HEALTH TECHNOLOGY ASSESSMENT REPORT

MOH/P/PAK/413.18(RR)-e

BONE TARGETING AGENTS (BTAs) IN PREVENTING SKELETAL RELATED EVENTS (SREs) FOR METASTATIC CANCERS OF SOLID TUMOURS AND ECONOMIC EVALUATION

HEALTH TECHNOLOGY ASSESSMENT SECTION (MaHTAS)
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH

DISCLAIMER

This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organizations. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review.

Please contact: htamalaysia@moh.gov.my, if you would like further information.

Published by
Malaysian Health Technology Assessment Section, (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Complex E, Precint 1
Federal Government Administrative Centre
62590, Putrajaya, Malaysia
Tel: 603 88831229
Fax: 603 8883 1230

Copyright
The copyright owner of this publication is the Malaysian Health Technology Assessment Section (MaHTAS), Medical Development Division, Ministry of Health Malaysia. Content may be reproduced in any number of copies and in any format or medium provided that a copyright acknowledgement to the Malaysian Health Technology Assessment Section (MaHTAS) is included and the content is not changed, not sold, nor used to promote or endorse any product or service, and not used in an inappropriate or misleading context.

ISBN:

Available on the MOH website: http://www.moh.gov.my/index.php/pages/view/1691

This HTA report was endorsed in HTA & CPG Council Meeting 2/2018 on 26 November 2018.

AUTHORS

Madam Atikah Shaharudin
Registered Pharmacist
Senior Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Dr. Hanin Farhana Kamaruzaman
(Decision Analytic Modelling for Economic Evaluation)
Senior Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Dr. Aidatul Azura Abdul Rani
Senior Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Mr. Syful Azlie Md Fuzi
Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

INFORMATION SPECIALIST

Madam Zamilah Mat Jusoh @Yusof
Nursing Officer
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

EXPERT COMMITTEE

Dr. Muthukkumaran Thiagarajan
Consultant Clinical Oncologist
Department of Oncology and Radiotherapy
Hospital Kuala Lumpur

Dr Akmal Naziah Ahmad
Senior Principal Assistant Director
Medical Services Unit
Medical Services Development Section
Medical Development Division
Ministry of Health Malaysia

Dr Junie Khoo Yu Yen
Consultant Clinical Oncologist
Department of Oncology and Radiotherapy
National Cancer Institute

Dr Soo Hoo Hwoei Fen
Consultant Clinical Oncologist
Department of Oncology and Radiotherapy
Hospital Pulau Pinang

Dato' Dr. (Mr) Mohammad Anwar Hau Abdullah
Surgeon
Consultant Orthopedics Surgery
Hospital Raja Perempuan Zainab II, Kota Bahru

Dr Malwinder Singh Sandhu
Consultant Clinical Oncologist
Department of Oncology and Radiotherapy
Hospital Kuala Lumpur

Dr Adlinda Alip
Consultant Clinical Oncologist & Senior Lecturer
Department of Clinical Oncology
University Malaya Medical Centre

Pn. Nurul Suhaida Badarudin
Senior Pharmacist
National Cancer Institute

Dr. Junainah Sabirin
(Public Health Physician)
Deputy Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

EXTERNAL REVIEWERS

Prof. Dr. Nur Aishah Taib
Senior Consultant Breast Surgeon
Department of Surgery
University Malaya Medical Centre

Dr. Azura Rozila Ahmad
Consultant Medical Oncology
Beacon International Specialist Hospital
Petaling Jaya

Prof. Dr. Wan Faisham Nu'man Wan Ismail
Professor of Orthopaedic
Department of Orthopaedic
Universiti Sains Malaysia

Prof. Dr. Sharifa Ezat Wan Puteh
Professor of Economic
Department of Community Health, UKM
Hospital Canselor Tuanku Muhriz

Prof. Madya Dr. Zafar Ahmed
Associate Professor of Economic
Faculty of Medicine and Health Science, UNIMAS
Sarawak

ACKNOWLEDGEMENT

The authors for this Health Technology Assessment Report would like to express their gratitude and appreciation to the following for their contribution and assistance:

- Health Technology Assessment and Clinical Practice Guidelines Council.
- Technical Advisory Committee for Health Technology Assessment.
- Technical Advisory Committee for Health Technologies Economic Evaluation (TACHTEE).

DISCLOSURE

The authors of this report have no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

EXECUTIVE SUMMARY

Background

According to WHO, cancer is the second leading causes of morbidity and mortality worldwide with approximately 9.6 million cancer related deaths in 2018. Worldwide, one in six deaths is due to cancer. The low and middle income countries account for 70% of the world's cancer deaths. In terms of incidence, cancers with high incidence of bone metastases namely lung, breast and prostate ranked 1st, 2nd and 4th commonest cancer diagnosed in 2018; indicating the importance of managing skeletal related morbidity amongst cancer patients. In Malaysia, National Cancer Registry Report reported a total of 64 275 cancer deaths within the period of 2007 and 2011 and over the years, the numbers have gradually increased. The major solid tumour types that tend to metastases to bone include breast, prostate, lung, kidney and thyroid cancers. Metastatic cancer of solid tumour cells in circulation interacts with the bone microenvironment causing a positive feedback loop of tumour growth, which mostly affects the skeleton and thus weakens bone integrity that lead to skeletal related events (SREs). Patients with an SRE are more likely to have a subsequent SRE and have a poorer prognosis, shorter overall survival than and impaired quality of life that consume more health resources compared with patients without SREs. There are two types of drugs currently used for the prevention and treatment of SREs that result from bone metastases that include Bisphosphonates and Denosumab. As these agents play an important role in preventing SREs, their effectiveness and cost implications need to be assessed for routine practice in Ministry of Health, Malaysia.

Technical features

Bisphosphonates are synthetic analogues of pyrophosphates, the natural regulator of bone mineral precipitation and dissolution. They are potent inhibitors of osteoclast activity that bind to the bone matrix. The four Bisphosphonates currently available are Clodronate, Pamidronate, Ibandronate and Zoledronic acid. The next generation of bone metastasis treatments is Denosumab. Denosumab is a fully human monoclonal antibody that inhibits osteoclast maturation, activation, and function by binding to receptor activator of nuclear factor kappa B ligand (RANKL), subsequently inhibits the mechanism of the resorption of the bone.

Policy question

In MOH practices, should Bone Targeting Agents (BTAs) be used in preventing SREs for metastatic cancers of solid tumours? Which BTAs should be used in routine clinical practice?

Objectives

1. To assess and compare the effectiveness, safety, economic implications, organizational or societal issues of BTAs in preventing SREs for metastatic cancers of solid tumours.
2. To conduct local economic evaluation of Bisphosphonates and Denosumab.

Methods

Systematic review of literatures

Studies were identified by searching the electronic database for published literatures pertaining to the use of BTAs in preventing SREs for metastatic cancers of solid tumours. The following databases were searched through the Ovid interface: MEDLINE, EBM Reviews-Cochrane Database of Systematic Reviews (2005 to April 18), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2018), EBM Reviews-Health Technology Assessment (4th Quarter 2016), EBM Reviews-DARE, EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2016) and Embase. Searches were also being conducted in PubMed, Horizon Scanning database, INAHTA database, and FDA database. Additional literatures were identified from the references of the retrieved articles. General search engine also be used to get additional web-based materials and information. The last search was run on 17 May 2018. All relevant literature was appraised using the Critical Appraisal Skills Programme (CASP) tool and Cochrane Collaboration Assessment tool. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force.

Decision analytic economic modelling

The economic evaluation was designed from provider perspective (Ministry of Health, Malaysia) based on mix-cased unit in general public hospital. The evaluation was conducted using literature-based Markov model (Excel) to compare the direct costs and quality adjusted life years (QALY) for hypothetical cohort of patients with primary solid tumour with bone metastases using the seven healths states in two disease conditions; stable and progressive within 3-month transition cycle and lifetime time horizon.

Results and conclusion

A. Systematic review of literature

A total of 74 relevant abstracts were screened using the inclusion and exclusion criteria. Twenty-two out of 74 full text studies comprising of one Health Technology Assessment (HTA), five Systematic Review (SR), 12 Randomised Controlled Trials (RCTs), one retrospective cohort study, one cross sectional survey, one SR on cost implication and one cost-effectiveness analysis were finally included in this review.

Effectiveness

- There was fair to good level of evidence to suggest:

Outcomes/ Group	BTAs vs placebo/ no treatment/ best supportive care (BSC)	Bisphosphonates vs alternate Bisphosphonates	Denosumab vs Bisphosphonates	Different regimen of BTAs (12-weekly vs 4-weekly)
Time to first SREs	Significantly delayed time to 1st SREs in all types of cancer except non-small cell lung cancer **(NSCLC)**	Zoledronic acid **(ZA)** was the most effective in delaying the time to 1st SREs followed with **Pamidronate** and **Ibandronate** in breast and lung cancer	Pooled data from meta-analysis showed that **Denosumab** delayed the time to 1st SREs by 18% for all types of cancer. [Hazard ratio (HR): 0.82, 95% CI: 0.77, 0.87]	No difference in time to 1st SREs for **ZA** in breast cancer (HR: 1.06, 95% CI: 0.70, 1.60)
Risk of first and subsequent SREs	**BTAs** reduced the risk of 1st and subsequent SREs in all types of cancer except NSCLC. Denosumab was superior in reducing risk of developing SREs followed by Zoledronic acid and Pamidronate.	**ZA** significantly reduced risk of 1st and subsequent SREs in patients with breast cancer only while no difference in other types of cancers	**Denosumab** significantly reduced the risk of 1st and subsequent SREs by 17% with for all types of cancer [Rate ratio: 0.83, 95% CI: 0.78, 0.88]	No difference for **ZA** in terms of risk of 1st and subsequent SREs in breast cancer and prostate cancer (HR: 0.97, 95% CI: 0.83, 1.12)
Number of patients with SREs	Bisphosphonates significantly reduced the number of patients with SREs in patients with breast and prostate cancer only.	The results were similar between all types of Bisphosphonates in patients with breast cancer for outcomes number of patients with SREs, number of events per year and SMR	-	No significant difference for **ZA** in overall number of patients with SREs (Risk ratio: 1.00, 95% CI: 0.88, 1.15) The evidence for **Denosumab** was limited due to the small sample size involved even though there was no significant difference in overall number of patients with SREs (Risk ratio: 1.96, 95% CI: 0.71, 5.38)
Number of events per year	**ZA** reduced the number of SREs compared with placebo in lung cancer		Not reported	Not reported
Skeletal morbidity rate	SMR occurred less frequent in breast, prostate cancer and OSTs for patients who received **ZA** and **Pamidronate**		-	-

Outcomes/ Group	BTAs vs placebo/ no treatment/ best supportive care (BSC)	Bisphosphonates vs alternate Bisphosphonates	Denosumab vs Bisphosphonates	Different regimen of BTAs (12-weekly vs 4-weekly)
Overall survival	Treatment with Bisphosphonates did not appear to affect overall survival in all types of cancer.	-	Overall survival was similar for all types of cancer (HR: 0.94, 95% CI: 0.87, 1.01) except for lung cancer where patients who received **Denosumab** significantly delayed by 21% (HR: 0.79, 95% CI: 0.65, 0.96)	Not reported
Disease progression	-	Not reported	No significant difference in all types of cancer (HR: 1.02, 95% CI: 0.96, 1.07)	Not reported
Pain relief	Significant pain relief with Bisphosphonates in breast and prostate cancer.	-	**Denosumab** was favourable in reducing pain in breast cancer, prostate cancer and other solid tumours	-
Quality of life (QoL)	Better QoL with Bisphosphonates in breast and prostate cancer.	-	**Denosumab** was found improve QoL in patients with breast cancer.	Not reported

- There was fair level of evidence to suggest:

Outcomes/ Group	BTAs vs placebo/ no treatment/ best supportive care (BSC)	Bisphosphonates vs alternate Bisphosphonates	Denosumab vs Bisphosphonates	Different regimen of BTAs (12-weekly vs 4-weekly)
Number of patients with SREs	-	-	**Denosumab** significantly reduced number of patients with SREs in breast cancer only while fewer SREs in prostate cancer.	-
Skeletal morbidity rate (SMR)	-	-	In terms of **(SMR), Denosumab** significantly reduced the rate by 22% compared to **ZA** in patients with breast cancer.	No significant difference in terms of **(SMR)** for **ZA** in patients with breast cancer
Overall survival	-	No significant difference in terms of overall survival in patients with breast cancer.	-	-

Outcomes/ Group	BTAs vs placebo/ no treatment/ best supportive care (BSC)	Bisphosphonates vs alternate Bisphosphonates	Denosumab vs Bisphosphonates	Different regimen of BTAs (12-weekly vs 4-weekly)
Disease progression	Bisphosphonates **(ZA)** reduced the number of events per year and delayed time to progression of disease in patients with lung cancer compared to placebo.	-	-	-
Pain relief	-	No significant difference in terms of pain reduction in patients with breast cancer.	-	No difference in terms of pain for **Pamidronate** in patients with breast cancer.
Quality of life (QoL)	-	No significant difference for QoL in patients with lung cancer.	-	-

Safety

- There was fair to good level of evidence to suggest:
  - No significant difference in few adverse events such as flu-like syndromes, hypocalcemia, impaired renal function and osteonecrosis when compared Bisphosphonates with placebo and alternate Bisphosphonates groups. The incidence of these adverse events are low and could be used safely under regular clinical monitoring.

  - Denosumab was associated with two time higher occurrence of hypocalcemia but with less renal toxicity compared with Zoledronic acid. However, both had similar occurrence of osteonecrosis of the jaw (ONJ) event.

  - No significant difference between12-weekly and 4-weekly regimens in adverse events for hypocalcemia and ONJ. However, less renal toxicity events found in 12-weekly Zoledronic acid for breast cancer and prostate cancer compared to 4-weekly Zoledronic acid.

Economic evaluation

- A SR on economic evaluation reported for breast cancer, Denosumab was the most effective but more costly compared to Zoledronic acid with lowest incremental cost per QALY in excess of £57, 000. The finding was similar for prostate cancer, however the costs were varied across countries and Denosumab is unlikely to represent value for money in the absence of patient assessment scheme (PAS). In line with above, for lung cancer, Denosumab

resulting in incremental cost per QALY >£68,000. Overall evidence suggest Zoledronic acid would result in gains in QALYs for a modest additional cost.

- A cost–effectiveness analysis performed in US in 2017 found that on base-case analysis, Denosumab was dominated and 12-weekly Zoledronic acid would be a dominant option. As QALYs was identical in all three treatments, 12-weekly Zoledronic acid was the optimal treatment as it was the least costly treatment. Eventhough sensitivity analysis was performed, the results did not lead Denosumab to being the least costly treatment.

Ethical/Social/Organizational

- One evidence was related to utilization pattern of BTAs and the impact of BTAs among metastatic solid tumour in real-world practice showed that patients treated with Denosumab were more likely compliant compared to Zoledronic acid. The number of percentage that switched agents was lower in the Denosumab group compared to Zoledronic acid group within first, second and third year of administration. Thus, the higher levels of compliance and persistence may improve treatment effectiveness.

B. Decision analytic economic modelling

Based on this decision analytic model, the use of bone targeting agents in preventing skeletal-related events among Stage IV solid tumour patients with bone metastases is a cost-effective strategy. Within this evaluation, the most cost-effective option was 12-weekly intravenous Zoledronic acid, yielding an ICER of RM 4,968.87 per QALY gained which is lower than the cost-effectiveness threshold of 1 GDP per capita. The estimated total financial implications for this strategy with 100% potential patients coverage was RM 8.8 million per year.

Recommendation

Based on this review, BTAs significantly delay the development of SREs among metastatic cancers of solid tumours and hence, directly preserving quality of life and improve morbidity rate. This effect is particularly significant with Zoledronic Acid and Denosumab. Twelve-weekly IV Zoledronic acid was found to be the most cost-effective option in preventing SREs among solid tumour patients with bone metastases. Current evidence on the use of 12-weekly Denosumab is still limited, thus, further good quality research is warranted. In general, BTAs were well tolerated with rare occasion of adverse events. However, creatinine clearance must be closely monitored in patients receiving Zoledronic acid in view of its potential side effect of renal impairment.

ABBREVIATIONS

BTA	: Bone targeting agent
BPs	: Bisphosphonates
BSC	: Best supportive care
CASP	: Critical Appraisal Skill Programme
CI	: Confidence interval
CCA	: Cost-consequences analysis
CDSR	: Cochrane Database of Systematic Reviews
CEA	: Cost-effectiveness analysis
CUA	: Cost-utility analysis
DP	: Disodium Pamidronate
HTA	: Health Technology Assessment
HRQoL	: Health related quality of life
ICER	: Incremental cost-effectiveness ratio
ITT	: Intention-to-treat
IV	: Intravenous
LYS	: Life years saved
MOH	: Ministry of Health
NSCLC	: Non-small cell lung cancer
OR	: Odds ratio
OST	: Other solid tumour
PAS	: Patient access scheme
RANKL	: Receptor activator of nuclear factor kappa B ligand
RCT	: Randomised controlled trial
RR	: Rate ratio
RR	: Relative risk
SC	: Subcutaneous
SCC	: Spinal cord compression
SCLC	: Small cell lung cancer
SMR	: Skeletal morbidity rate
SR	: Systematic review
SRE	: Skeletal related event
US FDA	: United States Food Drug Administration
QALY	: Quality-adjusted life year
QoL	: Quality of life
WHO	: World Health Organization
ZA	: Zoledronic acid

TABLE OF CONTENTS

	Disclaimer		i
	Authors and Information specialist		ii
	Expert committee		iii
	External reviewers		iv
	Acknowledgement and Disclosure		v
	Executive summary		vi
	Abbreviations		xi
1	CHAPTER 1: INTRODUCTION		1
	1.1	BACKGROUND	1
	1.2	TECHNICAL FEATURES	3
	1.3	POLICY QUESTION	4
2	CHAPTER 2: SYSTEMATIC REVIEW AND META-ANALYSIS		4
	2.1	OBJECTIVES	5
	2.2	RESEARCH QUESTIONS	5
	2.3	METHODS	5
	2.4	RESULTS	8
	2.4.1	RESULTS OF THE SEARCH	8
	2.4.2	DESCRIPTION OF THE INCLUDED STUDIES	9
	2.4.3	RISK OF BIAS ASSESSMENT	15
	2.4.4	EFFECTIVENESS	18
	2.4.5	SAFETY	52
	2.4.6	ECONOMIC EVALUATION	54
	2.4.7	SOCIAL/ETHICAL/ LEGAL/ ORGANIZATIONAL ISSUES	57
	2.5	DISCUSSION	59
	2.5.1	INTERPRETATION OF THE EVIDENCE	59
	2.5.2	QUALITY OF THE EVIDENCE	61
	2.5.3	STRENGTHS AND LIMITATIONS	62
3	CHAPTER 3: DECISION ANALYTIC ECONOMIC MODELLING		63
	3.1	OBJECTIVES	63
	3.2	METHODS	63
	3.2.1	MODEL STRUCTURE	63
	3.2.2	MODEL ESTIMATION	65
	3.2.3	SENSITIVITY ANALYSIS	67
	3.2.4	ASSUMPTIONS	68
	3.3	RESULTS AND DISCUSSIONS	68
	3.4	LIMITATIONS	72
4	CHAPTER 4: CONCLUSION AND RECOMMENDATIONS		74
	4.1	CONCLUSIONS	74

	4.1.1	SYSTEMATIC REVIEW AND META-ANALYSIS	74
	4.1.2	DECISION ANALYTIC ECONOMIC MODELLING	76
	4.2	RECOMMENDATION	77
5	REFERENCES		78
6	APPENDICES		85
		Appendix 1- Hierarchy of evidence for effectiveness studies	85
		Appendix 2- Health Technology Assessment Protocol	86
		Appendix 3- Search strategy	95
		Appendix 4- Assessment Tools	112
		Appendix 5- Total number of Stage IV patients in 13 solid tumour cancers	114
		Appendix 6- Evidence Table (Included studies)	115
		Appendix 7- List of excluded studies	176

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Cancer which spread from the primary site to other parts of the body is called metastatic cancer.[1] When cancerous cells break away from the primary site, they travel to other area of the body through either the bloodstream or lymphatic system. Bone is one of the common sites for the cancer cells to settle and start growing.[1,2] Tumour cells from metastatic cancer which are present in circulation interact with the bone micro-environmant, causing a positive feedback loop of tumour growth, which mostly affects the skeleton and weakens bone integrity and lead to skeletal related events (SREs).[1] SREs could be defined as spinal cord compression (SCC), pathological fracture, palliative radiation to the bone and bone surgery.[2-5] However, bone pain and hypercalcemia were included in the previous definition.[6-8] When SREs happen, the quality of life and life expectancy of a patient may be greatly reduced.

Carcinoma that commonly metastasize to the bone are prostate, breast, lung, thyroid and kidney.[1,2] The frequency of SREs may differ based on the site of the malignancy. It is estimated that 73% of breast cancer, 68% of prostate cancer, 36% of lung cancer, 42% of thyroid cancer and 35% of kidney cancer showed evidence of bone metastases at post-mortem examination,[1] but this prevalence was not available for Malaysian population. According to the Malaysian National Cancer Registry Report 2007-2011, prostate cancer was among the five most common cancers in male with incidence rate 6.6 per 100,000 population whereby 41.3% from 1592 were detected at stage four (658). While for female, breast cancer was the most common with incidence rate 31.1 per 100,000 population whereby 36.5% from 12011 cases were diagnosed at stage four (2411).[9] At the same period there were 4028 stage four lung cancer patients, 273 stage four thyroid cancer patients and 372 stage four kidney cancer patients.[9]

More hospital resources including treatment, physiology, rehabilitation and social support were needed when SREs develop in metastatic cancer patients. Studies conducted in Europe and the United States describe the substantial healthcare resource use required for the management of metastatic bone disease and the treatment of SREs in patients with advanced cancer in general.[10-13] A recent analysis of health databases in the United States found the cumulative incidence of SREs at 24 months was 54.2% among patients with breast cancer, 41.9% among patients with prostate cancer and 47.7% among patients with lung cancer.[14] The incidence rate for patients admitted following SREs were 211 per 1000 for breast cancer, 150 per 1000 for prostate cancer and 260 per 1000 for lung cancer in Spain.[15] Costs and hospital length of stays varied by type of SREs and ranged from €1187 to €40 948, depending on event type of cancer.[15] On

average, one of the major skeletal events occur every three to six months. Skeletal related events resulted in greatest morbidity which includes pain, hypercalcemia and pathological fracture affecting patients' quality of life over the years and may increase healthcare cost.[10,16,17] Survival rates for people with bone metastases vary depending on the primary tumour type. In breast cancer, median survival was 24 months with a 5-year survival rate of 20% and in prostate cancer there was a 5-year survival rate of 25% and a median survival of 40 months.[1,18] Thus, hospitalisation with SREs is associated with high health economic burden. [19,20] Therefore, reducing the incidence of metastatic bone disease associated with SREs may lead to less inpatient admissions, shorter lengths of stay and less cost.

There are two types of Bone targeting agents (BTAs) currently used for the prevention and treatment of SREs that result from bone metastases: Bisphosphonates and Denosumab, a receptor activator of nuclear factor kappa B ligand (RANKL). It is known that NICE published information through their guidelines that patients with lung cancer, metastatic spinal cord compression and advanced breast cancer to be given Bisphosphonates for prevention of SREs instead of receiving best supportive care. Bisphosphonates is not offered to prevent the complications of bone metastases in men with hormone-relapsed prostate cancer, however may be considered for pain relieve when treatments with analgesic and palliative radiotherapy have failed. Denosumab, is an alternative therapy to Bisphosphonates.[21-24]

In Ministry of Health (MOH), Malaysia, Drug Formulary, Ibandronic acid tablet and Denosumab injection was approved for the treatment of post-menopausal osteoporosis, while Zoledronic acid was approved for prevention of SREs only in patients with multiple myeloma involving multiple bone lesions.[20] Zoledronic acid might be less convenient to patients as it is delivered intravenously (IV) for 15 minutes compared to Denosumab which is administered subcutaneously (SC) and would be a better option but cost implications need to be taken into account.[25-29] As these agents play an important role in preventing SREs, their effectiveness and economic implications need to be assessed. Hence, this HTA was requested by Clinical Oncologist, Hospital Kuala Lumpur (HKL).

