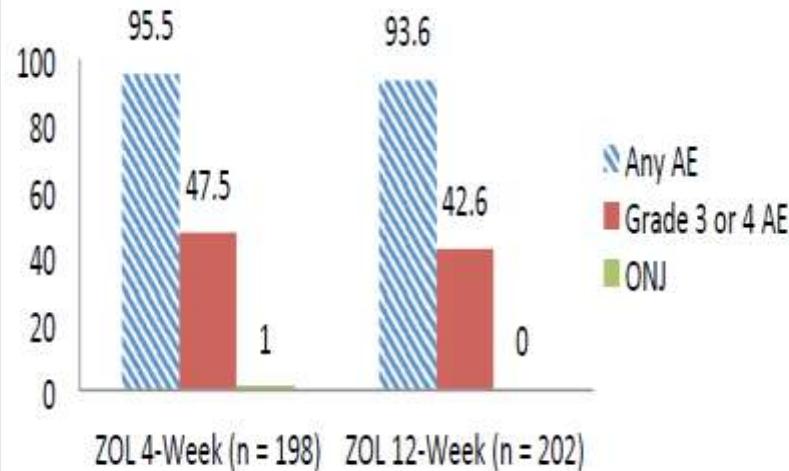
| | |
|---------------------|------------------------------------|
| Patient population | Breast cancer |
| Study design | Randomized, double-blind |
| Medication | Zoledronic acid |
| Dose | 4mg q 4 weeks vs 4mg q 12 weeks |
| Length of follow-up | 1 year |
| Result | Non-inferior |

Percentage of Patients With Any SRE



SRE = skeletal related event, ZOL = zoledronic acid

Percentage of Patients with Adverse Events



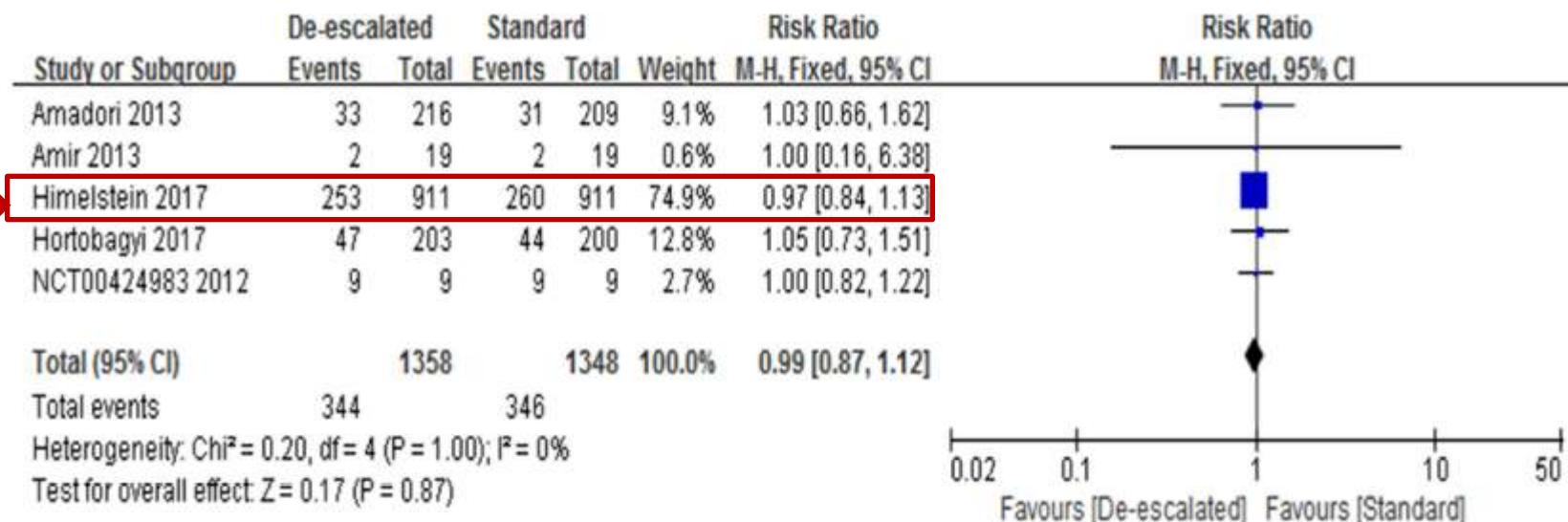
ZOL = zoledronic acid

FULL TEXT

JAMA Oncology

Is De-escalated Bisphosphonates Therapy a Suitable Alternative to Standard Dosing in Malignant Tumor Patients With Bone Metastases: A Systematic Review and Meta-Analysis

Qiuhua Luo ^{1†}, Peng Men ^{2†}, Zhiyong Liu ³, Suodi Zhai ^{2*} and Mingyan Jiang ^{1*}

