TABLE 121 Breast cancer studies

Study ID and country	Reason for exclusion	Participants (demographics)	Participants (cancer details)	Participants (bone metastasis details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Body 2003[71] (secondary publication Diel 2004[140]) Europe, Kuwait, Russian Federation, South Africa, USA	Definition of SRE used is not comparable	Total patients, *n*: 466 Mean age (SD): 54.5–56.1 (10.9–11.5) years No. of females: 466 Previous SREs: NR ECOG status: WHO performance –0 = 21% 1 = 57% 2 = 20% 3 = 1% 4 = <1%	Primary tumour type: breast cancer. Time from diagnosis of cancer to bone metastases: mean 46–54.7 (SD 50.2–59.0) months. Presence of other metastases: bone metastasis, lung metastases, other metastases	Time from diagnosis of bone metastases to randomisation: mean 15.4–17.4 (SD 19–21.8) months. Proportion lytic vs blastic: NR. Prior treatments: chemotherapy/ hormonal therapy = 84%; radiotherapy = 31%	Bone events were defined as any of vertebral fractures; pathological non-vertebral fractures; radiotherapy for bone complications (uncontrolled bone pain or impending fractures); or surgery for bone complications (fractures or impending fractures)	Length of intervention: 60 (min.) –96 (max.) weeks; length of follow-up: NR	Roche, Switzerland	A: 2 mg ibandronate intravenously every 3 or 4 weeks for 96 weeks (max.) or 60 weeks (min.) (*n* = 154) B: 6 mg ibandronate intravenously every 3 or 4 weeks for 96 weeks (max.) or 60 weeks (min.) (*n* = 154) C: placebo intravenously every 3 or 4 weeks for 96 weeks (max.) or 60 weeks (min.) (*n* = 158)

Study ID and country	Reason for exclusion	Participants (demographics)	Participants (cancer details)	Participants (bone metastasis details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Body 2004,[72] Europe, Australia, USA Secondary publication Tripathy 2004,[166] USA, Australia, New Zealand, Bulgaria, Russian Federation and South Africa	Definition of SRE used is not comparable (Definition did not include SCC)	Total patients, *n*: 564 (Body 2004); 435 (Tripathy 2004) Median age (range): 56 (26–87); 57 (27–92) years No. of females: 100% Previous SREs: 95 ECOG status: WHO grade 0 or 1 = 169 WHO grade 2 = 31	Primary tumour type: breast cancer. Time from diagnosis of cancer to first drug intake: median 3.44 to 3.87 years. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: median 0.46 to 0.48 years. Proportion lytic vs blastic: 16%–23%/8%–14% (Tripathy 2004). Prior treatments: 32.2–39.2% with cytotoxic drugs (Tripathy 2004)	Skeletal complications included vertebral fractures, pathological non-vertebral fractures, radiotherapy for bone complications (uncontrolled bone pain or impending fractures) and surgery for bone complications (fractures or impending fractures)	Length of intervention: 96 weeks (outcomes assessed at 4-weekly clinic visits). Length of follow-up: NR	Roche	A: 20 mg oral ibandronate once daily for 96 weeks (NR) B: 50 mg oral ibandronate once daily for 96 weeks (*n* = 287) C: placebo once daily for 96 weeks (n = 277)
Elomaa 1988[73] Finland	Definition of SRE used is not comparable (Measured new bone metastases, fractures and hypercalcaemia)	Total patients, *n*: 34 Median age (range): NR No. of females: 34 Previous SREs: NR ECOG status: NR	Primary tumour type: breast cancer. Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: multiple osteolytic bone metastases due to breast cancer	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs blastic: all lytic. Prior treatments: hormonal and cytotoxic therapy	Measured new bone metastases, pathological bone fracture and hypercalcaemia	Length of intervention: 12 months. Length of follow-up: 24 months	NR	A: 1.6g clodronate once daily for 12 months (*n* = 17) B: placebo (*n* = 17)
Heras 2009[74] Greece	Definition of SRE used is not comparable (Definition of SREs included 'change in antineoplastic therapy')	Total patients, *n*: 150 Mean age (SD): 58 (5) years No. of females: 148 (2 males) Previous SREs: NR ECOG status: NR	Primary tumour type: breast cancer. Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs blastic: NR. Prior treatments: NR	SREs included pathological bone fracture, SCC, radiation therapy to bone, change in antineoplastic therapy and surgery to bone	Length of intervention: 24 months. Length of follow-up: NR	NR	A: 6 mg ibandronate intravenously every 4 weeks for 24 months (NR) B: placebo (NR)

continued

TABLE 121 Breast cancer studies (*continued*)

