# MASCC/ISOO 2019

ANNUAL MEETING · SAN FRANCISCO

**21-23 JUNE 2019**

Supportive Care Makes Excellent Cancer Care Possible #MASCC19

***Epidemiology of Bone Health Issues in Patients With Cancer***

*Invited Speaker:* Beatrice Edwards, USA

14:05 - 14:25

***Functional and Psychosocial Consequences of Fractures***

*Invited Speaker:* Nelson Watts, USA

14:25 - 14:45

***Clinical Guidelines for the Management of Bone Health in Patients With Cancer***

*Invited Speaker:* Matti Aapro, Switzerland

14:45 - 14:55

***EFFECT OF FRACTURES ON OVERALL SURVIVAL IN CANCER PATIENTS: THE NHANES DATABASE***

*Speaker:* B. Edwards, USA

14:55 - 15:05

***PAIN FLARE-EFFECT PROPHYLAXIS WITH CORTICOSTEROIDS ON BONE RADIOTHERAPY TREATMENT: A SYSTEMATIC REVIEW***

*Speaker:* C. Fabregat Franco, Spain

# Clinical Guidelines for the Management of Bone Health in Patients With Cancer

*Matti S. Aapro*
*Cancer Center*
*Genolier*
*Switzerland*

# COI

Dr Aapro is/was a consultant for

Accord, Amgen, BMS, Celgene, Clinigen, Eisai, Genomic Health, G1, GSK, Helsinn, Hospira, JnJ, Novartis, Merck, Merck Serono, Pfizer, Pierre Fabre, Roche, Sandoz, Tesaro,Teva, Vifor

and has received honoraria for lectures at symposia of

Accord, Amgen, Angelini, Bayer Schering, Biocon, Cephalon, Chugai, DRL, Eisai, Genomic Health, Glenmark, GSK, Helsinn, Hospira, Ipsen, JnJ OrthoBiotech, Kyowa Hakko Kirin, Merck, Merck Serono,Mundipharma, Novartis, Ono Pharmaceuticals, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Tesaro, Taiho, Teva, Vifor

No responsibility accepted for involuntary errors or omissions.
The list may be incomplete, and does not reflect consultancy for NGOs, Universities, Governmental agencies, and others

# WHOM TO THANK?

Laura Biganzoli

**Jean-Jacques Body**

Robert Coleman

Luis Costa

Ingo Diel

Michael Gnant

Peyman Hadji

Juan Morote

Trevor Powles

Tiina Saarto

And many others

# Accepted Manuscript


General and Supportive Care

Bone health in the elderly cancer patient: a SIOG Position Paper

J.J. Body, E. Terpos, B. Tombal, P. Hadji, A. Arif, A. Young, M. Aapro, R. Coleman

PII: S0305-7372(16)30104-9
DOI: http://dx.doi.org/10.1016/j.ctrv.2016.10.004
Reference: YCTRV 1560

To appear in: *Cancer Treatment Reviews Cancer Treatment Reviews*

Received Date: 17 October 2016
Accepted Date: 19 October 2016

Please cite this article as: Body, J.J., Terpos, E., Tombal, B., Hadji, P., Arif, A., Young, A., Aapro, M., Coleman, R., Bone health in the elderly cancer patient: a SIOG Position Paper, *Cancer Treatment Reviews Cancer Treatment Reviews* (2016), doi: http://dx.doi.org/10.1016/j.ctrv.2016.10.004

# The menu

- Which guidelines, why?
- Messages from guidelines
- To conclude

# The menu

- **Which guidelines, why?**
- Messages from guidelines
- To conclude

# A HUGE THANKS TO

## Jim Koeller, MS

**Professor of Medicine, Oncology & Pharmacy**

**University of Texas at Austin & the Health Science Center, San Antonio**

# Goals of Guidelines

- To provide a framework and thought process for specific patient management
  - Should result in decreased variation
- Evaluate available evidence (establishing the quality and degree of concurrence by expert reviewers) and provide recommendations based of it
- Can provide expert ‘opinion’ when evidence is missing (based on guideline intent)

# CRITERIA FOR TRUSTWORTHY GUIDELINES

## The Institute of Medicine (IOM) Report 2011

### Trustworthy Clinical Practice Guidelines

According to the Institute of Medicine's clinical practice guidelines report, trustworthy guidelines should:

- Be based on a systematic review of the existing evidence
- Be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups
- Consider important patient subgroups and patient preferences, as appropriate
- Be based on an explicit and transparent process that minimizes distortions, biases, and conflicts of interest
- Provide a clear explanation of the logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of recommendations
- Be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations ■

**Reference:** Committee on Standards for Developing Trustworthy Clinical Practice Guidelines: Clinical Practice Guidelines We Can Trust. Washington, DC; Institute of Medicine, 2011.

See: www.iom.edu, *The ASCO Post,* Sept 15, 2011

# Proliferation Of GUIDELINES
## - Approaches to Guidelines Development -

- Evidence-based (expert panel)
  - ESMO; MASCC; ASCO ( international relevance )
- Consensus-based (opinion-expert panel)
  - NCCN ( should be only US but…)
- Economically-based

# The menu

- Which guidelines, why?
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# BONE…
# CANCER and ITS TREATMENT

