Title

Denosumab for treatment of bone metastases secondary to solid tumours: systematic review and network meta-analysis

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Abstract

Aim

To evaluate the evidence for denosumab for the treatment of bone metastases secondary to solid tumours and, using a network meta-analysis, indirectly compare denosumab with bisphosphonates and best supportive care.

Data sources

MEDLINE (1948 to April 2011), EMBASE (1980 to March 2011), Cochrane Library (all sections) (Issue 1, 2011) and Web of Science with Conference Proceedings (1970 to May 2011) and additional meeting abstracts (2010 and 2011) were searched.

Study eligibility, participants and interventions

Only randomised controlled trials assessing denosumab, bisphosphonates or best supportive care in patients with bone metastases from any solid tumour were included.

Synthesis

Direct evidence comparing denosumab and zoledronic acid was assessed for breast cancer, prostate cancer and other solid tumours. Denosumab was compared with pamidronate and best supportive care through a network meta-analysis for each tumour type. The primary outcomes were time to first skeletal related event (SRE) and time to first and subsequent SRE. Secondary outcomes were skeletal morbidity rate, pain, quality of life (QoL) and overall survival.

Results

Denosumab was found to be more effective in delaying the time to first SRE and reducing the risk of first and subsequent SREs compared to zoledronic acid, placebo and pamidronate. In breast and prostate cancer, denosumab was effective in reducing skeletal morbidity rate compared with placebo. The lack of published data on pain and QoL meant that firm conclusions could not be made. Denosumab did not appear to have an affect on overall survival.

Limitations

Network meta-analyses are subject to uncertainties and potential biases.

Conclusions

Denosumab is effective in preventing SREs, but the effect on pain and QoL is unclear.

Key words

upto 10 MESH keywords

denosumab, zoledronic acid, pamidronate, neoplasm metastasis, indirect estimation techniques

Introduction

The impact of bone metastases on cancer patients can be considerable. Complications, reduced mobility, pain and the effects of treatment reduce quality of life significantly. Complications may include pathological fracture, spinal cord compression and hypercalcaemia of malignancy.

Bone-targeted pharmacological treatments aim at preventing complications, reducing pain and improving quality of life. To date bisphosphonates have been the main pharmacological treatment option for patients with bone metastases. Currently licensed bisphosphonates include; zoledronic acid (any advanced malignancy involving bone), disodium pamidronate (breast cancer or multiple myeloma), sodium clodronate (breast cancer or multiple myeloma) and ibandronic acid (breast cancer). Bisphosphonates are administered either intravenously (zoledronic acid, pamidronate or ibandronic acid) or orally (clodronate or ibandronic acid) and have been associated with renal toxicity.[1] In the UK, the National Institute of Health and Clinical Excellence (NICE) currently recommends the use of bisphosphonates in all patients with bone metastases secondary to breast cancer,[2] patients with hormone resistant prostate cancer with painful bone metastases despite conventional analgesics[3] or as an option in lung cancer with bone metastases.[4] Patients who are not recommended for bisphosphonates would receive standard best supportive care.

Denosumab (Xgeva, Amgen) is a fully human monoclonal antibody, licensed for the prevention of skeletal related events (SRE) in bone metastases from solid tumours. It is administered by sub-cutaneous injection and does not require renal monitoring.[5]

The term ‘skeletal related event’ is a composite endpoint that has evolved over the past 20 years for use in clinical trials. Recent trials define SREs as pathological fracture (including asymptomatic vertebral collapse), spinal cord compression or need for radiotherapy or surgery to bone.[6-8] Other definitions have included hypercalcaemia or change in anti-neoplastic therapy.

Three pivotal trials have evaluated denosumab compared to zoledronic acid for the prevention of SREs.[6-8] There are no head-to-head trials of denosumab compared with other bisphosphonates or best supportive care. These comparisons are, nonetheless, important because of the wide variation in practice. Some centres use only zoledronic acid, some use a variety of bisphosphonates, while others do not use bisphosphonates at all (especially in cancer other than breast). Therefore the aim of this review is to evaluate the evidence for denosumab for the treatment of bone metastases in solid tumours and, using a network

meta-analysis, indirectly compare denosumab with other bisphosphonates and best supportive care.

Materials and methods

The review complies with PRIMSA guidelines.[9] A pre-specified protocol has been published on the NICE website.[10]

Literature search and eligibility criteria

Studies were identified by systematic searching of the following databases; MEDLINE (1948 to April 2011), EMBASE (1980 to March 2011), Cochrane Library (all sections) (Issue 1, 2011) and Web of Science with Conference Proceedings (1970 to May 2011). Additional meeting abstracts (2010 and 2011) were identified through searching American Society of Clinical Oncology, American Urological Association and San Antonio Breast Cancer symposium. Reference lists of all included studies were scanned to identify additional potentially relevant studies. The titles and abstracts of all papers identified by the search strategy were screened and full-text copies of all potentially relevant studies obtained.

The search strategy used for MEDLINE was; step 1) exp Diphosphonates, step 2) RANK Ligand, step 3) (denosumab or bisphosphonate* or ibandron* or clodron* or pamidron* or zoledron*).tw., step 4) (radiation or radiotherapy or radionuclide* or hormone therapy or strontium or samarium).ti., step 5) or/1-4, step 6) exp Neoplasms, step 7) (solid tumor or solid tumour* or cancer or carcinoma or myeloma).tw., step 8) or/6-7, step 9) 5 and 8, step 10) exp Bone Neoplasms, step 11) (((bone or osteolytic or lytic) adj lesion*) or (bone adj2 metast*)).tw., step 12) (skeletal or fracture*).tw., step 13) or/10-12, step 14) 9 and 13, step 15) randomized controlled trial.pt., step 16) 14 and 15 and, step 17) limit 16 to english language.

