Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Federal Department of Home Affairs
Federal Office of Public Health FOPH
Health and Accident Insurance Directorate
Section Health Technology Assessment

Health Technology Assessment (HTA)

Scoping Report

Title	Three-monthly vs monthly use of bone-targeting agents in patients with bone metastases
Author/Affiliation	Bubendorfer-Vorwerk H, PhD[1], Konstanski M, MSc[1], Kuchenbecker U, PhD[1], van Stiphout J, MSc[2] [1] Xcenda GmbH, Lange Laube 31, 30159 Hannover, Germany [2] Xcenda Switzerland GmbH, Basel, Switzerland

Bundesamt für Gesundheit
Sektion Health Technology Assessment
Schwarzenburgstrasse 157
CH-3003 Bern
Schweiz
Tel.: +41 58 462 92 30
E-mail: hta@bag.admin.ch

Technology	Bone-targeting agents (zoledronate, ibandronate, denosumab)
Date	08.12.2020
Type of Technology	Pharmaceuticals

Executive Summary

Zoledronate, ibandronate, and denosumab are licensed bone-targeting agents (BTAs) in Switzerland. Patients with bone metastases are treated with BTA every 3-4 week, mostly for the remainder of their life to, reduce cancer-induced pain, fracture risk, hypercalcaemia, and to increase quality of life. Long-term exposure to BTAs is linked to possible severe side effects like hypocalcaemia, renal failure, or osteonecrosis of the jaw. Therefore, the question occurs if the monthly administrations of BTAs in patients with bone metastases should be replaced with a three-monthly administration.

The aim of this scoping report was to assess volume and quality of the available published evidence related to the topic and evaluate the feasibility of conducting a health technology assessment (HTA). A systematic literature search was conducted in Medline, Embase, Evidence-Based Medicine Reviews, and Cochrane Central Register of Controlled Trials. From 5,119 results, 9 results were suitable for inclusion.

One existing economic model was identified but has limitations regarding the relevance for the Swiss context. No evidence was identified for organisational, legal, social, and ethical issues.

In conclusion, there is sufficient evidence to undertake a full HTA.

Zusammenfassung

Zoledronat, Ibandronat und Denosumab sind in der Schweiz zugelassene knochenerhaltende Wirkstoffe (bone-targeting agents, BTAs). Patientinnen und Patienten mit Knochenmetastasen werden alle 3–4 Wochen, meist für den Rest ihres Lebens, mit BTAs behandelt, um krebsbedingte Schmerzen, das Frakturrisiko und Hyperkalzämie zu verringern sowie die Lebensqualität zu erhöhen. Eine langfristige Exposition mit BTAs ist jedoch mit möglichen schweren Nebenwirkungen wie Hypokalzämie, Nierenversagen oder Osteonekrose des Kiefers verbunden. Daher stellt sich die Frage, ob die monatliche Gabe von BTAs bei Patientinnen und Patienten mit Knochenmetastasen

durch eine dreimonatliche Gabe ersetzt werden sollte.

Das Ziel dieses Scoping-Berichts war, Umfang und Qualität der verfügbaren publizierten Evidenz zum Thema zu bewerten und die Durchführbarkeit eines Health Technology Assessment (HTA) zu prüfen. Es wurde eine systematische Literaturrecherche in Medline, Embase, Evidence-Based Medicine Reviews und Cochrane Central Register of Controlled Trials durchgeführt. Von 5119 Ergebnissen waren 9 zur Einbeziehung geeignet.

Ein bestehendes ökonomisches Modell wurde identifiziert, weist jedoch Einschränkungen hinsichtlich der Relevanz für den Schweizer Kontext auf. Es wurde keine Evidenz zu organisatorischen, rechtlichen, sozialen und ethischen Fragen ermittelt.

Zusammenfassend lässt sich festhalten, dass es genügend Evidenz gibt, um ein vollständiges HTA durchzuführen.

Résumé

Le zolédronate, l'ibandronate et le denosumab sont des BTA (bone-targeting agents, en français « agents ciblant les os ») autorisés en Suisse. Les patients atteints de métastases osseuses sont traités avec des BTA toutes les trois à quatre semaines, généralement pendant le reste de leur vie, pour réduire la douleur causée par le cancer, le risque de fracture et l'hypercalcémie ainsi qu'améliorer leur qualité de vie. L'exposition à long terme aux BTA peut cependant produire des effets secondaires comme une hypocalcémie, une insuffisance rénale ou une ostéonécrose de la mâchoire. C'est pourquoi la question se pose de savoir si les administrations mensuelles de BTA chez des patients atteints de métastases osseuses devraient être remplacées par des administrations trimestrielles.

Le présent rapport de scoping vise à identifier la quantité et la qualité de preuves scientifiques publiées à ce sujet et d'évaluer la faisabilité d'une évaluation des technologies de la santé (ETS ou HTA pour health technology assessment). Une recherche bibliographique systématique a été effectuée dans Medline, Embase, Evidence-Based Medicine Reviews et Cochrane Central Register of Controlled Trials. Sur 5119 résultats, 9 ont été jugés adaptés.

Un modèle économique a été identifié, mais sa pertinence pour le contexte suisse est limité. Aucune étude n'a été identifiée concernant les aspects organisationnels, légaux, sociaux et éthiques.

En conclusion, il existe suffisamment de preuves publiées pour mener une HTA complète.

Executive Summary

Il zoledronato, l'ibandronato e il denosumab sono medicamenti omologati in Svizzera per l'inibizione del riassorbimento osseo (bone-targeting agents, BTA). I pazienti affetti da metastasi ossee sono trattati con BTA ogni 3-4 settimane, soprattutto per ridurre, per il resto della loro vita, il dolore causato dal cancro, il rischio di frattura, l'ipercalcemia e per aumentare la qualità della loro vita. Una lunga esposizione ai BTA è legata a possibili gravi effetti collaterali come ipocalcemia, insufficienza renale o osteonecrosi della mascella. Sorge pertanto la domanda se sia preferibile una somministrazione trimestrale invece che mensile di BTA in pazienti affetti da metastasi ossee.

L'obiettivo del presente rapporto di scoping era di valutare la quantità e la qualità dell'evidenza scientifica disponibile sull'argomento e di accertare la fattibilità di un Health technology assessment (HTA). Una ricerca sistematica della letteratura è stata svolta in Medline, Embase, in riviste mediche scientifiche nonché nel registro centralizzato Cochrane degli studi controllati). 9 dei 5119 risultati avevano i requisiti per essere inclusi nel rapporto. Le evidenze riscontrate sul zoledronato, sull'ibandronato e sul denosumab erano rispettivamente moderate oppure scarse o non erano disponibili.

È stato identificato un modello economico esistente, ma di rilevanza limitata per il contesto svizzero. Non sono state rilevate evidenze per gli aspetti organizzativi, legali, sociali ed etici.

Per concludere, vi è un'evidenza sufficiente per svolgere un HTA completo.

Table of contents

Abbreviations and acronyms

AE	adverse event
BC	breast cancer
BM	bone metastasis
BP	Bisphosphonate
BPI	Brief Pain Inventory
BTA	bone-targeting agent
CCTR	Cochrane Central Register of Controlled Trials
CDSR	Cochrane Database of Systematic Reviews
CHEC	Consensus Health Economics Checklist
CTX	C-terminal telopeptide
DARE	Database of Abstracts of Reviews of Effects
EBMR	Evidence-Based Medicine Reviews
ECOG	Eastern Cooperative Oncology Group
FOPH	Federal Office of Public Health
HAS	Haute Autorité de Santé
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IV	intravenous
LY	life-year
LYG	life-year gained
MA	meta-analysis
mBC	metastatic breast cancer
MM	multiple myeloma
mPC	metastatic prostate cancer
NA	not applicable
NHS	National Health Service
NHSEED	NHS Economic Evaluation Database
NTX	N-terminal telopeptide
ONJ	osteonecrosis of the jaw
PC	prostate cancer
PICO	population, intervention, comparator, outcome
PK	pharmacokinetics

P1NP	propeptide of type 1 procollagen
QALY	quality-adjusted life-year
RANKL	receptor activator of nuclear factor kappa-b ligand
RCT	randomized controlled trial
ROB	risk of bias tool
SC	subcutaneous
SLR	systematic literature review
SmPC	Summary of Medical Product Characteristics
SMR	skeletal morbidity rate
SRE	skeletal-related event
SSE	symptomatic skeletal event
US	United States
VRS	visual rating scale
ZA	zoledronate

Tables

Figures

Appendix

Objective of the HTA scoping report

The Federal Office of Public Health (FOPH) is reviewing the 12-weekly vs the 4-weekly use of bone-targeting agents (BTAs) in cancer patients with bone involvement.

The process to evaluate health technologies involves multiple phases: (1) the pre-scoping phase, (2) the scoping phase, and (3) the health technology assessment (HTA) phase. This document represents the outcome of the scoping phase. The objective of this scoping report is to identify evidence for comparing the 4-weekly vs. the 12-weekly use of BTAs in cancer patients with bone involvement by conducting a systematic literature search. To achieve that, a central research question and sub-questions are presented to determine the existing evidence for the main HTA domains (ie, clinical effectiveness/safety, costs/budget impact/cost-effectiveness, legal/social/ethical, and organisational issues). The target population, the appropriate comparator, and the relevant health outcomes are defined.

The systematic literature search strategy directs the amount and types of studies generated during the extraction. Based on quantity and quality of the extracted evidence, the feasibility of pursuing an HTA is judged. Analysis of the individual study outcomes is not the objective of the scoping report.

1 Policy question and context

The BTAs zoledronate, ibandronate, and denosumab are used in cancer patients with bone metastases. In combination with standard antineoplastic therapy the use is aimed to reduce risk of fracture and bone pain, hypercalcemia, and to increase the quality of life. A potential impact on tumour growth is also discussed. However, long-term exposure to these agents is associated with potentially severe side effects such as hypocalcaemia, renal failure, or osteonecrosis of the jaw (ONJ). Consequently, the question is whether the current indication of monthly administration of these 3 BTAs should be replaced by a 3-monthly administration, which would require an update in the Summary of Medical Product Characteristics (SmPC) and a subsequent limitation in reimbursement to 1 administration every 3 months.

2 Research questions

1) Is the administration of BTAs in cancer patients with bone involvement every 12 weeks (or longer) non-inferior to monthly administration?
    a. Is zoledronate or ibandronate infusion every 12 weeks (or longer) non-inferior to zoledronate or ibandronate infusion every 3 to 4 weeks?
    b. Is denosumab subcutaneously (SC) every 12 weeks (or longer) non-inferior to denosumab SC every 4 weeks?
2) What impact on healthcare does administration every 12 weeks (or longer) have compared to monthly administration from economic, legal, social, ethical, and organizational perspectives?

The term “non-inferior” refers to efficacy and means that a new experimental treatment (here: administration of BTAs every 12 weeks) is not unacceptably less efficacious within predefined margins than the control or standard treatment that is already in use (here: administration of BTAs every 3 to 4 weeks).[1 2]

3 Medical background

Bone is a frequent site of cancer metastases. The relative incidence of bone metastases (BM) in metastatic diseases has been reported to range between 65% and 75% in breast cancer (BC), 65% and 75% in prostate cancer (PC), 60% in thyroid cancer, 40% in bladder cancer, 20% and 25% in renal cell carcinoma, and 14% and 45% in melanoma. Some reported rates of BM may be even higher (eg, more than 90% of patients with certain forms of metastatic prostate cancer [mPC] have BM).[3] The most common primary cancer forms leading to BM are BC and PC.[3 4] Of all 56,506 new cancer cases estimated in 2018 in Switzerland, 7,029 (12.4%)

were cases with BC and 6,781 (12.0%) cases with PC. Being the 2 cancer types with the highest absolute incidence rate, BC and PC have the highest 5-year prevalence rates among all cancer forms.[5]

Bone is the stabilizing framework of the body and is formed by osteoblasts and osteoclasts. During bone development, osteoblasts built up new bone while osteoclasts disassemble and resorb old bone cells, which requires tight regulation of bone remodeling. Bone markers like N-terminal telopeptide (NTX) or propeptide of type 1 procollagen (P1NP) are indicative for bone resorption and bone formation, respectively, and thus facilitate monitoring of bone turnover.[6]

Two mechanisms contribute to malignant bone involvement of cancer patients. First, cancer cells can stimulate osteoclasts, leading to higher resorption rates of bone cells without new bone cells being built up. This de-stabilizes and weakens the bone structure so that the bone can more easily break. Second, stimulation of osteoblasts by cancer cells might lead to increased cell growth without older bone cells being resorbed first. Although this process hardens the bone, blastic lesions and sclerosis can occur, causing the affected bone to break more easily than normal bone. Thus, BM are classified as osteolytic, osteoblastic, or mixed according to the primary mechanism of interference with normal bone remodelling.[3]

Although for many cancers (eg, BC, PC), survival with BM is better compared to survival with, for example, metastases in the liver, the presence of BM significantly affects a patient's morbidity. BM can lead to skeletal-related complications, such as pain or pathologic fractures. Skeletal-related trial endpoints are composite measures of events collectively termed skeletal-related events (SREs). SREs are defined as pathologic fractures, spinal cord compression, necessity for radiation to bone (for pain or impending fracture), or surgery to bone.[7 8]

Pathological fractures occur in 10% to 30% of all cancer patients, with proximal parts of the long bones being the most frequent fracture site and the femur accounting for over half of all cases.[9] Pathologic fractures due to BM are especially reported for patients with BC (60%), leading to impaired mobility and suffering of pain.[9 10]

Bone pain from BM is caused by inflammatory or mechanical reasons like fractures and is one of the most common type of pain from cancer. Bone pain is poorly localized, worse at night, and not necessarily relieved with sleep or lying down.[11] Back pain caused by spinal cord compression is most commonly reported for BC (20%–30%) and lung cancer (15%).[3]

Other symptoms include bone marrow aplasia and hypercalcemia, with the latter as the most common metabolic complication of the disease.[4] In final stages, cancer-induced hypercalcemia can lead to cardiac arrhythmias, acute renal failure, severe neurological impairment, and death.[4 12]

Due to pain, impaired general health status, and restricted physical abilities, BM not only affect the morbidity of cancer patients but also significantly lower their quality of life.[13]