Study ID and country	Reason for exclusion	Participants (demographics)	Participants (cancer details)	Participants (bone metastasis details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Kristensen 1999[75] Denmark	Definition of SRE used is not comparable (skeletal events were defined as hypercalcaemia, fractures and radiotherapy)	Total patients, *n*: 100 Median age (range): 53.1–53.4 (34.0- 73.8) years No. of females: 100 Previous SREs: NR ECOG status: WHO performance- 0 = 39 1 = 32 2 = 22 3 = 4 4 = 3	Primary tumour type: adenocarcinoma of the breast and recurrence in bone either histologically or on X-ray. Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic/mixed/sclerotic/unknown: 33%/44%/22%/1%. Prior treatments: 30%	'Events related to the skeleton were defined as hypercalcaemia with serum Ca^{2+} >1.40 mmol/l, a new fracture or radiotherapy to a bone metastasis'	Length of intervention: 24 months. Length of follow-up: NR	NR	A: 400 mg of clodronate twice daily (*n* = 49) B: no clodronate in addition to chemotherapy and/or endocrine therapy (*n* = 51)
Paterson 1993[76] UK and Canada	Definition of SRE used is not comparable (measured hypercalcaemia, vertebral and non-vertebral fractures and requirement for radiotherapy for bone pain)	Total patients, *n*: 173 Median age (range): 58–61 (26–77) years No. of females: NR Previous SREs: NR ECOG status: NR	Primary tumour type: breast cancer. Time from diagnosis of cancer to metastases: 30–31 months. Presence of other metastases: metastatic skeletal disease	Time from diagnosis of bone metastases to randomisation: 12–15 months. Proportion lytic vs blastic: NR. Prior treatments: 66% (endocrine) 43% (chemotherapy)	Measured hypercalcaemia, vertebral and non-vertebral fractures and requirement for radiotherapy for bone pain	Length of intervention: 18 months. Length of follow-up: median 14 range (4–37) months for patients still alive	Medical research programme grant from the Breast Cancer Research Trust	A: 1600 mg of clodronate once daily (or 800 mg twice daily for gastrointestinal intolerance) for 18 months extended till 3 years (*n* = 85) B: Placebo (*n* = 88)

max., maximum; min., minimum; NR, not reported.

TABLE 122 Prostate cancer studies

Study ID and country	Reason for exclusion	Participants (demographics)	Participants (cancer details)	Participants (bone metastases details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Adami 1985[209] and 1989[77] Italy	Only painful metastases, intravenous clodronate	Total patients, *n*: 64 Mean age: 64 (42–79) years Previous SREs: NR ECOG status: NR	Primary tumour type: prostate cancer. Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs blastic: NR. Prior treatments: 18 orchidectomy and 16 estramustine	NA	Length of intervention: 2–11 weeks. Length of follow-up: 42 patient-years	NR	A: 300 mg intravenous clodronate daily for 2 weeks ($n = 13$) B: 100 mg intramuscular clodronate daily for 2 weeks ($n = 12$) C: 1200 mg oral clodronate for 2 weeks ($n = 11$) D: Placebo ($n = 6$) E: Maintenance therapy – intravenous clodronate (300 mg) followed by oral for 6 weeks (1200 mg) ($n = 18$)

continued

TABLE 122 Prostate cancer studies (*continued*)