1.2 TECHNICAL FEATURES

Bisphosphonates

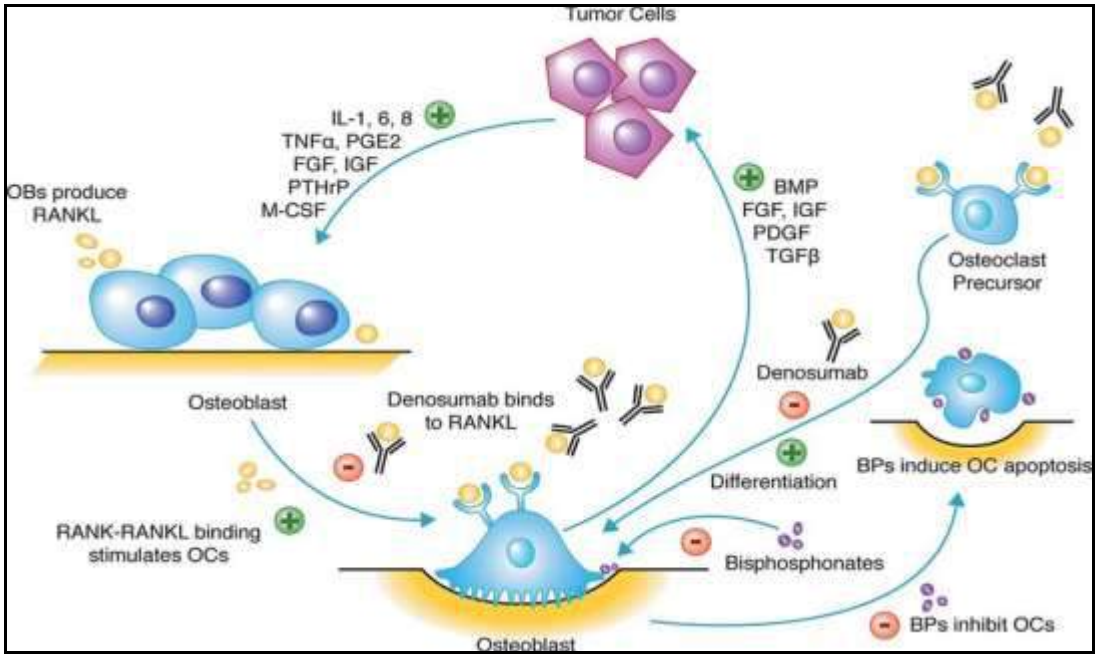
Bisphosphonates are synthetic analogues of pyrophosphates, the natural regulator of bone mineral precipitation and dissolution. They are potent inhibitors of osteoclast activity that bind to the bone matrix. They are released during bone resorption, and are subsequently internalised by osteoclasts, where they interfere with biochemical pathways and induce osteoclast apoptosis. Bisphosphonates also antagonise osteoclastogenesis and promote the differentiation of osteoblasts (Figure 1). As a result, Bisphosphonates inhibit tumour-induced osteolysis and reduce skeletal morbidity.[18]

There are four Bisphosphonates currently available: Clodronate; administered orally at a dose of 1.6-3.2 gram (g) daily, Pamidronate; administered by slow intravenous infusion (IV) at a dose of 90 milligram (mg) every four weeks, Ibandronate; administered either orally 150 mg monthly or IV 6 mg every three to four weeks and Zoledronic acid (ZA); administered by intravenous infusion 4 mg every three to four weeks. Absorption of oral Bisphosphonates is estimated at less than 6% of the active compound because of the low uptake from passive diffusion in the gastrointestinal tract. Location of treatment is important to patients. One study found that patients prefer administration at home, but this is not often possible with IV treatments.[30]

Bisphosphonates are generally well tolerated, although they are associated with osteonecrosis of the jaw, hypocalcaemia and renal toxicity, thus requiring routine monitoring of serum creatinine and other biochemical parameters and dose adjustments if necessary. Despite these concerns, Bisphosphonates are an important tool in the management of skeletal complications of cancer, providing benefits for the treatment of hypercalcemia, osteolytic lesions and fractures, as well as offering amelioration of pain and improvement in quality of life.[18,31]

Denosumab

Denosumab is a fully human monoclonal antibody that inhibits osteoclast maturation, activation, and function by binding to receptor activator of nuclear factor kappa B ligand (RANKL), subsequently inhibits the mechanism of the resorption of the bone (Figure 1).[32-34] Denosumab is currently approved for post-menopausal osteoporosis, administered by subcutaneous 60 mg every six months.



*Adapted from Lee et al., 2012 [35]

Figure 1. Mechanism of action of Denosumab and Bisphosphonates on vicious cycle of osteolytic metastases

Zoledronic acid with Zometa® trade name was approved by United States Food and drug Administration (US FDA) in 2001 for the treatment of patients with multiple myeloma and documented bone metastases from solid tumours in conjunction with standard therapy. While in United Kingdom (UK), Ibandronic acid is licensed for bone metastases in breast cancer only and Zoledronic acid is the only drug that is licensed for all cancers involving the bone.[19] Denosumab with Xgeva® trade name was approved on November 18, 2010 by US FDA for the prevention of SREs in patients with bone metastases from solid tumours.[19]

1.3 POLICY QUESTION

1. Should Bone Targeting Agents (BTAs) be used in preventing SREs for metastatic cancers of solid tumours?

2. Which BTAs should be used in routine clinical practice?

CHAPTER 2: SYSTEMATIC REVIEW AND META-ANALYSIS

2.1 OBJECTIVES

i. To assess and compare the effectiveness of BTAs in preventing SREs for metastatic cancers of solid tumours.

ii. To assess the safety of BTAs in preventing SREs for metastatic cancers of solid tumours.

iii. To assess the cost-effectiveness of BTAs in preventing SREs.

iv. To assess the organisational or societal issues related to the use of BTAs in preventing SREs for metastatic cancers of solid tumours.

2.2 RESEARCH QUESTIONS

i. What are the short and long term benefits of using BTAs in preventing SREs for metastatic cancers of solid tumours? Is there a subgroup of patients who is more likely to benefit from these agents (e.g. type of cancer, etc.)?

ii. How safe is BTAs in preventing SREs for metastatic cancers of solid tumours?

iii. What is the economic implication of using BTAs in preventing SREs compared to current best practice?

iv. What are organisational or societal issues related to the use of BTAs in preventing SREs for metastatic cancers of solid tumours?

2.3 METHODS

2.3.1 Literature search strategy

Studies were identified by searching the electronic database for published literatures pertaining to the use of BTAs in preventing SREs for metastatic cancers of solid tumours. The following databases were searched through the Ovid interface: MEDLINE, EBM Reviews-Cochrane Database of Systematic Reviews (2005 to April 18), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2018), EBM Reviews-Health Technology Assessment (4th Quarter 2016), EBM Reviews-DARE, EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2016) and Embase. Searches were also being conducted in PubMed, Horizon Scanning database, INAHTA database, and FDA database. Additional literatures were identified from the references of the retrieved articles. General search engine was also used to get additional web-based materials and information. The detail of the search strategy was presented in the Appendix 3.

2.3.2 Inclusion criteria

a. Population: Adult patients with metastatic cancers or stage IV cancers (breast cancer, prostate cancer, lung cancer and other solid tumours)

b. Intervention: Bisphosphonates or Receptor Activator of Nuclear Factor Kappa B Ligand (RANKL) inhibitor

c. Comparator: Placebo or best supportive care or Bisphosphonates or Chemotherapy

d. Outcome: Effectiveness:

i. Time to first SREs

ii. Risk of first and subsequent SREs

iii. No. of patients with first SREs

iv. No. of events per year

v. Quality of life

Safety:

i. Hypocalcaemia

ii. Osteonecrosis of the jaw

iii. Adverse events potentially associated with renal impairment

iv. Patients experiencing acute-phase reactions (acute pain, bone pain)

v. Gastrointestinal toxicity

Organisational issues (e.g. hospital admission, length of stay, day care)
Social issues (e.g. patient satisfaction, compliance)

e. Study design: HTA reports, Systematic Review, Randomised Controlled Trials for effectiveness and safety plus one cross-sectional survey for outcome bone pain. Another restrospective cohort for outcome social/ethical/psychological/organisational and studies which include economic evaluation.

f. English full text articles

2.3.3 Exclusion criteria

a. Study design: Non-randomised controlled trials, animal study, laboratory study, observational studies, narrative review, editorials, and letter to the editors.

b. Non English full text article.

Based on the above inclusion and exclusion criteria, study selection was carried out independently by two reviewers. Disagreement was resolved by discussion.

2.3.4 Critical Appraisal of Literature

The risk of bias (methodology quality) of all retrieved literatures was assessed using the relevant checklist of Cochrane Collaboration Assessment tools and Critical Appraisal Skill Programme (CASP) by two reviewers depending on the type of the study design. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force (Appendix 1).

2.3.5 Analysis and Synthesis of Evidence

Data extraction strategy

The following data was extracted:

i. Details of methods and study population characteristics.

ii. Details of intervention and comparators.

iii. Details of individual outcomes for safety, effectiveness, cost implication,

Organisational and societal issues associated with the use of bone targeting agents.

Data was extracted from selected studies by two reviewers using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion.

Methods of analysis/synthesis

Data on the effectiveness, safety and cost implication of using BTAs presented in tabulated format with narrative summaries. Meta-analysis was conducted for the RCTs that compared Denosumab with Zoledronic acid and BTAs between different regimen (12-weekly versus 4-weekly). The data were pooled using Review Manager (Revman) 5.3 if heterogeneity, I^2 is less than 80%.[36] Hazard ratio (HR), rate ratio (RR) and risk ratio (RR) were calculated using fixed–effect

method with 95% Confidence Interval (CI) were reported as appropriate. Statistical significance was set at $p<0.05$ for all outcomes.

2.4 RESULTS

2.4.1Results of the search

A total of 1,172 records were identified through the Ovid interface: MEDLINE, EBM Reviews-Cochrane Database of Systematic Reviews (2005 to April 18), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2018), EBM Reviews-Health Technology Assessment (4th Quarter 2016), EBM Reviews-DARE, EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2016) and Embase. Searches were also conducted in PubMed, Horizon Scanning database, INAHTA database, and FDA database. The last search was run on 17 May 2018.

Fifteen additional records were identified from references of retrieved studies. After removal of 233 duplicates, 954 records were screened through titles and abstracts. A further 880 records were excluded. Subsequently, 74 potentially relevant abstracts were retrieved in full text. Another 52 studies were excluded for not meeting the inclusion criteria (Figure 2). The studies were excluded due to irrelevant study design (n=20), irrelevant population (n=4), irrelevant intervention (n=3), irrelevant outcome (n=17) as well as those already included in the systematic reviews (n=8). The excluded studies are listed in Appendix 7.

Description of 22 full-text articles included in qualitative synthesis are presented in Table 1, Table 2 and Table 3. Number of full-text articles included in quantitative analysis are presented in Table 2.

2.4.2 Description of the included studies

Twenty two full text studies included in this review comprised of one Health Technology Assessment (HTA), five Systematic Review (SR), 12 Randomised Controlled Trials (RCTs), one cross-sectional survey, one retrospective cohort study, one SR on economic evaluation and one study on cost-effectiveness analysis. All studies included were published in English language between 2007 and 2018 and were mostly conducted in the U.S.A., United Kingdom, European, Japan, Australia, India and South Africa.

Of the 22 included articles, 19 studies were included in the effectiveness and safety sections in this review. The other two studies covers economic evaluation and one study related to social/ethical/psychological of BTAs in preventing SREs for metastatic cancers of solid tumours.

Types of primary tumour included were breast cancer (13 studies), prostate cancer (five studies), lung cancer (six studies) and other solid tumours (OST) (four studies). For RCTs of different regimen of BTAs, all studies were related to breast cancer except one study that includes prostate cancer (Himelstein et al. 2012).

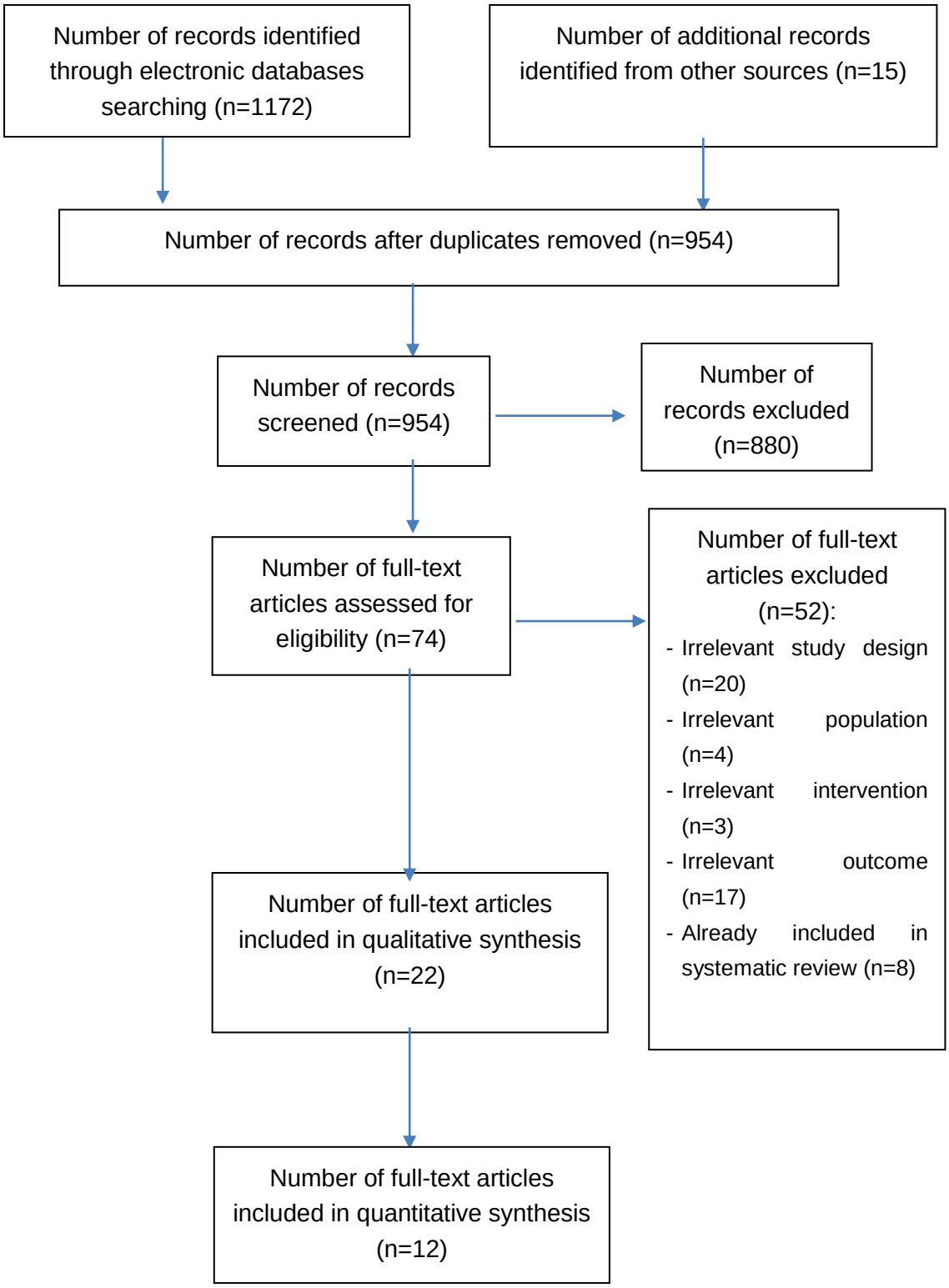


Figure 2: Flow chart of study selection

Table 1. Description of the included studies: types of primary tumour, number of patients, intervention and comparison and outcome measures.

Study	Types of primary tumour (number of studies included)	Number of patients	Intervention & Comparison	Outcome measures
Health Technology Assessment (HTA) with Network Meta-Analysis (NMA)				
Ford et al. (2013)[19]	Breast cancer (n=6) Prostate cancer (n=13) Other Solid Tumours (n=12)	More than 10200	Denosumab Bisphosphonates Best Supportive Care (BSC)	• Time to first on-study SREs • Risk of developing first and subsequent SREs • Skeletal morbidity rate (SMR) • Overall survival • Proportion of patients with on-study SREs • Pain • Quality of life
Systematic Review of RCTs				
O'Carrigan et al. (2017)[8]	Breast cancer (n=24)	10853 women	Denosumab Bisphosphonates Placebo	• Time to first SREs • Risk of developing SREs • Number of patients with SREs • Overall survival • Pain • Quality of life
LeVasseur et al. (2016)[37]	Lung cancer (n=15)	3379	Denosumab Bisphosphonates Placebo Best Supportive Care (BSC)	• Time to first on-study SREs • Annual incidence of SREs • Overall survival • Progression free survival • Time to progression • Quality of life • Safety
Wang et al. (2015)[31]	Breast cancer (n=9) Prostate cancer (n=3) OST & Non-small cell lung cancer (n=12)	10192 patients	Denosumab Bisphosphonates Placebo	• Reduction in SREs
Li et al (2014)[7]	Breast cancer (n=23)	More than 9330	Bisphosphonates Placebo	• Time to first SREs • Incidence and rate of SREs • Rate of first and subsequent SREs • SMR • Overall survival • Bone pain

Table 2. Description of the included studies: types of primary tumour, dosing, intervention and comparison, duration of follow-up and outcome measures

Study	Types of primary tumour (number of patients)	Dosing	Intervention & Comparison (number of patients)	Duration of follow-up	Outcome measures
Randomised Controlled Trials (RCTs): Denosumab versus Zoledronic acid (dosing for every 4 week)					
Lipton et al. (2016)[38]	Breast cancer (n=2046) Prostate cancer (n=1901) Other Solid Tumours (n=1596)	120 mg 4 mg	Denosumab (n=2775) Zoledronic acid (n=2768)	42 months	• First on-study SREs • Risk of first and subsequent on-study SREs
Scagliotti et al. (2012)[39]	Lung cancer	120 mg 4 mg	Denosumab (n=411) Zoledronic acid (n=400)	21 months	• Overall survival
Martin et al. (2012)[40]	Breast cancer	120 mg 4 mg	Denosumab (n=1026) Zoledronic acid (n=1020)	20 months	• First on-study SREs • First and subsequent on-study SREs • Number of patient with SREs • SREs by type • Quality of life
Fizazi et al. (2011)[41]	Castration-resistant prostate cancer	120 mg 4 mg	Denosumab (n=950) Zoledronic acid (n=951)	34 months	• Time to first on-study SREs • First and subsequent on-study SREs • Overall survival & disease progression • Number of patient with SREs
Henry et al. (2011)[42]	Non-small cell Lung Cancer Other Solid Tumour	120 mg 4 mg	Denosumab (n=799) Zoledronic acid (n=807)	34 months	• Time to first on-study SREs • First and subsequent on-study SREs • Overall survival & disease progression
Stopeck et al. (2010)[43]	Breast cancer	120 mg 4 mg	Denosumab (n=1026) Zoledronic acid (n=1020)	38 months	• Time to first on-study SREs • First and subsequent on-study SREs • Skeletal morbidity rate • Overall survival & disease progression

Table 2. Description of the included studies: Continued

Study	Types of primary tumour (number of patients)	Dosing	Intervention & Comparison (number of patients)	Duration of follow-up	Outcome measures
Randomised Controlled Trials (RCTs): Different regimen of BTAs (12-weekly versus 4-weekly)					
Himelstein et al. (2017)[44]	Breast cancer (n=855) Prostate cancer (n=689)	4 mg 4 mg	ZA 12 weeks (n=772) ZA 4 weeks (n=772)	24 months	• Proportion of patients having at least one SREs • Number of patients with SREs within 2 years • First and subsequent SREs • Safety (adverse events)
Hortobagyi et al. (2017)[45]	Breast cancer	4 mg 4 mg	ZA 12 weeks (n=203) ZA 4 weeks (n=200)	12 months	• Number of SREs • Time to first SREs • First and subsequent SREs • SRE-free survival • Skeletal morbidity rate • Adverse events
Amadori et al. (2013)[46]	Breast cancer	4 mg 4 mg	ZA 12 weeks (n=209) ZA 4 weeks (n=216)	12 months	• First and subsequent SREs • Number of patients with SREs within 2 years • Skeletal morbidity rate • Adverse events
Amir et al. (2013)[47]	Breast cancer	90 mg 90 mg	Pamidronate 12 weeks (n=19) Pamidronate 4 weeks (n=19)	48 weeks	• Skeletal morbidity rate • Number of patients with SREs within 2 years • First and subsequent SREs
Fizazi et al. (2009)[48]	Breast cancer	180 mg 180 mg	Denosumab 12 weeks (n=36) Denosumab 4 weeks (n=38)	57 weeks	• Time to first on-study SREs • First and subsequent on-study SREs • Overall survival & disease progression
Lipton et al. (2007)[49]	Breast cancer	60 & 80 mg 30, 120 & 180 mg	Denosumab 12 weeks (n=85) Denosumab 4 weeks (n=127)	56 weeks	• Time to first on-study SREs • First and subsequent on-study SREs • Skeletal morbidity rate • Overall survival & disease progression • Adverse events

Table 3. Description of included studies: types of primary tumour, intervention and comparison, duration of follow-up and outcome measures

Study	Types of study	Types of primary tumour (number of patients)	Intervention & Comparison (number of patients)	Duration of follow-up	Outcome measures
Additional studies for outcome effectiveness					
von Moos et al. (2018)[50]	Prospective, cross-sectional survey	Breast cancer (n=2984) Stage IV (n=2544) With BMs (n=1408) Non-BMs (n=1136)	BTAs (NR) No BTAs (NR)	6 months	• Bone pain
Additional study for outcome safety					
Chen et al. (2016)[32]	Systematic review & Meta-analysis	Metastatic cancer (13,733)	Denosumab 4-weekly (6880) Zoledronic acid 4-weekly (6853)	NA	• Adverse events
Study for outcome social/ethical/psychological/organisational					
Qian et al. (2017)[51]	Retrospective cohort	Metastatic cancer (14,881)	Denosumab 4-weekly (NR) Zoledronic acid 4-weekly (NR)	36 months after BTA initiation	• Compliant
Studies for outcome economic evaluation					
Andronis et al. (2018)[52]	Systematic review (24 studies)	Metastatic cancer (NR)	Denosumab Bisphosphonates	NA	• Cost-utility analyses (16) • Cost-effectiveness analyses (4) • CUA & CEA (3) • Cost-consequences analysis (1)
Shapiro et al. (2017)[53]	Cost-effectiveness analysis (CEA)	Breast cancer (10,000)	Zoledronic acid 4-weekly Zoledronic acid 12-weekly Denosumab 4-weekly	2-year time horizon	• Base-case analysis • Sensitivity analysis

2.4.3 Risk of Bias Assessment

Assessment for Systematic Review Studies Using Critical Appraisal Skills Programme (CASP) Checklist

Figure 3 shows the summary of the risk of bias of the seven included studies based on the Critical Appraisal Skill Programme (CASP) checklist. Four out of seven studies were overall at low risk of bias at all domain assessed. For LeVasseur et al., meta-analysis was done only for Zoledronic acid and no heterogeneity data available for the meta-analysis. There was no explanation why they did that, thus was judged as unknown for the last domain.

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Ford et al.[19]	+	+	+	+
O'Carrigan et al.[8]	+	+	+	+
LeVasseur et al.[37]	+	+	+	?
Wang et al.[31]	+	+	+	+
Li et al.[7]	+	-	-	?
Chen et al.[32]	+	+	-	+
Andronis et al.[52]	+	+	+	+

Notes:

+	Indicates YES (low risk of bias)
?	indicates UNKNOWN risk of bias
-	Indicates NO (high risk of bias)

Figure 3. Risk of bias summary for Systematic Review studies

Li et al. had more than one domain judged as high risk of bias as they did not mention the method that they used in searching the articles and no quality assessment done for the included studies as these are the important criteria for all systematic review studies. Chen et al. also did not assessed the quality of all included studies thus, was judged as high risk of bias for this domain.

Assessment for Randomised Controlled Trial Using Cochrane Collaboration's Tools

Figure 4 shows the summary of risk of bias of the 12 included studies based on the Cochrane Collaboration Tool for assessing risk of bias.[36] Four out of 12 studies were at low risk of bias for all six domains assessed.

Criteria assessed	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
Denosumab vs ZA						
Lipton et al. [38]	+	?	+	+	+	+
Scagliotti et al. [39]	?	?	?	+	+	+
Martin et al. [40]	+	+	+	+	+	+
Fizazi et al. [41]	+	+	+	+	+	+
Henry et al. [42]	+	+	+	+	+	+
Stopeck et al. [43]	?	?	+	+	+	+
Different regiment of BTAs						
Himelstein et al. [44]	+	+	?	+	+	+
Hortobagyi et al. [45]	+	+	+	+	+	+
Amadori et al. [46]	+	+	?	+	+	+
Amir et al. [47]	?	?	?	+	+	+
Fizazi et al. [48]	+	?	?	+	+	+
Lipton et al. [49]	+	?	+	+	+	+

Notes:

+	Indicates YES (low risk of bias)
?	indicates UNKNOWN risk of bias
-	Indicates NO (high risk of bias)

Figure 4. Risk of Bias Summary for RCTs

Of the 12 studies, two studies did not clearly state the method of generating the randomisation sequence, six studies did not mention the detail of allocation concealment method and thus they were classified as unclear risk of bias. Blinding was unclear in four studies and there was no blinding either in participants or personnel in one study. All articles carried out intention-to-treat (ITT) analysis as the final analysis have included all randomised patients and all outcomes measured were stated in the results section, thus were judged to have low risk of bias for these two domains. For domain of the other bias, baseline comparability was considered. All studies were judged to have low risk of bias as the baseline characteristics were comparable between the intervention and control groups.

2.4.4 EFFECTIVENESS

Eighteen studies related to the effectiveness of of BTAs in preventing SREs for metastatic cancers of solid tumours which met the inclusion criteria were included in this review. Twelve RCTs out of 17 studies were included in quantitative synthesis and were divided into two major groups of meta-analysis which are the comparison of Denosumab and Zoledronic acid and the comparison of two different regimens of BTAs (12-weekly versus 4-weekly).

The results were presented separately for studies involving intervention BTAs compared with placebo or no treatment or best supportive care, intervention involving Bisphosphonates compared with alternate Bisphosphonates, intervention involving Denosumab compared with Bisphosphonates and intervention involving different regimen of BTAs (12-weekly versus 4-weekly).

Within each types of interventions, the results were presented based on the different outcomes as follows; time to first SREs, risk of first and subsequent SREs, number of patients with SREs, number of events per year, skeletal morbidity rate, overall survival, disease progression, pain and quality of life. For each outcome, results will be divided into four main types of metastatic cancer; breast cancer, prostate cancer, lung cancer and other solid tumours.

Number of participants ranged from three thousand to more than ten thousand for HTA and SR and from 38 to more than five thousand for RCTs. The dosing that have been used in RCTs comparing Denosumab and Zoledronic acid were similar in all six studies while varied in Denosumab dosing for RCTs of different regimen of BTAs. Duration of study varied between 48 weeks and 42 months.

All studies reported at least one outcome of SREs for their primary outcomes such as time to first on-study SREs, first and subsequent on-study SREs, number of patients with SREs, number of events per year, overall survival, disease

progression, pain and quality of life. There was one study that only reported for bone pain and quality of life (von Moos et al.) where they compared patients who received BTAs with patients who do not received BTAs in real-world practice in six Eurepoean countries: Belgium, France, Germany, Italy, Spain and UK.

A. Effectiveness of BTAs (Bisphosphonates or Denosumab) versus placebo or no treatment or best supportive care (BSC)

One HTA and four SR reported these interventions which included 57 studies; six studies in Ford et al., 14 studies in O'Carrigan et al., eight studies in LeVasseur et al., eight in Wang et al. and 21 studies in Li et al. All results reported in Ford et al. which compared Denosumab with placebo and Denosumab with Pamidronate were derived from indirect Network Meta-analysis (NMA) (Figure 5). While all results reported in Wang et al. were derived from indirect NMA that involved studies with patients' naïve BTAs treatment.

One HTA (Ford et al.) and three SR studies (O'Carrigan et al., Wang et al. and Li et al.) reported on metastatic breast cancer patients, one HTA and one SR study (Ford et al. and Wang et al.) reported on metastatic castration-resistant prostate cancer, two SR studies (LeVasseur et al. and Wang et al.) reported on metastatic lung cancer and one HTA and one SR study (Ford et al. and Wang et al.) reported on OSTs.

