TABLE 124 Breast cancer

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Body 2003[71] (secondary publication: Diel 2004[140]) Europe, Kuwait, Russian Federation, South Africa, USA *Only reported in the study by Diel and colleagues[141]	2 mg ibandronate intravenously every 3 or 4 weeks for 96 weeks (max) or 60 weeks (min) ($n = 154$)	Time to first SRE: median 44.6 weeks Time to first and subsequent SRE (MEA): NR Incidence of SREs: 4.24 events per patient SMPR (events per patient-year): • All new bone events: 1.31 ($p = 0.152$) Proportion with SRE: 62.3%	Hypercalcaemia: NR Pain: mean change in the bone pain score between baseline and last assessment = 0.21(SD 0.09); mean change in analgesic score = 0.89 (SD NR) QoL (139): mean overall score between baseline and last assessment (functioning) = –18.1 Overall survival: median 116.4 (95% CI 104 to 133) weeks	Renal impairment: 0.7% ONJ, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	6 mg ibandronate intravenously every 3 or 4 weeks for 96 weeks (max) or 60 weeks (min) ($n = 154$)	Time to first SRE: 50.6 weeks Time to first and subsequent SRE (MEA): NR Incidence of SREs: 2.65 events per patient SMPR (events per patient-year): • All new bone events: 1.19 ($p = 0.004$) • Vertebral fractures: 0.71 ($p = 0.023$) • Non-vertebral fractures: 0.72 ($p = 0.396$) • Events requiring radiotherapy: 0.91 ($p = 0.011$) • Events requiring surgery: 0.56 ($p = 0.075$) Proportion with SRE: 50.6%	Hypercalcaemia: NR Pain: mean change in the bone pain score between baseline and last assessment = –0.28 (SD 1.11); mean change in analgesic score = 0.51(SD 1.54) QoL (137): mean overall score between baseline and last assessment (functioning) = –10.3 Overall survival: median 113.3 (95% CI 97 to 129) weeks	Renal impairment: 2.6% ONJ, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo intravenously every 3 or 4 weeks for 96 weeks (max) or 60 weeks (min) ($n = 158$)	Time to first SRE: 33.1 weeks Time to first and subsequent SRE (MEA): NR Incidence of SREs: 3.64 events per patient SMPR (events per patient-year): • All new bone events: 1.48 • Vertebral fractures: 0.82 • Non-vertebral fractures: 0.81 • Events requiring radiotherapy: 1.09 • Events requiring surgery: 0.62 Proportion with SRE: 62.0%	Hypercalcaemia: NR Pain: mean change in the bone pain score between baseline and last assessment = 0.19 (SD 0.11); mean change in analgesic score = 1.90 (SD 1.64) QoL (143): mean overall score between baseline and last assessment (functioning) = –45.4 Overall survival: median 106.7 (95% CI 95 to 124) weeks	Renal impairment: 1.3% ONJ, acute-phase reaction, hypocalcaemia or any other significant AE: NR

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Body 2004[72] (secondary report: Tripathy 2004[166]) Europe, Australia, USA *Only reported in the study by Tripathy and colleagues[167]	20 mg oral ibandronate once daily for 96 weeks (NR)	Time to first SRE: 76 weeks Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMPR (no. of 12-week periods with new skeletal complications/total observation time): • All new bone events: 0.99 ($p = 0.041$) Proportion with SRE: 46.5	Hypercalcaemia: NR Pain (LOCF bone pain score: change from baseline to study end point): –0.06 QoL: NR Overall survival: NR	Renal impairment: 3.5% Hypocalcaemia: 9% ONJ, acute-phase reaction, or any other significant AE: NR
	50 mg oral ibandronate once daily for 96 weeks ($n = 287$)	Time to first SRE: median 90.3 weeks ($p = 0.089$) Time to first and subsequent SRE (MEA): NR Incidence of SREs: No. of events per patient = 1.15 ($p = 0.008$) No. of 12-week periods with events per patient = 0.71 ($p = 0.015$) SMPR: • All new bone events = 0.99 ($p = 0.041$) • Vertebral fractures = 0.49 ($p = 0.145$) • Non-vertebral fractures = 0.51 ($p = 0.330$) • Need for radiotherapy = 0.80 ($p < 0.004$) • Need for surgery = 0.40 ($p = 0.098$) Proportion with SRE: 45.3% ($p = 0.122$)	Hypercalcaemia: NR Pain: 0.03 QoL: NR Overall survival: 20% died within 96 weeks	Renal impairment: 5.2% Hypocalcaemia: 9.4% ONJ, acute-phase reaction or any other significant AE: NR