Study ID and country	Reason for exclusion	Participants (demographics)	Participants (cancer details)	Participants (bone metastases details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Buchali 1988[78] Germany	SRE definition not reported	Total patients, *n*: 49 Mean age 67.4–66.5 years Previous SREs: NR ECOG status: NR	Primary tumour type: bioptically proven prostatic carcinoma with multiple skeletal metastases. Time from diagnosis of cancer to randomisation: 1.82–2.19 years. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs blastic: NR. Prior treatments: NR Pain: 84%	NR	Length of intervention: 12 months Length of follow-up: 12 months	NR	A: Three injections of 75 MBq strontium-89 chloride at monthly intervals ($n = 25$) B: Placebo ($n = 24$)
Dearnaley 2003[79] UK and New Zealand	Hormone-sensitive prostate cancer	Total patients, $n = 311$ Mean age: 71 (47–88) years Previous SREs: NR ECOG status: 0 = 65–66%, 1 = 30–27% and 2 = 5–7%	Primary tumour type: patients with prostate cancer who were commencing or showing positive response to first-line therapy. Time from diagnosis of cancer to randomisation: 5–5.5 months. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: 2.5–3 months. Proportion lytic vs blastic: NR. Prior treatments; NR. Pain: NR	'Similar to the "SRE" end point that has been used in other studies of Bps, except this definition includes evidence of asymptomatic disease progression'	Length of intervention: median 16.1–17.1 months Length of follow-up: median 59 months	MRC and Boehringer Mannheim	A: Oral clodronate 2080 mg daily ($n = 155$) B: Placebo ($n = 156$)
Elomma 1992[80] Finland	Only painful metastases	Total patients, $n = 75$ Mean age: 72–73 (60–83) years Previous SREs: NR ECOG status; NR	Primary tumour type: CRPC. Time from diagnosis of cancer to randomisation: 37–38 months. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs blastic: NR. Prior treatments: NR. Pain: 100%	NR	Length of intervention: 6 months Length of follow-up: 12 months	Finnish Cancer foundation and Leiras Pharmaceutical Company	A: Clodronate 3.2 g for 4 weeks then 1.6 g ($n = 36$) B: Placebo ($n = 39$)

Study ID and country	Reason for exclusion	Participants (demographics)	Participants (cancer details)	Participants (bone metastases details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Ernst 2003[81] Canada	Only painful metastases, unlicensed administration of clodronate	Total patients, $n = 209$ Median age: 70.1–70.6 years Previous SREs: NR ECOG status: 0 = 9–13%, 1 = 58–62%, 2 = 29–20%, 3 = 5%	Primary tumour type: hormone-resistant prostate cancer. Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs blastic: NR. Prior treatments: NR. Pain: 100%	Hypercalcaemia, pathological fractures and palliative radiotherapy	Length of intervention: NR. Length of follow-up: NR	Immunex Corporation	A: Clodronate 150 mg intravenously every 3 weeks plus mitoxantrone and prednisolone ($n = 104$) B: Placebo plus mitoxantrone and prednisolone ($n = 105$)
Kylmala 1993[82] Finland (similar data set to Elomma)	Only painful metastases	Total patients, $n = 99$ Mean age: 71–72 (47–90) years Previous SREs: NR ECOG status: NR	Primary tumour type: castration-resistant prostate. Time from diagnosis of cancer to randomisation: 37–38 months. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs blastic: NR. Prior treatments: NR. Pain: 100%	NR	Length of intervention: 6 months. Length of follow-up: 6 months	Finnish Cancer foundation and Leiras Pharmaceutical Company	A: Clodronate (3.2 g for 4 weeks then 1.6 g for 5 months) plus estramustine (280 mg twice daily) ($n = 50$) B: Estramustine alone (280 mg twice daily) ($n = 49$)
Kylama 1997[83] Finland	Only painful metastases and unlicensed dose of clodronate	Total patients, $n = 57$ Mean age: 74 (52–86) years Previous SREs: NR ECOG status: NR	Primary tumour type: prostate cancer. Time from diagnosis of cancer to randomisation: NA. Presence of other metastases: NA	Time from diagnosis of bone metastases to randomisation: Clodronate 6 months, placebo 5 months (median). Proportion lytic vs blastic: NA. Prior treatments: 74% orchidectomy, 21% oestrogen, 11% LHRH-agonist, 7% antiandrogens. Pain: 100%	NR	Length of intervention: 12 months. Length of follow-up: 12 months	Finnish Cancer Foundation, Finnish Medical Society Duodecim, Reino Lahtikari Foundation and Leiras Clinical Research	A: Clodronate 300 mg intravenously for 5 days followed by 1.6 g oral for 12 months plus estramustine 280 mg twice daily ($n = 28$) B: Placebo plus estramustine 280 mg twice daily ($n = 29$)