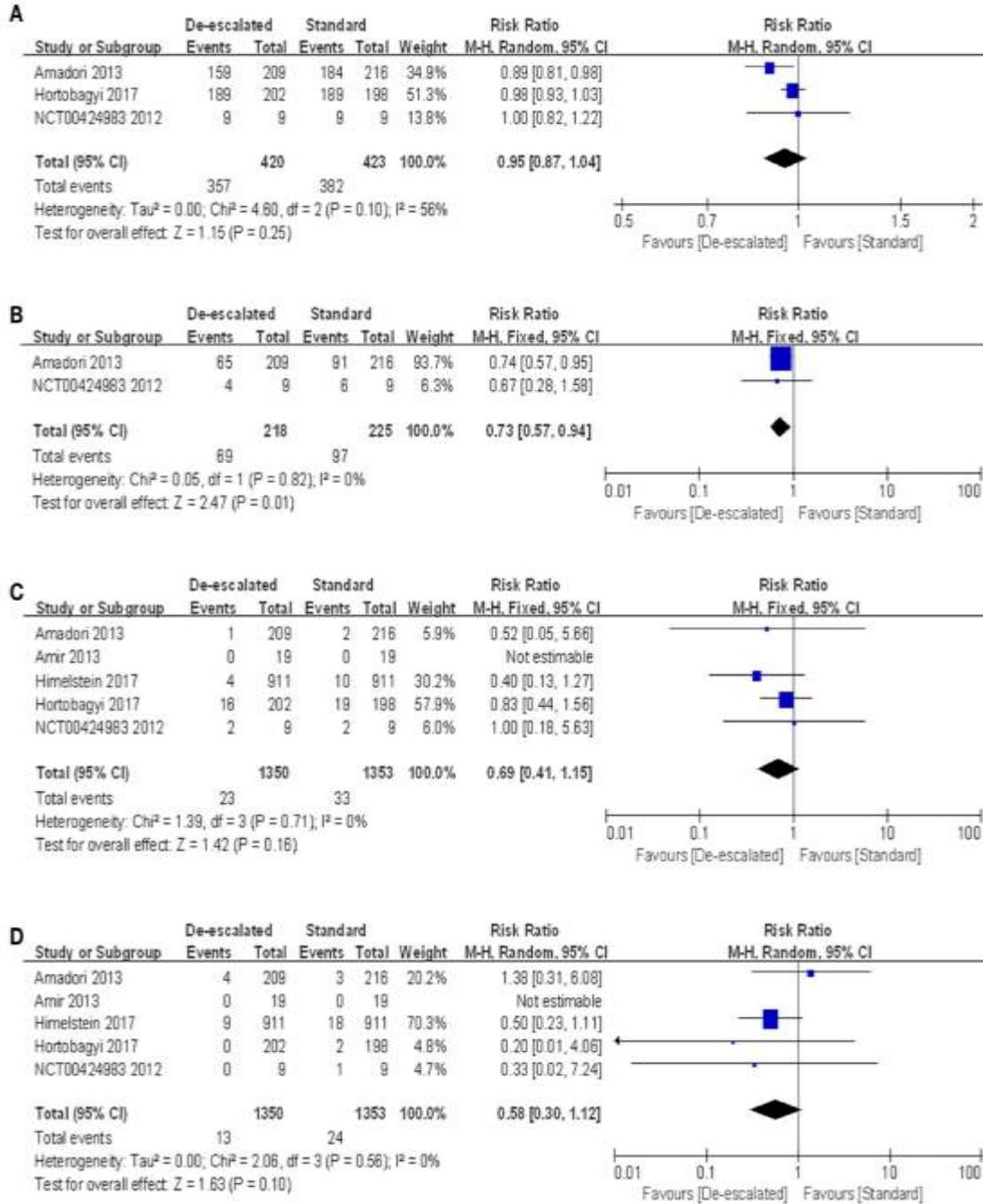


AEs

GASTROINTESTINAL DISORDERS

RENAL DYSFUNCTION

ONJ



Open Access Full Text Article

ORIGINAL RESEARCH

Efficacy and safety of de-escalation bone-modifying agents for cancer patients with bone metastases: a systematic review and meta-analysis

Table 2 Meta-analysis results for end points

| Study | BTAs | Outcomes (12-weekly/4-weekly dosage regimen) | | | | | | | | | | | | | | | |
|---------------------------------------|-------------|--|---------|---------------------|-------------|---------------------|-----------|--------------------------|-------------------|---------------------|--|---------------------|--|---------------------|--|---------------------|--|
| | | Total | SRE | AEs | Serious AEs | Bone pain | Renal AEs | Osteonecrosis of the jaw | Radiation to bone | uNTx | | | | | | | |
| Amadori et al (2013) ¹⁸ | Zoledronate | 209/216 | 31/33 | 159/184 | 21/29 | 11/13 | 1/2 | 4/3 | NA | NA | | | | | | | |
| Himelstein et al (2017) ¹⁹ | Zoledronate | 911/911 | 253/260 | NA | NA | NA | 4/10 | 9/18 | NA | NA | | | | | | | |
| Hortobagyi et al (2017) ²⁰ | Zoledronate | 203/200 | 47/44 | 189/189 | 51/50 | NA | 16/19 | 0/2 | 23/29 | NA | | | | | | | |
| Amir et al (2013) ²² | Pamidronate | 19/19 | 2/2 | NA | 1/2 | NA | 0/0 | 0/0 | 2/2 | NA | | | | | | | |
| Addison et al (2014) ²¹ | Pamidronate | 17/13 | 4/3 | NA | NA | NA | NA | NA | NA | NA | | | | | | | |
| Fizazi et al (2009) ²⁴ | Denosumab | 36/38 | 4/2 | NA | NA | NA | NA | NA | NA | 23/26 | | | | | | | |
| Lipton et al (2007) ²³ | Denosumab | 43/43 | 4/6 | NA | NA | NA | NA | 0/0 | NA | NA | | | | | | | |
| Lipton et al (2008) ²⁵ | Denosumab | 43/43 | NA | 41/40 | 15/16 | 4/6 | NA | NA | NA | 32/34 | | | | | | | |
| RR from meta-analysis with 95% CI | | 0.98 (0.87–1.12) | | 0.96 (0.89–1.04) | | 0.91 (0.70–1.17) | | 0.81 (0.42–1.55) | | 0.67 (0.39–1.16) | | 0.58 (0.30–1.12) | | 0.80 (0.49–1.30) | | 0.90 (0.75–1.08) | |
| β measure of heterogeneity | | 0% | | 66% | | 0% | | 0% | | 0% | | 0% | | 0% | | | |

Abbreviations: AEs, adverse events; BTAs, bone-targeting agents; NA, not available; RR, risk ratio; SRE, skeletal-related events; uNTx, urinary N-telopeptide.