continued

TABLE 124 Breast cancer (*continued*)

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
	Placebo once daily for 96 weeks ($n = 277$)	Time to first SRE: median 64.9 weeks Time to first and subsequent SRE (MEA): NR Incidence of SREs: No. of events per patient = 1.85 No. of 12-week periods with events per patient = 0.99 SMPR: • All new bone events = 1.15 • Vertebral fractures = 0.52 • Non-vertebral fractures = 0.52 • Need for radiotherapy = 0.98 • Need for surgery = 0.44 Proportion with SRE: 52.2%	Hypercalcaemia: NR Pain: 0.21 QoL: NR Overall survival: 15% died within 96 weeks	Renal impairment: 4.7% Hypocalcaemia: 5.1% ONJ, acute-phase reaction, or any other significant AE: NR
Elomaa 1988[73] Finland	1.6g clodronate once daily for 12 months ($n = 17$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: 3/17 during treatment; 11/17 after treatment SMR: NR Proportion of each SRE: 1 during treatment; 1 after treatment	Hypercalcaemia: 1 Pain: NR QoL: NR Overall survival: 11 patients	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo ($n = 17$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: 11/17 during treatment; 9/17 after treatment SMR: NR Proportion of each SRE: 4 during treatment; 9 after treatment	Hypercalcaemia: 4 Pain: NR QoL: NR Overall survival: 4 patients	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Heras 2009[74] Greece	6 mg ibandronate intravenously every 4 weeks for 24 months ($n = 150$)	Time to first SRE: median 457 days Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion with SRE: 36% Risk of developing SRE, MEA: HR = 0.69 (95% CI 0.42 to 0.79)	Hypercalcaemia: NR Pain: NR QoL: NR Overall survival: NR	ONJ: none Renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo	Time to first SRE: median 304 days Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion with SRE: 48%	Hypercalcaemia: NR Pain: NR QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
Kristensen 1999[75] Denmark	400 mg of clodronate twice daily ($n = 49$)	Time to first SRE: 15–20 months Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion with SRE: fracture 6%; radiotherapy 16%; hypercalcaemia 6%; total 29%	Hypercalcaemia: 6% Pain: NR QoL: NR Overall survival: NR	Hypocalcaemia: none ONJ, renal impairment, acute-phase reaction or any other significant AE: NR
	No clodronate in addition to chemotherapy and/or endocrine therapy ($n = 51$)	Time to first SRE: 3–5 months Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion with SRE: fracture 25%; radiotherapy 8%; hypercalcaemia 8%; total 41%	Hypercalcaemia: 8% Pain: NR QoL: NR Overall survival: NR	Hypocalcaemia: two patients ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR

continued

TABLE 124 Breast cancer (*continued*)

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Paterson 1993[76] UK and Canada	1600 mg of clodronate once daily (or 800 mg twice daily for gastrointestinal intolerance) for 18 months [extended till 3 years] ($n = 85$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs (events/100 patient-years): • Hypercalcaemic events: 27.9 • Non-vertebral fractures: 31.9 • Vertebral fractures: 84 • Vertebral deformity rate: 168 • No. of courses of radiotherapy: 74.8 SMR: 218.6/100 patient-years Proportion with SRE: patients requiring radiotherapy: 40% Total no. of hypercalcaemic episodes: 28 Total no. of vertebral fractures: 58	Hypercalcaemia: 24% Pain: NR QoL: NR Overall survival: at 1 year 62%; at 2 years 35%	Hypocalcaemia: three patients ONJ, renal impairment, acute-phase reaction, or any other significant AE: NR
	Placebo ($n = 88$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs (events/100 patient-years): • Hypercalcaemic events: 51.8 • Non-vertebral fractures: 39.8 • Vertebral fractures: 124.1 • Vertebral deformity rate: 252 • No. of courses of radiotherapy: 42 SMR: 304.8/100 patient-years Proportion of each SRE: patients requiring radiotherapy: 48% Total no. of hypercalcaemic episodes: 52 Total no. of vertebral fractures: 90	Hypercalcaemia: 35% Pain: NR QoL: NR Overall survival: at 1 year 54%; at 2 years 14%	Hypocalcaemia: two patients ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR

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

TABLE 125 Prostate cancer

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Adami 1985[209] and 1989[77] Italy	300 mg intravenous clodronate daily for 2 weeks ($n = 13$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 'most had bone pain relapse fairly soon' QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	100 mg intramuscular clodronate daily for 2 weeks ($n = 12$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 'significant fall in analgesic consumption but not [VAS] pain' QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	1200 mg oral clodronate for 2 weeks ($n = 11$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 'completely ineffective' QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo ($n = 6$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 'stopped early because of ethical reasons' QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	Maintenance therapy: intravenous clodronate (300 mg) followed by oral for 6 weeks (1200 mg) ($n = 18$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain 'relapse prevented' QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR

continued

TABLE 125 Prostate cancer (*continued*)

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Buchali 1988[78] Germany	Three injections of 75 MBq ^{89}Sr chloride at monthly intervals ($n = 25$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 7/19 had relief QoL: NR Overall survival: survival rate after 2 years 0.46	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo ($n = 24$)	Time to first SRE: NR Time to first and subsequent: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 11/22 had relief ($p = $ NS) QoL: NR Overall survival: survival rate after 2 years 0.04 ($p < 0.05$)	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
Dearnaley 2003[79] UK and New Zealand	Oral clodronate 2080 mg daily ($n = 155$)	Time to first SRE: median 23.6 months Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Analgesic consumption: Increased HR 1.12 (95% CI 0.86 to 1.45) compared with placebo QoL: NR Overall survival: 37.1 months HR 0.80 (95% CI 0.62 to 1.03) compared with placebo BPFS: 49.3% at 2 years HR 0.79 (95% CI 0.61 to 1.02) compared with placebo	Hypocalcaemia: 4% ONJ, renal impairment, acute-phase reaction or any other significant AE: NR
	Placebo ($n = 156$)	Time to first SRE: 19.3 months Time to first and subsequent (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: See above QoL: NR Overall survival: 28.4 months BPFS: 41% at 2 years	Hypocalcaemia: 0% ONJ, renal impairment, acute-phase reaction or any other significant AE: NR

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Elomaa 1992[80] Finland	Clodronate 3.2 g for 4 weeks then 1.6 g for remainder of trial ($n = 36$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 18% pain free and 18% required no analgesics QoL: NR Overall survival: no difference: NR	Renal impairment: 1/36 ONJ, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo ($n = 39$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 15% pain free and 23% required no analgesics QoL: NR Overall survival: no difference	Renal impairment: 0/39 ONJ, acute-phase reaction, hypocalcaemia or any other significant AE: NR
Ernst 2003[81] Canada	Clodronate 150 mg intravenously every 3 weeks plus mitoxantrone and prednisolone ($n = 104$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 46% achieved palliative response to pain (NS), 31% no longer needed analgesics QoL: no over difference in PROSQOLI Overall survival: 10.8 months HR 0.95 (95% CI 0.71 to 1.28) compared with placebo	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo plus mitoxantrone and prednisolone ($n = 105$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 39% achieved palliative response to pain, 25% no longer needed analgesics QoL: no over difference in PROSQOLI Overall survival: 11.5 months	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR

continued

TABLE 125 Prostate cancer (*continued*)

