VRAAG 1: WAT IS HET EFFECT VAN BEHANDELING MET BISFOSFONATEN OF DENOSUMAB OP PREVENTIE VAN HYPERCALCIËMIE BIJ PATIËNTEN MET MULTIPEL MYELOOM OF BOTMETASTASEN?

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Ford 2013	• Design: systematic review + meta-analysis • Funding: National Institute for Health Research Health Technology Assessment programme; CoI: see article • Search date: July 2011 • Databases: MEDLINE, EMBASE, The Cochrane Library and Web of Science with Conference Proceedings; 2010 and 2011 meeting abstracts of the American Society of Clinical Oncology (ASCO), American Urological Association and San Antonio Breast Cancer symposium • Study designs: RCTs • N included studies: N=39	• Eligibility criteria: patients with bone metastases from breast cancer, prostate cancer, non-small cell lung cancer (NSCLC) or other solid tumours	Denosumab	• Breast: ○ % hypercalcemia at 1y: Zoledronate 2.6% (3/114) vs. placebo 8.8% (10/113), no p-value (Kohno 2005) ○ % hypercalcemia at 2y: Pamidronate 6% (N=367) vs. placebo 13% (N=387), p=0.001 (Lipton 2000) • Prostate: no data reported • NSCLC: no data reported • Solid tumours: ○ % hypercalcemia: 0% vs. 3%, no p-value (Rosen 2003b)	• Review process done by independent reviewers • English articles only • Included relevant studies: ○ Breast: Kohno 2005, Lipton 2000, Rosen 2003a, Stopeck 2010 ○ Prostate: Fizazi 2011 ○ NSCLC: Rosen 2003b (but did not report hypercalcemia for lung cancer patients) ○ Solid tumours: Rosen 2003b, Rosen 2004
Jakob 2020	• Design: systematic review + meta-analysis • Funding: Federal Ministry for Education and Research (BMBF), Germany Grant no: 01KG1702; CoI: none • Search date: March 2020 • Databases: MEDLINE, EMBASE, The Cochrane Library; trial registers; abstract meetings 2013-2018	• Eligibility criteria: men with prostate cancer and bone metastases	Bisphosphonates or RANK-ligand-inhibitors	• Pamidronate vs. placebo: RR 0.54 (95%CI 0.05-5.85), 1/169 vs. 2/181 (Small 2003) • Zoledronate vs. Clodronate: RR 0.49 (0.05-5.31), 1/69 vs. 2/68 (Wang 2013) • Zoledronate vs. Denosumab: 0/16 vs. 0/33 (Fizazi 2009) • Zoledronate vs. placebo: RR 0.48 (0.06-3.69), 1/429 vs. 3/433 (Pan 2014, TRAPEZE 2016) • Network meta-analysis: ranking P-score, Zoledronate 0.67, Pamidronate 0.60, Clodronate 0.39, placebo 0.35	• High-quality review with review process done by independent reviewers • Included relevant studies: Small 2003, Wang 2013 (abstract), Fizazi 2009, Pan 2014, TRAPEZE 2016

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), Multinational Association of Supportive Care in Cancer (MASCC) • Study designs: RCTs • N included studies: N=25				
Kumar 2011	• Design: systematic review of systematic reviews • Funding: not reported; CoI: not reported • Search date: Nov 2009 • Databases: PubMed, Cochrane Database of Systematic Reviews • Study designs: systematic reviews of RCTs • N included studies: N=11	• Eligibility criteria: RCTs assessing the effect of treatments on multiple myeloma	Bisphosphonates	• Hypercalcemia: RR 0.79 (0.56-1.11), 80/932 vs. 106/1002, p=0.17	• Selection done by two independent reviewers, but unclear for data extraction • Included relevant reviews: Mhaskar 2010
Machado 2009	• Design: systematic review + meta-analysis • Funding: none; CoI: none • Search date: Jan 2009 • Databases: Medline, Embase, CENTRAL • Study designs: RCTs • N included studies: N=18	• Eligibility criteria: cancer patients with bone metastasis	Clodronate Pamidronate Zoledronate	• Clodronate: RR 0.73 (0.56-0.97), 69/533 vs. 99/546, 5 studies • Pamidronate: RR 0.60 (0.41-0.86), 44/1059 vs. 385/1068, 6 studies • Zoledronate: RR 0.27 (0.10-0.72), 5/380 vs. 18/363, 2 studies	• Review process done by independent reviewers • Quality assessment with Jadad scale • Included relevant RCTs: ○ Clodronate: Kristensen 1999 ○ Pamidronate: Berenson 1996, Hortobagyi 1996, Theriault 1999 ○ Zoledronate: Kohno 2005, Rosen 2003b
Mhaskar 2017	• Design: systematic review + meta-analysis • Funding: Leukämie-Initiative Bonn e.v., Germany, Cochrane Haematological Malignancies Group (CHMG), Germany; CoI: none • Search date: July 2017	• Eligibility criteria: patients with diagnosis of multiple myeloma	Bisphosphonates	• Incidence of hypercalcemia: RR 0.78 (0.56-1.09), 80/1054 vs. 108/1120, p=0.14	• High-quality review with review process done by independent reviewers • Included relevant RCTs: ○ Etidronate: Belch 1991 ○ Clodronate: Lahtinen 1992 ○ Pamidronate: Berenson 1998, Gimsing 2010, Musto 2003, Terpos 2000 ○ Ibandronate: Menssen 2002