This search strategy was adapted as appropriate for the other databases

Only randomised controlled trials evaluating denosumab, bisphosphonates or best supportive care were included. Best supportive care included trials evaluating radiotherapy, radionuclides, hormone therapy, strontium or samarium. Bone metastases secondary to any solid tumour were eligible.

Screening was performed by two independent authors and disagreements resolved by discussion. After piloting a data extraction form, data were extracted by one author and

checked by a second. Data included study characteristics, inclusion/exclusion criteria, results and adverse events. Quality was assessed using the Cochrane risk of bias tool.[11]

The primary outcomes were time to first SRE and time to first and subsequent SRE. Secondary outcomes were skeletal morbidity rate (SMR, , defined as ratio of the number of SREs per patient divided by the patient's time at risk), pain, quality of life and overall survival.

Network meta-analysis

Network meta-analysis (NMA) is a statistical technique used to indirectly compare two or more interventions. Generally, it is used in situations where there is an absence of head-to-head trials.

Studies meeting the inclusion criteria were assessed for eligibility of synthesis by network meta-analysis, by evaluating methodological heterogeneity. To be suitable for NMA, studies were required to be similar with respect to population, intervention, comparators, outcomes, SRE definition and time frame. Based on this assessment, networks were designed.

Networks were created for three primary cancer types; breast cancer, prostate cancer and other solid tumours including (OST). A subgroup of patients with non small cell lung cancer within OST was also explored.

The analyses followed methods for mixed treatment comparisons described by Lu and Ades.[12] and used the Bayesian software package, WinBUGS, which employs Markov chain Monte Carlo (MCMC) methods.

Outcomes analysed were time to first SRE (hazard ratios), time to first and subsequent SRE (rate ratios from Andersen-Gill[13] multiple event analyses reported in primary studies) and SMR ratios (for breast and prostate cancer only).

Fixed effects models were used for time to first SRE, adopting an approach recommended by the NICE Decision Support Unit[14] for modelling trial-based summary measures, which can be applied to modelling hazard ratios on the log hazard scale. The trial-level data included in the models comprised log hazard ratios and its standard error. Where hazard ratios were not reported or derivable in the primary study or related publications (e.g. publically available FDA documentation), Kaplan-Meier estimates and numbers at risk (if available) were used, applying the methods of Tierney[15] to estimate the hazard ratio. Pairwise hazard ratios were estimated from the median of the posterior distribution with

credible intervals taken from the 2.5% and 97.5% percentiles. Ten thousand MCMC simulations were used in the analysis following a burn-in of 10,000. The same approach was taken for modelling rate ratios in the analysis of time to first and subsequent SREs.

For SMR a random effects model was adopted using arm-based data. The data included in the SMR models were mean SMR and standard deviation along with the number of patients. Where standard deviations were not reported, values were imputed by taking the mean of reported SDs from other studies but for the same treatment. The robustness of the imputation was tested by comparing results with those obtained by treating missing data as an uncertain parameter. Posterior distributions for relative treatment effects were estimated from the absolute risks of outcome from the relevant individual treatments. Median estimates and credible intervals were taken from 10,000 MCMC simulations after a burn-in of 10,000.

In order to estimate the absolute risk of outcome in the analyses of arm-based data, it was necessary to include an estimate of the baseline risk of the control treatment in the models. Zoledronic acid was treated as the reference treatment in each analysis as it is the treatment common to the largest number of trials and is present in multiple included studies for each NMA. Single-arm meta-analyses of zoledronic acid were conducted to estimate baseline risk from studies included in the NMA that had zoledronic acid as one of its comparators. The data in the time-to-event analyses, however, were trial-based and baseline risk could not be estimated so the absolute effect of the reference treatment was set to zero in these models.

The quality of the models was examined by inspecting convergence using Gelman-Rubin-Brooks plots, assessing autocorrelation between iterations of the Markov chain and checking whether the MC error was less than 5% of the posterior standard deviation.

Results

Literature search

Results of the literature search are shown in figure 1. Thirty-eight studies met the inclusion criteria, most of which compared bisphosphonates with placebo. Of these 38 studies, 30 were excluded because they were not suitable for network meta-analysis (table 1). The characteristics and results of the eight studies included in the NMA are shown in table 2 and 3.

Study quality

The quality of the studies included in the NMA was high as shown in table 4. There was a low risk of bias for the majority of categories. Stopeck 2010[8] and Rosen 2003[16] failed to describe sequence generation or allocation concealment. Kohno 2005[17] and Rosen 2003[16] did not sufficiently address incomplete outcome data.

Study characteristics

Four studies included patients with breast cancer,[8,16-18] two with prostate cancer[6,19] and two with other solid tumours[7,20] (table 2). Henry 2011 included patients with multiple myeloma, in addition to patients with other solid tumours. Three studies compared denosumab with zoledronic acid,[6-8] three compared zoledronic acid with placebo,[17,19,20] one zoledronic acid with pamidronate[16] and one pamidronate with placebo.[18]

Six studies were international, one study only recruited patients from Japan[17] and one study recruited patients from the US.[18] Patients were youngest in the breast cancer studies and oldest in the prostate. The proportion of patients with a previous SRE at baseline ranged from 24%[6] to 73%.[20]

Direct SRE results

Denosumab statistically significantly delayed the time to first on-study SRE in breast cancer, prostate cancer and other solid tumours (table 3). The difference in mean months of time to first SRE between denosumab and zoledronic acid was 3.6 months in prostate cancer (HR

0.82 95%CI 0.71 to 0.95) and 4.3 months in other solid tumours (HR 0.84 95%CI 0.71 to 0.98) (in breast cancer this outcome was not reached (HR 0.82 9%%CI 0.71 to 0.95)).