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Kylmala 1993[82] Finland (similar data set to Elomma)	Clodronate (3.2 g for 4 weeks then 1.6 g for 5 months) plus estramustine (280 mg twice daily) ($n = 50$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 'pain relief within 1 month and reduction in analgesics more accentuated in the Clodronate group but NS' QoL: NR Overall survival: median 10 months (NS difference)	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	Estramustine alone (280 mg twice daily) ($n = 49$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 'pain relief within 1 month and reduction in analgesics more accentuated in the Clodronate group but NS' QoL: NR Overall survival: median 12 months	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
Kylmala 1997[83] Finland	Clodronate 300 mg intravenously for 5 days followed by 1.6 g oral for 12 months plus estramustine 280 mg twice daily ($n = 28$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: no statistically significant difference QoL: NR Overall survival: NR	Renal impairment: 0 ONJ, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo plus estramustine 280 mg twice daily ($n = 29$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: no statistically significant difference QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Nilsson 2005[84] Sweden	Strontium-89 chloride 150 MBq single dose at day 0 ($n = 18$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: Significantly lower than baseline ($p = 0.010$). No difference compared with FEM QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia: NR Any other significant 2/14 hospitalised because of side effects
	FEM (5-fluorouracil, epirubicin and mitomycin-C) two doses at day 0 and 1 ($n = 17$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: Significantly lower than baseline ($p = 0.039$). No difference compared strontium QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia: NR Any other significant: seven were hospitalised because of side effects
Porter 1993[85] Canada	Strontium-89 chloride 10.8 mCi single dose plus local radiotherapy	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: no significant difference between arms at 6 months. However, strontium significantly delayed onset of pain in asymptomatic patients QoL: overall strontium significantly improved QoL Overall survival: 27 weeks (median) NS	ONJ, renal impairment, acute-phase reaction, hypocalcaemia: NR Any other significant: higher incidence of thrombocytopenia in Strontium group. Two deaths because of haemorrhage
	Placebo plus local radiotherapy	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: no significant difference between arms at 6 months QoL: overall strontium significantly improved QoL Overall survival: 34 weeks (median) NS	ONJ, renal impairment, acute-phase reaction, hypocalcaemia: NR Any other significant: one death due to haemorrhage

continued

TABLE 125 Prostate cancer (*continued*)

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Quilty 1994[86] UK	Strontium-89 200 MBq intravenously and local field radiotherapy ($n = 76$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 65.1% had some pain relief, 39.7% reduced analgesic intake (NS) QoL: NR Overall survival: no statistical difference ($p = 0.1$)	Renal impairment: 1 patient ONJ, acute-phase reaction, hypocalcaemia: NR Any other significant: lower incidence of nausea and vomiting
	External beam radiotherapy and local field radiotherapy ($n = 72$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 66.7% had some pain relief, 33.3% reduced analgesic intake (NS) QoL: NR Overall survival: no statistical difference ($p = 0.1$)	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	Strontium-89 200 MBq intravenously and hemibody radiotherapy ($n = 77$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 70% had some pain relief, 28.3% reduced analgesic intake (NS) QoL: NR Overall survival: no statistical difference ($p = 0.1$)	ONJ, renal impairment, acute-phase reaction, hypocalcaemia: NR Any other significant: lower incidence of nausea and vomiting
	External beam radiotherapy and hemibody radiotherapy ($n = 80$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 67.4% had some pain relief, 34.8% reduced analgesic intake (NS) QoL: NR Overall survival: no statistical difference ($p = 0.1$)	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Small 2003[87] USA and international (pooled results of two RCTs)	Disodium pamidronate 90 mg intravenously every 3 weeks ($n = 182$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: 'similar between groups' Proportion of each SRE: no significant difference between intervention arms (25% vs 25%)	Hypercalcaemia: <1% Pain: no significant difference between intervention arms QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo intravenously every 3 weeks ($n = 196$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: 'similar between groups' Proportion of each SRE: no significant difference between intervention arms (25% vs 25%)	Hypercalcaemia: 1% Pain: no significant difference between intervention arms QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia: NR Any other significant: none
Smith 1989[88] USA	7.5 mg/kg etidronate intravenously for 3 days followed by etidronate 200 mg twice daily ($n = 14$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 2 patients had minor improvement, 0 had major improvement QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	7.5 mg/kg etidronate intravenously for 3 days followed by placebo ($n = 14$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 2 patients had minor improvement, 2 had major improvement QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	Intravenous placebo followed by etidronate 200 mg twice daily ($n = 15$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 1 patient had minor improvement, 1 had major improvement QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR

continued

TABLE 125 Prostate cancer (*continued*)