continued

TABLE 122 Prostate cancer studies (*continued*)

Study ID and country	Reason for exclusion	Participants (demographics)	Participants (cancer details)	Participants (bone metastases details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Nilsson 2005[84] Sweden	Only painful metastases and unlicensed dose of clodronate	Total patients, $n = 35$ Mean age: NR Previous SREs: NR ECOG status: NR	Primary tumour type: prostate cancer with persistent bone pain. Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs. blastic: NR. Prior treatments: NR. Pain: 100%	NR	Length of intervention: single dose. Length of follow-up: 12 weeks	NR	A: Strontium-89 chloride 150 MBq single dose at day 0 ($n = 18$) B: FEM (5-fluorouracil, epirubicin and mitomycin-C) two doses at day 0 and 1 ($n = 17$)
Porter 1992[85] Canada	Study investigating strontium	Total patients, $n = 126$ Mean age: 71.5/71.0 years Previous SREs: NR ECOG status: NR	Primary tumour type: CRPC. Time from diagnosis of cancer to randomisation: 21.5 months/ 25 months (median). Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: 11.0 months/ 11.5 months (median). Proportion lytic vs blastic: NR. Prior treatments: All patients had previous surgical orchidectomy or hormonal treatment. Pain: patients receiving. strong analgesics 56.3%/43.9%	NR	Length of intervention: single dose. Length of follow-up: NR	Amersham International	A: Atrontium-89 chloride 10.8 mCi single dose plus local radiotherapy B: Placebo plus local radiotherapy

Study ID and country	Reason for exclusion	Participants (demographics)	Participants (cancer details)	Participants (bone metastases details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Quilty 1994[86] UK	Only painful metastases	Total patients, $n = 305$ Mean age: 69, 68, 69, 70 years Previous SREs: NR ECOG status: NR	Primary tumour type: CRPC. Time from diagnosis of cancer to randomisation: 10, 9, 10, 13 months. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: 10, 10, 12, 11 months. Proportion lytic vs blastic. Prior treatments: orchidectomy or hormonal therapy. Pain: 100%	NR	Length of intervention: 12 weeks. Length of follow-up: 12 weeks	Amersham International	A: Strontium-89 200 MBq intravenously and local field radiotherapy ($n = 76$) B: External-beam radiotherapy and local field radiotherapy ($n = 72$) C: Strontium-89 200 MBq intravenously and hemibody radiotherapy ($n = 77$) D: External-beam radiotherapy and hemibody radiotherapy ($n = 80$)
Strang 1997[89] Sweden	Only painful metastases and unlicensed dose of clodronate	Total patients, $n = 52$ Mean age: NR Previous SREs: NR ECOG status: NR	Primary tumour type: hormone-refractory prostate cancer. Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs blastic: NR. Prior treatments Pain	NR	Length of intervention: 4 weeks. Length of follow-up: 4 weeks	Leiras OY and ASTRA Lakemedel	A: Clodronate 300 mg intravenously for 3 days followed by 3.2 g for 4 weeks ($n = 25$) B: Placebo ($n = 27$)

continued

TABLE 122 Prostate cancer studies (*continued*)

