Bone metastases from breast cancer

Study details	Participants	Cancer details	Intervention	Outcomes
Author, year: Kohno 2005[102] **Country:** Japan **Duration of study:** 12 months **Funding source:** Novartis Pharmaceuticals	**Primary solid tumour: breast cancer** **SRE definition:** pathological fracture, SCC, surgery to bone, radiation therapy to bone, and HCM (secondary efficacy analyses only). New vertebral compression fractures were diagnosed if there was a decrease in total, anterior, or posterior vertebral height of ≥25% from baseline **Demographics**	**Primary cancer details** **Bone metastases details**	**Intervention (A): zoledronic acid 4 mg** ($n = 114$) **Comparator (B): placebo** ($n = 113$) Both administered via 15-minute infusion. Infusions were administered every 4 weeks for 12 months	**SRE outcomes** *Ratio of SRE rate* (defined as the total number of SREs divided by the total years on study) for patients treated with zoledronic acid divided by the SRE rate for the placebo group (excluding HCM in definition) Proportion of patients experiencing at least one SRE Time to first SRE Multiple-event analysis by the Andersen–Gill method Risk ratio for developing SREs **Other outcomes** Change from baseline BPI composite pain scores and bone resorption markers **Adverse events of interest (AEs) or significant AEs** Hypocalcaemia Renal adverse events Hypophosphataemia Bone pain Pyrexia Fatigue Upper abdominal pain

Study details	Participants	Cancer details	Intervention	Outcomes
Author, year: 2000[103] (Aredia trial) Long-term follow-up of two RCTs (Hortobagi 1996,[22] 1998[107] and Theriault 1998[115]) **Country:** USA **Duration of study:** 24 months (24 cycles) **Funding:** Novartis Pharmaceuticals	**Primary solid tumour: breast cancer** **SRE definition:** Pathological fracture, irradiation of or surgery on bone, SCC or hypercalcaemia **Demographics**	**Primary cancer details** **Bone metastases details**	**Intervention (A): disodium pamidronate 90 mg** ($n = 367$) **Comparator (B): placebo** ($n = 384$) Both administered in 250 ml of 5% dextrose in water given as a 2-hour intravenous infusion every 3–4 weeks for 24 cycles	**SRE outcomes** *SMR* [number of skeletal complications per time on trial for each patient (events/year)]; the overall SMR was calculated with and without hypercalcaemia counted as a skeletal complication *Proportion of patient with skeletal complications* Time from randomisation to first SRE **Other outcomes** Bone pain score, analgesic use, ECOG performance status and quality of life measured as mean change from baseline to 24 months or last visit (any time during study); overall survival **Adverse events of interest (AEs) or significant AEs** Hypocalcaemia Allergic reaction in the left eye Interstitial pulmonary infiltrate Dyspnoea

Study details

Author, year: Rosen 2003[104]

Secondary reports: Rosen 2001,[108] Rosen 2004[109]

Rosen 2003:[104] extension phased – 25 month safety and efficacy of Rosen 2001.[108] Includes breast and myeloma patients but some breast cancer data reported separately

Country: multinational

Duration of study: 25 months (Rosen 2003[104]), 12 months (Rosen 2004[109])

Funding source: Novartis Pharmaceuticals

Participants

Primary solid tumour: breast cancer

SRE definition: pathological fracture, SCC, radiation therapy, or surgery to bone. HCM was not included in the definition of SREs, because zoledronic acid already has demonstrated efficacy in treating HCM. HCM was included as a SRE in some secondary analyses

Demographics

	A	B
Total, *n*	1130[a]	
Randomised, *n*	378	388
Age, median, years	58	56
ECOG status, *n* (%)		
0–1	328 (86.8)	316 (81.4
≥2	49 (13.0)	70 (18.0)
Pre-SREs, *n* (%)	232 (61.4)	244 (62.9)

a In June 2000, as a result of concerns over renal safety at the higher dose level, patients originally randomised to receive 8 mg of zoledronic acid were required to receive 4 mg of zoledronic acid instead; this arm is referred to hereafter as the 8/4-mg arm. For all efficacy variables analysed, only the 4-mg zoledronic acid arm was used to assess the effectiveness of treatment with zoledronic acid vs disodium pamidronate (because the 8/4-mg dose group was not homogeneous with regard to the dose delivered). There were 364 patients in the 8/4-mg group.