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Strang 1997[89] Sweden	Clodronate 300 mg intravenously for 3 days followed by 3.2 g for 4 weeks ($n = 25$)	Time to first SRE: NR Time to first and subsequents SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: no significant difference between groups QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo ($n = 27$)	Time to first SRE: NR Time to first and subsequents SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: no significant difference between groups QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo ($n = 14$)	Time to first SRE: NR Time to first and subsequents SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: one patient had minor improvement, one had major improvement, three recorded decrease in analgesic use QoL: NR Overall survival: NR	ONJ, renal impairment, acute-phase reaction, hypocalcaemia or any other significant AE: NR

NR, not reported; NS, not significant.

TABLE 126 Other solid tumours

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Arican 1999[90] Turkey	800 mg of clodronate once daily for 3 months ($n = 16$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion with SRE: radiotherapy = 2 patients; fracture = 0	Hypercalcaemia: 0 Pain score (% change 0 vs 3 months): –6.25 Performance status (% change 0 vs 3 months): –6.25 QoL: NR Overall survival: NR	Hypocalcaemia: 1 ONJ, renal impairment, acute-phase reaction, or any other significant AE: NR
	1600 mg of oral clodronate once daily for 3 months ($n = 17$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion with SRE: radiotherapy =1 patient; fracture = 0	Hypercalcaemia: 0 Pain score (% change 0 vs 3 months): –15.29 Performance status (% change 0 vs 3 months): –13.23 QoL: NR Overall survival: NR	Hypocalcaemia: 2 ONJ, renal impairment, acute-phase reaction, or any other significant AE: NR
	Placebo ($n = 17$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion with SRE: radiotherapy = 5 patients; fracture = 0	Hypercalcaemia: 1 Pain score (% change 0 vs 3 months): 0.6 Performance status (% change 0 vs 3 months): 0.0 QoL: NR Overall survival: NR	ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR

continued

TABLE 126 Other solid tumours (*continued*)

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Berenson 2001[91] USA and UK	0.4 mg zoledronic acid intravenously (as 2-hour infusion) every 4 weeks for up to 10 months ($n = 68$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion with SRE: Radiation to bone: 24% Any skeletal event + hypercalcaemia: 46% Any skeletal event – hypercalcaemia: 44% Pathological fractures: 28% SCC: 1% Surgery to bone: 7%	Hypercalcaemia: 7% Pain score (mean change from 0 to 18 months): –0.3 (SD 3.23) QoL: NR Overall survival: NR	ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR
	2.0 mg zoledronic acid intravenously (as 2-hour infusion) every 4 weeks for up to 10 months ($n = 72$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion with SRE: Radiation to bone: 19% Any skeletal event + hypercalcaemia: 35% Any skeletal event – hypercalcaemia: 32% Pathological fractures: 22% SCC: 0 Surgery to bone: 3%	Hypercalcaemia: 3% Pain score (mean change from 0 to 18 months): –0.6 (SD 2.19) QoL: NR Overall survival: NR	ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
	4.0 mg zoledronic acid intravenously (as 2-hour infusion) every 4 weeks for up to 10 months ($n = 67$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion with SRE: Radiation to bone: 21% Any skeletal event + hypercalcaemia: 33% Any skeletal event – hypercalcaemia: 33% Pathological fractures: 21% SCC: 3% Surgery to bone: 3	Hypercalcaemia: 0 score (mean change from 0 to 18 months): –0.7 (SD 3.33) QoL: NR Overall survival: NR	ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR
	90 mg disodium pamidronate intravenously (as 2-hour infusion) every 4 weeks for up to 10 months ($n = 73$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion with SRE: Radiation to bone: 18% Any skeletal event + hypercalcaemia: 30% Any skeletal event – hypercalcaemia: 30% Pathological fractures: 21% SCC: 3% Surgery to bone: 4%	Hypercalcaemia: 3% score (mean change from 0 to 18 months): 0.1 (SD 3.28) QoL: NR Overall survival: NR	ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR

continued

TABLE 126 Other solid tumours (*continued*)