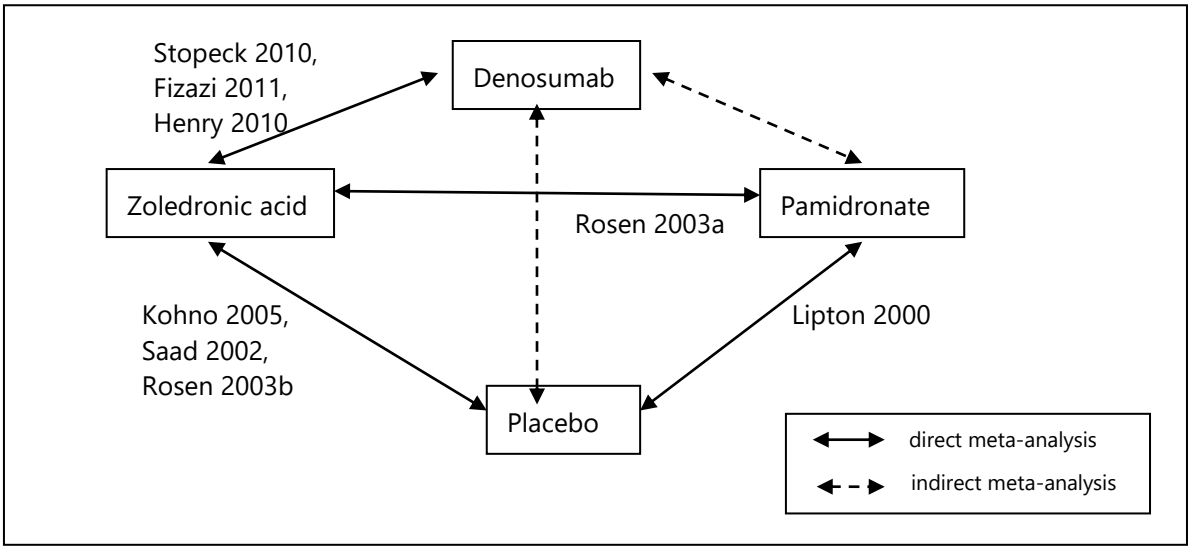


Figure 5. Network Meta-analysis studies in Ford et al. 2013

1. Time to first SREs

Out of one HTA and four SR, only three studies reported on this outcome. Wang et al. and Li et al. did not report on this outcome.

Breast cancer

Ford et al. conducted HTA with NMA reported that Bisphosphonates (ZA and Disodium Pamidronate) compared to placebo significantly delayed the time to first SREs in breast cancer (Table 4). Denosumab compared to placebo also significantly delayed the time to first SREs in breast cancer (Table 5).[19 level I]

O'Carrigan et al. conducted a SR and MA in breast cancer patients which involved Bisphosphonates versus no Bisphosphonates (three studies) and Bisphosphonates versus placebo (11 studies). Eleven out of 12 studies reported this outcome. They found that Bisphosphonates group (oral and IV Clodronate, IV Pamidronate, oral and IV Ibandronate and IV Zoledronate) significantly delayed the median time to first SREs with absolute effect that ranged from 8.7 to 20.8 months as compared to placebo group ranged from 4.9 to 14.9 months and median ratio 1.43 (Table 4).[8 level I]

Prostate cancer

Ford et al. reported that Bisphosphonates (ZA) and Denosumab compared to placebo significantly delayed the median time to first SREs in patient with prostate cancer (Table 4) reducing the risk of this event by 32% (ZA) and by 44% (Denosumab) compared to placebo (Table 5).[19 level I]

Lung cancer

Ford et al. reported no significant difference between Bisphosphonates (ZA) (Table 4) and Denosumab (Table 5) compared to placebo in patients with non-small cell lung cancer (NSCLC).[19 level I]

LeVasseur et al. conducted a SR in lung cancer patient. Five studies compared Bisphosphonates (Zoledronate and Clodronate) with placebo, two studies compared Bisphosphonates (Zoledronate and chemotherapy) with chemotherapy alone and one study compared Bisphosphonate (Zoledronic acid and Strontium) with placebo. Only four studies reported on this outcome. They reported a significant delay to first SREs with Bisphosphonates (ZA) as compared to placebo and reduced the risk of developing an SRE by 31% in one study (Table 4). Another two studies compared ZA 4/8 mg with placebo and ZA plus Strontium with placebo were also reported that the ZA groups significantly delayed the first SREs. One study did not identified any significant difference between Zoledronic acid and chemotherapy group and chemotherapy alone group (Table 4).[37 level I]

Other solid tumours (OSTs)

Ford et al. reported that the median time to developing a first SRE significantly longer in the Bisphosphonates (ZA) group than in the placebo group in OST excluding NSCLC and OST including NSCLC (Table 4) and reduced the risk by 21% (Table 5). However, they reported Denosumab as compared to placebo significantly delayed the time to first SREs in OST excluding NSCLC (p = 0.051) (Table 5).

When looking at the time to first SREs by different types of SREs, in patients with OSTs excluding NSCLC, they reported that the median time was not reached for individual SRE except for median time to first pathological fracture, which was longer in the Zoledronic acid group compared with the placebo group (238 days vs 161 days; p=0.031). They also reported that the time to first vertebral fracture and time to first radiation therapy significantly longer in the Zoledronic acid group (p = 0.05).[19] level I

Table 4. Different types of BTAs and primary tumour for outcome time to first SREs

Study	Types of BTAs	Breast cancer	Prostate cancer	Lung cancer	OST
Ford et al. (2013)	Zoledronic acid vs placebo	Not reached vs 364 days (p=0.007)	488 days vs 321 days (16.3 months vs 10.7 months)	NSCLC: 171 days vs 151 days (5.7 months vs 5 months) (p=0.188)	Excluding NSCLC: 314 days vs 168 days (p=0.051) (10.5 months vs 5.6 months) Including NSCLC: 230 days vs 163 days (p=0.023) (7.7 months vs 5.4 months)
	Disodium Pamidronate vs placebo	12.7 months (95% CI 9.6 to 17.2) vs 7.0 months (p< 0.001)			
O'Carrigan et al. (2017)	Bisphosphonates vs placebo	Median ratio 1.43 (95% CI: 1.29 to 1.58; p<0.00001)			
LeVasseur et al. (2016)	Zoledronic acid vs placebo			Median 469 days vs 307 days; (p=0.009) HR: 0.69; 95% CI: 0.42 to 0.79	
	Zoledronic acid 4/8 mg vs placebo			Median 236 & 219 days vs 155 days (p=0.023)	
	Zoledronic acid + Strontium vs placebo			Median 450 days (95% CI: 420-480 days) vs 240 days (95% CI 213-267 days); p<0.0001	
	Zoledronic acid + chemotherapy vs chemotherapy alone			Median 216 days (95% CI 147-321 days) vs 180 days (95% CI 132-255 days); p=0.84	

Notes: **HR;** Hazard ratio, **CI**; Confidence interval, **vs**; versus

Table 5. Network Meta-analysis (NMA) results for three main outcomes (Ford et al. 2013, European Journal of Cancer)

Tumour types	Intervention vs comparator	O1:Time to first SREs (Hazard Ratio)	O2:Risk of first and subsequent SREs (Risk Ratio)	O3:Skeletal Morbidity Rate (Rate ratio)
Direct NMA				
Breast cancer	Denosumab vs Zoledronic acid (Stopeck 2010)	**Significant reduced (HR 0.82; 95% CI 0.71 to 0.95)**	**Significant reduced (RR 0.77; 95% CI 0.66 to 0.89)**	No significant (favour Denosumab) (RR 0.90; 95% CI 0.67 to 1.09)
	Zoledronic acid vs Pamidronate (Rosen 2003a)	NR	NR	NR
	Pamidronate vs Placebo (Lipton 2000)	NR	NR	NR
	Zoledronic acid vs Placebo (Kohno 2005)	**Significant reduced (HR 0.56; 95% CI 0.36 to 0.86)**	**Significant reduced (RR 0.59; 95% CI 0.37 to 0.91)**	**Significant reduced (RR 0.52; 95% CI 0.32 to 0.70)**
Prostate cancer	Denosumab vs Zoledronic acid (Fizazi 2011)	**Significant reduced (HR 0.82; 95% CI 0.71 to 0.95)**	**Significant reduced (RR 0.82; 95% CI 0.71 to 0.94)**	No significant (favour Denosumab) (RR 0.95; 95% CI 0.46 to 1.47)
	Zoledronic acid vs Placebo (Saad 2002)	**Significant reduced (HR 0.68; 95% CI 0.50 to 0.91)**	**Significant reduced (RR 0.64; 95% CI 0.48 to 0.85)**	**Significant reduced (RR 0.54; 95% CI 0.11 to 0.83)**
Other Solid Tumours (OSTs) excluding NSCLC	Denosumab vs Zoledronic acid (Henry 2010)	**Significant reduced (HR 0.79; 95% CI 0.62 to 0.99)**	No significant (favour Denosumab) (RR 0.83; 95% CI 0.67 to 1.03)	NR
	Zoledronic acid vs Placebo (Rosen 2003b)	No significant (favour Zoledronic acid) (HR 0.37; 95% CI 0.14 to 1.01)	No significant (favour Zoledronic acid) (RR 0.74; 95% CI 0.49 to 1.10)	NR
Non-small cell lung cancer (NSCLC)	Denosumab vs Zoledronic acid (Henry 2010)	No significant (favour Denosumab) (HR 0.84; 95% CI 0.64 to 1.10)	No significant (favour Denosumab) (RR 0.87; 95% CI 0.68 to 1.12)	NR
	Zoledronic acid vs Placebo (Rosen 2003b)	No significant (favour Zoledronic acid) (HR 0.81; 95% CI 0.59 to 1.11)	No significant (favour Zoledronic acid) (RR 0.73; 95% CI 0.52 to 1.02)	NR
Indirect NMA				
Breast Cancer	Denosumab vs Pamidronate	**Significant reduced (HR 0.73; 95% CI 0.56 to 0.94)**	**Significant reduced (RR 0.62; 95% CI 0.48 to 0.80)**	No significant (favour Denosumab) (HR 0.73; 95% CI 0.41 to 1.06)
	Denosumab vs Placebo	**Significant reduced (HR 0.46; 95% CI 0.29 to 0.72)**	**Significant reduced (RR 0.45; 95% CI 0.28 to 0.72)**	**Significant reduced (RR 0.47; 95% CI 0.25 to 0.67)**
Prostate Cancer	Denosumab vs Placebo	**Significant reduced (HR 0.56; 95% CI 0.40 to 0.77)**	**Significant reduced (RR 0.53; 95% CI 0.39 to 0.72)**	**Significant reduced (RR 0.52; 95% CI 0.07 to 0.82)**
OSTs excluding NSCLC	Denosumab vs Placebo	**Significant reduced (HR 0.30; 95% CI 0.11 to 0.82)**	**Significant reduced (RR 0.61; 95% CI 0.39 to 0.97)**	NR
NSCLC	Denosumab vs Placebo	No significant (favour Denosumab) (HR 0.68; 95% CI 0.45 to 1.03)	**Significant reduced (RR 0.63; 95% CI 0.42 to 0.97)**	NR

Notes: **O1**: outcome first; **O2**: outcome second; **O3**: outcome third; **CI**: confidence interval; **NR**: not reported

2. Risk of first and subsequent SREs

One HTA and two SR reported on this outcome. O'Carrigan et al. and LeVasseur et al. did not report on this outcome.

Breast cancer

Ford et al. reported that Bisphosphonates (ZA) and Denosumab compared to placebo significantly reduced the risk of first and subsequent SREs in breast cancer (Table 5).

Specifically, in breast cancer, Wang et al. reported that BTAs compared with placebo, Denosumab was the superior in reducing risk of developing SREs (OR: 0.33, 95% CI: 0.15, 0.73), followed by Zoledronate (OR: 0.43, 95% CI: 0.26, 0.70) and Pamidronate (OR: 0.45, 95% CI: 0.29, 0.62). However, there was no statistically significant difference with Ibandronate (OR: 0.56, 95% CI: 0.25, 1.23). Denosumab and Pamidronate were associated with significant reduction of both pathologic fractures and the need for radiation compared with placebo in breast cancer patients. The effect of Zoledronate was limited to significantly reducing the risk of pathologic fractures in breast cancer patient. No significant reduction in the risk of surgery or spinal cord compression was observed for BTAs as compared to placebo.[19] level I

Li et al. in a SR involving breast cancer patients reported that Bisphosphonates compared to placebo significantly reduced the risk by 15% (Risk Ratio (RR): 0.85, 95% CI: 0.77–0.94; p = 0.001) compared to placebo. The ranking was as follows; IV Zoledronic acid 4 mg (RR 0.59), IV pamidronate 90 mg (RR 0.77), IV ibandronate 6 mg (RR 0.80), oral clodronate (RR 0.85) and oral ibandronate (RR 0.86).[7] level II-1

Prostate cancer

Ford et al. reported that Bisphosphonates (ZA) and Denosumab compared to placebo significantly reduced the risk by 36% (ZA, p=0.002) and by 47% (Denosumab) of first and subsequent SREs in patients with prostate cancer (Table 5).

Lung cancer

One study in Ford et al. reported that there was a 27% risk reduction of multiple SREs by the use of Bisphosphonates (ZA) compared to placebo, however, the reduction was not statistically significant (p=0.061) in patients with NSCLC (Table 5). However, when Denosumab compared to placebo, they reported Denosumab significantly reduced the risk of first and subsequent SREs in NSCLC (Table 5).[19] level I

Other solid tumours (OSTs)

Ford et al. reported a 26% reduction in the risk of developing multiple SREs for Bisphosphonates (ZA) group compared to placebo group but the difference was not significant (p=0.136) in patients with OSTs excluding NSCLC (Table 5). However, they reported Denosumab as compared to placebo significantly reduced the risk of first and subsequent SREs in OST excluding NSCLC (Table 5). While in patients with OSTs including NSCLC, they reported that Zoledronic acid significantly reduced the risk of multiple SREs by 27% compared with placebo (HR: 0.732; p=0.017).[19] level I

Wang et al. who conducted a SR with NMA reported that three BTAs significantly reduced the risk of first and subsequent SREs as compared to placebo in breast cancer, prostate cancer, NSCLC and OSTs. Denosumab was the superior in the rank (OR: 0.49; 95% CI: 0.31, 0.75) followed by Zoledronate (OR: 0.57; 95% CI: 0.41, 0.77) and Pamidronate (OR: 0.55; 95% CI: 0.41, 0.72). However, Ibandronate compared with placebo could not significantly reduce the risk of SREs (OR: 0.74; 95% CI: 0.40, 1.38).

In addition to that, Wang et al. also reported the risk of developing SREs by types. Denosumab and Zoledronate significantly reduced the risk of pathologic fractures, while Denosumab, Pamidronate and Zoledronate significantly reduced the need for bone radiation. However, only Pamidronate significantly reduced the risk of bone surgery and none of the four BTAs significantly reduced the risk of spinal cord compression (Table 6).[31] level I

Table 6. BTAs versus placebo by types of SRE according to ranking in all types of cancer

Pathologic fractures	Bone radiation	Bone surgery	Spinal cord compression
Denosumab- OR 0.50 (95% CI: 0.32, 0.79)	**Denosumab- OR 0.51 (95% CI: 0.35, 0.75)**	**Pamidronate- OR 0.60 (95% CI: 0.37, 0.98)**	Ibandronate- OR 0.48 (95% CI: 0.17, 1.43)
Zoledronate- OR 0.61 (95% CI: 0.43, 0.86)	**Pamidronate- OR 0.67 (95% CI: 0.52, 0.86)**	Denosumab- OR 0.63 (95% CI: 0.25, 1.50)	Denosumab- OR 0.55 (95% CI: 0.25, 1.21)
Ibandronate- OR 0.67 (95% CI: 0.36,1.29)	**Zoledronate- OR 0.70 (95% CI: 0.52 , 0.96)**	Zoledronate- OR 0.68 (95% CI: 0.32, 1.43)	Zoledronate- OR 0.56 (95% CI: 0.29, 1.04)
Pamidronate-OR 0.84 (95% CI: 0.64,1.18)	Ibandronate- OR 0.81 (95% CI: 0.48,1.30)	Ibandronate- OR 0.94 (95% CI: 0.33, 2.61)	Pamidronate- OR 0.95 (95% CI: 0.47, 1.91)

Notes: **OR**; Odds ratio, **CI**; Confidence interval

3. Number of patients with SREs

One HTA and one SR study reported on this outcome. LeVasseur et al., Wang et al. and Li et al. did not report on this outcome.

Breast cancer

In the HTA report by Ford et al., five studies reported that Bisphosphonates (ZA) was associated with lower number of patients with SREs as compared to placebo in breast cancer (29.8% versus 49.6%). Also, the disodium pamidronate group experienced a lower proportion of patients having any SREs compared with the placebo group (51% versus 64%) at two years.[19] level I

In line with above study, O'Carrigan et al. also found in breast cancer patients, nine studies of Bisphosphonates (Clodronate, Pamidronate, Ibandronate and Zoledronate) significantly reduced the number of patients with SREs (RR: 0.86 95% CI: 0.78 to 0.95). They also divided the Bisphosphonates groups into different types of dosage; intravenous and oral (Table 7).[8] level I

Table 7. Different types of dosage form comparing Bisphosphonates with placebo

Types of Bisphosphonates	**Overall results**	**IV Zoledronate vs placebo**	**IV Pamidronate vs placebo**	**IV Ibandronate vs placebo**
IV Bisphosphonates vs placebo (6 studies)	RR: 0.83, 95% CI: 0.73 to 0.95 (p=0.006)	RR: 0.59, 95% CI: 0.43 to 0.82 (p=0.002)	RR: 0.78, 95% CI: 0.69 to 0.88 (p<0.001)	RR: 0.80, 95% CI: 0.67 to 0.96 (p=0.01)
	Overall results	**Oral Clodronate vs placebo**	**Oral Pamidronate vs placebo**	**Oral Ibandronate vs placebo**
Oral Bisphosphonates vs placebo (5 studies)	RR: 0.84, 95% CI: 0.76 to 0.93 (p=0.007)	RR: 0.82, 95% CI: 0.71 to 0.96 (p=0.01)	RR: 0.86, 95% CI: 0.70 to 1.05 (p=0.14)	RR: 0.86, 95% CI: 0.73 to 1.02 (p=0.09)

Notes: **RR**; Risk ratio, **CI**; Confidence interval

Prostate cancer

Ford et al. reported a statistically significant fewer patient with SREs in the Bisphosphonates (ZA) as compared to placebo (33.2%, n=71/214 versus 44.2%, n=92/208; p=0.021). By looking at different types of SREs, the results showed that there was a significant difference in pathological fractures at 15 months of follow-up in Zoledronic acid group compared to placebo group (13.1%, n=28/214 versus 22.1%, n=46/208; p=0.021). The rest of SREs were similar among both groups (radiation therapy to bone: 22.9% versus 29.3%; p=0.136, surgery to bone: 2.3% versus 3.4%; p=0.514, SCC: 4.2% versus 6.7%; p=0.256; respectively).[19] level I

Lung cancer

One study in HTA report by Ford et al. reported that when Bisphosphonates (ZA) compared to placebo, there was no different between the two groups in patients with NSCLC (42% versus 45%). There was also no significant difference when Denosumab compared to placebo in NSCLC (RR: 0.83; 95% CI: 0.02 to 30.6).[19] level I

Other solid tumours (OSTs)

A study in the HTA by Ford et al. reported that Bisphosphonates (ZA) when compared to placebo, there was no different between the two groups in patients with OSTs excluding NSCLC (33% versus 43%; p=0.11) and OSTs including NSCLC (38% versus 44%; p=0.127). Similarly, there was also no significant difference when Denosumab compared to placebo in patients with OSTs excluding NSCLC (OR: 0.44; 95% CI: 0.01 to 17.13) and patients with OSTs including NSCLC (OR: 0.58; 95% CI: 0.02 to 19.48).[19 level I]

4. Number of events per year

One SR study reported this outcome. Ford et al., O'Carrigan et al., Wang et al. and Li et al. did not report this outcome. Only lung cancer data was available, the rest of other cancer types were not available.

Lung cancer

LeVasseur et al. reported that three studies involving metastatic lung cancer patients showed Bisphosphonates (ZA) reduced the number of SREs annually compared with placebo (39% in 4 mg arm versus 50%; p=0.029, 35% in 8/4 mg arm versus 44%; p=0.023, 24.4% in 4 mg arm versus 91.1%; p=0.00, respectively). However, one study did not found any statistically significant difference between combination of Zoledronic acid and chemotherapy versus chemotherapy alone (value not reported).[37 level I]

5. Skeletal morbidity rate (SMR)

One HTA reported on this outcome.

Breast cancer

Ford et al. reported that SREs occurred less frequently in Bisphosphonates group (ZA and Pamidronate) as compared to placebo (ZA versus placebo: 0.63 versus 1.1 events per year, Disodium Pamidronate versus placebo: 2.4 versus 3.7 events per year).[19 level I]

Prostate cancer

Ford et al. reported that the mean SMR was lower in prostate cancer patients who received Zoledronic acid than for those who received placebo for all SREs combined (0.80 versus 1.49) and for each individual type of SRE (pathological

fractures: 0.21 versus 0.45; radiation therapy to bone: 0.44 versus 0.88; surgery to bone: 0.03 versus 0.06; SCC: 0.14 versus 0.23; respectively) and significantly reduced in Zoledronic acid group as compared to placebo group (Table 5).[19 level I]

Lung cancer

Neither study reported on this outcome for lung cancer patients.

Other solid tumours (OSTs)

Neither study reported on this outcome for patients with OSTs excluding NSCLC. While in patients with OSTs including NSCLC, a study in a HTA reported by Ford et al. found a slightly lower number of events per year for Zoledronic acid than for placebo, however, the difference was non-significant (SMR 2.24, SD 9.12 vs 2.52, SD 5.11; p=0.069).[19 level I]

6. Overall survival

One HTA and three SR studies reported on this outcome. Wang et al. did not report on this outcome.

Breast cancer

Ford et al. reported overall median survival was slightly longer in the Disodium Pamidronate group (19.8 months) as compared to the placebo group (17.8 months) although the difference was not statistically significant (p=0.976).[19 level I] Treatment with Bisphosphonates (Clodronate, Pamidronate, Ibandronate and Zoledronate) did not appear to affect overall survival when compared to placebo in O'Carrigan et al. (RR: 1.01, 95% CI: 0.91 to 1.11; p=0.85).[8 level I] Another study by Li et al. also found that Bisphosphonates did not affect survival in breast cancer patient (RR: 1.01, 95% CI: 0.92 to 1.11).[7 level II-1]

Prostate cancer

Ford et al. reported median survival was 546 days (around 18.2 months) for the Zoledronic acid group and 464 days (around 15.5 months) for the placebo group (p = 0.091).[19 level I]

Lung cancer

LeVasseur et al. found no statistically significant difference when comparing Bisphosphonates groups with placebo (oral Clodronate: 240 days versus placebo: 240 days; Zoledronic acid: 187 days versus placebo: 157 days; Zoledronic acid plus chemotherapy: 312 days, 95% CI: 210 to 474 versus chemotherapy: 291 days, 95% CI: 183 to 375; p=0.62). However, they reported a significant difference in Zoledronic acid versus chemotherapy alone (ZA: 578 days, 95% CI: 454 to 701.8 versus chemotherapy: 384 days, 95% CI: 368 to 399.6; p<0.001) and combination of Zoledronic acid with Strontium versus placebo (ZA plus Strontium:

510 days, 95% CI: 480 to 543 versus placebo: 360 days, 95% CI: 324 to 396; p=0.00).[37 level I] No data was reported by Ford et al. in patients with NSCLC.

OST

Ford et al. reported that Bisphosphonates (ZA) was similar in time to median death when compared with placebo (203 days versus 183 days; p=0.623) for those with OSTs including NSCLC.[19 level I] No data was reported for patients with OSTs excluding NSCLC.

7. Disease Progression

One SR study reported on this outcome. Ford et al., O'Carrigan et al., Wang et al. and Li et al. did not report on this outcome. Only lung cancer data was available, the rest of other cancer types were not available.

Lung cancer

The result reported by LeVasseur et al. showed that there was a statistically significant difference in time to progression of bone lesions between Zoledronic acid and placebo (238 days versus 109 days) and time to progression of disease between combination of Zoledronic acid and chemotherapy versus chemotherapy alone (265 days, 95% CI: 240.5 to 289 versus 150 days, 95% CI: 56 to 244; p< 0.001). No significant difference in progression-free survival between Zoledronic acid and placebo (Median 89 days versus 84 days) and combination Zoledronic acid with chemotherapy versus chemotherapy alone (Median 81 days; 95% CI: 45 to 105 versus 78 days; 95% CI 30 to 102).[37 level I]

8. Pain

One HTA and two SR studies reported on this outcome. LeVasseur et al. and Wang et al. did not report on this outcome. In addition, there was one additional study reported only on this outcome (von Moos et al.).

Breast cancer

Ford et al. reported mean pain score decreased significantly in the Disodium Pamidronate group (–0.07; SD 3.07) compared with the placebo group (1.14; SD 3.42) over the 24 months (p = 0.015). Bone pain was evaluated using a scoring system that quantified both severity and frequency of bone pain. The bone pain score was determined by multiplying the bone pain severity score by the bone pain frequency score. At the last visit mean pain score was increased in both groups, but significantly lower in the Disodium Pamidronate group compared with the placebo group (p < 0.001).[19 level I]

In Li et al., one study reported that there was a significant pain relief among patients who received Bisphosphonate therapy compared to patients who received placebo (OR: 1.83, 95% CI: 1.11 to 3.04). In the subgroup analysis of the three

Bisphosphonates, the response was significant for oral Clodronate (OR 3.26, 95% CI 1.80–5.09), but not for IV Pamidronate (OR 2.35, 95% CI 0.77–7.15) and the trend was unfavorable for Etidronate (OR 0.28, 95% CI 0.01–7.67). However, two RCTs showed that Pamidronate significantly reduced the pain score (−0.07, p=0.015) and the analgesia score (−0.06, p=0.001) compared to placebo at 24 months of follow-up.[7 level II-1] O'Carrigan et al. reported that six studies from the Bisphosphonates group (Pamidronate, Ibandronate and Clodronate) showed significant reduction in bone pain (p< 0.05) as compared to placebo. However, five studies showed no significant difference (no value were reported).[8 level I]

One cross-sectional survey conducted by von Moos et al. in 2018 using the Brief Pain Inventory (BPI) revealed that patients who were receiving a BTA (Denosumab or Zoledronic acid) reported significantly lower average pain severity scores (2.7, 95% CI: 2.49–2.91 versus 3.5, 95% CI: 2.93–4.07; p=0.004) and interference scores (3.2, 95% CI: 2.96–3.44 versus 3.8, 95% CI: 3.16–4.44; p=0.036) than those who did not receive a BTA.[50 level II-3]

Prostate cancer

A study in the HTA report by Ford et al. used the Brief Pain Inventory (BPI) instrument, with the pain score a composite of four pain scores (worst pain, least pain, average pain of the last seven days, and pain right now), and was the primary efficacy variable for the quality-of-life assessments. They found that fewer patients in the Zoledronic acid group experienced bone pain than in the placebo group (51%, n=108/214 versus 61%, n=127/208; respectively).[19 level I]

Lung cancer

Neither study reported on this outcome for lung cancer patients.