LET US NOT FORGET
THE BACKGROUND

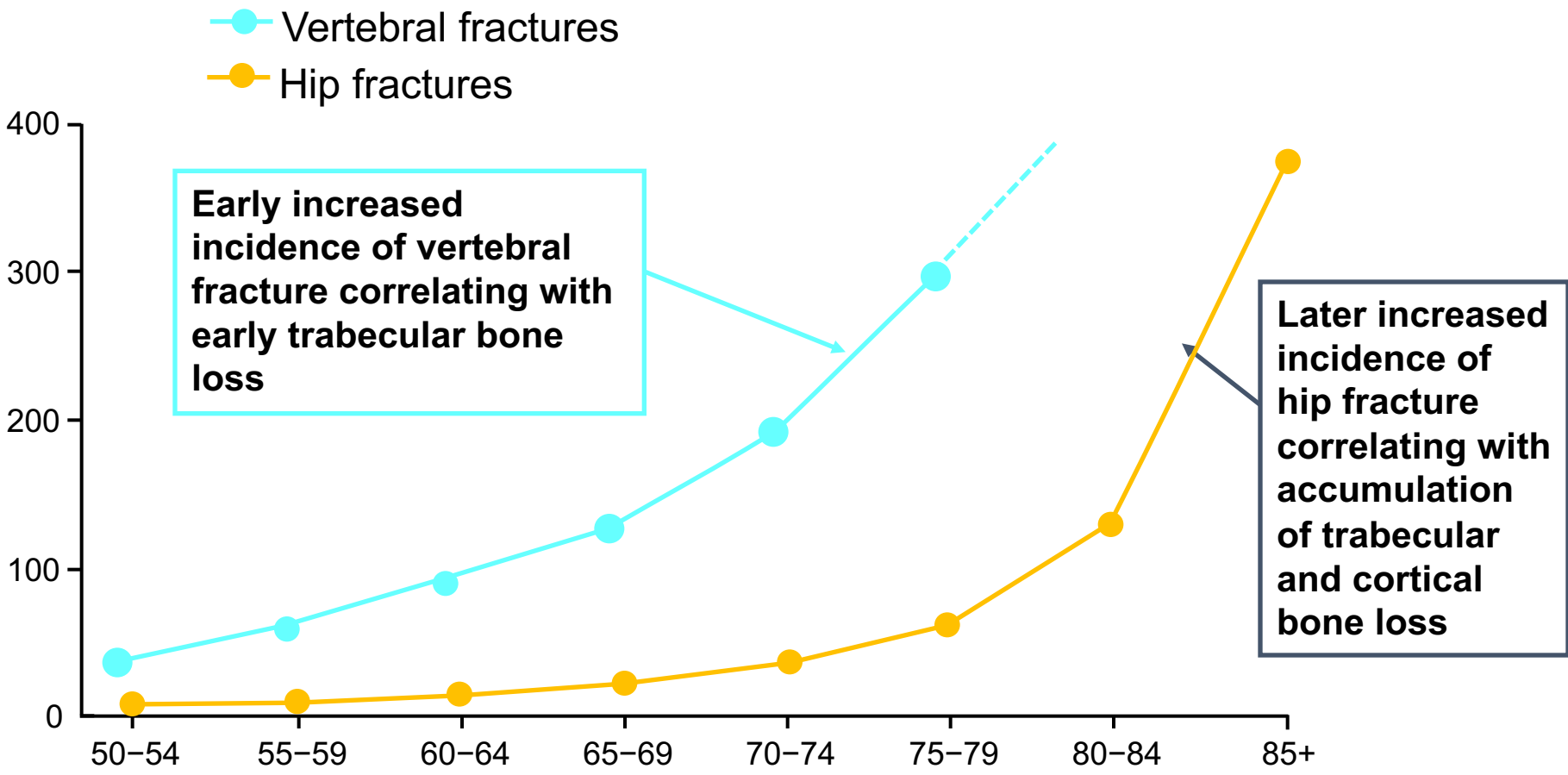
# Lifetime of osteoporosis related skeletal events:

| | Women | Men |
|---|---|---|
| Osteoporotic fracture[1,2] | 46-53% | 21-22% |
| Hip fracture[2,3] | 15-23% | 5-11% |
| Radiographic vertebral fracture[4] | 27% | 11% |
| Clinical vertebral fracture[2] | 15% | 8% |
| Breast cancer | 10-13% | |
| Prostate cancer | | 9-11% |

