Breast cancer

Direct evidence reporting denosumab or contributing data to the network meta-analysis

Kohno 2005

Kohno N, Aogi K, Minami H, Nakamura S, Asaga T, Iino Y, *et al*. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. *J Clin Oncol* 2005;**23**:3314–21.

Lipton 2000

Primary report

Lipton A, Theriault RL, Hortobagyi GN, Simeone J, Knight RD, Mellars K, *et al*. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer* 2000;**88**:1082–90.

Secondary reports

Hortobagyi GN, Theriault RL, Porter L, Blayney D, Lipton A, Sinoff C, *et al*. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N Engl J Med* 1996;**335**:1785–91.

Hortobagyi GN, Theriault RL, Lipton A, Porter L, Blayney D, Sinoff C, *et al*. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. *J Clin Oncol* 1998;**16**:2038–44.

Theriault RL, Lipton A, Hortobagyi GN, Leff R, Gluck S, Stewart JF, *et al*. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. *J Clin Oncol* 1999;**17**:846–54.

Rosen 2003

Primary report

Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, *et al*. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer* 2003;**98**:1735–44.

Secondary reports

Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, *et al*. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J* 2001;**7**:377–87.

Rosen LS, Gordon DH, Dugan W Jr, Major P, Eisenberg PD, Provencher L, *et al*. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer* 2004;**100**:36–43.

Stopeck 2010

Primary report

Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, *et al*. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* 2010;**28**:5132–9.

Secondary reports

Kidson S. *Clinical Study Report: 20050136. A randomized, double-blind, multicenter study of denosumab compared with zoledronic acid (Zometa) in the treatment of bone metastases in subjects with advanced breast cance*r. Thousand Oaks, CA: Amgen Inc.; 2009

Fallowfield L, Patrick D, Body JJ, Lipton A, Tonkin KS, Qian Y, *et al*. The effect of treatment with denosumab or zoledronic acid on health-related quality of life in patients with metastatic breast cancer. Proceedings of the 33rd Annual San Antiono Breast Cancer Symposium, 8–12 December 2010. URL: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=100&abstractID=60225 (accessed September 2011).

Fallowfield L, Patrick D, Body J, Lipton A, Tonkin KS, Qian Y, *et al*. Effects of denosumab versus zoledronic acid (ZA) on health-related quality of life (HRQL) in metastatic breast cancer: results from a randomized phase III trial. *J Clin Oncol* 2010;**28**(Suppl. 15):1025.

Martin M, Steger G, von Moos R, Stopeck A, de Boer R, Bourgeois H, *et al*. Benefit of denosumab therapy in patients with bone metastases from breast cancer: a number-needed-to-treat (NNT) analysis. *Breast* 2011;**20**:S85.

Stopeck A, Martin M, Ritchie D, Body JJ, Paterson A, Viniegra M, *et al*. Effect of denosumab versus zoledronic acid treatment in patients with breast cancer and bone metastases: Results from the extended blinded treatment phase. *Cancer Res* 2010;**70**(Suppl. 2):P6-14-01.

Stopeck A, Fallowfield L, Patrick D, Cleeland CS, de Boer RH, Steger GG, *et al*. Effects of denosumab versus zoledronic acid (ZA) on pain in patients (pts) with metastatic breast cancer: results from a phase III clinical trial. *J Clin Oncol* 2010;**28**(Suppl.):abstract no. 1024.

Stopeck A, Fallowfield L, Patrick D, Cleeland CS, de Boer RH, Steger GG, *et al*. Pain in patients (pts) with metastatic breast cancer: results from a phase III trial of denosumab versus zoledronic acid (ZA). Proccedings of the 33rd Annual San Antiono Breast Cancer Symposium, 8–12 December 2010. URL: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=100&abstractID=60225 (accessed September 2011).

Stopeck A, Lipton AA, Campbell-Baird C, von Moos R, Fan M, Haddock B, *et al*. Acute-phase reactions following treatment with zoledronic acid or denosumab: Results from a randomized, controlled phase 3 study in patients with breast cancer and bone metastases. *Cancer Res* 2010;**70**(Suppl. 2):P6-14-09.

Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, *et al*. Reply to V. Fusco *et al*. *J Clin Oncol* 2011;**29**:e523–4.

Meeting inclusion criteria but not included in network meta-analysis

Body 2003

Primary report

Body JJ, Diel IJ, Lichinitser MR, Kreuser ED, Dornoff W, Gorbunova VA, *et al*. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Ann Oncol* 2003;**14**:1399–405.

