Current strategies to maintain bone health, and emerging bone health issues in cancer patients

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Disclosures

- none

Aims

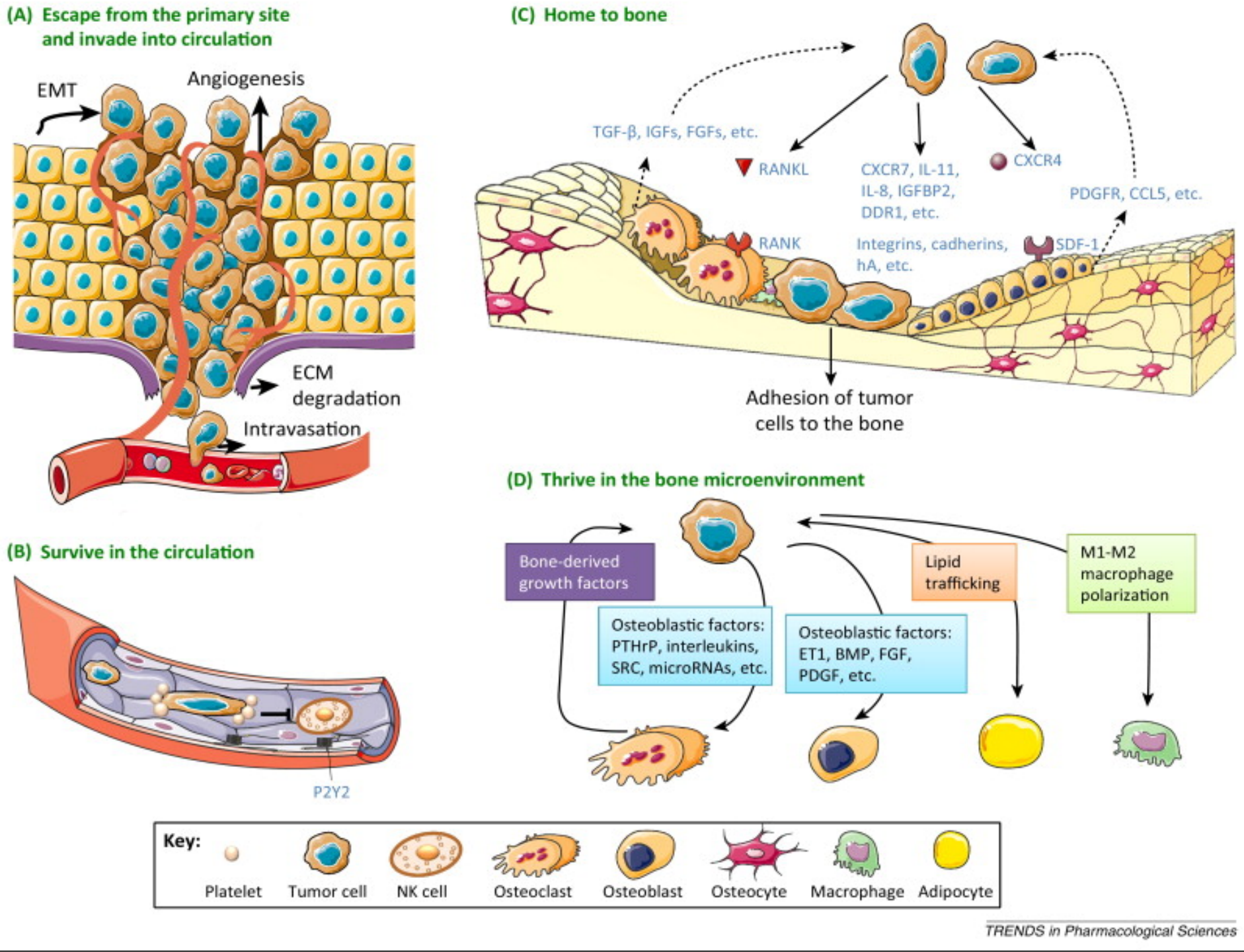
- To develop an understanding of the management of bone metastasis through a multidisciplinary approach
- Enable the learner to understand the guidelines of management of bone complications and the use of bisphosphonates and denosumab
- Describe the challenges in management of bone metastasis

About bone metastases

- One of the most common places for prostate or breast **cancer** to spread is to the bone
  - Approximately 65 to 75 per cent of people with advanced prostate or breast cancer experience bone metastases
- Growing cancer cells **weaken** and destroy bone around the tumour
- Can lead to debilitating **complications**