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Brown 2007[92] Europe (six centres)	800 mg, 1600 mg, 2400 mg or 3200 mg oral clodronate for 6 weeks ($n = 27$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 8 in 800 mg group; 9 in 1600 mg group; 8 in 2400 mg group; 7 in 3200 mg group; VAS studied but data not reported QoL: NR Overall survival: NR	Renal impairment: 1 (urinary retention in 3200 mg group) Hypocalcaemia: 1 (in 3200 mg group) ONJ, acute-phase reaction, or any other significant AE: NR
	Placebo for 6 weeks ($n = 24$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 7; VAS studied but data not reported QoL: NR Overall survival: NR	ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR
Heras 2007[93] Greece	6 mg intravenous ibandronate every 4 weeks for 9 months	Time to first SRE: median 279 days ($p = 0.009$) Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR (events/year): mean 2.36 ($p = 0.018$) Proportion with SRE: 39% ($p = 0.019$)	Hypercalcaemia: NR Pain: NR QoL: NR Overall survival: NR	'The incidence of renal adverse events was comparable to placebo' ONJ, hypocalcaemia, acute-phase reaction, or any other significant AE: NR
	Placebo	Time to first SRE: median 93 days Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR (events/year): mean 3.14 Proportion with SRE: 78%	Hypercalcaemia: NR Pain: NR QoL: NR Overall survival: NR	Renal adverse events: see above ONJ, hypocalcaemia, acute-phase reaction, or any other significant AE: NR

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Jagdev 2001[94] UK	1600 mg of oral clodronate once daily in two divided doses ($n = 18$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 4/16 showed improvement in clinical score in 3 months QoL: NR Overall survival: NR	ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR
	1500 mg of single intravenous clodronate + 1600 mg of oral clodronate once daily thereafter ($n = 15$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 2/11 showed improvement in clinical score in 3 months QoL: NR Overall survival: NR	ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR
	90 mg disodium pamidronate intravenously as a monthly infusion ($n = 18$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 9/16 showed improvement in clinical score in 3 months ($p < 0.01$ as compared with combination of above group) QoL: NR Overall survival: NR	ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR

continued

TABLE 126 Other solid tumours (*continued*)

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Lipton 2003[101] USA (retrospective subgroup analysis from RCT)	4 mg zoledronic acid infusion every 3 weeks for 9 months ($n = 27$)	Time to first SRE: not reached, $p = 0.006$; time to first pathological fracture: not reached, $p = 0.003$ Time to first and subsequent SRE (MEA): HR: 0.394, $p = 0.008$ Incidence of SREs: 37% ($p = 0.015$) SMR: mean 2.68 events per year, $p = 0.014$ Proportion of each SRE (with 21-day window): Any SRE = 15 Radiation to bone = 8 Vertebral pathological fracture = 1 Non-vertebral pathological fracture = 3 Surgery to bone = 3 SCC = 1 Proportion of each SRE (without 21-day window): Any SRE = 20 Radiation to bone = 11 Vertebral pathological fracture = 1 Non-vertebral pathological fracture = 3 Surgery to bone = 3 SCC = 2	Hypercalcaemia: NR Pain (bone): 14 QoL: NR Overall survival: median 295 days, $p = 0.179$	Renal impairment: 2/18; hypocalcaemia: 5; ONJ, acute-phase reaction, or any other significant AE: NR

