Common Drug Review
Clinical Review Report

November 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 solid tumours (other than breast and prostate cancer), including non–small cell lung cancer
Dosage form(s)	120 mg/1.7 mL solution for subcutaneous injection
NOC date	May 10, 2011
Manufacturer	Amgen Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in oncology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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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
CDR	CADTH Common Drug Review
CI	confidence interval
CNS	central nervous system
DB	double-blind
ECOG	Eastern Cooperative Oncology Group
EQ-5D	EuroQol 5-Dimensions Questionnaire
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
NCCN	National Comprehensive Cancer Network
NI	non-inferiority
NMA	network meta-analysis
PP	per-protocol
RANKL	receptor activator of nuclear factor kappa-B ligand
RCT	randomized controlled trial
SAE	serious adverse event
SC	subcutaneously
SD	standard deviation
SRE	skeletal-related event
WDAE	withdrawal due to adverse event

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]

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] Denosumab is not indicated for reducing the risk of developing SREs in patients with multiple myeloma.[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 solid tumours (except breast and prostate 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 solid tumours (except from breast cancer or prostate cancer).

Results and Interpretation

Included Studies

One published, manufacturer-sponsored, double-blind (DB), randomized controlled trial (RCT) was included in the systematic review. Other Solid Tumours Study 20050244 (Other Solid Tumours Study 244) (n = 1,776)[4,5] evaluated the non-inferiority and superiority of denosumab compared with zoledronic acid based on the first occurrence of an SRE in patients with advanced cancer (excluding breast and prostate 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 Other Solid Tumours Study 244 was the fact that a high proportion of patients in both treatment groups (80%) discontinued from the study, although event rates for death (35% versus 36%) and disease progression (14% versus 12%) were similar in both treatment groups. In addition, pain and health-related quality of life (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 ([redacted] $P = 0.03$), 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 the study was generalizability: approximately 10% of the trial population had multiple myeloma, a condition that is excluded from the Health Canada–approved indication for denosumab. In addition, the trial involved patients with a relatively good performance status at baseline compared with real-life patients, according to the clinical expert consulted by CDR; therefore, the effectiveness and safety observed may not be generalizable to patients with a poorer performance status.

Efficacy

Results from Other Solid Tumours Study 244 demonstrate the non-inferiority (NI) of denosumab compared with zoledronic acid to reduce the risk of a first SRE in patients with advanced cancer and bone metastases. The NI criterion was designed to demonstrate that denosumab would preserve at least 50% of the effect of zoledronic acid compared with placebo. With a hazard ratio (HR) of 0.84 (95% CI, 0.71 to 0.98), results for Other Solid Tumours Study 244 achieved the criteria for NI (P = 0.0007), but failed to demonstrate the superiority of denosumab over zoledronic acid (following adjustment for multiplicity (P = 0.0619). Nevertheless, in a secondary analysis in which patients with multiple myeloma were excluded from the analysis population, denosumab was associated with a significant reduction in the risk of a first SRE compared with zoledronic acid (HR 0.81; 95% CI, 0.68 to 0.96), which in this case achieved the criteria for superiority (P = 0.02).

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. 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. Other Solid Tumours Study 244 showed a statistically significant reduction in the risk of a ≥ 2-point increase from baseline on the Brief Pain Inventory (Short Form) (BPI-SF) "Worst Pain" item with denosumab; a finding considered clinically meaningful as a minimal clinically important difference (MCID) of 1.5 to 2.0 was estimated for this instrument. However, results for other patient-related outcomes did not differ between denosumab and zoledronic acid. Patients entering Other Solid Tumours Study 244 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 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, 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 cancer and bone metastases beyond the median time on study of seven months.

There is a lack of evidence with which to directly compare denosumab to drugs other than zoledronic acid used as treatment to reduce the risk of developing SREs in patients with bone metastases from solid tumours, 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.[6,7] assessed the comparative efficacy of denosumab versus zoledronic acid or best supportive care to reduce the risk of developing SREs in patients with bone metastases from solid tumours (except breast and prostate 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. This finding is consistent with the secondary analysis of the Other Solid Tumours Study 244 results after the exclusion of patients with multiple myeloma, but are not consistent with the primary analysis, in which denosumab was non-inferior to zoledronic acid. No data were available to compare denosumab versus pamidronate or clodronate.

Harms

Denosumab is approved for six indications and has been in use since 2010, and the overall harms in Other Solid Tumours Study 244 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 cancer and bone metastases beyond the median time on study of seven months.

Mortality as well as the overall incidence of serious adverse events (SAEs) during Other Solid Tumours Study 244 did not differ significantly between denosumab and zoledronic acid, and were not higher than would be expected in this patient population; the clinical expert consulted by CDR highlighted the high burden of the malignancy. The most commonly reported SAEs for both treatments (< 12%) included neoplasm progression, dyspnea, pneumonia, respiratory failure, metastases to the central nervous system (CNS), dehydration, general deterioration, spinal cord compression, pyrexia, anemia, pleural effusion, febrile neutropenia, and vomiting. The proportion of patients experiencing adverse events (AEs) was high but similar between denosumab and zoledronic acid. The most common AEs included nausea, anemia, dyspnea, fatigue, constipation, vomiting, back pain, cough, and asthenia. 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, osteonecrosis of the jaw, atypical femur fractures, and malignancies.[3] Results for osteonecrosis of the jaw (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 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 were available to directly compare the potential harms of denosumab versus other drugs used in patients with bone metastases from solid tumours. 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.

Conclusions

The results of Other Solid Tumours Study 244 suggest that denosumab is non-inferior to zoledronic acid with respect to reduction in time to a first SRE in patients with advanced cancer (excluding breast and prostate cancer) and bone metastases. In a secondary analysis in which patients with multiple myeloma were excluded from the analysis population, denosumab was associated with a significant reduction in the risk of a first SRE compared with zoledronic acid, achieving the criteria for superiority. Denosumab did not appear to be associated with improvements over zoledronic acid with respect to pain, HRQoL, or analgesic usage. Similar proportions of patients experienced ONJ, cardiovascular events, atypical femoral fractures, SAEs of infection, and dermatologic AEs in both treatment groups. The results of an indirect comparison in which the efficacy of denosumab was compared with zoledronic acid or placebo were consistent with the conclusion that denosumab is at least as effective as zoledronic acid and superior to placebo for reducing the risk of a first SRE in patients with advanced bone metastases from solid tumours.

TABLE 1: SUMMARY OF RESULTS

	Other Solid Tumours Study 244	
	Denosumab N = 886	**Zoledronic acid N = 890**
A. Skeletal-Related Events		
Time to First SRE — FAS population		
HR (95% CI)	**0.84 (0.71 to 0.98)**	
P value for NI	***P* = 0.0007**	
P value for superiority	non-adjusted *P* = 0.0309 and **adjusted *P* = 0.0619**[a]	
Time to First SRE — Excluding Patients with Multiple Myeloma		
HR (95% CI), *P* value for superiority	**0.81 (0.68 to 0.96), *P* = 0.0168**	
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	[redacted]	
≥ 2-point Increase from Baseline	0.85 ([redacted]), *P* = 0.0233	
Time to > 4-point	0.91 ([redacted]), *P* = 0.1092 (ns)	
Analgesic Score: Mean ± SD [Range]		
Baseline Value	[redacted]	[redacted]
Change from Baseline	0.4 ± 1.4 [–6 to 6]	0.5 ± 1.6 [–6 to 7]
FACT-G — Change from Baseline: Mean ± SD [Range]		
Physical Well-Being	[redacted]	[redacted]
Functional Well-Being	[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	Other Solid Tumours Study 244	
	Denosumab N=878	Zoledronic acid N=878
Mortality, n (%)	[redacted]	[redacted]
SAEs, n (%)	552 (62.9)	581 (66.2)
AEs, n (%)	841 (95.8)	842 (95.9)
WDAEs, n (%)	91 (10.4)	109 (12.4)
Notable Harms		
Infections: SAEs, n (%)	128 (14.6)	118 (13.4)
Hypocalcemia: AEs, n (%)	[redacted]	[redacted]
Cardiovascular Events: AEs, n (%)	[redacted]	[redacted]
Cardiovascular Events: SAEs, n (%)	[redacted]	[redacted]
ONJ: AEs, n (%)	10 (1.1)	11 (1.3)