Other solid tumours (OSTs)

One study in Ford et al. reported for patients with OSTs including NSCLC that compared Zoledronic acid with placebo, showed an increase in pain score from baseline to month 9 for mean BPI composite pain score and mean analgesic score in both groups, suggesting increased pain and use of analgesics. This study further reported that the mean composite pain score was decreased from baseline to month 9 for Zoledronic acid for those who had pain at baseline; however, no data were reported.[19 level I]

9. Quality of life

One HTA and one SR study reported on this outcome. LeVasseur et al., Wang et al. and Li et al. did not report on this outcome.

Breast cancer

In the HTA report by Ford et al., one study related to the Bisphosphonates group (Disodium Pamidronate) compared with placebo, reported a mean change in the quality-of-life scores from baseline to 24 months and to the last visit. Quality of life was evaluated using the Spitzer quality-of-life index. From baseline to the last visit the quality of life worsened in both the Disodium Pamidronate group and the placebo group (–1.80, SD: 2.81 versus –2.13, SD: 2.63; p=0.088).[19 level I]

Three studies in O'Carrigan et al. used Spitzer Quality-of-Life Index scores and EORTCQuality of Life Scale -Core 30 questionnaire (QLQ-C30) to evaluate QoL. They reported the Bisphosphonates group (Pamidronate and Ibandronate) showed a moderate quality evidence, however, the QoL scores decreased during the study (Pamidronate: p=0.057), though significantly less with Ibandronate than with placebo (-8.3, 95% CI: -20.6 to 4.1 versus -26.8, 95% CI: -39.4 to 14.3; p=0.03).[8 level I]

Prostate cancer

In HTA report by Ford et al., one study found that the total FACT-G score and EQ-5D scores decreased from baseline to the last measurement, with no statistically significant differences between the Zoledronic acid and placebo groups (value was not reported).[19 level I]

Lung cancer

Neither study reported on this outcome for lung cancer patients.

Other solid tumours (OSTs)

One study in Ford et al. for patients with OSTs including NSCLC stated that there were no statistically significant differences between Zoledronic acid and placebo with respect to any of these global quality-of-life outcomes and that changes in FACT-G scores were also comparable between treatment groups; however, no data were reported**.**

B. Effectiveness of Bisphosphonates versus alternate Bisphosphonates

One HTA and four SR reported these interventions which included 14 studies; one study in Ford et al., three studies in O'Carrigan et al. (one study was the same study in Ford et al. compared Zoledronic acid with Disodium Pamidronate), five studies in LeVasseur et al., three in Wang et al. and two studies in Li et al. (one study was the same in Ford et al. compared Zoledronic acid with Disodium Pamidronate). All results reported in Wang et al. were derived from indirect NMA that involved studies with patients' naïve BTAs treatment (upfront study).

One study in Ford et al. compared Zoledronic acid with Disodium Pamidronate. Two studies in O'Carrigan et al. compared oral Clodronate with IV Pamidronate

and oral Ibandronate with IV Zoledronate. Five studies in LeVasseur compared Zoledronate with Ibandronate (three studies), IV Ibandronate with oral Ibandronate and Clodronate with Pamidronate. Three studies in Wang et al. compared Zoledronate with Pamidronate (two studies) and Zoledronate with Ibandronate. One study in Li et al. compared Zoledronic acid with oral Ibandronate.

1. Time to first SRE

Out of one HTA and four SR, only three studies reported on this outcome. O'Carrigan et al. and Wang et al. did not report on this outcome. Result in Li et al. was the same with study in Ford et al. for Zoledronic acid group compared with Disodium Pamidronate group.

Breast cancer

One study in Ford et al. compared Zoledronic acid with Disodium Pamidronate. The result showed that Zoledronic acid significantly prolonged median time to first SREs compared with the Disodium Pamidronate (310 days versus 174 days; p=0.013) within the lytic metastases subgroup in the study.[19] level I

Prostate cancer

Neither study reported on this outcome for prostate cancer patients.

Lung cancer

One study in SR report by LeVasseur et al. reported that there was a statistically significant difference in median time to first SRE in patients who received Zoledronic acid compared with patients who received oral Ibandronate (306 days, range: 138-429 days versus 282 days, range: 171-483; p=0.034).[37] level I

Other solid tumours (OSTs)

Neither study reported on this outcome for OSTs patients.

2. Risk of first and subsequent SREs

One HTA and two SR studies reported on this outcome. O'Carrigan et al. and LeVasseur et al. did not report on this outcome. Result in Li et al. was the same with study in Ford et al. for Zoledronic acid group compared with Disodium Pamidronate group.

Breast cancer

One study in HTA report by Ford et al. compared Zoledronic acid with Disodium Pamidronate. The result showed that Zoledronic acid significantly reduced the risk of developing first and subsequent SREs by 20% compared with the Disodium Pamidronate (HR: 0.80; p=0.037) at 13 months of follow-up. From NMA results conducted by Wang et al., they found no significant difference in any SREs,

pathologic fractures and bone radiation in patients with breast cancer when different types of Bisphosphonates were compared (Table 8).[19 level I]

Table 8. NMA results when Bisphosphonates compared with alternate Bisphosphonates

Intervention	Any SREs	Pathologic fractures	Bone radiation
Zoledronate vs Pamidronate	OR 1.04 (95% CI: 0.75, 1.44)	OR 0.72 (95% CI: 0.46, 1.09)	OR 1.04 (95% CI: 0.70, 1.54)
Zoledronate vs Ibandronate	OR 0.77 (95% CI: 0.46, 1.28)	OR 0.91 (95% CI: 0.54, 1.55)	OR 0.87 (95% CI: 0.58, 1.31)
Ibandronate vs Pamidronate	OR 1.35 (95% CI: 0.74, 2.54)	OR 0.79 (95% CI: 0.39, 1.57)	OR 1.21 (95% CI: 0.69, 2.13)
Pamidronate vs Zoledronate	OR 0.94 (95% CI: 0.72 , 1.23**)**	OR 1.02 (95% CI: 0.45, 2.31)	OR 0.94 (95% CI: 0.72, 1.23)

Notes: **OR**; odds ratio, **CI**; confidence interval

Prostate cancer, lung cancer and other solid tumours (OSTs)

From NMA conducted by Wang et al., they found no significant difference in any SREs, pathologic fractures and bone radiation in patients with prostate cancer, NSCLC and OSTs when different types of Bisphosphonates were compared with alternate Bisphosphonates (Table 8).[31 level I]

3. Number of patients with SREs

One HTA and one SR study reported on this outcome. LeVasseur et al., Wang et al. and Li et al. did not report on this outcome.

Breast cancer

In HTA report by Ford et al., one study reported that proportion of patients with any SRE was similar between Zoledronic acid group and Disodium Pamidronate group (46% versus 49%; p=not reported).[19 level I]

By looking at the different types of SREs, one study in O'Carrigan et al. reported that a trend of increasing pathologic fractures with oral Clodronate (18%; 19 out of 107 women) compared to IV Clodronate (14%; 8 out of 105 women) or IV Pamidronate (7%; 8 out of 109 women).[8 level I]

Prostate cancer, lung cancer and other solid tumours (OSTs)

Neither study reported on this outcome for prostate cancer, lung cancer and OSTs patients.

4. Number of events per year

One HTA and two SR studies reported on this outcome. O'Carrigan et al. and Wang et al. did not report on this outcome.

Breast cancer

One study in HTA report by Ford et al. found that annual rates of SREs were 0.499 (95% CI 0.454 to 0.549) with oral Ibandronate and 0.435 (95%CI 0.393 to 0.480) with Zoledronate. The rate ratio for SREs was not statistically siginificant (1.148, 95% CI: 0.967 to 1.362). For study that compared Zoledronic acid with Disodium Pamidronate, for subgroup lytic metastases, the result showed a significant reduction in the SRE rate of 30% by Zoledronic acid (p=0.010).[19] level I

Another study in Li et al. reported that when Zoledronic acid compared to oral Ibandronate, it was shown that oral Ibandronate was inferior to Zoledronic acid in terms of SRE rate (0.543 versus 0.444, HR: 1.22, 95% CI: 1.04 to 1.45; p=0.017).[7] level II-1

Prostate cancer

Neither study reported on this outcome for prostate cancer patients.

Lung cancer

One study in LeVasseur et al. showed that there was a difference with SRE rate of 19.2% with Zoledronic acid group and 25.9% (p=0.034) with oral Ibandronate group in 14.5 months' follow-up (HR: 0.74, 95% CI: 0.27 to 2.00). However, another two studies in LeVasseur et al. found that there was no difference between Zoledronic acid and IV Ibandronate with regard to annual incidence (34% versus 37%; p=0.2 and 33% versus 39%; p=0.2).[37] level I

Other solid tumours (OSTs)

Neither study reported on this outcome for OSTs patients.

5. Skeletal morbidity rate (SMR)

One HTA and one SR study reported on this outcome. O'Carrigan et al., LeVasseur et al. and Wang et al. did not report on this outcome. Result in Li et al. was the same with study in Ford et al. for Zoledronic acid group compared with Disodium Pamidronate group.

Breast cancer

One study in HTA report by Ford et al. found that the SMR rate was lower for Zoledronic acid compared with Disodium Pamidronate but the difference was not statistically significant (0.9 events per year versus 1.49 events per year; p=0.125). When looking into the lytic metastases subgroup in the study, they reported a

significant reduction in skeletal morbidity rate (1.2 versus 2.4 events; p=0.008).[19] level I

Prostate cancer, lung cancer and other solid tumours (OSTs)

Neither study reported on this outcome for prostate cancer, lung cancer and OSTs patients.

6. Overall survival

One SR study reported on this outcome. Ford et al., O'Carrigan et al., LeVasseur et al. and Wang et al. did not report on this outcome.

Breast cancer

In the SR by O'Carrigan et al. one study that compared oral Ibandronate with IV Zoledronate, observed no significant difference in survival between the two groups (HR: 1.086, 95% CI: 0.948 to 1.245; p=0.24).[8] level I

Prostate cancer, lung cancer and other solid tumours (OSTs)

Neither study reported on this outcome for prostate cancer, lung cancer and OSTs patients.

7. Disease Progression

Neither study reported on this outcome for all types of cancer.

8. Pain

One SR study reported on this outcome. Ford et al., O'Carrigan et al., LeVasseur et al. and Wang et al. did not report on this outcome.

Breast cancer

In the SR by O'Carrigan et al., there were two studies which reported on this outcome. One study found no significant difference in pain scores between the IV Pamidronate group and IV or oral Clodronate (no value was reported). Another study reported there was also no difference in bone pain between Zoledronate and oral Ibandronate (no value was reported).[8] level I

Prostate cancer, lung cancer and other solid tumours (OSTs)

Neither study reported on this outcome for prostate cancer, lung cancer and OSTs patients.

9. Quality of life (QoL)

One SR study reported on this outcome. Ford et al., O'Carrigan et al., Wang et al. and Li et al. did not report on this outcome.

Breast cancer

Neither study reported on this outcome for breast cancer patients.

Prostate cancer

Neither study reported on this outcome for prostate cancer patients.

Lung cancer

One study in the SR by LeVasseur et al. reported an increase in mean total physical score in both the IV and oral Ibandronate groups (from 16 in each group to scores of 22.4 versus 22.5, respectively) at three months. The physical score was determined based on the functional assessment of cancer therapy-general scale (FACT-G; total physical and total function well-being scales), with a higher score indicating improved QoL. However, the difference was not statistically significant.[37 level I]

Other solid tumours (OSTs)

Neither study reported on this outcome for OSTs patients.

C. Effectiveness of Denosumab versus Bisphosphonates

One HTA and three SR studies reported these interventions which include 12 studies; four studies in Ford et al., three studies in O'Carrigan et al., two studies in LeVasseur et al. and three in Wang et al. No study in Li et al. reported on this intervention.

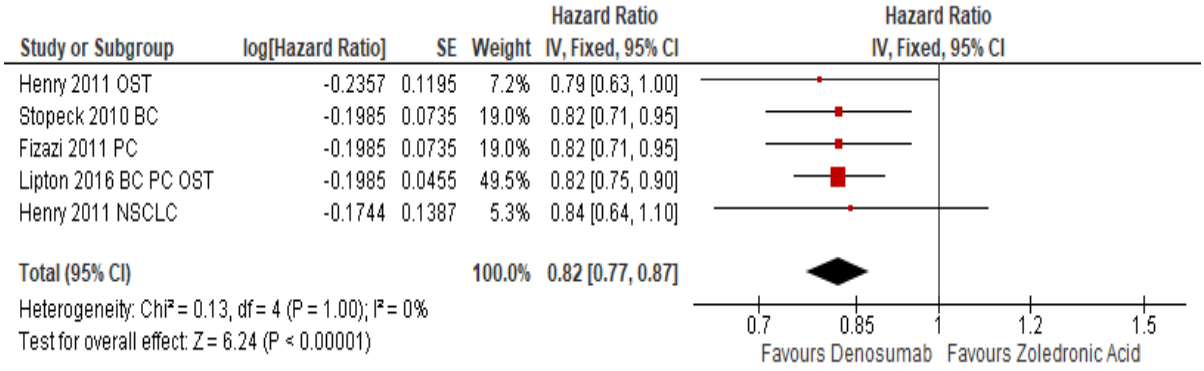
All studies in one HTA and three SR were from the same authors that compared Denosumab with Zoledronic acid, therefore pooling data for several studies was possible only for several similar outcomes, which have complete essential data reported. Data that were not similar will be reported in each outcome according to the types of cancer.

There were six studies; Lipton et al. 2016 involving breast cancer, prostate cancer and OSTs, Scagliotti et al. 2012 involving lung cancer, Martin et al. 2012 involving breast cancer, Fizazi et al. 2011 involving prostate cancer, Henry et al. 2011 involving NSCLC and OSTs and Stopeck et al. 2010 involving breast cancer.

1. Time to first SREs

Five out of six studies reported on this outcome. Scagliotti et al. did not report on this outcome. One study by Henry et al. (2011) reported two different results involving patients with OST and NSCLC. Pooled data from four studies showed

that Denosumab significantly delayed the time to first SREs by 18% as compared to Zoledronic acid (Figure 6). The results are presented as follows:



Notes: **OST**: other solid tumours; **BC**: breast cancer; **PC**: prostate cancer; **NSCLC**: non-small cell lung cancer

Figure 6. Denosumab versus Zoledronic acid (for all types of cancer); Outcome: Time to first SREs

Breast cancer

Only Lipton et al., Martin et al. and Stopeck et al. reported on this outcome involving breast cancer patients.

In Lipton et al. they found that treatment with Denosumab significantly reduced the risk of first on-study SRE compared with Zoledronic acid in breast cancer by 18% (Figure 6). Median time to first on-study SRE was longer with Denosumab compared with Zoledronic acid across all types of cancer (27.7 versus 19.4 months).[38 level I] This study was inline with Stopeck et al. that reported Denosumab delayed by 18% compared to Zoledronic acid (Figure 6). In extended four months of follow-up, they found that the median time to first on-study SRE was 27.4 months for Zoledronic acid and 32.4 months for Denosumab.[43 level I]

Martin et al. reported that Denosumab was superior to Zoledronic acid in prolonging the time to first on-study SRE and reducing the risk of first SREs by 48%. Fewer first SREs occurred in patients who received Denosumab than in patients who received Zoledronic acid (315 first SREs in 1,065 patient-years versus 372 first SREs in 1,040 patient-years; respectively). Number need to treat for Denosumab compared with Zoledronic acid was 16 patient-years.[40 level I]

Prostate cancer

Only Lipton et al. and Fizazi et al. reported on this outcome involving prostate cancer patients.

In Lipton et al. they found that treatment with Denosumab significantly reduced the risk of first on-study SRE compared with Zoledronic acid in prostate cancer by 18% (Figure 6). [38 level I]

Fizazi et al. reported that median time to first SREs was 20.7 (95% CI: 18·8, 24·9) months for Denosumab compared with 17.1 months for Zoledronic acid (95% CI: 15·0, 19·4). Denosumab delayed by 18% compared to Zoledronic acid (Figure 6). First SREs less in Denosumab compared to Zoledronic acid (n=341 versus 386).[41] level I

Lung cancer

Only Henry et al. reported on this outcome involving lung cancer patients. While Scagliotti et al. did not provide data on time to first SREs.

Henry et al. reported that Denosumab was non-inferior to Zoledronic acid in delaying time, representing 16% reduction in hazard (p=0.20) (Figure 6). Median time was longer for Denosumab group as compared to Zoledronic acid group (20.6 months versus 16.3 months).[42] level I

Other solid tumours (OSTs)

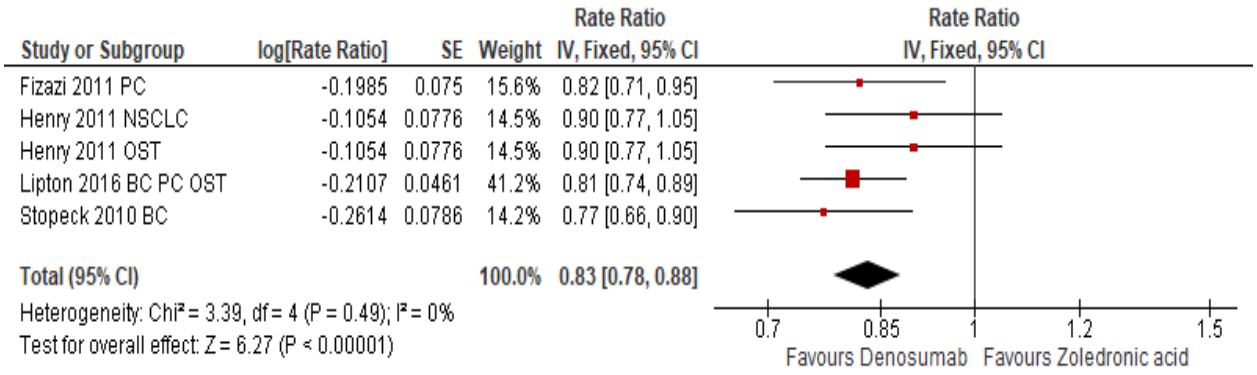
Only Lipton et al. and Henry et al. reported on this outcome involving OSTs patients.

In Lipton et al. they found that treatment with Denosumab significantly reduced the risk of first on-study SRE compared with Zoledronic acid in OSTs subgroups by 18% (Figure 6). [38] level I

Henry et al reported that Denosumab was non-inferior to ZA in delaying time, representing 21% reduction in hazard (p=0.04) (Figure 6). Median time to first SREs was longer for Denosumab as compared to Zoledronic acid (20.6 months versus 16.3 months; respectively).[42] level I

2. Risk of first and subsequent SREs

Five out of six studies reported on this outcome. Scagliotti et al. did not report on this outcome. Pooled data from four studies showed that Denosumab significantly reduced the risk of first and subsequent SREs by 17% as compared to Zoledronic acid (Figure 7). The results are presented as follows:



Notes: **PC**: prostate cancer; **NSCLC**: non-small cell lung cancer; **OST**: other solid tumours; **BC**: breast cancer

Figure 7. Denosumab versus Zoledronic acid (for all types of cancer); Outcome: Risk of first and subsequent SREs

Breast cancer

Only Lipton et al., Martin et al. and Stopeck et al. reported on this outcome involving breast cancer patients.

In Lipton et al. they found that treatment with Denosumab significantly reduced the risk of first and subsequent on-study SREs by 19% compared with Zoledronic acid in breast cancer (Figure 7), with the exception of the appendicular skeleton subgroup (the smallest subgroup assessed), which failed to meet nominal statistical significance (p=0.072) despite having a point estimate that was similar to the other metastasis locations.[38 level I]

Martin et al. reported that Denosumab was also superior to Zoledronic acid in preventing first-and-subsequent on-study SREs. Over the 1,353 patient-years observed in both treatment groups, 660 SREs occurred in the Denosumab group and 853 SREs in the Zoledronic acid group, yielding a number need to treat of 7 for Denosumab to prevent one first or subsequent SRE compared with Zoledronic acid.[40 level I]

Stopeck et al. reported that Denosumab reduced the risk of developing multiple SREs by 23% (p=0 .001) compared to Zoledronic acid (Figure 7).[43 level I]

Prostate cancer

Only Lipton et al. and Fizazi et al. reported on this outcome involving prostate cancer patients.

In Lipton et al. they found that treatment with Denosumab significantly reduced the risk of first and subsequent on-study SREs by 19% compared with Zoledronic acid in prostate cancer (Figure 7), with the exception of the appendicular skeleton subgroup (the smallest subgroup assessed), which failed to meet nominal

statistical significance (p=0.072) despite having a point estimate that was similar to the other metastasis locations.[38 level I]

Fizazi et al. reported that Denosumab reduced the risk of developing multiple SREs by 18% compared to ZA (n=494 versus 584; p=0.008) (Figure 8).[41 level I]

Lung cancer

Only Henry et al. reported on this outcome involving lung cancer patients. While Scagliotti et al. did not provide data on time to first SREs.

Henry et al. reported that Denosumab reduced the risk of developing multiple SREs by 10% compared to ZA (n=392 versus 436; p=0.14) (Figure 7).[42 level I]

Other solid tumours (OSTs)

Only Lipton et al. and Henry et al. reported on this outcome involving OSTs patients.

In Lipton et al. they found that treatment with Denosumab significantly reduced the risk of first and subsequent on-study SREs by 19% compared with Zoledronic acid in OSTs subgroup (Figure 7), with the exception of the appendicular skeleton subgroup (the smallest subgroup assessed), which failed to meet nominal statistical significance (p=0.072) despite having a point estimate that was similar to the other metastasis locations.[38 level I]

Henry et al. reported that Denosumab reduced the risk of developing multiple SREs by 10% compared to ZA. However this difference is not statistically significant (n=392 versus 436; p=0.14) (Figure 7).[42 level I]

3. Number of patients with SREs

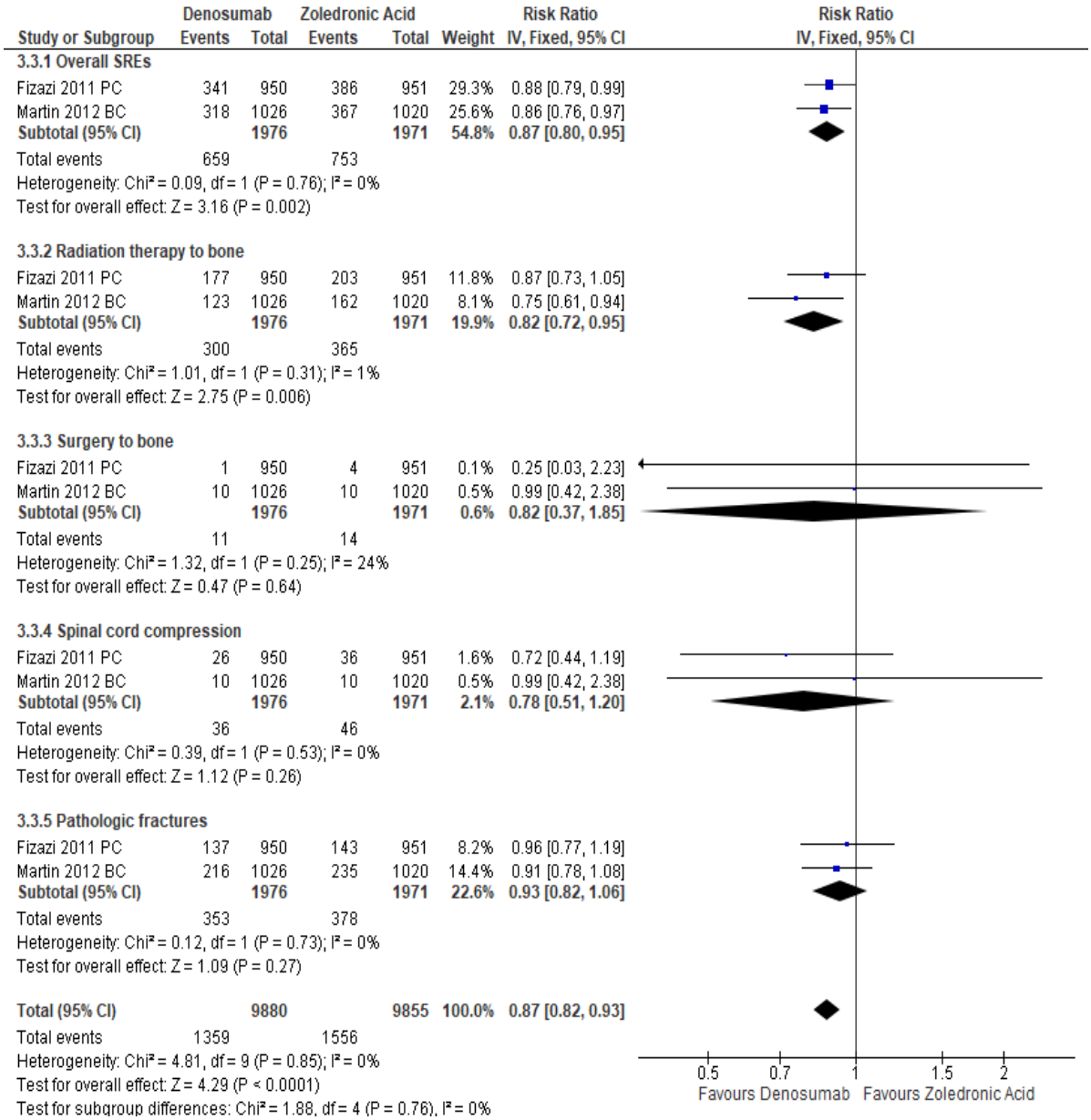
Only two out of six studies reported on this outcome. Lipton et al., Scagliotti et al. Henry et al. and Stopeck et al. did not report on this outcome. Pooled data from two studies showed that fewer number of patients with overall SREs in Denosumab group as compared to Zoledronic acid group (Figure 8). The results are presented as follows:

Breast cancer

Only Martin et al. reported on this outcome involving breast cancer patients. Fewer patients in the Denosumab group than in the Zoledronic acid group experienced an SRE (31%, 318 versus 36%, 367; p=0.006), and with multiple SREs (33%, 104) versus 38%, 141; p=0.016). In the subgroup of patients with a history of prior SRE at study entry, fewer patients in the Denosumab group than in the Zoledronic acid group experienced one or more subsequent SREs while on study (36% versus 44%; p=0.021). Similarly, among patients who had no history of SREs at study

entry, 28% of patients in the Denosumab group and 32% in the Zoledronic acid group experienced their first SRE (p=0.085).[40 level I]

By looking at the types of SREs, Denosumab prolonged the time to radiation therapy to bone by 26% (p=0.012) compared with Zoledronic acid. Fewer patients in the Denosumab group had pathologic fractures compared to Zoledronic acid group (21%, n=216 versus 23%, n=235). First SREs of surgery to bone and spinal cord compression were similar reported in approximately 1% (n=10) of patients in each treatment group.[40 level I]



Notes: **PC**: prostate cancer; **BC**: breast cancer

Figure 8. Denosumab versus Zoledronic acid (for breast cancer and prostate cancer); Outcome: Number of patients with SREs

Prostate cancer

Only Fizazi et al. reported on this outcome involving prostate cancer patients. Fewer patients in the Denosumab group than in the Zoledronic acid group experienced an SRE (36%, 341 versus 41%, 386), in radiation therapy to bone, surgery to bone, spinal cord compression and pathologic fractures. However, the difference was not significant in all results (Figure 8).[41 level I]

4. Number of events per year

Neither study reported on this outcome.