Study ID and country	Reason for exclusion	Participants (demographics)	Participants (cancer details)	Participants (bone metastases details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Smith 1989[88] USA	Only painful metastases	Total patients, $n = 57$ Mean age: NR Previous SREs: NR ECOG status: NR	Primary tumour type: prostate cancer. Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation. Proportion lytic vs. blastic. Prior treatments: all patients had undergone hormonal treatment. Pain: 100%	NR	Length of intervention: 'at least 1 month' then those who failed to respond crossed over for 6 months. Length of follow-up: NR	NR	A: 7.5 mg/kg etidronate intravenously for 3 days followed by etidronate 200 mg twice daily ($n = 14$) B: 7.5 mg/kg etidronate intravenously for 3 days followed by placebo ($n = 14$) C: Intravenous placebo followed by etidronate 200 mg twice daily ($n = 15$) D: Placebo ($n = 14$)
Small 2003[87] USA and international (pooled results of two RCTs)	Only painful metastases	Total patients, $n = 378$ Median age: 72, 71 years Previous SREs: 48%, 49% ECOG status: NR	Primary tumour type: CRPC. Time from diagnosis of cancer to randomisation: median 3.5, 4.3 years. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: 1.1, 1.6 years. Proportion lytic vs. blastic: NR. Prior treatments: 40%, 43% previous chemotherapy. Pain: 100%	Hypercalcaemia, a pathological fracture, requirement of radiation therapy to bone, surgery to bone, SCC, or need for a spinal orthotic brace	Length of intervention: 27 weeks. Length of follow-up: 27 weeks	Aredia	A: Disodium pamidronate 90 mg intravenously every 3 weeks ($n = 182$) B: Placebo intravenously every 3 weeks ($n = 196$)

NA, not applicable; NR, not reported.

TABLE 123 Other solid tumour studies

Study ID and country	Participants (demographics)	Participants (cancer details)	Participants (bone metastases details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Arican 1999[90] Turkey	Total patients, *n*: 50 Median age: 52–59 (range 27–70) years No. of females: 40 Previous SREs: all with bone pain ECOG status: 1 = 56% 2 = 44%	Primary tumour type: breast cancer (68%); NSCLC (22%); stomach cancer (6%); colorectal cancer (4%). Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic/ mixed: 48%/52%. Prior treatments: chemotherapy (58%); hormonal therapy (42%)	Skeletal morbidities including hypercalcaemia, radiotherapy need, pathological fracture, SCC were measured	Length of intervention: 3 months. Length of follow-up: NR	NR	A: 800 mg of clodronate once daily for 3 months (*n* = 16) B: 1600 mg of oral clodronate once daily for 3 months (*n* = 17) C: Placebo (*n* = 17)
Berenson 2001[91] USA and UK	Total patients, *n*: 280 Mean age: 56.5 (SD 13.6), 59.9 (SD 11.3) years No. of females: 213 Previous SREs: 82% ECOG status: 0 = 25% 1 = 56% 2 = 18% >2 = 1%	Primary tumour type: multiple myeloma (39%) breast carcinoma (61%). Time from diagnosis of cancer to randomisation: mean 63.6 (SD 67.8) – 71.2 (SD 81.9). Presence of other metastases: osteolytic lesion	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs blastic: NR. Prior treatments: NR	Skeletal events were defined as radiation to bone, pathological fracture, surgery to bone, SCC, or hypercalcaemia	Length of intervention; 10 months. Length of follow-up: NR	Novartis	A: 0.4 mg zoledronic acid intravenously (as 2 hour infusion) every 4 weeks for up to 10 months (*n* = 68) B: 2.0 mg zoledronic acid intravenously (as 2-hour infusion) every 4 weeks for up to 10 months (*n* = 72) C: 4.0 mg zoledronic acid intravenously (as 2-hour infusion) every 4 weeks for up to 10 months (*n* = 67) D: 90 mg disodium pamidronate intravenously (as 2-hour infusion) every 4 weeks for up to 10 months (*n* = 73)

continued

TABLE 123 Other solid tumour studies (*continued*)