As described above, considering that up to 75% of metastatic cancer patients may eventually develop BM, treatment of these patients remains an important health issue in Switzerland.[14]

4 Technology

4.1 Technology description

In potential cases of BM, basic screening needs to be performed when one of the signs and symptoms described in Section 3 are present: a complete blood cell count to evaluate for anaemia and myelosuppression, thrombocytopenia, albumin-corrected serum calcium, phosphorus, 25-hydroxyvitamin D, alkaline phosphatase, creatinine, and thyroid-stimulating hormone and, in some cases, parathyroid hormone level to identify bone turnover. This must be complemented with imaging data from, for example, radiographs, bone scintigraphy, tomography, and/or magnetic resonance.[3]

Treatment decisions depend on several factors like location and progression of the BM, pre-treatment history, and manifestation of symptoms and general health status but mostly include administration of BTAs such as zoledronate, ibandronate, or denosumab.[15] Bisphosphonates (BPs) like zoledronate and ibandronate inhibit osteoclast-mediated bone resorption, whereas denosumab as a receptor activator of the nuclear factor kappa B (RANK) ligand inhibitor reduces the activity of bone-resorbing osteoclasts.[16-18]

In Switzerland, the licensed BTAs are zoledronate (third-generation BP), ibandronate (second-generation BP), and denosumab. BTAs are administered in patients with BM from solid tumours or in patients with MM to prevent SREs and treat cancer-induced hypercalcaemia. Zoledronate and ibandronate are reimbursed by the compulsory health insurance. Zoledronate is approved for the prevention of SREs in patients with BM of solid tumours. Ibandronate is only licensed for BM due to BC. Denosumab is reimbursed by the compulsive health insurance and limited to the treatment of patients with bone metastases of solid tumours in combination with an antineoplastic standard of care.[16-18] According to the label, the approved dosing for ibandronate is 6 mg and for zoledronate is 4 mg during an infusion of 15 minutes every 3 to 4 weeks.[16 17] The approved dosing for denosumab is 120 mg every 4 weeks for malignant disease metastatic to the bone. It is injected SC. Unlike BPs, denosumab does not accumulate in the bone, and its effect is reversible in the short term after treatment discontinuation.[18]

The side effects are similar, including nausea, diarrhoea, weakness, and, in rare cases, ONJ which seems to be time and dose depending on the BTA administration.[15-18] For denosumab, fatal cases of hypocalcaemia have been reported.[19] Notably, studies in osteoporosis patients have shown a rapid rebound in bone turnover after denosumab treatment that is associated with an increase in vertebral fractures and this rebound effect

is also in discussion regarding the treatment with denosumab of cancer patients.[15 20] In Switzerland, however, 70.9% of physicians reported prescribing BTAs and initiating treatment with denosumab in 78.5% of patients.[14]

Recently published information showed that there is evidence that after an initial phase of 3 to 6 months, these agents may also be administered every 12 weeks, which could help to avoid adverse events (AEs) associated with 4-weekly administration.[21 22] Currently it is clinical practice in Switzerland that physicians initiate the admission of BTAs in cancer patients with BM as monthly therapy and might switch over to a less frequent dosing after one or two years. Both, patients and treating physicians, seem willing to optimize routine care with BTAs.[14]

It is therefore of interest to examine outcomes of a 12-weekly use of these BTAs compared to a 4-weekly use in patients with BM.

4.2 Alternative technologies

Treatment of BM in cancer patients often requires multidisciplinary therapy management. Beside BTAs, treatment may also include radiotherapy, radioisotope therapy, hormone therapy, chemotherapy, and surgical therapy.[14 15]

Radiotherapy is oftentimes the chosen treatment for localised bone pain caused by BM. Depending on the type of cancer, reported response rates go up to 85% and complete pain relief is attained in half of these patients. Radioisotope therapy can be performed in cancer patients with more diffuse bone pain and to save normal tissue for unnecessary irradiation. However, many patients experience widespread pain or a recurrence of bone pain after radiotherapy.[15 23]

Therapy with hormone therapy or chemotherapy is mainly applied to treat the primary cancer and thus depends on the cancer type, tumour growth rate, and general health of the patient. Consequently, both treatment procedures have an impact on both the primary tumour and their derived BM. Additionally, other primary cancer forms like PC can be treated by inhibition of the hormones needed for the tumour to grow.[24]

However, as a resistance to systemic treatment of the underlying cancer disease can arise over time and enables the development of metastases, a change of therapy might be necessary.[15]

If bone fractures, paralysis, or severe pain occur, surgery to can be performed to stabilize and reconstruct the broken part of the bone. For example, this might comprise injection of bone cement to the damaged bone as a minimally invasive surgery event.[25]

5 PICO

Population	• Patients with cancer-related BM from solid tumours • Patients with MM with bone involvement
Intervention	• I 1: Infusion of zoledronate (all Swissmedic-licensed medicinal products) every 3–4 weeks (dosing interval per SmPC) • I 2: Infusion of ibandronate (all Swissmedic-licensed medicinal products) every 3–4 weeks (dosing interval per SmPC) • I 3: SC injection of denosumab (all Swissmedic-licensed medicinal products) every 4 weeks (dosing interval per SmPC)
Comparator	• C 1: Infusion of zoledronate (all Swissmedic-licensed medicinal products) every 12 weeks (or longer intervals) • C 2: Infusion of ibandronate (all Swissmedic-licensed medicinal products) every 12 weeks (or longer intervals) • C 3: Subcutaneous injection of denosumab (all Swissmedic-licensed medicinal products) every 12 weeks (or longer intervals)
Outcomes (clinical)	• All-cause mortality • Quality of life • SREs, including fractures, spinal cord compression, surgery/operation, radiotherapy • Bone pain • Bone-related markers/markers of bone turnover, including bone mineral density, N-/C-telopeptide-related markers • Suppression of bone remodelling • Treatment-related AEs, specifically ONJ, cardiac events, toxicity (specifically, renal) / renal impairment, hypocalcaemia, study discontinuation due to AEs • Rebound effect
Outcomes (health economic)	• Costs (direct, medical, non-medical) • ICER, QALY; LY and budget impact • Costs per clinical event, LYG, QALY • Cost savings • Utilities • Healthcare resource utilization
Study designs/ types (clinical)	• RCTs and re-analysis of RCTs • HTA reports, SLRs, and meta-analyses from RCTs (for hand-searching of reference lists) • Non-randomized controlled trials (for long-term effects and if no RCTs are available)

Study designs/ types (health economic)	• All economic evaluations, such as:
	  ○ Budget-impact
	  ○ Cost-benefit
	  ○ Cost-utility
	  ○ Cost-effectiveness
	  ○ Cost-comparison
	  ○ Cost-minimization

Note: For assessment of the legal, social, ethical, and organizational aspects of the scoping, all relevant outcomes and study designs/types will be considered to help answer the research questions. **Key:** AE – adverse event; BM – bone metastases; TA – health technology assessment; ICER – incremental cost-effectiveness ratio; LY – life-year; LYG – life-year gained; MM – multiple myeloma; ONJ – osteonecrosis of the jaw; QALY – quality-adjusted life-year; RCT – randomized controlled trial; SC – subcutaneous; SLR – systematic literature review; SmPC – Summary of Medical Product Characteristics; SRE – skeletal-related event.	

6 HTA key questions

For the evaluation of the technology, the following key questions covering the central HTA domains, as designated by the European Network for Health Technology Assessment Core Model (clinical effectiveness, safety, costs, cost-effectiveness, budget impact, legal, social, ethical, and organisational aspects), are addressed:

1. Is the 12-weekly use of BTAs effective/efficacious compared to the 4-weekly use?
2. Is the 12-weekly use safe compared to the 4-weekly use of BTAs?
3. What are the costs of the 12-weekly use vs 4-weekly use?
4. How cost-effective is the less frequent use of BTAs?
5. What is the budget impact of the 12-weekly vs 4-weekly use?
6. Are there legal, social, or ethical issues related to the less frequent administration of BTAs?
7. Are there organisational issues related to the less frequent administration of BTAs?

6.1 Additional question(s)

None

7 Methodology of literature search

7.1 Databases and search strategy

The parameters described below will be applied to all questions, except when noted otherwise.

To address the introduced research questions, relevant literature in line with the population, intervention, comparators, and outcomes (PICO) scheme had to be obtained. Relevant literature was identified through a systematic literature search and additional hand search. For the systematic literature review, the following databases were searched via OVID:

- Medline
- Embase
- Cochrane Database of Systematic Reviews (CDSR)
- Database of Abstracts of Reviews of Effects (DARE)
- Health Technology Assessment (HTA)
- National Health Service (NHS) Economic Evaluation Database (NHSEED)

- Cochrane Central Register of Controlled Trials (CCTR)

The search strategies for each database were developed in consultation of an information specialist. A list of search terms based on the PICO scheme was compiled to support the development of the search strings. The queries were developed as a combination of keywords and subject headings in line with the respective database. Complete search strategies are shown in Appendix 1. No search filters were applied. The selection of relevant articles was done on the PIC level, whereas search filters typically are used for outcomes or study types. To test the search strategy, the search results were compared to a defined set of sentinel articles.

The database searches were conducted on 27 May 2020.

All publications between 2000 and the day of search (27th of May 2020) were included. For conference abstracts, the search was limited to the years 2015 to 2020. We included only publications in English, German, and French. For the screening of the database results, predefined inclusion and exclusion criteria were applied (Appendix 2). Duplicates (n=1,206) were removed before screening.

All hits were screened by 2 independent reviewers according to the inclusion and exclusion criteria. Differences in study selections were settled via consensus at each stage of the selection process. A third reviewer was consulted if no consensus could be reached. For the title and abstract screening, Distiller SR software was used. Reasons for exclusion were documented at the full-text review stage. A list of all these excluded hits with exclusion reason can be found in Appendix 3. During the full-text screening phase, reference lists were cross-checked to find any other studies or systematic reviews that were not captured with the literature search.

In the case that a reference identified in one domain was also of relevance for another domain, this reference was forwarded. Systematic literature reviews (SLRs) and meta-analyses were included to cross-check reference lists for further relevant publications.

If no full-text of an included reference was available, published data from official websites (clinicaltrial.gov or the company website) were used if accessible.

7.2 Other sources

Google Scholar was searched by hand to check for any publications possibly missed by the database search. Websites of major national HTA agencies (Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen [IQWiG], Canadian Agency for Drugs and Technologies in Health [CADTH], Haute Autorité de Santé [HAS], National Institute for Health and Care Excellence [NICE]) were searched for additional information. Relevant literature regarding the legal section of this report was obtained through a search on the Swiss legislation database. As search terms, names of the drugs (zoledronate, ibandronate, and denosumab) were entered into the database.

Conference abstracts were only searched for in the database search to make sure that the related full publications were included in the results. Therefore, Google Scholar was searched by hand for the corresponding publications of the identified conference abstracts. If no full publication was available, the reason of exclusion “no full text available” was noted.

7.3 Quality of evidence assessment

For the preliminary critical appraisal, the methodological quality of the included studies was assessed and summarized using recognized standards for the systematic evaluation of scientific studies.

The quality analysis of the selected randomized controlled trials (RCTs) was performed using the risk of bias (RoB) tool reported in the Cochrane Handbook for Systematic Reviews of Interventions.[26] An unclear RoB was determined in the case where not enough data for a precise assessment was present. If the RoB was evaluated as high, the quality of the evidence from this study was assumed to be low.

The quality analysis of the cost-effectiveness study was achieved using the Consensus Health Economics Checklist (CHEC). The CHEC is a 19-item checklist with questions regarding the economic evaluation that can be answered with “yes” and “no.” In the case of insufficient available data, the answer “no” was chosen.[27]

8 Synthesis of evidence base

8.1 Evidence base pertaining to efficacy, effectiveness, and safety

To identify evidence for efficacy, effectiveness, and safety, systematic literature searches in all the previously mentioned databases were performed. The results of the systematic literature searches that were performed are presented in Figure 1.

5,119 records were identified in all databases. Of those, 5,046 records were excluded based on their title and abstract, while 73 were reviewed for eligibility. By assessment of the full texts, 56 records were excluded (see Prisma flowchart for detailed exclusion details: Figure 1).

No further studies were identified through hand search or from reference lists of included SLRs (n=8).[21 22 28-32] An overview is presented in Appendix 4.