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Databases: MEDLINE, EMBASE, The Cochrane Library; trial registers; American Society of Hematology • Study designs: RCTs • N included studies: N=24				○ Zoledronate: Garcia-Sanz 2015, Sezer 2010 (abstract)
Ross 2003 Ross 2004	• Design: systematic review + meta-analysis • Funding: funded by a Health and Technology Assessment, NHS Research and Development Grant; CoI: not reported • Search date: June 2001 • Databases: MEDLINE, CANCERLIT, EMBASE, Science Citation Index Expanded, pre-MEDLINE, CENTRAL and DARE, Health Economic Evaluations Database, National Health Service Economic Evaluations Database • Study designs: RCTs • N included studies: N=30 RCTs (SRE review)	• Eligibility criteria: patients with malignancy and bony metastases	Oral or intravenous bisphosphonate in the experimental arm, compared to another bisphosphonate, another recognized treatment for hypercalcaemia, placebo or control group	• Hypercalcemia: OR 0.544 (0.364-0.814), p=0.003 (11 studies, N=3894) ○ 6-12m: OR 0.417 (0.235-0.741), p=0.003 (5 studies, N=1916) ○ 12-18m: OR 0.503 (0.282-0.898), p=0.02 (5 studies, N=1807) ○ 18-24m: OR 0.557 (0.266-1.165), p=0.12 (3 studies, N=1130) ○ ≥24m: OR 0.418 (0.342-0.511), p=0.0001 (2 studies, N=753) ○ Breast cancer: OR 0.427 (0.292-0.625), p=0.0001 (5 studies, N=1364) ○ Multiple myeloma: OR 0.968 (0.687-1.365), p=0.852 (3 studies, N=1079) ○ Pamidronate: OR 0.501 (0.287-0.875), p=0.015 (4 studies, N=1534) ○ Clodronate: OR 0.696 (0.481-1.006), p=0.054 (5 studies, N=811) ○ Zoledronate: OR 0.111 (0.028-0.445), p=0.002 (2 studies, N=1416)	• Review process performed by independent researchers • No language restriction • Included relevant RCTs: Belch 1991, Hortobagyi 1998, Theriault 1999, Berenson 1998, Elomaa 1983, Robertson 1995 (+ 2 unpublished studies)
Santini 2019	• Design: systematic review + meta-analysis • Funding: none; CoI: none • Search date: April 2019 • Databases: Medline, EMBASE and Cochrane Library • Study designs: RCTs • N included studies: N=3	• Eligibility criteria: patients with at least one site of histological confirmed bone metastasis from solid tumors	Zoledronate 12-week vs. 4-week schedule	• Hypercalcemia: 4-week 4/216 vs. 12-week 1/209, RR 3.87 (0.44-34.34)	• Data extraction done by two independent reviewers, but unclear for selection • Included relevant study: Amadori 2013

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Barrett-Lee 2014	• Design: RCT	• Eligibility criteria: 18 years or older; at least one	Ibandronate 50 mg/d for 96 weeks (N=704)	CRITICAL OUTCOMES	Level of evidence: high risk of bias