Secondary report

Diel IJ, Body JJ, Lichinitser MR, Kreuser ED, Dornoff W, Gorbunova VA, *et al*. Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. *Eur J Cancer* 2004;**40**:1704–12.

Body JJ, Diel IJ, Lichinitzer M, Lazarev A, Pecherstorfer M, Bell R, *et al*. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomized, placebo-controlled phase III studies. *Br J Cancer* 2004;**90**:1133–7.

Body 2004

Body JJ, Diel IJ, Bell R, Pecherstorfer M, Lichinitser MR, Lazarev AF, *et al*. Oral ibandronate improves bone pain and preserves quality of life in patients with skeletal metastases due to breast cancer. *Pain* 2004;**111**:306–12.

Secondary report

Tripathy D, Lichinitzer M, Lazarev A, MacLachlan SA, Apffelstaedt J, Budde M, *et al*. Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomized, double-blind, placebo-controlled trial. *Ann Oncol* 2004;**15**:743–50.

Elomaa 1988

Elomaa I, Blomqvist C, Porkka L, Holmström T, Taube T, Lamberg-Allardt C, *et al*. Clodronate for osteolytic metastases due to breast cancer. *Biomed Pharmacother* 1988;**42**:111–16.

Heras 2009

Heras P, Kritikos K, Hatzopoulos A, Georgopoulou AP. Efficacy of ibandronate for the treatment of skeletal events in patients with metastatic breast cancer. *Eur J Cancer Care* 2009;**18**:653–6.

Kristensen 1999

Kristensen B, Ejlertsen B, Groenvold M, Hein S, Loft H, Mouridsen HT. Oral clodronate in breast cancer patients with bone metastases: a randomized study. *J Intern Med* 1999;**246**:67–74.

Paterson 1993

Paterson AH, Powles TJ, Kanis JA, McCloskey E, Hanson J, Ashley S. Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. *J Clin Oncol* 1993;**11**:59–65.

Prostate cancer

Direct evidence reporting denosumab or contributing data to the network meta-analysis

Fizazi 2011

Primary report

Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L, *et al*. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 2011;**377**:813–22.

Secondary reports

Brown JE, Cleeland CS, Fallowfield LJ, Patrick DL, Fizazi K, Smith MR, *et al*. Pain outcomes in patients with bone metastases from castrate-resistant prostate cancer: results from a phase 3 trial of denosumab vs. zoledronic acid. *Eur Urol Suppl* 2011;**10**:336.

Tadros S. *Clinical Study Report: 20050103. A randomized, double-blind, multicenter study of denosumab compared with zoledronic acid (Zometa) in the treatment of bone metastases in men with hormone-refractory prostate*. Thousand Oaks, CA: Amgen Inc.; 2010.

Miller K, Fizazi K, Smith M, Moroto JP, Klotz L, Brown J, *et al*. Benefit of denosumab therapy in patients with bone metastases from castrate resistant prostate cancer: a number-needed-to-treat (NNT) analysis. *J Urol* 2011;**185**:e262.

Patrick D, Cleeland C, Fallowfield L, Smith MR, Trachtenberg J, Chilingirov P, *et al*. Effects of denosumab and zoledronic acid on pain interference with daily functioning in patients with castrate-resistant prostate cancer. *J Urol* 2011;**185**(Suppl. 4):e286.

Shore ND, Smith MR, Jievaltas M, Fizazi K, Damiao R, Chin J, *et al*. Effect of denosumab versus zoledronic acid in patients with castrate-resistant prostate cancer and bone metastases: subgroup analyses by prior SRE and baseline pain. *J Clin Oncol* 2011;**29**(Suppl.):4533.

Saad 2002

Primary report

Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, *et al*. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002;**94**:1458–68.

Secondary reports

European Medicines Agency. *Assessment report for zometa (zoledronic acid)*. European Medicines Agency; 2010. URL: www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000336/human_med_001182.jsp&mid=WC0b01ac058001d124# (accessed October 2011).

Saad F, Olsson C, Schulman CC. Skeletal morbidity in men with prostate cancer: quality-of-life considerations throughout the continuum of care. *Eur Urol* 2004;**46**:731–9.

Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, *et al*. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst* 2004;**96**:879–82.

Saad F. Clinical benefit of zoledronic acid for the prevention of skeletal complications in advanced prostate cancer. *Clin Prostate Cancer* 2005;**4**:31–7.

Saad F, Chen YM, Gleason DM, Chin J. Continuing benefit of zoledronic acid in preventing skeletal complications in patients with bone metastases. *Clin Genitourin Cancer* 2007;**5**:390–6.

Saad F, Lipton A, Cook R, Chen YM, Smith M, Coleman R. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. *Cancer* 2007;**110**:1860–7.

