Common Drug Review
Clinical Review Report

February 2016

Drug	denosumab (Xgeva)
Indication	Treatment to reduce the risk of developing skeletal-related events in patients with bone metastases from breast cancer, prostate cancer, non–small cell lung cancer, and other solid tumours
Listing request	Treatment to reduce the risk of developing skeletal-related events in patients with bone metastases from breast cancer
Dosage form(s)	120 mg/1.7 mL solution for subcutaneous injection
NOC date	May 10, 2011
Manufacturer	Amgen Canada Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
AQA	Analgesic Quantification Algorithm
BPI-SF	Brief Pain Inventory (Short Form)
CBCN	Canadian Breast Cancer Network
CCSN	Canadian Cancer Survivor Network
CI	confidence interval
CDR	CADTH Common Drug Review
DB	double-blind
ECOG	Eastern Cooperative Oncology Group
EQ-5D	EuroQol 5-Dimensions Questionnaire
FACT-B	Functional Assessment of Cancer Therapy–Breast
FACT-G	Functional Assessment of Cancer Therapy–General
HR	hazard ratio
HRQoL	health-related quality of life
IDC	indirect comparison
IV	intravenous
MCID	minimal clinically important difference
NMA	network meta-analysis
ONJ	osteonecrosis of the jaw
RANKL	human receptor activator of nuclear factor kappa-B ligand
RCT	randomized controlled trial
SAE	serious adverse event
SC	subcutaneous
SRE	skeletal-related event
ULN	upper limit of normal

EXECUTIVE SUMMARY

Introduction

Bone is a common site of metastasis for many cancers including breast, prostate, thyroid, lung, renal, and melanoma.[1] Skeletal metastatic disease is the cause of considerable morbidity in patients with advanced cancer and has been associated with an increase in cancer-related pain, hypercalcemia, fractures, spinal instability, and compression of the spinal cord.[2] Breast cancer is one of the primary tumour types that most frequently metastasize to bone.

Denosumab is a human monoclonal antibody binding to human receptor activator of nuclear factor kappa-B ligand (RANKL).[3] Denosumab has a Health Canada indication for reducing the risk of developing skeletal-related events (SREs) in patients with bone metastases from breast cancer, prostate cancer, non–small cell lung cancer, and other solid tumours.[3] The drug plans that participate in the CADTH Common Drug Review (CDR) process have requested that denosumab be evaluated for reimbursement for reducing the risk of developing SREs in patients with bone metastases from breast cancer. The objective of this report was to perform a systematic review of the beneficial and harmful effects of denosumab for reducing the risk of developing SREs in patients with bone metastases from breast cancer.

Results and Interpretation

Included Studies

One published, manufacturer-sponsored, double-blind (DB), randomized controlled trial (RCT) was included in the systematic review. Breast Cancer Study 20050136 (Breast Cancer Study 136) (n = 2,046)[4-6] evaluated the non-inferiority and superiority of denosumab compared with zoledronic acid based on the first occurrence of an SRE in patients with advanced breast cancer and bone metastases. Patients were randomized to receive either denosumab 120 mg administered by subcutaneous (SC) injection every four weeks, or zoledronic acid 4 mg administered by intravenous (IV) injection every four weeks. All patients received concomitant treatment with calcium (≥ 500 mg) and vitamin D (≥ 400 international units [IU]). The primary efficacy outcome was the time to the first occurrence of an SRE, defined as any of the following: pathological fracture, radiation therapy to the bone, surgery to the bone, or spinal cord compression.

One limitation of Breast Cancer Study 136 was the fact that a high proportion of patients in both treatment groups (55%) discontinued from the study, mostly due to death and disease progression. Although not unexpected in this patient population, the impact on the interpretation of the findings is uncertain. In addition, pain and health-related quality-of-life (HRQoL) outcomes were also likely confounded by unbalanced use of radiation to the bone, an effective treatment for bone pain due to metastasis, which was significantly more common in the zoledronic acid group, potentially biasing results in favour of zoledronic acid. Similar results were obtained with denosumab and zoledronic acid for these outcomes; therefore, this confounding factor undermines the potential for denosumab to show a between-group difference compared with zoledronic acid regarding pain and HRQoL outcomes. Other limitations of the study are related to generalizability. The trial involved patients with a relatively good performance status at baseline; therefore, the effectiveness and safety observed may not be generalizable to patients with a poorer performance status. In addition, patients with various comorbid conditions were excluded from the study, including those with a history of osteonecrosis of the jaw (ONJ), known brain metastases, prior other malignancy within three years, and known HIV or hepatitis B or C. Patients who received prior bisphosphonate treatment for bone metastases were also excluded from

the trial, so that the findings were observed in a population where denosumab was administered as first-line treatment.

Efficacy

Results from Breast Cancer Study 136 demonstrate the superiority of denosumab over zoledronic acid for reducing the risk of a first SRE in patients with advanced breast cancer and bone metastases. With a hazard ratio (HR) of 0.82 (95% confidence interval [CI], 0.71 to 0.95), results achieved the criteria for non-inferiority ($P < 0.001$) and superiority ($P = 0.01$). In Breast Cancer Study 136, denosumab was associated with improvements in median time to first on-study SRE of five months, and with an 18% reduction in HR; therefore, according to the literature and the clinical expert consulted by CDR, the magnitude of the clinical benefits of denosumab compared with zoledronic acid may be considered small but meaningful to patients. There is no consensus regarding the clinical relevance of improvement in time to first SRE. The oncology Scientific Advisory Group consulted by the European Medicines Agency (EMA) stated that the minimum effect size in terms of median time to first on-study SRE considered to be clinically relevant was three months,[7] whereas clinical advisors consulted by the National Health Service (NHS) National Institute for Health Research (NIHR) suggested that a minimal clinically significant change in terms of time to first SRE should reach a 20% reduction in HR.[8] However, the American Society of Clinical Oncology 2011 clinical practice guideline regarding the role of bone-modifying drugs in metastatic breast cancer state that there is insufficient evidence relating to efficacy to support one bone-modifying drug over another.[9]

Pain and HRQoL were identified as important outcomes for patients according to the patient input received by CADTH. These outcomes were measured using reliable and validated tools in Breast Cancer Study 136; however, it is uncertain whether the reduced risk of SREs observed with denosumab translates into improvements in pain or HRQoL, or into reductions in analgesic usage, due to mixed findings and limitations regarding the trial population and confounding factors. Results showed a statistically significant reduction in the risk of a > 4-point change on the Brief Pain Inventory (Short Form) (BPI-SF) "Worst Pain" item with denosumab compared with zoledronic acid; a finding considered clinically meaningful as it exceeds the minimal clinically important difference (MCID) of 1.5 to 2.0 estimated for this instrument. However, results for other patient-related outcomes did not differ between denosumab and zoledronic acid. Patients entering Breast Cancer Study 136 had a relatively good performance status, with consequently relatively low pain levels and limited analgesic use at baseline, as well as relatively little impairment in HRQoL compared with real-life patients, based on experience from specialists' clinical practice. In such circumstances, it may be difficult to detect significant improvements from baseline in these patient-reported outcomes throughout the course of the trial. An absence of worsening in pain or deterioration of HRQoL compared with baseline may also be perceived as a benefit for patients, as suggested by patient input, because the natural disease history in patients with metastatic breast cancer typically evolves toward disease progression. Finally, pain and HRQoL outcomes were also likely confounded by unbalanced use of concurrent treatments to control pain such as radiation to the bone, which was significantly more common in the zoledronic acid group (16% versus 12% with denosumab, $P = 0.0121$), potentially biasing results in favour of zoledronic acid. Similar results were obtained with denosumab and zoledronic acid for these outcomes; therefore, this confounding factor undermines the potential for denosumab to show a between-group difference compared with zoledronic acid regarding pain and HRQoL outcomes.

There are no data to inform on the sustainability of beneficial treatment effects observed with denosumab in patients with advanced breast cancer and bone metastases beyond the median trial duration of 17 months.

There is a lack of evidence with which to directly compare denosumab with drugs other than zoledronic acid used as treatment to reduce the risk of developing SREs in patients with bone metastases from breast cancer, including pamidronate and clodronate. To inform this evidence gap, CDR reviewed and critically appraised available indirect evidence. A literature search was undertaken by CDR to identify any relevant published indirect comparisons (IDCs). Two relevant publications were included, presenting data from one unique IDC. Ford et al.[8,10] assessed the comparative efficacy of denosumab versus zoledronic acid or pamidronate to reduce the risk of developing SREs in patients with bone metastases from breast cancer. No data were available to compare denosumab versus clodronate. The network meta-analysis (NMA) results suggest that the use of denosumab was associated with a statistically significant reduction in the risk of SREs compared with zoledronic acid and placebo. Although the NMA results favoured denosumab compared with pamidronate, statistical significance was not reached. The Ford et al.[8] IDC was likely conducted with methodological rigour; however, its major limitation was the small number of studies included in the IDCs, which results in a high degree of uncertainty regarding the findings of the IDCs. Therefore, the overall IDC results are consistent with the conclusion that denosumab is likely superior to zoledronic acid and placebo, and at least as effective as pamidronate to reduce the risk of developing SREs in patients with bone metastases from breast cancer.

Harms

Denosumab is approved for six indications and has been in use since 2010, and the overall harms in Breast Cancer Study 136 results did not raise any new safety concerns, as confirmed by the clinical expert consulted by CDR. However, there are no data to inform the long-term maintenance of safety of denosumab in patients with advanced breast cancer and bone metastases beyond the trial duration of 17 months.

Mortality as well as the overall incidence of serious adverse events (SAEs) during Breast Cancer Study 136 did not differ significantly between denosumab and zoledronic acid, and were not higher than would be expected in this patient population according to experience from specialists' clinical practice. The most commonly reported SAEs for both treatments (≤ 5%) included dyspnea, metastases to the central nervous system (CNS), vomiting, anemia, pleural effusion, hepatic failure, pyrexia, nausea, and metastases to liver. The proportion of patients experiencing adverse events (AEs) was high but similar between denosumab and zoledronic acid. The most common AEs included nausea, fatigue, arthralgia, back pain, diarrhea, dyspnea, vomiting, pain in extremity, and bone pain. Proportions of patients discontinuing due to AEs in the denosumab treatment group were, however, lower (10%), suggesting adequate tolerability.

Some AEs of particular interest were identified by CADTH based on the denosumab mechanism of action and Health Canada warnings, which have been issued with regard to the risks of hypocalcemia, infections, dermatologic AEs, ONJ, atypical femur fractures, and malignancies.[3] Results for ONJ, atypical femoral fractures, SAEs of infection, and dermatologic AEs are characterized by low and similar proportions of patients experiencing the event in both treatment groups. Cardiovascular events were relatively frequent but occurred in similar proportions of patients in both treatment groups. There were numerically more cases of hypocalcemia in the denosumab group compared with zoledronic acid; however, the difference did not seem to be clinically meaningful, according to the clinical expert consulted by CDR.

Experience from specialists' clinical practice and patient input received by CADTH suggest the need for pharmacological drugs with added convenience and tolerability for use in patients with advanced breast cancer and bone metastases. The fact that denosumab is administered subcutaneously, compared with zoledronic acid that needs to be administered intravenously, may provide benefits for patients in terms of accessibility and convenience, and may also contribute to reducing the burden on the health care system by eliminating the need for a visit to a facility for administration. However, the double-dummy design prevented the objective assessment of whether the SC administration of denosumab is a significant benefit to patients compared with IV administration.

No data are available to directly compare the potential harms of denosumab versus other drugs used in patients with bone metastases from breast cancer. Potential harms were not analyzed in the IDC that was identified by CDR to compare the safety of denosumab with other comparators than zoledronic acid.

Conclusions

The results of Breast Cancer Study 136 suggest that compared with zoledronic acid, denosumab is associated with a statistically significant, clinically meaningful reduction in the time to a first SRE in patients with advanced breast cancer and bone metastases. [redacted] Similar proportions of patients experienced ONJ, [redacted], SAEs of infection, and dermatologic AEs in both treatment groups. The generalizability of the results of Breast Cancer Study 136 is limited by the fact that the trial involved patients with a relatively good performance status at baseline. The results of an IDC in which the efficacy of denosumab was compared with zoledronic acid, pamidronate, or placebo were consistent with the conclusion that denosumab is superior to zoledronic acid and placebo, and at least as effective as pamidronate, for reducing the risk of a first SRE in patients with advanced breast cancer and bone metastases, although these findings are associated with a high degree of uncertainty.

TABLE 1: SUMMARY OF RESULTS

	Breast Cancer Study 136	
	Denosumab (N = 1,026)	**Zoledronic Acid (N = 1,020)**
a) Skeletal-Related Events		
Time to First SRE — FAS Population		
HR (95% CI)	**0.82 (0.71 to 0.95)**	
P value for NI	***P* < 0.0001**	
P value for superiority	***P* = 0.0101**	
b) Pain Control and Analgesic Use		
BPI-SF Pain Scores — Change from Baseline Mean ± SD (Range)		
Pain Right Now	[redacted]	[redacted]
Pain Interference with General Activity	[redacted]	[redacted]
Pain Severity Score	[redacted]	[redacted]
Pain Interference Score	[redacted]	[redacted]
Worst Pain	[redacted]	[redacted]
BPI-SF Pain Scores — Time-to-Event Analyses: HR (95% CI), *P* Value		
≥ 2-point decrease from baseline	1.02 (0.91 to 1.15), *P* = 0.7245 (ns)	
≥ 2-point increase from baseline	0.90 (0.80 to 1.01), *P* = 0.0822 (ns)	
Time to > 4-point	[redacted]	

	Breast Cancer Study 136	
	Denosumab (N = 1,026)	Zoledronic Acid (N = 1,020)
Analgesic Score: Mean ± SD (Range)		
Baseline value	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]
c) Health-Related Quality of Life		
FACT-B — Change from Baseline: Mean ± SD (Range)		
Physical Well-Being	[redacted]	[redacted]
Functional Well-Being	[redacted]	[redacted]
Trial Outcome Index	[redacted]	[redacted]
Total Score	[redacted]	[redacted]
EQ-5D — Change from Baseline: Mean ± SD (Range)		
Health Index Score	[redacted]	[redacted]
VAS Score	[redacted]	[redacted]
Key Harms Outcomes	**Breast Cancer Study 136**	
	Denosumab (N = 1,020)	**Zoledronic Acid (N = 1,013)**
Mortality, n (%)	[redacted]	[redacted]
SAEs, n (%)	**453 (44.4)**	**471 (46.5)**
AEs, n (%)	**977 (95.8)**	**985 (97.2)**
WDAEs, n (%)	**98 (9.6)**	**125 (12.3)**
Notable Harms		
Infections: SAEs, n (%)	71 (7.0)	83 (8.2)
Hypocalcemia: AEs, n (%)	[redacted]	[redacted]
Cardiovascular events: AEs, n (%)	[redacted]	[redacted]
Cardiovascular events: SAEs, n (%)	[redacted]	[redacted]
Cardiovascular events: fatal events, n (%)	[redacted]	[redacted]
ONJ: AEs, n (%)	20 (2.0)	14 (1.4)

AE = adverse event; BPI-SF = Brief Pain Inventory (Short Form); CI = confidence interval; EQ-5D = EuroQol 5-Dimensions Questionnaire; FACT-B = Functional Assessment of Cancer Therapy–Breast; FAS = full analysis set; HR = hazard ratio; NI = non-inferiority; ns = non-significant; ONJ = osteonecrosis of the jaw; SAE = serious adverse event; SD = standard deviation; SRE = skeletal-related event; VAS = visual analogue scale; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report.[11]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Bone is a common site of metastasis for many cancers including breast, prostate, thyroid, lung, renal, and melanoma.[1] Skeletal metastatic disease is the cause of considerable morbidity in patients with advanced cancer and has been associated with an increase in cancer-related pain, hypercalcemia, fractures, spinal instability, and compression of the spinal cord.[2] Breast cancer is one of the primary tumour types that most frequently metastasize to bone; the associated morbidity is increasingly prevalent because survival in the metastatic breast cancer population can be years due to advances in systemic therapy and palliation.