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	• Funding: Roche Products Ltd (educational grant), supported by National Institute for Health Research Cancer Network, following endorsement by Cancer Research UK (CRUKE/04/022).; CoI: none • Setting: multicentre trial, UK • Sample size: N=1404 • Duration: median follow-up 92 vs. 91 weeks; recruitment Jan 2006 – Oct 2010	radiologically confirmed bone metastasis from a histologically confirmed breast cancer; clinical decision to treat with bisphosphonates within the 3 months before randomisation; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; written informed consent • Exclusion criteria: CNS metastases; current active dental problems; known active peptic ulcer; pregnant or lactating; creatinine clearance lower than 30 mL/min (Cockcroft-Gault); serum bilirubin higher than 1.5 x upper limit of normal (ULN) or aspartate aminotransferase/alanine aminotransferase higher than 3.0 x ULN; bisphosphonate therapy in the previous 6 months; or history of bisphosphonate hypersensitivity • *A priori* patient characteristics: ○ M/F: 11/692 vs. 7/690 ○ Median age: 61 vs. 61y	vs. Zoledronate 4 mg IV every 4 weeks for 96 weeks (N=697)	• Hypercalcaemia: ○ 75/704 (11%) vs. 65/697 (9%) ○ Events: 142 vs. 108	• Central randomisation • Open-label trial • Industry-sponsored
Berenson 2001	• Design: RCT • Funding: supported by a grant from Novartis Pharmaceuticals Corp., East Hanover, NJ; CoI: see artocle • Setting: multicentre study, US and UK • Sample size: N=280 • Duration: 10 months	• Eligibility criteria: patients with a histologically confirmed diagnosis of metastatic breast carcinoma or multiple myeloma and with radiologic evidence of at least one osteolytic lesion; patients with multiple myeloma also were required to have had a previous skeletal event (radiation to bone, pathologic fracture, surgery to bone, spinal cord compression, or hypercalcemia) or to have failed first-line chemotherapy; patients with breast carcinoma had at least 1 osteolytic lesion that measured at least 1 cm in dimension, and multiple myeloma patients had at least	Zoledronic acid 0.4 mg IV every 4 weeks (N=68) vs. Zoledronic acid 2 mg IV every 4 weeks (N=72) vs. Zoledronic acid 4 mg IV every 4 weeks (N=67) vs.	CRITICAL OUTCOMES • Hypercalcaemia: ○ 5/68 (7%) vs. 2/72 (3%) vs. (0/67) 0% vs. 2/73 (3%), no p-value	Level of evidence: unclear risk of bias • Randomisation method not reported • Only the pharmacist at each study center was aware of treatment assignment • ITT analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		1 examinable osteolytic lesion; patients were to have a life expectancy of at least 10 months and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 • Exclusion criteria: patients were excluded if they had osteolytic lesions only in previously radiated areas, had received previous bisphosphonate treatment, had participated in a previous pamidronate protocol, had received other investigational drugs within 30 days, or had a recent history of hypercalcemia or bisphosphonate allergy or sensitivity • *A priori* patient characteristics: ○ M/F: 67/213 ○ Mean age: 57.6 vs. 56.5 vs. 59.9 vs. 57.7y	Pamidronate 90 mg IV every 4 weeks (N=73)		
Choudhury 2011	• Design: RCT • Funding: none; CoI: none • Setting: single centre, India • Sample size: N=256 • Duration: recruitment June 2008 – May 2011	• Eligibility criteria: patients with painful bone metastasis arising from solid tumors, at least 18y; normal renal (serum creatinine less than 1.5 mg/dl) and hepatic function, ECOG performance status 1–4, life expectancy of at least 3 months, normal serum calcium or asymptomatic hypercalcemia, pain score of at least 5 [pain assessed with the worst pain score from the Brief Pain Inventory (BPI): patients must have a 'worst pain score' of ≥5 on a scale of 10 (as scored on the BPI question no. 3: 0 = no pain; 10 = worst possible pain)], pain corresponding to the area of bone metastases • Exclusion criteria: nephrotoxic drugs or osteoclast activity modulators, with the target lesions that were not	Zoledronic acid 4 mg IV every 3-4 weeks (N=84) vs. Ibandronate 6 mg IV every 3-4 weeks (N=89) vs. Pamidronate 90 mg IV every 3-4 weeks (N=83)	CRITICAL OUTCOMES • Hypercalcaemia: 17/60 (28.3%) vs. 29/65 (44.6%) vs. 31/62 (50%)	Level of evidence: high risk of bias • Unclear allocation concealment • Open-label trial • No ITT analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		detectable by conventional techniques, the painful area had received prior radiation or surgery, pathologic fracture, clinical or radiographic evidence of spinal cord compression or cauda equina syndrome, with hematological malignancy, with pregnancy or lactation and if were unlikely to cooperate fully during the study • *A priori* patient characteristics: ○ M/F: 50/10 vs. 53/12 vs. 51/11 ○ Mean age: 53.1 vs. 51.8 vs. 53.3y ○ Cancer type: lung N=78, breast N=29, prostate, N=16			
Clemons 2021a Clemons 2021b	• Design: RCT • Funding: supported by the Rethinking Clinical Trials Program (REaCT), the Canadian Institute of Health Research (Patient Oriented Research grant), Cancer Care Ontario – Government of Ontario (Clinical Programs and Quality Initiatives grant 2017 and 2018 competitions), the Ottawa Hospital Foundation and its generous donors, and the Canadian Cancer Clinical Trials Network (3CTN); CoI: none • Setting: multicentre study, Canada • Sample size: N=263 • Duration: maximum follow-up 3.7 vs. 3.6y; recruitment Aug 2016 – June 2018	• Eligibility criteria: patients with bone metastases from either metastatic breast or castration resistant prostate cancer, who were either going to start or were already receiving bone-targeted agents (either denosumab, pamidronate, or zoledronate) • *A priori* patient characteristics: ○ M/F: 52/81 vs. 51/79 ○ Median age: 67 vs. 68y ○ Cancer type: breast N=160, prostate N=103	4-weekly bone-targeted agents for 2y (N=133) vs. 12-weekly bone-targeted agents for 2y (N=133)	CRITICAL OUTCOMES • Hypercalcaemia: 4/133 (3.0%) vs. 4/130 (3.1%)	Level of evidence: unclear risk of bias • Web-based randomisation system, but unclear allocation concealment • Stratification by tumour type • After enrolment, neither investigators nor participants were masked to treatment allocation
Diel 2015	• Design: combined analysis of 2 RCTs	• Eligibility criteria: patients with a primary diagnosis of either breast cancer (N = 2046), other solid tumours or multiple	Denosumab 120 mg IV every 4 weeks (N=1912)	CRITICAL OUTCOMES • Hypercalcaemia: 32/1912 (1.7%) vs. 52/1910 (2.7%)	Level of evidence: low risk of bias