AE = adverse event; EQ-5D = EuroQol 5-Dimensions Questionnaire; BPI-SF = Brief Pain Inventory (Short Form); CI = confidence interval; FACT-G = Functional Assessment of Cancer Therapy–General; 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.
[a] *P* values were adjusted for multiplicity according to a hierarchical testing strategy.
Source: Clinical Study Report.[8]

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-related events (SREs) include the following complications from bone metastases: pathological fractures, spinal cord compressions, and radiotherapy and surgery to the bone. 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 impaired function and diminished quality of life.[2,6]

1.2 Standards of Therapy

Current treatment strategies aim to prevent SREs in most patients. Conventional pain management with acetaminophen, nonsteroidal anti-inflammatory drugs, opioids, or steroids aims to balance pain control against side effects of pharmacotherapy, but does not generally influence the likelihood of developing most SREs; therefore, the use of bone-modifying drugs is recommended. The National Comprehensive Cancer Network (NCCN) recommends the use of denosumab, pamidronate, or zoledronic acid for patients with cancer and evidence of bone metastasis, and suggests the use of clinical judgment to determine the most appropriate treatment for each individual patient.[9] Experience from specialists' clinical practice suggests that patients with bone metastases from solid tumours, other than breast or prostate cancer, present with a very heterogeneous disease, depending on the site of the primary tumour, especially in terms of life expectancy. In some end-of-life patients, best supportive care may be considered an adequate palliative treatment option.

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 solid tumours (except breast and prostate 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. A separate CDR report focuses on the breast cancer indication; in this CDR report, we review 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.[10]

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

	Denosumab[3]	Bisphosphonates Zoledronic Acid (Zometa), Pamidronate, and Clodronate[11-13]
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; SRE = skeletal-related event.
[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 solid tumours (except from breast cancer or prostate 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 solid tumours (including lung cancer but excluding breast cancer and prostate cancer[a])
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 adverse events
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 injection; WDAE = withdrawal due to adverse event.

[a] The Canadian Expert Drug Advisory Committee recommended in 2011 that denosumab be reimbursed for the prevention of skeletal-related events in patients with castrate-resistant prostate cancer with one or more documented bony metastases and good performance status, in jurisdictions that list zoledronic acid for the same indication. A separate CADTH Common Drug Review report focuses on the breast cancer indication and is concomitantly prepared. 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 through Ovid; Embase (1974–)through 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 (RCTs) 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 (https://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 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 2 and described in Section 3.2. A list of excluded studies is presented in 0.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

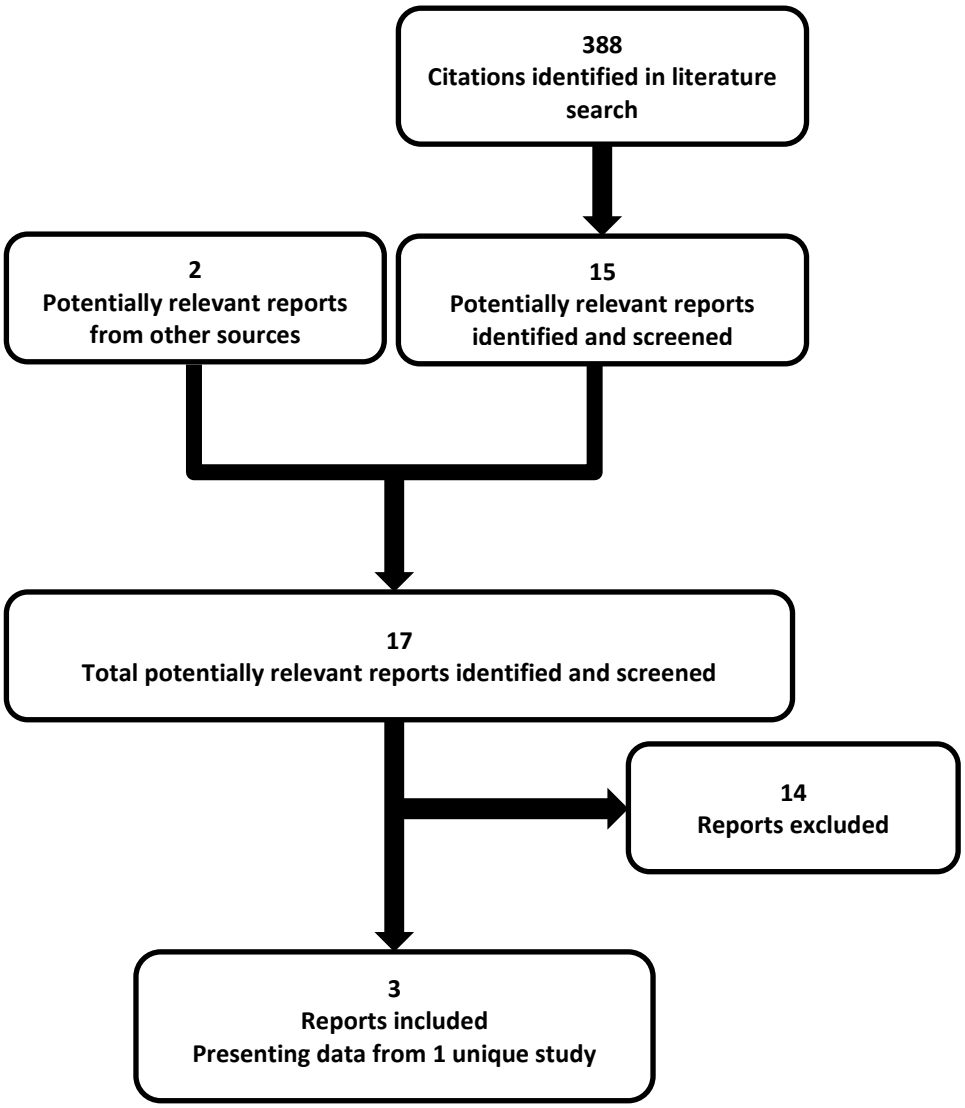


TABLE 4: DETAILS OF INCLUDED STUDY

		Other Solid Tumours Study 20050244
DESIGNS & POPULATIONS	**Study Design**	DB RCT with active comparator
	Locations	Multi-centre (321 study sites in 33 countries): Europe, US, Canada (n = 65), Latin America, India, Australia, South Africa
	Randomized (N)	1,776
	Inclusion Criteria	Adult patients with advanced cancers (including solid tumours, multiple myeloma, and lymphoma) and evidence of at least 1 bone metastasis (or lytic bone lesion from multiple myeloma). 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	**Diagnosis of breast or prostate cancer.** 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 7 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-G, EQ-5D, analgesic use • Safety outcomes: AEs and SAEs
NOTES	**Publications**	Henry et al. 2011,[4] Vadhan-Raj et al. 2012[5]

AE = adverse event; BPI-SF = Brief Pain Inventory (Short Form); DB = double-blind; ECOG = Eastern Cooperative Oncology Group; EQ-5D = EuroQol 5-Dimensions Questionnaire; FACT-G = Functional Assessment of Cancer Therapy–General; IV = intravenous; 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.[8]
Source: Clinical Study Report.[8]

3.2 Included Studies

3.2.1 Description of studies

One published, manufacturer-sponsored, double-blind (DB) RCT was included in the systematic review. Other Solid Tumours Study 20050244 (Other Solid Tumours Study 244) (n = 1,776)[4,5] evaluated the non-inferiority and superiority of denosumab compared with zoledronic acid based on the first occurrence of an SRE in patients with advanced cancer (excluding breast and prostate 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 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 Other Solid Tumours Study 244 if they were adults with histologically or cytologically confirmed advanced cancers including solid tumours, multiple myeloma, and lymphoma with current or prior radiographic evidence of at least one bone metastasis or lytic bone lesion.