1.2 Standards of Therapy

Current treatment strategies aim to prevent skeletal-related events (SREs), which include the following bone complications: pathological fractures, spinal cord compressions, and radiotherapy and surgery to the bone. These complications of bone metastases are associated with pain, impaired function, and diminished quality of life in patients with metastatic cancer. Conventional pain management with acetaminophen, nonsteroidal anti-inflammatory drugs, opioids, or steroids aims to balance pain control against side effects of pharmacotherapy, but do not generally influence the likelihood of developing most SREs; therefore, the use of bone-modifying drugs is recommended. The American Society of Clinical Oncology (ASCO) 2011 clinical practice guideline regarding the role of bone-modifying drugs in metastatic breast cancer recommends the use of denosumab, pamidronate, or zoledronic acid for patients with breast cancer and evidence of bone metastasis; however, ASCO indicates in its clinical practice guideline that there is insufficient evidence relating to efficacy, which precludes the recommendation of one bone-modifying drug over another.[9] The National Comprehensive Cancer Network (NCCN) also recommends any of these three drugs, suggesting the use of clinical judgment to determine the most appropriate treatment for each individual patient.[12]

1.3 Drug

Denosumab is a human monoclonal antibody binding with affinity and specificity to human receptor activator of nuclear factor kappa-B ligand (RANKL).[3] Increased osteoclast activity, stimulated by RANKL, is a key mediator of bone disease in metastatic tumours; by neutralizing the activity of RANKL, denosumab inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and interrupting cancer-induced bone destruction.[3] Denosumab has a Health Canada indication for reducing the risk of developing SREs in patients with bone metastases from breast cancer, prostate cancer, non–small cell lung cancer, and other solid tumours.[3] Denosumab is not indicated for reducing the risk of developing SREs in patients with multiple myeloma.[3] The recommended dose of denosumab is a 120 mg subcutaneous (SC) injection every four weeks.[3]

Indication under review
Treatment to reduce the risk of developing SREs in patients with bone metastases from breast cancer, prostate cancer, non-small cell lung cancer, and other solid tumours
Listing criteria requested by participating drug plans
Treatment to reduce the risk of developing SREs in patients with bone metastases from breast cancer

The drug plans that participate in the CADTH Common Drug Review (CDR) process have requested that denosumab be evaluated for reimbursement for reducing the risk of developing SREs in patients with bone metastases from breast cancer and other solid tumours. In this CDR report, we review only the breast cancer indication; a separate CDR report focuses on the solid tumours indication, with the exception of breast and prostate cancer. Indeed, the CADTH Canadian Drug Expert Committee (CDEC) recommended in its 2011 Final Recommendation that denosumab be listed for the prevention of SREs in patients with castrate-resistant prostate cancer with one or more documented bony metastases and good performance status (Eastern Cooperative Oncology Group [ECOG] performance status score of 0, 1, or 2), in jurisdictions that list zoledronic acid for the same indication.

Denosumab (Xgeva) is also indicated for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.[3] Finally, denosumab is available in a different product formulation (Prolia) that is indicated for reducing the incidence of fractures in postmenopausal women with osteoporosis, as well as for increasing bone mass in men with osteoporosis at high risk for fracture, and in women and men receiving hormonal therapy for non-metastatic breast or prostate cancer who also are at high risk for fracture.[13]

TABLE 2: KEY CHARACTERISTICS OF DENOSUMAB AND BISPHOSPHONATES INDICATED IN PATIENTS WITH BONE METASTASES

	Denosumab[3]	Bisphosphonates Zoledronic Acid (Zometa), Pamidronate, and Clodronate[14-16]
Mechanism of Action	Human monoclonal antibody that inhibits osteoclast-mediated bone resorption	Synthetic analogues of pyrophosphate that bind to the hydroxyapatite found in bones and inhibit osteoclast-mediated bone resorption
Indication[a]	Reducing the risk of developing SREs in patients with bone metastases from solid tumours Of note, denosumab is not indicated for reducing the risk of developing SREs in patients with multiple myeloma	• Zoledronic acid: treatment of patients with bone metastases from solid tumours and patients with osteolytic lesions of multiple myeloma in conjunction with standard care to prevent or delay complications from the bone lesions • Pamidronate: conditions associated with increased osteoclast activity, predominantly lytic bone metastases and multiple myeloma • Clodronate: as an adjunct in the management of osteolysis resulting from bone metastases of malignant tumours
Route of Administration	SC injection	• Zoledronic acid: IV • Pamidronate: IV • Clodronate: PO
Recommended Dose	120 mg SC every 4 weeks	• Zoledronic acid: 4 mg IV every 3 to 4 weeks • Pamidronate: 90 mg IV every 3 to 4 weeks • Clodronate: 1,600 mg up to 3,200 mg PO q.d.
Common Serious Side Effects/Safety Issues	Osteonecrosis of the jaw, atypical femoral fractures, hypocalcemia	
Particular Serious Side Effects/Safety Issues	Infections, dermatologic AEs	Deterioration in renal function, musculoskeletal pain, cardiovascular and gastrointestinal AEs

AE = adverse event; IV = intravenous; PO = orally; q.d. = once daily; SC = subcutaneous; SREs = skeletal-related events.
[a] Relevant Health Canada indications.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of denosumab for reducing the risk of developing SREs in patients with bone metastases from breast cancer.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with bone metastases from breast cancer
Intervention	Denosumab 120 mg SC every 4 weeks
Comparators	Bisphosphonates: • Zoledronic acid (Zometa) 4 mg IV every 3 to 4 weeks • Pamidronate 90 mg IV every 3 to 4 weeks • Clodronate 1,600 mg up to 3,200 mg PO q.d. Placebo with best supportive care
Outcomes	**Key Efficacy Outcomes** Skeletal-related events including but not limited to: • spinal cord compression • pathological fractures • surgery to the bone • radiation to the bone Pain control Analgesic use Health-related quality of life **Harms Outcomes** Mortality SAEs WDAEs AEs including but not limited to: • osteonecrosis of the jaw • atypical femoral fractures • infections • hypocalcemia • dermatologic AEs
Study Design	Published RCTs

AE = adverse event; IV = intravenous; PO = orally; q.d. = once daily; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; WDAE = withdrawal due to adverse event.
Note: Denosumab is not indicated for reducing the risk of developing skeletal-related events in patients with multiple myeloma.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was denosumab (Xgeva). Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. This report makes use of a literature search conducted in June 2011 for the original Xgeva CDR review. For the current report, database searches were rerun on June 15, 2015 to capture any articles published since the initial search date. Conference abstracts were excluded from the search results.

Regular alerts were established to update the search until the CDEC meeting on January 20, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH Grey Matters checklist (www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine): health technology assessment agencies, health economics, clinical practice guidelines, drug regulatory approvals, advisories and warnings, drug class reviews, and databases (free). Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Appendix 3: Excluded Studies.

3. RESULTS

3.1 Findings From the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in Appendix 3: Excluded Studies.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

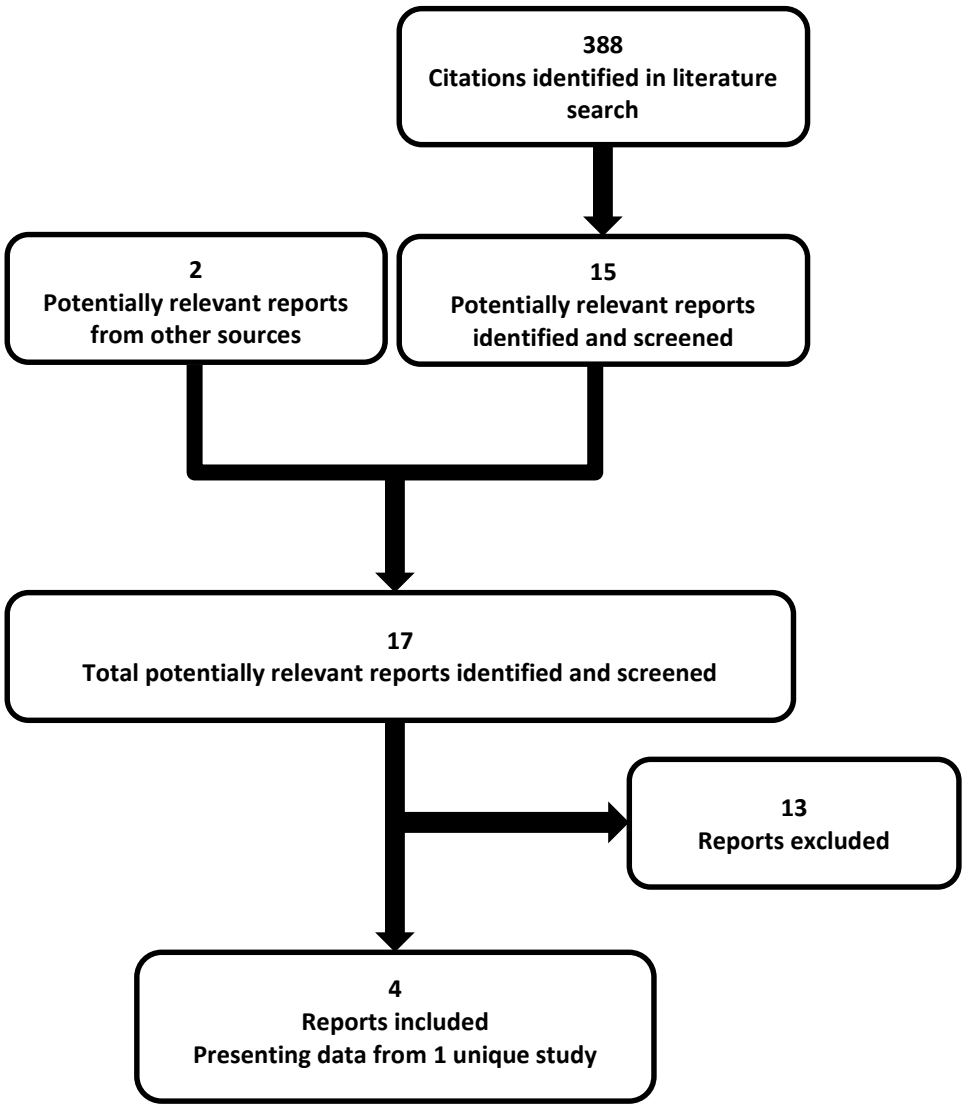


TABLE 4: DETAILS OF INCLUDED STUDY

		Breast Cancer Study 20050136
DESIGNS & POPULATIONS	**Study Design**	DB RCT with active comparator
	Locations	Multi-centre (322 study sites in 35 countries): Europe, US, Canada (n = 97), Latin America, Japan
	Randomized (N)	2,046
	Inclusion Criteria	Adult patients (men or women) with breast adenocarcinoma and evidence of at least 1 bone metastasis. Other inclusion criteria include: • ECOG performance status 0 to 2 • adequate organ function (including creatinine clearance ≥ 30 mL/min and albumin-adjusted serum calcium ≥ 2.0 mmol/L and ≤ 2.9 mmol/L).
	Exclusion Criteria	Current or prior administration of denosumab, IV bisphosphonate, or oral bisphosphonate for bone metastases; planned radiation therapy or surgery to bone; known brain metastases; life expectancy < 6 months; prior or current ONJ; planned or non-healed oral surgery; prior malignancy (except breast cancer, basal cell carcinoma, or in situ cervical cancer) within 3 years; known HIV or active hepatitis B or C.
DRUGS	**Intervention**	Denosumab 120 mg SC every 4 weeks; and zoledronic acid **placebo** IV every 4 weeks. Given concomitantly with strongly recommended daily supplementation of calcium (≥ 500 mg) and vitamin D (≥ 400 IU).
	Comparator(s)	Zoledronic acid 4 mg IV every 4 weeks; and denosumab **placebo** SC every 4 weeks. Given concomitantly with strongly recommended daily supplementation of calcium (≥ 500 mg) and vitamin D (≥ 400 IU).
DURATION	**Phase**	
	Double-blind	Median of 17 months on-study
	Follow-up	2-year follow-up
OUTCOMES	**Primary End Point**	• Time to first SRE (tested for non-inferiority)
	Other End Points	• Time to first SRE (tested for superiority) • Proportion of patients with SRE • Overall survival • Disease progression (overall and in bone) • Patient-reported outcomes: BPI-SF, FACT-B, EQ-5D, analgesic use • Safety outcomes: AEs and SAEs
NOTES	**Publications**	Stopek et al. 2010,[4] Cleeland et al. 2013,[5] Martin et al. 2012[6]

AE = adverse event; BPI-SF = Brief Pain Inventory (Short Form); DB = double-blind; EQ-5D = EuroQol 5-Dimensions Questionnaire; ECOG = Eastern Cooperative Oncology Group; FACT-B = Functional Assessment of Cancer Therapy–Breast; IV = intravenous; IU = international units; ONJ = osteonecrosis of the jaw; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; SRE = skeletal-related event.
Note: One additional report was included.[11]
Source: Clinical Study Report.[11]

3.2 Included Studies

3.2.1 Description of Studies

One published, manufacturer-sponsored, double-blind (DB), randomized controlled trial (RCT) was included in the systematic review. Breast Cancer Study 20050136 (Breast Cancer Study 136) (n = 2,046)[4-6] evaluated the non-inferiority and superiority of denosumab compared with zoledronic acid based on the first occurrence of an SRE in patients with advanced breast cancer and bone metastases. Patients were randomized to receive either denosumab 120 mg administered by SC injection every four weeks, or zoledronic acid 4 mg administered by intravenous (IV) injection every four weeks. All patients received concomitant treatment with calcium (≥ 500 mg) and vitamin D (≥ 400 IU).

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients were eligible for Breast Cancer Study 136 if they were adults (men or women) with histologically or cytologically confirmed breast adenocarcinoma with current or prior radiographic or magnetic evidence of at least one bone metastasis.

Participation in the trial also required an ECOG performance status of 0, 1, or 2, and adequate organ function as defined by the following criteria:

- serum aspartate aminotransferase ≤ 5 × upper limit of normal (ULN)
- serum alanine aminotransferase ≤ 5 × ULN
- serum total bilirubin ≤ 2 × ULN
- creatinine clearance ≥ 30 mL/min
- albumin-adjusted serum calcium ≥ 2.0 mmol/L and ≤ 2.9 mmol/L.