ZOOM

OPTIMIZE-2

CALGB 70604

- **NON INFERIORITA'**
- **APERTI**
- **NON A DOPPIO CIECO**

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

Stopeck AT, Lipton A, Body JJ, et al. *J Clin Oncol* 2010;28:5132-9.

Martín M, Bell R, Bourgeois H, et al. *Clin Cancer Res* 2012;18:4841-9.

Cleeland CS, Body JJ, Fallowfield L, et al. *Cancer* 2013;119:832-8.

Stopeck AT, Fizazi K, Body JJ, et al. *Support Care Cancer* 2016;24:447-55.

Lipton A, Smith MR, Fizazi K, et al. *Clin Cancer Res* 2016;22:5713-21.

Additional meeting abstracts, posters and oral presentations.

Study Design: International, Randomized, Double-Blind, Active-Controlled Study

Key inclusion criteria:

- Patients aged ≥ 18 years with
- Histologically or cytologically confirmed breast adenocarcinoma
- Evidence of 1 or more bone metastases
- Adequate organ function
- ECOG PS 0, 1, or 2

Key exclusion criteria:

- Current or prior IV BP treatment

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Denosumab 120 mg SC and
Placebo IV* Q4W
(n=1026)

Zoledronic acid 4 mg IV* and
Placebo SC Q4W
(n=1020)

Recommended: Daily supplementation with calcium (≥ 500 mg) and vitamin D (≥ 400 U)

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Primary Endpoint: Time to first on-study skeletal-related event (SRE) (non-inferiority)

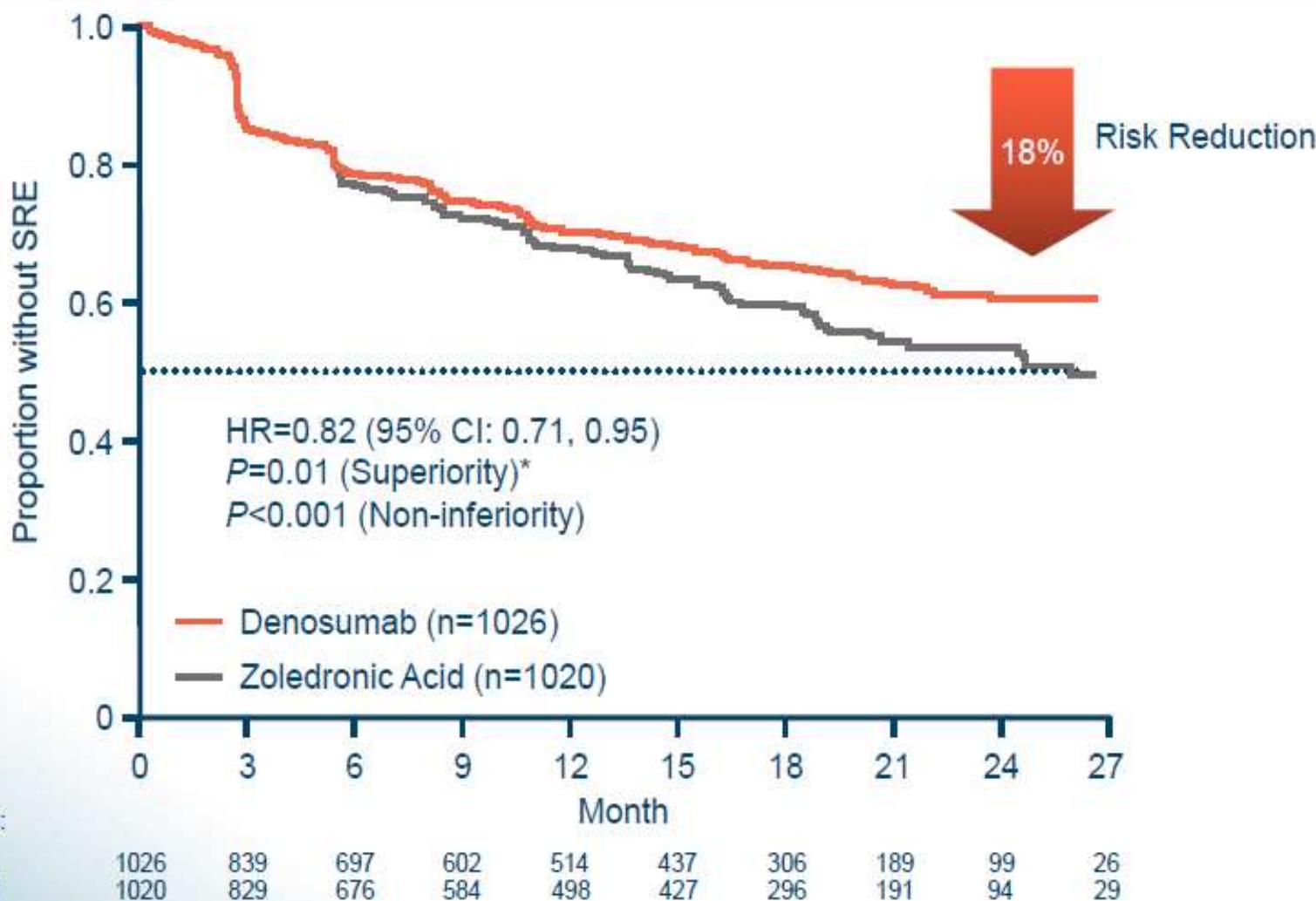
Secondary : Time to first on-study SRE (superiority), time to first and subsequent on-study SRE(s) (multiple event analysis)

*Per protocol and Zometa® label, IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine; No SC dose adjustments made due to increased serum creatinine.