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Funding: Amgen Inc; CoI: list provided in article • Setting: multicentre, Europe and US • Sample size: N=3822 • Duration: median time on-study 12.9 months; recruitment Apr 2006 – May 2008	myeloma (N = 1776) with radiographic evidence of at least one bone metastasis; an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 1 or 2; and adequate organ function • Exclusion criteria: creatinine clearance <30 mL/min, if they had received IV bisphosphonates for bone metastases, or if they had hypercalcemia of malignancy • *A priori* patient characteristics: ○ M/F: 596/1316 vs. 561/1349 ○ Mean age: 58 vs. 59y ○ Cancer type: breast N=2046, NSCLC N=702, multiple myeloma N=180	vs. Zoledronic acid 4 mg IV every 4 weeks (N=1910)	○ Breast: 19/1026 vs. 31/1020 ○ NSCLC: 11/350 vs. 9/352 ○ Multiple myeloma: 1/87 vs. 6/93	• Interactive voice response system • Stratification by tumour type • Study sponsors and personnel, investigators and patients remained blinded to treatment assignment through completion of the primary analysis of each study
Elomaa 1983	• Design: RCT • Funding: supported by grants from Cancer Society of Finland, the Finnish Cultural Foundation, and Nordisk Insulin Foundation; CoI: not reported • Setting: single university centre, Finland • Sample size: N=34 • Duration: 12 months	• Eligibility criteria: normocalcaemic women with multiple osteolytic bone metastases due to breast cancer • *A priori* patient characteristics: ○ M/F: 0/100 ○ Mean age: 52y	Clodronate 1600 mg/d po for 3-9 months (N=17) vs. Placebo (N=17)	CRITICAL OUTCOMES • Hypercalcaemia: 1/17 vs. 4/17, no p-value	Level of evidence: unclear risk of bias • Unclear randomisation method and allocation concealment • Unclear blinding
Glover 1994	• Design: RCT • Funding: Supported by CIBA-GEIGY Pharmaceuticals, Summit, New Jersey; CoI: not reported • Setting: multicentre trial, US • Sample size: N=61 • Duration: 3 months	• Eligibility criteria: ambulatory female patients age 18 years or older with breast cancer metastatic to bone and a life expectancy of at least 3 months • *A priori* patient characteristics: ○ M/F: 0/100 ○ Mean age: 53.6 vs. 50.1 vs. 52.1 vs. 54.1y	Pamidronate 30 mg IV every 2 weeks for 12 weeks (N=14) vs. Pamidronate 60 mg IV every 4 weeks for 12 weeks (N=17) vs. Pamidronate 60 mg IV every 2 weeks for 12 weeks (N=14) vs.	CRITICAL OUTCOMES • Hypercalcaemia: no clinical episodes of hypercalcemia were observed during the trial	Level of evidence: high risk of bias • Computer-generated randomization list • Unclear allocation concealment • Open label trial