Similarly, denosumab statistically significantly reduced the risk of time to first and subsequent SRE for prostate cancer (rate ratio 0.82 95%CI 0.71 to 0.94) and breast cancer (rate ratio 0.77, 95%CI 0.66 to 0.89). In other solid tumours, the result favoured denosumab but was not statistically significant (rate ratio 0.90 95%CI 0.77 to 1.04).

Stopeck 2010[8] was the only trial evaluating denosumab to report SMR. Denosumab was associated with a lower SMR compared with zoledronic acid (0.45 compared with 0.58, p value 0.004) in patients with breast cancer.

In the bisphosphonate trials, zoledronic acid and pamidronate were associated with delayed time to first SRE, time to first and subsequent SRE and SMR. In the only trial comparing zoledronic acid and pamidronate,[16] the authors found that zoledronic acid statistically significantly reduced the time to first SRE in hormone-treated breast cancer patients (415 days versus 370 days, p = 0.047) and risk of time to first and subsequent SRE in all breast cancer patients (RR = 0.80 (0.66 to 0.97).

Pain study results

Stopeck 2010[8] reported that the median time to developing moderate/severe pain in women with breast cancer, in patients with no/mild pain at baseline, was longer in denosumab compared with zoledronic acid (295 days versus 176 days; HR 0.78, 95%CI 0.67 to 0.92)

Pain outcomes for denosumab compared with zoledronic acid in other solid tumours is available in abstract form.[21] Denosumab was found to delay the time to clinically significant pain (more than 2 point increase from baseline on brief pain inventory) compared to zoledronic acid (169 days compared with 143 days HR 0.85, 95% CI: 0.73-0.98).

In prostate cancer, pain data have also been published in abstract form.[22] In the subgroup of patients with no/mild pain at baseline, there was no statistically significant difference in the time to moderate/severe in denosumab compared to zoledronic acid (177 days versus 148 days; HR 0.89, 95% CI 0.77, 1.04).

Quality of life study results

In breast cancer, quality of life data for denosumab have been published in abstract form.[23] The authors report that over the 18 month period an average of 4.1% more (range -0.6% to 9.3%) patients treated with denosumab, compared with zoledronic acid, experienced a meaningful improvement in quality of life (5 or more increase in FACT-G score).

No quality of life data are available for prostate cancer or other solid tumours.

Overall survival study results

There was no significant difference in overall survival between denosumab and zoledronic acid in breast cancer and prostate cancer. Henry 2010[24] also reported no significant difference; however on ad hoc analysis the authors found that denosumab was associated with an increased overall survival in non small cell lung cancer (HR 0.79, 95%CI 0.65 to 0.95). Notably the authors also reported a decrease in overall survival in the ad hoc analysis of multiple myeloma patients (HR 2.26, 95%CI 1.13 to 4.50).

Safety

For breast, prostate and other solid tumours denosumab, compared with zoledronic acid, was associated with lower renal impairment (0.4% versus 2.2%, 16% versus 15%, 8.3% versus 10.9%) and acute phase reaction (10.4% versus 27.3%, 8% versus 18%, 6.9% versus 14.5%). However, denosumab was associated with higher incidence of hypocalcaemia (not reported, 13% versus 6%, 2.3% versus 1.0%) and osteonecrosis of the jaw (2.0% versus 1.4%, 2 versus 1%, 1.1% versus 1.3%).

Network meta-analysis results

Network diagrams for breast cancer, prostate cancer and other solid tumours are shown in figures 2, 3 and 4. The same network was used for the subgroup of non small cell lung cancer as other solid tumours. The results of these analyses are summarised in tables 5, 6 and 7.

Denosumab versus placebo

NMA results suggest that denosumab, compared with placebo, reduces the time to first SRE in breast, prostate cancer and other solid tumours. In non small cell lung cancer the result favoured denosumab, but was not statistically significant (HR 0.68, 95%CI 0.45 to 1.03). Similarly denosumab statistically significantly reduced the risk of first and subsequent SRE in breast cancer, prostate cancer, other solid tumours and non small cell lung cancer, compared to placebo. Additionally, denosumab reduced the skeletal morbidity rate compared with placebo in all groups.

Denosumab versus pamidronate

The comparison of denosumab versus pamidronate was only possible in breast cancer. For skeletal morbidity rate the result favours denosumab, but there was no significant difference. There was a significant difference in time to first SRE and time to first and subsequent SRE when denosumab was compared with pamidronate (HR 0.73 95%CI 0.56 to 0.94 and rate ratio 0.62 95%CI 0.48 to 0.80, respectively).

Discussion

Statement of key findings

Based on the review of direct evidence and network meta-analysis, denosumab, compared with zoledronic acid or placebo, statistically significantly delays time to first SRE, time to first and subsequent SRE and skeletal morbidity rate. Denosumab appears to be more effective than pamidronate for these outcomes, but the results have mixed statistical significance.

Although denosumab has demonstrated its effectiveness in delaying SREs, a lack of published data means that conclusions about pain and quality of life cannot be made. There was no statistically significant difference in overall survival for denosumab compared with zoledronic acid for prostate and breast cancer. However in an ad hoc analysis of the trial including various tumour types, denosumab was found to improve the overall survival in non-small cell lung cancer.