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 x upper limit of normal (ULN)
- serum alanine aminotransferase ≤ 5 x ULN
- serum total bilirubin ≤ 2 x ULN
- creatinine clearance ≥ 30 mL/min.

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 Other Solid Tumours Study 244 had a mean age of 60 years. A total of [redacted] of patients were under 60 years of age, while 36% were 65 years or older. A total of 64% of patients were men and 87% were Caucasian.

Most patients had an ECOG performance status of 0 (27%) or 1 (56%) at study entry; 16% of participants had an ECOG score of 2. The most common primary tumour types were non–small cell lung cancer (40%), multiple myeloma (10%), [redacted] Primary tumour stage at diagnosis ranged from [redacted]; the presence of visceral metastasis was observed in 52% of patients. Concomitant chemotherapy was administered in [redacted] of patients. A total of [redacted] of patients had sustained a previous SRE. The most frequent individual events were [redacted]

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Baseline Characteristics	Other Solid Tumours Study 244	
	Denosumab N = 886	Zoledronic Acid N = 890
Age		
Mean ± SD, years	59.3 (11.4)	60.6 (10.7)
Age Categories, n (%)		
< 60 years	[redacted]	[redacted]
≥ 60 years	[redacted]	[redacted]
Geriatric Age Categories, n (%)		
≥ 65 years	299 (33.7)	336 (37.8)
≥ 75 years	[redacted]	[redacted]
Gender, n (%)		
Male	588 (66.4)	552 (62.0)
Female	298 (33.6)	338 (38.0)
Ethnic Group, n (%)		
Caucasian	770 (86.9)	770 (86.5)
Black	20 (2.3)	29 (3.3)
Hispanic or Latino	49 (5.5)	36 (4.0)
Asian	36 (4.1)	44 (4.9)
Japanese	3 (0.3)	1 (0.1)
American Indian or Alaska Native	0	2 (0.2)
Other	8 (0.9)	8 (0.9)
ECOG Performance Status at Study Entry, n (%)		
0	240 (27.1)	236 (26.5)
1	508 (57.3)	492 (55.3)
2	135 (15.2)	157 (17.6)
3	NR	NR
Missing	5 (0.6)	3 (0.3)
Primary Tumour Type, n (%)		
NSCLC	350 (39.5)	352 (39.6)
Multiple myeloma	87 (9.8)	93 (10.4)
Other	449 (50.7)	445 (50.0)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Primary Tumour Stage at Diagnosis, n (%)		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	[redacted]	[redacted]
Other	[redacted]	[redacted]

Baseline Characteristics	Other Solid Tumours Study 244	
	Denosumab N = 886	Zoledronic Acid N = 890
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]
Mixed	[redacted]	[redacted]
Unable to evaluate	[redacted]	[redacted]
Not seen	[redacted]	[redacted]
Presence of Visceral Metastases, n (%)		
All	474 (53.5)	449 (50.4)
Liver	172 (19.4)	167 (18.8)
Lung	239 (27.0)	162 (18.2)
Other	320 (36.1)	341 (38.3)
Concomitant Chemotherapy, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
SRE History, n (%)		
Any SRE	[redacted]	[redacted]
Radiation to bone	[redacted]	[redacted]
Pathological fracture	[redacted]	[redacted]
Spinal cord compression	[redacted]	[redacted]
Surgery to bone	[redacted]	[redacted]

ECOG = Eastern Cooperative Oncology Group; NR = not reported; NSCLC = non–small cell lung cancer; SD = standard deviation; SRE = skeletal-related event.
Source: Clinical Study Report, p. 131, 133-5, 282.[8]

3.2.3 Interventions

Other Solid Tumours Study 244 evaluated the efficacy and safety of denosumab compared with zoledronic acid in patients with advanced metastatic cancer (excluding breast and prostate 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 for advanced cancer with bone metastasis or multiple myeloma 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 Other Solid Tumours Study 244 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–General (FACT-G)
- 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 below. The change from baseline in analgesic usage over the course of the study was assessed through to the time when 50% 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 mg to 150 mg OME per day
5	strong opioids > 150 mg to 300 mg OME per day
6	strong opioids > 300 mg to 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 below. 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-G questionnaire is a widely used disease-specific HRQoL instrument considered valid and reliable in patients with cancer. The questionnaire consists of 27 questions evaluating 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 consisting 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 their 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 Other Solid Tumours Study 244 was to test for non-inferiority of denosumab compared with zoledronic acid in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma and bone metastasis for the outcome of SRE, based on the time to first on-study occurrence. For the primary outcome, inclusion of 1,690 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 1.40; 95% confidence interval [CI], 1.11 to 1.77). 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. 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. The multiplicity was adjusted for according to a hierarchical testing strategy: testing a null hypothesis for primary end point first, and if rejected, testing secondary end points via Hochberg procedure. 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 16. A total of 1,779 patients were enrolled and 1,776 patients were randomized in Other Solid Tumours Study 244; of these, 80% 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 (35% with denosumab and 36% with zoledronic acid), disease progression (14% and 12%, respectively) and consent withdrawn (14% and 16%).

TABLE 6: PATIENT DISPOSITION

	Other Solid Tumours Study 244	
	Denosumab	Zoledronic Acid
Enrolled, N	1,779	
Randomized — Overall	1,776	
Randomized — Per group	886	890
Randomized and Treated, n (%)	878 (99)	878 (99)
Completed study through primary data analysis cut-off date, n (%)	180 (20)	178 (20)
Discontinued, n (%)	706 (80)	712 (80)
Most frequent reasons for discontinuation, n (%)		
Death	310 (35)	316 (36)
Disease progression	126 (14)	104 (12)
Consent withdrawn	124 (14)	143 (16)
Subject request	22 (3)	31 (4)
Adverse event	36 (4)	48 (5)
Other	44 (5)	36 (4)
Administrative decision	2 (< 1)	1 (< 1)
Noncompliance	17 (2)	15 (2)
Lost to follow-up	22 (3)	16 (2)
Protocol deviation	2 (< 1)	0
Ineligibility determined	1 (< 1)	2 (< 1)
Analysis sets		
FAS, N	886	890
PP, N	[redacted]	[redacted]
Safety, N	878	878

FAS = full analysis set; PP = per-protocol.
Source: Clinical Study Report, p. 126, 139, 275.[8]

3.4 Exposure to Study Treatments

Details regarding baseline characteristics are provided in Table 7. Patients in Other Solid Tumours Study 244 spent a median time on study of seven months in each treatment group, which was, however, associated with a relatively wide range of 0 months to 33 months.