NB: variable between countries

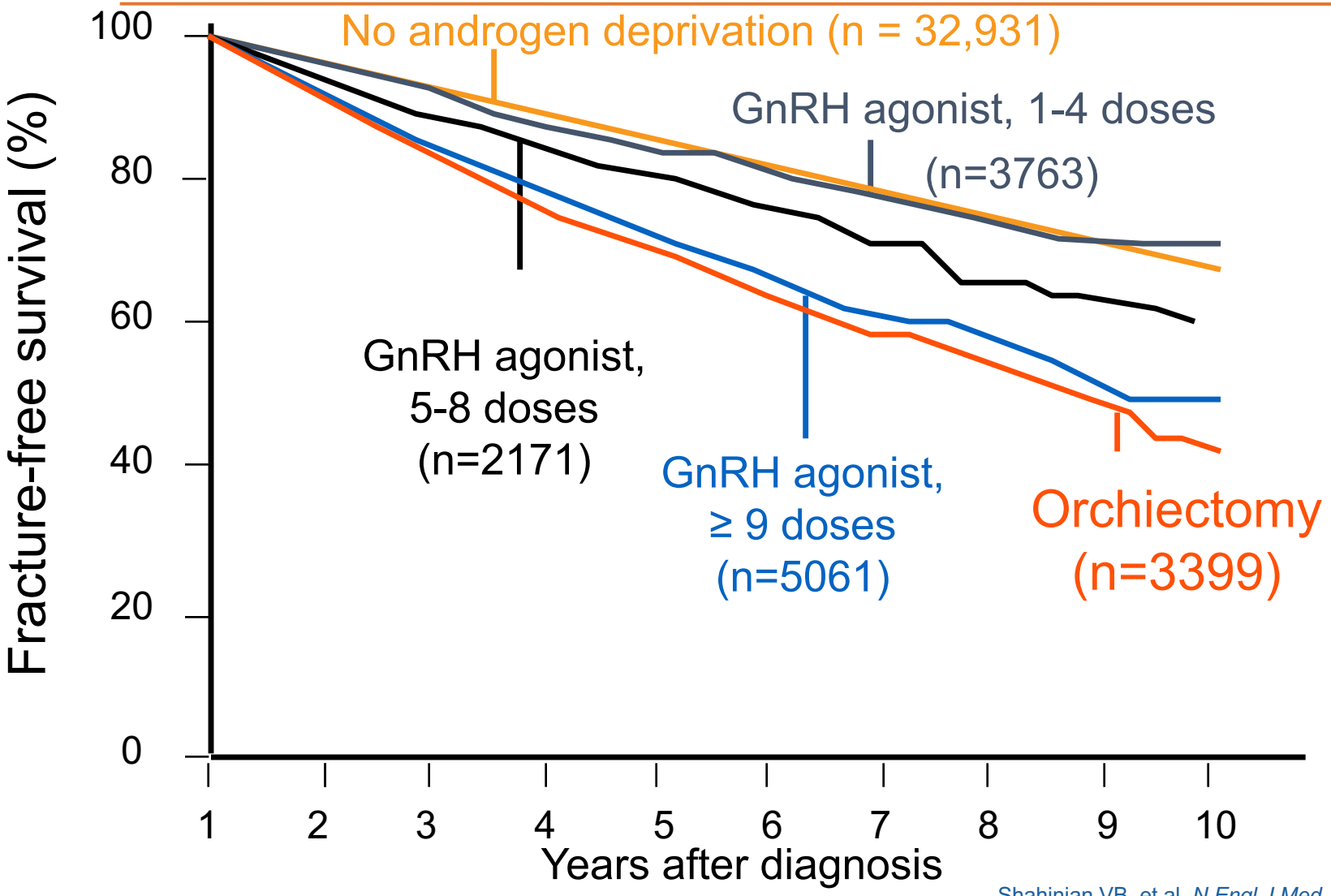

1. Van Staa TP et al (2001) Bone 29: 517
2. Kanis JA et al (2000) Osteoporos Int 11: 669
3. Samelson E et al 92007) J Bone Miner Res 22: 1449
4. Samelson EL et al (2006) J Bone Miner Res 21: 1207

# As trabecular and cortical bone loss progresses, vertebral and hip fracture rates increase exponentially




Adapted from: Sambrook P & Cooper C. *Lancet* 2006;367:2010–2018

# Risk of fracture after androgen deprivation for prostate cancer




Shahinian VB, et al. *N Engl J Med.* 2005


257-8426

# Toxicity of Adjuvant Endocrine Therapy in Postmenopausal Breast Cancer Patients: A Systematic Review and Meta-analysis

Eitan Amir, Bostjan Seruga, Saroj Niraula, Lindsay Carlsson, Alberto Ocaña

7 trials; 30.023 patients

Table 2. Absolute differences and number needed to harm associated with one adverse event of each type

| | ↑ Cardiovascular disease | | = Cerebrovascular disease | | ↓ Venous thrombosis | | ↑ Bone fractures | | ↓ Endometrial Carcinoma | |
|---|---|---|---|---|---|---|---|---|---|---|
| Trial (reference) | Absolute difference, % | NNH | Absolute difference, % | NNH | Absolute difference, % | NNH | Absolute difference, % | NNH | Absolute difference, % | NNH |
| ATAC (5) | 0.8 | 129 | −0.8 | −115 | −1.8 | −59 | 4.6 | 22 | −0.6 | −163 |
| BIG01-98 (3) | 0.9 | 107 | 0 | ∞ | −1.8 | −56 | 2.8 | 36 | −0.5 | −204 |
| IES (13) | 1.3 | 79 | 0 | ∞ | −1.2 | −84 | 2.1 | 48 | −0.2 | −479 |
| ABCSG8/ARNO (4) | <0.1† | 1643† | NS | NS | −0.6 | −179 | 1.1 | 91 | −0.3 | −268 |
| ITA (2) | 1.3 | 72 | NS | NS | −2.3 | −40 | NS | NS | −2.2 | −46 |
| N-SAS BC03 (14) | −0.3 | −354 | NS | NS | 0.3 | 347 | −1.2 | −85 | −0.3 | −349 |
| TEAM (15) | 0.7 | 139 | 0.4 | 311 | −1.1 | −91 | 1.6 | 63 | −0.2 | −485 |
| Pooled | 0.8 | 132 | −0.1 | −974 | −1.3 | −79 | 2.2 | 46 | −0.4 | −258 |

Limitations:

- Literature rather than individual patient data meta-analysis
- Reports of trials with different durations of follow-up
- Information on the potentially confounding baseline host factors (eg, obesity, hypertension, diabetes, and family history of events of interest) or the use of concurrent medications was not reported

J Natl Cancer Inst 2011;103:1299–1309

# ESMO BONE 2020 GUIDELINES
# ASCO 2020 BONE GUIDELINES

# Summary of Recommendations

*Recommendations Unchanged From 2011 Guideline Update*

- BMAs are recommended for patients with metastatic breast cancer with evidence of bone destruction.
- One BMA is not recommended over another.
- Mechanism of action, as well as the potential benefits and harms, should be taken into account when considering long-term use of BMA.
- In patients with creatinine clearance > 60 mL/min, no change in dosage, infusion time, or interval is required; monitor creatinine level with each intravenous 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 BMA.
- Use of biochemical markers to monitor BMA use is not recommended for routine care.