Cancer details

Primary cancer details

	A	B
Time since diagnosis, mean (SD), months	78 (67)	71(62)

Bone metastases details

	A	B
Lesion type, *n* (%)		
Lytic lesion	190 (50.3)	162 (41.6)
Non-lytic lesion	188 (49.5)	226 (58.3)
Primary therapy, *n* (%)		
Chemotherapy	178 (47.1)	181 (46.7)
Hormone therapy	200 (53.0)	207 (53.4)

Intervention

Intervention (A): zoledronic acid 4 mg or 8 mg

(*n* = 378)

Comparator (B): disodium pamidronate 90 mg

(*n* = 388)

Both administered as an intravenous infusion depending on the scheduling of other antineoplastic treatments every 3–4 weeks for 24 months

Zoledronic acid was initially infused over 5 minutes in 50 ml hydration solution; however, because of safety concerns over renal safety a protocol amendment in June 1999 changed the infusion time to 15 minutes and increased infusion volume to 100 ml

Outcomes

SRE outcomes

Proportion of patients who experienced at least one SRE during 25-month study period (HCM not included)

Proportion of patients experiencing any SRE (including HCM)

Time to first SRE

SMR

Multiple-event analysis

(For SMR and multiple event analysis, a 21-day event window was used for counting SREs, such that any event occurring within 21 days of a previous event was not counted. Analyses were performed using the SRE end point with and without inclusion of HCM.) Efficacy analysis, A, *n* = 377; B, *n* = 389

Other outcomes

None reported

Adverse events of interest (AEs) or significant AEs

Bone pain

Renal impairment (a change from baseline)

Study details

Author, year: Stopeck 2010[31]

(secondary reports – Fallowfield 2010,[106] Fallowfield 2010,[105] Martin 2011,[116] Stopeck 2010[110–114])

Country: Europe, North America, South America, Japan, Australia, India and South Africa

Duration of study: from first patient enrolment to primary analysis ~ 34 months

Funding source: Amgen and Daiichi Sankyo

Participants

Primary solid tumour: breast cancer

SRE definition: pathological fracture, radiation or surgery to bone, or SCC

Demographics

	A	B
Randomised, *n*	1026	1020
Age, mean, years	57	56
No. of females (%)	1018 (99.2)	1011 (99.1)
No. of postmenopausal women (%)	839 (82.3)	831 (81.8)
ECOG status, *n* (%)		
0	504 (49.1)	488 (47.8)
1	451 (44.0)	444 (43.5)
2	68 (6.7)	82 (8.0)
Missing or other	3 (< 1)	6 (< 1)
Pre-SREs, *n* (%)	378 (36.8)	373 (36.6)

Cancer details

Primary cancer details

	A	B
Time from cancer diagnosis to initial diagnosis of bone metastases		
Median, months	32.8	35.4
Presence of other metastases, *n* (%)		
Lung	216 (21.1)	210 (20.6)
Liver	211 (20.6)	182 (17.8)
Other	369 (36.0)	369 (36.2)

Bone metastases details

	A	B
Time from initial diagnosis of bone metastases to random assignment		
Median, months	2.1	2.0
More than two metastases bone lesions, *n* (%)	242 (23.6)	240 (23.5)
Prior treatment, *n* (%)		
Hormonal	755 (73.6)	728 (71.4)
Chemotherapy	831 (81)	825 (80.9
Recent chemotherapy	410 (40.0)	410 (40.2)
Oral BPs	42 (4.1)	38 (3.8)

Intervention

Intervention (A): denosumab 120 mg (subcutaneous injection) + placebo (intravenous infusion)

(*n* = 1026)

Comparator (B): zoledronic acid 4 mg (intravenous infusion, lasting no less than 15 minutes) + **placebo** (subcutaneous injection)

(*n* = 1020)