BP=bisphosphonate; ECOG PS=Eastern Cooperative Oncology group performance status; IV=intravenous; Q4W=every 4 weeks; SC=subcutaneous; SRE=skeletal-related event.

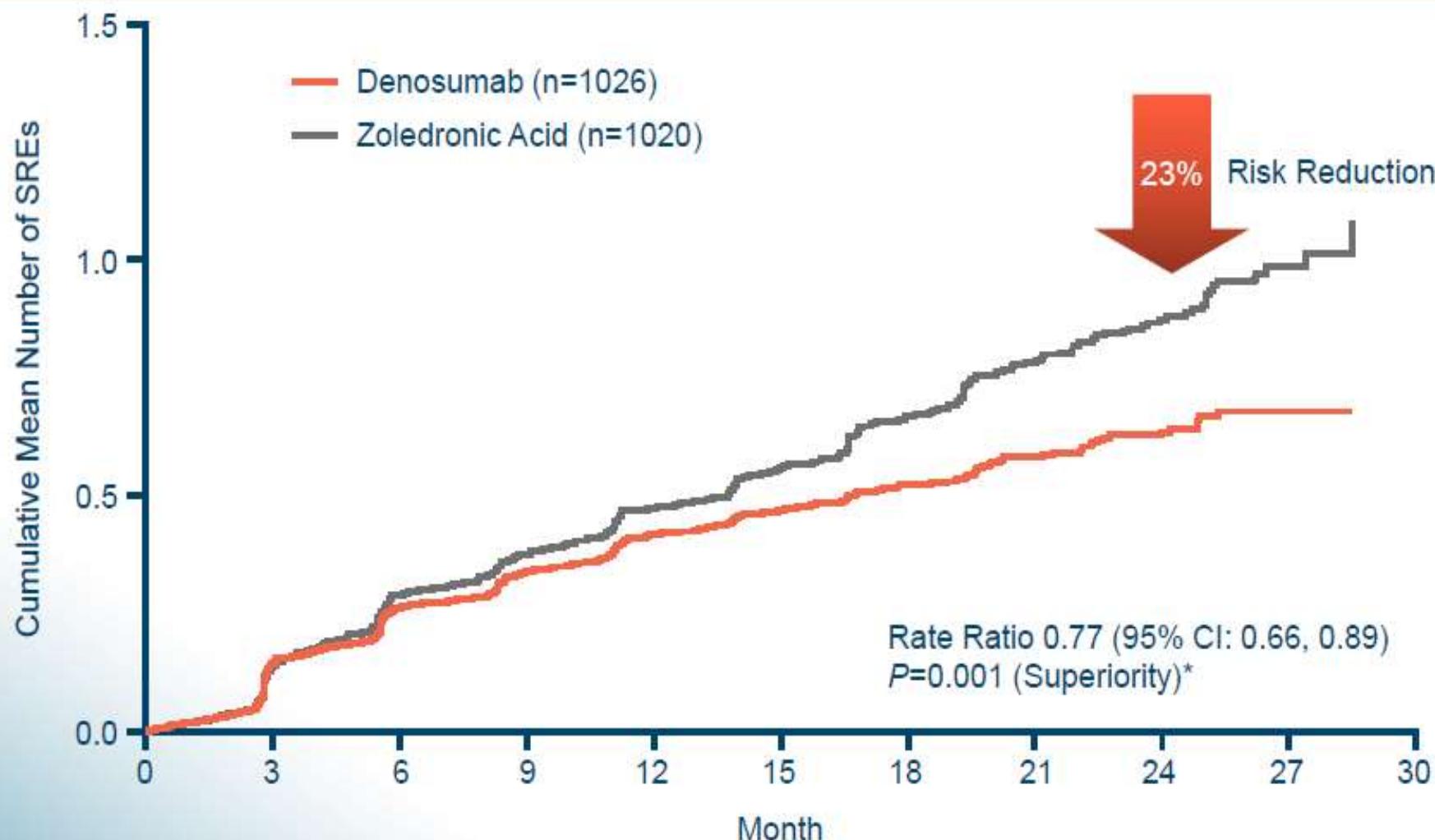
Adapted from Stopeck AT, Lipton A, Body JJ, et al. J Clin Oncol 2010;28:5132-9.

Primary Endpoint: Time to First On-Study SRE



*Adjusted for multiplicity. CI=confidence interval; HR=hazard ratio.
Stopeck AT, Lipton A, Body JJ, et al. J Clin Oncol 2010;28:5132-9.