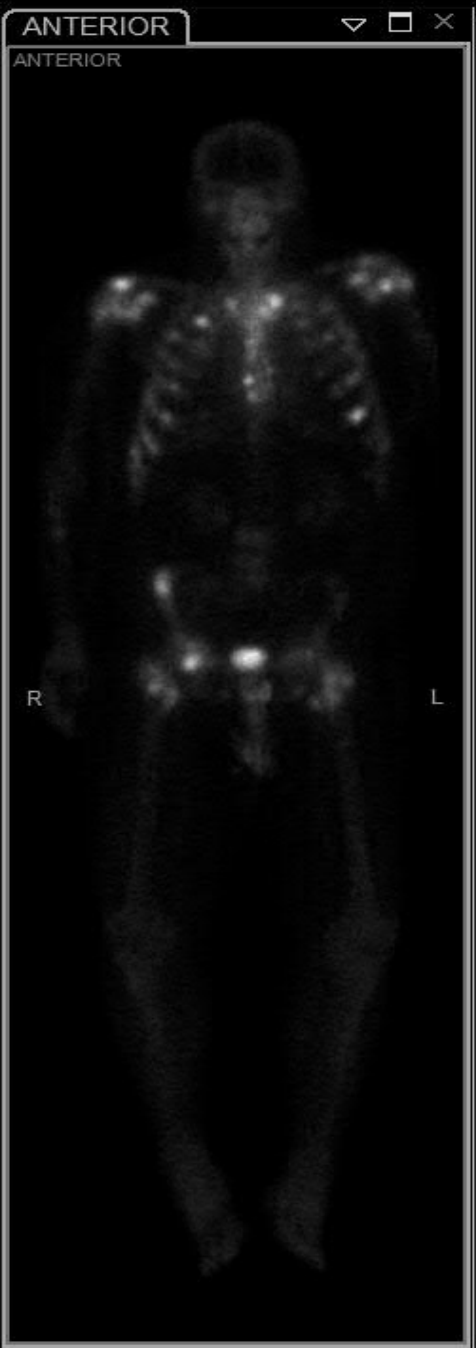
Bone metastasis

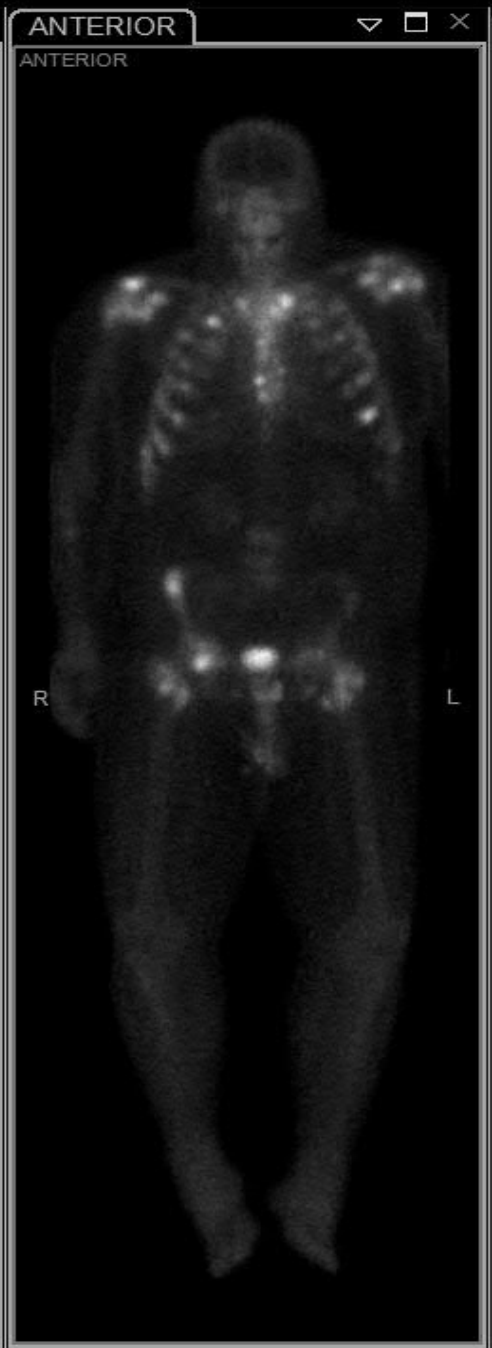
- most prevalent in advanced breast (70–80%), prostate (70–80%), thyroid (60%), lung (10–50%) and renal cancers (30%)
- The consequences of bone metastases include reduced survival, morbidity and pain that negatively affect the patient's quality of life (QoL) as well as skeletal-related events (SREs)

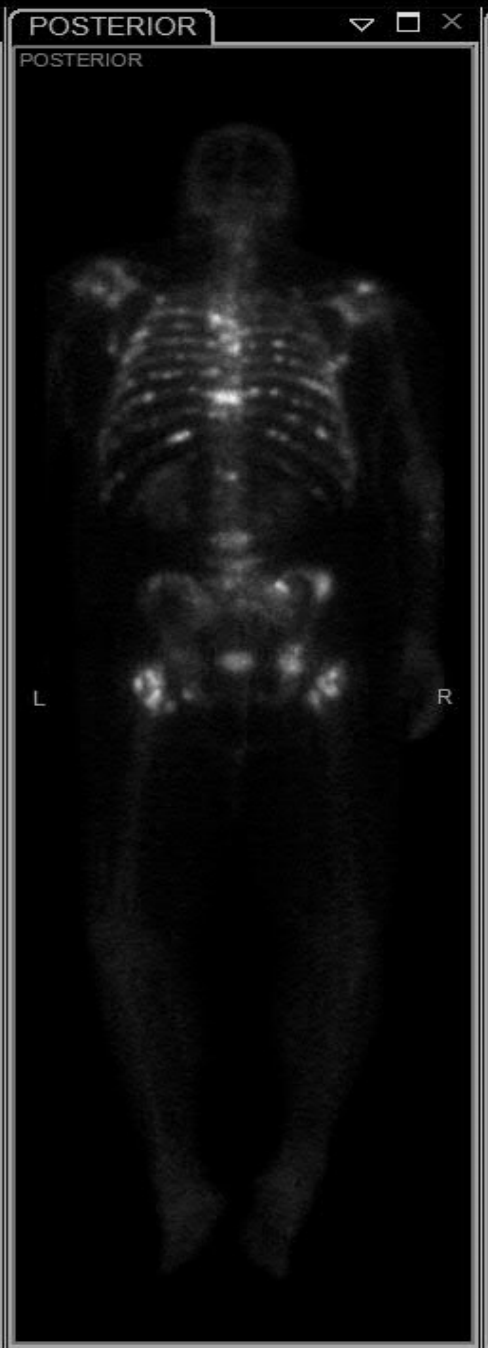

(A) Escape from the primary site and invade into circulation
EMT
Angiogenesis
ECM degradation
Intravasation
(B) Survive in the circulation
P2Y2
(C) Home to bone
TGF-β, IGFs, FGFs, etc.
RANKL
CXCR7, IL-11, IL-8, IGFBP2, DDR1, etc.
CXCR4
PDGFR, CCL5, etc.
RANK
Integrins, cadherins, hA, etc.
SDF-1
Adhesion of tumor cells to the bone
(D) Thrive in the bone microenvironment
Bone-derived growth factors
Osteoblastic factors: PTHrP, interleukins, SRC, microRNAs, etc.
Osteoblastic factors: ET1, BMP, FGF, PDGF, etc.
Lipid trafficking
M1-M2 macrophage polarization
Key:
Platelet
Tumor cell
NK cell
Osteoclast
Osteoblast
Osteocyte
Macrophage
Adipocyte