TABLE 7: EXTENT OF EXPOSURE

	Other Solid Tumours Study 244	
	Denosumab N = 886	Zoledronic Acid N = 890
Number of Months on Study[a]		
Mean ± SD	[redacted]	[redacted]
Median	7[redacted]	7[redacted]
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	7.0	7.0
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. 185-6.[8]

3.5 Critical Appraisal

3.5.1 Internal validity

a) Study design, intervention, and comparator

Other Solid Tumours Study 244 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 solid tumours. 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 ([redacted] $P = 0.0256$) 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

Other Solid Tumours Study 244 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 tumour type, previous SRE, and systemic anticancer therapy. 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 (80%) 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, but likely limited.

c) Outcome measures

The outcome measures and definitions 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-G, and EQ-5D, are considered valid and reliable.

d) Statistical analysis

Other Solid Tumours Study 244 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. Approximately 10% of the trial population were patients with multiple myeloma, a condition that is excluded from the Health Canada–approved indication for denosumab; however, the results of an analysis excluding patients with multiple myeloma were reported.

Other Solid Tumours Study 244 involved patients with a relatively good performance status at baseline compared with real-life patients, according to the clinical expert consulted by CDR. A total of 27% of patients had an ECOG performance status of 0, 56% of patients had an ECOG performance status of 1, and 16% of patients had an ECOG performance status of 2. 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 Other Solid Tumours Study 244 were observed in a population where denosumab was administered as first-line treatment.

The trial population was homogenous, with the exception of primary tumour type. Apart from multiple myeloma, a total of 40% of patients had non–small cell lung cancer, while the rest of the trial population had a wide range of primary tumour type.

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 Other Solid Tumours Study 244 are not generalizable to these patients.

b) Treatment regimen and length of follow-up

Other Solid Tumours Study 244 used an appropriate and realistic denosumab treatment regimen for patients with bone metastases from solid tumours. 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 seven months was considered sufficient to see the effect of both treatments on SREs. Findings from Other Solid Tumours Study 244, as well as experience from specialists' clinical practice, suggest that the disease in this patient population may progress quickly; as a result, the magnitude of the potential benefits of denosumab on outcomes such as HRQoL may be limited to some degree. 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 are reported (section 2.2, Table 3). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Skeletal-related events

Results of Other Solid Tumours Study 244 for the primary efficacy outcome of time to first SRE demonstrated that the use of denosumab was associated with a reduction in the risk of a first SRE compared with zoledronic acid, as shown by the HR of 0.84 (95% CI, 0.71 to 0.98; FAS population), achieving the criteria for non-inferiority (*P* = 0.0007), but failing to demonstrate the superiority of denosumab over zoledronic acid once results were adjusted for multiplicity (adjusted *P* = 0.0619). [redacted]

However, with patients with multiple myeloma excluded from the analysis, the use of denosumab was associated with a significant reduction in the risk of a first SRE compared with zoledronic acid, as shown by the HR of 0.81 (95% CI, 0.68 to 0.96), achieving the criteria for superiority (*P* = 0.0168).

The median time to first SRE was [redacted][8] The proportions of patients experiencing an event was 31% (n = 278 patients) in the denosumab group compared with 36% (n = 323 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. However, Other Solid Tumours Study 244 did not have sufficient power to show a significant difference in individual types of SRE.

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. [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,[14,15] the clinical significance of these results is uncertain.

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. Denosumab was associated with a statistically significant reduction in the risk of a ≥ 2-point increase from baseline compared with zoledronic acid, as shown by the HR of 0.85 ([redacted] $P = 0.0233$); however, there was no statistically significant difference between treatment groups for the outcomes of time to ≥ 2-point decrease from baseline and time to > 4-point change.

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 50% of patients withdrew from the trial, which is approximately [redacted]. Results for mean change from baseline did not seem to differ between denosumab and zoledronic acid; however, no statistical analysis between treatment groups was reported.

3.6.3 Health-related quality of life

HRQoL was assessed using the FACT-G 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 for both outcome measures did not seem to differ between denosumab and zoledronic acid with respect to any of the reported items; however, no statistical analysis between treatment groups regarding change from baseline was reported. Outcome measures including HRQoL instruments are reviewed in Appendix 5. Considering that an MCID of 3 to 7 was estimated for the FACT-G questionnaire,[16,17] and that an MCID of 0.06 was estimated for the EQ-5D utility scores,[18,19] the clinical significance of these results is uncertain.

TABLE 8: KEY EFFICACY OUTCOMES

	Other Solid Tumours Study 244	
	Denosumab N = 886	Zoledronic Acid N = 890
C. Skeletal-Related Events		
Time to First SRE — FAS population		
HR (95% CI)	**0.84 (0.71 to 0.98)**	
P value for NI	***P* = 0.0007**	
P value for superiority	non-adjusted *P* = 0.0309 and **adjusted *P* = 0.0619**[a]	
Time to First SRE — PP population		
HR (95% CI)	[redacted]	
P value for NI	[redacted]	
P value for superiority	[redacted]	
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	[redacted]	
Time to First SRE — Excluding Patients with Multiple Myeloma		
HR (95% CI), *P* value for superiority	**0.81 (0.68 to 0.96), *P* = 0.0168**	
Time to First and Subsequent SRE — FAS population		
HR (95% CI), *P* value	0.90 (0.77 to 1.04), *P* = 0.1447 (ns)	
D. 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	[redacted]	
≥ 2-point Increase from Baseline	0.85 ([redacted]), ***P* = 0.0233**	
Time to > 4-point	0.91 ([redacted]), *P* = 0.1092 (ns)	
Analgesic Score: Mean ± SD [Range]		
Baseline Value	[redacted]	[redacted]
Change from Baseline	[redacted]	[redacted]
E. Health-Related Quality of Life		
FACT-G — Change from Baseline: Mean ± SD [Range]		
Physical Well-Being	[redacted]	[redacted]
Functional Well-Being	[redacted]	[redacted]
Total Score	[redacted]	[redacted]
EQ-5D — Change from Baseline: Mean ± SD [Range]		
Mean ± SD	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]

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

[a] *P* values were adjusted for multiplicity according to a hierarchical testing strategy.

Source: Clinical Study Report.[8]

3.7 Harms

Only those harms identified in the review protocol are reported below (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 in both treatment groups died during Other Solid Tumours Study 244. 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 Other Solid Tumours Study 244, with a total of 63% and 66% of patients in the denosumab and zoledronic acid group, respectively. The most common SAEs reported (< 12% in each treatment group) included neoplasm progression, dyspnea, pneumonia, respiratory failure, metastases to central nervous system (CNS), dehydration, general deterioration, spinal cord compression, pyrexia, anemia, pleural effusion, febrile neutropenia, and vomiting.

3.7.3 Adverse events

Similar proportions of patients experienced AEs in both treatment groups in Other Solid Tumours Study 244, with a total of 96% of patients in both treatment groups. The most common AEs reported (< 33% in each treatment group) included nausea, anemia, dyspnea, fatigue, constipation, vomiting, back pain, cough, and asthenia.

3.7.4 Withdrawal due to adverse events

The proportion of patients discontinuing Other Solid Tumours Study 244 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 (≤ 1% in each treatment group) were malignant disease progression, dyspnea, fatigue, general physical health deterioration, osteonecrosis, and hypocalcemia.

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, atypical femoral fractures, and dermatologic AEs in both treatment groups; these were reported by low proportions of patients in Other Solid Tumours Study 244. A total of 15% of patients randomized to denosumab reported SAEs of infection compared with 13% of patients receiving zoledronic acid. 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 (AEs: 11% versus 6%, respectively; SAEs: 1.4% versus 0.9%, respectively).