Key exclusion criteria included current or prior administration of denosumab, IV bisphosphonate, or oral bisphosphonate for bone metastases. Patients were also excluded if they had any planned radiation therapy or surgery to bone, known brain metastases, or a life expectancy under six months. The presence of the following comorbidities also excluded patients from participating in the trial: prior or current osteonecrosis of the jaw (ONJ); planned or non-healed oral surgery; prior malignancy (except breast cancer, basal cell carcinoma, or in situ cervical cancer) within three years; known HIV or active hepatitis B or C.

b) Baseline Characteristics

Details regarding baseline characteristics are provided in Table 5. Baseline characteristics were balanced between treatment groups. Patients in Breast Cancer Study 136 had a mean age of 57 years. A total of [redacted] of patients were under 50 years of age, while [redacted] were 65 years or older. Almost all patients were women and 80% were Caucasian.

A total of 92% of patients had an ECOG performance status of 0 (48%) or 1 (44%) at study entry. Only 7% of participants had an ECOG score of 2. Primary tumour stage at diagnosis ranged from [redacted]. Most patients (76%) had two bone metastases or fewer at baseline; however, based on the inclusion criteria, patients were to have at least one bone metastasis. The presence of visceral metastasis was observed in 53% of patients. Concomitant chemotherapy was administered in 40% of patients.

A total of [redacted] of patients in Breast Cancer Study 136 sustained a previous SRE. The most frequent individual events were [redacted].

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Baseline Characteristics	Breast Cancer Study 136	
	Denosumab (N = 1,026)	Zoledronic Acid (N = 1,020)
Age		
Mean ± SD, years	56.8 ± 11.5	56.6 ± 11.6
Age Categories, n (%)		
< 50 years	[redacted]	[redacted]
≥ 50 years	[redacted]	[redacted]
Geriatric Age Categories, n (%)		
≥ 65 years	[redacted]	[redacted]
≥ 75 years	[redacted]	[redacted]
Gender, n (%)		
Male	8 (0.8)	9 (0.9)
Female	1,018 (99.2)	1,011 (99.1)
Ethnic Group, n (%)		
Caucasian	822 (80.1)	813 (79.7)
Black	26 (2.5)	25 (2.5)
Hispanic or Latino	59 (5.8)	59 (5.8)
Asian	32 (3.1)	37 (3.6)
Japanese	70 (6.8)	69 (6.8)
Native Hawaiian or Other Pacific Islander	1 (< 0.1)	1 (< 0.1)
Other	16 (1.6)	6 (1.6)
ECOG Performance Status at Study Entry, n (%)		
0	504 (49)	488 (48)
1	451 (44)	444 (44)
2	68 (7)	82 (8)
3	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Primary Tumour Stage at Diagnosis, n (%)		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Time from Primary Cancer Diagnosis to Initial Bone Metastasis		
Mean ± SD, months	[redacted]	[redacted]
Time from Initial Bone Metastasis to Randomization		
Mean ± SD, months	[redacted]	[redacted]
Number of Metastatic Lesions in Bone at Baseline, n (%)		
≤ 2	[redacted]	[redacted]
> 2	[redacted]	[redacted]
Type of Bone Lesion at Baseline		
Osteoblastic	[redacted]	[redacted]
Osteolytic	[redacted]	[redacted]

Baseline Characteristics	Breast Cancer Study 136	
	Denosumab (N = 1,026)	Zoledronic Acid (N = 1,020)
Mixed	[redacted]	[redacted]
Unable to evaluate	[redacted]	[redacted]
Not seen	[redacted]	[redacted]
Presence of Visceral Metastases, n (%)		
All	552 (54)	525 (51)
Liver	211 (21)	182 (18)
Lung	[redacted] (21)	210 (21)
Other	369 (36)	369 (36)
Concomitant Chemotherapy, n (%)		
Yes	410 (40)	408 (40)
No	616 (60)	612 (60)
SRE History, n (%)		
Any SRE	[redacted]	[redacted]
Radiation to bone	258 (25.1)	280 (27.5)
Pathological fracture	[redacted]	[redacted]
Spinal cord compression	[redacted]	[redacted]
Surgery to bone	[redacted]	[redacted]

ECOG = Eastern Cooperative Oncology Group; SD = standard deviation; SRE = skeletal-related event.
Source: Clinical Study Report p. 134, 136–7, 266.[11]

3.2.3 Interventions

Breast Cancer Study 136 evaluated the efficacy and safety of denosumab compared with zoledronic acid in patients with advanced metastatic breast cancer. The study was conducted in a DB fashion; therefore, all randomized patients received matching placebo:

- Patients randomly assigned to the denosumab group received a 120 mg SC injection of denosumab and the zoledronate placebo (IV) every four weeks until the event-driven analysis cut-off date.
- Patients randomly assigned to the zoledronate group received 4 mg of zoledronic acid intravenously as a single minimum 15-minute infusion every four weeks until the primary analysis cut-off date. These patients were also administered the denosumab placebo (SC) every four weeks. The dosage of zoledronate (or matching placebo) was to be adjusted for patients with baseline creatinine clearance ≤ 60 mL/min.

Concomitant treatment with calcium (≥ 500 mg) and vitamin D (≥ 400 IU) was strongly recommended for all patients, unless documented hypercalcemia developed during the study (i.e., albumin-adjusted serum calcium > 2.9 mmol/L or > 11.5 mg/dL or ionized calcium > 1.5 mmol/L). Investigators were permitted to prescribe chemotherapy or hormonal therapy for metastatic breast cancer and any other concomitant medication or treatment that they deemed necessary to provide adequate supportive care, with the exception of any bisphosphonate other than study treatment. All concomitant medications received during the study were recorded for each patient.

3.2.4 Outcomes

a) Primary Efficacy Outcome — Skeletal-Related Events

The primary efficacy outcome for Breast Cancer Study 136 was the time to the first occurrence of an SRE, defined as any of the following:

- pathological fracture (vertebral or non-vertebral)
- radiation therapy to bone (including the use of radioisotopes)
- surgery to bone
- spinal cord compression.

Patients who experienced an SRE continued on the study treatments and a multiple-event analysis (time to first-and-subsequent on-study SRE) was performed as a secondary outcome. To be included in the analysis, subsequent events had to occur ≥ 21 days after the previous SRE to ensure that potentially related events, such as surgical procedures for a fracture that are likely scheduled within 21 days, were not counted as separate events.

Pathological fractures were defined as new bone fractures that occurred spontaneously and not as a result of severe trauma. The nature of the trauma was to be determined by the investigator. Fractures were assessed by skeletal surveys (X-rays) every 12 weeks, or by unscheduled radiographic assessments taken in the course of standard of care during the study, and were identified or confirmed centrally and independently. The skeletal surveys included the following examinations:

- lateral skull
- posterior-anterior chest
- anterior-posterior and lateral cervical, thoracic, and lumbar spine
- anterior-posterior pelvis and extremities — upper (shoulder to elbow) and lower (hip to knee).

Surgery to bone included procedures to set or stabilize a fracture, or to prevent an imminent fracture or spinal cord compression. **Radiation therapy** to bone included radiation for pain control, to treat or prevent pathologic fractures, or to treat or prevent spinal cord compression. **Spinal cord compression** events were confirmed centrally and independently using appropriate radiographic imaging.

b) Secondary Efficacy Outcomes — Patient-Reported Outcomes

Relevant secondary efficacy outcomes included the following patient-reported outcomes:

- analgesic use
- Brief Pain Inventory (Short Form) (BPI-SF)
- Functional Assessment of Cancer Therapy–Breast (FACT-B)
- EuroQol 5-Dimensions Questionnaire (EQ-5D).

Analgesic use was scored on a numerical scale ranging from 0 (no analgesic) to 7 (strong opioids) based on oral morphine equivalent per day, as shown in the table that follows. The change from baseline in analgesic usage over the course of the study was assessed through to the time when 30% of patients withdrew from the trial.

Scale	Description
0	No analgesics
1	Non-opioid analgesics
2	Weak opioids (codeine, meperidine, tramadol)
3	Strong opioids ≤ 75 mg OME per day
4	Strong opioids > 75–150 mg OME per day
5	Strong opioids > 150–300 mg OME per day
6	Strong opioids > 300–600 mg OME per day
7	Strong opioids > 600 mg OME per day

OME = oral morphine equivalents.

Pain and health-related quality of life (HRQoL) were measures using the validated tools described in the following section. Assessments were to be completed before any other study procedures were performed.

The BPI-SF was specifically designed to assess pain in cancer and is considered reliable. The questionnaire is used to assess the intensity of pain (pain severity) and the degree to which pain interferes with function (pain interference). The FACT-B questionnaire consists of the 27-item Functional Assessment of Cancer Therapy–General (FACT-G) questionnaire, a widely used disease-specific HRQoL instrument considered valid and reliable in patients with cancer, with 10 additional questions on breast cancer. The questionnaire evaluates the HRQoL domains of physical well-being, functional well-being, social/family well-being, and emotional well-being in patients with cancer. The EQ-5D is a widely used, generic HRQoL instrument composed of six questions allowing for estimation of health utility. The first five questions address various quality-of-life dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety /depression. The last question is represented by a visual analogue scale (EQ-5D VAS), scored from 0 to 100 asking the patient to mark his or her health state today.

c) Harms Outcomes

Safety outcomes included adverse events (AEs) and serious adverse events (SAEs), clinical laboratory results, and vital signs.

3.2.5 Statistical Analysis

The primary objective of Breast Cancer Study 136 was to test for non-inferiority of denosumab compared with zoledronic acid in patients with advanced breast cancer and bone metastases for the outcome of SRE, based on the time to first on-study occurrence. For the primary outcome, inclusion of 1,960 patients (745 patients experiencing ≥ 1 SRE) provided 97% power to detect that denosumab is non-inferior to zoledronic acid with a true hazard ratio (HR) of 0.9, based on a synthesis approach designed to demonstrate that denosumab would preserve at least 50% of the effect of zoledronic acid compared with placebo (HR 1.58; 95% confidence interval [CI], 1.23 to 2.02). Superiority testing was pre-specified as a secondary outcome and would be tested only if denosumab was found to be non-inferior to zoledronic acid, following a hierarchical testing strategy. The planned sample size would provide 90% power to detect that denosumab is superior to zoledronic acid with a true HR of 0.8.

The analysis of time to the first occurrence of an SRE was performed using the Kaplan–Meier method and the HR was estimated using the stratified Cox proportional hazard model. The significance level for the analysis of the primary end point was 0.05. Patients completing the study and not experiencing the event(s) of interest were considered censored to those event(s).

a) Analysis Populations

The **primary analysis population (full analysis set [FAS] population)** included all randomized patients, analyzed according to their randomized treatment assignment, regardless of treatment received. A supportive analysis used **the per-protocol analysis population**, which included all patients with a protocol-defined diagnosis and no major protocol violations who received at least one dose of active investigational product.

The **safety analysis population** included all randomized patients who received at least one dose of active investigational product; patients in this analysis set were analyzed according to the treatment received, based on the first investigational product dose administered.

3.3 Patient Disposition

Details regarding baseline characteristics are provided in Table 6. A total of 2,049 patients were enrolled and 2,046 patients were randomized in Breast Cancer Study 136; of these, 55% of patients discontinued the study before the primary data analysis cut-off date. Discontinuation rates throughout the study duration, as well as reasons for discontinuation, were balanced between treatment groups. The most frequent reasons for discontinuation were death (17% in each treatment group), disease progression (12% in each group), and consent withdrawn (12% in each group).

TABLE 6: PATIENT DISPOSITION

	Breast Cancer Study 136	
	Denosumab	Zoledronic Acid
Enrolled, N	2,049	
Randomized — overall	2,046	
Randomized — per group	1,026	1,020
Randomized and treated, n (%)	[redacted]	[redacted]
Completed study through primary data analysis cut-off date, n (%)	468 (46)	461 (45)
Discontinued, n (%)	558 (54)	559 (55)
Most Frequent Reasons for Discontinuation, n (%)		
Death	174 (17)	169 (17)
Disease progression	124 (12)	124 (12)
Consent withdrawn	118 (12)	117 (12)
Subject request	61 (6)	57 (6)
Adverse event	28 (3)	43 (4)
Other	18 (2)	21 (2)
Administrative decision	14 (1)	15 (2)
Noncompliance	10 (1)	4 (< 1)
Lost to follow-up	8 (< 1)	7 (< 1)
Protocol deviation	2 (< 1)	0
Ineligibility determined	1 (< 1)	2 (< 1)
Analysis Sets		
FAS, N	1,026	1,020
PP, N	[redacted]	[redacted]
Safety, N	[redacted]	[redacted]

FAS = full analysis set; PP = per-protocol.
Source: Clinical Study Report p. 129, 141, 261.[11]

3.4 Exposure to Study Treatments

Details regarding baseline characteristics are provided in Table 7. Patients in Breast Cancer Study 136 spent a median time on study of 17 months in each treatment group, which was, however, associated with a relatively wide range of 0 months to 34 months.

TABLE 7: EXTENT OF EXPOSURE

	Breast Cancer Study 136	
	Denosumab (N = 1,026)	Zoledronic Acid (N = 1,020)
Number of Months on Study[a]		
Mean ± SD	[redacted]	[redacted]
Median	16.85	16.97
Range	[redacted]	[redacted]
Cumulative Exposure, Months[b]		
Mean ± SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Number of Doses Received		
Mean ± SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]

SD = standard deviation.
[a] Defined as the time period from the first dose of investigational product, or randomization date if patients did not take any dose, to the end of study date or primary data cut-off date, whichever comes first.
[b] Exposure is defined as the time from the first dose to the last dose of investigational product and adding 28 days.
Source: Clinical Study Report p. 179-80.[11]

3.5 Critical Appraisal

3.5.1 Internal Validity

a) Study Design, Intervention and Comparator

Breast Cancer Study 136 was a DB, active-controlled randomized trial that was likely conducted with methodological rigour. Zoledronic acid is a valid comparator, but uncertainty remains regarding the effects of denosumab compared with other drugs recommended as treatment to reduce the risk of developing SREs in patients with bone metastases from breast cancer. To inform this gap, additional evidence was gathered in the form of indirect comparisons.

There was unbalanced use of concurrent treatments to control pain; indeed, radiation to the bone was significantly more common in the zoledronic acid group (16% versus 12% with denosumab, *P* = 0.0121) and, according to the clinical expert consulted by CDR, radiotherapy is considered an effective treatment for bone pain due to metastasis. Therefore, it is possible that outcomes related to pain and HRQoL were affected by this confounding factor and that results favour zoledronic acid. Similar results were obtained with denosumab and zoledronic acid for these outcomes; therefore, this confounding factor undermines the potential for denosumab to show a between-group difference compared with zoledronic acid regarding pain and HRQoL outcomes.

b) Selection, Allocation and Disposition of Patients

Breast Cancer Study 136 was performed using appropriate allocation strategies. Patients were randomized in a 1:1 allocation to receive denosumab or zoledronic acid; the randomization schedule was stratified by previous SRE, prior oral bisphosphonate use, current chemotherapy, and region. The randomization schedule used randomly permuted blocks and was performed centrally. The trial was conducted in a DB fashion and used matching placebos, which is appropriate; however, the double-dummy design prevented the objective measurement of the potential benefits of SC versus IV administration. There was no indication of unplanned sources of unblinding.