During the screening, we also identified ongoing RCTs that would fulfil our predefined inclusion criteria but are not finished yet (Appendix 5). These ongoing RCTs might be considered as additional data sources if the results are published before the end of the HTA. Notably, the SAKK96/12 trial is a non-inferiority phase 3 trial led by the Swiss Group for Clinical Cancer Research with recruitment sites in Switzerland, Austria, and

Germany. Thus, the data would especially provide evidence for the utilization of BTAs in Switzerland. The estimated completion date of the trial is December 2022.[33]

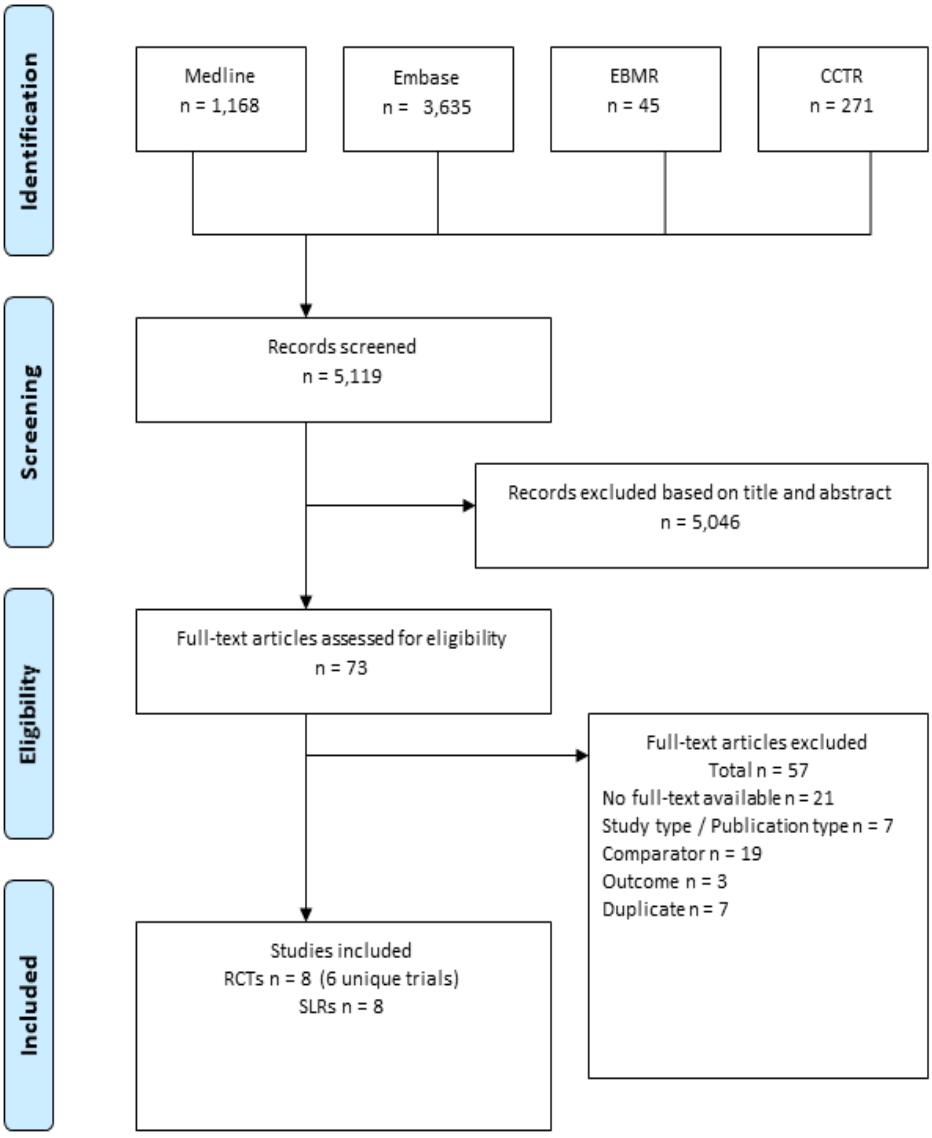
In total, we identified 6 unique RCTs (from 8 publications) reporting on clinical efficacy, effectiveness, and safety of administration of less frequent dosing with BTAs (every 12 weeks or greater intervals) compared to the standard dosing regimen (every 3–4 weeks) (Table 1). The majority of RCT information was found for zoledronate, followed by denosumab. No trial was identified for ibandronate.

Table 1. Included studies identified by the systematic literature search

	Ibandronate	Zoledronate	Denosumab
Identified trials	No trials identified	4 RCTs[34-37]	2 RCTs[38-41]

8.1.1 PRISMA flow diagram

Figure 1. PRISMA flowchart of the efficacy, effectiveness, and safety systematic literature search



Key: CCTR – Cochrane Central Register of Controlled Trials; EBMR – Evidence-Based Medicine Reviews; RCT – randomized controlled trial; SLR – systematic literature review.

8.1.2 Evidence table

The characteristics of the included RCTs are presented in Table 2 (zoledronate) and Table 3 (denosumab).

Table 2. RCTs with zoledronate: study characteristics

Trial/reference	Study design	Population/N	Intervention	Comparator	Efficacy outcomes	Safety outcomes	RoB
Hortobagyi et al (2017)[37] OPTIMIZE-2 *NCT00320710*	• Phase 3, randomized (1:1), double-blind, multicentre, national, non-inferiority • 102 centres in the US • 1 year of study treatment • 1 year of follow-up	• mBC • Pretreated with BPs n=416	Zoledronate (IV) every 4 weeks n=200	Zoledronate (IV) every 12 weeks n=203 Placebo n=13	• SREs • Pain (BPI, analgesic score) • Bone markers • SMRs	Incidence of AEs	Low
Himelstein et al (2017)[36] CALGB 70604 *NCT00869206*	• Phase 3, randomized (1:1), open-label, multicentre, national, non-inferiority • 269 sites in the US • 2 year of study treatment • 2 years of follow-up	• mBC, mPC, MM with bone involvement • Pretreated with BPs n=1,822	Zoledronate (IV) every 4 weeks n=260	Zoledronate (IV) every 12 weeks n=253	• SREs • Pain (BPI) • ECOG PS • SMRs • Bone markers	Incidence of AEs, especially ONJ and renal dysfunction	Moderate
Amadori et al (2013)[35] ZOOM *NCT00375427*	• Phase 3, randomized (1:1), open-label, multicentre, national, non-inferiority • Study sites in Italy • 1 year of study treatment • 1 year of follow-up	• mBC • Pretreated with zoledronate n=430 (n=425 finished the study)	Zoledronate (IV) every 4 weeks n=216	Zoledronate (IV) every 3 months n=209	• SMRs • SREs • Pain (BPI, VRS, analgesic score) • ECOG PS	Incidence of AEs, especially ONJ and renal dysfunction	Moderate
Novartis (2012)[34] *NCT00424983*	• Phase 1, randomized (1:1), open-label, multicentre, national • 7 study sites in the US • 1 year of study treatment	• mBC, MM with bone involvement • Pretreated with zoledronate n=18	Zoledronate (IV) every 4 weeks	Zoledronate (IV) every 12 weeks	• SREs • PK parameters	Incidence of AEs	High

Key: AE – adverse event; BM – bone metastases; BP – bisphosphonate; BPI – Brief Pain Inventory; ECOG PS – Eastern Cooperative Oncology Group performance status; IV – intravenous; mBC – metastatic breast cancer; MM – multiple myeloma; mPC – metastatic prostate cancer; ONJ – osteonecrosis of the jaw; PK – pharmacokinetics; RCT – randomized controlled trial; RoB – risk of bias; SMR – skeletal morbidity rate; SRE – skeletal-related event; US – United States; VRS – visual rating scale.

Table 3. RCT with denosumab: study characteristics

Trial/reference	Study design	Population/N	Intervention	Comparator	Efficacy outcomes	Safety outcomes	RoB
Lipton et al (2007 and 2008)[40 41] *NCT00091832*	• Phase 2, randomized (1:1:1:1:1:1), multidose, multicentre, international • Blinding of assigned dose and frequency for patients receiving denosumab • 56 centres in North America, Australia, and Europe • 24 weeks of treatment • 32 weeks of follow-up	• mBC • Treatment-naïve n=255	Denosumab (SC) every 4 weeks (30 mg [n=43], 120 mg [n=42] or 180 mg [n=42])	Denosumab (SC) every 12 weeks (60 mg [n=42] or 180 mg [n=42] or BP [IV] every 4 weeks [n=43])	• SREs • Bone markers	Incidence of AEs, especially hypercalcaemia	High
Fizazi et al (2009 and 2013)[38 39] *NCT00104650*	• Phase 2, randomized (1:1:1), open-label, multicentre, international • 26 centres in North America and Europe • 25 weeks of treatment • 32 weeks of follow-up	• mBC, mPC, MM with BM • Pretreated with BPs n=111	BP (IV) every 4 weeks (n=17)	Denosumab (SC) 180 mg every 12 weeks (n=16) or 4 weeks (n=17)	• SREs • Bone markers	Incidence of AEs, especially hypercalcaemia	High
Key: AE – adverse event; BM – bone metastases; BP – bisphosphonate; IV – intravenous; mBC – metastatic breast cancer; MM – multiple myeloma; mPC – metastatic prostate cancer; RCT – randomized controlled trial; RoB – risk of bias; SC – subcutaneous; SR – skeletal-related event.							

8.1.3 Findings regarding efficacy, effectiveness, and safety

Findings regarding efficacy, effectiveness, and safety of de-escalated zoledronate

Of the 4 RCTs investigating the de-escalation of zoledronate, 3 were phase 3 studies with 416 (OPTIMIZE-2),[37] 430 (ZOOM),[35] and 1,822 patients (CALGB 70604)[36], while 1 trial (NCT00424983)[34] was a phase 1 study with 18 patients. In total, 2,642 patients were treated with zoledronate in all identified RCTs. In all 4 studies, the patients were randomly assigned (1:1) to either 4-weekly or 12-weekly treatment with zoledronate. OPTIMIZE-2 was the only double-blinded study; the other trials were open-label. National studies were performed in multiple centres in the United States (US) (OPTIMIZE-2, CALGB 70604, or NCT00424983) or in Italy (ZOOM). Patients with metastatic breast cancer (mBC) were included in all studies. Patients with BM due to MM were additionally included in the NCT00424983 trial and patients with metastatic prostate cancer (mPC) to the CALGB 70604 trial. All patients were previously treated with BPs before entering the study. Thus, most evidence for zoledronate is available for pretreated BC patients with BM.

Regarding clinical outcomes, all 4 studies comparatively investigated the incidence of SREs. No clear distinction between asymptomatic and symptomatic fractures were made in 3[34 35 37] of 4 studies. Differences in skeletal morbidity rates (SMRs) were analysed in all phase 3 RCTs. Additionally, these studies also analysed changes in pain by using the Brief Pain Inventory (BPI) questionnaire. Furthermore, 2 studies (CALGB 70604, ZOOM) monitored changes in general health via the Eastern Cooperative Oncology Group (ECOG) performance status (PS). All phase 3 studies compared bone turnover by analysis of bone markers as surrogate endpoints. For safety outcomes, the incidence of AEs was assessed in all 4 trials.

However, limitations exist that affect the quality of evidence. The NCT00104650 trial is a phase 1 study with only 9 patients in each treatment arm, resulting in low statistical study power. The treatment duration varied between the phase 3 trials, although study treatment duration was at least 1 year for all of them. Importantly, the CALGB 70604 and ZOOM trials are open-label studies with differences in frequency of clinic visits that were mainly determined by the dosing schedule. On one hand, this could introduce a detection bias for AEs in the 4-week group, but on the other hand, patient-reported outcomes in the 12-week group like the pain assessment could be biased as well. Notably, most data are present for patients with mBC. Additionally, none of the trials were international and/or included patients from Switzerland. Thus, convincing evidence of the effectiveness of 12-week dosing vs 4-week dosing with zoledronate is limited for Swiss patients with PC or MM and BM. The full RoB assessment can be found in Appendix 6.

Findings regarding efficacy, effectiveness, and safety of de-escalated denosumab

We identified 2 phase 2 studies investigating the treatment effects of different denosumab doses with 255 (NCT00091832)[40 41] and 111 patients (NCT00104650).[38 39] Both multidose studies composed treatment arms of 4-weekly dosing (NCT00091832: 43 patients; NCT00104650: 38 patients) and 12-weekly dosing (NCT00091832: 43 patients; NCT00104650: 36 patients) with 180 mg denosumab, although they were not designed as non-inferiority studies. However, it should be noted that denosumab is licensed in Switzerland as monthly therapy with 120 mg. The identified studies did not provide a comparison of 4-weekly treatment with 120 mg vs. 12-weekly treatment with 120 mg denosumab, thus the comparison of the 180 mg denosumab dosing schedules were considered. The patients of both studies were randomly assigned to one of the treatment arms, although information whether the allocation was concealed is missing. While the patients in the NCT00091832 trial were blinded regarding their treatment with denosumab, NCT00104650 was an open-label trial. Both studies were performed internationally, including study centres in North America and Europe. Only patients with mBC were included in NCT00091832, while NCT00104650 additionally included patients with mPC and MM with bone involvement. Moreover, patients in NCT00091832 were treatment-naïve while the patients in NCT00104650 were pre-treated with BPs.

Regarding clinical outcome, both studies analysed the incidence of SREs. SREs were defined as ≥ 1 of the following: pathological bone fracture, spinal cord compression, surgery, or radiation therapy to bone (including the use of radioisotopes). No differentiation between asymptomatic and symptomatic fractures were made. Additionally, both studies investigated bone turnover by analysis of the bone markers NTX and CTX as surrogate endpoints. For safety outcomes, the incidences of AEs, especially hypercalcaemia and hypocalcaemia, were assessed in both trials.

Several factors limit the quality of evidence due to the heterogeneity of the studies. In NCT00091832, the focus was on the dosing and frequency of denosumab administration, explaining the multiple study arms. In NCT00104650, the focus was on the comparison of denosumab vs BPs and thus results of both denosumab arms were compared to those of the zoledronate. Consequently, the number of patients comparing 4-weekly dosing with 12-weekly dosing of denosumab is quite low, resulting in low statistical power, especially regarding rare events, such as severe AEs. Additionally, the patients differed between both studies regarding pre-treatment with BPs. Moreover, the open-label nature of NCT00104650 may lead to reporting bias. The full RoB assessment can be found in Appendix 6.

8.2 Evidence base pertaining to costs, cost-effectiveness, and budget impact

Search and selection regarding costs, budget impact, and cost-effectiveness were conducted in Medline, Embase, and Evidence-Based Medicine Reviews (EBMR), which includes the databases CDSR, DARE, HTA, and NHSEED.