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
	8/4 mg zoledronic acid (8 mg reduced to 4 mg) every 3 weeks for 9 months ($n = 28$)	Time to first SRE: mean 140 days, $p = 0.016$; time to first pathological fracture: not reached, $p = 0.027$ Time to first and subsequent (MEA): NR Incidence of SREs: 50% ($p = 0.108$) SMR: mean 1.67 events per year, $p = 0.026$ Proportion of each SRE: NR	Hypercalcaemia: NR Pain (bone): 11 QoL: NR Overall survival: NR	Renal impairment: 4/21; hypocalcaemia: 0 ONJ, acute-phase reaction, or any other significant AE: NR
	Placebo every 3 weeks for 9 months ($n = 19$)	Time to first SRE: mean 72 days; time to first pathological fracture: mean 168 days Time to first and subsequent (MEA) Incidence of SREs: 74% SMR: mean 3.38 per year Proportion of each SRE (with 21-day window): Any SRE = 20 Radiation to bone = 9 Vertebral pathological fracture = 4 Non-vertebral pathological fracture = 9 Surgery to bone = 4 SCC = 3 Proportion of each SRE (without 21-day window): Any SRE = 35 Radiation to bone = 12 Vertebral pathological fracture = 5 Non-vertebral pathological fracture = 11 Surgery to bone = 4 SCC = 3	Hypercalcaemia: NR Pain (bone): 12 QoL: NR Overall survival: median 216 days	Renal impairment: 3/15 Hypocalcaemia: 0 ONJ, acute-phase reaction, or any other significant AE: NR

continued

TABLE 126 Other solid tumours (*continued*)

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Mystakidou 2008[95] Greece	50 mg oral ibandronic acid once daily every 28 days ($n = 26$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 'bone pain scores decreased'; pain in general activity decreased by 65%; interference of pain in enjoyment of life was decreased by 75% QoL (mean increase from baseline at 6 months): physical score 7.5; functional score 6.5; physical 8 and functional 8 scores decreased Overall survival: 7 deaths in 6 months ('not related to drug')	ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR
	6 mg intravenous ibandronic acid infused over 15 minutes every 28 days ($n = 26$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain: 'bone pain scores decreased'; pain in general activity decreased by 66%; interference of pain in enjoyment of life was decreased by 80% QoL (mean increase from baseline at 6 months): physical score 6.0; functional score 6.5; physical 8 and functional 8 scores decreased Overall survival: 2 deaths in 6 months ('not related to drug')	ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
O'Rourke 1995[96] UK	400 mg oral sodium clodronate once daily for 4 weeks ($n = 20$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain score (mean change): 0.1 QoL: NR Overall survival: NR	ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR
	1600 mg oral sodium clodronate once daily for 4 weeks ($n = 19$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain score (mean change): –0.7 QoL: NR Overall survival: NR	ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR
	3200 mg oral sodium clodronate once daily for 4 weeks ($n = 20$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain score (mean change): –0.5 QoL: NR Overall survival: NR	Hypocalcaemia: 1 Any other significant AE: flatulence = 3 ONJ, renal impairment, acute-phase reaction: NR
	Placebo for 4 weeks ($n = 21$)	Time to first SRE: NR Time to first and subsequent SRE (MEA): NR Incidence of SREs: NR SMR: NR Proportion of each SRE: NR	Hypercalcaemia: 2 Pain score (mean change): –1.5 QoL: NR Overall survival: NR	Any other significant AE: flatulence = 0 ONJ, hypocalcaemia, renal impairment, acute-phase reaction: NR

continued

TABLE 126 Other solid tumours (*continued*)