5. Skeletal morbidity rate (SMR)

Only one out of six studies reported on this outcome. Lipton et al., Scagliotti et al. Martin et al., Fizazi et al. and Henry et al. did not report on this outcome.

Breast cancer

Only Stopeck et al. reported on this outcome involving breast cancer patients. Skeletal morbidity rate was defined as ratio of the number of SREs per patient divided by the patient's time at risk. Denosumab reduced SMR by 22% compared to Zoledronic acid (0.45 events versus 0.58 events per patient per year; p=0.004).[43 level I]

6. Overall survival

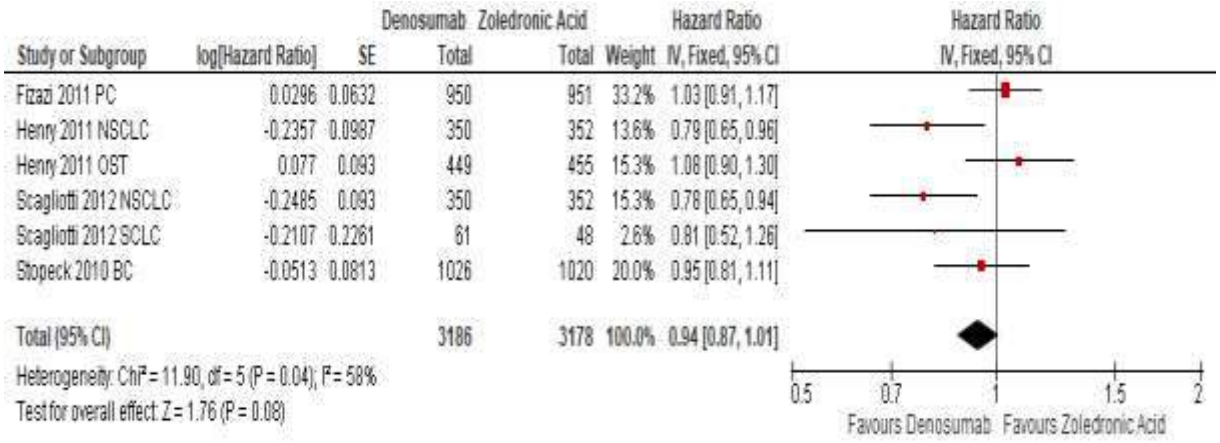
Four out of six studies reported on this outcome. Lipton et al. and Martin et al. did not report on this outcome. Pooled data from four studies showed that the overall survival was similar between Denosumab and Zoledronic acid (Figure 9). The results are presented as follows:

Breast cancer

Only Stopeck et al. reported on this outcome involving breast cancer patients. There was no significant difference in the overall survival between Denosumab and Zoledronic acid (p=0.49) (Figure 9).[43 level I]

Prostate cancer

Only Fizazi et al. reported on this outcome involving prostate cancer patients. There was no significant difference in the overall survival between Denosumab and Zoledronic acid (p=0.65) (Figure 9).[41 level I]



Notes: **PC**: prostate cancer; **NSCLC**: non-small cell lung cancer; **OST**: other solid tumour; **BC**: breast cancer

Figure 9. Denosumab versus Zoledronic acid (for all types of cancer); Outcome: Overall survival

Lung cancer

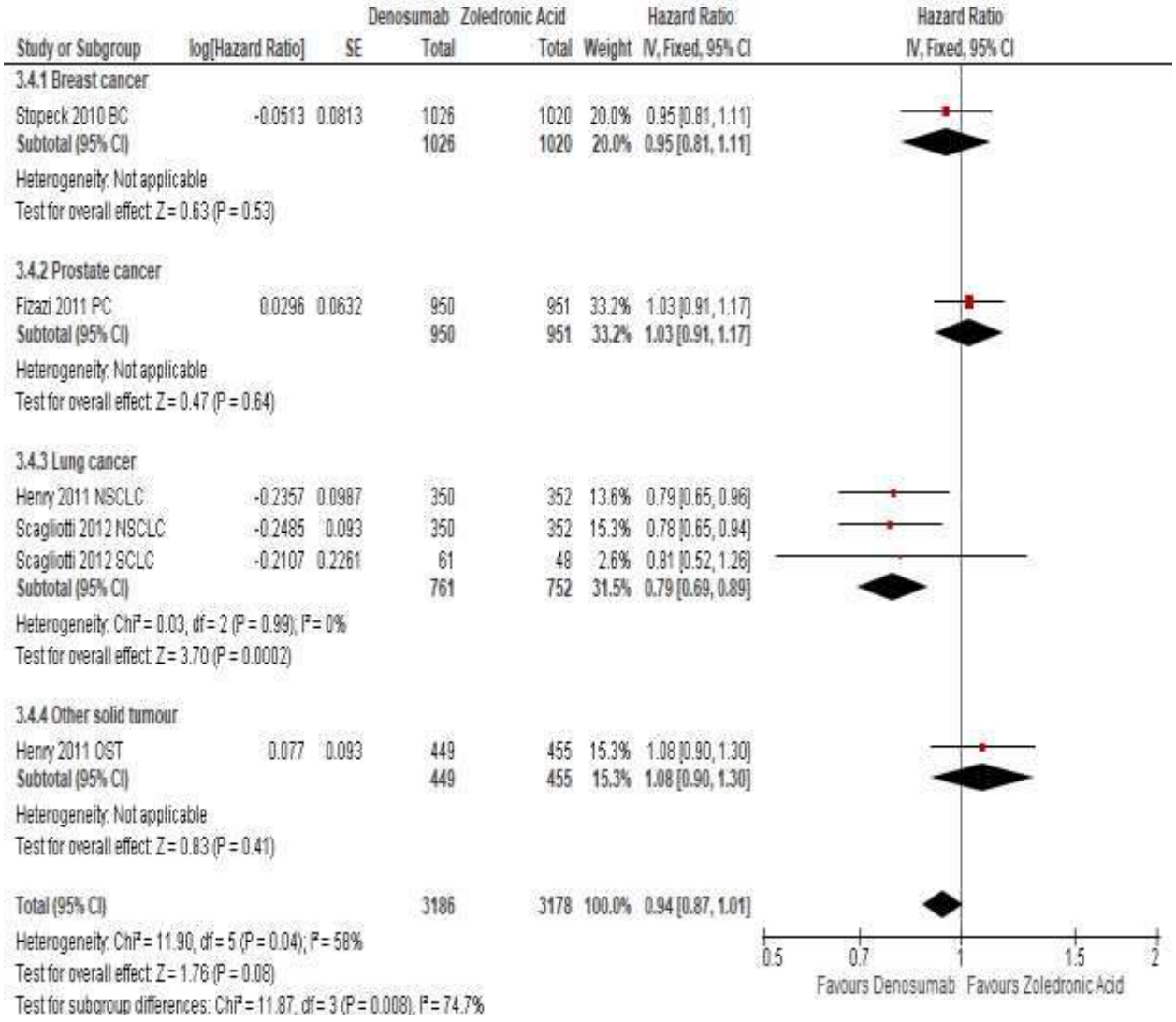
Scagliotti et al. and Henry et al. reported on this outcome involving lung cancer patients (Figure 9). In general, overall median survival in Scagliotti et al. showed that Denosumab increased with a difference of 1.2 months compared with Zoledronic acid (median: 8.9 months versus 7.7 months; p=0.01). During subgroup analysis Denosumab also has significant improvement of overall survival when compared to Zoledronic acid in NSCLC (median: 9.5 months versus 8.0 months; p=0.01). Having said so the difference of overall survival is not significant in SCLC (median: 7.6 months versus 5.1 months; p=0.36).[39 level I]

This was inline with the study reported by Henry et al. showed that there was a significant difference between the two groups for NSCLC (p=0.017).[42 level I]

Other solid tumours (OSTs)

Only Henry et al. reported on this outcome involving OSTs patients. There was no significant difference in the overall survival between Denosumab and Zoledronic acid (p=0.41) (Figure 9).[42 level I]

Pooled data in Figure 9 showed a substantial heterogeneity (I^2=58%) across all types of cancer group.[36] We conducted a subgroup analyses to explore the heterogeneity and found that it comes from the differences results from lung cancer subgroup and the other types of cancer subgroup (breast cancer, prostate cancer and other solid tumours). Therefore, there were two different results on this outcome, where only non-small cell lung cancer subgroup showed the significant difference in overall survival between Denosumab and Zoledronic acid (Figure 10). The results showed that there was a high substantial heterogeneity between the subgroup differences (I^2=74.7%).



Notes: **PC**: prostate cancer; **NSCLC**: non-small cell lung cancer; **OST**: other solid tumour; **BC**: breast cancer

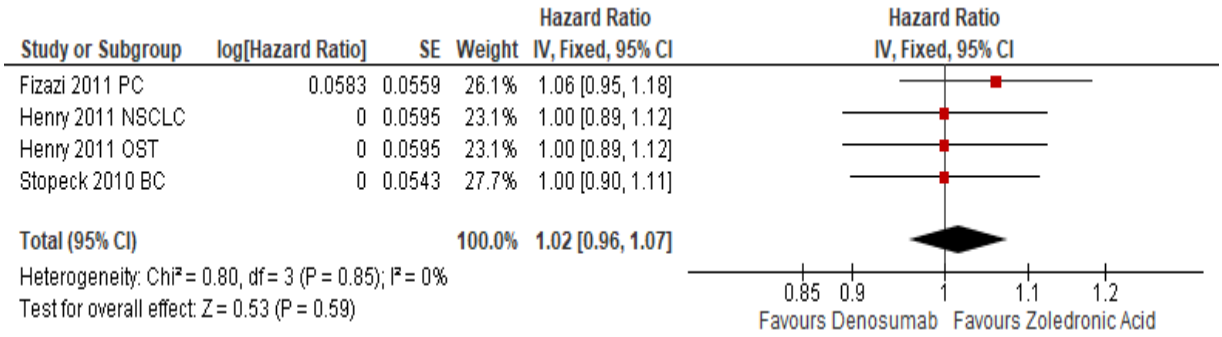
Figure 10. Subgroup analyses (for all types of cancer); Outcome: Overall survival

7. Disease Progression

Three out of six studies reported on this outcome. Lipton et al., Scagliotti et al. and Martin et al. did not report on this outcome. Pooled data from three studies showed that the disease progression was similar between Denosumab and Zoledronic acid in all types of cancer (Figure 11). The results are presented as follows:

Breast cancer

Only Stopeck et al. reported on this outcome involving breast cancer patients. There was no significant difference in the disease progression between Denosumab and Zoledronic acid (p=0.93) (Figure 11).[43 level I]



Notes: **PC**: prostate cancer; **NSCLC**: non-small cell lung cancer; **OST**: other solid tumour; **BC**: breast cancer

Figure 11. Subgroup analyses (for all types of cancer); Outcome: Disease progression

Prostate cancer

Only Fizazi et al. reported on this outcome involving prostate cancer patients. There was no significant difference in the disease progression between Denosumab and Zoledronic acid (p=0.30) (Figure 11).[41 level I]

Lung cancer

Only Henry et al. reported on this outcome involving lung cancer patients. The results showed that there was no significant difference in the disease progression between Denosumab group and Zoledronic acid group for non-small cell lung cancer (p=1.0) (Figure 11).[42 level I]

Other solid tumours (OSTs)

Only Henry et al. reported on this outcome involving OSTs patients. There was no significant difference in the disease progression between Denosumab and Zoledronic acid (p=1.0) (Figure 11).[31 level I]

8. Pain

One HTA reported on this outcome involving this intervention.

Breast cancer

One study in Ford et al. reported the pain outcome by dividing it into groups. The results are as follows:

i. The median time to developing moderate/severe pain

In patients with no/mild pain at baseline, Denosumab delayed time to development of moderate or severe worst pain (worst pain score of > 4 points) compared with Zoledronic acid (295 days versus 176 days; HR 0.78; 95% CI 0.67 to 0.92; p = 0.0024).[19 level I]

ii. The median time to worsening pain

The median time to worsening pain (≥ 2-point increase from baseline in BPI-SF worst pain score) was non-significantly favoured Denosumab compared with Zoledronic acid (8.5 months versus 7.4 months, p = 0.822).[19 level I]

iii. Time to pain improvement

Was similar between groups for (median 82 days versus 85 days; HR 1.02; 95% CI 0.91 to 1.15; p = 0.7245).[19 level I]

Prostate cancer

One study in Ford et al. reported the pain outcome by dividing it into groups. The results are as follows:

i. Time to development of moderate or severe pain

Denosumab delayed in patients with no or mild pain at baseline by around one month compared with Zoledronic acid (median 5.8 months vs 4.9 months) although the difference was not statistically significant (HR: 0.89, 95% CI: 0.77 to 1.04; p=0.1416). Denosumab also significantly decreased the proportion of patients with no/ mild pain at base who progressed to moderate or severe pain (relative decrease).[19 level I]

ii. The median time to worsening pain

The median time to worsening pain (≥ 2-point increase from baseline in BPI-SF worst pain score) was similar in the Denosumab and Zoledronic acid groups.[19 level I]

iii. Time to pain improvement

There was no significant difference in time to pain improvement (≥ 2-point decrease from baseline) between Denosumab and Zoledronic acid.[19 level I]

Lung cancer

Neither study reported on this outcome involving lung cancer patients.

Other solid tumours (OSTs)

One study in Ford et al. reported the pain outcome by dividing it into groups. The results are as follows:

i. Time to development of moderate or severe worst pain

Denosumab delayed time to development of moderate or severe worst pain (worst pain score of > 4 points) compared with Zoledronic acid OSTs including NSCLC (HR: 0.81, 95% CI: 0.66 to 0.99; median: 3.7 months versus 2.8 months; p=0.038).[19 level I]

ii. The median time to worsening pain

Denosumab delayed (≥ 2-point increase from baseline in BPI-SF worst pain score) compared with Zoledronic acid (4.7 months versus 3.9 months; p=0.040).[19 level I]

9. Quality of life

One HTA and one RCT reported on this outcome involving this intervention.

Breast cancer

One study in Ford et al. reported that Denosumab delayed time to development of moderate or severe worst pain (worst pain score of > 4 points) compared with Zoledronic acid (median: 9.7 months versus 5.8 months; p=0.0024). In all three studies, in terms of quality of life, overall mean Functional Assessment of Cancer Therapy (FACT) scores remained similar between the groups. An average of 3.2% (range 1% to 7%) more patients in the Denosumab group experienced a clinically meaningful improvement in quality of life (≥ 5-point increase in FACT-G total score) from week 5 through to week 73.[19 level I]

A RCT reported by Martin et al. showed that an average of 10% more patients in the Denosumab group compared with the Zoledronic acid group had a clinically meaningful improvement in HRQoL (≥5-point increase in FACT-G total score) over the course of the study (34% versus 31%). An average of 7% fewer patients in the Denosumab group than in the Zoledronic acid group had worsening of HRQoL on study. Among patients with no or mild pain at baseline (BPI-SF score 0 to 4), the relative overall improvement in HRQoL was 14% greater with Denosumab compared with Zoledronic acid. Among patients who had moderate or severe pain at baseline (BPI-SF score 5 to 10), the relative overall improvement in HRQoL was 9% greater with Denosumab than with Zoledronic acid. ECOG performance status was comparable in the Denosumab and Zoledronic acid groups (59% versus 55%, respectively). Worsened ECOG performance status was reported for 36% of patients in the Denosumab group and 41% of patients in the Zoledronic acid group; improved ECOG status was reported in 5% and 4% of patients in the Denosumab and Zoledronic acid groups, respectively.[40 level I]

Prostate cancer

Neither study reported on this outcome involving prostate cancer patients.

Lung cancer

Neither study reported on this outcome involving lung cancer patients.

Other solid tumours (OSTs)

Neither study reported on this outcome involving OSTs patients.

D. Effectiveness of the different regimen of BTAs (12-weekly versus 4-weekly)

Six RCTs related to assess the effectiveness of less frequent dosing of BTAs which are 12-weekly compared to the standard dosing 4-weekly. They are Himelstein et al. 2017 involving breast cancer and prostate cancer, Hortobagyi et al. 2017 involving breast cancer, Amadori et al. 2013 involving breast cancer, Amir et al. 2013 involving breast cancer, Fizazi et al. 2009 involving breast cancer, prostate cancer and other solid tumours and Lipton et al. 2007 involving breast cancer. No studies reported involving lung cancer.

Participants who naïve to the the standard dosing (up-front)

There are three RCTs involving patients that did not received any standard dosing of BTAs prior intervention; Himelstein et al. 2017, Fizazi et al. 2009 and Lipton et al. 2007.

Participants who have received standard dosing (4-weekly)

There are three RCTs involving patients that had received any standard dosing of BTAs prior intervention; Hortobagyi et al. 2017, Amadori et al. 2013 and Amir et al. 2013. In this group, patients had received standard dosing of Zoledronic acid or Pamidronate 9 doses or more during the first nine to 15 months at study entry before enrolment to 12-weekly dosing. They have been follow-up until 48 weeks to two years.

1. Time to first SREs

Only one RCT reported on this outcome. Himelstein et al., Amadori et al., Amir et al., Fizazi et al. and Lipton et al. did not report on this outcome. The result is presented as follow:

Breast cancer

Only Hortobagyi et al. reported on this outcome involving breast cancer patients. The study reporting on Zoledronic acid 12-weekly compared to Zoledronic acid 4-weekly. They reported that there was no statistically significant difference between Zoledronic acid 12-weekly and 4-weekly (HR: 1.06, 95% CI: 0.70-1.60; p=0.79).[45] level I

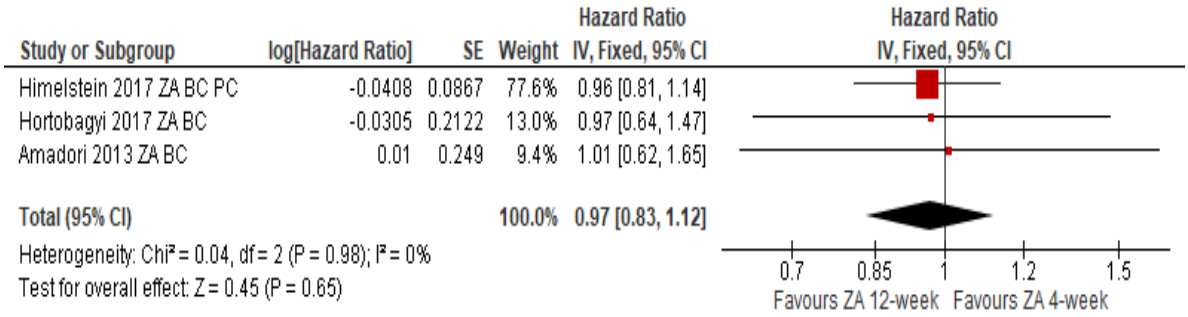
2. Risk of first and subsequent SREs

Three out of six RCTs reported on this outcome. Amir et al., Fizazi et al. and Lipton et al. did not report on this outcome. Pooled data from three studies showed that there was no significant different between Zoledronic acid 12-weekly and Zoledronic acid 4-weekly (Figure 12). The results are presented as follows:

Breast cancer

Himelstein et al., Hortobagyi et al. and Amadori et al. reported on this outcome involving breast cancer patients.

Himelstein reported that there were 256 patients with SREs in the Zoledronic acid every 4-week dose group and 246 patients in the every 12-week dose group. The median follow-up was 15.7 months in the Zoledronic acid every 4-week dose group and 16.8 months in the every 12-week dose group.[44 level I] Hortobagyi et al. and Amadori et al. only reported that there was no significant difference between the two groups without any numerical values (Figure 12).[45,46 level I]



Notes: **BC**: breast cancer; **PC**: prostate cancer; **ZA**: Zoledronic acid

Figure 12. Zoledronic acid 12-weekly versus Zoledronic acid 4-weekly (for breast and prostate cancer); Outcome: Risk of first and subsequent SREs

Prostate cancer

Only Himelstein et al. reported on this outcome involving lung cancer patients. Himelstein reported that there were 256 patients with SREs in the Zoledronic acid every 4-week dose group and 246 patients in the every 12-week dose group (Figure 12). The median follow-up was 15.7 months in the Zoledronic acid every 4-week dose group and 16.8 months in the every 12-week dose group.[44 level I]

Lung cancer

Neither study reported on this outcome involving lung cancer patients.

Other solid tumours (OSTs)

Neither study reported on this outcome involving OSTs patients.

3. Number of patients with SREs

All six RCTs reported on this outcome. Three study reporting on Zoledronic acid (Himelstein et al., Hortobagyi et al. and Amadori et al.), two studies reporting on Denosumab et al. (Fizazi et al. and Lipton et al.) and one study reporting on Pamidronate (Amir et al.). The results are presented as follows:

Breast cancer

All six RCTs reported on this outcome involving breast cancer patients. In terms of number of patients, three RCTs (Himelstein et al., Hortobagyi et al. and Amadori et al.) showed that the results were similar between Zoledronic acid 12-weekly and Zoledronic acid 4-weekly (302 patients versus 301 patients; respectively) (Figure 13).

As for Denosumab, two RCTs (Fizazi et al. and Lipton et al.) demonstrated that more patients with SREs in Denosumab 12-weekly compared to Denosumab 4-weekly (9 patients versus 6 patients), however the difference was not significant (Figure 13).[48,49 level I]

Amir et al. reported that over the 48-week follow-up period for Pamidronate, only two symptomatic SREs were observed in each treatment group (Figure 13). Both required radiation therapy to control bone pain.[47 level I]

Prostate cancer

Only two RCTs reported on this outcome involving prostate cancer patients. Himelstein et al. reporting on Zoledronic acid and Fizazi et al. reporting on Denosumab. Both results showed that there was no significant difference between the two regimens of dosing (Figure 13).[44,48 level I]

Lung cancer

Neither study reported on this outcome involving lung cancer patients.

Other solid tumours (OSTs)

Only one RCT reported on this outcome involving OSTs patients. Fizazi et al. found that there was no significant difference between the two groups (Figure 13).[48 level I]

4. Number of events per year

Neither study reported on this outcome.

5. Skeletal morbidity rate (SMR)

Two out of six RCTs reported on this outcome involving breast cancer patients only.

Breast cancer

Hortobagyi et al. reported that the mean SMR was not statistically significant between the Zoledronic acid 4-weekly and Zoledronic acid 12-weekly (0.46, SD: 1.06 versus 0.50, SD: 1.50 events per year; p=0.85).[45 level I] Another RCT by Amadori et al. reported that the SMR was higher in 12-week ZA group compared to 4-week ZA group (0·26, 95% CI: 0·15 to 0·37 versus 0·22, 95% CI: 0·14 to 0·29, respectively).[46 level I]

Prostate cancer, lung cancer and other solid tumours (OSTs)

Neither study reported on this outcome involving patients with prostate cancer, lung cancer and OSTs.

6. Overall survival

Neither study reported on this outcome.

7. Disease Progression

Neither study reported on this outcome.

8. Pain

Only one RCT reported this outcome on Pamidronate.