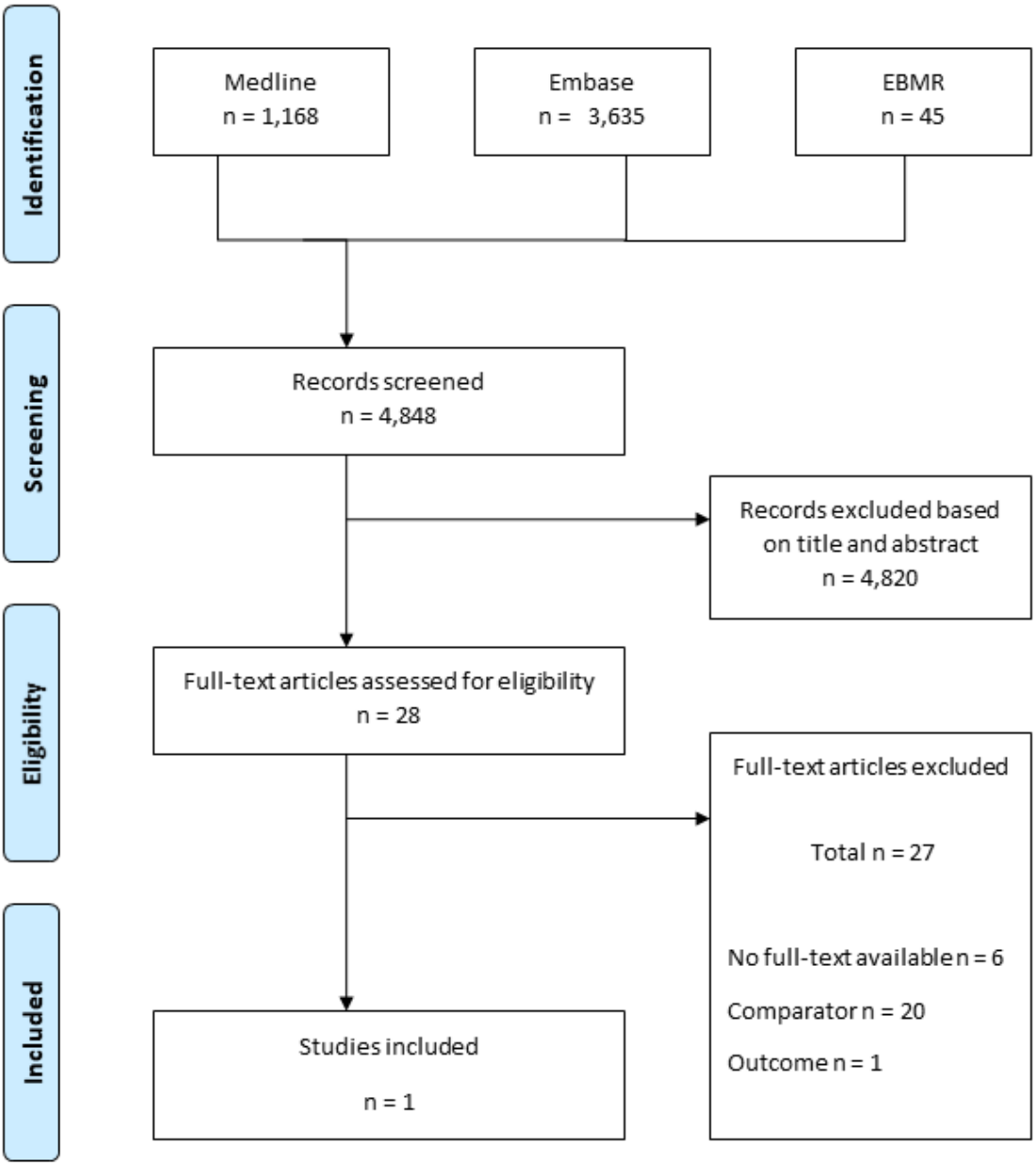
The costs, budget impact, and cost-effectiveness searches resulted in 4,848 unique records (Medline: 1,168 records; Embase: 3,635 records; EBMR: 45 records). In total, 4,820 records were excluded by title abstract screening, resulting in 28 full-text articles to be assessed for eligibility. No additional literature was found by hand search. In total, 27 full-text articles were excluded based on no full-text availability (n=6), no comparator of interest (n=20), and no outcome of interest (n=1).

One study assessed the cost-effectiveness of 4-weekly zoledronate, 12-weekly zoledronate, and 4-weekly denosumab in women with BC and BM and was therefore included (Shapiro, 2017).[42] Study characteristics are shown in Table 4.

No additional studies or systematic reviews were identified by hand searching the reference lists. The PRISMA flow diagram is shown in Figure 2.

8.2.1 PRISMA flow diagram

Figure 2. PRISMA flowchart of the costs, cost-effectiveness, and budget impact of the systematic literature search



Key: EBMR – Evidence-Based Medicine Reviews.

8.2.2 Evidence table

Table 4. Economic study: study characteristics

Author/affiliation	Charles L. Shapiro, Icahn School of Medicine, Mt Sinai, NY; James P. Moriarty, Paul J. Novotny, and Bijan J. Borah, Mayo Clinic Cancer Center; Paul J. Novotny, Mayo Clinic, Rochester, MN; Stacie Dusetzina, University of North Carolina at Chapel Hill, Chapel Hill, NC; Andrew L. Himelstein, Helen F. Graham Cancer Center and Research Institute; Stephen S. Grubbs, Christiana Care NCI Community Oncology Research Program, Newark, DE; and Jared C. Foster, University of Michigan, Grand Rapids, MI
Title	Cost-effectiveness analysis of monthly zoledronic acid, zoledronic acid every 3 months, and monthly denosumab in women with breast cancer and skeletal metastases: CALGB 70604 (alliance)
Year of publication	2017
Publication source	Journal of Clinical Oncology
Study design	Cost-effectiveness study
Sample size and population	Hypothetical cohort of 10,000 women with breast cancer and bone metastases for SRE prevention
Intervention	Monthly zoledronate
Comparator	Every-3-months zoledronate and monthly denosumab
Outcomes	Mean costs, mean SREs, QALY year 1, QALY year 2, cost per SRE avoided with monthly ZA, and ZA every 3 months as reference
Country, Perspective	US payer's perspective
Time horizon	A 2-year time horizon was used
Discount rates	Future costs are discounted at an annual rate of 3%
Clinical parameters	For annual probabilities of first SREs and subsequent SREs associated with denosumab from Xie et al[43] (referring to Stopeck et al[44]) and for monthly ZA and ZA every 3 months from NCT00869206[36]
Costs parameters	Drug costs; administration costs; costs associated with having an SRE, bone surgery, pathologic fracture, spinal cord compression, radiation to bone
Sources	Monthly probabilities, utilities, and costs from published literature and Centers for Medicare & Medicaid Services reimbursement rates
Main cost-effectiveness findings	ZA every 3 months is dominant and denosumab is dominated
Key: SRE – skeletal-related event; QALY– quality-adjusted life-year; US – United States; ZA – zoledronate	

8.2.3 Findings regarding costs, cost-effectiveness, and budget impact

One cost-effectiveness study (Shapiro 2017)[42] was included after the full-text screening as described in Section 8.2. The authors assessed the cost-effectiveness of 4-weekly zoledronate, 12-weekly zoledronate, and 4-weekly denosumab in women with BC and skeletal metastases. A Markov model was used to assess the cost effectiveness of 4-weekly zoledronate vs 12-weekly zoledronate, and 4-weekly denosumab. The model consisted of 11 distinct health states starting with patients with no SREs and no history of SREs. Patients could move from the first state to SRE status (no SRE, first on-study SRE, subsequent SRE, no SRE but history of SRE) and from SRE status to SRE type (pathologic fracture, radiation to the bone, surgery to the bone, spinal cord compression) and finally to the death state.

The cost-effectiveness analysis was conducted from the US payer's perspective using a 2-year time horizon. Monthly probabilities, utilities, and costs came from published literature and Centers for Medicare & Medicaid Services reimbursement rates. Included cost parameters were drug costs; administration costs; and costs associated with having an SRE, bone surgery, pathologic fracture, spinal cord compression, and radiation to bone. All costs before 2015 were inflated to 2015 US dollars. Future costs were discounted by an annual rate of 3%. Costs of the death state were not counted due to similar mortality among the 3 treatment groups, Sensitivity analyses were conducted to estimate the results of different scenarios using different SRE probabilities for denosumab and zoledronate.

Limitations were the use of a 2-year time horizon; the lack of differentiation between a vertebral and a non-vertebral (hip) fracture; and the fact that costs of ONJ, atypical femoral fractures, and the laboratory tests were not included.

8.3 Evidence base pertaining to legal, social, and ethical issues

Legal

There were no relevant articles identified that could help answer the research questions.

Social and Ethical

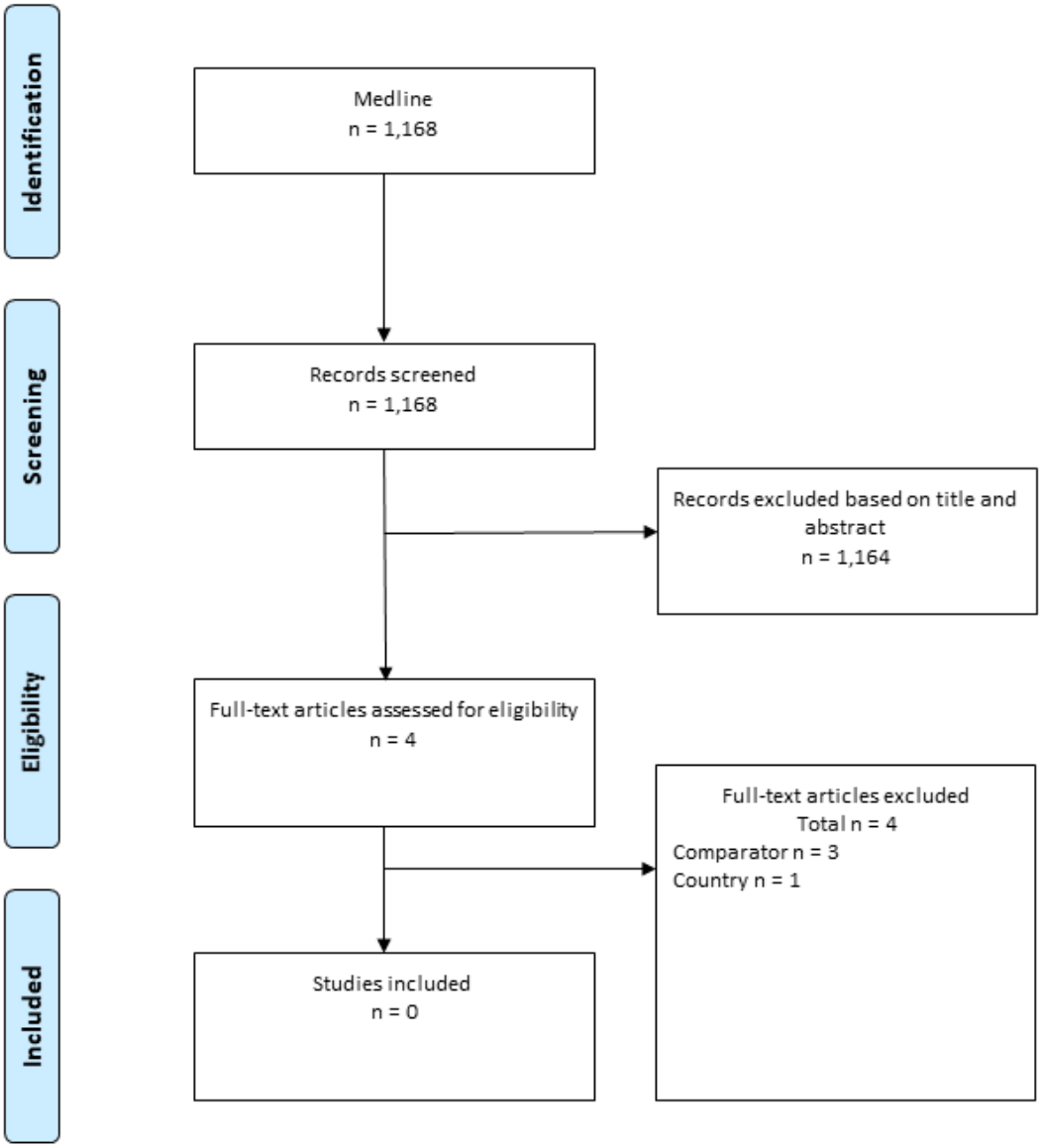
There were no relevant articles identified that could help answer the research questions.

Ethical

There were no relevant articles identified that could help answer the research questions.

8.3.1 PRISMA flow diagram

Figure 3. PRISMA flowchart of the legal, social, and ethical issues of the systematic literature search



8.3.2 Evidence table

N.A.

8.3.3 Findings regarding legal, social, and ethical issues

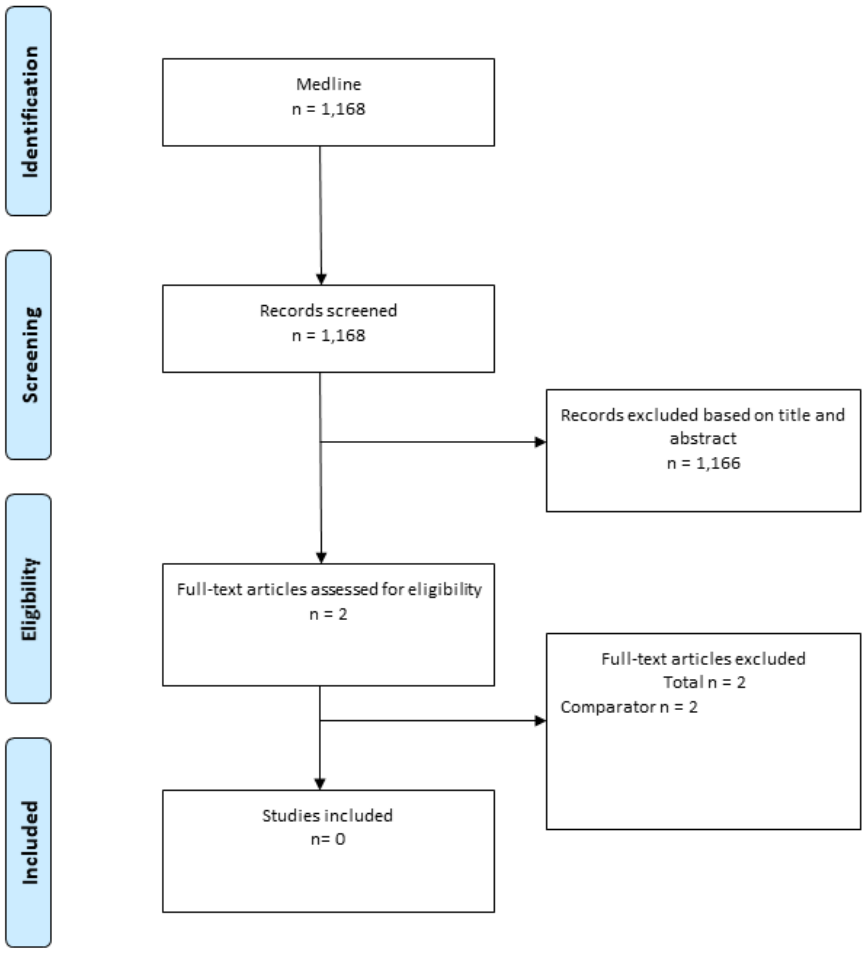
N.A.