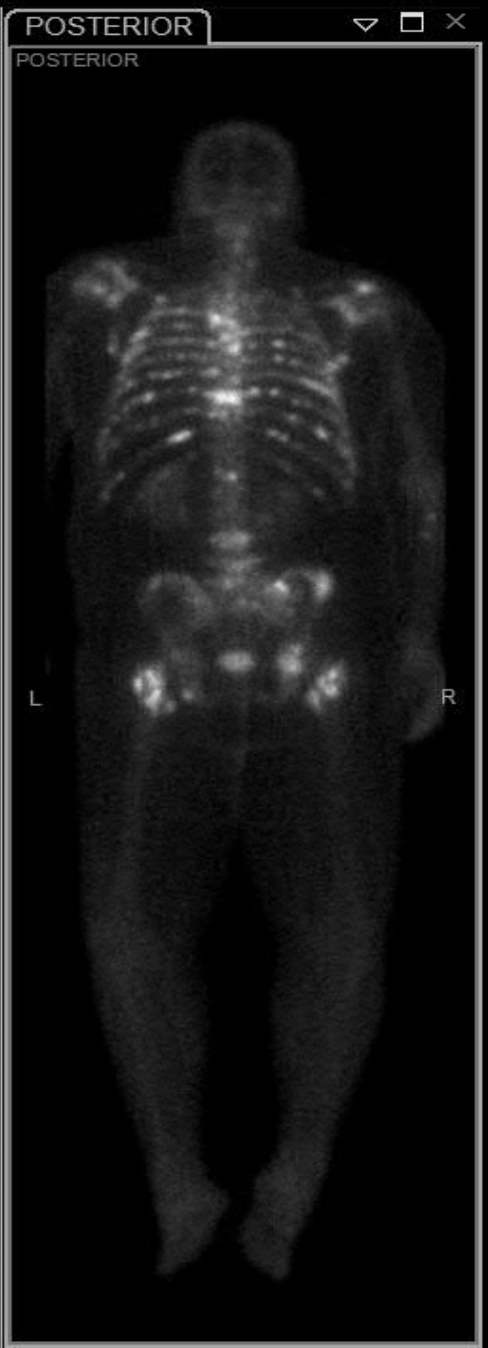
04-Feb-1952 M HLH

Bone Sequence 14-Sep-2015









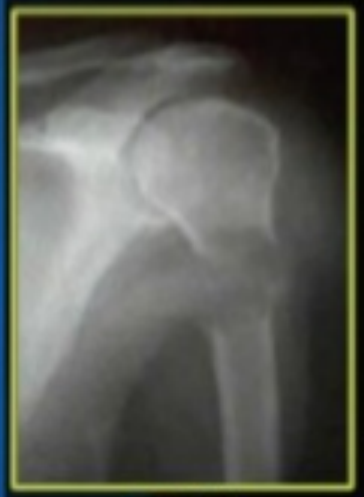
Signs

- Asymptomatic
- Bone pain
- Fracture
- hypercalcemia

Skeletal Related Events (SREs) in Cancer Have Potentially Severe Consequences

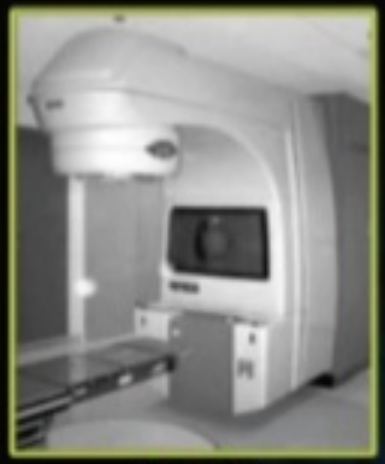
Pain
50-90% of patients with bone metastases[1]

Pathologic fracture[3]



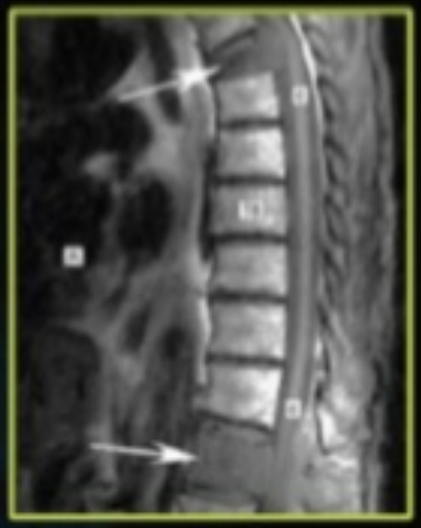
22%[2]

Radiotherapy to bone[4]



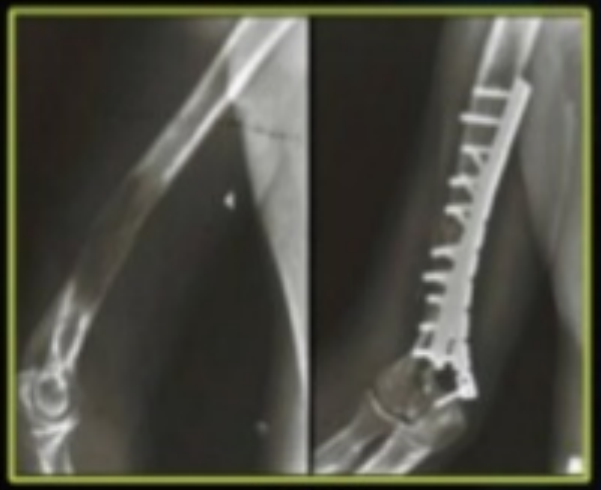
29%[2]

Spinal cord compression[5]



7%[2]

Surgery to bone[6]



3%[2]

1. Clemons et al. *Oncologist* 2006;11:227-33. 2. Saad et al. *J Natl Cancer Inst* 2002;94:1458-68.

ASTRO Guideline 2017

External beam radiotherapy (EBRT) continues to be the mainstay for the treatment of pain and/or prevention of morbidity caused by bone metastases.

The evidence for the safety and efficacy of re-treatment to previously irradiated areas of peripheral bone metastases pain is derived from both prospective studies and retrospective data, and it has been shown to be safe and effective.

Guideline statement

- Multiple prospective randomized trials have shown pain relief equivalency for dosing schema including 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and a single 8 Gy fraction for patients with previously un-irradiated painful bone metastases.
- Fractionated treatment courses are associated with an 8% re-treatment to the same anatomic site due to recurrent pain versus 20% after a single fraction, while the single fraction treatment approach optimizes patient and caregiver convenience.

Efficacy of single dose radiation

- All of the completed studies for either a single 8 Gy fraction or multiple fractions have confirmed similar rates of pain relief varying from 50%-85% for peripheral and vertebral bone metastases.

Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol. 2007 Apr10;25:1423-1436.