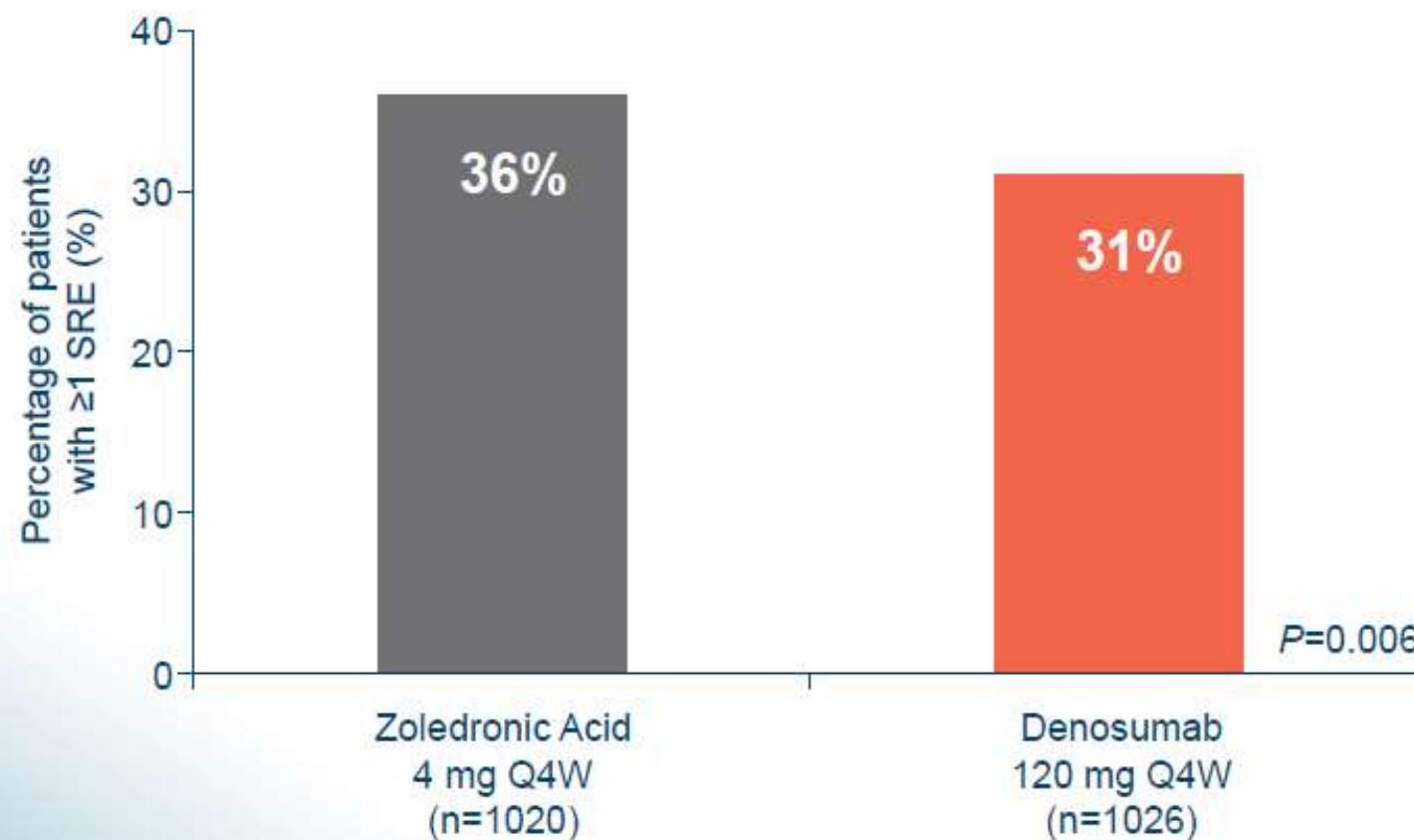
Time to First and Subsequent SREs



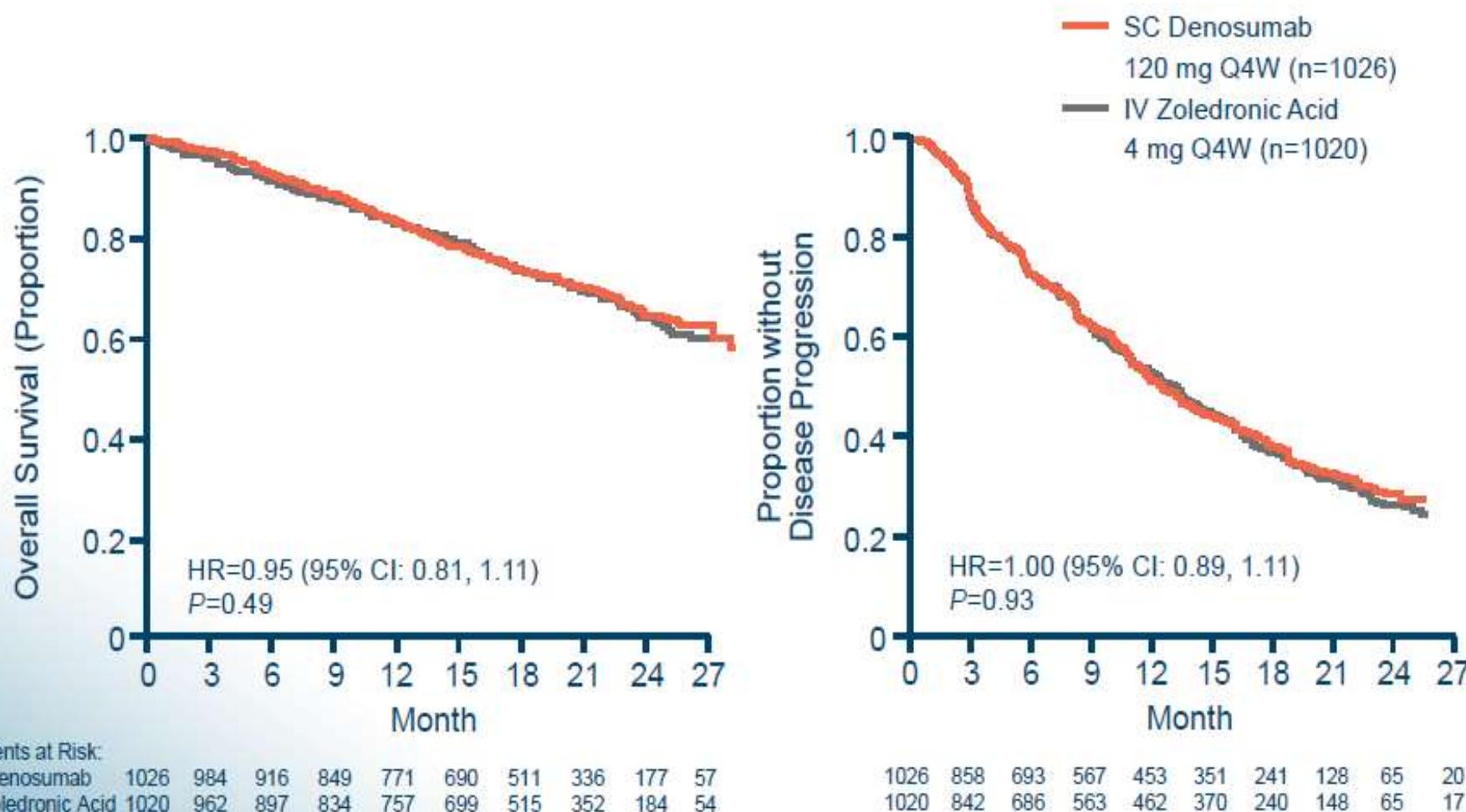
*Adjusted for multiplicity.