8.4 Evidence base pertaining to organisational issues

Regarding organisational outcomes, we could not identify any relevant publication to answer our research questions.

8.4.1 PRISMA flow diagram

Figure 4. PRISMA flowchart of the organisational issues of the systematic literature search



8.4.2 Evidence table

N.A.

8.4.3 Findings regarding organisational issues

N.A.

9 Feasibility of an HTA

The aim of this scoping report was to identify the existing evidence regarding the use of 12-weekly BTAs vs the use of BTAs every 3 to 4 weeks in cancer patients with bone involvement. Most evidence is available for zoledronate (4 RCTs), whereas less evidence is available for denosumab (2 RCTs). No evidence was found regarding ibandronate. In the identified trials, most participants had mBC and a minority had PC and/or MM. Additionally identified SLRs evaluate the use of BTAs in patients with only mBC[21 29 30 32] or mBC, mPC[31], and MM with BM[22 45].

Only 1 economic evaluation assessing the cost-effectiveness from the US payer perspective was identified. Based on the structure with distinct health states, a health economic model could be developed but a longer time horizon should be considered.

No evidence was identified for organisational, legal, social, and ethical issues. Physicians in Switzerland prefer to prescribe denosumab instead of other BTAs. One-third of physicians are extending intervals to 12 weeks after an initial 2 years of treatment, and a minority use smaller intervals.[14] From the current findings, the preference of patients, what impact it may have on adherence, and optimal time to extend the treatment interval are still unknown.

Conducting a full HTA report would be feasible but with consideration of the known heterogeneity of the trials and limitations related to the existing trial information (eg, low statistical power, varying treatment duration, no Swiss patients included, most data for mBC, some trials with open-label study design). No adaption of the PICO scheme for the HTA is needed. A key focus of the HTA might be the different cancer types to determine whether specific dosing frequencies should be limited to specific patient subgroups. The HTA should also present an economic analysis. To support this HTA, the data search will be expanded and also include non-RCTs for safety and effectiveness data. The ongoing trials may procure relevant information.

10 Outlook

Clinical Evaluation

This scoping report has identified evidence investigating the use of BTAs with different administration frequencies in cancer patients with bone involvement. The evidence is restricted by numbers and has substantial uncertainties eg regarding the definition / operationalisation of endpoints. A meta-analysis can be performed, but limitations due to the described heterogeneity must be considered. No evidence was identified regarding the benefits of monthly pre-treatment with BTAs before switching to less

frequent administration of BTAs, which should be closer evaluated in the HTA as well as the time/dose dependent risk of ONJ. A rebound effect of denosumab is described for osteoporosis and also discussed for cancer patients[15] although no evidence was identified in context of the scoping. Thus, such rebound effects of denosumab in the treatment of cancer patients with bone involvement should also be considered in the HTA.

To overcome the limitations of the current findings additional data will be needed.

There are 2 ongoing trials that might be of interest for the HTA, the REaCT-BTA trial and the SAKK96/12 (REDUSE) trial. The REaCT-BTA trial is sponsored by the Ottawa Hospital Research Institute. The estimated end date of the REaCT-BTA trial is stated as April 2020, so first results can be anticipated soon. This trial includes patients with mBC and mPC and is currently capturing data for denosumab and zoledronate.[46] In the SAKK96/12 trial, which is sponsored by the Swiss Group for Clinical Cancer Research, patients are recruited from different sites across Switzerland (as well as Germany and Austria). In this trial, only patients with at least 3 BM from BC or PC are enrolled. The trial is planned to be finished by the end of 2022. The anticipated sample size is n=1,380. For these trials[33] [46]the dosing schedules are 120 mg every 4 weeks vs. 120 mg every 12 weeks. If possible, interim data should be requested. If the final dataset is available, the meta-analysis should be updated.

Economic Evaluation

The decision to conduct a cost-effectiveness analysis will be based on the results related to the comparative effectiveness and safety assessment. Assuming similar results (no significant differences) in efficacy and safety, a cost-minimisation study might be a sufficient approach. The 12-weekly administration of BTAs is convincingly confirmed as non-inferior compared to administration every 3 to 4 weeks, with a very low probability of significantly higher clinical event rates. Therefore, a cost-minimisation study might not be necessary, and a budget impact analysis might be sufficient. If a possibility of significantly higher clinical event rates with the 12-weekly dosing administration remains, then a full cost-effectiveness analysis could be conducted. But the prerequisite for this would be to have sufficient data to overcome the weaknesses of the current findings of the scoping report. Otherwise, it is likely to maintain the substantial uncertainties due to limitations of existing data.

The budget impact model would be conducted to estimate the impact of 12-weekly BTA administration compared to 4-weekly use on the Swiss healthcare budget. The perspective of the model will be the perspective of the Swiss third-party payer for cancer patients with bone involvement. The time horizon for the budget impact model could be 5 years depending on the treatment situation in Switzerland and the time to the first event (ie, SREs). The budget impact analysis would include costs associated with SRE management, AEs, and drug administration and acquisition. The incremental costs would be calculated as the difference between a new administration schedule scenario (12-weekly dosing) and

the current administration schedule (every 3–4 weeks). Robust sensitivity analyses for uncertainties would need to be performed to investigate the uncertainty around the financial impact of the different treatments. The model should allow for flexibility in testing the population, resource utilization, costs, and market share inputs to reflect any changes in the current and future market. The ongoing SAKK 95/16 trial[33] might provide additional information of what to include (ie, an evaluation of health-related quality of life and a health economic analysis are planned).

Social, legal, ethical, and organisational issues

No evidence was found regarding social, legal, ethical, and organisational issues. A survey on patient preferences should be considered and could include a targeted consultation survey among patients and physicians during the HTA phase. For all aspects mentioned, it needs to be discussed if input from stakeholder groups (manufacturers, trial groups) should be requested through collaboration with the FOPH. In the full HTA, the search for legal and ethical databases and additional grey literature databases should be extended to collect evidence from comparable regions.

11 References

1. European Medicines Agency. Choice of a non-inferiority margin 2005 [Available from: https://www.ema.europa.eu/en/choice-non-inferiority-margin accessed 27.09.2020 2020.

2. Hahn S. Understanding noninferiority trials. *Korean J Pediatr* 2012;55(11):403-07. doi: http://dx.doi.org/10.3345/kjp.2012.55.11.403

3. Macedo F, Ladeira K, Pinho F, et al. Bone Metastases: An Overview. *Oncol Rev* 2017;11(1):321. doi: 10.4081/oncol.2017.321

4. Cecchini M, Wetterwald A, Van der Pluijm G, et al. Molecular and biological mechanisms of bone metastasis. *EAU Update Series* 2005;3(4):214-26. doi: 10.1016/j.euus.2005.09.006

5.Observatory TGC. Switzerland Fact Sheet 2019 [Available from: https://gco.iarc.fr/today/data/factsheets/populations/756-switzerland-fact-sheets.pdf accessed 20.07.2020 2020.

6. Ferreira A, Alho I, Casimiro S, et al. Bone remodeling markers and bone metastases: From cancer research to clinical implications. *BoneKEy Reports* 2015;4:1-9. doi: doi:10.1038/bonekey.2015.35

7. Hussain A, Lee RJ, Graff JN, et al. The evolution and understanding of skeletal complication endpoints in clinical trials of tumors with metastasis to the bone. *Crit Rev Oncol Hematol* 2019;139:108-16. doi: 10.1016/j.critrevonc.2019.04.020

8. Ibrahim A, Scher N, William G, et al. Approval Summary for Zoledronic Acid for Treatment of Multiple Myeloma and Cancer Bone Metastases. *Clinical Cancer Research* 2003;9:2394-99.

9. Selvaggi G, Scagliotti GV. Management of bone metastases in cancer: a review. *Crit Rev Oncol Hematol* 2005;56(3):365-78. doi: 10.1016/j.critrevonc.2005.03.011

10. Hadji P, Aapro MS, Body JJ, et al. Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment. *Ann Oncol* 2011;22(12):2546-55. doi: 10.1093/annonc/mdr017

11.Clohisy DR, P. M. Bone Cancer Pain. *Cancer* 2003;97(S3):866-73. doi: https://doi.org/10.1002/cncr.11144

12. Seccareccia D. Cancer-related hypercalcemia. *Canadian family physican Medecin de famile canadien* 2010;56(3):244-46.

13. Tharmalingam S, Chow E, Harris K, et al. Quality of life measurement in bone metastases: A literature review. *J Pain Res* 2008;1:49-58. doi: 10.2147/jpr.s4572

14. Mark M, Thurlimann B, Ribi K, et al. Patterns of care for patients with metastatic bone disease in solid tumors: A cross-sectional study from Switzerland (SAKK 95/16). *Journal of bone oncology* 2020;21:100273. doi: https://dx.doi.org/10.1016/j.jbo.2019.100273

15. Coleman RE, Body JJ, Aapro MS, et al. Bone health in cancer patients: ESMO Clinical Practice Guidelines. *Supportive and Palliative Care* 2014;25(S3):III124-III37. doi: https://doi.org/10.1093/annonc/mdu103

16. Swissmedic. Zometa: SmPC 2020 [Available from: https://www.swissmedicinfo.ch/ accessed 27.07.2020.

17. Swissmedic. Bondronat: SMPC 2020 [Available from: https://www.swissmedicinfo.ch/ accessed 27.07.2020.

18. Swissmedic. Xgeva: SmPC 2020 [Available from: https://www.swissmedicinfo.ch/ accessed 27.07.2020.

19. Adnan MM, Bhutta U, Iqbal T, et al. Severe Hypocalcemia due to Denosumab in Metastatic Prostate Cancer. *Case Reports in Nephrology* 2014;2014:1-3. doi: http://dx.doi.org/10.1155/2014/565393

20. Tyan A, Patel SP, Block S, et al. Rebound Vertebral Fractures in a Patient With Lung Cancer After Oncology-Dose Denosumab Discontinuation: A Cautionary Tale. *Mayo CLin Proc Innov Qual Outcomes* 2019;3(2):235-37.

21. Awan AA, Hutton B, Hilton J, et al. De-escalation of bone-modifying agents in patients with bone metastases from breast cancer: a systematic review and meta-analysis. *Breast cancer research and treatment* 2019;176(3):507. doi: https://dx.doi.org/10.1007/s10549-019-05265-1

22. Luo Q, Men P, Liu Z, et al. Is De-escalated Bisphosphonates Therapy a Suitable Alternative to Standard Dosing in Malignant Tumor Patients With Bone Metastases: A Systematic Review and Meta-Analysis. *Frontiers in oncology* 2019;9:774. doi: https://dx.doi.org/10.3389/fonc.2019.00774

23. De Felice F, Piccioli A, Musio D, et al. The role of radiation therapy in bone metastases management. *Oncotarget* 2017;8(15):25691-99.

24. Deutsche Krebsgesellschaft. Knochenmetastasen: Wie lassen sie sich behandeln? 2020 [Available from: https://www.krebsgesellschaft.de/onko-internetportal/basis-informationen-krebs/nebenwirkungen-der-therapie/knochenmetastasen.html accessed 27.07.2020.

25. Kurth A. Knochenmetastasen: Aktuelle Therapieoptionen. *Deutsches Ärzteblatt* 2020;117(11):4-10. doi: DOI:10.3238/PersOnko.2020.03.13.01

26. Higgins JP, Savović J, Page MJ, et al. Assesing risk of bias in a randomized trial. In: Higgins JP, Thomas J, Chandler J, et al., eds.: Cochrane, 2019.

27. Evers S, Goossens M, de Vet H, et al. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *International Journal of technology assessment in health care* 2005;21(2):240-45.

28. Cao L, Yang YJ, Diao JD, et al. Systematic review and meta-analysis comparing zoledronic acid administered at 12-week and 4-week intervals in patients with bone metastasis. *Oncotarget* 2017;8(52):90308. doi: http://dx.doi.org/10.18632/oncotarget.19856

29. Ibrahim MFK, Mazzarello S, Shorr R, et al. Should de-escalation of bone-targeting agents be standard of care for patients with bone metastases from breast cancer? A systematic review and meta-analysis. *Annals of oncology : official journal of the European Society for Medical Oncology* 2015;26(11):2205. doi: https://dx.doi.org/10.1093/annonc/mdv284

30. O'Carrigan B, Wong MH, Willson ML, et al. Bisphosphonates and other bone agents for breast cancer. *The Cochrane database of systematic reviews* 2017;10:CD003474. doi: https://dx.doi.org/10.1002/14651858.CD003474.pub4

31. Santini D, Galvano A, Pantano F, et al. How do skeletal morbidity rate and special toxicities affect 12-week versus 4-week schedule zoledronic acid efficacy? A systematic review and a meta-analysis of randomized trials. *Critical reviews in oncology/hematology* 2019;142:68. doi: https://dx.doi.org/10.1016/j.critrevonc.2019.07.013

32. Yang M, Yu X. Management of bone metastasis with intravenous bisphosphonates in breast cancer: a systematic review and meta-analysis of dosing frequency. *Supportive Care in Cancer* 2020;28(6):2533. doi: http://dx.doi.org/10.1007/s00520-020-05355-7

33. ClinicalTrials.gov. Prevention of Symptomatic Skeletal Events With Denosumab Administered Every 4 Weeks Versus Every 12 Weeks: U. S. National Library of Medicine; 2020 [Available from: https://clinicaltrials.gov/ct2/show/NCT02051218 accessed 24.07.2020.

34. Novartis. A stratified, randomized, open-label, multi-center comparative 2-arm trial of pharmacokinetics (PK), pharmacodynamics (PD), and safety of Zometa® infusions administered monthly vs. every 3-month, in multiple myeloma patients with malignant bone lesions, and breast cancer patients with bone metastasis, who have received 9 to 12 doses of Zometa® over the prior year. 2012 [Available from: https://www.novctrd.com/CtrdWeb/searchbystudyid.nov#CZOL446E2105 accessed 27.07.2020.