Overall, baseline characteristics were balanced between treatment groups. A high proportion of patients (55%) discontinued from the study, mostly due to death and disease progression, which is not unexpected in this patient population. However, withdrawals were evenly distributed between treatment groups. The impact of this limitation on the interpretation of the findings is uncertain.

c) Outcome Measures

The outcome measure and definition for efficacy outcomes, i.e., time to SREs, are considered appropriate to evaluate treatment response in clinical practice. SREs include pathological fractures and spinal cord compression — which were considered the individual outcomes with the most clinical consequences for patients, according to the clinical expert consulted by CDR — as well as radiation therapy and surgery to the bone. Pathological fractures were assessed radiographically; however, the clinical expert noted that not all radiographically assessed fractures are clinically meaningful, depending on the level of pain and if function is affected. Patient-reported outcome measures, i.e., analgesic score, BPI-SF, FACT-B, and EQ-5D are considered valid and reliable.

d) Statistical Analysis

Breast Cancer Study 136 had sufficient power to demonstrate statistical significance for testing of the primary non-inferiority hypothesis and secondary superiority hypothesis. The time-to-event analyses were performed using the Kaplan–Meier method and hazard ratios were estimated using the stratified Cox proportional hazard model.

3.5.2 External Validity

a) Patient Selection

Inclusion and exclusion criteria appeared relevant and reasonable. Breast Cancer Study 136 involved patients with a relatively good performance status at baseline (i.e., 92% of patients had an ECOG performance status of 0 or 1); therefore, the effectiveness and safety observed in the trial may not be generalizable to patients with a poorer performance status.

The trial excluded patients who received prior bisphosphonate treatment for bone metastases; as a result, the findings from Breast Cancer Study 136 were observed in a population where denosumab was administered as first-line treatment.

Various groups of patients with comorbid conditions were excluded, including but not limited to prior or current ONJ; known brain metastases; prior other malignancy within three years (with exceptions); and known HIV, hepatitis B or C. Therefore, the findings from Breast Cancer Study 136 are not generalizable to these patients.

b) Treatment Regimen and Length of Follow-up

Breast Cancer Study 136 used an appropriate and realistic denosumab treatment regimen for patients with bone metastases from breast cancer. There is a gap in the evidence as the trial does not inform on how denosumab compares with other drugs recommended in this indication.

The median on-study duration of 17 months was considered sufficient to see the effect of both treatments on SREs and HRQoL. The sustainability of beneficial treatment effects and long-term safety beyond the trial duration remain uncertain.

c) Outcome Measures

Although considered valid and reliable, experience from specialists' clinical practice suggests that the instruments selected for assessment of patient-reported outcomes may not be routinely used outside specialized clinics.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (section 2.2, Table 3) are reported . See Appendix 4 for detailed efficacy data.

3.6.1 Skeletal-Related Events

Results of Breast Cancer Study 136 for the primary efficacy outcome of time to first SRE demonstrated that the use of denosumab was associated with a statistically significant reduction in the risk of a first SRE compared with zoledronic acid, as shown by the HR of 0.82 (95% CI, 0.71 to 0.95; FAS population), achieving the criteria for non-inferiority ($P < 0.0001$) and superiority ($P = 0.0101$). Findings in the per-protocol (PP) population [redacted].

The median time to first SRE was 32.4 months in patients randomized to denosumab and 27.4 months for patients receiving zoledronic acid (data not shown).[11] The proportions of patients experiencing an event was 31% (n = 315 patients) in the denosumab group compared with 37% (n = 372 patients) in the zoledronic acid group (Appendix 4, Table 10).

Results for the secondary outcome of time to first and subsequent SRE were consistent with those for the primary outcome. Detailed results as well as data for individual types of SRE are provided in Table 8, as well as in Appendix 4, Table 10. [redacted] As for other efficacy outcomes, [redacted][11]

3.6.2 Pain Control and Analgesic Use

Pain-related outcomes were assessed using BPI-SF. Detailed outcome data are provided in Appendix 4, Table 11 and Table 12. Results for mean change from baseline [redacted]. Outcome measures including the BPI-SF questionnaire are reviewed in Appendix 5. Considering that a minimal clinically important difference (MCID) of 1.5 to 2.0 was estimated for this instrument,[17,18] [redacted].

A time-to-event analysis was also reported for the BPI-SF "Worst Pain" item, which is ranked from 0 to 10, with a higher score indicating a less preferred health status. There was no statistically significant difference between treatment groups for the outcome of time to a ≥ 2-point decrease or increase from baseline; [redacted].

Analgesic use was scored on a numerical scale ranging from 0 (no analgesic) to 7 (strong opioids) based on oral morphine equivalent per day and assessed through to the time when 30% of patients withdrew from the trial, which is approximately at week 73. Results for mean change from baseline [redacted].

3.6.3 Health-Related Quality of Life

HRQoL was assessed using the FACT-B questionnaire and the EQ-5D utility scores. Detailed outcome data are provided in Appendix 4, Table 14 and Table 15, respectively. Results for mean change from baseline [redacted]. Outcome measures including HRQoL instruments are reviewed in Appendix 5. Considering that an MCID of 7 to 8 was estimated for the FACT-B questionnaire,[19,20] and that an MCID of 0.06 was estimated for the EQ-5D utility scores,[21,22] [redacted].

TABLE 8: KEY EFFICACY OUTCOMES

	Breast Cancer Study 136	
	Denosumab (N = 1,026)	Zoledronic Acid (N = 1,020)
Skeletal-Related Events		
Time to First SRE — FAS Population		
HR (95% CI)	**0.82 (0.71, 0.95)**	
P value for NI	***P* < 0.0001**	
P value for superiority	***P* = 0.0101**	
Time to First SRE — by Individual Event Type: HR (95% CI), *P* value		
Spinal cord compression	[redacted]	
Pathological fracture	[redacted]	
Surgery to bone	[redacted]	
Radiation to bone	0.74 (0.59 to 0.94), ***P* = 0.0121**	
Time to First and Subsequent SRE — FAS Population		
HR (95% CI), *P* value	0.77 (0.66 to 0.89), [redacted] for superiority	
Pain Control and Analgesic Use		
BPI-SF Pain Scores — Change from Baseline: Mean ± SD (Range)		
Pain Right Now	[redacted]	[redacted]
Pain Interference with General Activity	[redacted]	[redacted]
Pain Severity Score	[redacted]	[redacted]
Pain Interference Score	[redacted]	[redacted]
Worst Pain	[redacted]	[redacted]
BPI-SF Pain Scores — Time-to-Event Analyses: HR (95% CI), *P* value		
≥ 2-point decrease from baseline	1.02 (0.91 to 1.15), *P* = 0.7245 (ns)	

	Breast Cancer Study 136	
	Denosumab (N = 1,026)	Zoledronic Acid (N = 1,020)
Skeletal-Related Events		
≥ 2-point increase from baseline	0.90 (0.80 to 1.01), *P* = 0.0822 (ns)	
Time to > 4-point	[redacted]	
Analgesic Score: Mean ± SD (Range)		
Baseline value	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]
Health-Related Quality of Life		
FACT-B — Change from Baseline: Mean ± SD (Range)		
Physical Well-Being	[redacted]	[redacted]
Functional Well-Being	[redacted]	[redacted]
Trial Outcome Index	[redacted]	[redacted]
Total Score	[redacted]	[redacted]
EQ-5D — Change from Baseline: Mean ± SD (Range)		
Health Index Score	[redacted]	[redacted]
VAS Score	[redacted]	[redacted]

BPI-SF = Brief Pain Inventory (Short Form); CI = confidence interval; EQ-5D = EuroQol 5-Dimensions Questionnaire; FACT-B = Functional Assessment of Cancer Therapy–Breast; FAS = full analysis set; HR = hazard ratio; NI = non-inferiority; ns = non-significant; SD = standard deviation; SRE = skeletal-related event; VAS = visual analogue scale.
Source: Clinical Study Report.[11]

3.7 Harms

Only those harms identified in the review protocol are reported (see 2.2.1, Protocol). See Appendix 4: Detailed Outcome Data for detailed harms data.

3.7.1 Mortality

A total of [redacted] of patients randomized to denosumab [redacted] died during Breast Cancer Study 136, compared with [redacted] of patients receiving zoledronic acid [redacted]. The most frequently reported causes of death were [redacted].

3.7.2 Serious Adverse Events

Similar proportions of patients experienced SAEs in both treatment groups in Breast Cancer Study 136, with a total of 44% and 47% of patients in the denosumab and zoledronic acid group, respectively. The most common SAEs reported (≤ 5% in each treatment group) included dyspnea, metastases to central nervous system (CNS), vomiting, anemia, pleural effusion, hepatic failure, pyrexia, nausea, and metastases to liver.

3.7.3 Adverse Events

Similar proportions of patients experienced AEs in both treatment groups in Breast Cancer Study 136, with a total of 96% and 97% of patients in the denosumab and zoledronic acid group, respectively. The most common AEs reported (< 40% in each treatment group) included nausea, fatigue, arthralgia, back pain, diarrhea, dyspnea, vomiting, pain in extremity, and bone pain.

3.7.4 Withdrawals Due to Adverse Events

The proportion of patients discontinuing Breast Cancer Study 136 due to AEs was 10% in the denosumab group and 12% in the zoledronic acid group. The most frequent reasons for discontinuation due to AEs reported [redacted] were [redacted]

3.7.5 Notable Harms

Several AEs of particular interest were identified by CADTH and by the manufacturer based on the denosumab mechanism of action and Health Canada warnings. Detailed outcome data are provided in Appendix 4, Table 17. Similar proportions of patients experienced ONJ, [redacted] in both treatment groups; these were reported by low proportions of patients in Breast Cancer Study 136. A total of 7% of patients randomized to denosumab reported SAEs of infection compared with 8% of patients receiving zoledronic acid. Cardiovascular events [redacted]. There were numerically more cases of hypocalcemia in the denosumab group compared with zoledronic acid [redacted].

TABLE 9: HARMS

	Breast Cancer Study 136	
	Denosumab (N = 1,020)	Zoledronic Acid (N = 1,013)
Mortality, n (%)	[redacted]	[redacted]
Most common reasons:		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
SAEs, n (%)	**453 (44.4)**	**471 (46.5)**
Most common SAEs:		
Dyspnea	53 (5.2)	38 (3.8)
Metastases to CNS	47 (4.6)	46 (4.5)
Vomiting	31 (3.0)	31 (3.1)
Anemia	27 (2.6)	32 (3.2)
Pleural effusion	24 (2.4)	25 (2.5)
Hepatic failure	24 (2.4)	16 (1.6)
Pyrexia	21 (2.1)	26 (2.6)
Nausea	21 (2.1)	23 (2.3)
Metastases to liver	20 (2.0)	28 (2.8)
AEs, n (%)	**977 (95.8)**	**985 (97.2)**
Most common AEs:		
Nausea	356 (34.9)	384 (37.9)
Fatigue	301 (29.5)	324 (32.0)
Arthralgia	250 (24.5)	291 (28.7)
Back pain	241 (23.6)	264 (26.1)
Diarrhea	231 (22.6)	207 (20.4)
Dyspnea	222 (21.8)	190 (18.8)

	Breast Cancer Study 136	
	Denosumab (N = 1,020)	**Zoledronic Acid (N = 1,013)**
Vomiting	212 (20.8)	238 (23.5)
Pain in extremity	204 (20.0)	222 (21.9)
Bone pain	186 (18.2)	238 (23.5)
WDAEs, n (%)	**98 (9.6)**	**125 (12.3)**
Most common WDAEs:		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Notable Harms		
Infections: SAEs, n (%)	71 (7.0)	83 (8.2)
Hypocalcemia: AEs, n (%)	[redacted]	[redacted]
Cardiovascular events: AEs, n (%)	[redacted]	[redacted]
Cardiovascular events: SAEs, n (%)	[redacted]	[redacted]
Cardiovascular events: Fatal events, n (%)	[redacted]	[redacted]
ONJ: AEs, n (%)	20 (2.0)	14 (1.4)

AE = adverse event; CNS = central nervous system; ONJ = osteonecrosis of the jaw; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report.[11]

4. DISCUSSION

4.1 Summary of Available Evidence

One published, manufacturer-sponsored, DB RCT was included in the systematic review. Breast Cancer Study 136 (n = 2,046)[4-6] evaluated the non-inferiority and superiority of denosumab compared with zoledronic acid based on the first occurrence of an SRE in patients with advanced breast cancer and bone metastases. Patients were randomized to receive either denosumab 120 mg SC every four weeks, or zoledronic acid 4 mg IV every four weeks. All patients received concomitant treatment with calcium (≥ 500 mg) and vitamin D (≥ 400 IU).

Breast Cancer Study 136 was conducted with methodological rigour, but was not without limitations. One limitation of the study was the fact that a high proportion of patients in both treatment groups (55%) discontinued from the study, mostly due to death and disease progression. Although this is not unexpected in this patient population, the impact on the interpretation of the findings is uncertain. The double-dummy design prevented the objective assessment of whether the SC administration of denosumab is a significant benefit to patients compared with IV administration, as highlighted by the patient input received by CADTH. In addition, pain and HRQoL outcomes were likely confounded by unbalanced use of radiation to the bone, an effective treatment for bone pain due to metastasis, which was significantly more common in the zoledronic acid group (16% versus 12% with denosumab, $P = 0.0121$), potentially biasing results in favour of zoledronic acid. Similar results were obtained with denosumab and zoledronic acid for these outcomes; therefore, this confounding factor undermines the potential for denosumab to show a between-group difference compared with zoledronic acid regarding pain and HRQoL outcomes.

Another limitation of Breast Cancer Study 136 is related to generalizability. The trial involved patients with a relatively good performance status at baseline; therefore, the effectiveness and safety observed may not be generalizable to patients with a poorer performance status. In addition, patients with various comorbid conditions were excluded from the study, including those with a history of ONJ, known brain metastases, prior other malignancy within three years, and known HIV or hepatitis B or C. Considering that patients who received prior bisphosphonate treatment for bone metastases were excluded from the trial, the findings from Breast Cancer Study 136 were observed in a population where denosumab was administered as first-line treatment.