Strengths and limitations

There are a number of strengths of this review. A comprehensive and robust search strategy was used. A rigorous inclusion/exclusion criteria was used which only included high quality evidence (RCTs). Undertaking a NMA means that estimates of effectiveness can be made when no direct evidence is available. This was the case for comparing denosumab with placebo and pamidronate. Excluding studies with a different definition of what constitutes an SRE resulted in a smaller but more robust NMA.

Although NMA allows indirect estimates to be calculated, they can be subject to potential biases and uncertainties.[25] Network meta-analyses are not randomised comparisons, but rather observational findings across studies and therefore should be interpreted with due caution. The quality of any NMA is only as good as the weakest link in the network. All studies included in this NMA were of good quality (table 4), improving the validity of the NMA results. Some published studies did not report full results, therefore some treatment effects were estimated, for example using the method described by Teirney and colleagues.[15] However when these parameters were treated as uncertain, the impact on the results was negligible. A key limitation was the small number of studies included. This resulted in an unstable model when a random effects model was used for time to first SRE and time to first and subsequent SRE. Therefore a fixed effects model was used, which assumes no variability between studies.

Meaning of the results

Our analysis indicates that denosumab is effective in delaying first and first-and-subsequent SREs when compared to zoledronic acid, placebo and pamidronate. NMA analysis results in reduced power and therefore less precision. Non-statistically significant results for skeletal morbidity rate for denosumab compared with pamidronate should not be interpreted as evidence that there is no effect. Only if higher powered NMA were possible could this conclusion be made.

The validity of these results relies on, firstly, the SRE outcome and, secondly, the analysis of it. The SRE outcome is useful because it allows for increased power and therefore efficiency. It would be impractical to power trials to detect differences in each component of the SRE outcome, especially with regard to spinal cord compression and need for surgery to bone (as these are rare events). However, the composite outcome is of little use to patients since it incorporates a wide spectrum of clinical events, ranging from asymptomatic pathological fracture (identified during routine on-study skeletal surveys) to paraplegic spinal cord compression. Furthermore, the outcome does not directly measure mobility or bone pain, although it could be argued that the need for radiotherapy is an indirect measure of bone pain. In addition, for many patients, radiotherapy will be a highly effective treatment for bone pain.

Using time to event and multiple event analyses (time to first and subsequent SRE) allows smaller differences between treatments to be identified. This may be warranted when comparing active comparators; however, researchers and healthcare staff should ensure that statistically significant differences are clinically meaningful. In addition, the method used in these trials for the multiple event analysis (Andersen-Gill[13]) has been criticised because it does not differentiate between participants who died and who leave the study for another reason.[26] These issues have been discussed in greater detail elsewhere.[27]

A key issue is whether the delay in SREs results in a reduction in pain and improvement in quality of life. Ideally, the improved SRE outcomes with denosumab, would be interpreted alongside pain and quality of life data. Unfortunately, the lack of published pain and quality of life data means that this association could not be established. The data published from the three pivotal trials are only available in abstract form and generally only reports subgroups. For breast cancer there was a statistically significant delay to moderate/severe pain in

patients with no/mild pain, however in prostate cancer the difference was not statistically significant.

Denosumab has the added advantage of being given as a sub-cutaneous injection which does not require renal monitoring. Denosumab could potentially be administered in the community. Zoledronic acid is an intra-venous administration and requires renal monitoring with dose adjustment if renal impairment present. In terms of adverse events, denosumab has lower renal toxicity and does not appear to be associated with acute phase reactions. However, there is a marginally higher incidence of osteonecrosis of the jaw. In addition, there is a higher incidence of hypocalcaemia but this can be easily corrected with appropriate treatment.

Future research needs

In common with most findings for bisphosphonates in advanced cancer, from available evidence denosumab does not appear to affect overall survival. In the Henry 2010 trial,[24] there was a statistically significant improvement in overall survival in the ad hoc analysis for non small cell lung cancer. The reason for this is not clear and it may be a chance finding. Further trials in this subgroup would be needed to establish the validity of this result..

The place for denosumab in treatment pathways is unclear. Much of this will depend on local budgets and on economic evaluations.[28,29] One option may be as a second line agent in patients who suffer an SRE on bisphosphonates. A randomised controlled trial looking at this specific population may be informative.

Conclusion

Denosumab compared with zoledronic acid, placebo and, pamidronate, is effective in delaying time to first SRE and reducing the risk of first and subsequent SRE. However, conclusion about its impact on pain reduction and quality of life cannot be reached because of the lack of published data.

Financial and disclosure statement

The Health Services Research Unit, University of Aberdeen was commissioned by the NIHR HTA Programme on behalf of NICE to undertake a systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours. *This project was funded by the NIHR Health Technology Assessment programme (project number* 08/236/01*) and will be published in full in Health Technology Assessment. See the HTA programme website for further project information.* The Health Services Research Unit, Institute of Applied Health Sciences, University of Aberdeen is core-funded by the Chief Scientist Office of the Scottish Government Health Directorates. *The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme, the Department of Health or Chief Scientist Office* Any errors are the responsibility of the authors.