Saad F, Eastham J. Zoledronic Acid improves clinical outcomes when administered before onset of bone pain in patients with prostate cancer. *Urology* 2010;**76**:1175–81.

Weinfurt KP, Anstrom KJ, Castel LD, Schulman KA, Saad F. Effect of zoledronic acid on pain associated with bone metastasis in patients with prostate cancer. *Ann Oncol* 2006;**17**:986–9.

Meeting inclusion criteria but not included in network meta-analysis

Adami 1989

Primary report

Adami S, Mian M. Clodronate therapy of metastatic bone disease in patients with prostatic carcinoma. *Recent Results Cancer Res* 1989;**116**:67–72.

Secondary report

Adami S, Salvagno G, Guarrera G. Dichloromethylene-diphosphonate in patients with prostatic carcinoma metastatic to the skeleton. *J Urol* 1985;**134**:1152–4.

Buchali 1988

Buchali K, Correns HJ, Schuerer M, Schnorr D, Lips H, Sydow K. Results of a double blind study of 89-strontium therapy of skeletal metastases of prostatic carcinoma. *Eur J Nuclear Med* 1988;**14**:349–51.

Dearnaley 2003

Dearnaley DP, Sydes MR, Mason MD, Stott M, Powell CS, Robinson AC, *et al*. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). *J Natl Cancer Inst* 2003;**95**:1300–11.

Elomaa 1992

Elomaa I, Kylmala T, Tammela T, Viitanen J, Ottelin J, Ruutu M, *et al*. Effect of oral clodronate on bone pain. A controlled study in patients with metastatic prostatic cancer. *Int Urol Nephrol* 1992;**24**:159–66.

Ernst 2003

Ernst DS, Tannock IF, Winquist EW, Venner PM, Reyno L, Moore MJ, *et al*. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. *J Clin Oncol* 2003;**21**:3335–42.

Kylmala 1993

Kylmala T, Tammela T, Risteli L, Risteli J, Taube T, Elomaa I. Evaluation of the effect of oral clodronate on skeletal metastases with type 1 collagen metabolites. A controlled trial of the Finnish Prostate Cancer Group. *Eur J Cancer* 1993;**29A**:821–5.

Kylmala 1997
Kylmala T, Taube T, Tammela TL, Risteli L, Risteli J, Elomaa I. Concomitant i.v. and oral clodronate in the relief of bone pain – a double-blind placebo-controlled study in patients with prostate cancer. *Br J Cancer* 1997;**76**:939–42.

Nilsson 2005
Nilsson S, Strang P, Ginman C, Zimmermann R, Edgren M, Nordstrom B, *et al*. Palliation of bone pain in prostate cancer using chemotherapy and strontium-89. A randomized phase II study. *J Pain Sympt Manag* 2005;**29**:352–7.

Porter 1993
Porter AT, McEwan AJ, Powe JE, Reid R, McGowan DG, Lukka H, *et al*. Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. *Int J Rad Oncol Biol Physics* 1993;**25**:805–13.

Quilty 1994
Quilty PM, Kirk D, Bolger JJ, Dearnaley DP, Lewington VJ, Mason MD, *et al*. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. *Radiother Oncol* 1994;**31**:33–40.

Small 2003
Small EJ, Smith MR, Seaman JJ, Petrone S, Kowalski MO. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol* 2003;**21**:4277–84.

Smith 1989
Smith JA Jr. Palliation of painful bone metastases from prostate cancer using sodium etidronate: results of a randomized, prospective, double-blind, placebo-controlled study. *J Urol* 1989;**141**:85–7.

Strang 1997
Strang P, Nilsson S, Brandstedt S, Sehlin J, Borghede G, Varenhorst E, *et al*. The analgesic efficacy of clodronate compared with placebo in patients with painful bone metastases from prostatic cancer. *Anticancer Res* 1997;**17**:4717–21.

Other solid tumours

Direct evidence reporting denosumab or contributing data to the network meta-analysis

Henry 2011

Primary report
Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J, *et al*. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol* 2011;**29**:1125–32.

Secondary reports
O'Neill S. *Clinical Study Report: 20050244. A randomized, double-Blind, multicenter study of denosumab compared with zoledronic acid (Zometa) in the treatment of bone metastases in subjects with advanced cancer excluding breast and prostate Cancer) or multiple myeloma*. Thousand Oaks, CA: Amgen Inc.; 2010.