35. Amadori D, Aglietta M, Alessi B, et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a

phase 3, open-label, randomised, non-inferiority trial. *The Lancet Oncology* 2013;14(7):663. doi: https://dx.doi.org/10.1016/S1470-2045(13)70174-8

36. Himelstein AL, Foster JC, Khatcheressian JL, et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases: A Randomized Clinical Trial. *JAMA* 2017;317(1):48. doi: https://dx.doi.org/10.1001/jama.2016.19425

37. Hortobagyi GN, Van Poznak C, Harker WG, et al. Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in Women With Breast Cancer Metastatic to Bone: The OPTIMIZE-2 Randomized Clinical Trial. *JAMA oncology* 2017;3(7):906. doi: https://dx.doi.org/10.1001/jamaoncol.2016.6316

38. Fizazi K, Bosserman L, Gao G, et al. Denosumab treatment of prostate cancer with bone metastases and increased urine N-telopeptide levels after therapy with intravenous bisphosphonates: results of a randomized phase II trial. *The Journal of urology* 2013;189(1 Suppl):S51. doi: https://dx.doi.org/10.1016/j.juro.2012.11.022

39. Fizazi K, Lipton A, Mariette X, et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009;27(10):1564. doi: https://dx.doi.org/10.1200/JCO.2008.19.2146

40. Lipton A, Steger GG, Figueroa J, et al. Extended efficacy and safety of denosumab in breast cancer patients with bone metastases not receiving prior bisphosphonate therapy. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2008;14(20):6690. doi: https://dx.doi.org/10.1158/1078-0432.CCR-07-5234

41. Lipton A, Steger GG, Figueroa J, et al. Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2007;25(28):4431.

42. Shapiro CL, Moriarty JP, Dusetzina S, et al. Cost-Effectiveness Analysis of Monthly Zoledronic Acid, Zoledronic Acid Every 3 Months, and Monthly Denosumab in Women With Breast Cancer and Skeletal Metastases: CALGB 70604 (Alliance). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2017;35(35):3949. doi: https://dx.doi.org/10.1200/JCO.2017.73.7437

43. Xie J, Diener M, Sorg R, et al. Cost-effectiveness of denosumab compared with zoledronic acid in patients with breast cancer and bone metastases. *Clin Breast Cancer* 2012;12(4):247-58. doi: 10.1016/j.clbc.2012.04.001

44. Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* 2010;28(35):5132-9. doi: 10.1200/JCO.2010.29.7101

45. Liu C, Wang L, Liu L, et al. Efficacy and safety of de-escalation bone- modifying agents for cancer patients with bone metastases: a systematic review and meta-analysis. *Cancer management and research* 2018;10:3809. doi: https://dx.doi.org/10.2147/CMAR.S176811

46. ClinicalTrials.gov. 4-weekly Versus 12-weekly Administration of Bone-targeted Agents in Patients With Bone Metastases (REaCT-BTA): U. S. National Library of Medicine; 2020 [Available from: https://clinicaltrials.gov/ct2/show/NCT02721433 accessed 27.04.2020.

47. Liu C, Wang L, Zhuang J, et al. Should de-escalation of bone-targeting agents be standard of care for patients with bone metastases from breast cancer? A systematic review and meta-analysis. *Annals of oncology : official journal of the European Society for Medical Oncology* 2018;29(5):1329. doi: https://dx.doi.org/10.1093/annonc/mdy067

12 Appendices

Appendix 1. Search strategies for the different databases

Database:	**Medline and Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Daily and Versions**	
Interface:	**Ovid**	
Time segment:	**1946 to May 26, 2020**	
Date of search:	**27.05.2020**	
#	**Searches**	**Results**
1	exp Bone Neoplasms/ and exp Neoplasm Metastasis/ and exp Neoplasms/	11463
2	(bone* adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	12490
3	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	2628
4	1 or 2 or 3	24307
5	exp Bone Neoplasms/ and exp Neoplasm Metastasis/	11463
6	((bone* neoplasm* or (bone* adj3 (cancer* or carcinom* or tumo?r*))) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	7576
7	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (cancer* or carcinom* or tumo?r*) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	1107
8	(bone* adj3 (metasta* or micrometasta*)).mp.	23345
9	5 or 6 or 7 or 8	34283
10	exp Multiple Myeloma/ or exp Plasmacytoma/	47581
11	(solid* adj3 (malign* or neoplasm* or tumo?r*)).mp.	62869
12	((multiple* adj4 myelom*) or (Kahler* adj2 diseas*) or (morbus adj2 kahler*) or (myeloma adj4 multiplex) or myelomatos#s or plasm##ytom* or ((plasma cell or plasmacell) adj4 myelom*)).mp.	59663
13	10 or 11 or 12	121768
14	9 and 13	1851

15	4 or 14	24839
16	(bone target* adj4 (therap* or agent*)).mp.	452
17	(bone modif* adj4 (therap* or agent*)).mp.	111
18	(BTA or BMA).ti,ab.	4008
19	exp Zoledronic Acid/	3399
20	(Zoledronic acid or Zoledronat? or Zometa or Zolacin or Aclasta or Orazol or Reclast or Zomera or cgp 42446 or cgp 42446a or cgp42446 or cgp42446a or zol 446 or zol446).mp. or ZA.ti,ab.	6577
21	exp Ibandronic Acid/	720
22	(Ibandronic acid or Ibandronat? or Bondronat? or Boniva or Bonviva or Ibandronico or bondenza or destara or iasibon or "BM-21.0955" or "BM21.0955" or BM-210955 or BM210955 or RPR-102289A or RPR102289A or r 484 or r484).mp.	1192
23	(((receptor activator adj3 nuclear factor kappa B ligand) or RANKL or RANK-L or RANK ligand) adj4 (antibod* or inhibit*)).mp.	2187
24	exp Denosumab/	1595
25	(Denosumab or Xgeva or Prolia or Amgiva or amg 162 or amg162).mp.	3023
26	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	15678
27	exp Standard of Care/	3704
28	(standard* adj4 (treatment* or care)).mp.	112439
29	((health care or healthcare) adj4 (evaluation or quality)).mp.	158034
30	exp Drug Therapy/	1348878
31	((Drug adj1 Therap*) or Chemotherap* or Pharmacotherap*).mp.	2550233
32	(dosing* or dosag* or dosis* or dose* or administration?).mp.	3763798
33	((drug adj2 infiltration*) or (drug adj2 injection*)).mp.	9745
34	((drug* or administration* or dos*) adj4 (schedule* or interval*)).mp.	129766
35	((De-escal* or deescal*) adj4 (therap* or treatment*)).mp.	908
36	(Dose-respons* adj4 evaluation*).mp.	341
37	((less adj4 intens*) or (frequen* adj4 treat*)).mp.	42582
38	(3-4 week* or 3-4week* or 4 week* or 4week* or three week* or four week* or monthly or 1month*).mp.	246666
39	(12 week* or 12week* or twelve week* or 3 month* or 3month* or three month*).mp.	337219
40	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	6045410
41	15 and 26 and 40	1323
42	41 and (exp Humans/ or human?.mp.)	1185

43	41 not (exp Animals/ or (animal? or non-human? or nonhuman?).mp.)	121
44	42 or 43	1286
45	limit 44 to (english or german or french)	1187
46	limit 45 to yr=2000-2020	**1170**
47	remove duplicates from 46	**1168**

Database:	**Embase**	
Interface:	**Ovid**	
Time segment:	**1974 to 26 May, 20202**	
Date of search:	**27.05.2020**	
#	**Searches**	**Results**
1	exp bone metastasis/ and exp malignant neoplasm/	44054
2	(bone* adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	33892
3	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	3358
4	1 or 2 or 3	52173
5	exp bone metastasis/	44054
6	((bone* neoplasm* or (bone* adj3 (cancer* or carcinom* or tumo?r*))) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	11959
7	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (cancer* or carcinom* or tumo?r*) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	1635
8	(bone* adj3 (metasta* or micrometasta*)).mp.	57998
9	5 or 6 or 7 or 8	60429
10	exp solid tumor/	1627267
11	exp multiple myeloma/ or exp plasmacytoma/	82377
12	(solid* adj3 (malign* or neoplasm* or tumo?r*)).mp.	119488
13	((multiple* adj4 myelom*) or (Kahler* adj2 diseas*) or (morbus adj2 kahler*) or (myeloma adj4 multiplex) or myelomatos#s or plasm##ytom* or ((plasma cell or plasmacell) adj4 myelom*)).mp.	91083

14	10 or 11 or 12 or 13	1769204
15	9 and 14	26878
16	4 or 15	56250
17	(bone target* adj4 (therap* or agent*)).mp.	734
18	(bone modif* adj4 (therap* or agent*)).mp.	197
19	(BTA or BMA).ti,ab.	4572
20	exp zoledronic acid/	16173
21	(Zoledronic acid or Zoledronat? or Zometa or Zolacin or Aclasta or Orazol or Reclast or Zomera or cgp 42446 or cgp 42446a or cgp42446 or cgp42446a or zol 446 or zol446).mp. or ZA.ti,ab.	17575
22	exp ibandronic acid/	5268
23	(Ibandronic acid or Ibandronat? or Bondronat? or Boniva or Bonviva or Ibandronico or bondenza or destara or iasibon or "BM-21.0955" or "BM21.0955" or BM-210955 or BM210955 or RPR-102289A or RPR102289A or r 484 or r484).mp.	5441
24	(((receptor activator adj3 nuclear factor kappa B ligand) or RANKL or RANK-L or RANK ligand) adj4 (antibod* or inhibit*)).mp.	3515
25	exp denosumab/	8697
26	(Denosumab or Xgeva or Prolia or Amgiva or amg 162 or amg162).mp.	9129
27	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	32776
28	exp health care quality/	3174936
29	(standard* adj4 (treatment* or care)).mp.	189704
30	((health care or healthcare) adj4 (evaluation or quality)).mp.	261073
31	exp drug therapy/	2784378
32	exp drug dose/	643402
33	exp drug administration/	1191647
34	((Drug adj1 Therap*) or Chemotherap* or Pharmacotherap*).mp.	4835683
35	(dosing* or dosag* or dosis* or dose* or administration?).mp.	4992988
36	((drug adj2 infiltration*) or (drug adj2 injection*)).mp.	14261
37	((drug* or administration* or dos*) adj4 (schedule* or interval*)).mp.	57919
38	((De-escal* or deescal*) adj4 (therap* or treatment*)).mp.	1856
39	(Dose-respons* adj4 evaluation*).mp.	460
40	((less adj4 intens*) or (frequen* adj4 treat*)).mp.	62953
41	(3-4 week* or 3-4week* or 4 week* or 4week* or three week* or four week* or monthly or 1month*).mp.	379508

42	(12 week* or 12week* or twelve week* or 3 month* or 3month* or three month*).mp.	548785
43	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42	10400230
44	16 and 27 and 43	5753
45	44 not Medline.cr.	5534
46	45 and (exp human/ or human?.mp.)	5255
47	45 not (exp animal/ or (animal? or non-human? or nonhuman?).mp.)	182
48	46 or 47	5411
49	limit 48 to (english or german or french)	5262
50	limit 49 to yr=2000-2020	5211
51	50 and Conference Abstract.pt.	981
52	limit 51 to yr=1974-2014	582
53	50 not 52	**4629**
54	remove duplicates from 53	**3650**

Database:	**Cochrane Database of Systematic Reviews (CDSR)** **Database of Abstracts of Reviews of Effects (DARE)** **Health Technology Assessment (HTA)** **NHS Economic Evaluation Database (NHSEED)**	
Interface:	**Ovid**	
Time segment:	**CDSR - 2005 to date May 21, 2020** **DARE - 1st Quarter 2016**	**HTA – 4th Quarter 2016** **NHSEED – 1st Quarter 2016**
Date of search:	**27.05.2020**	

#	Searches	Results
1	exp Bone Neoplasms/ and exp Neoplasm Metastasis/ and exp Neoplasms/	8
2	(bone* adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	101
3	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	24
4	1 or 2 or 3	120
5	exp Bone Neoplasms/ and exp Neoplasm Metastasis/	8
6	((bone* neoplasm* or (bone* adj3 (cancer* or carcinom* or tumo?r*))) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	89
7	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (cancer* or carcinom* or tumo?r*) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	18
8	(bone* adj3 (metasta* or micrometasta*)).mp.	175
9	5 or 6 or 7 or 8	195

10	exp Multiple Myeloma/ or exp Plasmacytoma/	111
11	(solid* adj3 (malign* or neoplasm* or tumo?r*)).mp.	334
12	((multiple* adj4 myelom*) or (Kahler* adj2 diseas*) or (morbus adj2 kahler*) or (myeloma adj4 multiplex) or myelomatos#s or plasm##ytom* or ((plasma cell or plasmacell) adj4 myelom*)).mp.	275
13	10 or 11 or 12	570
14	9 and 13	38
15	4 or 14	132
16	(bone target* adj4 (therap* or agent*)).mp.	5
17	(bone modif* adj4 (therap* or agent*)).mp.	5
18	(BTA or BMA).ti,ab.	10
19	exp Zoledronic Acid/	0
20	(Zoledronic acid or Zoledronat? or Zometa or Zolacin or Aclasta or Orazol or Reclast or Zomera or cgp 42446 or cgp 42446a or cgp42446 or cgp42446a or zol 446 or zol446).mp. or ZA.ti,ab.	103
21	exp Ibandronic Acid/	0
22	(Ibandronic acid or Ibandronat? or Bondronat? or Boniva or Bonviva or Ibandronico or bondenza or destara or iasibon or "BM-21.0955" or "BM21.0955" or BM-210955 or BM210955 or RPR-102289A or RPR102289A or r 484 or r484).mp.	54
23	(((receptor activator adj3 nuclear factor kappa B ligand) or RANKL or RANK-L or RANK ligand) adj4 (antibod* or inhibit*)).mp.	11
24	exp Denosumab/	0
25	(Denosumab or Xgeva or Prolia or Amgiva or amg 162 or amg162).mp.	77
26	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	179
27	15 and 26	**45**

Database:	**Cochrane Central Register of Controlled Trials (CCTR)**	
Interface:	**Ovid**	
Time segment:	**April 2020**	
Date of search:	**27.05.2020**	
#	**Searches**	**Results**
1	exp Bone Neoplasms/ and exp Neoplasm Metastasis/ and exp Neoplasms/	191
2	(bone* adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	2146
3	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	214
4	1 or 2 or 3	2363
5	exp Bone Neoplasms/ and exp Neoplasm Metastasis/	191
6	((bone* neoplasm* or (bone* adj3 (cancer* or carcinom* or tumo?r*))) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	1892