All administered every 4 weeks

Intravenous products (placebo or zoledronic acid) were dose-adjusted on the basis of baseline creatinine clearance 60 ml/minute and were held for renal function deterioration on-study (until serum creatinine returned to within 10% of baseline values), per zoledronic acid prescribing information

Outcomes

SRE outcomes

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

Time to first on-study SRE (superiority test)

Time to first and subsequent on-study SREs (multiple event analysis)

[Subsequent events must have occurred at least 21 days from the most recent event to ensure that linked events (e.g. surgery to repair a fracture or multiple doses of radiation during a course of treatment) were not counted as separate SREs]

Other outcomes

Overall survival

Disease progression

SMR [allowing one event per assessing period (3 weeks)]

Per cent change from baseline to week 13 in urinary collagen type 1 procollagen peptide (uNTx) and BSAP levels

Adverse events of interest (AEs) or significant AEs

Incidence of anti-denosumab antibodies

ONJ

Acute-phase reaction

Renal impairment

Bone pain

Bone metastases from prostate cancer

Author, year: Fizazi 2011[29]

Country: 39 countries (multinational)

Duration of study: between May 2006 and October 2009; from enrolment to discontinuation for individual patients, or until the primary analysis cut-off date (27 months), whichever occurred first

Funding source: Amgen

Primary solid tumour: prostate cancer

SRE definition: pathological fracture (excluding fractures from severe trauma), radiation therapy to bone (including use of radioisotopes), surgery to bone, or SCC. New bone metastases (symptomatic or asymptomatic) were not included

Demographics

	A	B
Randomised, *n*	950	951
Age, median (IQR), years	71 (64–77)	71 (66–77)
Age ≥65 years, *n* (%)	697 (73)	735 (77)
Ethnicity, *n* (%)		
White	829 (87)	810 (85)
Other	121 (13)	141 (15)
No. of females (%)	1018 (99.2)	1011 (99.1)
ECOG status, *n* (%)		
0–1	882 (93)	886 (93)
Pre-SREs, *n* (%):	232 (24)	231 (24)
Gleason score at diagnosis, *n* (%)		
2–6	175 (18)	180 (19)
7	273 (29)	280 (29)
8–10	394 (41)	408 (43)
Missing	108 (11)	83 (9)

Primary cancer details

	A	B
Time from diagnosis to randomisation		
Median (IQR), months	37.5 (18.1–75.4)	41.2 (18.3–82.0)
Presence of visceral metastases, *n* (%)	161 (17)	181 (19)

Bone metastases details

	A	B
Time from diagnosis of bone metastases to randomisation		
Median (IQR), months	3.94 (1.22–15.67)	5.19 (1.31–16.10)
Prior treatment, *n* (%)		
Recent chemotherapy	132 (14)	132 (14)

Intervention (A): denosumab 120 mg (subcutaneous) + **placebo** (intravenous for at least 15 minutes)

(*n* = 950)

Comparator (B): zoledronic acid 4 mg (intravenous for at least 15 minutes) + **placebo** (subcutaneous)

(*n* = 951)

For every 4 weeks until the primary analysis cut-off date

Intravenous products (placebo or zoledronic acid) were dose-adjusted on the basis of baseline creatinine clearance 60 ml/minute and were held for renal function deterioration on-study (until serum creatinine returned to within 10% of baseline values), per zoledronic acid prescribing information

SRE outcomes

Time to first on-study SRE; assessed for non-inferiority

If testing of the primary end point showed non-inferiority, then the same outcome was further tested as a secondary end point, together with the secondary end point of time to first and subsequent on-study SREs (multiple events), for superiority

Other outcomes

Overall survival

Overall disease progression (encompassing visceral distant metastatic disease, locoregional progression, and biochemical progression, and excluding SREs)

PSA concentration during the study (assessed every 12 weeks)

Change in bone turnover markers from baseline (assessed every 13 weeks)

Pain

Adverse events of interest (AEs) or significant AEs

Hypocalcaemia, ONJ, infectious adverse events, new primary malignant disease

Author, year:
Saad 2002[117]