Stereotactic radiation

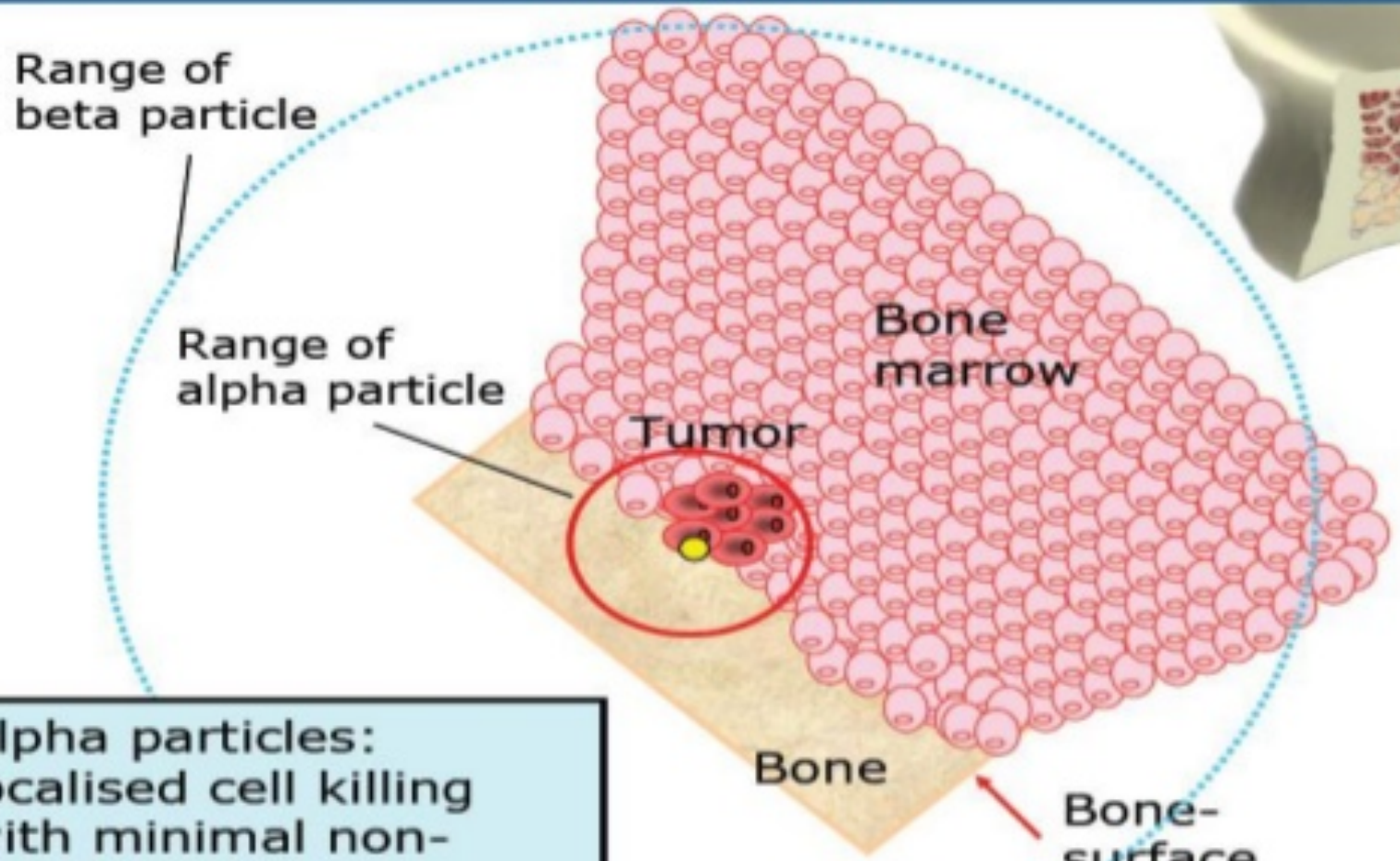
The use of stereotactic body radiotherapy was seen to hold theoretical promise in the treatment of new or recurrent spine lesions, though the Task Force recommended that its use be limited to selected patients preferably treated on a prospective trial.

ASTRO Guideline 2017

Surgical decompression and post-operative radiotherapy is recommended for spinal cord compression or spinal instability in highly selected patients with sufficient performance status and life expectancy.

The use of bisphosphonates, radionuclides, vertebroplasty and kyphoplasty for the treatment or prevention of cancer related symptoms does not obviate the need for EBRT in appropriate patients.

Mechanism

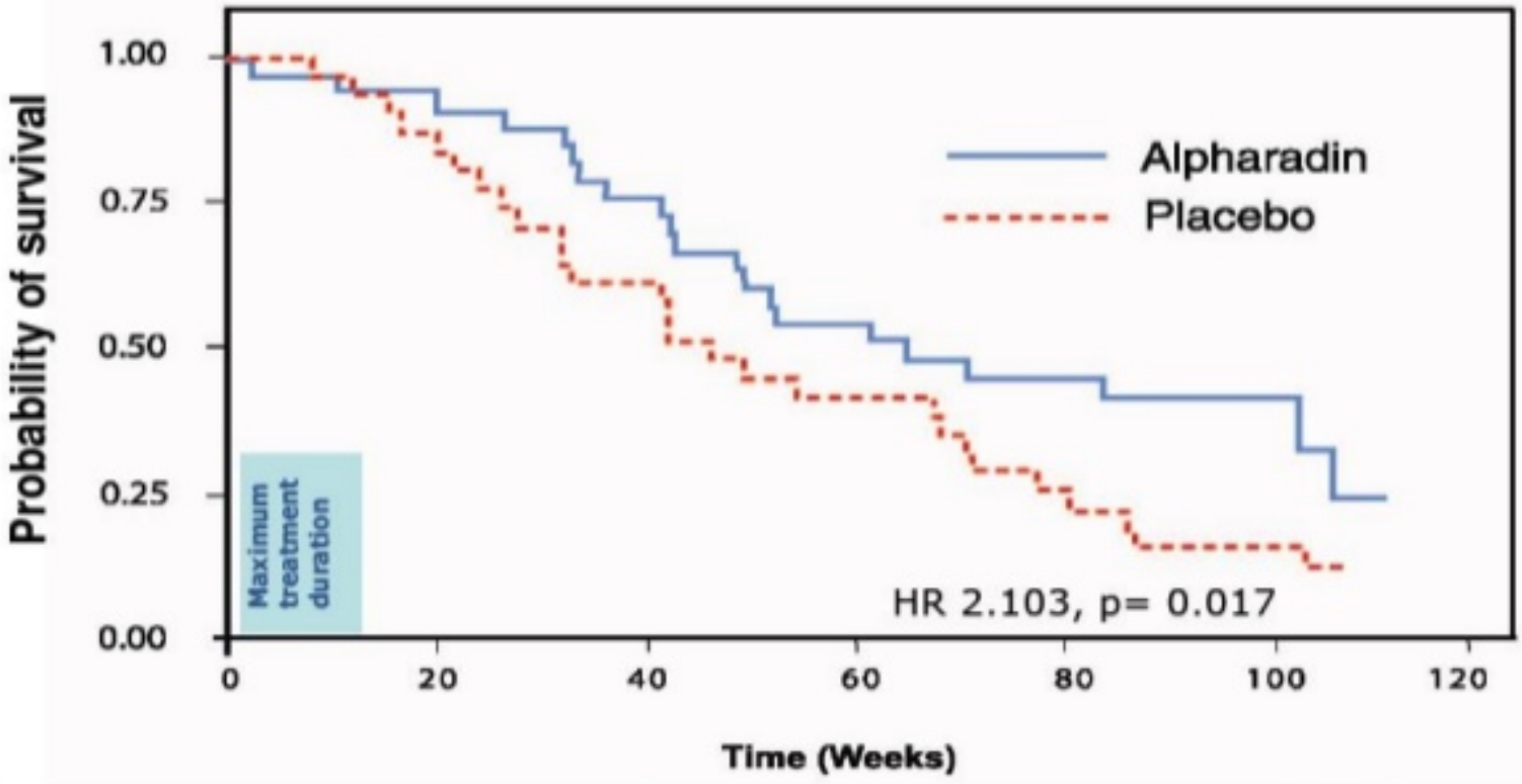


Alpha particles:
localised cell killing
with minimal non-
target toxicity

Radium 223 and prostate cancer

- Most recently, this has been evident in studies examining the radiopharmaceutical radium-223 dichloride (Xofigo) in patients with mCRPC.
- The ALSYMPCA trial, which was the basis for the 2013 FDA approval of radium-223, showed a median overall survival (OS) of 14 months with radium-223 versus 11.2 months with placebo (HR, 0.70; $P = .00185$) in patients.