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
			Pamidronate 90 mg IV every 4 weeks for 12 weeks (N=15)		
Hortobagyi 1996 Hortobagyi 1998	• Design: RCT • Funding: not reported; CoI: not reported • Setting: multicentre study, US, Australia, Canada • Sample size: N=382 • Duration: median follow-up 25.7 vs. 27.8 months	• Eligibility criteria: women with stage IV metastatic breast cancer and at least one predominantly lytic metastatic bone lesion at least 1 cm in diameter • Exclusion criteria: patients were ineligible for the study if they had a skeletal complication (a pathologic fracture, the need for radiation to bone or bone surgery, or spinal cord compression due to vertebral collapse) or a corrected serum calcium concentration (corrected for serum albumin concentration) above 12.0 mg per deciliter (3.0 mmol per liter) during the two weeks before enrollment, a serum creatinine concentration above 2.5 mg per deciliter (220 mmol per liter), ascites or a serum total bilirubin concentration above 2.5 mg per deciliter (43 mmol per liter), or a New York Heart Association (NYHA) ranking of class III or IV; patients were also excluded from the study if they were treated with a bisphosphonate (except as part of the study) during the 60 days before enrollment or at any time during the trial or if they had been treated for bone pain with radiation, corticosteroids (except as part of the patient's chemotherapeutic regimen), calcitonin, or plicamycin during the 2 weeks before enrollment • *A priori* patient characteristics: ○ M/F: 0/382 ○ Mean age: 57 vs. 56y	Pamidronate 90 mg IV every 4 weeks, 12 times (N=185) vs. Placebo (N=197)	CRITICAL OUTCOMES • Hypercalcaemia: ○ After 3 cycles: 2/185 (1%) vs. 11/195 (6%), p=0.02 ○ After 6 cycles: 9/185 (5%) vs. 15/195 (6%), p=0.26 ○ After 9 cycles: 10/185 (5%) vs. 22/195 (11%), p=0.04 ○ After 12 cycles: 11/185 (6%) vs. 24/195 (12%), p=0.03 ○ 15 months: 11/185 (6%) vs. 28/195 (14%), p=0.007 ○ 18 months: 11/185 (6%) vs. 30/195 (15%), p=0.003 ○ 21 months: 11/185 (6%) vs. 30/195 (15%), p=0.003 ○ 24 months: 13/185 (7%) vs. 30/195 (15%), p=0.01	Level of evidence: low risk of bias • A site-specific, computer-generated randomization list was provided in advance to the study pharmacist at each site • Study personnel, as well as the patients and investigators, remained unaware of the treatment assignments • Two patients assigned to the placebo group did not have bone metastases and were not included in the efficacy analyses