Secondary reports: Saad 2004,[123] Saad 2004,[121] Saad 2005,[120] Saad 2007,[19] Saad 2007,[211] Saad 2010,[118] Weinfurt 2006[128]

Country: USA, Europe, South America and Australasia

Duration of study: treatment exposure: 15 months; A, mean (SD) 8.8 (5.3) to 9.4 (5.8) months; B, 9.0 (5.4) months

Follow-up bone scans were done 6 and 15 months after enrolment (Saad 2004[121] report 24-month outcome)

Extension phase: 24 months (from months 15 to 24) (i.e. the extension phase only)

Funding: Novartis Pharmaceuticals

Primary solid tumour: prostate cancer

SRE definition: pathological bone fractures (vertebral or non-vertebral), SCC, surgery to bone, radiation therapy to bone (including the use of radioisotopes) or a change of antineoplastic therapy to treat bone pain

Demographics

	A	B
Total, *n*	643	
Randomised, *n*	214	208
Age, mean (SD), years	71.8 (7.9)	72.2 (8.0)
Ethnicity, *n* (%)		
White	178 (83)	173 (83)
Black	24 (11)	19 (9)
Other	12 (6)	17 (8)
ECOG performance status, *n* (%)		
0	85 (39.7)	93 (44.7)
1	112 (52.3)	97 (46.6)
>2	17 (7.9)	18 (8.7)
Missing	0	0
Pre-SREs, *n* (%)	66 (30.8)	78 (37.5)

Primary cancer details

	A	B
Time since diagnosis, mean (SD	62.2 (43.5)	66.6 (46.9)
Presence of metastases, *n* (%)		
Bone	212 (99.1)	205 (98.6)
Distant lymph nodes	29 (13.6)	15 (7.2)
Lung	6 (2.8)	5 (2.4)
Liver	1 (0.5)	1 (0.5)

Bone metastases details

	A	B
Time since first bone metastases diagnosis		
Mean (SD), months	23.8 (26.1)	28.4 (30.7)
Median, months	16.1	17.8

Intervention (A): zoledronic acid 4 mg

(*n* = 214)

Comparator (B): placebo

(*n* = 208)

Administered every 3 weeks for 15 months (20 cycles). Initially 5-minute infusion (in 50 ml), changed to 15-minute infusion (in 100 ml) in 1999

SRE outcomes

The proportion of patients having at least one SRE

Time to first SRE

SMR

Proportion of patients with individual SREs

Other outcomes

Time to disease progression

Objective bone lesion response

Bone biochemical markers

Quality-of-life parameters [quality-of-life parameters included a pain score assessed with the BPI (26), analgesic scores, ECOG performance status, and two quality-of-life questionnaires: FACT-G, version 4 (27) and EURO Quality of Life EQ-5D (EURO QOL)]

Adverse events of interest (AEs) or significant AEs

Bone pain

ONJ

Hypocalcaemia

Renal impairment

Bone metastases from other solid tumours

Author, year: Henry 2011[30]

(Henry 2010 abstract,[132] von Moos 2010 abstract[134])

Country: multicentred and multinational

Duration of study: patients were observed for survival for 2 years after the last dose of blinded investigational product, primary analysis was conducted 34 months after enrolment initiated

Patients were evaluated on study day 1 and every 4 weeks thereafter. Oral examinations were conducted at baseline and every 6 months thereafter

Median time on-study (months) = 7

Funding: Amgen

Primary solid tumour: OSTs

SRE definition: Pathological fracture, radiation or surgery to bone, SCC. A subsequent SRE was defined as an event occurring 21 days after the previous SRE

Demographics

	A	B
Total, *n*	1779	
Randomised, *n*	890	886
Age, median (range) years	61 (22–87)	60 (19–89)
Sex, male, *n* (%)	552 (62)	588 (66)
ECOG status, *n* (%)		
0	236 (27)	240 (27)
1	492 (55)	508 (57)
2	157 (18)	136 (15)
Missing	5 (<1)	2 (<1)
Primary tumour type, *n* (%)		
NSCLC	352 (40)	350 (39)
Multiple myeloma	93 (10)	87 (10)
Other	455 (50)	449 (51)
Prior SRE	446 (50)	440 (50)