Ontario
Cancer Care Ontario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Annals of Oncology Advance Access published April 29, 2014

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. Coleman[1], J. J. Body[2], M. Aapro[3], P. Hadji[4] & J. Herrstedt[5] on behalf of the ESMO Guidelines Working Group*

[1]Weston Park Hospital, Cancer Research-UK/Yorkshire Cancer Research Sheffield Cancer Research Centre, Sheffield, UK; [2]CHU Brugmann, Université Libre de Bruxelles, Brussels, Belgium; [3]Multidisciplinary Oncology Institute, Genolier, Switzerland; [4]Department of Gynecology, Endocrinology and Oncology, Philipps-University of Marburg, Marburg, Germany; [5]Department of Oncology, Odense University Hospital, Odense, Denmark

# ESMO clinical practice guideline: Bone health in cancer patients


Annals of Oncology Advance Access published April 29, 2014

clinical practice guidelines

**Bone health in cancer patients: ESMO Clinical Practice Guidelines†**

- Clinicians treating cancer patients need to be aware of:
  - Treatments to reduce skeletal morbidity in metastatic disease
  - Strategies to minimise cancer treatment-induced skeletal damage
- ESMO guidelines "provide a framework for maintaining bone health in patients with cancer"

Coleman R et al. *Ann Oncol* 2014;00:1–14.

# Diagnosis: Recommended techniques

## Isotope bone scan

- Sensitive test used to detect presence of skeletal pathology
- Gives little information about nature of damage/metastatic disease

## CT and MRI

- Recommended for obtaining structural information on skeletal damage from metastatic bone disease

## PET

- Provides functional information that may aid in diagnosis

## DXA scan

- Recommended for patients at risk of fracture or cancer treatment-induced bone loss

## *Plain radiographs*

- *An insensitive test for metastasis – lesions need to be >1cm with bone mineral loss of ~50% to be recognized*

# COMMENTS

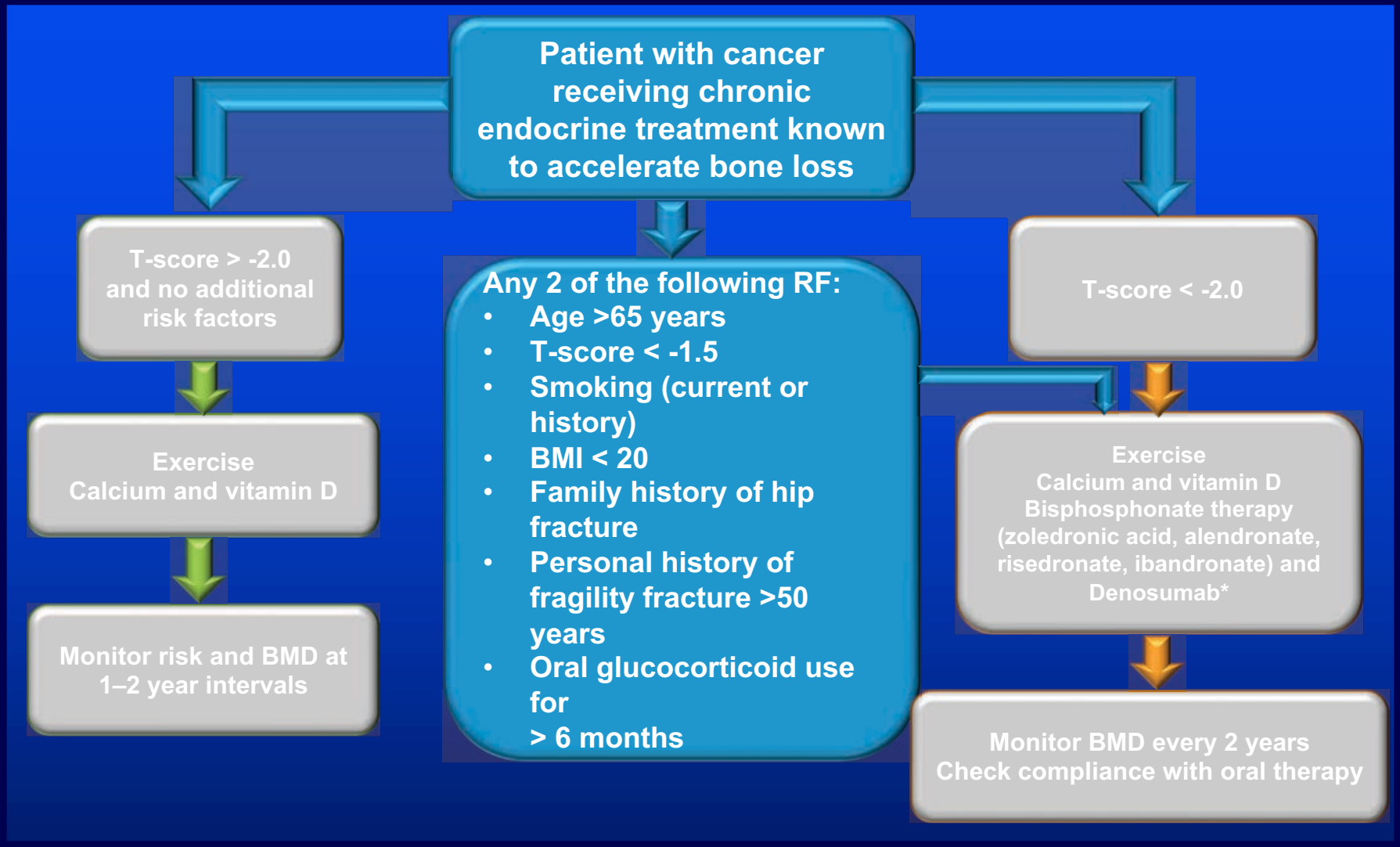
**Isotopic bone scanning**

- Not useful for monitoring treatment response

**Biochemical markers**

- e.g. amino (N) and carboxy (C) cross-linked telopeptides of type I collagen (NTC, CTX)
- May provide information on prognosis and response to treatments but are not recommended for routine clinical use

# ESMO – 2014 Algorithm for managing Bone Health during Breast Cancer Treatment




*in view of ABCSG-18 data

Coleman R. , Hadji P. et al. *Ann Oncol* 2014;00:1–14.