7	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (cancer* or carcinom* or tumo?r*) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	142
8	(bone* adj3 (metasta* or micrometasta*)).mp.	3022
9	5 or 6 or 7 or 8	3547
10	exp Multiple Myeloma/ or exp Plasmacytoma/	1572
11	(solid* adj3 (malign* or neoplasm* or tumo?r*)).mp.	7342
12	((multiple* adj4 myelom*) or (Kahler* adj2 diseas*) or (morbus adj2 kahler*) or (myeloma adj4 multiplex) or myelomatos#s or plasm##ytom* or ((plasma cell or plasmacell) adj4 myelom*)).mp.	5412
13	10 or 11 or 12	12561
14	9 and 13	361
15	4 or 14	2464
16	(bone target* adj4 (therap* or agent*)).mp.	67
17	(bone modif* adj4 (therap* or agent*)).mp.	7
18	(BTA or BMA).ti,ab.	263
19	exp Zoledronic Acid/	0
20	(Zoledronic acid or Zoledronat? or Zometa or Zolacin or Aclasta or Orazol or Reclast or Zomera or cgp 42446 or cgp 42446a or cgp42446 or cgp42446a or zol 446 or zol446).mp. or ZA.ti,ab.	1751
21	exp Ibandronic Acid/	0
22	(Ibandronic acid or Ibandronat? or Bondronat? or Boniva or Bonviva or Ibandronico or bondenza or destara or iasibon or "BM-21.0955" or "BM21.0955" or BM-210955 or BM210955 or RPR-102289A or RPR102289A or r 484 or r484).mp.	495
23	(((receptor activator adj3 nuclear factor kappa B ligand) or RANKL or RANK-L or RANK ligand) adj4 (antibod* or inhibit*)).mp.	254
24	exp Denosumab/	0
25	(Denosumab or Xgeva or Prolia or Amgiva or amg 162 or amg162).mp.	985
26	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	3193
27	exp Standard of Care/	251
28	(standard* adj4 (treatment* or care)).mp.	54788
29	((health care or healthcare) adj4 (evaluation or quality)).mp.	9513
30	exp Drug Therapy/	139105
31	((Drug adj1 Therap*) or Chemotherap* or Pharmacotherap*).mp.	301218
32	(dosing* or dosag* or dosis* or dose* or administration?).mp.	474101
33	((drug adj2 infiltration*) or (drug adj2 injection*)).mp.	2760
34	((drug* or administration* or dos*) adj4 (schedule* or interval*)).mp.	39401
35	((De-escal* or deescal*) adj4 (therap* or treatment*)).mp.	231
36	(Dose-respons* adj4 evaluation*).mp.	293
37	((less adj4 intens*) or (frequen* adj4 treat*)).mp.	14924
38	(3-4 week* or 3-4week* or 4 week* or 4week* or three week* or four week* or monthly or 1month*).mp.	93952
39	(12 week* or 12week* or twelve week* or 3 month* or 3month* or three month*).mp.	150124
40	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	794077
41	15 and 26 and 40	500
42	41 and (exp Humans/ or human?.mp.)	390
43	41 not (exp Animals/ or (animal? or non-human? or nonhuman?).mp.)	364
44	42 or 43	500
45	limit 44 to yr=2000-2020	496
46	remove duplicates from 45	271

Appendix 2. Inclusion and exclusion criteria

Search	Inclusion Criteria		Exclusion Criteria
Population	• Cancer patients with bone involvement • Solid tumours (eg, breast cancer, prostate cancer, lung cancer) • MM • Patients aged ≥18 years		• Cancer patients without bone metastases • Cancer patients with bone metastases not related to solid cancer/MM • Patients with diseases other than solid tumours and MM • Patients aged <18 years
Interventions	• Standard treatment with BTAs licenced in Switzerland • Bisphosphonates • Zoledronate (intravenously every 3–4 weeks) • Ibandronate (intravenously every 3–4 weeks) • Receptor activator of nuclear factor kappa-B ligand • Denosumab (subcutaneously every 4 weeks) • Standard dosing with BTA		All other interventions
Comparators	• De-escalated treatment with BTA (every 12 or more weeks) • De-escalated dosing with BTA • Reduced-frequency BTA • Longer-interval dosing • Placebo	Bisphosphonates • Zoledronate (intravenously every 12 or more weeks) • Ibandronate (intravenously every 12 or more weeks) Receptor activator of nuclear factor kappa-B ligand • Denosumab (subcutaneously, every 12 or more weeks)	• Standard treatment with BTAs • BTA dosing intervals <12 weeks • Treatment with another comparator than BTAs • Failed treatments (eg, study discontinuation) due to consent withdrawal and disease progression

Search	Inclusion Criteria		Exclusion Criteria
Outcomes (clinical)	Efficacy: • All-cause mortality • SRE (**critical**) • New bone metastases • Skeletal morbidity rate • Recurrence of bone metastases • Bone pain • Usage of pain medication • General (health) condition/ performance status • Change of bone-related marker/marker of bone turnover (NTX, CTX), bone-specific alkaline phosphatase • Bone mineral density • Quality of life measures	Safety • Incidence of treatment-related AEs • Any AE • Severe AEs • Serious AEs • AEs leading to treatment discontinuation • AEs leading to study withdrawal/drop-out • Fatal AEs/on-treatment deaths AEs include: • ONJ • Hypercalcaemia of malignancy • Infusion-related side effects • Renal toxicity (eg, renal failure, renal impairment, decreased estimated glomerular filtration rate, decreased renal clearance) • Cardiovascular events	All other outcomes
Outcomes (economic)	• Budget impact • Costs (direct, medical, non-medical) • ICER, QALY; LY and budget impact • Utilities • Costs per clinical event, LYG, QALY • Cost savings • Healthcare resource utilization		All other outcomes

Search	Inclusion Criteria		Exclusion Criteria
Study design/type	Clinical • RCTs and non-randomized controlled study • Systematic reviews/ metanalyses • Cohort studies • Cross-sectional studies • Database studies • Surveys • Observational studies (eg, database studies, prospective cohorts, surveys, and cross-sectional studies) Economic • Randomized controlled and other trials that report cost or healthcare resource use data	Health economic All economic evaluations, such as: • Budget-impact • Cost-benefit • Cost-utility • Cost-effectiveness • Cost-comparison Any relevant SLRs and meta-analyses will also be included for hand-searching of the reference lists	• Single-arm studies • Narrative review • Case reports, case series (N≤5) • *In vitro* studies • Animal studies • Non-pertinent publication types (eg, editorials, expert opinions, letters to editor, conference/meeting abstracts, theses, and dissertations)
Publication language	English, French, German		All other
Publication type	Full publication		All other
Setting	Clinical: Global	All other parts: Switzerland and focus on Western countries (Europe/United Kingdom, United States of America, Canada, Australia)	All other

Key: AE – adverse event; BTA – bone-targeting agent; CTX – c-terminal telopeptide; ICER – incremental cost-effectiveness ratio; LY – life-year; LYG – life-year gained; MM – multiple myeloma; NTX – n-terminal telopeptide; ONJ – osteonecrosis of the jaw; QALY – quality-adjusted life-year; SLR – systematic literature review; SRE – skeletal-related event.

Appendix 3. List of excluded references

No full-text available

Comparison of the efficacy of Denosumab when administered only every 12 weeks instead of every 4 weeks related to the prevention of complications on the bone skeleton. Prevention of Symptomatic Skeletal Events with Denosumab Administered every 4 Weeks versus every 12 Weeks - A Non-Inferiority Phase III trial. 2017 http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2014-001189-87-DE *

Comparison of Two Schedules of Zoledronic Acid in Treating Patients With Breast Cancer That Has Spread to the Bone. Cost-Effective Use of Bisphosphonates in Metastatic Bone Disease - A Comparison of Bone Marker Directed Zoledronic Acid Therapy to a Standard Schedule. 2007

https://clinicaltrials.gov/show/NCT00458796 *

4-weekly Versus 12-weekly Administration of Bone-targeted Agents in Patients With Bone Metastases. A Pragmatic Randomised, Multicentre Trial Comparing 4-weekly Versus 12-weekly Administration of Bone-targeted Agents in Patients With Bone Metastases From Either Castration-resistant Prostate Cancer or Breast Cancer - The REaCT-BTA Study. 2016 https://clinicaltrials.gov/show/NCT02721433

Clemons MJ, Ong M, Stober C, Ernst DS, et al. A randomized trial comparing four-weekly versus 12-weekly administration of bone-targeted agents (denosumab, zoledronate, or pamidronate) in patients with bone metastases from either breast or castration-resistant prostate cancer. Journal of Clinical Oncology J. Clin. Oncol. 2019;37(15) http://dx.doi.org/10.1200/JCO.2019.37.15_suppl.11501

Muller A, Templeton AJ, Hayoz S, Hawle H, et al. Incidence of hypocalcemia in patients with metastatic breast cancer under treatment with denosumab: A non-inferiority phase III trial assessing prevention of symptomatic skeletal events (SSE) with denosumab administered every 4 weeks versus every 12 weeks: SAKK 96/12 (REDUSE). Cancer Res 2019, 79(4 Supplement 1). http://dx.doi.org/10.1158/1538-7445.SABCS18-P1-18-01

Gralow J, Lipton A, Fizazi K, Gao G, et al. Effects of denosumab treatment in breast cancer patients with bone metastases and elevated bone resorption levels after therapy with intravenous bisphosphonates: results of a phase 2 randomized trial. 2008

Clemons M, Stober C, Mates M, Joy AA, et al. A pragmatic, randomized, multicenter trial comparing 4-weekly vs. 12-weekly administration of bone-targeted agents (denosumab, zoledronate or pamidronate) in patients with bone metastases". Ann. Oncol.2019;30(3) http://dx.doi.org/10.1093/annonc/mdz118.002

Peterson MC, Jang G, Kim W, Gurrola E, et al. Selection of a phase 3 dose regimen for denosumab based on pharmacokinetic (PK), pharmacodynamic (PD), and safety data from multiple subcutaneous (SC) dosing regimens in breast cancer patients (pts) with bone metastases (BM). Journal of clinical oncology : ASCO annual meeting proceedings. 2006. 24(18), 142

Himelstein AL, Qin R, Novotny PJ, Seisler DK, et al. CALGB 70604 (Alliance): A randomized phase III study of standard dosing vs. Longer interval dosing of zoledronic acid in metastatic cancer. Journal of clinical oncology. 2015 33(15)

Hortobagyi GN, Sallas W, Zheng M, Mohanlal RW. An indirect evaluation of bone saturation with zoledronic acid after long-term Q4 week dosing using plasma and urine pharmacokinetics. Journal of clinical oncology. 2015; 33(15)

Hortobagyi GN, Lipton A, Chew HK, Gradishar WJ. et al. Efficacy and safety of continued zoledronic acid every 4 weeks versus every 12 weeks in women with bone metastases from breast cancer: Results of the OPTIMIZE-2 trial. Journal of clinical oncology. 2014; 32(15)

Coleman RE, Wright J, Houston S, Agrawal R. et al. Randomized trial of marker-directed versus standard schedule zoledronic acid for bone metastases from breast cancer. Journal of clinical oncology. 2012; 30(15).

National Horizon Scanning Centre. Denosumab (AMG162) for prevention of bone metastases in prostate cancer (Structured abstract). Health Technology Assessment Database. 2016;(Issue 4)

National Horizon Scanning Centre. "Denosumab (AMG 162) for bone metastases from solid tumours and multiple myeloma (Structured abstract). Health Technology Assessment Database 2016; (Issue 4)

Health Technology Assessment. Denosumab for the treatment of bone metastases from solid tumours and multiple myeloma (Project record). Health Technology Assessment Database 2016;(Issue 4)

Hernandez-Vasquez, A, Pichon-Riviere, A, Augustovski, F, Garcia Marti, S, et al. Denosumab for the treatment of solid tumor bone metastasis (Structured abstract). Health Technology Assessment Database 2016; (Issue 4)

Centre for Reviews and Dissemination. Cost-effectiveness of zoledronic acid for the prevention of skeletal complications in patients with prostate cancer (Structured abstract). NHS Economic Evaluation Database (NHSEED) 2004;(Issue 2)

Centre for Reviews and Dissemination. Use of bisphosphonates in women with breast cancer (Structured abstract). Database of Abstracts of Reviews of Effects. 2015;(2)

Campbell-Baird C, Lipton A, Sarkeshik M, Ma H, Jun S. Incidence of acute phase adverse events following denosumab or intravenous bisphosphonates: Results from a randomized, controlled phase II study in patients with breast cancer and bone metastases. Community Oncol. 2010;7(2), 85 http://www.communityoncology.net/journal/articles/0702085.pdf http://dx.doi.org/10.1016/S1548-5315(11)70560-5

Study Type / Publication Type

Fornier M N. Less intense dosing schedule for a bone-modifying agent. JAMA Oncol. 2017;3(7), 893 http://oncology.jamanetwork.com/journal.aspx http://dx.doi.org/10.1001/jamaoncol.2016.6240

Hong B Y, Ibrahim M F K, Fernandes R, Mazzarello S, et al. De-escalation of bone-targeted agents for metastatic prostate cancer. Curr. Oncol. 2016;23(1), e77 http://www.current-oncology.com/index.php/oncology/article/download/2913/2003 http://dx.doi.org/10.3747/co.23.2913

Campagnaro, E, Reimers, M, Qin, Al, Alva, A et al. Use of Bone-Modifying Agents in Myeloma and Bone Metastases: How Recent Dosing Interval Studies Have Affected Our Practice. J Oncol Pract 2018

Liu, C, Wang, L, Zhuang, J, Liu, L et al. Should de-escalation of bone-targeting agents be standard of care for patients with bone metastases from breast cancer? A systematic review and meta-analysis. Ann Oncol 2018;29(5), 1329 https://dx.doi.org/10.1093/annonc/mdy067

Van Poznak, C, Somerfield, M, Barlow, W, Biermann, JS, et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update.J Clin Oncol 2017;35(35), 3978 https://dx.doi.org/10.1200/JCO.2017.75.4614 Systematic review without further data