Stopeck AT, Lipton A, Body JJ, et al. *J Clin Oncol* 2010;28:5132-9.

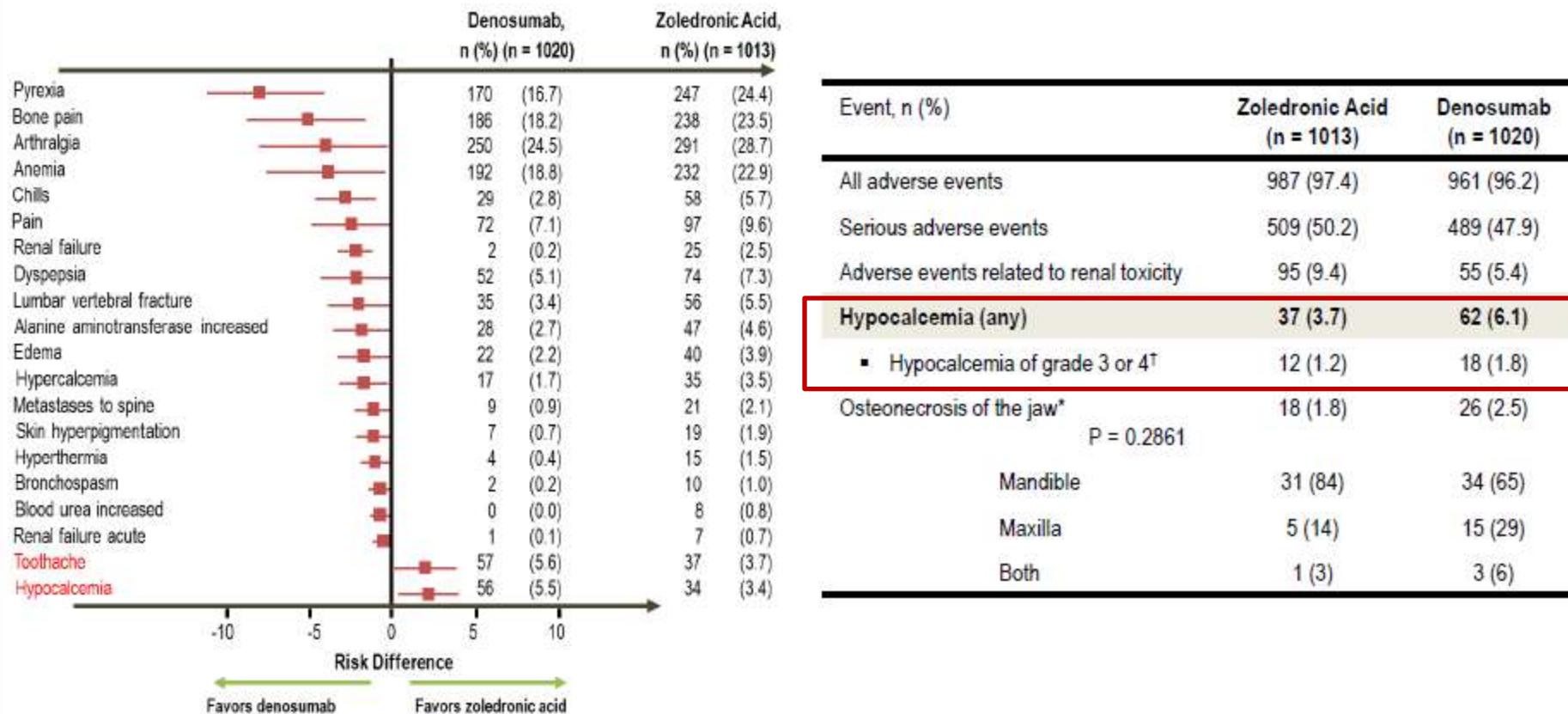
Proportion of Patients With at Least 1 On-Study SRE