4.2 Interpretation of Results

4.2.1 Efficacy

Results from Breast Cancer Study 136 demonstrate the superiority of denosumab over zoledronic acid to reduce the risk of a first SRE in patients with advanced breast cancer and bone metastases. With an HR of 0.82 (95% CI, 0.71 to 0.95), results achieved the criteria for non-inferiority ($P < 0.0001$) and superiority ($P = 0.0101$). In Breast Cancer Study 136, denosumab was associated with an improvement in the median time to first on-study SRE of five months, which is likely clinically meaningful to patients according to the literature and the clinical expert consulted by CDR. There is no consensus regarding the clinical relevance of improvement in time to first SRE. The oncology Scientific Advisory Group consulted by the European Medicines Agency (EMA) stated that the minimum effect size in terms of median time to first on-study SRE considered to be clinically relevant was three months,[7] whereas clinical advisors consulted by the NHS National Institute for Health Research suggested that a minimal clinically significant change in terms of time to first SRE should reach a 20% reduction in HR.[8] However, the American Society of Clinical Oncology 2011 clinical practice guideline regarding the role of bone-

modifying drugs in metastatic breast cancer state that there is insufficient evidence relating to efficacy to support one bone-modifying drug over another.[9]

Pain and HRQoL were identified as important outcome for patients according to the patient input received by CADTH. These outcomes were measured using reliable and validated tools. However, it is uncertain whether the reduced risk of SREs observed with denosumab translates into improvements in pain or HRQoL, or into reductions in analgesic usage, due to mixed findings and limitations regarding the trial population and confounding factors. Breast Cancer Study 136 showed a statistically significant reduction in the risk of a > 4-point change on the BPI-SF "Worst Pain" item with denosumab compared with zoledronic acid; a finding considered clinically meaningful as it exceeds the MCID of 1.5 to 2.0 estimated for this instrument. [redacted] results for other patient-related outcomes [redacted]

A few key interpretation points should be noted. Experience from specialists' clinical practice suggests that patients entering Breast Cancer Study 136 had a relatively good performance status, with consequently relatively low pain levels and limited analgesic use at baseline, as well as relatively little impairment in HRQoL. In such circumstances, it may be difficult to detect significant improvements from baseline in these patient-reported outcomes throughout the course of the trial. Considering that the natural disease history in patients with metastatic breast cancer typically evolves toward disease progression, the patient input received by CADTH suggests that an absence of worsening in pain or deterioration of HRQoL compared with baseline may also be perceived as a benefit for patients. In addition, radiation to the bone was more common in the zoledronic acid group (16% versus 12% with denosumab, $P = 0.0121$) and, according to the clinical expert consulted by CDR, radiotherapy is considered an effective treatment for bone pain due to metastasis; therefore, it is possible that outcomes related to pain were confounded by unbalanced use of concurrent treatments to control pain, potentially biasing results in favour of zoledronic acid. Similar results were obtained with denosumab and zoledronic acid for these outcomes; therefore, this confounding factor undermines the potential for denosumab to show a between-group difference compared with zoledronic acid regarding pain and HRQoL outcomes. It should be noted that most pain and HRQoL results are associated with wide ranges; therefore, it is likely that some patients may experience various level of improvement (or deterioration) for each of these particular outcomes.

The sustainability of beneficial treatment effects observed with denosumab in patients with advanced breast cancer and bone metastases remain uncertain, as there are no data to inform on the effectiveness of denosumab beyond the median trial duration of 17 months.

There is a lack of evidence with which to directly compare denosumab with drugs other than zoledronic acid used as treatment to reduce the risk of developing SREs in patients with bone metastases from breast cancer, including pamidronate and clodronate. To inform this evidence gap, CDR reviewed and critically appraised available indirect evidence. A literature search was undertaken by CDR to identify any relevant published indirect comparisons (IDCs). Two relevant publications were included, presenting data from one unique IDC. Ford et al.[8,10] assessed the comparative efficacy of denosumab versus zoledronic acid and pamidronate as treatment to reduce the risk of developing SREs in patients with bone metastases from breast cancer. The network meta-analysis (NMA) results suggest that the use of denosumab was associated with a statistically significant reduction in the risk of SREs compared with zoledronic acid and placebo. Although results favoured denosumab compared with pamidronate, statistical significance was not reached. There were no data available to assess the comparative effectiveness of denosumab versus clodronate. Pain, HRQoL, and AEs figured as secondary outcomes;

however, no NMA results were reported. The Ford et al.[8] IDC was likely conducted with methodological rigour; however, its major limitation was the small number of studies included in the IDCs, which results in a high degree of uncertainty regarding the findings of the IDCs. Therefore, the overall results of the IDCs are consistent with the conclusion that denosumab is likely superior to zoledronic acid and placebo, and at least as effective as pamidronate to reduce the risk of developing SREs in patients with bone metastases from breast cancer.

4.2.2 Harms

Denosumab is approved for six indications and has been in use since 2010, and the overall harms in Breast Cancer Study 136 results did not raise any new safety concerns, as confirmed by the clinical expert consulted by CDR. However, there are no data to inform on the long-term maintenance of safety of denosumab in patients with advanced breast cancer and bone metastases beyond the trial duration of 17 months.

Mortality as well as the overall incidence of SAEs during Breast Cancer Study 136 did not differ significantly between denosumab and zoledronic acid, and were not higher than would be expected in this patient population according to experience from specialists' clinical practice. The most commonly reported SAEs for both treatments were relatively infrequent (≤ 5%). The proportion of patients experiencing AEs was high but similar between denosumab and zoledronic acid. The most common AEs included nausea, fatigue, arthralgia, back pain, diarrhea, dyspnea, vomiting, pain in extremity, and bone pain. Proportions of patients discontinuing due to AEs in the denosumab treatment group were lower (10%), however, suggesting adequate tolerability.

Some AEs of particular interest were identified by CADTH based on the denosumab mechanism of action and Health Canada warnings, which have been issued with regard to the risks of hypocalcemia, infections, dermatologic AEs, ONJ, atypical femur fractures, and malignancies.[3] Results for ONJ, [redacted], SAEs of infection, and dermatologic AEs are characterized by low and similar proportions of patients experiencing the event in both treatment groups. Cardiovascular events [redacted]. There were numerically more cases of hypocalcemia in the denosumab group compared with zoledronic acid; however, the difference did not seem to be clinically meaningful, according to the clinical expert consulted by CDR.

Experience from specialists' clinical practice and patient input received by CADTH suggest the need for pharmacological drugs with added convenience and tolerability for use in patients with advanced breast cancer and bone metastases. The fact that denosumab is administered subcutaneously, compared with zoledronic acid that needs to be administered intravenously, provides benefits in terms of accessibility and convenience. In palliative patients, the availability of an option with an SC route of medication delivery, often eliminating the need for a visit to a facility for administration, is a communicated advantage in terms of quality of life for all cancer types, in addition to reducing the burden on the health care system. This advantage of denosumab could not be captured in Breast Cancer Study 136; due to the double-dummy design, all patients received both SC and IV administrations. Denosumab also has the advantage that no dose adjustment is necessary in patients with renal impairment,[3] while bisphosphonates such as zoledronic acid are associated with an increased risk of clinically significant deterioration in renal function.[14]

No data are available to directly compare the potential harms of denosumab versus other drugs used in patients with bone metastases from breast cancer. Potential harms were not analyzed in the IDC that was identified by CDR to compare the safety of denosumab with comparators other than zoledronic acid.

4.3 Potential Place in Therapy

This section is based on information provided in draft form by the clinical expert consulted by CDR for the purpose of this review. Bone metastases and their associated complications burden patients with devastating bone pain, and their management is a challenging and growing clinical problem to health care providers, patients, and caregivers. Survival in the metastatic breast cancer population can now be in the order of years due to advances in systemic therapy and palliation; therefore, the morbidity associated with bone metastases is increasingly becoming more prevalent. There exists a need to further decrease pain and impairments on functional status, and increase quality of life for many patients.

Current treatment strategies are essentially reactive. Conventional pain management with palliative treatment options such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDS), opioids, or steroids, aims to balance pain control against side effects of pharmacotherapy, but does not generally influence the likelihood of developing most SREs. Considering the potential adverse impacts resulting from SREs, the best treatment approach includes a preventive component. The most commonly employed standard for the prevention of SREs are bisphosphonates. They are used to reduce bone pain, decrease the incidence of pathologic fracture, and decrease the need for radiotherapy.[23,24]

In clinical practice, consideration is usually given to prescribe denosumab based on the evidence that the drug delays time to SREs; therefore, in patients with breast cancer and bone metastases, it would be reasonable to consider denosumab as a first-line treatment option, especially considering that denosumab is administered subcutaneously, compared with zoledronic acid that needs to be administered intravenously, which provides benefits in terms of accessibility and convenience. Denosumab also has the advantage that no dose adjustment is necessary in patients with renal impairment,[3] while bisphosphonates such as zoledronic acid are associated with an increased risk of clinically significant deterioration in renal function.[14]

5. CONCLUSIONS

The results of Breast Cancer Study 136 suggest that denosumab is associated with a statistically significant, clinically meaningful reduction in the time to a first SRE in patients with advanced breast cancer and bone metastases compared with zoledronic acid. [redacted] Similar proportions of patients experienced ONJ, [redacted] SAEs of infection, and dermatologic AEs in both treatment groups. The generalizability of the results of Breast Cancer Study 136 is limited by the fact that the trial involved patients with a relatively good performance status at baseline. The results of an IDC in which the efficacy of denosumab was compared with zoledronic acid, pamidronate, or placebo were consistent with the conclusion that denosumab is superior to zoledronic acid and placebo, and at least as effective as pamidronate, for reducing the risk of a first SRE in patients with advanced breast cancer and bone metastases, although these findings are associated with a high degree of uncertainty.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

CADTH received three patient input submissions from the following patient groups:

- The Canadian Cancer Survivor Network (CCSN) is a national network of patients, families, survivors, friends, community partners, funders, and sponsors who have come together to promote the very best standards of care. The CCSN connects patients, survivors, and other stakeholder groups with decision-makers and the wider community to engage in discussion and to act on evidence-based best practices to alleviate the medical, emotional, financial, and social costs of cancer and encourage research on ways to overcome barriers to optimal cancer care for survivors in Canada.
- The Canadian Breast Cancer Network (CBCN) is a national, survivor-driven organization that aims to champion the voices of Canadian breast cancer patients and survivors through the promotion of education and information, networking, and advocacy activities.
- Rethink Breast Cancer is a national charity that brings bold, relevant awareness to people in their 40s and under, fosters a new generation of young and influential breast cancer supporters, and responds to the unique needs of young women going through it.

Conflict of interest declaration reported by CCSN included: Amgen, Astellas, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, Janssen, Lilly, Merck, and Novartis. As part of its conflict of interest declaration, CBCN reported a close working relationship with Amgen Canada and other pharmaceutical companies. Conflict of interest reported by Rethink Breast Cancer included: Roche, Novartis, Amgen, Allergan, Genomic Health, Astra Zeneca, and Pfizer.

Each group independently prepared and submitted its input. Information presented in this patient input summary was gathered from several sources:

- Two different surveys — one conducted by the CCSN (12 responses), and the other was the 2012 Metastatic Breast Cancer Patient and Caregiver Survey (2012 Survey), conducted by CBCN and Rethink Breast Cancer (87 responses)
- A review of current studies and grey literature conducted by CBCN
- A one-to-one interview conducted by CBCN
- Five online/telephone interviews conducted by Rethink Breast Cancer.

2. Condition-Related Information

Bone metastasis is when the cancerous cell growth spreads to the bone. CBCN indicated that approximately 75% to 80% of women with advanced breast cancer will develop bone metastases during their disease. Bone metastasis has many serious physical, psychological, social, and financial consequences. The participants in the CCSN survey identified bone pain, weakness, fractures, sleeping problems, insomnia, and spinal compression as the most difficult physical consequences of bone metastasis to control.

While not specific to bone metastasis, patients who responded to the 2012 Survey identified fatigue, insomnia, pain, problems concentrating, and depression as some cancer-related symptoms with significant or debilitating impact on their quality of life.

For patients with bone metastases, managing the symptoms of pain and loss of movement associated with metastatic cancer is especially critical to stabilize their disease and improve overall quality of life. Most patients with such a diagnosis understand the limitations of current treatment options on survival, and seek to live their remaining months and years with the best possible quality of life that they can achieve.

The consequences of weakness, fatigue, and pain extend further to affect social and financial aspects of patients' life. Significant restrictions in the ability to work, ability to take care of their children, ability to engage in family and social events, and ability to spend quality time with loved ones are all common themes reported as social consequences in patient groups' submissions. On the financial side, many patients had difficulties affording the cost of medication, as many patients are self-employed, not eligible for their corporate health care plan, or face confusing and time-consuming application processes to access corporate or government assistance plans. The cost of alternative treatments (i.e., massage, physiotherapy, etc.) to manage symptoms and side effects, and the time and cost required to travel to treatment had a significant or debilitating impact on their quality of life.

"Many of the next step treatments are very expensive [and not covered by government programs] and it is a HUGE struggle to get [coverage]. […] When dealing with an incurable disease the last thing you want to have to do is spend time on a letter-writing campaign to argue about whether or not you should receive the drugs [recommended by your physician]. At about $1,500.00 a week, I don't know many who can afford that." – Patient

Caregivers are also affected; more than half of the 2012 survey respondents indicated experiencing anxiety, fatigue, problems with concentration, depression, insomnia, restrictions in their ability to work and pursue career plans, and ability to spend time with their loved ones, to take care of children and dependants, and to participate in social events and activities.

"I do not want to be a burden on my family. I would not want my family to decline/lose good opportunities in their careers and restrict them in any way on my behalf/condition." – Patient

3. Current Therapy-Related Information

Patients with bone metastases often go through several therapy options to control progression and stabilize their condition. The main goals of the therapy are usually to extend life and reduce cancer-related symptoms. Typically, many patients are treated with bisphosphonates, including pamidronate and zoledronic acid. However, these bisphosphonate therapies have been associated with severe flu-like symptoms and renal complications. Many patients find these symptoms intolerable and desire alternative therapies with fewer adverse effects that would allow for a greater quality of life.

"I was first put on pamidronate to improve the strength of my bones, but right away I developed a high fever and had to be hospitalized. My symptoms were so severe and I was incredibly weak and debilitated. I am the poster child for why patients need more options beyond pamidronate!" – Patient

Patients reported a variety of side effects related to bone metastases treatment, including fatigue, muscle weakness, bone pain, joint pain, anemia, rash of eczema, nausea and vomiting, and shortness of breath.

The value to patients of stabilizing their condition cannot be overestimated. Patients living with metastatic cancer are aware that their advanced disease will progress with worsening symptoms until death, and embrace opportunities to try new treatments that will improve their quality of life and stave off further complications. Patients acknowledge the importance of having the energy to attend their children's activities and to spend time with family and friends. A number of patients expressed concern over the costs of the treatment, indicating that new treatments often come with high costs that must be covered by patients out-of-pocket, or that require lengthy processes for public and private insurance to secure approval for the expense.

4. Expectations About the Drug Being Reviewed

There is an expectation that denosumab will delay and prevent skeletal-related events (SREs) in patients with breast cancer with bone metastases and will be generally well tolerated. By reducing the risk of developing SREs in patients with bone metastases, treatment can improve a patient's quality of life. When living with no or with minimal cancer-related symptoms, and with minimal side effects from the treatment, patients are able to reduce the impact of cancer on their ability to care for children and dependents, continue with their employment and earn income, spend time with loved ones and participate in their life in a meaningful way by engaging in social activities, travelling, maintaining friendships, and pursuing personal interests.

In the CCSN patient input, six patients indicated experience with Xgeva. When asked what issues are better managed on Xgeva than on their previous therapy, four patients responded "ease of use"; three responded "better able to control symptoms"; three responded "stop disease progression"; two responded "reduction in side effects from current medication or treatment, including digestive issues"; and one responded that there was no difference.