Henry DH, von Moos R, Hungria V, Costa L, Woll PJ, Scagliotti G, *et al*. Delaying skeletal-related events in a randomized phase III study of denosumab versus zoledronic acid in patients with advanced cancer. *J Clin Oncol* 2010;**28**(Suppl. 15):9133.

von Moos R, Patrick D, Fallowfield L, Cleeland CS, Henry DH, Qian Y, *et al*. Effects of denosumab versus zoledronic acid (ZA) on pain in patients (pts) with advanced cancer (excluding breast and prostate) or multiple myeloma (MM): results from a randomized phase III clinical trial. *J Clin Oncol* 2010;**28**(Suppl. 15):9043.

Rosen 2003b

Primary report

Rosen LS, Gordon D, Tchekmedyian S, Yanagihara R, Hirsh V, Krzakowski M, *et al*. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumours: a phase III, double-blind, randomized trial – the Zoledronic Acid Lung Cancer and Other Solid Tumours Study Group. *J Clin Oncol* 2003;**21**:3150–7.

Secondary reports

Rosen LS, Gordon D, Tchekmedyian NS, Yanagihara R, Hirsh V, Krzakowski M, *et al*. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumours: a randomized, Phase III, double-blind, placebo-controlled trial. *Cancer* 2004;**100**:2613–21.

Schulman CC. Efficacy of zoledronic acid in the treatment of bone metastases secondary to renal cell carcinoma. *Eur Urol Suppl* 2004;**3**:40–5.

Meeting inclusion criteria but not included in network meta-analysis

Arican 1999

Arican A, Icli F, Akbulut H, Cakir M, Sencan O, Samur M, *et al*. The effect of two different doses of oral clodronate on pain in patients with bone metastases. *Medical Oncol* 1999;**16**:204–10.

Berensen 2001

Berenson JR, Rosen LS, Howell A, Porter L, Coleman RE, Morley W, *et al*. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases.[Erratum appears in *Cancer* 2001;**91**:1956.] *Cancer* 2001;**91**:1191–200.

Brown 2007

Brown JE, McCloskey EV, Dewar JA, Body JJ, Cameron DA, Harnett AN, *et al*. The use of bone markers in a 6-week study to assess the efficacy of oral clodronate in patients with metastatic bone disease. *Calcif Tissue Int* 2007;**81**:341–51.

Heras 2007

Heras Rincon, I, Zubillaga RI, Castrillo Tambay M, Montalvo Moreno JJ. [Osteonecrosis of the jaws and bisphosphonates. Report of fifteen cases. Therapeutic recommendations.] *Med Oral Patol Oral Cir Bucal* 2007;**12**:E267–71.

Jagdev 2001

Jagdev SP, Purohit P, Heatley S, Herling C, Coleman RE. Comparison of the effects of intravenous pamidronate and oral clodronate on symptoms and bone resorption in patients with metastatic bone disease. *Ann Oncol* 2001;**12**:1433–8.

Lipton 2003

Lipton A, Zheng M, Seaman J. Zoledronic acid delays the onset of skeletal-related events and progression of skeletal disease in patients with advanced renal cell carcinoma. *Cancer* 2003;**98**:962–9.

Mystakidou 2008

Mystakidou K, Stathopoulou E, Parpa E, Kouloulias V, Kouskouni E, Vlahos L. Oral versus intravenous ibandronic acid: a comparison of treatment options for metastatic bone disease. *J Cancer Res Clin Oncol* 2008;**134**:1303–10.

O'Rourke 1995

O'Rourke N, McCloskey E, Houghton F, Huss H, Kanis JA. Double-blind, placebo-controlled, dose–response trial of oral clodronate in patients with bone metastases. *J Clin Oncol* 1995;**13**:929–34.

Piga 1998

Piga A, Bracci R, Ferretti B, Sandri P, Nortilli R, Acito L, *et al*. A double blind randomized study of oral clodronate in the treatment of bone metastases from tumours poorly responsive to chemotherapy. *J Exp Clin Cancer Res* 1998;**17**:213–17.

Robertson 1995

Robertson AG, Reed NS, Ralston SH. Effect of oral clodronate on metastatic bone pain: a double-blind, placebo-controlled study. *J Clin Oncol* 1995;**13**:2427–30.

Zaghloul 2010

Zaghloul MS, Boutrus R, El-Hossieny H, Kader YA, El-Attar I, Nazmy M. A prospective, randomized, placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer. *Int J Clin Oncol* 2010;**15**:382–9.

Zhao 2011

Zhao YY, Xue C, Hou X, Liao H, Li S, Zhao HY, *et al*. Changes of bone resorption marker (NTX) in chemotherapy plus zoledronic acid versus chemotherapy alone for nasopharyngeal cancer patients with bone metastases. *Eur J Cancer* 2011;**47**:848–53.