TABLE 9: HARMS

	Other Solid Tumours Study 244	
	Denosumab N = 878	Denosumab N = 878
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 (%)	**552 (62.9)**	**581 (66.2)**
Most common SAEs:		
[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]
AEs, n (%)	**841 (95.8)**	**842 (95.9)**
Most common AEs:		
Nausea	248 (28.2)	266 (30.3)
Anemia	242 (27.6)	286 (32.6)
Dyspnea	220 (25.1)	200 (22.8)
Fatigue	211 (24.0)	220 (25.1)
Constipation	191 (21.8)	214 (24.4)
Vomiting	186 (21.2)	183 (20.8)
Back pain	173 (19.7)	196 (22.3)
[redacted]	[redacted]	[redacted]
Asthenia	172 (19.6)	180 (20.5)
WDAEs, n (%)	**91 (10.4)**	**109 (12.4)**
Most common WDAEs:		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	Other Solid Tumours Study 244	
	Denosumab N = 878	Denosumab N = 878
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Infections: SAEs, n (%)	128 (14.6)	118 (13.4)
Hypocalcemia: AEs, n (%)	[redacted]	[redacted]
Cardiovascular events: AEs, n (%)	[redacted]	[redacted]
Cardiovascular events: SAEs, n (%)	[redacted]	[redacted]
ONJ: AEs, n (%)	10 (1.1)	11 (1.3)

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.[8]

4. DISCUSSION

4.1 Summary of Available Evidence

One published, manufacturer-sponsored, DB RCT was included in the systematic review. Other Solid Tumours Study 244 (n = 1,776)[4,5] evaluated the non-inferiority and superiority of denosumab compared with zoledronic acid based on the first occurrence of an SRE in patients with advanced cancer (excluding breast and prostate 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).

Other Solid Tumours Study 244 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 (80%) discontinued from the study, mostly due to death and disease progression. Although this is not unexpected in a trial population with a wide range of advanced solid tumours, the impact on the interpretation of the findings is uncertain, but likely limited. Findings from Other Solid Tumours Study 244, as well as experience from specialists' clinical practice, suggest that the disease in this patient population may progress quickly, considering the median on-study duration of seven months. As a result, the magnitude of the potential benefits of denosumab on outcomes such as HRQoL may vary on an individual patient level in an end-of-life setting. 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 ([redacted] *P* = 0.0256), 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 Other Solid Tumours Study 244 is related to generalizability. Approximately 10% of the trial population were patients with multiple myeloma, a condition that is excluded from the Health Canada–approved indication for denosumab. The product monograph for denosumab states that mortality was higher with denosumab in a subgroup analysis of patients with multiple myeloma, with an HR of 2.26 (95% CI, 1.13 to 4.50); n = 180.[3] This has contributed to regulatory decisions to exclude multiple myeloma from the approved indication. However, the results of an analysis excluding patients with multiple myeloma were reported.

The trial involved patients with a relatively good performance status at baseline compared with real-life patients, according to the clinical expert consulted by CDR; 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 Other Solid Tumours Study 244 were observed in a population where denosumab was administered as first-line treatment.

4.2 Interpretation of Results

4.2.1 Efficacy

Results from Other Solid Tumours Study 244 demonstrate the non-inferiority of denosumab compared with zoledronic acid to reduce the risk of a first SRE in patients with advanced cancer and bone metastases. The NI criterion was based on a synthesis approach designed to demonstrate that denosumab would preserve at least 50% of the effect of zoledronic acid compared with placebo. With an HR of 0.84 (95% CI, 0.7 to 0.98), results achieved the criteria for non-inferiority (*P* = 0.0007), but failed to demonstrate the superiority of denosumab over zoledronic acid once results were adjusted for multiplicity (adjusted *P* = 0.0619). However, with patients with multiple myeloma excluded from the analysis, the use of denosumab was associated with a significant reduction in the risk of a first SRE compared with zoledronic acid, as shown by the HR of 0.81 (95% CI, 0.68 to 0.96), achieving in this case the criteria for superiority (*P* = 0.0168).

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. 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. Other Solid Tumours Study 244 showed a statistically significant reduction in the risk of a ≥ 2-point increase from baseline on the BPI-SF "Worst Pain" item with denosumab; a finding considered clinically meaningful as an MCID of 1.5 to 2.0 was estimated for this instrument. However, results for other patient-related outcomes did not differ between denosumab and zoledronic acid, despite the absence of further statistical comparison.

A few key interpretation points should be noted. Experience from specialists' clinical practice suggests that patients entering the trial had a relatively good performance status compared with real-life patients, with consequently relatively lower pain levels and 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 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 ([redacted] *P* = 0.0256) 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 cancer and bone metastases remain uncertain, as there are no data to inform on the effectiveness of denosumab beyond the median time on study of seven 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 solid tumours, 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.[6,7] assessed the comparative efficacy of denosumab versus zoledronic acid and best supportive care or placebo as treatment to reduce the risk of developing SREs in patients with bone metastases from solid tumours (except breast and prostate 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. There were no data available to assess the comparative effectiveness of denosumab versus pamidronate or clodronate. Pain, HRQoL, and AEs figured as secondary outcomes; however, no NMA results were reported. The Ford et al.[6] IDC was likely conducted with methodological rigour; however, some major limitations affect our level of confidence in the findings. NMA results for the direct comparison of denosumab versus zoledronic acid were not consistent with those reported by the included study comparing the two treatments, where denosumab was non-inferior to zoledronic acid; access to additional data from the manufacturer of denosumab, including a post hoc analysis, may have had an impact on the findings. This significant difference in the conclusions between analyses further highlights the need to view the results with caution, considering the high level of uncertainty surrounding the NMA brought by the small number of included studies.

4.2.2 Harms

Denosumab is approved for six indications and has been in use since 2010, and the overall harms in Other Solid Tumours Study 244 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 cancer and bone metastases beyond the median time on study of seven months.

Mortality as well as the overall incidence of SAEs during Other Solid Tumours Study 244 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 < 12%. The clinical expert consulted by CDR highlighted the high burden of the malignancy in this patient population. The proportion of patients experiencing AEs was high but similar between denosumab and zoledronic acid. The most common AEs included nausea, anemia, dyspnea, fatigue, constipation, vomiting, back pain, cough, and asthenia. 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, 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 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 a subcutaneous 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 Other Solid Tumours Study 244; 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.[11]

No data are available to directly compare the potential harms of denosumab versus other drugs used in patients with bone metastases from solid tumours. 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. There exists a need to further decrease pain and impairments on functional status, and increase quality of life for many patients. However, translating this into clinical practice is often complicated by the fact that patients with bone metastases from solid tumours other than breast or prostate cancer present with a very heterogeneous disease, depending on the site of the primary tumour, especially in terms of disease severity and life expectancy.

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.[20,21]

In clinical practice, access to denosumab would be beneficial in select patients if the indication to delay time to SREs arose, based on the evidence that denosumab is non-inferior to zoledronic acid. In addition, 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.[11] However, in some end-of-life patients, best supportive care may be considered as an adequate palliative treatment option.

5. CONCLUSIONS

The results of Other Solid Tumours Study 244 suggest that denosumab is non-inferior to zoledronic acid with respect to reduction the time to a first SRE in patients with advanced cancer (excluding breast and prostate cancer) and bone metastases. In a secondary analysis in which patients with multiple myeloma were excluded from the analysis population, denosumab was associated with a significant reduction in the risk of a first SRE compared with zoledronic acid, and achieved the criteria for superiority. Denosumab did not appear to be associated with improvements over zoledronic acid with respect to pain, HRQoL, or analgesic usage. Similar proportions of patients experienced ONJ, cardiovascular events, atypical femoral fractures, SAEs of infection, and dermatologic AE in both treatment groups. The results of an indirect comparison in which the efficacy of denosumab was compared with zoledronic acid or placebo were consistent with the conclusion that denosumab is at least as effective as zoledronic acid and superior to placebo for reducing the risk of a first SRE in patients with bone metastases from solid tumours.