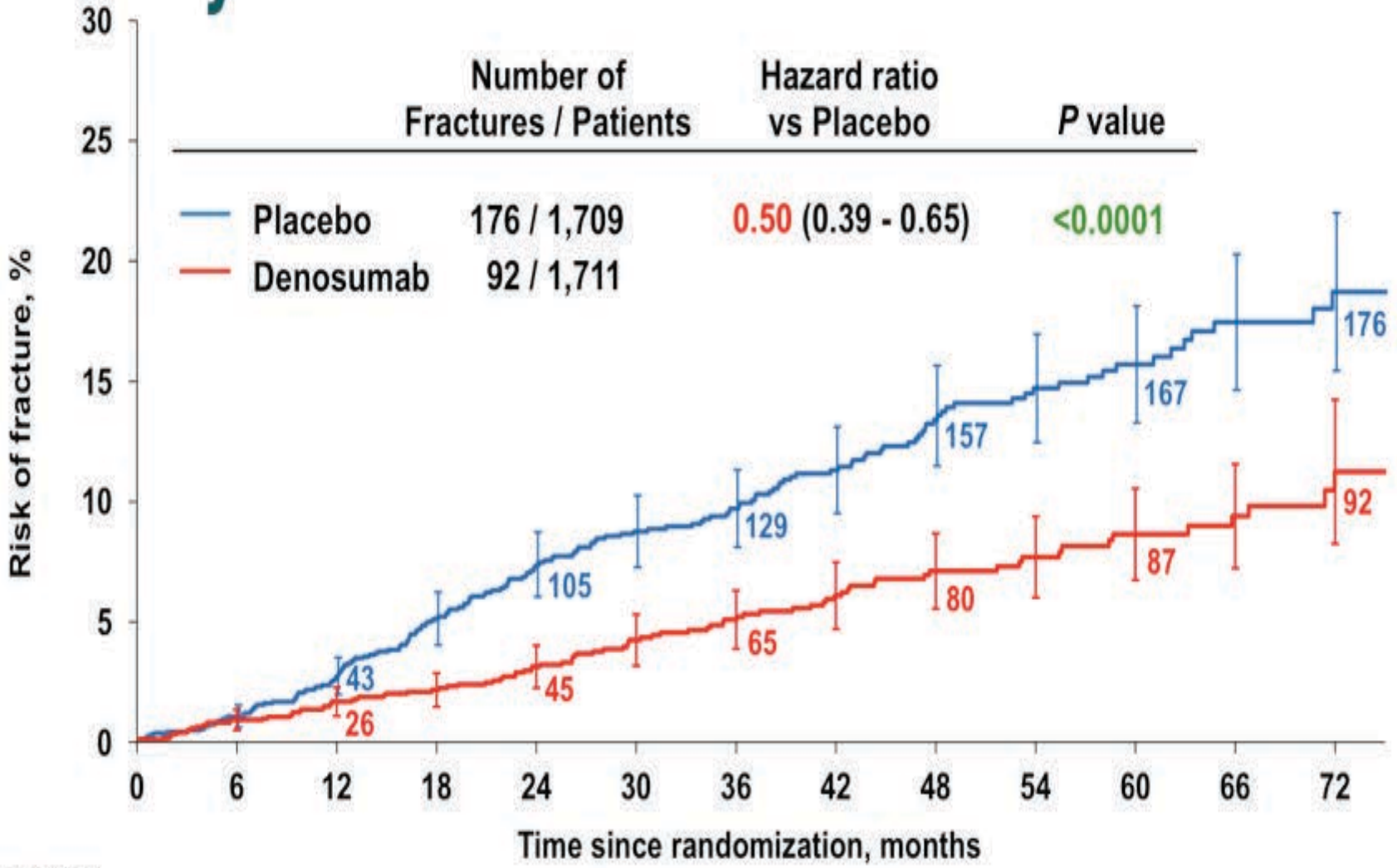
# Guideline for Bisphosphonates as Adjuvant: St Gallen/Vienna 2019 ( notes taken by Aapro )

Is bisphosphonate treatment, such as zoledronic acid q 6 months or oral clodronate, during adjuvant endocrine therapy *indicated to improve DFS irrespective of BMD*?

- In postmenopausal patients? YES 83.7%

Should adjuvant denosumab (60 mg twice a year) substitute for bisphosphonate? NO 75%

# Primary End Point Results




Patients at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 1709 | 1660 | 1470 | 1265 | 1069 | 921 | 785 | 637 | 513 | 384 | 275 | 185 | 112 |
| Denosumab | 1711 | 1665 | 1488 | 1297 | 1118 | 965 | 823 | 688 | 549 | 432 | 305 | 221 | 116 |