Hutton, B, Addison, C L, Campbell, K, Fergusson, D, et al. A systematic review of dosing frequency with bone-targeted agents for patients with bone metastases from breast cancer. J Bone Oncol 2013; 2(3), 123 https://dx.doi.org/10.1016/j.jbo.2013.05.001

Zhao, Xinmin, Hu, Xichun. Dosing of zoledronic acid with its anti-tumor effects in breast cancer. J Bone Oncol. 2015; 4(3), 98 https://dx.doi.org/10.1016/j.jbo.2015.08.001

Comparator

Ford, J, Cummins, E, Sharma, P, Elders, A, et al. Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours (Structured abstract). Health Technology Assessment Database 2016;(Issue 4)

Centre for Reviews and Dissemination. Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours (Provisional abstract). NHS Economic Evaluation Database (NHSEED). 2013;(2015 Issue 2)

Centre for Reviews and Dissemination. Cost-effectiveness of zoledronic acid in the prevention of skeletal-related events in patients with bone metastases secondary to advanced renal cell carcinoma: application to France, Germany, and the United Kingdom (Structured abstract). NHS Economic Evaluation Database (NHSEED). 2011; (2015 Issue 2)

Centre for Reviews and Dissemination. Cost-effectiveness of zoledronic acid in the management of skeletal metastases in patients with lung cancer in France, Germany, Portugal, the Netherlands,

and the United Kingdom (Structured abstract). NHS Economic Evaluation Database (NHSEED). 2011;(2015 Issue 2)

Centre for Reviews and Dissemination. Cost effectiveness of zoledronic acid in the management of skeletal metastases in hormone-refractory prostate cancer patients in France, Germany, Portugal, and the Netherlands (Structured abstract). NHS Economic Evaluation Database (NHSEED); 2011 (2015 Issue 2)

Centre for Reviews and Dissemination. Cost effectiveness of bisphosphonates in the management of breast cancer patients with bone metastases (Structured abstract). NHS Economic Evaluation Database (NHSEED) 2006;(2015 Issue 2)

Centre for Reviews and Dissemination. Zoledronate for metastatic bone disease and pain: a meta-analysis of randomized clinical trials (Structured abstract). Database of Abstracts of Reviews of Effects. 2015;(2)

Centre for Reviews and Dissemination. Denosumab for treatment of bone metastases secondary to solid tumours: systematic review and network meta-analysis (Provisional abstract). Database of Abstracts of Reviews of Effects. 2015;(2)

Centre for Reviews and Dissemination. Bisphosphonates in the treatment of patients with lung cancer and metastatic bone disease: a systematic review and meta-analysis (Structured abstract). Database of Abstracts of Reviews of Effects 2015;(2)

Centre for Reviews and Dissemination. Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer (Structured abstract). Database of Abstracts of Reviews of Effects. 2015;(2)

Tesfamariam, M. Y., Macherey, S., Kuhr, K., Becker, I., et al. Bisphosphonates or RANK-ligand-inhibitors for men with prostate cancer and bone metastases: a Cochrane Review and network meta-analysis. Cochrane Database Syst Rev. 2018; (5) doi: 10.1002/14651858.CD013020

Macherey, S., Monsef, I., Jahn, F., Jordan, K., et al. Bisphosphonates for advanced prostate cance. Cochrane Database Syst Rev. 2017; (12) doi: 10.1002/14651858.CD006250.pub2

Centre for Reviews and Dissemination. Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours (Provisional abstract). NHS Economic Evaluation Database (NHSEED) 2013; (2015 Issue 2)

Yu Z, Liu Y, Cui Y, Ma R, et al. Cost-effectiveness of standard utilization of zoledronic acid for bone metastases from advanced lung cancer in China. J. Comp. Eff. Res. 2019;8(7), 487 http://dx.doi.org/10.2217/cer-2018-0127

Body JJ, Lipton A, Gralow J, Steger G.G, et al. Effects of denosumab in patients with bone metastases with and without previous bisphosphonate exposure. J. Bone Miner. Res.2010;25(3), 440 http://www3.interscience.wiley.com/cgi-bin/fulltext/123323887/PDFSTART http://dx.doi.org/10.1359/jbmr.090810

Stopeck A, Brufsky A, Kennedy L, Bhatta S, et al. Cost-effectiveness of denosumab for the prevention of skeletal-related events in patients with solid tumors and bone metastases in the United States. J. Med. Econ. 2020; 23(1), 37 http://www.tandfonline.com/loi/ijme20 http://dx.doi.org/10.1080/13696998.2019.1651122

Terpos E, Jamotte A, Christodoulopoulou A, Campioni M, et al. A cost-effectiveness analysis of denosumab for the prevention of skeletal-related events in patients with multiple myeloma in four European countries: Austria, Belgium, Greece, and Italy. Med. Econ. 2019; 22(8), 766 http://www.tandfonline.com/loi/ijme20 http://dx.doi.org/10.1080/13696998.2019.1606002

Ross J.R., Saunders Y., Edmonds P.M., Patel S., Wonderling D., Normand C., Broadley K. A systematic review of the role bisphosphonates in metastatic disease. Health Technology Assessment Health Technol. Assess. 2004; 8(4), http://dx.doi.org/10.3310/hta8040

Yano, A, Arai, Y, Kitayama, S, Otsuka, Y, et al. Effect of zoledronic acid dosing every 3 months in patients with prostate cancer with skeletal metastases: A multicenter prospective exploratory study with matched historical controls. Int J Urol 2018;25(8), 758 https://dx.doi.org/10.1111/iju.13703

Yerram, P, Moore, R, Wolf, S, Barbour, Sally Y. Incidence of skeletal related events in patients with bone metastasis receiving denosumab every four weeks compared to intervals greater than every four weeks. J Oncol Pharm Pract 2019; 25(3), 529 https://dx.doi.org/10.1177/1078155217743074

Mark, M, Thurlimann, B, Ribi, K, Schar, C, et al. Patterns of care for patients with metastatic bone disease in solid tumors: A cross-sectional study from Switzerland (SAKK 95/16). J Bone Oncol. 2020; 21, 100273 https://dx.doi.org/10.1016/j.jbo.2019.100273

Saad, F, Fleshner, N, So, A, Le L, et al. The burden of symptomatic skeletal events in castrate-resistant prostate cancer patients with bone metastases at three Canadian uro-oncology centres. Can Urol Assoc J. 2018;12(12), https://dx.doi.org/10.5489/cuaj.5053

Schroder, J, Fietz, T, Kohler, A, Petersen, V, et al. Treatment and pattern of bone metastases in 1094 patients with advanced breast cancer - Results from the prospective German Tumour Registry Breast Cancer cohort study. Eur J Cancer. 2017; 79, 139 https://dx.doi.org/10.1016/j.ejca.2017.03.031

von Moos, R, Body, J, Rider, A, de Courcy, J, et al. Bone-targeted agent treatment patterns and the impact of bone metastases on patients with advanced breast cancer in real-world practice in six European countries. J Bone O ncol 2018; 11, 1 https://dx.doi.org/10.1016/j.jbo.2017.11.004 Good general overview how many receive less frequent dosing in Europe but no subgroup comparison about effects in care or complications

Body, J, Gatta, F, De C, Erwin, T, Sunning, K. et al. An observational time and motion study of denosumab subcutaneous injection and zoledronic acid intravenous infusion in patients with

metastatic bone disease: results from three European countries. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer Support Care Cancer 2017; 25(9), 2823 https://dx.doi.org/10.1007/s00520-017-3697-5

Outcome

Hortobagyi G.N., Zheng M., Mohanlal R. Indirect Evaluation of Bone Saturation with Zoledronic Acid After Long-Term Dosing. Oncologist. 2019; 24(2), 178 http://theoncologist.alphamedpress.org http://dx.doi.org/10.1634/theoncologist.2018-0218

Tella SH, Kommalapati A, Singhi R.K., Wu S.-G. Cost-effectiveness in managing skeletal related events in breast cancer: A strategy of less-intense dosing schedule of bone modifying agents. Transl. Cancer Res. 2018; 7(Supplement1), S81 http://tcr.amegroups.com/article/download/18411/pdf http://dx.doi.org/10.21037/tcr.2018.01.07

Doshi, S, Sutjandra, L, Zheng, J, Sohn, W, et al. Denosumab dose selection for patients with bone metastases from solid tumors. Clin Cancer Res. 2012; 18(9), 2648 https://dx.doi.org/10.1158/1078-0432.CCR-11-2944.

Duplicate

Continued Efficacy and Safety of Zoledronic Acid (q 4 Wks vs. q 12 Wks) in the 2nd Year of Treatment in Patients With Bone Metastases From Breast Cancer.
A Prospective, Randomized, Double-blind, Stratified, Multi-center, 2-arm Trial of the Continued Efficacy and Safety of Zoledronic Acid (Every 4 Weeks vs. Every 12 Weeks) in the 2nd Year of Treatment in Patients With Documented Bone Metastases From Breast Cancer. 2006. https://clinicaltrials.gov/show/NCT00320710.

Zoledronic Acid in Treating Patients With Metastatic Breast Cancer, Metastatic Prostate Cancer, or Multiple Myeloma With Bone Involvement.
A Randomized, Phase III Study of Standard Dosing Versus Longer Dosing Interval of Zoledronic Acid in Metastatic Cancer. 2009. https://clinicaltrials.gov/show/NCT00869206

Safety and Efficacy of Zoledronic Acid in Patients With Breast Cancer With Metastatic Bone Lesions. A Prospective, Randomized, Multi-center Comparative 2-arm Trial of Efficacy and Safety of Zoledronic Acid (Every 3-months vs. Every 4 Weeks) Beyond Approximately 1 Year of Treatment With Zoledronic Acid in Patients With Bone Lesions From Breast Cancer. 2006 https://clinicaltrials.gov/show/NCT00375427

Denosumab (AMG 162) in Bisphosphonate Naive Metastatic Breast Cancer. A Randomized Active-controlled Study of AMG 162 in Breast Cancer Subjects With Bone Metastasis Who Have Not Previously Been Treated With Bisphosphonate Therapy. 2004. https://clinicaltrials.gov/show/NCT00091832

A randomized active controlled study of AMG 162 in breast cancer subjects with bone metastases who have not previously been treated with bisphosphonate therapy. 2004 http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2004-000509-24-AT

A prospective, randomized, multi-center comparative 2-arm trial on efficacy and safety of zoledronic acid every 3-months vs. every 4 weeks beyond approximately 1 year of treatment with zoledronic acid in patients with bone lesions from breast cancer - ND". 2006 http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2005-004942-15-IT

Fizazi, K, Bosserman, L, Gao, G, Skacel, T, Markus, R. Denosumab treatment of prostate cancer with bone metastases and increased urine N-telopeptide levels after therapy with intravenous bisphosphonates: results of a randomized phase II trial. J Urol 2009; 182(2), 509 https://dx.doi.org/10.1016/j.juro.2009.04.023 seems to be same as Fizazi

Country

Hutton, B, Morretto, P, Emmenegger, U, Mazzarello, S, et al. Bone-targeted agent use for bone metastases from breast cancer and prostate cancer: A patient survey. J Bone Oncol. 2013; 2(3),105. http://dx.doi.org/10.21037/tcr.2018.01.07.

Studies that were in the first screening step included for more than one HTA domain and excluded for the same reason multiple times, where only listed once.

**Ongoing Trials*

Appendix 4. Overview of the SLRs and MAs that included the identified RCT

SLR+MA / RCT	Yang et al. 2020[32] P: mBC I/C: BP	Cao et al. 2017[28] P: cancer-related BM I/C: zoledronate	Awan et al. 2019[21] P: mBC I/C: BTA	Santani et al. 2019[31] P: BM in solid cancer I/C: zoledronate	O'Carrigan et al. 2017[30] P: mBC I/C: BTA	Ibrahim et al. 2015[29] P: mBC I/C: BTA	Luo et al. 2019[22] P: cancer-related BM I/C: BP	Lui et al. 2018[47] P: cancer-related BM I/C: BTA
Hortobagyi et al. 2017[37] P: mBC I/C: zoledronate	X	X	X	X	X	X	X	X
Himelstein et al. 2017[36] P: cancer-related BM I/C: zoledronate	X	X	X	X	X	-	X	X
Amadori et al. 2013[35] P: mBC I/C: zoledronate	X	X	X	X	X	X	X	X
Novartis 2012[34] P: mBC + myeloma with BM I/C: zoledronate	-	-	-	-	-	-	X	-
Lipton[40 41] et al. 2007+2008 P: mBC I/C: denosumab	-	-	X	-	-	X	-	X
Fizazi et al. 2009+2013[38 39] P: cancer-related BM I/C: denosumab	-	-	-	-	X	X	-	X

Key: BM – bone metastasis; BP – bisphosphonates; BTA– bone-targeting agent; I/C – intervention/comparator; MA – meta-analysis; mBC – metastatic breast cancer; P – population; RCT – randomized controlled trial; SLR – systematic literature review.

Appendix 5. List of ongoing RCTs fitting the inclusion criteria

Trial name/registry ID	Study design	Population; n	Intervention	Comparator	Outcomes	Estimated completion date; status
SAKK 96/12[33] *NCT02051218*	• Phase 3, randomized, open-label, multicentre, international, non-inferiority • 50 centres in Switzerland, Germany and Austria	• mBC • mPC • Not previously treated with BTA n=1,380	Denosumab every 4 weeks	Denosumab every 12 weeks	• SSEs • SMRs • Overall survival • Quality of life measures • Bone markers • AEs/toxicity • Economic evaluations	December 2022; recruiting
REaCT-BTA[46] *NCT02721433*	• Phase 4, randomized, open-label, multicentre, national, non-inferiority • Centres in Canada	• mBC • mPC No information about pretreatment available n=250	Pamidronate/ denosumab/ zoledronate every 4 weeks	Pamidronate/ denosumab/ zoledronate every 12 weeks	• SSEs • Health-related quality of life scores • AEs/toxicity • Economic evaluations	April 2020; active, not recruiting
Key: AE – adverse event; BTA – bone-targeting agent; mBC – metastatic breast cancer; mPC – metastatic prostate cancer; SMR – skeletal morbidity rate; SSE – symptomatic skeletal event.						

Appendix 6: Risk of bias assessment