One Canadian patient living with metastatic breast cancer and receiving denosumab therapy once a month mentioned to CBCN that denosumab had made a drastic difference in managing her bone pain.

"I am very happy on this treatment. I had so much bone pain and complications related to the metastases to my bone and I lost so much of my ability to move and function normally. It impacted my ability to care for my daughter or work. But after being on this treatment, my pain has subsided and I have been able to fully regain my mobility." – Patient

She also mentioned that she appreciated the ease of use of denosumab: the treatment can be administered at home since the drug is administrated via subcutaneous injection, which gave her greater flexibility, comfort, and discretion.

One patient also noted the discrepancy between inequitable coverage of denosumab for prostate cancer patients, while breast cancer patients are not always able to access the treatment.

Rethink Breast Cancer gathered information through an interview conducted with five patients who have direct experience with the treatment under review. All five patients have very positive experiences taking Xgeva. For four out of five patients Xgeva is being used as a first-line therapy, and for one patient as a second line of therapy, due to an adverse reaction to the first therapy. None of the patients surveyed have experienced adverse side effects from Xgeva. The drug has helped with their quality of life and has kept their bone metastases stable.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to June 15, 2015 MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 15, 2015
Alerts:	Biweekly search updates until January 20, 2016
Study Types:	Randomized controlled trials, controlled clinical trials
Limits:	Records added to the databases since June 2011 (original Xgeva submission search date) No language limits were used Conference abstracts were excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.pt	Publication type
.kw	Keywords defined by the author
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.rn	CAS registry number
.nm	Name of substance word
.ed	Entry date; date in which the document was indexed as a MEDLINE record
.dp	Date of publication; date of publication for a citation in MEDLINE
.dc	Date created; the date that processing of the record begins in MEDLINE
.ep	Electronic date of publication; the date the record was sent to NLM for inclusion in MEDLINE
.dd	Date delivered; date that the record was issued on Embase
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
Line #	**Search Strategy**	**Results**
1	(Xgeva* or Prolia* or Pralia* or Ranmark* or denosumab* or AMG162 or AMG 162 or 4EQZ6YO2HI or 615258-40-7 or 847987-83-1).ti,ot,ab,kw,sh,rn,hw,nm.	5560
2	(201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014* or 2015*).ed,dp,dc,ep.	5470182
3	1 and 2	1359
4	3 use pmez	983

MULTI-DATABASE STRATEGY		
Line #	**Search Strategy**	**Results**
5	*denosumab/	1253
6	(Xgeva* or Prolia* or Pralia* or Ranmark* or denosumab* or AMG162 or AMG 162).ti,ab.	3326
7	or/5-6	3420
8	(201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014* or 2015*).dd.	5968459
9	7 and 8	1752
10	9 not conference abstract.pt.	983
11	10 use oemezd	983
12	4 or 11	1966
13	(Randomized Controlled Trial or Controlled Clinical Trial).pt.	482935
14	Randomized Controlled Trial/	774726
15	Randomized Controlled Trials as Topic/	174255
16	"Randomized Controlled Trial (topic)"/	75828
17	Controlled Clinical Trial/	480838
18	Controlled Clinical Trials as Topic/	9504
19	"Controlled Clinical Trial (topic)"/	4432
20	Randomization/	150533
21	Random Allocation/	150533
22	Double-Blind Method/	254594
23	Double Blind Procedure/	123622
24	Double-Blind Studies/	215814
25	Single-Blind Method/	41062
26	Single Blind Procedure/	20412
27	Single-Blind Studies/	41062
28	Placebos/	303516
29	Placebo/	270474
30	Control Groups/	77569
31	Control Group/	77569
32	(random* or sham or placebo*).ti,ab,hw.	2456149
33	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	412099
34	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	1034
35	(control* adj3 (study or studies or trial*)).ti,ab.	789589
36	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.	67073
37	allocated.ti,ab,hw.	96046
38	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.	56670
39	or/13-38	3087667
40	12 and 39	618
41	remove duplicates from 40	437

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	May 5–7, 2015
Keywords:	Denosumab, Xgeva, Prolia, bone metastases
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
van Moos et al. 2013[25]	Inappropriate study design
Lipton et al. 2012[26]	
Henry et al. 2014[27]	
Scagliotti et al. 2012[28]	
Lipton et al. 2012[29]	
Perez-Lopez 2014[30]	
Shapiro 2013[31]	
Lippuner et al. 2014[32]	Inappropriate population
Schmitz-Drager et al. 2013[33]	
Smith et al. 2015[34]	
Gnant et al. 2015[35]	
Diel et al. 2015[36]	Inappropriate outcome
Vadhan-Raj et al. 2012[37]	Second screening by indication — breast cancer only

APPENDIX 4: DETAILED OUTCOME DATA

Efficacy Outcomes

TABLE 10: SKELETAL-RELATED EVENTS

	Breast Cancer Study 136	
	Denosumab (N = 1,026)	Zoledronic Acid (N = 1,020)
Time to First SRE:		
FAS Population Analysis		
n (%) at data cut-off	315 (30.7)	372 (36.5)
HR (95% CI)	0.82 (0.71 to 0.95)	
P value for NI	*P* < 0.0001	
P value for superiority	*P* = 0.0101	
PP Population Analysis		
HR (95% CI)	[redacted]	
P value for NI	[redacted]	
P value for superiority	[redacted]	
Time to First SRE — by Individual Type (FAS Population Analysis):		
Spinal Cord Compression		
n (%) at data cut-off	[redacted]	[redacted]
HR (95% CI)	[redacted]	
P value	[redacted]	
Pathological Fracture		
n (%) at data cut-off	[redacted]	[redacted]
HR (95% CI)	[redacted]	
P value	[redacted]	
Surgery to Bone		
n (%) at data cut-off	[redacted]	[redacted]
HR (95% CI)	[redacted]	
P value	[redacted]	
Radiation to Bone		
n (%) at data cut-off	123 (12.0)	162 (15.9)
HR (95% CI)	0.74 (0.59 to 0.94)	
P value	0.0121	
Time to First and Subsequent SRE:		
FAS Population Analysis		
Number of events at data cut-off	[redacted]	[redacted]
HR (95% CI)	0.77 (0.66 to 0.89)	
P value for superiority	[redacted]	
PP Population Analysis		
Number of events at data cut-off	[redacted]	[redacted]
HR (95% CI)	[redacted]	
P value for superiority	[redacted]	

CI = confidence interval; FAS = full analysis set; HR = hazard ratio; NI = non-inferiority; ns = non-significant; PP = per-protocol; SRE = skeletal-related event.
Source: Clinical Study Report p. 143 and tables starting p. 286.[11]

Patient-Reported Outcomes

TABLE 11: BRIEF PAIN INVENTORY (SHORT FORM) PAIN SCORES

	Breast Cancer Study 136	
	Denosumab (N = 1,026)	Zoledronic Acid (N = 1,020)
Pain You Have Right Now:		
Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
30% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Change from Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Pain Interference with General Activity:		
Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
30% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Change from Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Pain Severity Score:		
Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
30% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Change from Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Pain Interference Score:		
Baseline		
Mean ± SD	3.11 ± 2.66	3.10 ± 2.59
Range	[redacted]	[redacted]
30% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Change from Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]

SD = standard deviation.

[a] Table presents data up to the visit when ≥ 30% of patients have withdrawn due to death, disease progression, or consent withdrawn, which is approximately at week 73.

Source: Clinical Study Report tables starting p. 365.[11]

TABLE 12: BRIEF PAIN INVENTORY (SHORT FORM) PAIN SCORES — WORST PAIN

	Breast Cancer Study 136	
	Denosumab (N = 1,026)	Zoledronic Acid (N = 1,020)
Worst Pain:		
Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
30% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Change From Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Time to ≥ 2-point Decrease From Baseline		
HR (95% CI)	1.02 (0.91 to 1.15)	
P value	*P* = 0.7245 (ns)	
Time to ≥ 2-point Increase From Baseline		
HR (95% CI)	0.90 (0.80 to 1.01)	
P value	*P* = 0.0822 (ns)	
Time to > 4-point		
HR (95% CI)	[redacted]	
P value	[redacted]	

HR = hazard ratio; ns = non-significant; SD = standard deviation.
[a] Table presents data up to the visit when ≥ 30% of patients have withdrawn due to death, disease progression, or consent withdrawn, which is approximately at week 73.
Note: The range of worst pain is 0 to 10; a higher score indicates a less preferred health status.
Source: Clinical Study Report tables starting p. 365, 432.[11]

TABLE 13: ANALGESIC USE

	Breast Cancer Study 136	
	Denosumab (N = 1,026)	Zoledronic Acid (N = 1,020)
Analgesic Score at Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Analgesic Score at 30% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Change from Baseline in Analgesic Score at 30% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]

SD = standard deviation.
[a] Table presents data up to the visit when ≥ 30% of patients have withdrawn due to death, disease progression, or consent withdrawn, which is approximately at week 73.
Source: Clinical Study Report p. 355, 362.[11]

TABLE 14: FUNCTIONAL ASSESSMENT OF CANCER THERAPY SCORES

	Breast Cancer Study 136	
	Denosumab (N = 1,026)	Zoledronic Acid (N = 1,020)
FACT-B — Physical Well-Being: Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
30% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Change from Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
FACT-B — Functional Well-Being: Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
30% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Change from Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
FACT-G — Total Score: Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
30% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Change from Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
FACT-B — Trial Outcome Index: Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
30% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Change from Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
FACT-B — Total Score: Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
30% Dropout[a]		
Mean ± SD	[redacted]	[redacted]

	Breast Cancer Study 136	
	Denosumab (N = 1,026)	Zoledronic Acid (N = 1,020)
Range	[redacted]	[redacted]
Change from Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]

FACT-B = Functional Assessment of Cancer Therapy–Breast; FACT-G = Functional Assessment of Cancer Therapy–General; SD = standard deviation.
[a] Table presents data up to the visit when ≥ 30% of patients have withdrawn due to death, disease progression, or consent withdrawn, which is approximately at week 73.
Source: Clinical Study Report tables starting p. 432.[11]

TABLE 15: EUROQOL 5-DIMENSIONS QUESTIONNAIRE UTILITY SCORES

	Breast Cancer Study 136	
	Denosumab (N = 1,026)	Zoledronic Acid (N = 1,020)
EQ-5D — Health Index Score:		
Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
30% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Change from Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
EQ-5D — VAS Score:		
Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
30% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Change from Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]

EQ-5D = EuroQol 5-Dimensions Questionnaire; SD = standard deviation; VAS = visual analogue scale.
[a] Table presents data up to the visit when ≥ 30% of patients have withdrawn due to death, disease progression, or consent withdrawn, which is approximately at week 73.
Source: Clinical Study Report p. 498.[11]

Harms Outcomes

TABLE 16: MORTALITY

	Breast Cancer Study 136	
	Denosumab (N = 1,020)	Zoledronic Acid (N = 1,013)
Mortality		
n (%)	[redacted]	[redacted]
Most Frequently Reported Reasons — > 5 Patients in at Least 1 Treatment Group, n (%):		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CNS = central nervous system.
Source: Clinical Study Report p. 182, 797.[11]

TABLE 17: NOTABLE OR CLINICALLY SIGNIFICANT HARMS

	Breast Cancer Study 136	
	Denosumab (N = 1,020)	Zoledronic Acid (N = 1,013)
Infections		
SAEs, n (%)	71 (7.0)	83 (8.2)
Most Frequently Reported Reasons — ≥ 1% of Patients in at Least 1 Treatment Group, n (%):		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Hypocalcemia		
AEs, n (%)	[redacted]	[redacted]
Skin Infections		
AE of skin infection, n (%)	[redacted]	[redacted]
AE of serious skin infection, n (%)	[redacted]	[redacted]
Cardiovascular Events		
AEs, n (%)	[redacted]	[redacted]
SAEs, n (%)	[redacted]	[redacted]
Fatal events, n (%)	[redacted]	[redacted]
Eczema		
AEs, n (%)	[redacted]	[redacted]
ONJ		
AEs, n (%)	20 (2.0)	14 (1.4)

	Breast Cancer Study 136	
	Denosumab (N = 1,020)	Zoledronic Acid (N = 1,013)
Atypical Femoral Fractures		
AE of femur fracture, n (%)	[redacted]	[redacted]
SAE of femur fracture, n (%)	[redacted]	[redacted]
New Malignancies		
AEs, n (%)	5 (0.5)	5 (0.5)

AE = adverse event; ONJ = osteonecrosis of the jaw; SAE = serious adverse event.
Source: Clinical Study Report p. 192-202 (tables p. 1345, 1328, 1341-3, 197-8, 1338, 560, 189, 1340).[11]

TABLE 18: SERIOUS ADVERSE EVENTS

	Breast Cancer Study 136	
	Denosumab (N = 1,020)	Zoledronic Acid (N = 1,013)
SAEs		
n (%)	**453 (44.4)**	**471 (46.5)**
Most Frequently Reported SAEs — ≥ 1 Patient in at Least 1 Treatment Group, n (%):		
Dyspnea	53 (5.2)	38 (3.8)
Metastases to CNS	47 (4.6)	46 (4.5)
Vomiting	31 (3.0)	31 (3.1)
Anemia	27 (2.6)	32 (3.2)
Pleural effusion	24 (2.4)	25 (2.5)
Hepatic failure	24 (2.4)	16 (1.6)
Pyrexia	21 (2.1)	26 (2.6)
Nausea	21 (2.1)	23 (2.3)
Metastases to liver	20 (2.0)	28 (2.8)
Pneumonia	20 (2.0)	25 (2.5)
Respiratory failure	20 (2.0)	20 (2.0)
General deterioration	20 (2.0)	15 (1.5)
Diarrhea	19 (1.9)	16 (1.6)
Osteonecrosis	18 (1.8)	11 (1.1)
Febrile neutropenia	17 (1.7)	22 (2.2)
Neutropenia	16 (1.6)	14 (1.4)
Abdominal pain	15 (1.5)	14 (1.4)
Fatigue	15 (1.5)	5 (0.5)
Dehydration	13 (1.3)	24 (2.4)
Asthenia	12 (1.2)	14 (1.4)
Thrombocytopenia	12 (1.2)	11 (1.1)
Pulmonary embolism	11 (1.1)	18 (1.8)
Disease progression	11 (1.1)	12 (1.2)
Bone pain	10 (1.0)	13 (1.3)
[redacted]	[redacted]	[redacted]
Multi-organ failure	9 (0.9)	9 (0.9)
Back pain	8 (0.8)	14 (1.4)
Pain in extremity	8 (0.8)	3 (0.3)
Urinary tract infection	7 (0.7)	9 (0.9)
Spinal cord compression	6 (0.6)	8 (0.8)
[redacted]	[redacted]	[redacted]
Cardiac failure	6 (0.6)	7 (0.7)

	Breast Cancer Study 136	
	Denosumab (N = 1,020)	Zoledronic Acid (N = 1,013)
Cachexia	6 (0.6)	7 (0.7)
Chest pain	5 (0.5)	9 (0.9)
Hypocalcemia	5 (0.5)	2 (0.2)
Pain	4 (0.4)	8 (0.8)
Deep vein thrombosis	4 (0.4)	8 (0.8)
Sepsis	2 (0.2)	4 (0.4)
Renal failure	1 (< 0.1)	9 (0.9)
Urinary retention	1 (< 0.1)	0 (0.0)
Renal failure acute	0 (0.0)	6 (0.6)