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

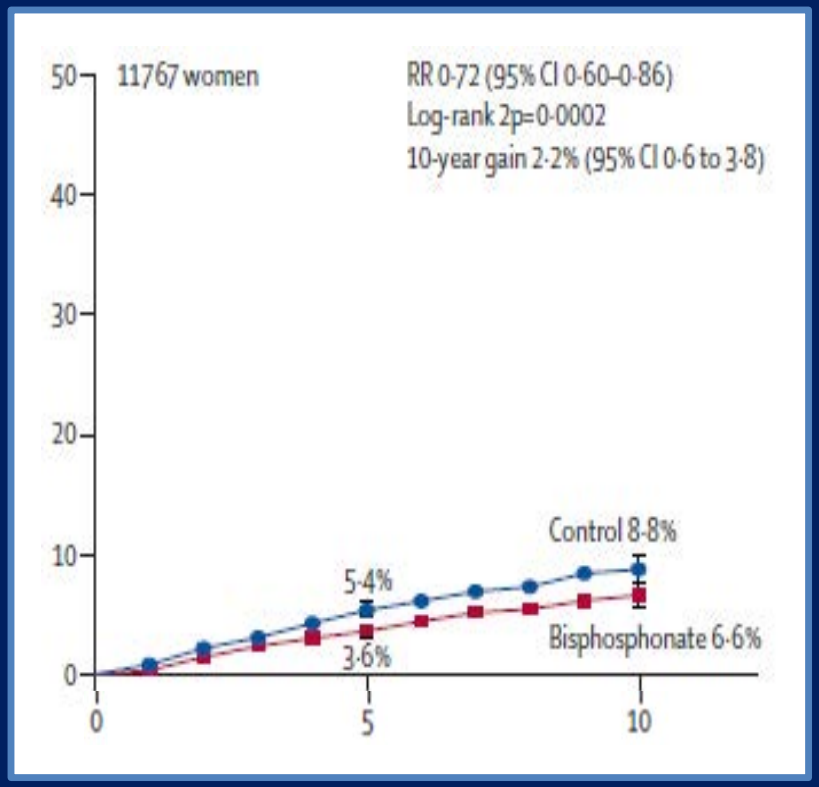
# Effects Of Bisphosphonate Treatment On Recurrence And Cause-specific Mortality In Women With Early Breast Cancer: A Meta-analysis Of Individual Patient Data From Randomised Trials

R Coleman, M Gnant, A Paterson, T Powles, G von Minckwitz, K Pritchard, J Bergh, J Bliss, J Gralow, S Anderson, D Cameron, V Evans, H Pan, R Bradley, C Davies, R Gray.

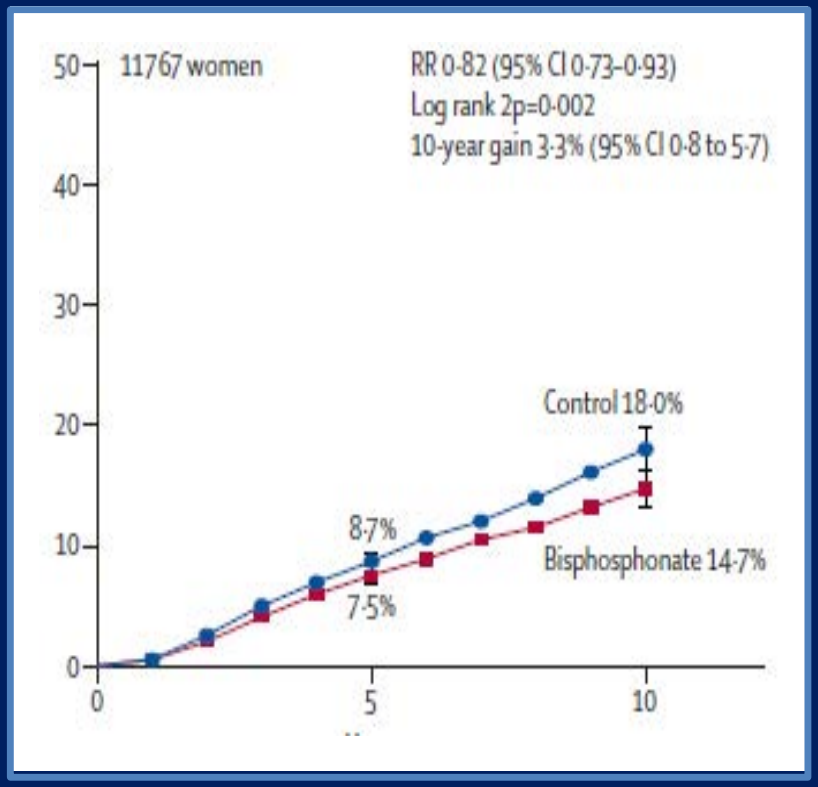
Early Breast Cancer Trialists' Collaborative Group (EBCTCG)'s Bisphosphonate Working Group.

Published in Lancet Oncology 2014

# Adjuvant bisphosphonates reduce the rate of bone metastasis and improve breast cancer survival in **post-menopausal patients**