Survival


Probability of survival
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
100
120
Time (Weeks)
Alpharadin
Placebo
Maximum treatment duration
HR 2.103, p= 0.017

ASCO/Cancer Care Ontario- Breast Adjuvant Guidelines

- "It is recommended that, if available, zoledronic acid (4 mg intravenously [over 15 minutes or longer] every 6 months [for 3 to 5 years]) or clodronate (1,600 mg/d orally [for 2 to 3 years]) be considered as adjuvant therapy for postmenopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy

Dhesy-Thind S, Flecther GG, Blanchette S et al. Use of Bisphosphonates and other disease modifying agents in breast cancer JCO 2017 ;35:18 2062-2081

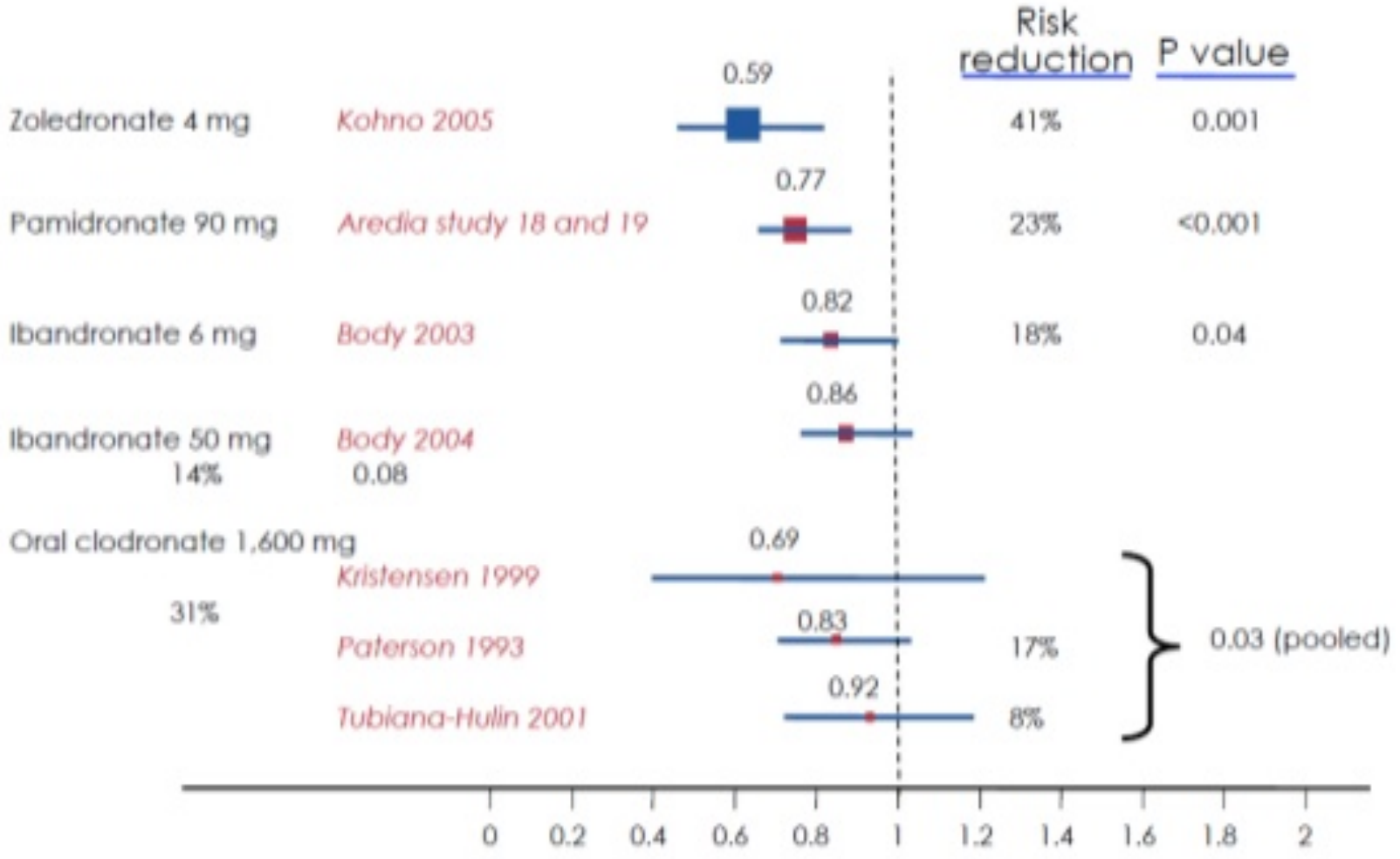
Breast Cancer Guidelines

1.Postmenopausal women in the decade after beginning treatment, 5 years of AI therapy reduces the risk of dying from breast cancer by around 40%, compared with no endocrine therapy (and reduces the risk for breast cancer mortality by about 15% compared with tamoxifen).

2. 2 to 5 years of bisphosphonates adjuvant, reduces the risk of dying from breast cancer by 18%

Early Breast Cancer Trialist Collaborative Group 2017

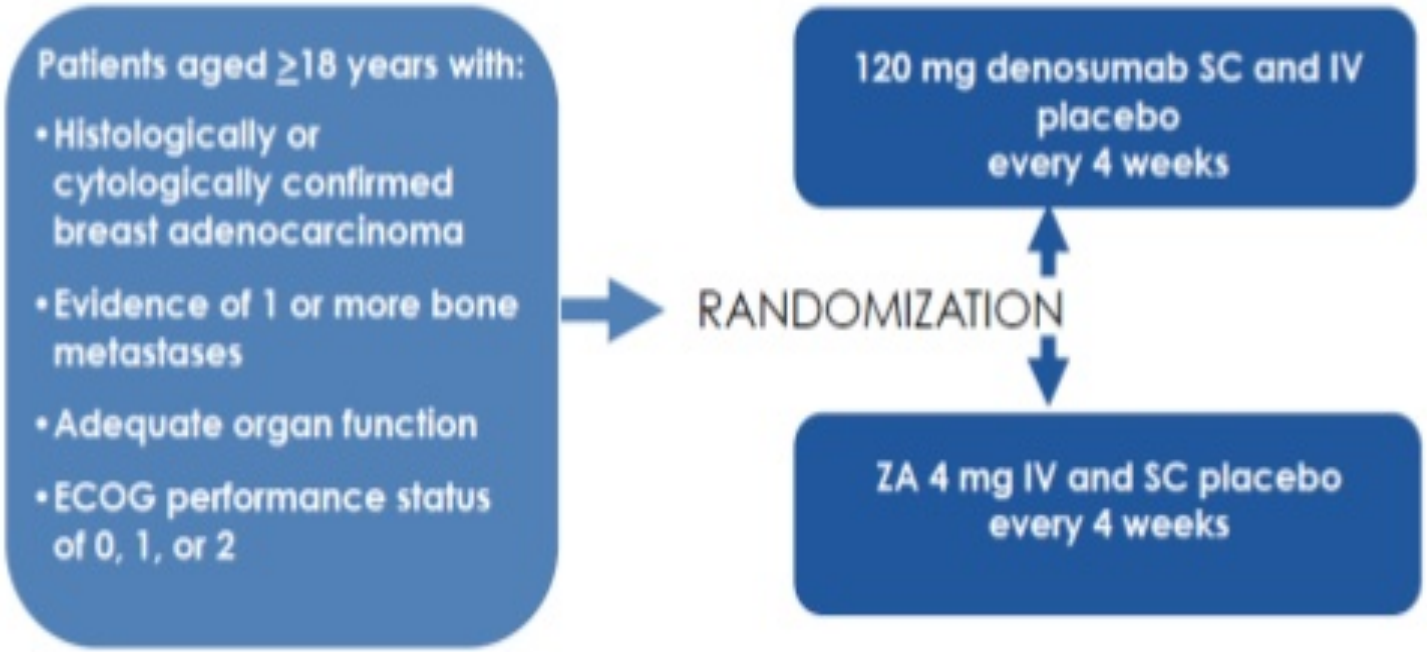
Bisphosphonates reduce the risk of SREs in breast cancer patients