Breast cancer

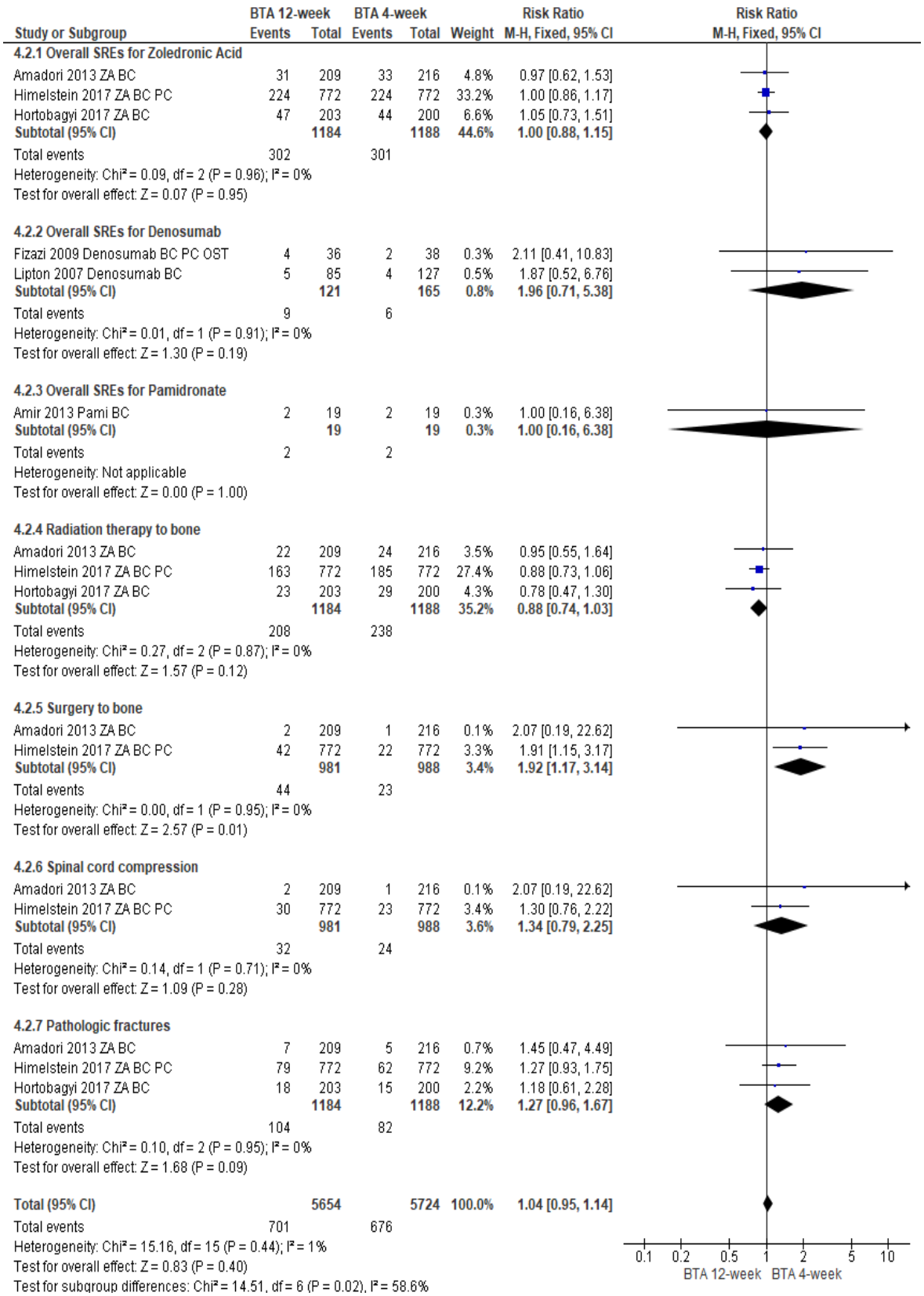
Only Amir et al. reported on this outcome involving breast cancer patients. They reported that pain scores as measured by BPI and FACT-BP remained generally stable over time in both the Pamidronate 4-weekly and Pamidronate 12-weekly groups. There were no statistically significant differences between groups in cumulative pain scores as measured by BPI (p=0.21) or by FACT-BP (p=0.59).[47] level I

Prostate cancer, lung cancer and other solid tumours (OSTs)

Neither study reported on this outcome involving patients with prostate cancer, lung cancer and OSTs.

9. Quality of life

Neither study reported on this outcome.



Notes: **BC**: breast cancer; **PC**: prostate cancer; **OST:** other solid tumour **ZA**: Zoledronic acid

Figure 13. 12-weekly versus 4-weekly Zoledronic acid (for breast, prostate cancer and other solid tumours); Outcome: Number of patients with SREs

2.4.5 SAFETY

Seven articles related to the safety of BTAs for prevention of SREs were included in this review; two SR studies and five RCTs. The articles were published between 2007 and 2017. One SR reporting on Bisphosphonates compared with placebo, Bisphosphonates compared with alternate Bisphosphonates and Denosumab compared with Zoledronic acid (LeVasseur et al. 2016), one SR reporting on Denosumab compared with Zoledronic acid (Chen et al. 2016) and five RCTs reporting on different regimen of BTAs (12-weekly compared with 4-weekly) (Himelstein et al. 2017, Hortobagyi et al. 2017, Amadori et al. 2013, Fizazi et al. 2009 and Lipton et al. 2007). Two studies in LeVasseur et al. that compared Denosumab with Zoledronic acid were also included in SR by Chen et al.

A. Safety of BTAs (Bisphosphonates or Denosumab) versus placebo or no treatment or best supportive care (BSC)

Adverse events that commonly associated with Bisphosphosnates reported by four studies in LeVasseur et al. were flu-like symptoms including pyrexia, bone pain, gastrointestinal upset and fatigue, hypocalcaemia, osteonecrosis of the jaw (ONJ) and renal toxicity. One study reported numerical values for these events where pyrexia and flu-like symptoms were the most common with Bisphosphonates, that ranging from 12.5% to 39%. The same four studies also reported on hypocalcemia, ONJ and renal impairment (Table 9).[37 level I] Hypocalcemia was more common in Bisphosphonates (Clodronate and Zoledronic acid) compared with placebo and chemotherapy. While renal toxicity was more common with Zoledronic acid when compared to placebo and to chemotherapy (Docetaxel/Carboplatin).

Table 9. Adverse events for Bisphosphonates versus placebo or best supportive care

Intervention versus control	Hypocalcemia (%)	ONJ (%)	Renal impairment (%)
Bisphosphonates vs placebo			
Clodronate vs placebo	7 vs 0	NR	NR
Zoledronic acid vs placebo	NR	NR	13 vs 7
Bisphosphonates & chemotherapy vs chemotherapy alone			
Zoledronic acid & docetaxel vs docetaxel	76 vs 30	0 vs 0	14 vs 26
Zoledronic acid & docetaxel/carboplatin vs docetaxel/carboplatin	NR	5 vs 0	5 vs 0

Notes: **ONJ;** osteonecrosis of the jaw **NR**; not reported, **vs**; versus

B. Safety of Bisphosphonates versus alternate Bisphosphonates

Adverse events that were commonly associated with Bisphosphosnates reported by three studies in LeVasseur et al. were flu-like symptoms including pyrexia, bone pain, gastrointestinal upset and fatigue, hypocalcaemia, ONJ and renal toxicity. All of them reported numerical values for these events found that pyrexia and flu-like symptoms were the most common with Bisphosphonates, that ranging from 12.5%

to 39%. The same three studies also reported on hypocalcemia, ONJ and renal impairment (Table 10). Hypocalcemia, ONJ and renal impairment results varied between Zoledronic acid and IV Ibandronic acid (hypocalcemia ranging from 3-8% while rates of ONJ remained low with Bisphosphonates). However, renal impairment was more common in Zoledronic acid compared with oral Ibandronate.[37 level I]

Table 10. Adverse events for Bisphosphonates versus alternate Bisphosphonates

Intervention versus control	Hypocalcemia (%)	ONJ (%)	Renal impairment (%)
IV Ibandronic acid vs Zoledronic acid	4 vs 5	0 vs 0	0 vs 0
Zoledronic acid vs oral Ibandronate	NR	4 vs 0	15 vs 4
Zoledronic acid vs Ibandronic acid	8 vs 3	0 vs 0	NR

Notes: **ONJ;** osteonecrosis of the jaw **NR**; not reported, **vs**; versus

C. Safety of Denosumab versus Bisphosphonates

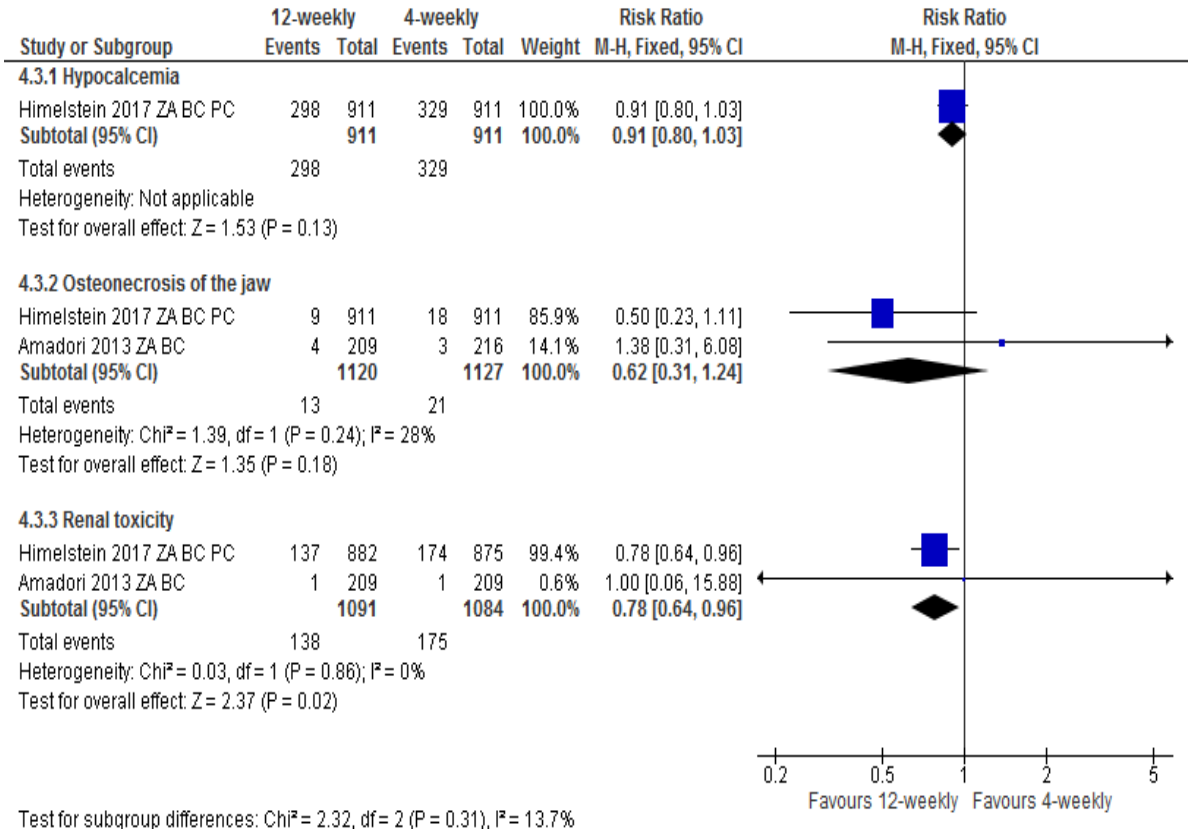
For this group, the safety data that compared Denosumab with Zoledronic acid only was reported. No data for other types of Bisphosphonates was available. Chen et al. conducted a systematic review involving 13,733 patients with bone metastases reported that Zoledronic acid associated with a decreased risk of hypocalcemia while Denosumab associated with decreased risk of renal toxicity. Denosumab has two times occurrence of hypocalcemia as compared to Zoledronic acid (OR: 2.17, 95% CI: 1.84, 2.56) and every 100 patients with Denosumab, 74 patients will have renal toxicity (OR: 0.74, 95% CI: 0.64, 0.85). While there was no significant difference in the rate of ONJ between Denosumab and Zoledronic acid (OR: 1.29, 95% CI: 0.95, 1.76).[32 level I]

Occurences of other adverse events such as back pain, nausea, fatigue, constipation, bone pain, asthenia, arthralgia and vomitting were generally similar between Denosumab and Zoledronic acid except anemia and anorexia. Denosumab is associated with a decreased risk of anaemia (OR: 0.86, 95% CI: 0.79, 0.94) and anorexia (OR: 0.90, 95% CI: 0.82, 0.98).[32 level I]

D. Safety of the different regimen of BTAs (12-weekly versus 4-weekly)

For Zoledronic acid, one RCT (Himelstein et al.) reported that the adverse events less occurred in 12-weekly regimen compared to 4-weekly regimen,[44 level I] while two RCTs (Hortobagyi et al. and Amadori et al.) reported that there were comparable between 12-weekly and 4-weekly regimen.[45,46 level I] No hypocalcemia result reported in Amadori et al. Pooled data from two RCTs showed that there was no significant different in hypocalcemia and ONJ events between 12-weekly Zoledronic acid and 4-weekly Zoledronic acid while 12-weekly regimen significantly decreased the event of renal toxicity compared to 4-weekly regimen (Figure 14).

For Denosumab, two RCTs (Fizazi et al. and Lipton et al.) found that the rates of adverse events were comparable between the Denosumab 4-weekly and 12-weekly groups (no value was available). The treatment related adverse events in general reported by Lipton et al. was fewer in 12-weekly regimen of Denosumab compared to 4-weekly regimen (15%, n=13/85 versus 22%, n=28/127).[49] level I



Notes: **BC**: breast cancer; **PC**: prostate cancer; **ZA**: Zoledronic acid

Figure 14. 12-weekly versus 4-weekly Zoledronic acid (for breast and prostate cancer); Outcome: Adverse events

2.4.6 ECONOMIC EVALUATION

Two articles related to the cost implication of BTAs in preventing SREs for metastatic cancers of solid tumours were included in this review; one SR of economic evaluation (Adronis et al.) and one cost-effectiveness analysis (Shapiro et al.).

The SR of economic evaluation was conducted in 2018 to review and appraise all published economic evaluations on treatments for the management of bone metastases. Seventeen out of 24 studies from 20 different countries involving four most common primary tumours; prostate (n=8), breast (n=7), lung (n=1) and renal (n=1) while seven reported results for various primary tumours. No economic

evaluations on treatment options for bone metastases secondary to thyroid cancer were identified.[52 level I]

The types of cost analysis were; cost-utility analyses (CUAs, n=16), reporting outcomes in terms of quality-adjusted life-years (QALYs), cost-effectiveness analysis (CEAs, n=4), reporting outcomes such as instances of SREs prevented, both CUA and CEA analyses (n=3), and cost-consequences analysis (CCA, n=1). In relation to the analytic approach adopted, 18 of the identified evaluations involved synthesising information from various sources (evidence published in the literature, estimates drawn from patient-level data, expert opinion, and other secondary sources) through some form of a decision analytic structure. The remaining six studies involved using statistical methods to analyse patient-level data collected from a single clinical trial (most often RCTs).[52 level I]

The perspective of the analyses (the viewpoint from which costs and benefits were calculated) varied across studies. Half of the studies reported results from the perspective of the healthcare system in the countries they related to, with eight studies adopting a third-party payer perspective, under which costs and consequences were included if they were deemed relevant to the entity covering the cost of the provided care. A societal perspective, which is meant to encompass all costs and consequences accruing across the society, was stated as the adopted viewpoint in three studies while one study did not report the perspective of the presented analysis.[52 level I]

The time frame over which results were calculated varied across studies. One study reported results over a time horizon shorter than 12 months, eight studies looked at costs and benefits accruing between 12 and 24 months, eight studies reported results over time horizons equal to or longer than 24 months, while four studies produced results over a lifetime horizon. One study analysed costs and benefits accruing over different lengths of time, while in another study, the length of time horizon varied according to the type of primary cancer investigated. Discounting was carried out to account for positive time preference in 11 studies that had time horizons more than 12 months. Discounting was not performed in nine studies.[52 level I]

In general, for breast cancer, evidence suggests that Bisphosphonate treatments were more effective in improving QoL and reducing the occurrence of SREs when compared with placebo. While such treatments were also more costly, the estimated additional cost per QALY gained values were typically lower than commonly cited cost-effectiveness thresholds. Denosumab was shown to be more effective but considerably more costly than ZA, with the lowest incremental costs per QALY value reported being in excess of €57,000. Denosumab dominated ZA,

being less costly and more effective, only when access to patient access scheme (PAS) was considered.[52 level I]

In prostate cancer, they suggest that Zoledronic acid (ZA) leads to fewer SREs and a greater number of QALYs but associated with higher costs, the magnitude of which appears to be contingent on the acquisition cost of ZA. Denosumab, a newer alternative to bisphosphonates was invariably found to be marginally more effective than ZA in preventing SREs and improving patients' QoL. Nonetheless, findings suggest that superior effectiveness comes at a considerable additional cost; while this cost varies across studies and countries, there was an agreement between authors that, in the absence of special arrangements such as PAS, Denosumab was unlikely to represent 'value for money'.[52 level I]

With regard to lung cancer, findings suggest that, in comparison with placebo, ZA leads to QALY gains at an additional cost that was relatively low. In line with findings for breast and prostate cancer, Denosumab was seen to be more effective but substantially more costly than ZA, resulting in incremental cost per QALY values >$68,000, unless a PAS arrangement was in place. In addition, in the only economic study on bone metastases for renal cancer, evidence suggests that ZA would result in gains in QALYs for a modest additional cost (or cost savings in some countries).[52 level I]

Another cost-effectiveness analysis by Shapiro et al. that constructed a-monthly cycle of markov model (a total of 24 simulated months) to analyze the CE of three treatment strategies (4-weekly ZA, 12-weekly ZA, and 4-weekly Denosumab), each using a hypothetical cohort of 10,000 women with breast cancer and bone metastases for SRE prevention. The CEA was conducted from the US payer's perspective. A 2-year time horizon was used to correspond with the length of the trial comparing 4-weekly ZA with 12-weekly ZA. On the base-case analysis, Denosumab was found to be the greatest mean costs and mean number of SREs and was dominated, relative to 4-weekly ZA and 12-weekly ZA. Twelve-weekly ZA was less expensive and had slightly fewer SREs than 4-weekly ZA and would be considered the dominant option. QALYs were virtually identical in all the three treatment arms; hence, the optimal treatment would be 12-weekly ZA because it was the least costly treatment.[53 level I]

The sensitivity analyses were performed into three groups, where the first one was by assuming 4-weekly Denosumab had transition probabilities equal to 4-weekly ZA and 12-weekly ZA in the base-case scenario. Although this assumption results in Denosumab having fewer SREs than 4-weekly ZA or 12-weekly ZA, and consequently lower costs, the overall findings were unchanged from the base-case analysis. Twelve-weekly ZA still had the lowest costs. The second group was assuming Denosumab SRE probabilities were 50%, 75%, and 90% lower than 4-

weekly ZA and 12-weekly ZA. Denosumab had fewer SREs than 4-weekly ZA and 12-weekly ZA. However, this did not lead to Denosumab being less costly. Compared with 4-weekly ZA, the mean incremental costs per mean SRE avoided for Denosumab ranged from $137,905 to $283,109. Likewise, compared with 12-weekly ZA, the mean incremental costs per mean SRE avoided for Denosumab ranged from $162,918 to $347,655. The third group was assuming 4-weekly ZA and 12-weekly ZA SRE probabilities were higher than 4-weekly Denosumab by 50% and 100%. The incremental differences in SREs for 4-weekly ZA and 12-weekly ZA relative to Denosumab were high enough to make the mean costs more comparable. The mean incremental costs per SRE avoided for Denosumab when compared with 4-weekly ZA ranged from $6,072 to $41,432. Similarly, compared with 12-weekly ZA mean incremental costs per SRE avoided for Denosumab ranged from $8,628 to $46,896.[53 level I]

2.4.7 SOCIAL/ETHICAL /LEGAL /ORGANIZATIONAL ISSUES

Only one article (Qian et al.) conducted in US related to utilization pattern of BTAs and the impact of BTAs among metastatic solid tumour was included in this review.[51 level II-2] Compliance and persistence outcomes were assessed during the first, second and third year after BTAs initiation. Denosumab patients were more likely to be male and older age which reflect mainly usage among prostate cancer patients compared to Zoledronic acid (30.4% versus 21%; p<0.0001). While in breast cancer and lung cancer, ZA used among patients was more than Denosumab (33.4% versus 32.6%; p=0.39 and 29.4% versus 22.3%; p<0.0001, respectively). Majority of patients (92.0%) initiated BTAs within three months of bone metastasis diagnosis.[51 level II-2]

The evidence showed that patients treated with Denosumab were more compliant to BTAs by receiving at least 12 administrations in a 1-year period compared to ZA administration (Table 11). Patients that used Denosumab were less likely to switch. In the first year of follow-up, 4% Denosumab patients' switched agent compared to 14% patients of ZA switched to Denosumab. In the 2nd and 3rd year, 3% and 1% of Denosumab patients switched compared with 12% and 11% of ZA patients. By using the 90-day therapy gap, the result found that the median time to non-persistence over the entire 36-month follow-up was longer for Denosumab compared with ZA (25.9 months versus 17.2 months; p<0.0001).[51 level II-2]

Table 11. Percentage of patients' compliant to BTAs administration

Types of BTAs	1st year (%)	2nd year (%)	3rd year (%)
Denosumab	50.4	36.6	30.9
Zoledronic acid	40.7	25.9	5.8

In each of the three 1-year periods evaluated, a greater percentage of Denosumab patients were compliant compared with Zoledronic acid users. Denosumab patients also had longer durations of persistent therapy use. These higher levels of compliance and persistence may improve treatment effectiveness.[51 level II-2]

2.5 DISCUSSION

For effectiveness and safety outcome, our systematic review included one HTA, five SR, 12 RCTs and one cross-sectional survey on the effects of Bone Targeting Agents (BTAs) in preventing SREs for metastatic cancers of solid tumours. Evidence was grouped into four groups of interventions: BTAs versus placebo or no treatment or best supportive care, Bisphosphonates versus alternate Bisphosphonates, Denosumab versus Bisphosphonates and the different regimen of BTAs. We also divided into four large groups of solid tumours: breast cancer, prostate cancer, lung cancer and OSTs. In general, we found that BTAs produced favourable outcomes in solid tumours. This finding is in agreement with the HTA published in 2013.[19]

2.5.1 Interpretation of the evidence

The findings on the first group of intervention showed BTAs significantly delayed the time to first SREs and significantly reduced the risk of first and subsequent SREs in breast cancer, prostate cancer, lung cancer and OSTs except for NSCLC patients where Ford et al. found that there was no significant difference between the two groups. Bone targeting agents were also associated with lower number of patients with SREs in breast cancer and prostate cancer. However, there was no difference in lung cancer and OSTs. The evidence for number of events per year, SMR and QoL was limited however, there was evidence that favoured BTAs among all types of cancer.[37] While for disease progression, evidence showed that time to bone lesions was longer in patients with BTAs. At the same time, BTAs were also found to significantly reduce pain score in breast cancer and prostate cancer patients.

In terms of effectiveness, evidence showed that Zoledronic acid was the most effective in delaying the time to first SREs and reduction in SRE rate followed by Pamidronate and Ibandronate in breast cancer and lung cancer.[7,19,37] However, Zoledronic acid significantly reduced the risk of first and subsequent SREs only in patients with breast cancer[19] while there was no difference in patients with prostate cancer, lung cancer and OSTs compared with other types of Bisphosphonates used.[31]

Pooled data from meta-analysis that compared between Denosumab and Zoledronic acid showed that Denosumab delayed the time to first SREs by 18% for all types of cancer. Denosumab also significantly reduced the risk of first and

subsequent SREs by 17% for all types of cancer. This analysis was inline with the study in the HTA report by Ford et al. among breast cancer, prostate cancer and OSTs. However, for NSCLC, the result was favoured to Denosumab although there was no significant difference.[19] It was also in agreement with SR by LeVasseur et al. among lung cancer patients.[37] Overall survival and disease progression were similar for all types of cancer except overall survival for lung cancer where patients who received Denosumab significantly delayed by 21%. For pain outcome, Denosumab was favourable compared to Zoledronic acid in breast cancer and OSTs only. As the evidence for quality of life was very limited whereby only breast cancer data available and showed that Denosumab was superior to Zoledronic acid in improving QoL.

For all outcomes reported in the different regimens of BTAs, there was no difference in time to first SRE, risk of subsequent SREs and number of patients with SREs in breast, prostate cancer and other solid tumors. This results showed no difference between the three RCTs that involving naïve patients (for Zoledronic acid and Denosumab)[44,48,54] and another three RCTs (that involved Zoledronic acid and Pamidronate) who had prior treatment with the standard dosing 4-weekly before they swithched to less frequent dosing, 12-weekly. Thus, the effect of the standard dosing might not interfere with the 12-weekly results. However, with a small sample size for Denosumab, caution must be applied as the findings might not be the same with the bigger population.[48,54]

For all seven articles which reported on the safety profiles, there was no significant difference in all adverse events when compared Bisphosphonates with placebo and alternate Bisphosphonates.While we found Denosumab had two times higher occurrence of hypocalcemia but it was associated with less renal toxicity compared with Zoledronic acid. Both Denosumab and Zoledronic acid were similar in the occurrence of ONJ event. No significant difference between12-weekly and 4-weekly regimens in adverse events for hypocalcemia and ONJ. However, less renal toxicity events were found in 12-weekly Zoledronic acid for breast cancer and prostate cancer compared to 4-weekly Zoledronic acid. Given that the occurrence of adverse events mostly similar in all BTAs group, it seems that BTAs were well tolerated without serious unwanted effects except for Zoledronic acid, whereby creatinine clearance must be closely monitored in patients with renal impairment and was contraindicated when creatinine clearance was less than 0.5mL/s.[41,55] Nephrotoxicity has been shown to be associated with Zoledronic acid treatment, therefore some studies set a limit that patients with creatinine clearance of less than 30 mL/min will be contraindicated to Zoledronic acid.[19,43,56]

One of the main reasons for using of BTAs in prevention of SREs is due to the economic burden of bone metastases that was associated with SREs.[57,58] In US, National Institutes of Health reported the cost burden for patients with metastatic

bone disease accounted about 17% of the $74 billion of total direct medical cost which was estimated at $12.6 billion.[57] The evidence on economic evaluation suggested that Denosumab was the most effective intervention compared to Zoledronic acid but associated with higher cost for all types of cancer. Also, when comparing between 4-weekly, 12-weekly Zoledronic acid and 4-weekly Denosumab, 12-weekly Zoledronic acid would be the optimal treatment with least costly compared to others.

2.5.2 Quality of the evidence

To ensure reliability of the evidence on the effectivenss and safety, we have decided to include HTA, SR and RCTs for this review. Thus, we were able to include only 18 articles with these study design on the effectiveness and safety. However, we also included another one recent evidence (cross-sectional study) in 2018 related to the outcome of bone pain in real-world practice among European countries.[50]

Some articles were of good quality and some articles were of moderate quality. One SR had more than one domain judged as high risk of bias. Poor reporting of allocation concealment and blinding was common among these articles. For example, six articles did not adequately report allocation concealment which might lead to selection bias.[38,39,43,47,48,59] Additionally, five articles did not completely described how blinding of participants, researchers or healthcare providers and outcome assessors was carried out in the studies.[39,44,46-48] Insufficient allocation concealment and poor blinding conducted in any trial could lead to higher estimation effects of treatment.[60] Blinding in a trial should be performed on as many parties as possible including participants, clinicians, data collectors, outcomes assessors, and data analysts to minimize differentials interventions and outcome biased assessments.[61]

The diversity of the studies such as cancer types and the intervention given is useful rather than a problem because the findings could be generalisable to a broader group of patients.[62]

2.5.3 Strengths and limitations

The main strength of this review is the degree of rigour in the conduct of the review. The methods were in accordance with those proposed by the Cochrane Collaboration for conducting systematic review of interventions and the PRISMA statement.[36,63] Additionally we assessed the quality of the included trials.