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Piga 1998[97] Italy	1600 mg oral clodronate once daily for 12 months ($n = 27$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: 'no difference in bone responses and rate of skeletal complications was detectable between the two groups' SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain score (change from baseline and at 3 months): –1.1 ($p = 0.424$) QoL: NR Overall survival: NR Karnofsky performance status: 20% increase = 4.2% ($p = 0.323$) 20% decrease = 20.8% stable or minor change = 75%	ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR
	Placebo once daily for 12 months ($n = 23$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: 'no difference in bone responses and rate of skeletal complications was detectable between the two groups' SMR: NR Proportion of each SRE: NR	Hypercalcaemia: NR Pain score (change from baseline and at 3 months): 1.3 QoL: NR Overall survival: NR Karnofsky performance status: 20% increase = 0.0% 20% decrease = 38.1% stable or minor change = 61.9%	ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR
Robertson 1995[98] UK	1600 mg oral clodronate disodium (400-mg capsules) once daily in divided doses ($n = 27$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: Chemotherapy/radiotherapy = 30% Fracture = 15% SCC = NR	Hypercalcaemia: NR Pain (change in bone pain from entry to the average score on subsequent visits) median (range): –0.9 (–2.6 to –0.4), $p = 0.03$ QoL (change in well-being from entry), median (range): 0.3 (–1.0 to 1.2) Overall survival, median (range) days: 240 (25–518)	Hypocalcaemia: 2 ONJ, renal impairment, acute-phase reaction, or any other significant AE: NR

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
	Placebo ($n = 28$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: Chemotherapy/radiotherapy = 32% Fracture = 7% SCC = 11%	Hypercalcaemia: 7% Pain (change in bone pain from entry to the average score on subsequent visits) median (range): 0.4 (–1.0 to 4.0) QoL (change in well-being from entry), median (range): 0.0 (–1.2 to 0.8) Overall survival, median (range) days: 240 (20–486)	Hypocalcaemia: 0 ONJ, hypocalcaemia, renal impairment, acute-phase reaction, or any other significant AE: NR
Zaghloul 2010[99] Egypt	4 mg intravenous zoledronic acid monthly for 6 months ($n = 20$) + radiotherapy	Time to first SRE, median weeks: 16 (4–65), $p = 0.0001$ Time to first and subsequent SRE: HR 0.413, $p = 0.008$ Incidence of SREs, mean (SD): 0.95 (0.9) per person-year, $p = 0.001$ SMR: NR Proportion with >1 SRE: 60%, $p = 0.010$; 1 SRE = 35%; 2 SREs = 15%; 3 SREs = 10%	Hypercalcaemia: NR Pain score, mean (SD): 2.95 (0.3), $p = 0.015$ QoL: NR Overall survival: 36.3 (11.2), $p = 0.004$; 1-year SRE-free survival rate: 27.8 (10.4), $p = 0.001$	ONJ: 0 Renal impairment (elevated Scr): 7 Acute-phase reaction: NR Hypocalcaemia: NR Any other significant: NR
	Placebo ($n = 20$) + radiotherapy	Time to first SRE, median weeks: 8 (4–16) Time to first and subsequent SRE: see intervention group Incidence of SREs, mean (SD): 2.05 (1.0) per person-year SMR: NR Proportion with >1 SRE: 90%; 1 SRE = 20%; 2 SREs: 30%; 3 SREs = 35%; 4 SREs = 5%	Hypercalcaemia: NR Pain score, mean (SD): 4.37 (0.7) QoL: NR Overall survival: 0; 1-year SRE-free survival rate: 0	ONJ: 0 Renal impairment (elevated Scr): 5 Acute-phase reaction: NR Hypocalcaemia: NR Any other significant: NR

continued

TABLE 126 Other solid tumours (*continued*)

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Zhao 2011[210] China	4 mg intravenous zoledronic acid three times in 4 weeks + chemotherapy ($n = 30$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: 4	Hypercalcaemia: NR Pain: NR QoL: NR Overall survival: median 20 months, $p = 0.27$	ONJ: 0 Renal impairment: 0 Acute-phase reaction: NR Hypocalcaemia: NR Any other significant: vomiting = 16.7% anaemia = 13.3% thrombocytopenia = 6.7%
	Chemotherapy ($n = 29$)	Time to first SRE: NR Time to first and subsequent SRE: NR Incidence of SREs: NR SMR: NR Proportion of each SRE: 4	Hypercalcaemia: NR Pain: NR QoL: NR Overall survival: median 30 months	ONJ: 0 Renal impairment: 0 Acute-phase reaction: NR Hypocalcaemia: NR Any other significant: vomiting = 10.3%, anaemia = 17.2%, thrombocytopenia = 3.4%

NR, not reported.