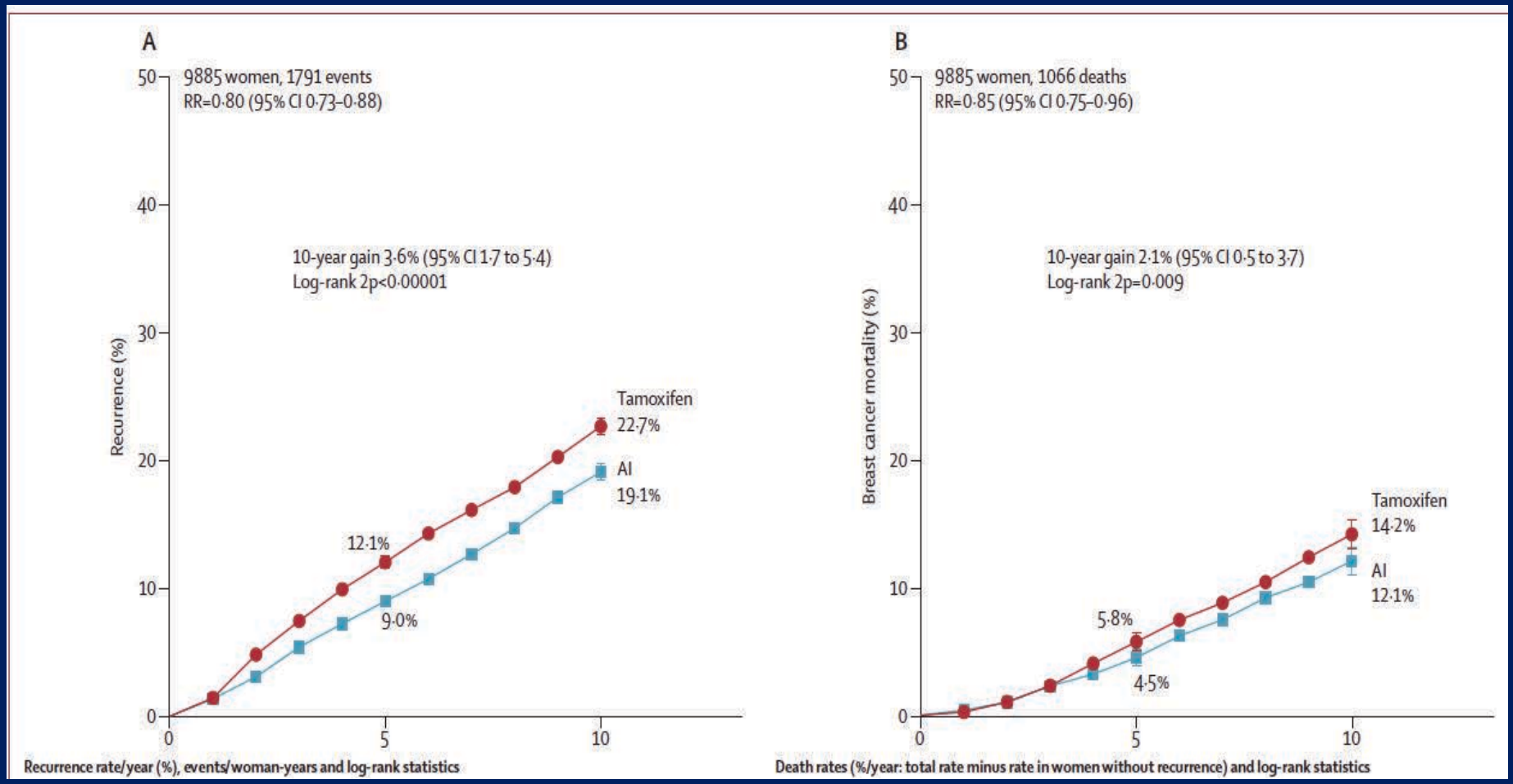

Bone Recurrence




Breast Cancer Mortality

*EBCTCG Lancet 2014*

# Adjuvant AIs reduce the relapse rate and improve breast cancer survival in **post-menopausal patients compared to tamoxifen**




*EBCTCG Lancet 2015*

# A NICE REVIEW

Current Breast Cancer Reports (2018) 10:241–250
https://doi.org/10.1007/s12609-018-0295-6

SYSTEMIC THERAPIES (M LIU AND T HADDAD, SECTION EDITORS)

## Bone-Modifying Agents in Early-Stage and Advanced Breast Cancer

Arielle Heeke[1] • Maria Raquel Nunes[2] • Filipa Lynce[3,4]

# WHAT DOSE OF BPs TO USE in M1 BrCA

***SEVERAL STUDIES***

***INDICATE THAT MONTHLY ZOLEDRONIC ACID MAY NOT BE NEEDED FOR LONG-TERM CONTROL OF SREs***

***HOWEVER EXPERT CONSENSUS MIGHT SUGGEST MONTHLY FOR 3-6 MONTHS***

***before 3 monthly***

Amadori Lancet 2014; Hortobagyi ASCO 2014; Himelstein ASCO 2015

# Himelstein ASCO 2015

| | Q Month N = 911 | Q 3 Months N = 911 | HR (P-value) |
|---|---|---|---|
| **Total ZA dose (median)** | 56 mg | 24 mg | — (< 0.01) |
| **Dose delays** | 62% | 37% | — (< 0.01) |
| **Any SRE** | 260 | 253 | 1.05 (0.60) |
| **Any SRE – breast pts (N = 820)** | 113 | 119 | 0.90 (0.43) |
| **Any SRE – prostate pts (N = 660)** | 107 | 101 | 1.15 (0.31) |
| **Any SRE – myeloma pts (N = 265)** | 35 | 30 | 1.30 (0.29) |
| **Bone RT** | 185 | 163 | 1.16 (0.18) |
| **Bone fractures** | 62 | 79 | 0.78 (0.13) |
| **Spinal cord compression** | 23 | 30 | 0.75 (0.30) |
| **Bone surgery** | 22 | 42 | 0.51 (0.01) |
| **Jaw osteonecrosis** | 18 | 9 | — (0.08) |
| **Grade 2-4 creatinine increase** | 11 | 5 | — (0.46) |

## BUT A RECENT REVIEW ( JOP 2018 )

# Use of Bone-Modifying Agents in Myeloma and Bone Metastases: How Recent Dosing Interval Studies Have Affected Our Practice

*Erica Campagnaro, Melissa A. Reimers, Angel Qin, Ajjai S. Alva, Bryan J. Schneider, and Catherine H. Van Poznak*

COMMENTED IN JOP 2018

# De-Escalation of Bone-Modifying Agents in Patients With Bone Metastases: The Best of Times and the Worst of Times?

*Arif A. Awan, Alexander Paterson, and Mark Clemons*

# …AND
# A META-ANALYSIS

Breast Cancer Res Treat. 2019 Aug;176(3):507-517. doi: 10.1007/s10549-019-05265-1. Epub 2019 May 11.