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Kristensen 1999	• Design: RCT • Funding: by a grant from Astra Denmark A/S.; CoI: not reported • Setting: single university centre, Denmark • Sample size: N=100 • Duration: unclear	• Eligibility criteria: women were eligible if they had histologically verified adenocarcinoma of the breast and recurrence in bone either histologically or on X-ray; if they were previously untreated or had received firstline systemic antineoplastic treatment for less than 6 months; if they had a life expectancy of more than 6 months; and if they gave informed consent • Exclusion criteria: patients could not participate if they were younger than 18 years, had serum ionized calcium (S-Ca2+) above 1.40 mmol/L, had fractures in weight-bearing bones, had a known metabolic bone disease, were treated with hypocalcaemic drugs less than 1 month before randomization, had known intolerance to bisphosphonates, had another malignant disease except in situ carcinoma of the uterine cervix and basocellular carcinoma of the skin, predictable low compliance, or had been admitted into the trial previously • *A priori* patient characteristics: ○ M/F: 0/100 ○ Median age: 53.1 vs. 53.4y	Clodronate 800 mg po 2x/d, for a maximum of 2 years (N=49) vs. No Clodronate (N=51)	CRITICAL OUTCOMES • Hypercalcaemia (as first skeletal event): 3/49 vs. 4/51, no p-value	Level of evidence: high risk of bias • Computer-generated randomization list • Unclear allocation concealment • Open label trial
Murakami 2014	• Design: RCT • Funding: not reported; CoI: see article for list • Setting: multicentre study, Japan • Sample size: N=100 • Duration: 1 year follow-up	• Eligibility criteria: patients were required to be histologically or cytologically diagnosed with NSCLC and bone metastases (at least one bone metastasis that had not been treated with radiation therapy) and to have had previous treatment with one or two chemotherapy regimens; age of ≥20 years, Eastern Cooperative Oncology Group performance status of	Zoledronic acid 4 mg IV every 3 weeks (N=50) vs. No Zoledronic acid (N=50)	CRITICAL OUTCOMES • Hypercalcaemia: 2/49 (4%) vs. 8/50 (16%)	Level of evidence: high risk of bias • Unclear randomisation method and allocation concealment • Open label trial

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		0–2, measurable disease, no history of chemotherapy with docetaxel, no history of prior treatment with zoledronic acid, adequate baseline organ function (leukocyte count ≥3500/mm3; absolute neutrophil count ≥2000/mm3; hemoglobin ≥9.0 g/dL; platelet count ≥100 000/mm3; total bilirubin ≤2.0 mg/dL; aspartate aminotransferase and alanine aminotransferase levels ≤100 IU/L; creatinine clearance, ≥30 mL/min; and SpO2 under room air, ≥90%) • Exclusion criteria: active concomitant malignancy, space fluid collection requiring drainage, radiographic signs of interstitial pneumonia or pulmonary fibrosis, active SRE at the time of registration, hypercalcemia requiring prompt treatment, active periodontal disease or severe comorbidities (active infectious disease, severe heart disease, uncontrolled diabetes mellitus, gastrointestinal bleeding, intestinal paralysis, bowel obstruction or psychiatric disease), or a history of drug allergy; patients receiving systemic steroid medication and pregnant or breast-feeding women were also excluded • *A priori* patient characteristics: ○ M/F: 31/19 vs. 32/18 ○ Median age: 62 vs.63y			
Pivot 2011	• Design: RCT • Funding: Roche SA; CoI: some authors work for Roche • Setting: multicentre study, France • Sample size: N=334 • Duration: 28 days	• Eligibility criteria: adult females having a breast adenocarcinoma, documented by histology, with one or more bone metastases confirmed by imaging • Exclusion criteria: creatinine clearance <30 mL/min, Karnofsky index <60, life	Ibandronate 6 mg IV over 15 min (N=165) vs. Ibandronate 6 mg IV over 60 min (N=169)	CRITICAL OUTCOMES • Hypercalcaemia was reported five times in three patients and considered serious in one case; no real comparison reported	Level of evidence: high risk of bias • Randomization was performed using a minimization algorithm, taking into account the center, baseline creatinine clearance and time since