Overall Survival and Disease Progression

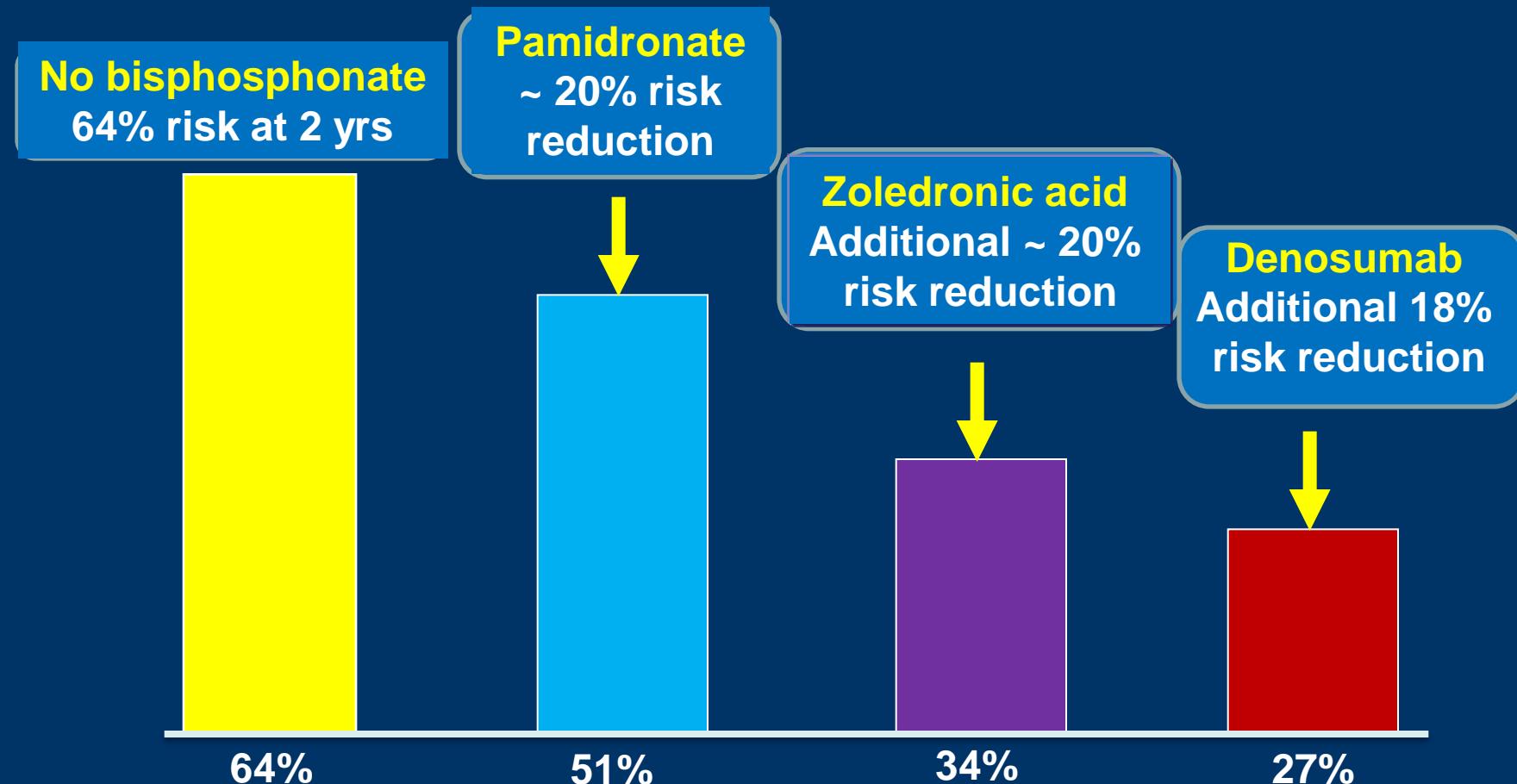


Bisphosphonate vs. denosumab



- No difference in OS and DFS

SKELETAL COMPLICATION RISK: INCREMENTAL BENEFITS IN BREAST CANCER



Lipton A, et al. Cancer. 2000;88:3033-3037. Rosen LS, et al. Cancer. 2003;100:36-43. Stopeck A, et al. ECCO/ESMO 2009. Abstract 2LBA. Stopeck AT, et al. J Clin Oncol. 2010;28:5132-5139.

Open Access Full Text Article

ORIGINAL RESEARCH

Efficacy and safety of de-escalation bone-modifying agents for cancer patients with bone metastases: a systematic review and meta-analysis