Study ID and country	Participants (demographics)	Participants (cancer details)	Participants (bone metastases details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Brown 2007[92] Europe (six centres)	Total patients: 125 Median age (range): 64 (28–81) years No. of females: 87 Previous SREs: radiation therapy = 82% ECOG status: Zubrod 0 = 26% Zubrod 1 = 58% Zubrod 2 = 16% (Zubrod is equivalent to ECOG status)	Primary tumour type: breast (70%); prostate (26%); other (4%). Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: bone metastases = 107(86%), liver metastases = 11 (9%), lung metastases = 12 (10%), other metastases = 19 (15%)	Median duration of bone metastases: 10.9 months. Proportion of bone metastases type: lytic/mixed = 58%; sclerotic = 39%; missing = 3%. Prior treatments: BPs = 10%	NR	Length of intervention: 6 weeks. Length of follow-up: NR	NR	A: 800 mg, 1600 mg, 2400 mg or 3200 mg oral clodronate for 6 weeks ($n = 27$) B: Placebo for 6 weeks ($n = 24$)
Heras 2007[93]	Total patients: 73 Age: ≥21 years No. of females: NR Pre-SREs: NR ECOG status: NR	Primary tumour type: colorectal cancer. Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR Proportion lytic vs blastic: NR Prior treatments: NR	SREs were defined as pathological fracture, SCC, radiation therapy to bone, change in antineoplastic therapy and surgery to bone	Length of intervention: 9 months. Length of follow up: NR	NR	A: 6 mg intravenous ibandronate every 4 weeks for 9 months B: Placebo
Jagdev 2001[94] UK	Total patients: 51 Median age (range): 63 (46–79); 58.5 (38–72); 66.5 (38–78) years No. of females: 30 Previous SREs: NR ECOG status: 0 = 6% 1 = 51% 2 = 43%	Primary tumour type: breast (43%); prostate (31%); renal (2%); lung (10%); thyroid (2%); other (12%). Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs blastic: NR. Prior treatments: NR	NR	Length of intervention: 3 months. Length of follow-up	NR	A: 1600 mg of oral clodronate once daily in two divided doses ($n = 18$) B: 1500 mg of single intravenous clodronate + 1600 mg of oral clodronate once daily thereafter ($n = 15$) C: 90 mg disodium pamidronate intravenously as a monthly infusion ($n = 18$)

Study ID and country	Participants (demographics)	Participants (cancer details)	Participants (bone metastases details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Lipton 2003[101] USA (retrospective subgroup analysis from RCT)	Total randomised patients: 766; subset analysed: 74 Median age: 64 years; 65 years No. of males: 59 Previous SREs: 85% ECOG status: ≤1: 85% ≥2: 15%	Primary tumour type: lung carcinoma (381); renal cell carcinoma (74); unknown primary (43); head and neck (17); thyroid (11); other (240). Time from diagnosis of cancer to randomisation: median 25.5; 22.7; 21.2 months. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs blastic: NR. Prior treatments: immunotherapy=58% hormonal therapy= 4%	SREs were defined as pathological fracture; SCC; surgery to bone; or radiation therapy to bone	Length of intervention: 9 months. Length of follow-up: NR	Novartis Pharmaceuticals	A: 4 mg zoledronic acid infusion every 3 weeks for 9 months ($n = 27$) B: 8/4 mg zoledronic acid (8 mg reduced to 4 mg) every 3 weeks for 9 months ($n = 28$) C: Placebo every 3 weeks for 9 months ($n = 19$)
Mystakidou 2008[95] Greece	Total patients: 52 Mean age (SD): 66.9 (10.7), 65.8 (10.7) years No. of males/females: 24/28 Previous SREs: NR ECOG status: NR	Primary tumour type: breast (27%); lung (23%); urogenital (13%); colon (13%); prostate (10%); other (13%). Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: only bone metastases	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs blastic: NR. Prior treatments: surgery (42%); radiotherapy (85%)	NR	Length of intervention: 6 months. Length of follow-up: NR	No funding source	A: 50 mg oral ibandronic acid once daily every 28 days ($n = 26$) B: 6 mg intravenous ibandronic acid infused over 15 minutes every 28 days ($n = 26$)
O'Rourke 1995[96] UK	Total patients: 84 Median age (range): 57 (28 to 80) years No. of male/female: 12/72 Previous SREs: NR ECOG status: NR	Primary tumour type: breast (82%); prostate (7%); lung (4%); kidney (2%); other (6%). Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs blastic: NR. Prior treatments: NR	NR	Length of intervention: 4 weeks. Length of follow-up: 4 weeks	Part funded by Boehringer Mannheim	A: 400 mg oral sodium clodronate once daily for 4 weeks ($n = 20$) B: 1600 mg oral sodium clodronate once daily for 4 weeks ($n = 19$) C: 3200 mg oral sodium clodronate once daily for 4 weeks ($n = 20$) D: Placebo for 4 weeks ($n = 21$)

continued

TABLE 123 Other solid tumour studies (*continued*)