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		expectancy <6 months, tooth/jaw disorder or surgery in the past six week, history of osteonecrosis of the jaw or delayed healing after dental surgery, uncontrolled brain metastasis, severe sepsis, systemic disease involving renal lesions, rapidly progressive renal failure, uncontrolled cardiac disorder, calcaemia <2.0 mmol/L or v>2.7 mmol/L, concomitant nephrotoxic chemotherapy (methotrexate > 50 mg/m2 or cisplatin) eligibility for hematopoietic stem cell transplantation, bisphosphonate therapy in the past three weeks, pregnancy or lactation, and hypersensitivity to bisphosphonates • *A priori* patient characteristics: ○ M/F: 0/334 ○ Mean age: 59 vs. 60y			diagnosis of bone metastases • Computer-generated randomization list • Unclear allocation concealment • Open label trial • ITT population: N=315
Robertson 1995	• Design: RCT • Funding: Supported by Boehringer Mannheim, Livingston, United Kingdom; CoI: not reported • Setting: single university centre, UK • Sample size: N=55 • Duration: unclear	• Eligibility criteria: patients with proven malignant disease and judged to have bone pain in association with progressing bone metastases that had been resistant to first-line antitumour therapy • Exclusion criteria: life expectancy less than 2 months, inability to swallow oral medication, presence of significant renal dysfunction (creatinine concentration > 250 pmol/L), and previous or current treatment with bisphosphonates • *A priori* patient characteristics: ○ M/F: unclear ○ Mean age: 60 vs. 65y ○ Cancer type: breast N=28, lung N=4, prostate N=4, myeloma/lymphoma N=4	Clodronate 1600 mg/day po (N=27) vs. Placebo (N=28)	CRITICAL OUTCOMES • Hypercalcaemia: ○ 0/27 (0%) vs. 2/28 (7%), no p-value	Level of evidence: unclear risk of bias • Randomisation method and allocation concealment unclear • Double-blind, but unclear if outcome assessors were blinded

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Theriault 1999	• Design: RCT • Funding: supported by a grant from Novartis Pharmaceuticals, East Hanover, NJ.; CoI: not reported • Setting: multicentre study, US, Australia, Canada • Sample size: N=371 • Duration: median follow-up 36.8 vs. 37.1 months	• Eligibility criteria: ambulatory women 18 years of age or older with a confirmed diagnosis of breast cancer and two or more predominantly lytic metastatic bone lesions • Exclusion criteria: patients were not to have had a skeletal event in the 2 weeks before trial entry and were to have an estimated life expectancy of 9 months with no significant renal, hepatic, or cardiac impairment • *A priori* patient characteristics: ○ M/F: 0/371 ○ Mean age: 60 vs. 62y	Pamidronate 90 mg IV every 4 weeks for 24 cycles (N=182) vs. Placebo (N=189)	CRITICAL OUTCOMES • Hypercalcaemia: (skeletal morbidity rate, i.e. N complications/year) ○ After 6 cycles: 0.03 vs. 0.11, p=0.169 ○ After 12 cycles: 0.05 vs. 0.14, p=0.143 ○ After 18 cycles: 0.06 vs. 0.15, p=0.095 ○ After 24 cycles: 0.06 vs. 0.17, p=0.037	Level of evidence: unclear risk of bias • Site-specific, computer-generated randomization list • Unclear allocation concealment • Study personnel, as well as the patients and investigators, remained unaware of the treatment assigned
van Holten-Verzantvoort 1993 van Holten-Verzantvoort 1987	• Design: RCT • Funding: grants from the Dutch Cancer Society, Amsterdam, The Netherlands, ((KVO 83/09) and the Prevention Fund, The Hague, The Netherlands, (28-B/141).; CoI: not reported • Setting: multicentre study, the Netherlands • Sample size: N=161 • Duration: median follow-up 18 vs. 21 months	• Eligibility criteria: patients with breast cancer and established (predominantly) osteolytic metastases, with or without other sites of metastases • *A priori* patient characteristics: ○ M/F: 0/161 ○ Mean age: 61.0 vs. 61.4y	Pamidronate 300 mg/d (N=81) vs. No Pamidronate (N=80)	CRITICAL OUTCOMES • Hypercalcaemia: mean event rate 0.5 vs. 1.6, p=0.003	Level of evidence: high risk of bias • Unclear randomisation method and allocation concealment • Open label trial

Abbreviations: 95%CI: 95% confidence interval; CoI: conflict of interest; IV: intravenous; ITT: intention to treat; M/F: male/female;; po: per os; NSCLC: non-small cell lung cancer; RCT: randomised controlled trial; RR: relative risk; SC: subcutaneously; SD: standard deviation; US: United States.

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