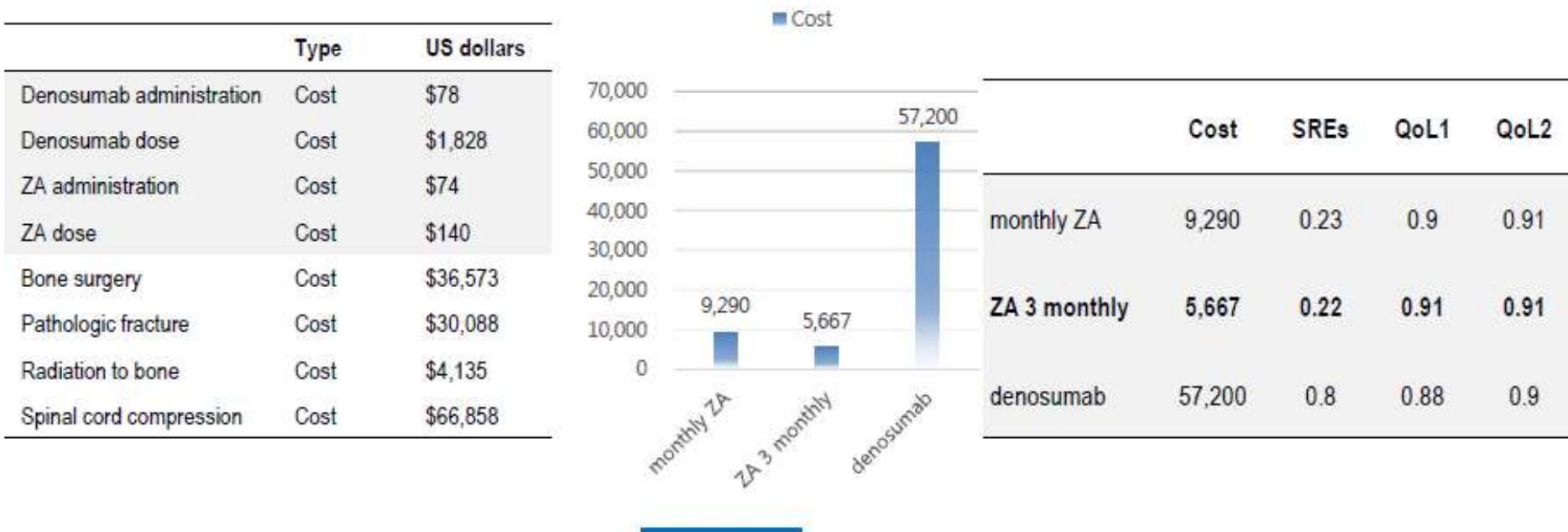
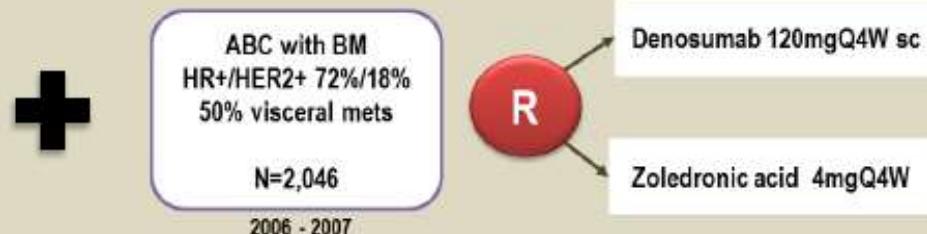
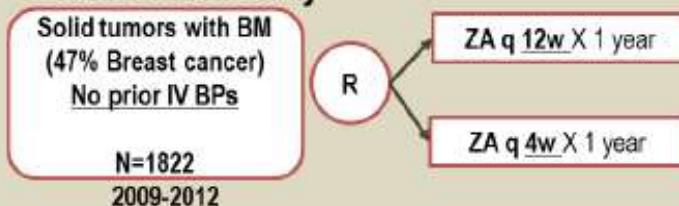
Table 2 Meta-analysis results for end points

| Study | BTAs | Outcomes (12-weekly/4-weekly dosage regimen) | | | | | | | | |
|---------------------------------------|-------------|--|---------------------|---------------------|---------------------|---------------------|---------------------|--------------------------|---------------------|-------|
| | | Total | SRE | AEs | Serious AEs | Bone pain | Renal AEs | Osteonecrosis of the jaw | Radiation to bone | uNTx |
| Amadori et al (2013) ¹⁸ | Zoledronate | 209/216 | 31/33 | 159/184 | 21/29 | 11/13 | 1/2 | 4/3 | NA | NA |
| Himelstein et al (2017) ¹⁹ | Zoledronate | 911/911 | 253/260 | NA | NA | NA | 4/10 | 9/18 | NA | NA |
| Hortobagyi et al (2017) ²⁰ | Zoledronate | 203/200 | 47/44 | 189/189 | 51/50 | NA | 16/19 | 0/2 | 23/29 | NA |
| Amir et al (2013) ²² | Pamidronate | 19/19 | 2/2 | NA | 1/2 | NA | 0/0 | 0/0 | 2/2 | NA |
| Addison et al (2014) ²¹ | Pamidronate | 17/13 | 4/3 | NA | NA | NA | NA | NA | NA | NA |
| Fizazi et al (2009) ²⁴ | Denosumab | 36/38 | 4/2 | NA | NA | NA | NA | NA | NA | 23/26 |
| Lipton et al (2007) ²³ | Denosumab | 43/43 | 4/6 | NA | NA | NA | NA | 0/0 | NA | NA |
| Lipton et al (2008) ²⁵ | Denosumab | 43/43 | NA | 41/40 | 15/16 | 4/6 | NA | NA | NA | 32/34 |
| RR from meta-analysis with 95% CI | | 0.98 (0.87–1.12) | 0.96 (0.89–1.04) | 0.91 (0.70–1.17) | 0.81 (0.42–1.55) | 0.67 (0.39–1.16) | 0.58 (0.30–1.12) | 0.80 (0.49–1.30) | 0.90 (0.75–1.08) | |
| β measure of heterogeneity | | 0% | 66% | 0% | 0% | 0% | 0% | 0% | 0% | |

Abbreviations: AEs, adverse events; BTAs, bone-targeting agents; NA, not available; RR, risk ratio; SRE, skeletal-related events; uNTx, urinary N-telopeptide.

Cost-effectiveness: ZA vs. denosumab

CALGB 70604 study



ASCO : no superiority among BMAs against the others

La nuova schedula di Acido Zoledronico ogni 3 mesi upfront nei tumori della mammella, prostata e il mieloma multiplo, con i limiti dell'unico studio disponibile oggi riportati sopra, potrebbe rappresentare 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.

GRAZIE PER LA VOSTRA ATTENZIONE

A photograph of an underwater scene. A scuba diver in dark gear is swimming towards the right side of the frame. Sunlight filters down from the surface in bright rays, illuminating a coral reef structure. Several small, colorful tropical fish are scattered throughout the scene, some near the top left and others near the center.

Exploring uncharted territories—
bringing advances in oncology to light