This review has several limitations since it relied on the methods and quality of the included reviews and the limitations of the primary studies themselves. The comprehensiveness of this review is inevitably limited by the comprehensiveness

and quality of the source reviews (HTA and SR). It is presumed that each review generally included the full available and eligible evidence that data extraction was accurate, and that analyses were scientifically sound. Most studies did not mention whether they enrolled participants who actually naïve BTAs or have received BTAs prior to the studies, thus the exact differences between these two groups are unknown. Most of the included studies within each review were conducted in the U.S, United Kingdom and other parts of Europe which poses questions to the applicability of the results to Malaysian population. Although there was no restriction in language during the search but only English full text articles were included in the report.

CHAPTER 3: DECISION ANALYTIC ECONOMIC MODELLING

3.1 OBJECTIVES

The general objective of this economic evaluation was to assess the cost-effectiveness of bone targeting agents in prevention of skeletal-related events in metastatic cancer of solid tumours. The specific objectives were:

i. To calculate the incremental cost-effectiveness ratio (ICER) between various bone targeting agents (Zoledronic acid and Denosumab) with current best supportive care in prevention of SREs among patients with metastatic solid tumours.
ii. To estimate the budget impact and financial implications when patients with bone metastases secondary to solid tumours transitioned from usual care (no prophylaxis) to intravenous Zoledronic acid as SRE-prophylaxis.

3.2 METHODS

A literature-based state transition model (Markov cohort simulation) was developed using Microsoft Excel Workbook 2007 to estimate the lifetime costs and quality adjusted life years (QALYs) of using bone targeting agents as prevention of SRE in patients with bone metastases secondary to solid tumours. This type of model was chosen for its ability to extrapolate efficacy data from short-term clinical trials in metastatic solid tumours to longer term cost-effectiveness results.

Based on the systematic review and meta-analysis conducted in this HTA report earlier, there was no significant difference in terms of the effectiveness outcomes when comparing 4-weekly and 12-weekly intravenous Zoledronic acid. Hence, for economic evaluation, only 12-weekly regime of Zoledronic acid was assessed. A hypothetical cohort of 1000 stage IV cancer patients with bone metastases were simulated in three strategies:-

i) usual care / best supportive care (no bone targeting agents given)
ii) 12-weekly intravenous Zoledronic acid 4mg
iii) 4-weekly subcutaneous Denosumab 120mg

3.2.1 Model Structure

The model structure was constructed with reference to other published studies[14, 64-65] and in consultation with expert committees consist of multidisciplinary experts namely clinical oncologists, orthopaedic oncologist, health economists, public health physicians and pharmacists. In general, this Markov model included seven health states in two disease conditions, namely stable metastatic and progressive metastatic disease, with dead as the absorption state (Figure 15).
The simulated clinical pathways are as follow:

i. Patients entered the model in the post-diagnosis state after confirming presence of bone metastases and without SRE (cancer with metastases, no SRE). In the usual care / best supportive care cohort, no bone targeting agent was given in preventing SRE and all patients were managed according to standard care.
ii. In the cohorts of patients receiving bone targeting agent, 12-weekly intravenous Zoledronic acid 4mg or 4-weekly subcutaneous Denosumab 120mg were given as prevention of SRE once the patients confirmed as Stage IV cancer with bone metastases. Once patient developed SRE, the same bone targeting agent was given as treatment. Calcium supplementation was also given to patients who received bone targeting agents.
iii. Patients would either remain in stable metastatic disease (without progression) or having disease progression before experiencing the first episode of SRE and/or subsequent SRE.
iv. The health outcome and economic impact related to drug-induced severe adverse events were not included in the model due to its rarity (<1%)[65]
v. In patients receiving Zoledronic acid, renal monitoring test was performed prior to each treatment in view of possible complication of renal toxicity[64]
vi. All patients received palliative care and follow-up in oncology specialists clinic was 3-monthly.
vii. Death was only possible due to metastatic cancer and not other causes.

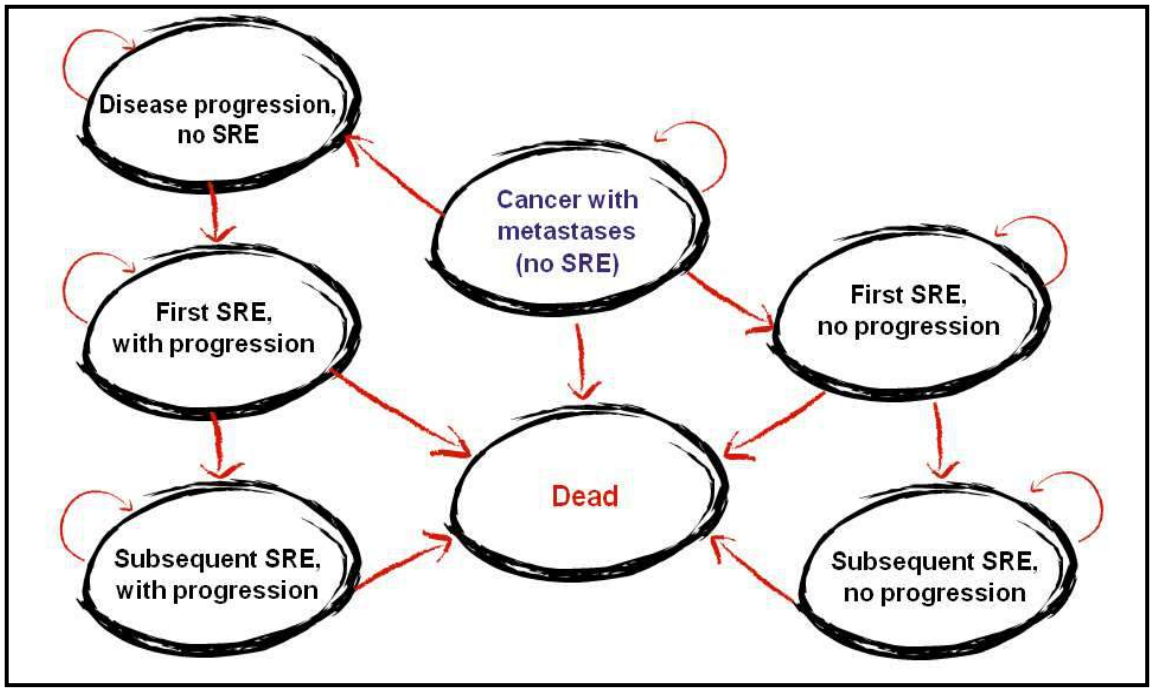


Figure 15. Markov model of bone targeting agents versus usual care in prevention of skeletal related events.

The model decision analyses were projected to lifetime horizon (84 months) and the transition cycle was quarter year or equal to 13 weeks.

3.2.2 Model Estimation

The epidemiological and disease-related data were obtained from local sources of data whenever available, or literature review when local data was not available.

a. Effectiveness Data and Transitional Probabilities

The effectiveness parameters in this study were obtained from published clinical trials as shown in **Table 12**. The main outcomes from these clinical trials were median time to first SRE and skeletal morbidity rate. No significant difference in overall survival and progression-free survival,[30, 66] hence, these two parameters were not included in this model.

Transitional probabilities among different states were derived primarily from the efficacy results of the phase 3 clinical trial comparing Denosumab and Zoledronic acid which being used in an economic evaluation by Xie et al.[30, 64] Probabilities for usual care arm were obtained from a clinical trial comparing Zoledronic acid and placebo, which then utilised in an economic evaluation by Carter et al.[14, 66]

Table 12. Effectiveness data and transitional probabilities

Parameter	Usual care	ZA	Denosumab	Reference
Median time to first SRE in months (SD)	11 (0.8)	17.1 (1.1)	20.7 (1.6)	14, 30, 64, 66
Skeletal morbidity rate	3.05	1.71	1.20	64, 65
Risk of hypocalcaemia	-	6%	13%	30
Increased risk of having first SRE and subsequent SRE due to progression	2.14	2.14	2.14	64
Transitional probabilities				
From stable metastases to disease progression	0.221	0.221	0.221	64
First SRE among patients without progression	0.245	0.115	0.096	14, 64
Subsequent SRE among patients without progression	0.355	0.167	0.137	14, 64
From any health states to death	0.271	0.271	0.271	64

Notes: **SD:** standard deviation; **SRE**: skeletal related events; **ZA**: Zoledronic acid

b. Utility Data

Utilities for the health states represented in the model were obtained from a time trade-off (TTO) exercise by Dranitsaris and Hsu, which was the only published empirically-based estimate of utilities for bone targeting agents and SRE for patients with advanced breast cancer receiving pamidronate, a type of biphosphonates.[67] These utility values were incorporated in other published economic evaluations related to prevention and treatment of SRE in Stage IV cancers with bone metastases.[16, 65] Hence, the same utilities were used in patients receiving any type of bone targeting agents. These values were compared with the utility value from ACTION study which was a longitudinal study on health-related quality of life among cancer survivors in Southeast Asia including Malaysia.[68] Utility for progressive disease was obtained from another health-state utilities study on metastatic breast cancer patients.[69] All the utility values incorporated in the model were as shown in **Table 13**.

Table 13. Utility inputs

Health states	Base-case value	95%CI	Reference
No SRE, receive BTA	0.64	0.53 - 0.76	16, 65, 67
No SRE, receive usual care	0.56	0.45 - 0.68	16, 65, 67
SRE, receive BTA	0.46	0.37 - 0.54	16, 65, 67
SRE, receive usual care	0.31	0.23 - 0.38	16, 65, 67
Stage IV with progressive disease	0.39	0.33 - 0.45	69
Stage IV at diagnosis	0.65	SD = 0.24	68

Notes: **BTA:** bone targeting agent

c. Resources and Cost Data

The costs used in this analysis were based on MOH Consumer Price Guide from Pharmaceutical Services Program[70], Malaysian DRG Casemix costing (severity illness 2), MOH Investigation Charges from website,[71] published literature using local data[72-75] and personal communication with pharmacists from MOH. Direct medical costs included were cost of drugs, cost of procedures such as IV and subcutaneous administration of drugs, cost of investigations such as renal profile, cost of SRE related management (pathological fracture, radiotherapy to the bone and spinal cord compression requiring instrumentation), cost of specialist clinic follow-ups and palliative care. All costs are expressed in Malaysian Ringgit (RM) and adjusted accordingly to costs of the year 2017. For the drugs, the most recent costs in 2018 were used in the model. All the parameters for cost inputs are

presented in **Table 14**. All results were presented as incremental cost-effectiveness ratio (ICER).

Table 14. Cost parameters

Cost description	Base case estimate	Reference / Source
Tablet calcium carbonate 500mg (per month)	RM 180.00	MOH Consumer Price Guide [70]
Renal profile (per test)	RM 5.00 (third class charge)	MOH Investigation Charges [71]
Total cost IV Zoledronic acid 4mg (per dose)	RM 472.00	National Cancer Institute, 72
Total cost SC Denosumab 120mg (per dose)	RM 1,239.14	National Cancer Institute, 72
Stable / Progressive Stage IV disease (per year)	RM 21,830.77	MalaysianDRG (severity illness 2), 73, 74
Average cost of first SRE related treatment	RM 5,132.04	MalaysianDRG (severity illness 2), 75

Notes: **IV**: intravenous; **SC**: subcutaneous

3.2.3 Sensitivity Analysis

Deterministic sensitivity analysis was performed as one-way sensitivity analysis to evaluate the impact of variations in key model inputs on the model results. Input parameters were varied over a specified range, standard deviation or using values of reported upper and lower limit of 95% confidence interval. Input parameters tested in sensitivity analyses were:

- annual discounting rate (0-5%)
- transition probability of subsequent SRE among patients without progression in Zoledronic acid group (per cycle)
- utility values for usual care and Zoledronic acid groups
- cost of first SRE-related managements (range: RM 1,845 to RM 8,745)
- cost of stable/progressive Stage IV disease (range: RM 17,710 to RM 31,552)

3.2.4 Assumptions

It is a common approach to use assumptions based on available published literature or expert consultations in economic modelling. The following key assumptions were used in this model:

i. The same bone targeting agent is given as prevention and treatment of SRE in the cohort (no switch of treatment once patient has SRE).

ii. The quality of life benefits (utility) of all bone targeting agents were assumed to be similar.[65]
iii. Utility values in disease progression states are lower than in stable metastases.
iv. No more than one SRE could occur within each cycle, making the maximum SRE that may occur in a year is four times.[64]
v. The type of subsequent SRE was not dependent on the first SRE.[14]
vi. Stable and progressive metastases states incur the same cost.
vii. Average cost of SRE-related treatments is the same regardless whether it is first SRE or subsequent SRE.
viii. Skeletal-related events did not change the mortality rate.

3.3 RESULTS AND DISCUSSIONS

3.3.1 Base-Case Analysis

The results of this Markov model reflected the incremental cost-effectiveness ratios if bone targeting agents (12-weekly Zoledronic acid and 4-weekly Denosumab) were used as prophylaxis in prevention of skeletal related events in Stage IV solid tumours patients with bone metastases. The base case results of the evaluated strategies were presented in **Table 14**. The mean total discounted cost and QALY per patient receiving 12-weekly Zoledronic acid was RM 37,314.89 and 2.5836 respectively, while for 4-weekly Denosumab was RM 57,231.09 and 2.7582. For usual care group in which no prophylaxis was given, the mean discounted cost and QALY was RM 32,544.36 and 1.6235 respectively.

Table 14. Incremental cost-effectiveness ratios (ICERs) for base-case

Strategies	Total cost per patient	Total QALY per patient	Increment. cost	Increment. QALY	ICER (compared to usual care)
Usual care	RM 32,544.36	1.6235	-	-	-
ZA	RM 37,314.89	2.5836	RM 4,770.53	0.9601	**RM 4,968.87**
Denosumab	RM 57,231.09	2.7582	RM 24,686.73	1.1348	**RM 21,754.66**

The base case analysis indicated that the deterministic ICER for 12-weekly Zoledronic acid was **RM 4,968.87 per QALY gained**. Over the lifetime of the patients cohort (approximately 7 years), there was a marginal cost increase of RM 4,770.53 and a marginal benefit of 0.9601 QALYs per patient when 12-weekly Zoledronic acid was given as prevention of SRE in Stage IV solid tumour patients with bone metastases compared with no prophylaxis. The ICER for 4-weekly Denosumab was RM 21,754.66 with slightly higher incremental QALY gained of 1.1348 compared with Zoledronic acid.

Both of these ICERs were below the cost-effectiveness threshold of one gross domestic product (GDP) per capita per QALY gained for Malaysia. However, 12-weekly Zoledronic acid was the most cost-effective option with lower ICER compared with Denosumab. If generic Zoledronic acid is to be used, whereby the price of this generic is lower than the originator drug by 60%, the estimated ICER is RM 3,718.01. This estimate was based on an assumption that the generic drug and the originator drug is of the same effectiveness.

3.3.2 Sensitivity Analysis

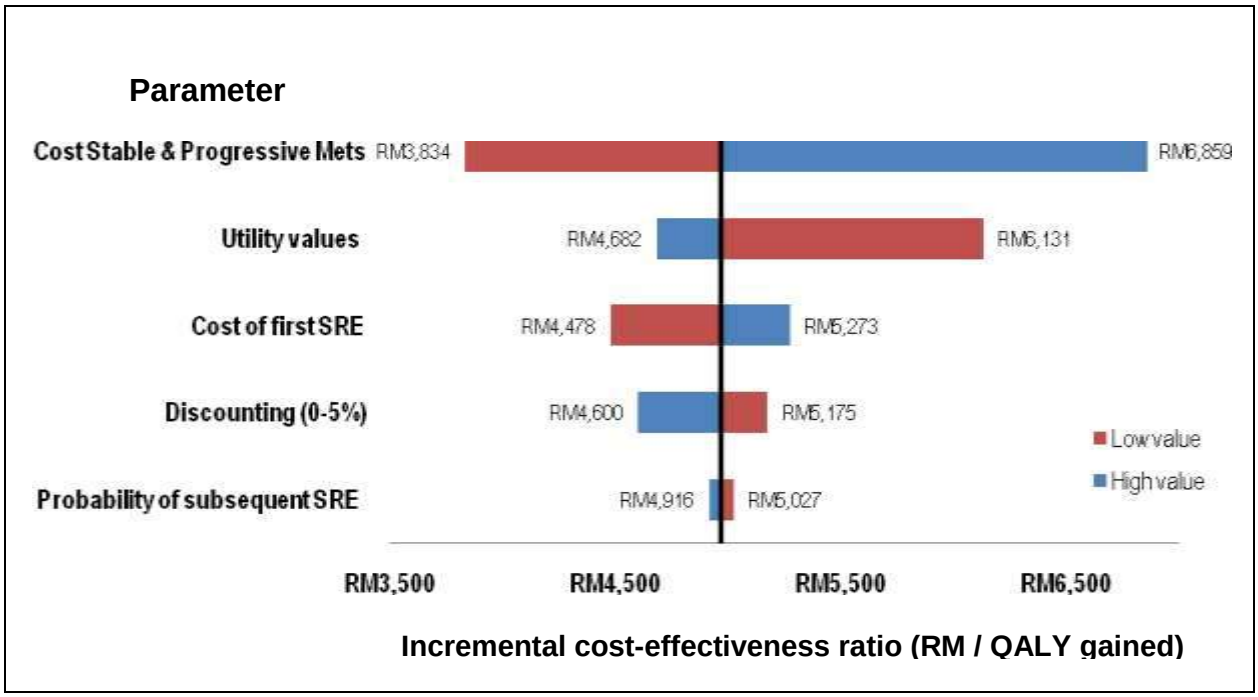
One-way sensitivity analysis was performed around key model parameters including discounting rate, clinical parameters, utility parameters as well as cost parameters for usual care and 12-weekly Zoledronic acid cohorts. The findings from the analysis were presented in **Table 15** and plotted as tornado diagram (**Figure 16**) to illustrate the differences in ICERs obtained given the range of parameter estimates being tested.

Table 15. Sensitivity analysis of key model parameters (usual care vs Zoledronic acid)

Parameters	95% CI limit / Range / SD	ICER of lower value input	ICER of higher value input
Annual discounting rate	0 – 5%	RM 5,174.74	RM 4,600.12
Transition probability of subsequent SRE in patients without progression (ZA group)	SD = 0.019	RM 5,026.56	RM 4,915.89
Utility values for usual care and ZA groups	Refer to **Table 13**	RM 6,131.09	RM 4,681.52
Cost of first SRE-related managements	RM 1,845 - RM 8,745	RM 4,478.36	RM 5,273.47
Total cost of stable and progressive Stage IV disease	RM 17,710 - RM 31,552	RM 3,834.01	RM 6,858.80

Notes: **SD**: standard deviation

By varying the input parameters, the estimated ICERs ranged from a lower bound of RM 3,834.01 per QALY gained to an upper bound of RM 6,858.80 when comparing usual care or best supportive care to prophylaxis Zoledronic acid. All the ICERs generated were lower than one GDP per capita per QALY gained.



Notes: Central axis = base-case ICER (RM 4,968.87)

Figure 16. Tornado diagram Zoledronic acid (one-way sensitivity analysis)

From the sensitivity analysis, the most sensitive input parameter in this model was the total cost of management for stable and progressive Stage IV disease with bone metastases **(Figure 16)**. Utility values, cost of first SRE-related management and discounting rate had moderate impact on the ICER as shown in the tornado diagram. In contrast, the result was not sensitive to different transition probability values of subsequent SRE in these patients.

3.3.3 Budget Impact Analysis / Financial Implication

This analysis will assess the cost implications per patient, per year and to predict the potential annual budget impact when patients with bone metastases secondary to solid tumours at risk of SRE are transitioned from usual care with no SRE prophylaxis to 12-weekly Zoledronic acid.

It is estimated that approximately 70% of patients with breast or prostate cancer are affected by metastatic disease to the bone,[1, 41] although no reliable incidence or prevalence figures were available for Malaysian population. From Malaysian National Cancer Registry Report (2007-2011), the total number of Stage IV patients among 13 solid tumour cancers was 14,671 and the average number of Stage IV patients per year was 2,934 (**Appendix 5**).[9] Hence, approximately **2,054** patients with Stage IV solid tumours in Malaysia are affected by metastatic

disease to the bone each year for these 13 type of cancers, assuming that the number of patients per year did not differ significantly.

Intravenous Zoledronic acid 12-weekly as SRE prophylaxis incurred a total cost of **RM 4,289.82** per patient per year for the drug and its administration / management while a 4-weekly strategy of the same drug would incur **RM 9,081.90** per patient per year. Comparing these two strategies, 12-weekly prophylaxis would generate 52.77% cost saving per patient per year. Assuming that all patients with Stage IV solid tumour with bone metastases are given 12-weekly Zoledronic acid, the total financial implication per year was approximately **RM 8.8 million**. If 4-weekly strategy was to be given to the same number of patients, the total financial implication per year was estimated to be RM 18.7 million.

The total annual budget implications for patients transition from usual care to prophylactic Zoledronic acid depends on the actual transition rate strategy by the stakeholders. **Table 16** outlined the total annual budget implications following transition of patients by 20% each year from usual care to 12-weekly Zoledronic acid.

Table 16. Annual budget implications of transition from usual care to 12-weekly Zoledronic acid by percentage of patients

Year (% of patients)	Year 1 (20%)	Year 2 (40%)	Year 3 (60%)	Year 4 (80%)	Year 5 (100%)
Budget implications	RM 1.7 million	RM 3.5 million	RM 5.3 million	RM 7.0 million	RM 8.8 million

Five most common types of primary cancer that metastasise to the bone are prostate, breast, lung, renal and thyroid cancer.[76] If the strategy is to offer 12-weekly Zoledronic acid SRE-prophylaxis to these patients first before widening the coverage to all Stage IV patients with bone metastases, the budget needed was estimated to be **RM 4.6 million**

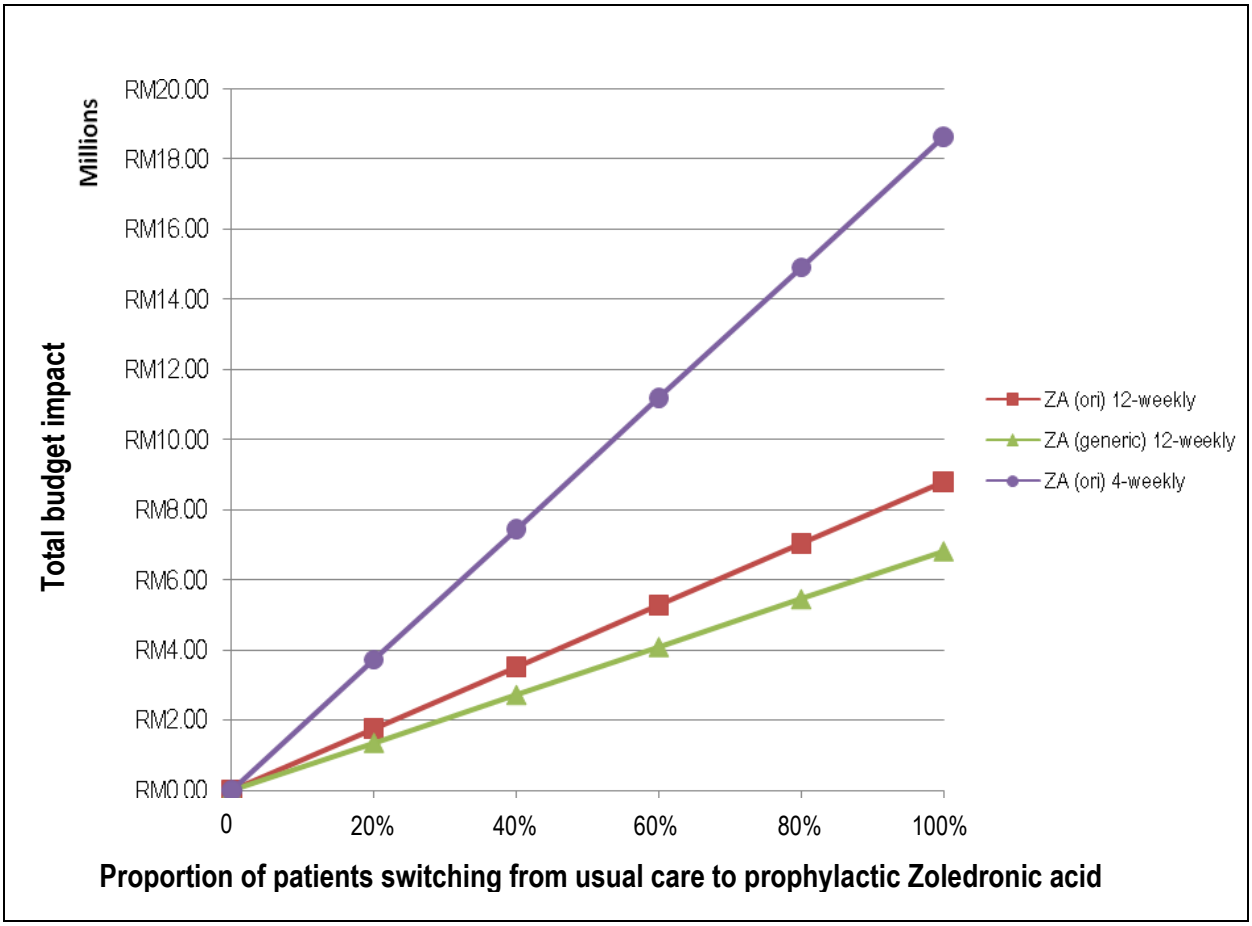


Figure 17. Total budget implications following transition from usual care to different strategies of SRE-prophylaxis with Zoledronic acid

Figure 17 illustrates the total budget implications following transition from usual care (no prophylaxis) to different strategies of SRE-prophylaxis with Zoledronic acid by phases from 20% coverage to 100% coverage of patients. By using 12-weekly Zoledronic acid compared with 4-weekly strategy, the predicted total cost-savings for every 20% patient transitions ranged from RM 2.0 million to RM 9.8 million. However, a more cost-saving impact would be achieved if 12-weekly generic drug of Zoledronic acid is to be used as SRE-prophylaxis in Stage IV solid tumour patients with bone metastases (from RM 394,356.00 to RM 2.0 million).

The estimated benefit cost ratio if IV Zoledronic acid is given for prevention of SRE compared to usual care is greater than one, which indicates that the benefits outweigh its costs. By using originator Zoledronic acid, for every RM 1.00 spent, the cost-saving from SRE-related treatment is RM 1.50 while the saving is greater (RM 2.00) if generic Zoledronic acid is used.