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 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 CBNC
- 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. The 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' lives. 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 $1500.00 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 & restrict them in anyway 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
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" (https://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[22]	Inappropriate study design
Lipton et al. 2012[23]	
Henry et al. 2014[24]	
Scagliotti et al. 2012[25]	
Lipton et al. 2012[26]	
Perez-Lopez 2014[27]	
Shapiro 2013[28]	
Lippuner et al. 2014[29]	Inappropriate population
Schmitz-Drager et al. 2013[30]	
Smith et al. 2015[31]	
Gnant et al. 2015[32]	
Diel et al. 2014[33]	Inappropriate outcome
Cleeland et al. 2013[34]	Second screening by indication — other solid tumours only (breast cancer and prostate cancer excluded)
Martin et al. 2012[35]	

APPENDIX 4: DETAILED OUTCOME DATA

Efficacy Outcomes

TABLE 10: SKELETAL-RELATED EVENTS

	Other Solid Tumours Study 244	
	Denosumab N = 886	Zoledronic Acid N = 890
Time to First SRE: FAS Population Analysis		
n (%) at data cut-off	278 (31.4)	323 (36.3)
HR (95% CI)	0.84 (0.71 to 0.98)	
P value for NI	*P* = 0.0007	
P value for superiority	non-adjusted *P* = 0.0309 and adjusted *P* = 0.0619[a]	
PP Population Analysis		
HR (95% CI)		
P value for NI		
P value for superiority		
Time to First SRE — by Individual Type (FAS Population Analysis): Spinal Cord Compression		
n (%) at data cut-off		
HR (95% CI)		
P value		
Pathological Fracture		
n (%) at data cut-off		
HR (95% CI)		
P value		
Surgery to Bone		
n (%) at data cut-off		
HR (95% CI)		
P value		
Radiation to Bone		
n (%) at data cut-off		
HR (95% CI)		
P value		
Time to First SRE: FAS Population Analysis Excluding Patients with Multiple Myeloma		
n (%) at data cut-off		
HR (95% CI)	0.81 (0.68 to 0.96)	
P value for superiority	*P* = 0.0168	
Time to First and Subsequent SRE: FAS Population Analysis		
Number of events at data cut-off	392	436
HR (95% CI)	0.90 (0.77 to 1.04)	
P value for superiority	*P* = 0.1447 (ns)	
PP Population Analysis		
Number of events at data cut-off		
HR (95% CI)		
P value for superiority		

CI = confidence interval; FAS = full analysis set; HR = hazard ratio; NI = non-inferiority; ns = non-significant; PP = per-protocol; SRE = skeletal-related event.

[a] *P* values were adjusted for multiplicity according to a hierarchical testing strategy: testing null hypothesis for primary end point first, and if rejected, testing secondary end points via Hochberg procedure.

Source: Clinical Study Report p. 141 and tables starting p. 301, 2015.[8]

Patient-Reported Outcomes

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

	Other Solid Tumours Study 244	
	Denosumab N = 886	Zoledronic Acid N = 890
Pain you Have Right Now:		
Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
50% 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]
50% 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]
50% 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	[redacted]	[redacted]
Range	[redacted]	[redacted]
50% 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 ≥ 50% of patients have withdrawn due to death, disease progression or consent withdrawn, which is approximately at week 45.
Source: Clinical Study Report, tables starting p. 375.[8]

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

	Other Solid Tumours Study 244	
	Denosumab N = 886	Zoledronic Acid N = 890
Worst Pain:		
Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
50% 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)	[redacted]	
P value	[redacted]	
Time to ≥ 2-point Increase from Baseline		
HR (95% CI)	0.85 ([redacted])	
P value	*P* = 0.0233	
Time to > 4-point		
HR (95% CI)	0.91 ([redacted])	
P value	*P* = 0.1092 (ns)	

HR = hazard ratio; SD = standard deviation.
The range of "Worst Pain" is 0 to 10; a higher score indicates a less preferred health status.
[a] Table presents data up to the visit when ≥ 50% of patients have withdrawn due to death, disease progression or consent withdrawn, which is approximately at week 45.
Source: Clinical Study Report, tables starting p. 375, 430.[8]

TABLE 13: ANALGESIC USE

	Other Solid Tumours Study 244	
	Denosumab N = 886	Zoledronic Acid N = 890
Analgesic Score at Baseline		
Mean ± SD	2.0 ± [redacted]	2.0 ± [redacted]
Range	0 to 7	0 to 7
Analgesic Score at 50% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Change from Baseline in Analgesic Score at 50% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]

SD = standard deviation.
[a] Table presents data up to the visit when ≥ 50% of patients have withdrawn due to death, disease progression or consent withdrawn, which is approximately at week 45.
Source: Clinical Study Report, p. 363, 368.[8]

TABLE 14: FUNCTIONAL ASSESSMENT OF CANCER THERAPY SCORES

	Other Solid Tumours Study 244	
	Denosumab N = 886	Zoledronic Acid N = 890
FACT-G — Physical Well-Being: Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
50% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Change from Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
FACT-G — Functional Well-Being: Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
50% 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]
50% Dropout[a]		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Change from Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]

FACT-G = Functional Assessment of Cancer Therapy–General; SD = standard deviation.
[a] Table presents data up to the visit when ≥ 50% of patients have withdrawn due to death, disease progression or consent withdrawn, which is approximately at week 45.
Source: Clinical Study Report, tables starting p. 430.[8]

TABLE 15: EUROQOL 5-DIMENSIONS QUESTIONNAIRE UTILITY SCORES

	Other Solid Tumours Study 244	
	Denosumab N = 886	Zoledronic Acid N = 890
EQ-5D — Health Index Score:		
Baseline		
Mean ± SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
50% 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]
50% 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; WDAE = withdrawal due to adverse event.

[a] Table presents data up to the visit when ≥ 50% of patients have withdrawn due to death, disease progression or consent withdrawn, which is approximately at week 45.

Source: Clinical Study Report, p. 470.[8]

Harms Outcomes

TABLE 16: MORTALITY

	Other Solid Tumours Study 244	
	Denosumab N = 878	Zoledronic Acid N = 878
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]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CNS = central nervous system.
Source: Clinical Study Report, p. 188, 738.[8]

TABLE 17: NOTABLE OR CLINICALLY SIGNIFICANT HARMS

	Other Solid Tumours Study 244	
	Denosumab N = 878	Zoledronic Acid N = 878
Infections		
SAEs, n (%)	128 (14.6)	118 (13.4)
Most Frequently Reported Reasons — ≥ 1% of Patients in at Least 1 Treatment Group, n (%):		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Cardiovascular Events		
AEs, n (%)	[redacted]	[redacted]
SAEs, n (%)	[redacted]	[redacted]
Fatal events, n (%)	[redacted]	[redacted]
Hypocalcemia		
AEs, n (%)	[redacted]	[redacted]
Skin Infections		
AE of skin infection, n (%)	[redacted]	[redacted]
AE of serious skin infection, n (%)	[redacted]	[redacted]
Eczema		
AEs, n (%)	[redacted]	[redacted]
ONJ		
AEs, n (%)	10 (1.1)	11 (1.3)
Atypical Femoral Fractures		
AE of femur fracture, n (%)	[redacted]	[redacted]
SAE of femur fracture, n (%)	[redacted]	[redacted]
New Malignancies		
AEs, n (%)	5 (0.6)	3 (0.3)