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679 Table 1: Studies meeting inclusion criteria but unsuitable for NMA

Primary tumour	Study ID	Intervention	Comparator	Reason for exclusion
***BP vs placebo/ another BP* (n=27)**				
Breast	Body 2004[30] Body 2004[31] Tripathy 2004[32]	Ibandronate (oral)	Placebo	SRE definition not comparable
	Body 2003,[33] Diel 2004[34]	Ibandronate (iv)	Placebo	SRE definition not comparable
	Heras 2009[35]	Ibandronate (iv)	Placebo	SRE definition not comparable
	Elomaa 1988[36]	Clodronate (oral)	Placebo	SRE definition not comparable
	Paterson 1993[37]	Clodronate (oral)	Placebo	SRE definition not comparable
	Kristensen 1999[38]	Clodronate (oral)	Open	SRE definition not comparable
Prostate	Dearnaley 2003[39]	Clodronate (oral)	Placebo	Hormone sensitive prostate cancer
	Elomaa 1992[40]	Clodronate (iv)	Placebo	Only painful metastases
	Kylmala 1993[41]	Clodronate (iv)	Open	Only painful metastases
	Ernst 2003[42]	Clodronate (iv)	Placebo	Unlicensed administration of clodronate
	Adami 1989,[43] Adami 1985[44]	Clodronate (iv+im+oral)	Placebo	Only painful metastases
	Kylmala 1997[45]	Clodronate (iv+oral)	Placebo	Only painful metastases
	Strang 1997[46]	Clodronate (iv)	Placebo	Only painful metastases
	Small 2003[47]	Pamidronate (iv)	Placebo	Only painful metastases
	Smith 1989[48]	Etidronate (iv+oral)	Placebo	Only painful metastases
OST	Arican 1999[49]	Clodronate (oral)	Placebo	SRE definition not comparable
	Brown 2007[50]	Clodronate (oral)	Placebo	Outcomes not relevant
	O'Rourke 1995[51]	Clodronate (oral)	Placebo	Outcomes not relevant
	Piga 1998[52]	Clodronate (oral)	Placebo	Outcomes not relevant
	Robertson 1995[53]	Clodronate (oral)	Placebo	SRE definition not comparable
	Jagdev 2001[54]	Clodronate (oral)	Pamidronate (iv)	Outcomes not relevant
	Mystakidou 2008[55]	Ibandronate (oral)	Ibandronate (iv)	Outcomes not relevant
	Heras 2007[56]	Ibandronate (iv)	Placebo	SRE definition not comparable
	Berenson 2001[57]	Zoledronic acid (iv)	Pamidronate (iv)	SRE definition not comparable
	Zaghloul 2010[58]	Zoledronic acid (iv)	Placebo	SRE definition not comparable
	Zhao 2011[59]	Zoledronic acid (iv)	Open	SRE definition not comparable

Primary tumour	Study ID	Intervention	Comparator	Reason for exclusion
BSC vs placebo/ another BSC (n=4)				
Prostate	Buchali 1988[60]	Strontium chloride (iv)	Placebo	SRE definition not comparable
	Nilsson 2005[61]	Strontium chloride (iv)	FEM	Only painful metastases
	Porter 1993[62]	Strontium chloride (iv)	Placebo	Only painful metastases
	Quilty 1994[63]	Strontium chloride (iv)	Radiotherapy	Only painful metastases

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682 Table 2: Characteristics of studies included in NMA

Author, year, country and duration	Cancer type	Interventions	Participants		Outcomes	Comments
			Age	Prev SRE, n (%)		
Kohno 2005[17] Country: Japan Duration: 12 months	Breast	Zoledronic acid 4 mg (n=114)	mean 54.3	39 (34.2)	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	Both administered via 15-minute infusion. Infusions were administered every 4 weeks for 12 months
		Placebo (n=113)	mean 53.5	47 (41.6)		
Lipton 2000[18,64-66] Country: US Duration: 24 months (24 cycles)	Breast	Pamidronate 90 mg (n=367)	<50 years 25% 51-65 years 42% >65 years 33%	NR	SRE outcomes *SMR* (number of skeletal complications per time on trial for each patient (events/year); the overall SMR was calculated with and without hypercalcemia 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	Both administered in 250 mL of 5% dextrose in water given as a 2-hour intravenous infusion every 3-4 weeks for 24 cycles.
		Placebo (n=384)	<50 years 29% 51-65 years 38% >65 years 34%	NR		
Rosen 2003a[16,67,68] Country: Multinational Duration: 25	Breast cancer	Zoledronic acid 4 mg (n=378)	median 58	232 (61.4)	SRE outcomes *Proportion of patients who experienced at least 1 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* Other outcomes	Both administered as an intravenous infusion depending on the scheduling of other antineoplastic
		Pamidronate 90 mg (n=388)	median 56	244 (62.9)		

months					None reported	treatments every 3–4 weeks for 24 months
Stopeck 2010[8,69-75] **Country: Multinational Duration: 34 months**	Breast	**Denosumab 120 mg** (subcutaneous injection) + **placebo** (intravenous infusion) (n=1026)	mean 57	378 (36.8)	**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 apart from the most recent event to ensure that linked events (eg, 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 Skeletal morbidity rate Percent change in uNTx and BSAP levels.	Intravenous products (placebo or zoledronic acid) were dose-adjusted on the basis of baseline creatinine clearance 60 mL/min and were held for renal function deterioration on-study as per zoledronic acid prescribing information
		Zoledronic acid 4 mg (intravenous infusion) + **placebo** (subcutaneous injection) (n=1020)	mean 56	373 (36.6)		
Fizazi 2011[6] **Country: Multinational Duration: 27 months**	Prostate	**Denosumab 120 mg** (subcutaneous) + **placebo** (n=950)	median 71	232 (24)	**SRE outcomes** *Time to first on-study skeletal-related event; assessed for non-inferiority* If testing of the primary endpoint showed non-inferiority, then the same outcome was further tested as a secondary endpoint, together with the secondary endpoint of time to first and subsequent on-study skeletal-related events (multiple events), for superiority **Other outcomes** Overall survival Overall disease progression Prostate-specific antigen concentration during the study Change in bone turnover markers from baseline Pain	Interventions given every 4 weeks until the primary analysis cut off date. Dose adjustment as per Stopeck 2010
		Zoledronic acid 4 mg + **placebo** (subcutaneous) (n=951)	median 71	231 (24)		
Saad 2002[19,76-82] **Country: Multinational**	Prostate	**Zolendronic acid 4mg** (n=214)	mean 72	66 (30.8)	**SRE outcomes** *The proportion of patients having at least one skeletal-related event* Time to the first skeletal- related event Skeletal morbidity rate Proportion of patients with individual skeletal-related events **Other outcomes**	Administered every 3 weeks for 15 months (20 cycles). Initially 5 min infusion (in
		Placebo	mean 72	78 (37.5)		