CNS = central nervous system; SAE = serious adverse event.
Source: Clinical Study Report p. 189.[11]

TABLE 19: ADVERSE EVENTS

	Breast Cancer Study 136	
	Denosumab (N = 1,020)	Zoledronic Acid (N = 1,013)
AEs		
n (%)	**977 (95.8)**	**985 (97.2)**
Most Frequently Reported AEs — ≥ 10% of Patients in at Least 1 Treatment Group, n (%):		
Nausea	356 (34.9)	384 (37.9)
Fatigue	301 (29.5)	324 (32.0)
Arthralgia	250 (24.5)	291 (28.7)
Back pain	241 (23.6)	264 (26.1)
Diarrhea	231 (22.6)	207 (20.4)
Dyspnea	222 (21.8)	190 (18.8)
Vomiting	212 (20.8)	238 (23.5)
Pain in extremity	204 (20.0)	222 (21.9)
Headache	197 (19.3)	214 (21.1)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Bone pain	186 (18.2)	238 (23.5)
[redacted]	[redacted]	[redacted]
Constipation	176 (17.3)	205 (20.2)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

AE = adverse event.
Source: Clinical Study Report p. 204, 697.[11]

TABLE 20: WITHDRAWALS DUE TO ADVERSE EVENTS

	Breast Cancer Study 136	
	Denosumab (N = 1,020)	Zoledronic Acid (N = 1,013)
WDAEs[a]		
n (%)	**98 (9.6)**	**125 (12.3)**
Most Frequently Reported Reasons — ≥ 4 Patients in at Least 1 Treatment Group, n (%):		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CNS = central nervous system; WDAE = withdrawal due to adverse event.
[a] Discontinuation of study drug.
Source: Clinical Study Report p. 186, 775.[11]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim

To summarize the validity of the following outcome measures:

- skeletal-related events (SREs)
- spinal cord compression
- pathological fractures
- Analgesic Quantification Algorithm (AQA)
- Brief Pain Inventory (Short Form) (BPI-SF)
- Functional Assessment of Cancer Therapy–Breast (FACT-B)
- EuroQoL 5-Dimensions Questionnaire (EQ-5D)

Findings

Table 21 provides a detailed summary of the findings.

TABLE 21: VALIDITY OF OUTCOMES

Instrument	Type	Validated	MCID	References
Spinal cord compression	A clinical and radiological diagnosis of indentation of the thecal sac that causes variety of associated pain, mobility, and neurological problems.	Unknown	Unknown	No references on validity or MCID were found
Pathological fractures	Pathological fractures are new bone fractures that occurred spontaneously and not as a result of severe trauma.	Unknown	Unknown	No references on validity or MCID were found
Analgesic Quantification Algorithm (AQA)	An 8-point analgesic scoring system based on four categories of daily morphine use.	Yes	Unknown	[38]
Brief Pain Inventory (Short Form) (BPI-SF)	A 9-item self-administered questionnaire to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily function.	Yes	1.5 to 2.0	[5,17,18,39]
Functional Assessment of Cancer Therapy–Breast (FACT-B)	Breast–cancer specific health-related quality-of-life measure. A 44-item self-administered questionnaire with a 5-point Likert scale response, assessing 4 categories: physical well-being, functional well-being, and a composite domain with breast–cancer specific questions.	Yes	7 to 8	[11,19,20]
EuroQoL 5-Dimensions Questionnaire (EQ-5D)	A 5-item self-administered, standardized, preference-based, health outcome measure instrument, assessing 5 dimensions: mobility, self-care, usual activities, pain, and depression.	Yes	0.06	[21,22,40]

MCID = minimal clinically important difference.

Skeletal-Related Events
This primary outcome was defined as the occurrence of one of the following: pathologic fracture (vertebral or non-vertebral), radiation therapy to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression. Generally, these events are considered hard outcomes and objective in nature. Our clinical expert, however, informed us that pathological fractures in patients with bone metastases do not necessarily require intervention, and the effect of these fractures on pain levels and quality of life varies in nature. The clinical expert expressed that only fractures that required an intervention are clinically important.

Spinal Cord Compression
Spinal cord compressions are the result of an abnormal mass exerting pressure on the spinal cord. This can be due to a number of reasons, including a fractured vertebra, herniated disk, or tumour metastases. Spinal cord compression can cause clinical manifestations of varying degrees of intensity, ranging from numbness and weakness to loss of limb function. The definitive diagnosis of spinal cord compression is based on radiologic findings. This outcome can be considered objective, although the extent of the clinical importance of milder cases of spinal compression is not clear.

Pathological Fractures
Pathological fractures are bone fractures that happen in the absence of serious trauma. In patients with metastatic cancer, this can manifest clinically as sudden pain, and can cause varying degrees of loss of function and deterioration in quality of life. In other cases, pathological fractures can be asymptomatic and discovered incidentally in radiographic diagnostics for other indications. The definitive diagnosis of this outcome occurs through radiographic findings, with a high degree of objectiveness in these findings. Due to the variability in the severity of presentation, the clinical expert consulted on this review was of the opinion that only fractures that require an active intervention with surgery or radiotherapy are clinically significant.

Analgesic Quantification Algorithm
AQA is an analgesic score that captures the daily intensity of the analgesic used in pain management. It consists of a minimum score of 0 (no analgesic) and up to 7 (strong opioid > 600 mg oral morphine equivalent [OME] per day) as shown in Table 22.

TABLE 22: ANALGESIC SCORE

Scale	Description
0	No analgesics
1	Non-opioid analgesics
2	Weak opioids (codeine, meperidine, tramadol)
3	Strong opioids ≤ 75 mg OME per day
4	Strong opioids > 75–150 mg OME per day
5	Strong opioids > 150–300 mg OME per day
6	Strong opioids > 300–600 mg OME per day
7	Strong opioids > 600 mg OME per day

OME = oral morphine equivalents.

Chung and colleagues[38] have shown that the AQA is a sensitive measure to capture analgesic use by comparing AQA with an older established tool (World Health Organization [WHO] analgesic treatment ladder) using the history of analgesics use in patients enrolled in a randomized controlled trial (RCT) comparing denosumab with zoledronic acid in patients with non-breast or prostate cancer metastatic tumour.[41] No other validation parameters or minimal clinically important difference (MCID) were found for AQA.

Brief Pain Inventory (Short Form)
Designed specifically to capture pain in cancer patients, the BPI-SF mainly assesses pain intensity and pain interference with a patient's life. It mainly consists of eight questions, with the patient indicating the severity and effects of pain on a scale from 0 (No pain/ no interference) to 10 (Worst ever pain/ complete interference).

The BPI-SF tool has been validated and shown to be reliable in many studies.[5,17,39] In addition, a recent study established the MCID at 1.5 to 2.0.[18]

Functional Assessment of Cancer Therapy–Breast
The FACT-B questionnaire is a health-related quality-of-life instrument that is specific to patients with breast cancer. It is built on the FACT-G questionnaire with the same 27 questions evaluating four aspects of a patient's quality of life, namely: physical well-being, functional well-being, social/family well-being, and emotional well-being. In addition to these 27 questions from FACT-G, FACT-B adds 10 more questions that are specific to patients with breast cancer.

The tool has been shown to valid and reliable by Brady et al. using two validation samples and assessing sensitivity to change, internal consistency, test-retest reliability, convergent, divergent, and known group validity.[19] In addition, an MCID for FACT-B was established at 7 to 8.[20]

EuroQoL 5-Dimensions Questionnaire
EQ-5D is a non–disease specific health-related quality-of-life instrument that is commonly used to estimate health utility. With a total of six questions, the first five cover mobility, self-care, usual activities, pain/ discomfort, and anxiety/ depression. The last question is a visual analogue scale where patients mark their health state on a 20 cm strip scored from 0 to a 100, where 0 is the worst possible health state and 100 is the best possible health state.

A structured review by Lin et al. attempted to synthesize the validity, reliability, and utility of EQ-5D from the literature. The review included 12 studies that assessed EQ-5D in cancer patients. The reviewers were in support of using the EQ-5D tool in cancer patients.[40] In addition, an MCID has been established for EQ-5D at 0.06.[21,22]

Conclusion
SREs, spinal cord compression, and bone fracture are objective outcomes with possible clinical symptoms and signs and a definitive diagnosis with radiographic signs. BPI-SF, FACT-B, and EQ-5D are commonly used patient-reported outcome measures that have been validated in cancer patients and that have an MCID established. For AQA, although validated in cancer patients, an MCID is not known.

APPENDIX 6: SUMMARY OF INDIRECT COMPARISONS

The objective of this section is to summarize and critically appraise indirect comparisons (IDCs) identified by CADTH for the purpose of this review.

Introduction

Background

There is a lack of evidence to directly compare denosumab with other drugs used as treatment to reduce the risk of developing skeletal-related events (SREs) in patients with bone metastases from breast cancer. To inform this evidence gap, CADTH Common Drug Review (CDR) reviewed and critically appraised available indirect evidence.

Methods

A literature search was undertaken by CDR to identify any relevant published IDCs. Two relevant publications,[8,10] presenting data from one unique IDC, were included in this section.

The manufacturer provided CADTH with two additional documents consisting of one network meta-analysis (NMA) that was, however, already captured by Ford et al., and also referenced one summary of an NMA that was submitted to the Institut national d'excellence en santé et en services sociaux (INESSS).

Description of Indirect Comparisons identified

Ford et al. assessed the comparative efficacy of denosumab versus zoledronic acid and pamidronate as treatment to reduce the risk of developing SREs in patients with bone metastases from breast cancer. Studies were selected for inclusion based on the selection criteria presented in Table 23.

TABLE 23: INCLUSION CRITERIA FOR FORD ET AL.

Patient Population	Adult patients with confirmed carcinoma of the breast and evidence of ≥ 1 bone metastasis
Intervention	Denosumab (Xgeva) 120 mg SC every 4 weeks
Relevant Comparators	Bisphosphonates: • Clodronate • Pamidronate • Zoledronic acid
Relevant Outcomes	• Skeletal-related events • Pain • Health-related QoL • AEs
Study Design	Published systematic reviews and RCTs; observational studies (for QoL and safety only)

AE = adverse event; QoL = quality of life; RCT = randomized controlled trial; SC = subcutaneous.

Review and Appraisal of Indirect Comparisons

Review of Ford et al.

Objectives and Rationale

Ford et al.[8,10] had the objective of assessing the clinical effectiveness of denosumab as treatment to reduce the risk of developing SREs in patients with bone metastases from a range of solid tumours. Considering that denosumab offers an alternative treatment option to bisphosphonates or best

supportive care, the authors aimed to document the place of denosumab in therapy compared with these other drugs recommended in similar indications.

Methods

Study Eligibility and Selection Process

A systematic literature search was conducted by the authors using several databases (MEDLINE, EMBASE, Cochrane, and conference proceedings), relevant websites, and contact with clinical experts. Systematic reviews and randomized controlled trials (RCTs) were considered for inclusion; observational studies were used to obtain additional data on quality of life (QoL) and safety. The study selection process involved independent duplicate reviewers screening titles, abstracts, and full-text publications.

Data Extraction

Data extraction was performed by one reviewer; a second reviewer was responsible for data check. Studies were selected for inclusion based on the selection criteria presented in Table 23. A total of four RCTs were included in the systematic review: Stopeck et al.[4] (denosumab versus zoledronic acid; n = 2,046), Kohno et al.[42] (zoledronic acid versus placebo; n = 227), Rosen et al.[43] (zoledronic acid versus pamidronate; n = 766) and Lipton et al.[44] (pamidronate versus placebo; n = 754). Details for all included studies are presented in Table 24. All included trials enrolled patients with breast cancer and at least one bone metastasis. Age was similar between trials and ranged from mean or median 54 to 58 years (age categories in Lipton et al.). The majority of patients in all trials had an Eastern Cooperative Oncology Group (ECOG) status of 0 to 1.

TABLE 24: CHARACTERISTICS OF THE INCLUDED STUDIES AND POPULATION IN FORD ET AL.

Studies	Population	Interventions	Outcome
Stopeck et al., 2010[4]	• Adults with confirmed breast cancer and ≥ 1 bone metastasis • Multi-centre: Europe, America, Japan, Australia, India, and South Africa • Median age = 57 years (denosumab) and 56 years (zoledronic acid) • ECOG Status 0 to 1 = 93% (denosumab) and 92% (zoledronic acid) • Previous SREs = 37% in both groups	**Denosumab 120 mg q.4w. (n = 1,026)** or **Zoledronic acid 4 mg q.4w. (n = 1,020)** for 17 months	**Primary outcome:** SREs
Kohno et al., 2005[42]	• Adults with ≥ 1 osteolytic bone metastasis from breast cancer • Multi-centre: Japan • Mean age = 54 years in both groups • ECOG status 0 to 1 = 89% in both groups • Previous SREs = 34% (zoledronic acid) and 42% (placebo)	**Zoledronic acid 4 mg q.4w. (n = 114)** or **Placebo (n = 113)** for 12 months	**Primary outcome:** SREs
Rosen et al., 2003a[43]	• Women with ≥ 1 bone metastasis from stage IV breast cancer • Multi-centre: international • Median age = 58 years (zoledronic acid) and 56 years (pamidronate) • ECOG status 0 to 1 = 87% (zoledronic acid) and 81% (pamidronate) • Previous SREs = 62% (zoledronic acid) and 63% (pamidronate)	**Zoledronic acid 4 mg q.3w.–4w. (n = 378)** or **Pamidronate 90 mg q.3w.–4w. (n = 388)** for 24 months	**Primary outcome:** SREs

Studies	Population	Interventions	Outcome
Lipton et al., 2000[44]	• Women with stage IV breast cancer and ≥ 1 lytic metastasis bone lesion ≥ 1 cm • Multi-centre: US, Canada, Oceania • Age < 50 years = 25% (pamidronate) and 29% (placebo) • Age 51 to 65 years = 42% (pamidronate) and 38% (placebo) • Age > 65 years = 33% in both groups • ECOG status 0 to 1 = 72% (pamidronate) and 69% (placebo) • Previous SREs NR	**Pamidronate 90 mg q.3w.–4w. (n = 367)** or **Placebo (n = 387)** for 24 months	**Primary outcome:** Skeletal morbidity rate

ECOG = Eastern Cooperative Oncology Group; NR = not reported; q.3w.–4w. = every three to four weeks; q.4w. = every four weeks; SRE = skeletal-related event.
Source: Ford et al.[8]

Comparators

Comparators in the included studies were zoledronic acid (direct evidence against denosumab), pamidronate, and placebo. Included comparators are the ones with most interest to Canadian decision-makers.