AE = adverse event; ONJ = osteonecrosis of the jaw; SAE = serious adverse event.
Source: Clinical Study Report, p. 200–13 (tables p. 1275, 1258, 1270–4, 207, 527, 558, 1268).[8]

TABLE 18: SERIOUS ADVERSE EVENTS

	Other Solid Tumours Study 244	
	Denosumab N = 878	Zoledronic Acid N = 878
SAEs		
n (%)	**552 (62.9)**	**581 (66.2)**
Most Frequently Reported SAEs — ≥ 1 Patient in at Least 1 Treatment Group, n (%):		
Neoplasm progression	103 (11.7)	100 (11.4)
Dyspnea	55 (6.3)	54 (6.2)
Pneumonia	52 (5.9)	44 (5.0)
Respiratory failure	45 (5.1)	40 (4.6)
Metastases to CNS	43 (4.9)	44 (5.0)
Dehydration	35 (4.0)	34 (3.9)
General deterioration	26 (3.0)	38 (4.3)
Spinal cord compression	27 (3.1)	26 (3.0)
Pyrexia	26 (3.0)	21 (2.4)
Anemia	25 (2.8)	49 (5.6)
Pleural effusion	23 (2.6)	27 (3.1)
Febrile neutropenia	21 (2.4)	31 (3.5)
Vomiting	21 (2.4)	24 (2.7)
Asthenia	21 (2.4)	16 (1.8)
Pulmonary embolism	19 (2.2)	18 (2.1)
Abdominal pain	18 (2.1)	17 (1.9)
Thrombocytopenia	17 (1.9)	23 (2.6)
Metastases to liver	16 (1.8)	13 (1.5)
Sepsis	16 (1.8)	11 (1.3)
Back pain	15 (1.7)	19 (2.2)
Deep vein thrombosis	15 (1.7)	13 (1.5)
Nausea	14 (1.6)	16 (1.8)
Diarrhea	14 (1.6)	13 (1.5)
Neutropenia	14 (1.6)	11 (1.3)
Chest pain	14 (1.6)	10 (1.1)
Hypocalcemia	12 (1.4)	8 (0.9)
Pain	12 (1.4)	6 (0.7)
Fatigue	11 (1.3)	6 (0.7)
Bone pain	11 (1.3)	15 (1.7)
Renal failure acute	10 (1.1)	15 (1.7)
Renal failure	10 (1.1)	13 (1.5)
Multi-organ failure	10 (1.1)	8 (0.9)
Cardiac failure	10 (1.1)	5 (0.6)
Urinary tract infection	9 (1.0)	9 (1.0)
Disease progression	8 (0.9)	13 (1.5)
Hematuria	8 (0.9)	2 (0.2)
[redacted]	[redacted]	[redacted]

	Other Solid Tumours Study 244	
	Denosumab N = 878	Zoledronic Acid N = 878
Osteonecrosis	7 (0.8)	4 (0.5)
Pain in extremity	5 (0.6)	7 (0.8)
Cachexia	4 (0.5)	10 (1.1)
Urinary retention	3 (0.3)	9 (1.0)
Hepatic failure	2 (0.2)	4 (0.5)

CNS = central nervous system; SAE = serious adverse event.
Source: Clinical Study Report, p. 197–8.[8]

TABLE 19: ADVERSE EVENTS

	Other Solid Tumours Study 244	
	Denosumab N = 878	Zoledronic Acid N = 878
AEs		
n (%)	**841 (95.8)**	**842 (95.9)**
Most Frequently Reported AEs — ≥ 10% of Patients in at Least 1 Treatment Group, n (%):		
Nausea	248 (28.2)	266 (30.3)
Anemia	242 (27.6)	286 (32.6)
Dyspnea	220 (25.1)	200 (22.8)
Fatigue	211 (24.0)	220 (25.1)
Constipation	191 (21.8)	214 (24.4)
Vomiting	186 (21.2)	183 (20.8)
Back pain	173 (19.7)	196 (22.3)
[redacted]	[redacted]	[redacted]
Asthenia	172 (19.6)	180 (20.5)
[redacted]	[redacted]	[redacted]
Anorexia	165 (18.8)	195 (22.2)
[redacted]	[redacted]	[redacted]
Pyrexia	139 (15.8)	182 (20.7)
[redacted]	[redacted]	[redacted]

AE = adverse event.
Source: Clinical Study Report, p. 215, 643.[8]

TABLE 20: WITHDRAWAL DUE TO ADVERSE EVENTS

	Other Solid Tumours Study 244	
	Denosumab N = 878	Zoledronic Acid N = 878
WDAEs[a]		
n (%)	**91 (10.4)**	**109 (12.4)**
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]

CNS = central nervous system; WDAE = withdrawal due to adverse event.
[a] Discontinuation of study drug.
Source: Clinical Study Report, p. 194, 748.[8]

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
- spinal cord compression
- pathological fractures
- Analgesic Quantification Algorithm (AQA)
- Brief Pain Inventory (Short Form) (BPI-SF)
- Functional Assessment of Cancer Therapy–General (FACT-G)
- 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.	UNKOWN	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.	UNKOWN	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	[36]
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	[14,15,34,37]
Functional Assessment of Cancer Therapy–General (FACT-G)	Cancer-specific health-related quality of life measure. A 44-item self-administered questionnaire with a 5-point Likert scale response, assessing four categories: physical well-being domain, functional well-being domain, and a composite domain with cancer-specific questions.	YES	3 to 7	[16,38,39]

Instrument	Type	Validated	MCID	References
EuroQol 5-Dimensions Questionnaire (EQ-5D)	A 5-item self-administered, standardized, preference-based, health outcome measure instrument, assessing five dimensions: mobility, self-care, usual activities, pain, and depression.	YES	0.06	[18,19,40]

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 the 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 mg to 150 mg OME per day
5	strong opioids > 150 mg to 300 mg OME per day
6	strong opioids > 300 mg to 600 mg OME per day
7	strong opioids > 600 mg OME per day

OME = oral morphine equivalents.

Chung et al.[36] 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.[4] 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 patients 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.[14,34,37] In addition, a recent study established the MCID at 1.5 to 2.0.[15]

Functional Assessment of Cancer Therapy–General
The FACT-G questionnaire is a health-related quality of life instrument for patients with cancer. FACT-G consists of 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 1993, Cella et al. developed the FACT-G tool and assessed its reliability and validity with 854 cancer patients and 15 oncology specialists. FACT-G was found to be valid, reliable, and sensitive to change.[16] FACT-G has since been used in many RCTs for cancer therapy.[38] The MCID for the FACT-G ranges from 3 to 7.[39]

EuroQoL 5-Dimensions Questionnaire
The 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.[18,19]

Conclusion

Skeletal-related events, 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-G, and EQ-5D are commonly used patient-reported outcome measures that have been validated in cancer patients and for which an MCID has been 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.

1. Introduction

1.1 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 solid tumours (except breast and prostate cancer). To inform this evidence gap, CADTH Common Drug Review (CDR) reviewed and critically appraised available indirect evidence.

1.2 Methods

A literature search was undertaken by CDR to identify any relevant published IDCs. Two relevant publications,[6,7] presenting data from one unique IDC, were included in this section.