Duration : 15 months		(n=208)			Time to disease progression Objective bone lesion response Bone biochemical markers Quality-of-life parameters Pain	50ml), changed to 15 min infusion (in 100ml) in 1999
Henry 2011[7,21,24] **Country: Multinational** **Duration : 7 months (median time on-study**	Other solid tumours	**Denosumab 120 mg** (n=890)	median 61	446 (50)	**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** Bone turnover markers Overall survival Overall disease progression.	Zoledronic acid administered intravenously monthly with subcutaneous placebo.
		Zoledronic acid 4 mg (n=886)	median 60	440 (50)		
Rosen 2003b[20,83,84] **Country: Multinational** **Duration of study: 9 months**	Other solid tumours	**Zoledronic acid 4 mg** (n=257)	median 64	166 (65)	**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** Pain score Analgesic use ECOG performance status Best bone lesion response and time to progression of bone lesions Biochemical markers of bone resorption Time to progression of overall disease and survival. Quality of life	Interventions administered intravenously every 3 weeks for 9 months
		Placebo (n=250)	median 64	179 (73)		

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Table 3: Results of individual studies included in the NMA

Cancer	Study	Intervention	TTF SRE		p value	TTF+S SRE	SMR	p value
Breast	**Kohno 2005[17]**	Zoledronic acid (n=114)	Not reached	N/R	0.007	RR 0.59 (0.38 to 0.91)	0.63	0.016
		Placebo (n=113)	364 days (~12.1 months)				1.1	
	Lipton 2000[18]	Pamidronate (n=367)	12.7 months (95%CI 9.6 to 17.2)	N/R	<0.001	NR	2.4 (5.5)	<0.001
		Placebo (n=387)	7.0 months (95%CI 6.2 to 8.5)				3.7 (5.5)	
	Rosen 2003a[16]	Zoledronic acid (n=378)	349 days(chemo treated) 415 days(hormone treated)	N/R	0.826 (chemo) 0.047 (hormone)	RR = 0.80 (0.66 to 0.97)	0.9	0.125
		Pamidronate (n=388)	366 days (chemo treated) 370 days(hormone treated)				1.49	
	Stopeck 2010[8]	Denosumab (n=1026)	Not reached	HR 0.82 95%CI 0.71 to 0.95	<0.001	RR *0.77 (0.66 to 0.89)	0.45	0.004
		Zoledronic acid (n=1020)	26.4 months				0.58	
Prostate	**Fizazi 2011[6]**	Denosumab (n=950)	20.7 months	HR 0.82, 95%CI 0.71 to 0.95	0.0002	RR* 0.82 (95% CI 0.71 to 0.94)	NR	NR
		Zoledronic acid (n=951)	17.1 months				NR	
	Saad 2002[19]	Zoledronic acid (n=214)	361 days (prev SRE) 499 days (no prev SRE)	N/R	0.066 (prev SRE) 0.065 (no prev SRE)	RR 0.64 (95% CI not reported, p value 0.002)	0.80	0.006
		Placebo (n=208)	258 days (prev SRE) 337 days (no prev SRE)				1.49	
Other solid tumours	**Henry 2011[7]**	Denosumab (n=886)	20.6 months	HR 0.84, 95%CI 0.71 to 0.98	0.0007	RR*† 0.90 (0.77 to 1.04)	NR	NR
		Zoledronic acid (n=890)	16.3 months				NR	
	Rosen 2003[20]	Zoledronic acid	230 days	N/R	0.023	HR 0.732, p=0.017	2.24	0.069
		Placebo	163 days				2.52	

RR = risk ratio, RR* = rate ratio, HR = hazard ratio, † = includes multiple myeloma, N/R = not reported, TTF SRE = time to first skeletal related event, TTF+S SRE = time to first and subsequent skeletal related events

688 Table 4: Risk of bias of studies included in NMA

Study id	Q1 Adequate sequence generation?	Q2 Adequate allocation concealment?	Q3 Blinding?	Q4 Incomplete outcome data addressed?	Q5 Free of selective reporting?
Breast cancer					
Lipton 2000[18]	Low	Low	Low	Unclear	Unclear
Kohno 2005[17]	Low	Low	Low	High	Low
Stopeck 2010[8]	Unclear	Unclear	Low	Low	Low
Rosen 2003a[16]	Low	Low	Low	Low	Low
Prostate cancer					
Fizazi 2011[6]	Low	Low	Low	Low	Low
Saad 2002[19]	Low	Low	Low	Low	Low
Other solid tumours					
Henry 2011[7]	Low	Low	Low	Low	Low
Rosen 2003b[20]	Unclear	Unclear	Low	High	Low

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Table 5: Breast cancer NMA results