Cochrane database comparing placebo-controlled trials in breast cancer setting.

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

Study Schema



Primary end point

- Time to first on-study SRE (non-inferiority test)

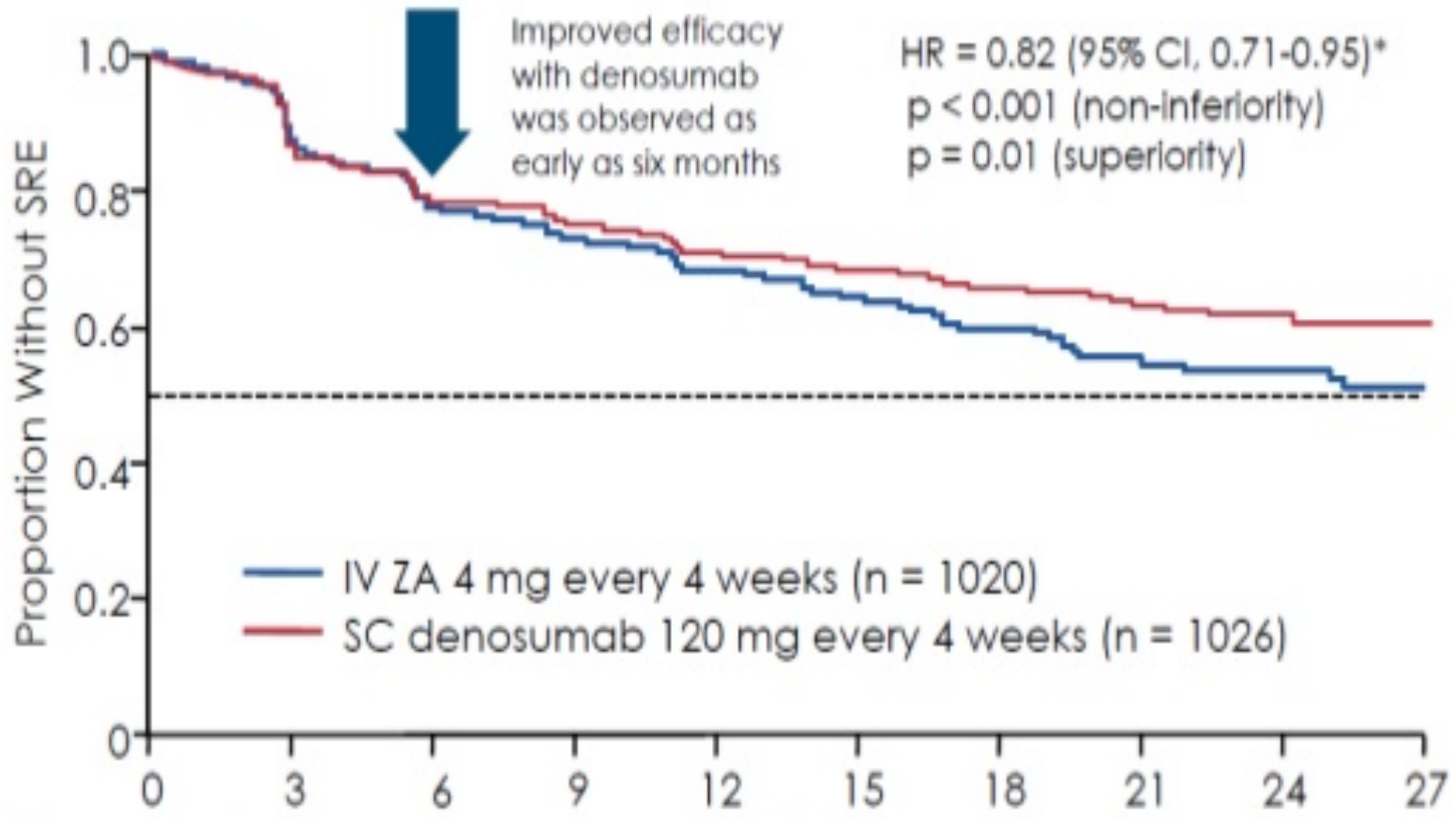
Secondary end points

- Time to first on-study SRE (superiority)
- Time to first and subsequent on-study SRE (superiority)

BSAP = Bone-specific alkaline phosphatase
ECOG = Eastern Cooperative Oncology Group
SC = Subcutaneous