The manufacturer provided CADTH with one additional document consisting of a network meta-analysis (NMA) that was, however, already captured by Ford et al.[6,7]

2. Description of Indirect Comparisons Identified

Ford et al.[6,7] assessed the comparative efficacy of denosumab and zoledronic acid and best supportive care or placebo as treatment to reduce the risk of developing SREs in patients with bone metastases from solid tumours (except breast and prostate cancer). Studies were selected for inclusion based on the selection criteria presented in Table 23.

TABLE 23: INCLUSION CRITERIA FOR FORD ET AL.[6,7]

Patient Population	Adult patients with confirmed carcinoma of other solid tumours and evidence of ≥ 1 bone metastasis
Intervention	Denosumab (Xgeva) 120 mg SC every 4 weeks
Relevant Comparators	Bisphosphonates: • Clodronate • Pamidronate • Zoledronic acid Best supportive care
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.

3. Review and Appraisal of Indirect Comparisons

3.1 Review of Ford et al.[6,7]

3.1.1 Objectives and rationale

Ford et al.[6,7] 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.

3.2 Methods

3.2.1 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.

3.2.2 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 two RCTs were included in the systematic review: Henry et al.[4] (denosumab versus zoledronic acid; n = 1,776) and Rosen et al. [41] (zoledronic acid versus placebo; n = 507). For the included study by Henry et al.,[4] the authors of the IDC reported that they had access to data from the manufacturer of denosumab, including a post hoc analysis of the study that excluded patients with multiple myeloma. Details for all included studies are presented in Table 24. Both included trials enrolled adult patients with solid tumours and at least one bone metastasis. Age was similar between trials and ranged from median 60 to 64 years. The majority of patients in all trials had an Eastern Cooperative Oncology Group (ECOG) status of 1 or lower. Non–small cell lung cancer was the most frequent primary tumour type.

TABLE 24: CHARACTERISTICS OF THE INCLUDED STUDIES AND POPULATION IN FORD ET AL.[6]

Studies	Population	Interventions	Outcome
Henry et al. 2011[4]	• Patients aged ≥ 18 years with confirmed solid tumours (except breast and prostate) or multiple myeloma and ≥ 1 bone metastasis or osteolytic lesion • Multi-centre: International • Median age = 60 (18 to 89) years (denosumab) and 61 (22 to 87) years (ZA) • ECOG Status 1 or below = 84% (denosumab) and 82% (ZA) • Primary tumours type: NSCLC = 40% (denosumab) and 39% (ZA); Other = 50% (denosumab) and 51% (ZA) • Previous SREs = 50% in both groups	**Denosumab 120 mg q.4w. (n = 886)** or **Zoledronic acid 4 mg q.4w. (n = 890)** for 7 months	**Primary outcome:** SREs
Rosen et al. 2003b[41]	• Patients aged ≥ 18 years with bone metastases from solid tumours (excluding breast and prostate cancer) • Multi-centre • Median age = 64 years in both groups • ECOG Status 1 or below = 83% (ZA) and 87% (PL) • Primary tumours type: NSCLC = 49%; Other = 51%; in both groups • Previous SREs = 65% (ZA) and 73% (PL)	**Zoledronic acid 4 mg q.3w. (n = 257)** or **Placebo (n = 250)** for 9 months	**Primary outcome:** SREs

ECOG = Eastern Cooperative Oncology Group; NR = not reported; NSCLC = non–small cell lung cancer; PL = placebo; q.3w. = every three weeks; q.4w. = every four weeks; SRE = skeleton-related event; ZA = zoledronic acid.
Source: Ford et al.[6]

3.2.3 Comparators

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

3.2.4 Outcomes

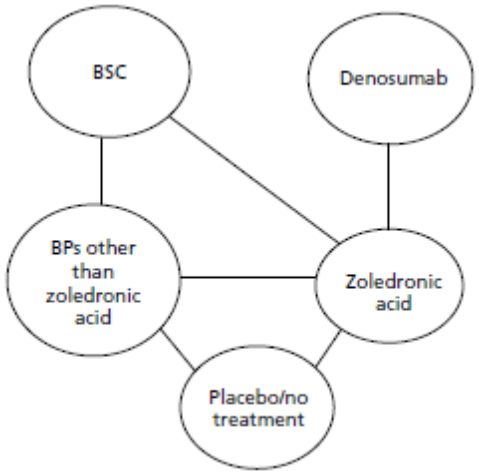
The primary outcomes in all included trials were SREs or skeletal morbidity rates. Pain, health-related quality of life (HRQoL), and adverse events (AEs) figured as outcomes included in the NMA, but were not consistently reported in all included studies.

3.2.5 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.

3.2.6 Evidence network

FIGURE 2: ILLUSTRATING DIAGRAM FOR FORD ET AL. — OTHER SOLID TUMOURS[6]



BP = bisphosphonate.
Source: Ford et al.[6]

3.3 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.

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.

3.4 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 (HR 0.81; 95% CI, 0.68 to 0.96) and placebo (HR 0.49; 95% CI, 0.30 to 0.78).

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 placebo (HR 0.49; 95% CI, 0.30 to 0.78). Results favoured denosumab compared with zoledronic acid, but statistical significance was not reached (HR 0.85; 95% CI, 0.72 to 1.00).

Pain, HRQoL, and AEs figured as secondary outcomes; however, no NMA results were reported. The Ford et al. publication[6,7] 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 Henry et al.,[4] which is already detailed in the main body of this review report.

3.5 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 solid tumours and bone metastasis with a relatively good performance status — possibly better, however, than the majority of real-life patients. Denosumab and zoledronic acid dosing strategies are in line with the Health Canada–approved labels for the products.

The Ford et al.[6] 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. It is unclear what data the authors used for Henry et al.[4] (published versus unpublished data, with or without multiple myeloma) to directly compare denosumab versus zoledronic acid, as the NMA findings were not consistent with those reported by the published study comparing the two treatments (Henry et al.[4]).

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. Two studies were included in the other solid tumours evidence network, which is a small number of trials in relation to the number of nodes of this network. A further layer was added to this uncertainty due to the fact that the populations included a wide range of primary tumour types, increasing heterogeneity significantly.

4. 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. The IDC was likely conducted with methodological rigour; however, some major limitations affect our level of confidence in the findings. NMA results for the direct comparison of denosumab versus zoledronic acid were not consistent with those reported by the included study comparing the two treatments (Henry et al.[4]). Indeed, the findings from Henry et al.[4] demonstrated that denosumab was non-inferior to zoledronic acid with regard to time to first SRE, but the results failed to demonstrate the superiority of denosumab over zoledronic acid once results were adjusted for multiplicity. However, the authors of the NMA conclude that denosumab was associated with a statistically significant reduction in the risk of SREs compared with zoledronic acid. The authors report that they had access to additional data from the manufacturer of denosumab, including a post hoc analysis of the study by Henry et al. that excluded patients with multiple myeloma. This significant difference in the conclusions between analyses further highlights the need to view the results with caution, considering the high level of uncertainty surrounding the NMA brought by the small number of included studies.

5. 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 solid tumours (other than breast and prostate 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.[6,7] assessed the comparative efficacy of denosumab versus zoledronic acid and placebo as treatment to reduce the risk of developing SREs in patients with bone metastases from solid tumours. 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. Pain, HRQoL, and AEs figured as secondary outcomes; however, no NMA results were reported. The Ford et al.[6] IDC was likely conducted with methodological rigour; however, some limitations affect our level of confidence in the findings. This finding is consistent with the secondary analysis of Other Solid Tumours Study 244 results after the exclusion of patients with multiple myeloma, but is not consistent with the primary analysis in which denosumab was non-inferior to zoledronic acid.

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