**De-escalation of bone-modifying agents in patients with bone metastases from breast cancer: a systematic review and meta-analysis.**

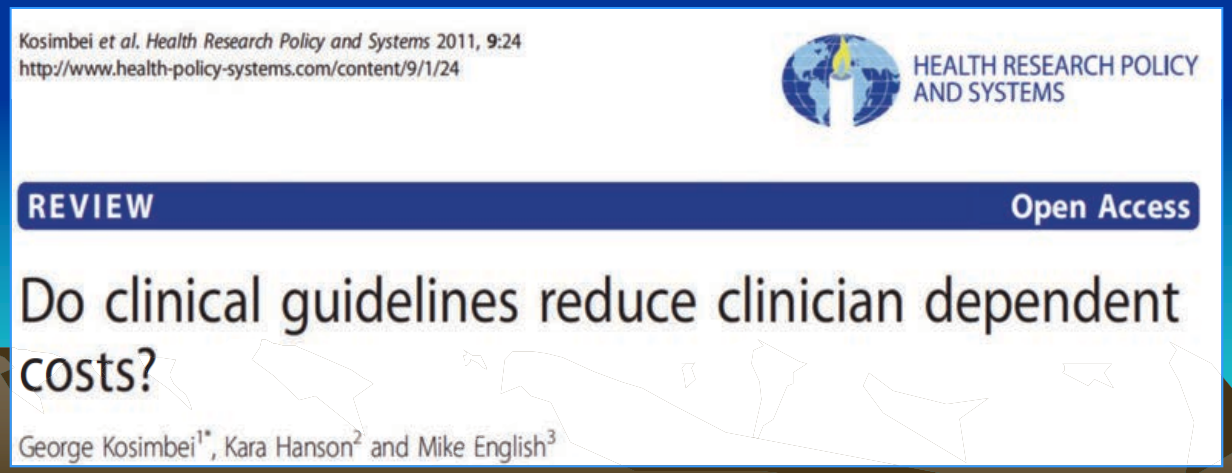
Awan AA[1], Hutton B[2], Hilton J[1], Mazzarello S[3], Van Poznak C[4], Vandermeer L[3], Bota B[3], Stober C[3], Sienkiewicz M[3], Fergusson D[2], Shorr R[5], Clemons M[6,7,8].

# The menu

- Which guidelines, why?
- Messages from guidelines
- **To conclude**

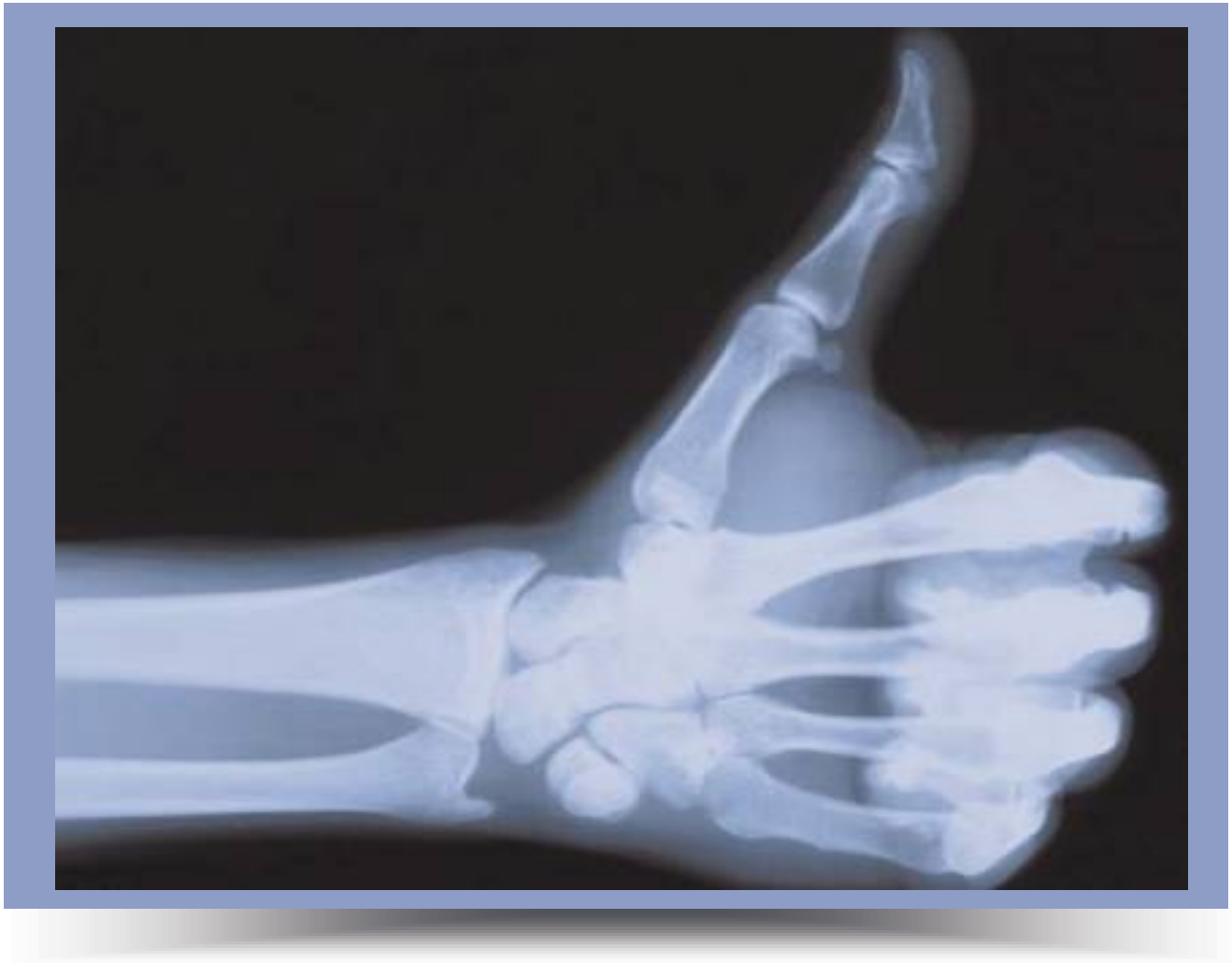
# Guidelines use can reduce health care costs

- Implementation of guidelines has resulted in observed improvements in care and absolute improvements in performance
- The reported degree of financial savings ranging from 6% to 57% (costs on drug, hospital, managing, etc.)




Kosimbei G, et al. Health Res Policy Syst. 2011;9:24.

# ! Thank you !



Courtesy of JJ Body