Stopeck AT, et al. J Clin Oncol 2010;28:5132-9

Primary End Point: Time to First On-Study SRE



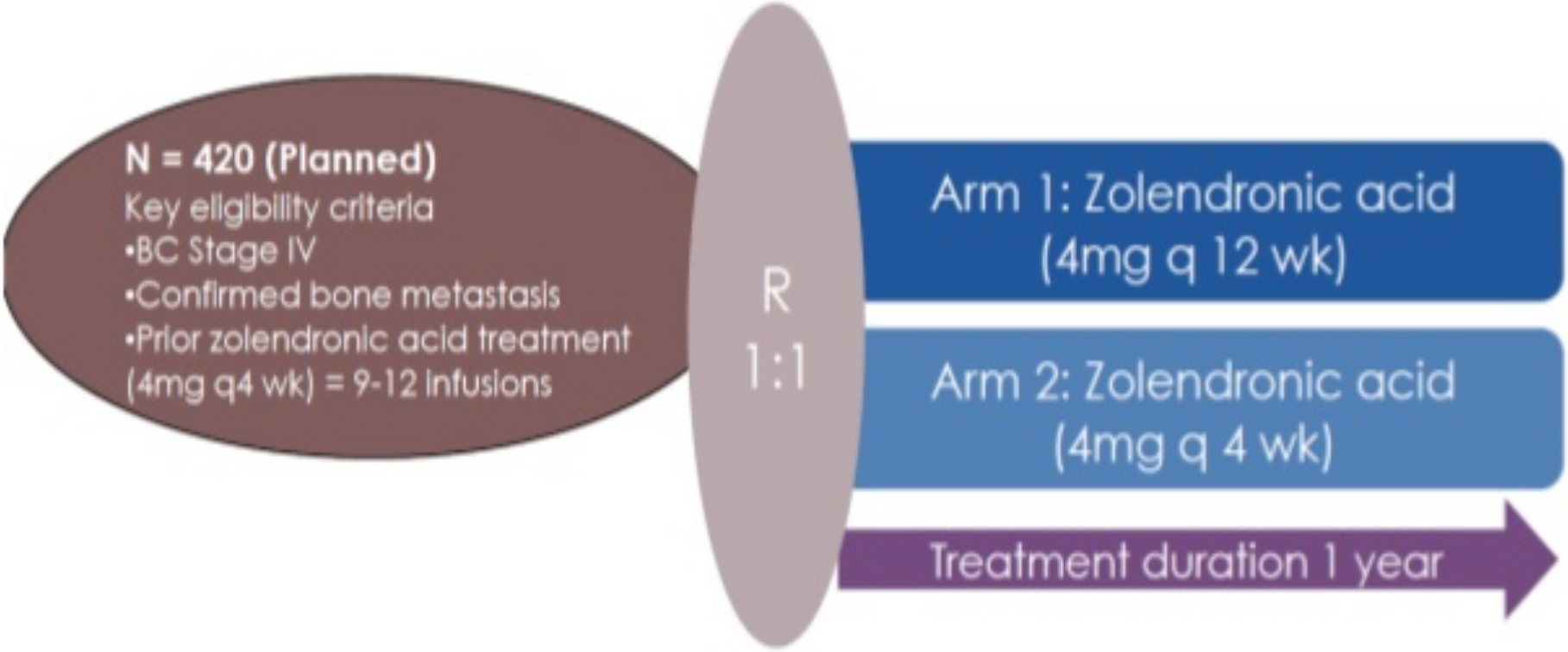
*Adjusted for multiplicity

No. at risk										
IV ZA	1020	829	676	584	498	427	296	191	94	29
SC denosumab	1026	839	697	602	514	437	306	189	99	26

CI = Confidence interval; HR = Hazard ratio.

Stopeck AT, et al. J Clin Oncol 2010;28:5132-9

ZOOM: A Prospective, Randomized Trial of ZA for Long-Term Treatment of Bone-metastatic BrCa after 1 Year of ZA Treatment



Endpoints:
Primary: Skeletal morbidity rate (SMR)
Secondary: Proportion of patients experiencing SREs (overall and by event), time to first SRE, SMR by event, bone pain, use of analgesics, bone marker levels, safety

Accrual: February 2006 – February 2010

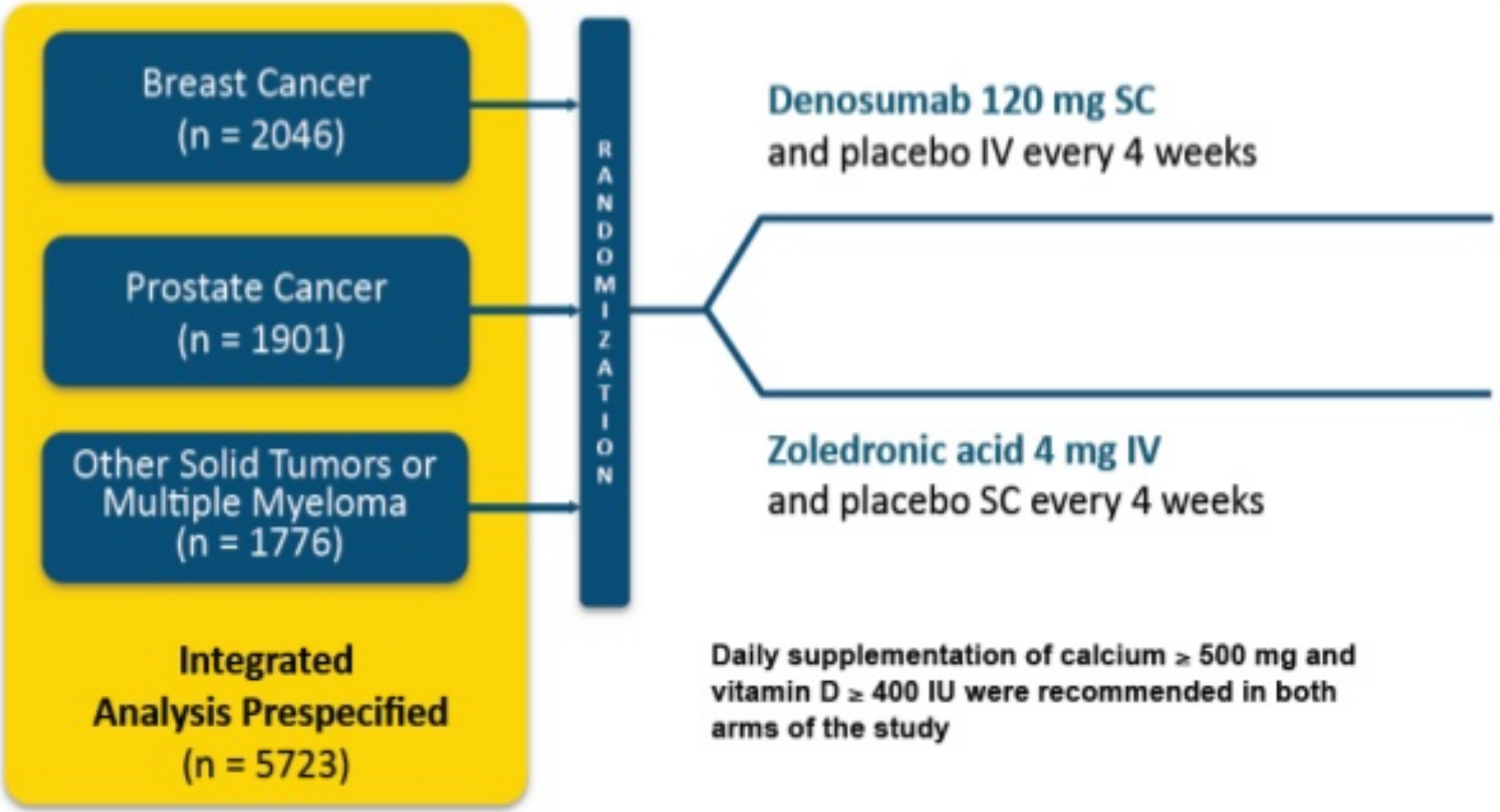
ZOOM: Primary Efficacy Analysis: SMR

	ZOL q 12 wk (Arm 1)	ZOL q 4 wk (Arm 2)
N (ITT population)	209	216
Mean SMR (95% CI)	0.26 (0.15, 0.37)	0.22 (0.14, 0.29)
95% CI	-0.09 to 0.17	

The upper limit of the CI (0.17) was less than the recalculated non-inferiority margin of 0.19. This result indicates that the efficacy of the q 12 wk arm was not inferior to the q 4 wk arm.