Outcomes

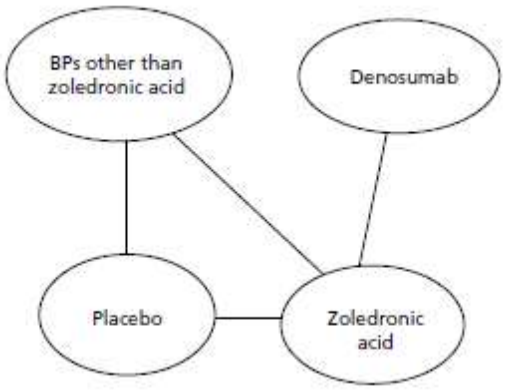
The primary outcomes in all included trials were SREs or skeletal morbidity rates. Pain, health-related quality of life (HRQoL), and adverse events (AEs) figured as outcomes included in the NMA, but were not consistently reported in all included studies.

Quality Assessment of Included Studies

The authors evaluated the risk of bias in the included studies. Independent duplicate reviewers performed study assessment using the Cochrane risk-of-bias tool for RCTs. All included studies were assessed by the authors as generally of good quality.

Evidence Network

FIGURE 2: ILLUSTRATING DIAGRAM FOR FORD ET AL. — BREAST CANCER



BP = bisphosphonate.
Reproduced from: *Ford J, Cummins E, Sharma P, Elders A, Stewart F, Johnston R, et al. Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours. Health Technol Assess [Internet]. 2013 Jul [cited 2015 Aug 31];17(29):1-386. Available from: http://www.ncbi.nlm.nih.gov/books/NBK260765/pdf/Bookshelf_NBK260765.pdf*.[8]

Indirect Comparison Methods

Authors indicate that the NMA was carried out using methods for mixed treatment comparisons and employed the Bayesian software package WinBUGS with Markov chain Monte Carlo methods for the analyses. For the primary outcome of time to first SRE, the authors used fixed effects models. There was a need for data conversion into time-to-event analysis for two of the four included studies (Rosen et al.[43] and Kohno et al.[42]).

Heterogeneity assessment was performed for all included studies regarding population, intervention, comparators, outcomes, SRE definition, and time frame. Separate analyses were performed according to primary cancer type.

Results

The primary outcome was time to first SRE. NMA results show that the use of denosumab was associated with a statistically significant reduction in the risk of SREs compared with zoledronic acid (hazard ratio [HR] 0.82; 95% confidence interval [CI], 0.71 to 0.95) and placebo (HR 0.46; 95% CI, 0.29 to 0.72). Results favoured denosumab compared with pamidronate, but statistical significance was not reached (HR 0.79; 95% CI, 0.61 to 1.03).

For the secondary outcome of time to first and subsequent SRE, the use of denosumab was associated with a statistically significant reduction in the risk of SREs compared with zoledronic acid (HR 0.77; 95% CI, 0.66 to 0.89), pamidronate (HR 0.62; 95% CI, 0.48 to 0.80), and placebo (HR 0.45; 95% CI, 0.28 to 0.72).

Pain, HRQoL, and AEs figured as secondary outcomes; however, no NMA results were reported. The Ford et al. publication presents a summary of results for these outcomes for each of the individual studies. Therefore, the only comparison available for pain, HRQoL, and AEs that includes denosumab is versus zoledronic acid in Stopeck et al.,[4] which is already detailed in the main body of this review report.

Critical Appraisal

The included studies had similar patient population in terms of age and disease severity, based on ECOG performance status. According to the clinical expert consulted by CDR, the patient characteristics for the included studies reflect the profile of patients with breast cancer and bone metastasis with a relatively good performance status — possibly better, however, than the majority of real-life patients. Denosumab, zoledronic acid, and pamidronate dosing strategies are in line with the Health Canada–approved labels for the products. NMA results for the direct comparison of denosumab versus zoledronic acid were consistent with those from the included study comparing the two treatments (Stopeck et al.[4]).

The Ford et al.[8] IDC was likely conducted with methodological rigour, but was not without limitations. Outcomes included in the NMA were limited to SREs; clinical outcomes directly relevant to patients such as pain, HRQoL, and safety outcomes were presented as a summary of results for each included studies. Therefore, no indirect comparisons were reported for these outcomes. Despite adequate reporting quality, the main limitation was the small number of studies included in the IDCs, which results in a high degree of uncertainty regarding the findings of the IDCs. Four studies were included in the breast cancer evidence network, which is a small number of trials in relation to the four nodes of this network. A further layer was added to this uncertainty due to the fact that results for two of the included studies had to be converted to time-to-event data, requiring the authors to make assumptions.

Discussion

The NMA results show that the use of denosumab was associated with a statistically significant reduction in the risk of SREs compared with zoledronic acid and placebo. Results favoured denosumab compared with pamidronate, but statistical significance was not reached. The IDC was likely conducted with methodological rigour, and the fact that results of the NMA for the comparison of denosumab versus zoledronic acid are consistent with the direct evidence available is reassuring. However, there is considerable uncertainty surrounding these findings due to the limited number of included studies. The fact that superiority was achieved for denosumab versus zoledronic acid, but not versus pamidronate, reflects the amount of uncertainty associated with the conclusion of the NMA, as results from Rosen et al.[43] reported in the Ford publication suggest that zoledronic acid may be superior to pamidronate in some subgroups of patients. Therefore, the results should be viewed with caution.

Conclusion

There is a lack of evidence with which to directly compare denosumab with other drugs used as treatment to reduce the risk of developing SREs in patients with bone metastases from breast cancer. To inform this evidence gap, CDR reviewed and critically appraised available indirect evidence. A literature search was undertaken by CDR to identify any relevant published IDCs. Two relevant publications were included, presenting data from one unique IDC. Ford et al.[8,10] assessed the comparative efficacy of denosumab versus zoledronic acid, pamidronate, and placebo as treatment to reduce the risk of developing SREs in patients with bone metastases from breast cancer. NMA results show that the use of denosumab was associated with a statistically significant reduction in the risk of SREs compared with zoledronic acid and placebo. Results favoured denosumab compared with pamidronate, but statistical significance was not reached. Pain, HRQoL, and AEs figured as secondary outcomes; however, no NMA results were reported. The Ford et al.[8] IDC was likely conducted with methodological rigour; however, its major limitation was the small number of studies included in the IDCs, which results in a high degree of uncertainty regarding the findings of the IDCs. Therefore, the overall results of the IDCs are consistent with the conclusion that denosumab is likely superior to zoledronic acid and placebo, and at least as effective as pamidronate to reduce the risk of developing SREs in patients with bone metastases from breast cancer.

REFERENCES

1. Suva LJ, Washam C, Nicholas RW, Griffin RJ. Bone metastasis: mechanisms and therapeutic opportunities. Nat Rev Endocrinol. 2011 Apr;7(4):208-18.
2. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006 Oct 15;12(20 Pt 2):6243s-9s.
3. [Pr]Xgeva® (denosumab) 120 mg/1.7 mL solution for injection single-use vial [product monograph]. Mississauga (ON): Amgen Canada Inc.; 2015 Mar 31.
4. 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 [Internet]. 2010 Dec 10 [cited 2015 May 27];28(35):5132-9. Available from: http://jco.ascopubs.org/content/28/35/5132.full.pdf+html
5. Cleeland CS, Body JJ, Stopeck A, von Moos R, Fallowfield L, Mathias SD, et al. Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer [Internet]. 2013 Feb 15 [cited 2015 Jul 2];119(4):832-8. Available from: http://onlinelibrary.wiley.com/doi/10.1002/cncr.27789/epdf
6. Martin M, Bell R, Bourgeois H, Brufsky A, Diel I, Eniu A, et al. Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab versus zoledronic acid. Clin Cancer Res [Internet]. 2012 Sep 1 [cited 2015 Jul 2];18(17):4841-9. Available from: http://clincancerres.aacrjournals.org/content/18/17/4841.full.pdf+html
7. European Medicines Agency (EMA). European Public Assessment Report (EPAR): Xgeva [Internet]. London: EMA; 2011. [cited 2015 Oct 20]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002173/WC500110384.pdf
8. Ford J, Cummins E, Sharma P, Elders A, Stewart F, Johnston R, et al. Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours. Health Technol Assess [Internet]. 2013 Jul [cited 2015 Aug 31];17(29):1-386. Available from: http://www.ncbi.nlm.nih.gov/books/NBK260765/pdf/Bookshelf_NBK260765.pdf
9. Van Poznak CH, Temin S, Yee GC, Janjan NA, Barlow WE, Biermann JS, et al. American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. J Clin Oncol [Internet]. 2011 Mar 20 [cited 2015 Jun 26];29(9):1221-7. Available from: http://jco.ascopubs.org/content/29/9/1221.full.pdf+html
10. Ford JA, Jones R, Elders A, Mulatero C, Royle P, Sharma P, et al. Denosumab for treatment of bone metastases secondary to solid tumours: systematic review and network meta-analysis. Eur J Cancer. 2013 Jan;49(2):416-30.
11. 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 cancer. [Primary analysis]. [**CONFIDENTIAL** internal manufacturer's report]. Thousand Oaks (CA): Amgen Inc; 2009 Oct 29.
12. Gralow JR, Biermann JS, Farooki A, Fornier MN, Gagel RF, Kumar R, et al. NCCN task force report: bone health in cancer care. J Natl Compr Canc Netw. 2013 Aug;11 Suppl 3:S1-50.
13. [Pr]Prolia® (denosumab) 60 mg/mL solution for injection. Prefilled syringe or vial [product monograph]. Mississauga (ON): Amgen Canada Inc.; 2014 Oct 20.

14. [Pr]Zometa® concentrate (zoledronic acid for injection) 4 mg zoledronic acid/5 mL incorporated as the monohydrate for intravenous infusion [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2014 Dec 5.
15. [Pr]Aredia® (pamidronate disodium for injection) 30 mg, 90 mg for i.v. infusion only [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2014 Apr 17.
16. [Pr]Bonefos® clodronate disodium for injection 60 mg/mL for slow intravenous infusion only and clodronate disodium capsules 400 mg/capsule [product monograph]. Toronto: Bayer Inc.; 2011 Sep 22.
17. Atkinson TM, Rosenfeld BD, Sit L, Mendoza TR, Fruscione M, Lavene D, et al. Using confirmatory factor analysis to evaluate construct validity of the Brief Pain Inventory (BPI). J Pain Symptom Manage. 2011 Mar;41(3):558-65.
18. Mathias SD, Crosby RD, Qian Y, Jiang Q, Dansey R, Chung K. Estimating minimally important differences for the worst pain rating of the Brief Pain Inventory-Short Form. J Support Oncol. 2011 Mar;9(2):72-8.
19. Brady MJ, Cella DF, Mo F, Bonomi AE, Tulsky DS, Lloyd SR, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. J Clin Oncol. 1997 Mar;15(3):974-86.
20. Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, et al. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol. 2004 Sep;57(9):898-910.
21. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70.
22. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res. 2005 Aug;14(6):1523-32.
23. Body JJ, Facon T, Coleman RE, Lipton A, Geurs F, Fan M, et al. A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. Clin Cancer Res [Internet]. 2006 Feb 15 [cited 2015 May 26];12(4):1221-8. Available from: http://clincancerres.aacrjournals.org/content/12/4/1221.long
24. Pavlakis N, Schmidt R, Stockler M. Bisphosphonates for breast cancer. Cochrane Database Syst Rev. 2005;(3):CD003474.
25. von Moos R, Body JJ, Egerdie B, Stopeck A, Brown JE, Damyanov D, et al. Pain and health-related quality of life in patients with advanced solid tumours and bone metastases: integrated results from three randomized, double-blind studies of denosumab and zoledronic acid. Support Care Cancer. 2013 Dec;21(12):3497-507.
26. Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer. 2012 Nov;48(16):3082-92.
27. Henry D, Vadhan-Raj S, Hirsh V, von Moos R, Hungria V, Costa L, et al. Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors. Support Care Cancer. 2014 Mar;22(3):679-87.
28. Scagliotti GV, Hirsh V, Siena S, Henry DH, Woll PJ, Manegold C, et al. Overall survival improvement in patients with lung cancer and bone metastases treated with denosumab versus zoledronic acid: subgroup analysis from a randomized phase 3 study. J Thorac Oncol. 2012 Dec;7(12):1823-9.

29. Lipton A, Smith MR, Ellis GK, Goessl C. Treatment-induced bone loss and fractures in cancer patients undergoing hormone ablation therapy: efficacy and safety of denosumab. Clin Med Insights Oncol [Internet]. 2012 [cited 2015 Jul 2];6:287-303. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3427033/pdf/cmo-6-2012-287.pdf

30. Perez-Lopez FR. Effects of denosumab in patients with bone metastases from solid cancers. Climacteric. 2014;17(5):616-8.

31. Shapiro CL. Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. Breast Diseases. 2013;24(3):220-1.

32. Lippuner K, Wolff JM, Hadji P, Braun A, Ke C, Steinle T, et al. Risk reduction for vertebral fractures in patients with normal to osteopenic bone mineral density receiving denosumab: a subgroup analysis of the HALT Prostate Cancer Trial. Osteologie. 2014;23(2):117-22.

33. Schmitz-Drager BJ, Weiss C, Ebert T, Dorsam J, Bismarck E. Skeletal-related events in metastatic prostate cancer and the number needed to treat: a critical consideration. Urol Int. 2013;90(3):329-33.

34. Smith MR, Coleman RE, Klotz L, Pittman K, Milecki P, Ng S, et al. Denosumab for the prevention of skeletal complications in metastatic castration-resistant prostate cancer: comparison of skeletal-related events and symptomatic skeletal events. Ann Oncol [Internet]. 2015 Feb [cited 2015 Jul 2];26(2):368-74. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4304378/pdf/mdu519.pdf

35. Gnant M, Pfeiler G, Dubsky PC, Hubalek M, Greil R, Jakesz R, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2015 Aug 1;386(9992):433-43.

36. Diel IJ, Body JJ, Stopeck AT, Vadhan-Raj S, Spencer A, Steger G, et al. The role of denosumab in the prevention of hypercalcaemia of malignancy in cancer patients with metastatic bone disease. Eur J Cancer. 2015 Jul;51(11):1467-75.

37. Vadhan-Raj S, von Moos R, Fallowfield LJ, Patrick DL, Goldwasser F, Cleeland CS, et al. Clinical benefit in patients with metastatic bone disease: results of a phase 3 study of denosumab versus zoledronic acid. Ann Oncol [Internet]. 2012 Dec [cited 2015 Jul 2];23(12):3045-51. Available from: http://annonc.oxfordjournals.org/content/23/12/3045.full.pdf+html

38. Chung KC, Barlev A, Braun AH, Qian Y, Zagari M. Assessing analgesic use in patients with advanced cancer: development of a new scale--the Analgesic Quantification Algorithm. Pain Med. 2014 Feb;15(2):225-32.

39. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994 Mar;23(2):129-38.

40. Pickard AS, Wilke CT, Lin HW, Lloyd A. Health utilities using the EQ-5D in studies of cancer. Pharmacoeconomics. 2007;25(5):365-84.

41. 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 [Internet]. 2011 Mar 20 [cited 2015 May 27];29(9):1125-32. Available from: http://jco.ascopubs.org/content/29/9/1125.full.pdf+html

42. 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 May 20;23(15):3314-21.

43. 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 Oct 15;98(8):1735-44.

44. 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 Mar 1;88(5):1082-90.