Comparison	TTF SRE HR (95% CI)	TTF+S Risk Ratio (95% CI)	SMR Rate Ratio (95% CI)
Denosumab versus zoledronic acid	0.82 (0.71 to 0.95)	0.77 (0.66 to 0.89)	0.90 (0.67 to 1.09)
Denosumab versus pamidronate	0.79 (0.61 to 1.03)	0.62 (0.48 to 0.80)	0.73 (0.41 to 1.06)
Denosumab versus placebo	0.46 (0.29 to 0.72)	0.45 (0.28 to 0.72)	0.47 (0.25 to 0.67)
Zoledronic acid versus placebo	0.56 (0.36 to 0.86)	0.59 (0.37 to 0.91)	0.52 (0.32 to 0.70)

TTF SRE = time to first skeletal related event, TTF+S SRE = time to first and subsequent skeletal related events, SMR = skeletal morbidity rate

Table 6: Prostate cancer NMA results

	TTF SRE HR (95%CI)	**TTF+S Risk Ratio (95% CI)**	**SMR Rate Ratio (95% CI)**
Denosumab versus zoledronic acid	0.82 (0.71 to 0.95)	0.82 (0.71 to 0.94)	0.95 (0.46 to 1.47)
Denosumab versus placebo	0.56 (0.40 to 0.77)	0.53 (0.39 to 0.72)	0.52 (0.07 to 0.82)
Zoledronic acid versus placebo	0.68 (0.50 to 0.91)	0.64 (0.48 to 0.85)	0.54 (0.11 to 0.83)

TTF SRE = time to first skeletal related event, TTF+S SRE = time to first and subsequent skeletal related events, SMR = skeletal morbidity rate

Table 7: Other solid tumours and non small cell lung cancer NMA results

	Other solid tumours		NSCLC	
	TTF SRE HR (95%CI)	**TTF+S SRE RR (95%CI)**	**TTF SRE HR (95%CI)**	**TTF+S SRE RR (95%CI)**
Denosumab versus zoledronic acid	0.79 (0.62 to 0.99)	0.83 (0.67 to 1.03)	0.84 (0.64 to 1.10)	0.87 (0.68 to 1.12)
Denosumab versus placebo	0.30 (0.11 to 0.82)	0.61 (0.39 to 0.97)	0.68 (0.45 to 1.03)	0.63 (0.42 to 0.97)
Zoledronic acid versus placebo	0.37 (0.14 to 1.01)	0.74 (0.49 to 1.10)	0.81 (0.59 to 1.11)	0.73 (0.52 to 1.02)

TTF SRE = time to first skeletal related event, TTF+S SRE = time to first and subsequent skeletal related events, SMR = skeletal morbidity rate

Figure 1: PRISMA flow diagram

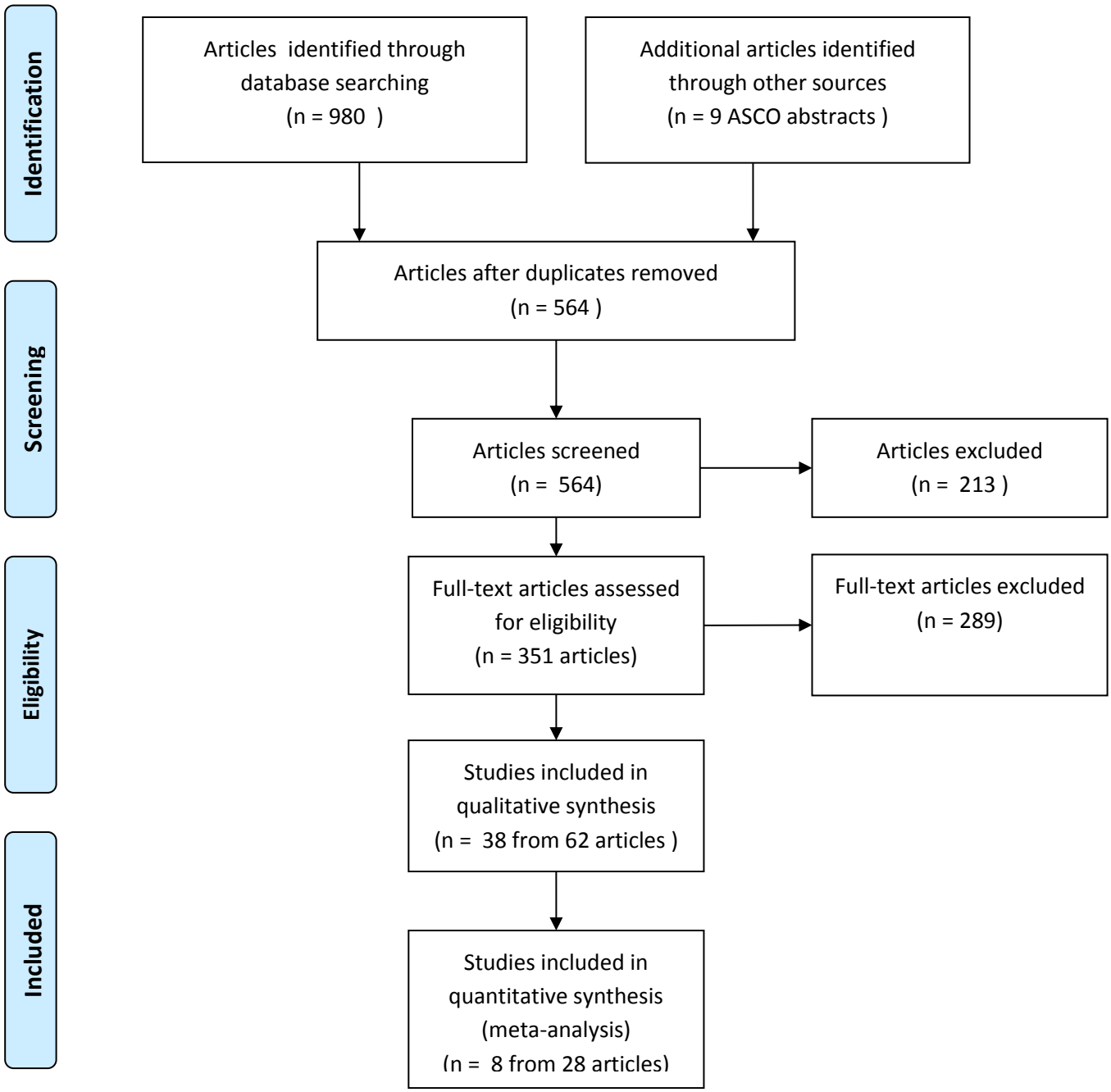
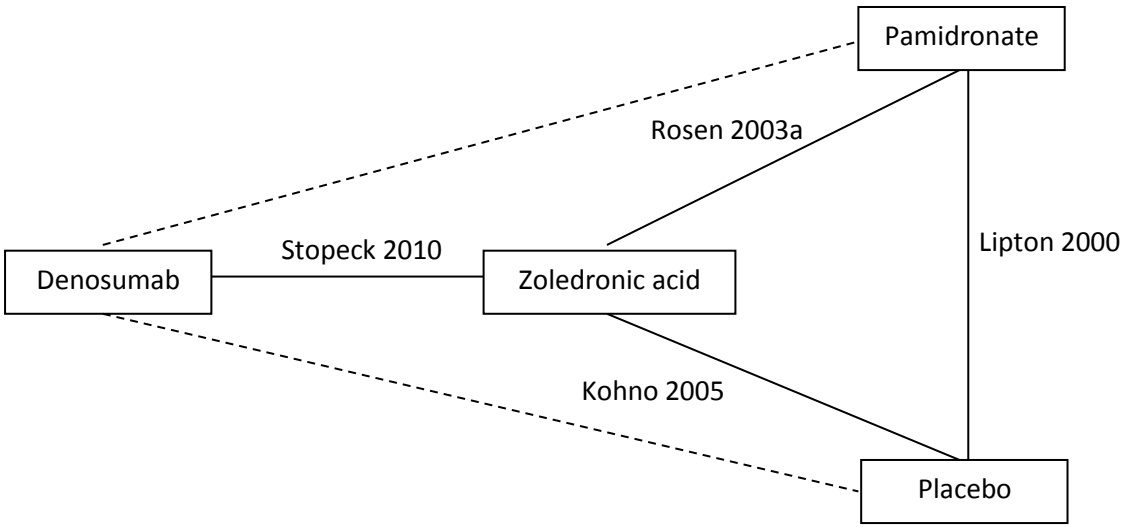