Primary cancer details

	A	B
Presence of other metastases, *n* (%)		
Liver	167 (19)	171 (19)
Lung	162 (18)	239 (27)
Other	340 (38)	319 (36)
Total	448 (50)	474 (54)

Bone metastases details

	A	B
Time from diagnosis of bone metastases to randomisation, median (range)	2 (0–130)	2 (0–152)
Prior treatment, *n* (%)		
Antineoplastic treatment	855 (96)	845 (95)
Systemic anticancer therapy	770 (87)	767 (87)
Radiotherapy	353 (40)	324 (37)
Surgery	406 (46)	409 (46)
Other	20 (2)	15 (2)
Prior BP use	24 (3)	28 (3)

Intervention (A): denosumab 120 mg

(*n* = 890)

Denosumab administered subcutaneously monthly with intravenous placebo

Comparator (B): zoledronic acid 4 mg

(*n* = 886)

Zoledronic acid administered intravenously monthly with subcutaneous placebo

Co-intervention: calcium (>500 mg) and vitamin D (>400 U) strongly recommended in each group

SRE outcomes

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

Time to first on-study SRE (superiority tests)

Time to first and subsequent SRE (multiple-event analysis)

Other outcomes

Exploratory end points included bone turnover markers (measured at baseline and week 13), overall survival, and overall disease progression

Adverse events of interest (AEs) or significant AEs

Acute-phase reactions, hypocalcaemia, renal adverse events, adjudicated positive ONJ, SAEs reported

Author, year: Rosen 2003[130]

(Rosen 2004,[133] Schulman 2004[135])

Country: USA, Canada, Australia and Poland

Duration of study: 9 months

Funding: Novartis

Primary solid tumour: OSTs

SRE definition: Pathological fracture, radiation therapy to bone, surgery to bone and SCC. For secondary analyses hypercalcaemia was included in the definition

Demographics

	A	B
Randomised, *n*	257	250
Age, median (range) years	64	64
Sex, male, *n* (%)	158 (61)	159 (64)
ECOG status, *n* (%)		
1 or less	211 (83)	215 (87)
2 or more	42 (17)	32 (13)
Missing	4 (>1)	3 (>1)
Primary tumour type, *n* (%)		
NSCLC	124 (49)	120 (49)
SCLC	17 (7)	19 (8)
Renal cell carcinoma	27 (11)	19 (8)
Unknown primary	18 (7)	17 (7)
Head and neck	6 (2)	4 (2)
Thyroid	2 (1)	4 (2)
Other	60 (24)	64 (26)
Prior SRE	166 (65)	179 (73)

Primary cancer details

	A	B
Median time from initial diagnosis, months	3.8	2.5

Bone metastases details

	A	B
Prior treatment, *n* (%)		
Chemotherapy	207 (82)	197 (80)
Hormonal therapy	3 (1)	2(1)

Patients were also excluded if they had more than a single exposure to a BP within 30 days

Intervention (A): zoledronic acid 4 mg

(*n* = 257)

Administered intravenously every 3 weeks for 9 months (initially over 5 minutes in 50 ml but changed to over 15 minutes in 100 ml)

Comparator (B): placebo

(*n* = 250)

Administered intravenously for every 3 weeks for 9 months

Co-intervention: calcium (500 mg) and a multivitamin tablet containing vitamin D (400–500 U) to all patients throughout the study

SRE outcomes

Proportion of patients with at least one SRE

Time to first SRE

SMR (defined as the number of SREs per year)

Multiple event analysis

Other outcomes

Change from baseline in BPI composite pain score, analgesic use, ECOG performance status, best bone lesion response, time to progression of bone lesions, changes from baseline in biochemical markers of bone resorption, time to progression of overall disease, and survival

Quality of life was measured using the Function Assessment of Cancer Therapy – General (FACT-G) instrument, and analysed using a random effect pattern mixture model

Adverse events of interest (AEs) or significant AEs

Bone pain reported

BPI, Brief Pain Inventory.