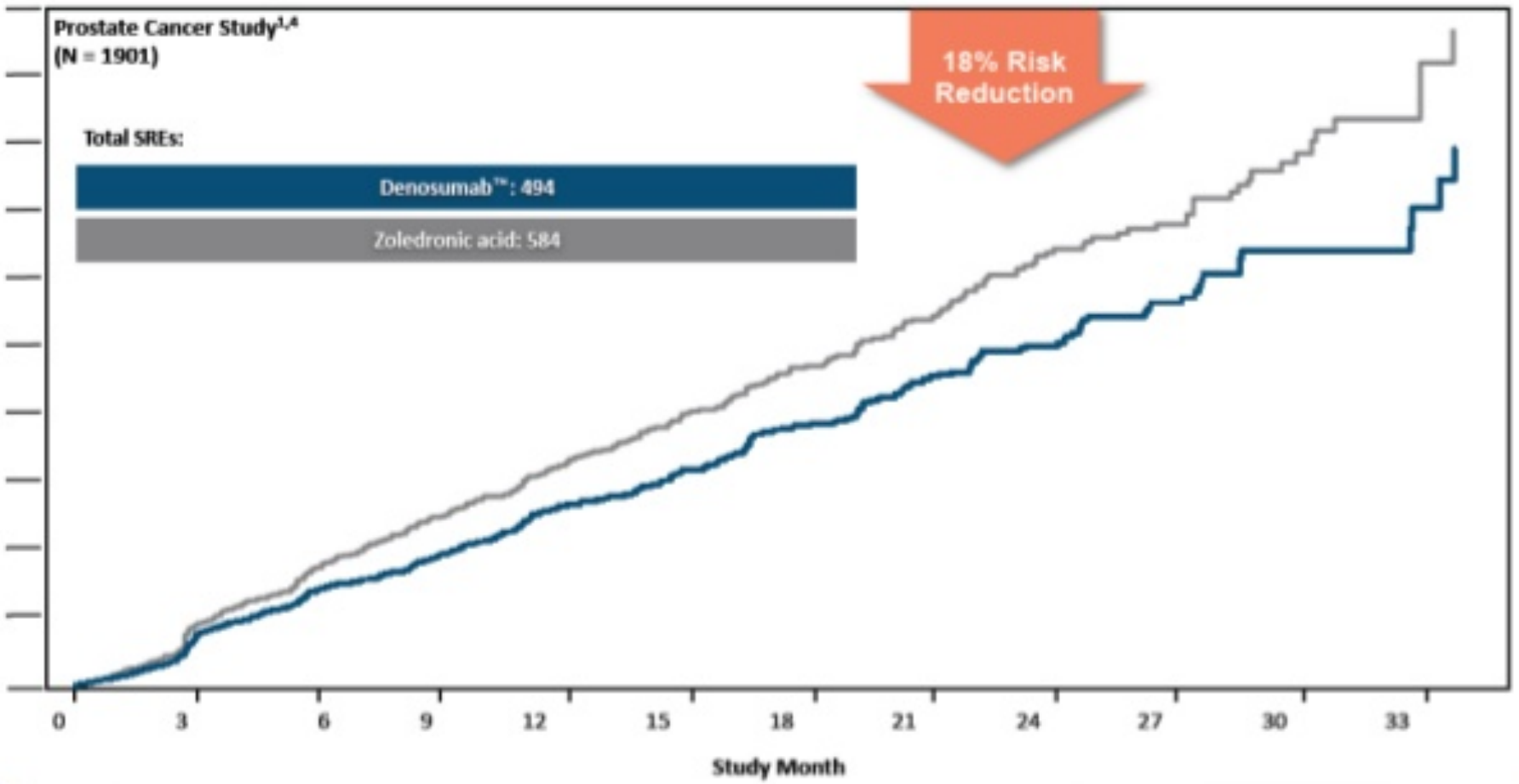
Amadori D, et al. J Clin Oncol 2012 ;30(suppl)Abstr 9005

Three Identically Designed Head-to-Head StudiesComparing Denosumab vs Zoledronic Acid



Daily supplementation of calcium ≥ 500 mg and vitamin D ≥ 400 IU were recommended in both arms of the study

First and Subsequent SRE



Questions and Challenges

Basic Science

Are osteoclasts the only stromal cell type that should be targeted therapeutically?

Are there new cancer/bone-stromal targets that should be developed?

What is our understanding of the biological mechanisms of pain associated with bone metastasis?

Clinical

What are the major issues affecting cancer patients with bone metastasis?

What do patients, nurses and clinicians feel are the most immediate concerns (bone pain, mobility issues, and survival)?

Why do bisphosphonates and denosumab for metastatic bone cancers fail to prolong overall survival?

Preclinical Studies

- Experimentally, the most frequent route of injection of cancer cells is intracardiac (into left cardiac ventricle), which permits seeding and colonization of tumor cells in metaphyses of the long bones.
- Intratibial (intraosseous) injection of tumour cells directly into the marrow space is often used to examine tumour stromal interactions during the growth of bone metastatic lesions.
- optical imaging systems (IVIS), radiography, μCT and MRI) have been used to assess the growth of bone metastatic lesions and the effect on bone resorption/destruction.

Mechanism of bone metastasis

- isolate new bone metastatic-derived cancer cell lines, to test drug combinations in ex vivo bone metastatic tumour tissues and to develop patient derived xenograft models. There remain challenges in translating these models into the clinical practice, such as a need to improve quantitative assays for tumour burden and ultimately evaluate response to treatment in vivo and models that can better mimic to the human in vivo phenotype

Cabozantinib

- Cabozantinib (XL184) is an orally bioavailable tyrosine kinase inhibitor with potent activity against MET and VEGFR2. In early clinical studies in patients with metastatic prostate cancer, cabozantinib demonstrated significant and rapid effects on bone scan lesions as well as on markers of bone formation and resorption, bone pain and narcotic use. In addition, statistically significant improvement in progression-free survival was seen with cabozantinib compared with placebo. While the subsequent larger registration study was negative in terms of overall survival

Cabozantinib

- Inhibitor of MET and VEGFR-2
- Phase II results
- 76% showed bone metastasis shrinking
- 108 patients, 21 demonstrated complete resolution of bone lesions and 61 had partial shrinkage

Choueri T et al 2018

Radium 223

- Radium 223 and pembrolizumab
- Prepare the microenvironment
- Principles and challenges

Apalutamide

- First drug in prostate cancer to prevent metastasis

Thank You

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