Figure 2: Breast cancer network diagram

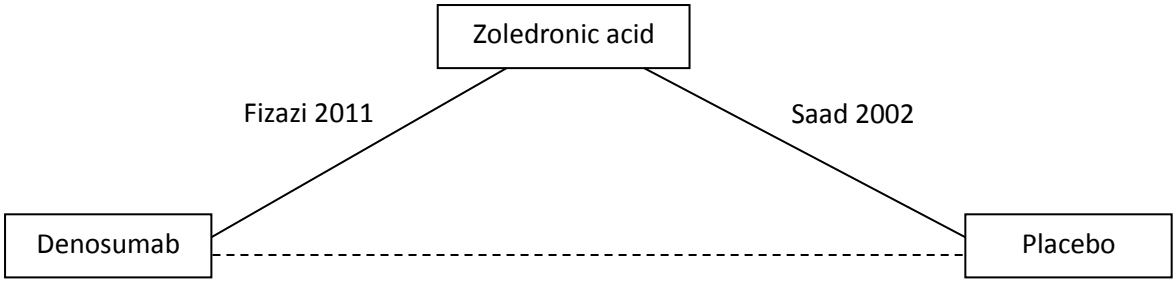


——— = direct evidence

- - - - - - - = indirect evidence from NMA

Note: Lipton 2000 data was only available for the SMR outcome.

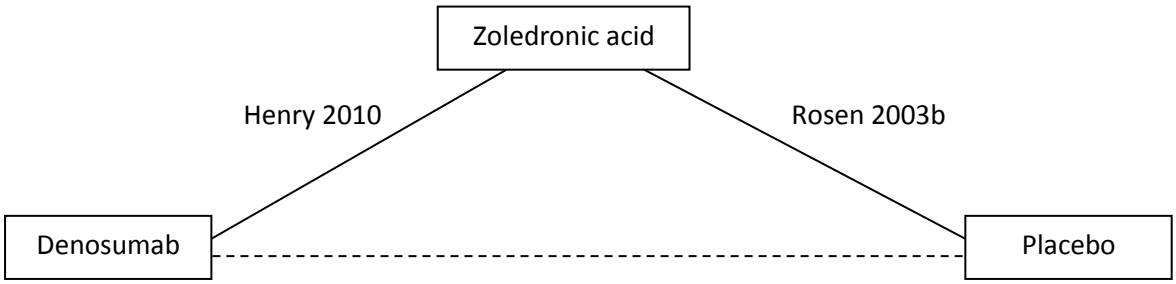
Figure 3: Prostate cancer network diagram



——— = direct evidence

- - - - - - - = indirect evidence from NMA

Figure 4: Other solid tumours network



——— = direct evidence

- - - - - - - = indirect evidence from NMA