Study ID and country	Participants (demographics)	Participants (cancer details)	Participants (bone metastases details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Piga 1998[97] Italy	Total patients: 50 Median age: 65, 63 years Previous SREs: NR ECOG status: NR	Primary tumour type: lung (34%); colon (20%); kidney (2%); melanoma (6%); unknown (6%); stomach (12%); others (12%). Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs. blastic: NR. Prior treatments: NR	Bone responses measured	Length of intervention: 12 months. Length of follow-up: NR	NR	A: 1600 mg oral clodronate once daily for 12 months ($n = 27$) B: Placebo once daily for 12 months ($n = 23$)
Robertson 1995[98] UK	Total patients, *n*: 55 Mean age (SEM): 60 (4.6); 65 (3.8) years Previous SREs: NR ECOG status: NR WHO grade; 0 = 7% 1 = 43–48% 2 = 18–19% 3 = 7–14%	Primary tumour type: breast (48% to 53%); lung (7%); prostate (7%); myeloma/ lymphoma (7%); other cancers (25% to 26%). Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs blastic: NR. Prior treatments: tamoxifen 22 to 29%; progestogen 14 to 17%; other hormonal 11 to 14%; chemotherapy 11 to 17%. Bone pain (VAS score, median (range): 3.2 (1.6–7.5); 4.8 (2.1–6.9)	Changes in severity of bone pain measured; outcomes on chemotherapy/ radiotherapy, fracture, hypercalcaemia, cord compression reported	Length of intervention, median (range), days: 56 (28–135); 57 (25–171). Length of follow-up: NR	Boehringer Mannheim	A: 1600 mg oral clodronate disodium (400 mg capsules) once daily in divided doses ($n = 27$) B: Placebo ($n = 28$)

Study ID and country	Participants (demographics)	Participants (cancer details)	Participants (bone metastases details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Zaghloul 2010[99] Egypt	Total patients: 40 Median age: 53 (42–70); 55 (41–66) years No. of males: 31 Previous SREs: radiotherapy- 2 fractions (65%); 5 fractions (35%) ECOG status: NR	Primary tumour type: bladder cancer. Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: 25%	Time from diagnosis of bone metastases to randomisation: 1–6 months (57%); ≥7 months (25%). Proportion lytic vs blastic: NR. Prior treatments: palliative radiotherapy given to all patients; analgesics	SREs defined as pathologic fractures, SCC, HCM and the need for radiation or bone surgery	Length of intervention: 6 months. Length of follow-up: 12 month; median 24 (range 8–65) weeks	NR	A: 4 mg intravenous zoledronic acid monthly for 6 months (20) + radiotherapy B: Placebo (20) + radiotherapy
Zhao 2011[100] China	Total patients: 60 Mean age: 47 (30–70); 45 (20–63) years No. of males: 52 Previous SREs: NR ECOG status: 1–2: 7% 3: 38% 4: 47% other: 10%	Primary tumour type: nasopharyngeal carcinoma. Time from diagnosis of cancer to randomisation: NR. Presence of other metastases: NR	Time from diagnosis of bone metastases to randomisation: NR. Proportion lytic vs blastic: NR. Prior treatments: chemotherapy 77%	Radiation to the bone ($n = 7$) and SCC reported ($n = 1$)	Length of intervention: 3 months. Length of follow-up: median 17 months	NR	A: 4 mg intravenous zoledronic acid three times in 4 weeks + chemotherapy (30) B: Chemotherapy (29)

NR, not reported.