3.4 LIMITATIONS

One of the main limitations of these analyses was the use of trial-based clinical parameters (SRE rates, transition probability, utility values) obtained from the literature review due to lack of real world local data. These parameters could diverge from the national reality in absolute terms and hence, the final outcomes i.e. ICER could be under- or overestimated.

Another potential limitation is an assumption that was applied in estimating the cost of stable and progressive disease. Various cost estimates were available for management of malignancy-related condition in case-mix data or Malaysian DRG, depending on the types of cancer. Since most of the literatures evaluated the effect of SRE-prophylaxis on breast and prostate cancer, malignancy-related costs from Malaysian DRG were taken from these two groups of patients. These limitations, however, were dealt through variation in the sensitivity analyses. In this decision analytic model, the cost of severe adverse events related to bone targeting agents were not included in the analysis due to its infrequent occurrence (<1%). However, if the costs of any of these severe adverse events (such as osteonecrosis of the jaw and severe hypocalcaemia) were taken into consideration, the total cost for bone targeting agents would be higher.

For budget impact and financial implication analyses, the data for number of Stage IV solid tumour patients were obtained from Malaysian National Cancer Registry Report 2007-2011. This report was fairly outdated, given the latest year of patients registry was in 2011. The most recent registry that reported patients from year 2012-2016 is still in analysis phase and hence, could not be utilised for this economic evaluation. The most striking limitation in this registry report was low number of established reported stage of cancers. The percentages of recorded stage in this report ranged from 35% to 65% for the 13 solid tumours; hence, the budget analysis estimates could be higher than the calculated amount.

CHAPTER 4: CONCLUSIONS & RECOMMENDATIONS

4.1 CONCLUSIONS

4.1.1Systematic Review and Meta-analysis

A total of 74 relevant abstracts were screened using the inclusion and exclusion criteria. Twenty-two out of 74 full text studies comprising of one Health Technology Assessment (HTA), five Systematic Review (SR), 12 Randomised Controlled Trials (RCTs), one retrospective cohort study, one cross sectional survey, one SR on cost implication and one cost-effectiveness analysis were finally included in this review.

Effectiveness

- There was fair to good level of evidence to suggest:
  - BTAs (Denosumab and oral or IV Bisphosphonates) significantly delayed time to first SREs, reduced the risk of first and subsequent SREs in all types of cancer except non-small cell lung cancer (NSCLC). Denosumab was superior in reducing risk of developing SREs followed by Zoledronic acid and Pamidronate. Bisphosphonates significantly reduced the number of patients with SREs in patients with breast and prostate cancer only. Treatment with Bisphosphonates did not appear to affect overall survival in all types of cancer. However, there was a significant pain relief and better quality of life in Bisphosphonates group compared to placebo group in breast and prostate cancer.

  - Between the different types of Bisphosphonates, Zoledronic acid was the most effective in delaying the time to first SREs followed with Pamidronate and Ibandronate in breast cancer and lung cancer. However, in reducing risk of first and subsequent SREs, Zoledronic acid significantly reduced in patients with breast cancer only while no difference in other types of cancers. In terms of number of patients with SREs, the number of events per year and skeletal morbidity rate, the results were similar between all types of Bisphosphonates in patients with breast cancer.

  - Pooled data from meta-analysis that compared between Denosumab and Zoledronic acid showed that Denosumab delayed the time to first SREs by 18% with Hazard ratio (HR): 0.82, 95% CI: 0.77, 0.87 for all types of cancer. Denosumab also significantly reduced the risk of first and subsequent SREs by 17% with Rate ratio (RR): 0.83, 95% CI: 0.78, 0.88 for all types of cancer. Overall survival was similar for all types of cancer (HR: 0.94, 95% CI: 0.87, 1.01) except for lung cancer (HR: 0.79, 95% CI: 0.69, 0.89) where patients who received Denosumab significantly delayed by 21%. For disease

progression, there was also no significant difference between the two groups in all types of cancer (HR: 1.02, 95% CI: 0.96, 1.07). In terms of pain, Denosumab was favourable in reducing pain compared to Zoledronic acid in breast cancer, prostate cancer and other solid tumours while Denosumab was found improve quality of life in patients with breast cancer.

- Comparison between the two different regimens (12-weekly and 4-weekly) showed that no difference in time to first SREs for Zoledronic acid in breast cancer (HR: 1.06, 95% CI: 0.70, 1.60). Similar result for Zoledronic acid in terms of risk of first and subsequent SREs (HR: 0.97, 95% CI: 0.83, 1.12) in breast cancer and prostate cancer. Also, no significant difference, between the two regimens for Zoledronic acid in overall number of patients with SREs (Risk ratio: 1.00, 95% CI: 0.88, 1.15). The evidence on the two different regimens of Denosumab was limited eventhough there was no significant difference for Denosumab in overall number of patients with SREs (Risk ratio: 1.96, 95% CI: 0.71, 5.38) due to the small sample size involved.

- There was fair level of evidence to suggest:
  - Bisphosphonates (ZA) reduced the number of events per year and delayed time to progression of disease in patients with lung cancer compared to placebo.

  - There was no significant difference between different types of Bisphosphonates in terms of overall survival and pain in patients with breast cancer. The result for quality of life also found no significant difference between the Bisphosphonates types in patients with lung cancer.

  - Comparison between Denosumab and Zoledronic acid found that Denosumab significantly reduced number of patients with SREs in breast cancer only while no significant difference in prostate cancer. In terms of skeletal morbidity rate, Denosumab significantly reduced the rate by 22% compared to Zoledronic acid in patients with breast cancer.

  - For different regimen of BTAs (12-weekly versus 4-weekly), there was no significant difference in terms of skeletal morbidity rate for Zoledronic acid in patients with breast cancer and no difference in terms of pain for Pamidronate in patients with breast cancer.

Safety

- There was fair to good level of evidence to suggest:
  - No significant difference in all adverse events when compared Bisphosphonates with placebo and alternate Bisphosphonates.

- Denosumab was associated with two time higher occurrence of hypocalcemia but with less renal toxicity compared with Zoledronic acid. However, both had similar occurrence of ONJ event.

- No significant difference between12-weekly and 4-weekly regimens in adverse events for hypocalcemia and ONJ. However, less renal toxicity events found in 12-weekly Zoledronic acid for breast cancer and prostate cancer compared to 4-weekly Zoledronic acid.

Economic evaluation

- A SR on economic evaluation reported for breast cancer, Denosumab was the most effective but more costly compared to Zoledronic acid with lowest incremental cost per QALY in excess of £57, 000. The finding was similar for prostate cancer, however the costs were varied across countries and Denosumab is unlikely to represent value for money in the absence of patient assessment scheme (PAS). In line with above, for lung cancer, Denosumab resulting in incremental cost per QALY >£68,000. Overall evidence suggest Zoledronic acid would result in gains in QALYs for a modest additional cost.

- A cost–effectiveness analysis performed in US in 2017 found that on base-case analysis, Denosumab was dominated and 12-weekly Zoledronic acid would be a dominant option. As QALYs was identical in all three treatments, 12-weekly Zoledronic acid was the optimal treatment as it was the least costly treatment. Eventhough sensitivity analysis was performed, the results did not lead Denosumab to being the least costly treatment.

Ethical/Social/Organizational

One evidence was related to utilization pattern of BTAs and the impact of BTAs among metastatic solid tumour in real-world practice showed that patients treated with Denosumab were more likely compliant compared to Zoledronic acid. The number of percentage that switched agents was lower in the Denosumab group compared to Zoledronic acid group within first, second and third year of administration. Thus, the higher levels of compliance and persistence may improve treatment effectiveness.

4.1.2 Decision Analytic Economic Modelling

Based on this decision analytic model, the use of bone targeting agents in preventing skeletal-related events among Stage IV solid tumour patients with bone metastases is a cost-effective strategy. Within this evaluation, the most cost-effective option was 12-weekly intravenous Zoledronic acid, yielding an ICER of **RM 4,968.87 per QALY gained** which is lower than the cost-effectiveness

threshold of one GDP per capita. The estimated total financial implications for this strategy with 100% potential patients coverage was **RM 8.8 million per year.**

4.2 RECOMMENDATION

Based on this review, BTAs significantly delay the development of SREs among metastatic cancers of solid tumours and hence, directly preserving quality of life and improve morbidity rate. This effect is particularly significant with Zoledronic Acid and Denosumab. Twelve-weekly IV Zoledronic acid was found to be the most cost-effective option in preventing SREs among solid tumour patients with bone metastases. Current evidence on the use of 12-weekly Denosumab is still limited, thus, further good quality research is warranted. In general, BTAs were well tolerated with rare occasion of adverse events. However, creatinine clearance must be closely monitored in patients receiving Zoledronic acid in view of its potential side effect of renal impairment.

5 REFERENCES

1. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006;12 (20 Suppl):6243s-6249s

2. Ibrahim A, Scher N, Williams G, et al. Approval summary for Zoledronic acid for treatment of multiple myeloma and cancer bone metastases. Clin Cancer Res 2003;9(7):2394-2399.World Health Organisation. Cancer fact sheets. Available at: http://www.who.int/news-room/fact-sheets/detail/cancer. Accessed on 6/9/2018.

3. Onukwugha E, Kwok Y, Ciezki JP, et al. Skeletal-related events and mortality among men diagnosed with advanced prostate cancer: The impact of alternative measures of radiation to the bone. PloS one. 2017;12(4):e0175956.

4. Wilkinson AN, Viola R, Brundage MD. Managing skeletal related events resulting from bone metastases. BMJ. 2008;337.

5. Clemons M, Gelmon KA, Pritchard KI, et al. Bone-targeted agents and skeletal-related events in breast cancer patients with bone metastases: the state of the art. Curr Oncol. 2012;19(5):259-268.

6. Domchek SM, Younger J, Finkelstein DM, et al. Predictors of skeletal complications in patients with metastatic breast carcinoma. Cancer: Interdisciplinary Inter J Am Cancer Soc. 2000;89(2):363-368

7. Li BT, Wong MH, Pavlakis N. Treatment and Prevention of Bone Metastases from Breast Cancer: A Comprehensive Review of Evidence for Clinical Practice. J Clin Med. 2014;3:1-24.

8. O'Carrigan B, Wong MHF, Willson ML, et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database of Systematic Reviews. 2017(10).

9. Cancer National Institute. National Cancer Registry Department. National Cancer Registry Report 2007-2011. Malaysia: Ministry of Health; 2017.

10. Barlev A, Song X, Ivanov B, et al. Payer costs for inpatient treatment of pathologic fracture, surgery to bone, and spinal cord compression among patients with multiple myeloma or bone metastasis secondary to prostate or breast cancer. J Manag Care Pharm. 2010;16(9):693-702.

11. Hechmati G, Cure S, Gouepo A, et al. Cost of skeletal-related events in European patients with solid tumours and bone metastases: data from a prospective multinational observational study. J Med Econ. 2013;16(5):691-700.

12. Hagiwara M, Delea T, Saville M, et al. Healthcare utilization and costs associated with skeletal-related events in prostate cancer patients with bone metastases. Prostate Cancer Prostatic Dis. 2013;16(1):23.

13. Pereira J, Body J-J, Gunther O, et al. Cost of skeletal complications from bone metastases in six European countries. J Med Econ. 2016;19(6):611-618.

14. Oster G, Lamerato L, Glass AG, et al. Natural history of skeletal-related events in patients with breast, lung, or prostate cancer and metastases to bone: a 15-year study in two large US health systems. Support Care Cancer. 2013;21(12):3279-3286.

15. Pockett R, Castellano D, McEwan P, et al. The hospital burden of disease associated with bone metastases and skeletal-related events in patients with breast cancer, lung cancer, or prostate cancer in Spain. Eur J Cancer Care. 2010;19(6):755-760.

16. DePuy V, Anstrom KJ, Castel LD, et al. Effects of skeletal morbidities on longitudinal patient-reported outcomes and survival in patients with metastatic prostate cancer. Support Care Cancer. 2007;15(7):869-876.

17. Major PP, Cook R. Efficacy of bisphosphonates in the management of skeletal complications of bone metastases and selection of clinical endpoints. Am J Clin Oncol. 2002;25(6 Suppl 1):S10-18.

18. Berenson JR, Rajdev L, Broder M. Treatment strategies for skeletal complications of cancer. Cancer Biol Ther. 2006;5(9):1074-1077.

19. Ford J, Cummins E, Sharma P, et al. Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of Denosumab for the treatment of bone metastases from solid tumours. Health Technol Assess. 2013;17(29):1-386.

20. Formulari Ubat Kementerian Kesihatan Malaysia. 2017. Available at: https://www.pharmacy.gov.my/v2/ms/apps/fukkm. Accessed on 13/2/2018.

21. National Institute for Health and Care Excellence (NICE). CG121: The diagnosis and the treatment of lung cancer (update). London: NICE; 2011.

22. National Institute for Health and Care Excellence (NICE). CG175: Prostate Cancer: diagnosis and treatment. London: NICE; 2014.

23. National Institute for Health and Care Excellence (NICE). CG75: Metastatic spinal cord compression: diagnosis and management of patients at risk of or with metastatic spinal cord compression. London: NICE; 2008.

24. National Institute for Health and Care Excellence (NICE). CG81: Advanced breast cancer: diagnosis and treatment. London: NICE; 2009.

25. Carter JA, Joshi AD, Kaura S, et al. Pharmacoeconomics of Bisphosphonates for Skeletal-Related Event Prevention in Metastatic Non-Breast Solid Tumours. Pharmacoeconomics 2012;30(5):373-386.

26. Reed SD, Radeva JI, Glendenning GA, et al. Cost-effectiveness of Zoledronic acid for the prevention of skeletal complications in patients with prostate cancer. J Urol. 2004;171(4):1537-1542.

27. Carter J, Joshi A, Kaura S, et al. Cost effectiveness of Zoledronic acid in the management of skeletal metastases in hormone-refractory prostate cancer patients in France, Germany, Portugal, and the Netherlands. J Med Econ. 2011;14(3):288-298.

28. Joshi AD, Carter JA, Botteman MF, et al. 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. Clin Ther. 2011;33(3):291-304. e298.

29. Botteman M, Meijboom M, Foley I, et al. 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. Eur J Health Econ. 2011;12(6):575-588.

30. Chern B, Joseph D, Joshua D, et al. Bisphosphonate infusions: patient preference, safety and clinic use. Support Care Cancer. 2004;12(6):463-466.

31. Wang Z, Qiao D, Lu Y, et al. Systematic Literature Review and Network Meta-Analysis Comparing Bone-Targeted Agents for the Prevention of Skeletal-Related Events in Cancer Patients With Bone Metastasis. Oncologist. 2015;20(4):440-449.

32. Chen F, Pu F. Safety of Denosumab Versus Zoledronic acid in Patients with Bone Metastases: A Meta-Analysis of Randomized Controlled Trials. Oncol Res Treat. 2016;39(7-8):453-459.

33. Castellano D, Sepulveda JM, Garcia-Escobar I, et al. The role of RANK-ligand inhibition in cancer: the story of Denosumab. Oncologist. 2011;16(2):136-145.

34. Ford JA, Jones R, Elders A, et al. Denosumab for treatment of bone metastases secondary to solid tumours: systematic review and network meta-analysis. Eur J Cancer. 2013;49(2):416-430.

35. Lee BL, Higgins MJ, Goss PE. Denosumab and the current status of bone-modifying drugs in breast cancer. Acta Oncol. 2012;51(2):157-167.

36. Higgins J, Green S. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. UK: John Wiley & Sons.; 2012.

37. LeVasseur N, Clemons M, Hutton B, et al. Bone-targeted therapy use in patients with bone metastases from lung cancer: A systematic review of randomized controlled trials. Cancer Treat Rev. 2016;50:183-193.

38. Lipton A, Fizazi K, Stopeck A, et al. Effect of Denosumab versus Zoledronic acid in preventing skeletal-related events in patients with bone metastases by baseline characteristics. Eur J Cancer. 2016;53:75-83.

39. Scagliotti GV, Hirsh V, Siena S, et al. Overall survival improvement in patients with lung cancer and bone metastases treated with Denosumab versus Zoledronic acid subgroup analysis from a randomized phase 3 study. J Thorac Oncol. 2012;7(12):1823–1829.

40. Martin M, Bell R, Bourgeois H, et al. Bone-related complications and quality of life in advanced breast cancer: Results from a randomized phase III trial of Denosumab versus Zoledronic acid. Clin Cancer Res. 2012;18(17):4841-4849.

41. Fizazi K, Carducci M, Smith M, et al. Denosumab versus Zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011;377(9768):813-822.

42. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of Denosumab versus Zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol. 2011;29(9):1125-1132.

43. 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):5132-5139.

44. 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):48-58.

45. 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 Oncol. 2017;3(7):906-912.

46. 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. Lancet Oncology. 2013;14(7):663-670.

47. Amir E, Freedman O, Carlsson L, et al. Randomized feasibility study of de-escalated (Every 12 wk) versus standard (every 3 to 4 wk) intravenous pamidronate in women with low-risk bone metastases from breast cancer. Am J Clin Oncol. 2013;36(5):436-442.

48. 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. J Clin Oncol. 2009;27(10):1564-1571.

49. 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. J Clin Oncol. 2007;25(28):4431-4437.

50. von Moos R, Body J-J, Rider A, 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 Oncol. 2018;11:1-9.National Institute for Health and Care Excellence (NICE). CG75: Metastatic spinal cord compression: diagnosis and management of patients at risk of or with metastatic spinal cord compression. London: NICE; 2008.

51. Qian Y, Bhowmik D, Kachru N, et al. Longitudinal patterns of bone-targeted agent use among patients with solid tumors and bone metastases in the United States. Support Care Cancer. 2017;25(6):1845-1851.

52. Andronis L, Goranitis I, Bayliss S, et al. Cost-Effectiveness of Treatments for the Management of Bone Metastases: A Systematic Literature Review. Pharmacoeconomics. 2018;36(3):301-322.

53. 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). J Clin Oncol. 2017;35(35):3949-3955.

54. Lipton A. Efficacy and safety of intravenous bisphosphonates in patients with bone metastases caused by metastatic breast cancer. Clin Breast Cancer. 2007;7(SUPPL. 1):S14-S20.

55. Novartis. Zometa (Zoledronic acid) package insert East Hanover: NJ: Novartis 2013. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/Zometa.pdf. Accessed on 12/02/2018.

56. Stopeck AT, Fizazi K, Body J-J, et al. Safety of long-term Denosumab therapy: results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer. Support Care Cancer. 2016;24(1):447-455.

57. Schulman KL, Kohles J. Economic burden of metastatic bone disease in the US. Cancer. 2007;109(11):2334-2342.

58. Saad F, Fleshner NE, So A, 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).

59. Lipton A, Cook RJ, Major P, et al. Zoledronic acid and survival in breast cancer patients with bone metastases and elevated markers of osteoclast activity. Oncologist. 2007;12(9):1035-1043.

60. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-634.

61. Karanicolas PJ, Farrokhyar F, Bhandari M. Blinding: Who, what, when, why, how? Can J Surg. 2010;53(5):345.

62. Borenstein M, Hedges LV, Higgins JP, et al. Introduction to meta-analysis: John Wiley & Sons; 2011.Hagiwara M, Delea T, Saville M, et al. Healthcare utilization and costs associated with skeletal-related events in prostate cancer patients with bone metastases. Prostate Cancer Prostatic Dis. 2013;16(1):23.

63. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. I J Surg. 2010;8(5):336-341.

64. Xie J, Namjoshi M, Wu EQ, et al. Economic evaluation of Denosumab compared with Zoledronic acid in hormone-refractory prostate cancer patients with bone metastases. J Manag Care Pharm. 2011 Oct;17(8):621-43.

65. Botteman M, Barghout V, Stephens J, et al. Cost effectiveness of bisphosphonates in the management of breast cancer patients with bone metastases. Ann Oncol. 2006 Jul;17(7):1072-82.

66. Saad F, Gleason DM, Murray R, et al; Zoledronic acid Prostate Cancer Study Group. Long-term efficacy of Zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst. 2004 Jun 2;96(11):879-82.

67. Dranitsaris G, Hsu T. Cost utility analysis of prophylactic pamidronate for the prevention of skeletal related events in patients with advanced breast cancer. Support Care Cancer. 1999 Jul;7(4):271-9.

68. ACTION Study Group. Health-related quality of life and psychological distress among cancer survivors in Southeast Asia: results from a longitudinal study in eight low- and middle-income countries. BMC Med. 2017 Jan 13;15(1):10.

69. Nafees B, Patel C, Ray D, e al. An Assessment of Health-State Utilities in Metastatic Breast Cancer in the United Kingdom. Value in Health. 2016 May 1;19(3):A157.

70. Consumer Price Guide. Pharmaceutical Services Programme, Ministry of Health Malaysia. Available at: https://www.pharmacy.gov.my/v2/en/apps/drug-price. *(Accessed : 17 July 2018)*

71. MOH Investigation Charges. Ministry of Health Malaysia. Available at: http://www.moh.gov.my/english.php/pages/view/155 . *(Accessed : 17 July 2018)*

72. Lee WC, Haron MR, Yu KL, et al. Economic analysis of intravenous vs. subcutaneously administered trastuzumab for the treatment of HER2+ early breast cancer in Malaysia. Advances in Breast Cancer Research. 2016 Jan 11;5(01):1.

73. Dranitsaris G, Truter I, Lubbe MS, et al. Using pharmacoeconomic modelling to determine value-based pricing for new pharmaceuticals in malaysia. Malays J Med Sci. 2011 Oct;18(4):32-43.

74. Zainal R, Mahat M. Estimating The Costs Of Specialist Out-Patient Services In A Public Hospital. Value Health. 2014 Nov;17(7):A790.

75. Hwa YS, Shatar AK, Hashim H. THE SOCIOECONOMIC IMPACTS OF BREAST CANCER ON BREAST CANCER PATIENTS IN PENANG. Kajian Malaysia: Journal of Malaysian Studies. 2011 Dec 1;29(2).

76. Coleman RE. Skeletal complications of malignancy. Cancer. 1997;80(8):1588-94.

6 APPENDICES

Appendix 1

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomised controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

Appendix 2

PTK – BOR– 11

HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL
BONE TARGETING AGENTS IN PREVENTING
SKELETAL RELATED EVENTS FOR METASTATIC CANCERS
OF SOLID TUMOURS AND ECONOMIC EVALUATION

1. BACKGROUND INFORMATION

Cancer which spread from the primary site to other parts of the body is called metastatic cancer.[1] When cancerous cells break away from the primary site, they travel to other area of the body through either the bloodstream or lymphatic system. Bone is one of the common sites for the cancer cells to settle and start growing. The human skeleton which made up of 206 bones is one of the common sites of metastases.[1,2] Metastatic cancer of solid tumour cells in circulation interact with the bone microenvironment causing a positive feedback loop of tumour growth, which mostly affects the skeleton and thus weakens bone integrity that lead to skeletal related events (SREs).[1] Skeletal related events are skeletal complications from bone metastases such as spinal cord compression (SCC), pathological fracture, bone pain, hypercalcemia, palliative radiation to the bone and bone surgery.[2-5] Thus, when SREs happen, the quality of life and life expectancy of a patient may be greatly reduced.

According to the Malaysian National Cancer Registry Report 2007-2011, prostate cancer was among the five most common cancers in male with incidence rate 6.6 per 100,000 population whereby 60% from 1592 were detected at stage three and four. While for female, breast cancer was the most common with incidence rate 31.1 per 100,000 population whereby 43% from 11938 cases were diagnosed at stage three and four.[6] Carcinoma that commonly metastasise to the bone originate from the prostate, breast, lung, thyroid and kidney.[1, 2] The frequency of SREs may differ based on the site of the malignancy. Breast cancer accounts for 68%, prostate cancer accounts for 49%, lung cancer accounts for 48% while multiple myeloma accounts for 51%.[2]

NICE recommended in their Clinical Guidelines whereby patients with lung cancer, metastatic spinal cord compression and advanced breast cancer to be given Bisphosphonates for prevention of SREs instead of receiving best supportive care depending on the type of primary care which may include palliative radiotherapy, chemotherapy, antibiotics, analgesics, steroids or surgery. Bisphosphonates is not offered to prevent the complications of bone metastases in men with hormone-relapsed prostate cancer. However, Bisphosphonates may be considered for pain relief in men with hormone-relapsed prostate cancer when treatments with analgesic and palliative radiotherapy have failed. Denosumab, a different group of drug is an alternative therapy to Bisphosphonates. [7-10]

Bisphosphonates

Bisphosphonates are synthetic analogues of pyrophosphates, the natural regulator of bone mineral precipitation and dissolution. They are potent inhibitors of osteoclast activity that bind to the bone matrix. They are released during bone resorption, and are subsequently internalised by osteoclasts, where they interfere with biochemical pathways and induce osteoclast apoptosis. Bisphosphonates also antagonise osteoclastogenesis and promote the differentiation of osteoblasts. As a result, Bisphosphonates inhibit tumour-induced osteolysis and reduce skeletal morbidity.[11]

The four Bisphosphonates currently available are Clodronate; administered orally at a dose of 1.6-3.2 gram (g) daily, Pamidronate; administered by slow intravenous infusion (IV) at a dose of 90 milligram (mg) every four weeks, Ibandronate; administered either orally 150 mg monthly or IV 6 mg every three to four weeks and Zoledronic acid (ZA); administered by intravenous infusion 4 mg every three to four weeks. Absorption of oral Bisphosphonates is estimated at less than 6% of the active compound because of the low uptake from passive diffusion in the gastrointestinal tract. Location of treatment is important to patients. One study found that patients prefer administration at home, but this is not often possible with IV treatments.[12]

Bisphosphonates are generally well tolerated, although they have recently been associated with osteonecrosis of the jaw, hypocalcaemia and renal toxicity, thus requiring routine monitoring of serum creatinine and other biochemical parameters and dose adjustments. Despite these concerns, Bisphosphonates are an important tool in the management of skeletal complications of cancer, providing benefits for the treatment of hypercalcemia, osteolytic lesions and fractures, as well as offering amelioration of pain and improvement in quality of life.[11, 13]

Denosumab

The next generation of bone metastasis treatments is Denosumab. Denosumab is a fully human monoclonal antibody that inhibits osteoclast maturation, activation, and function by binding to receptor activator of nuclear factor kappa B ligand (RANKL), subsequently inhibits the mechanism of the resorption of the bone.[14-16] Denosumab is currently approved for post-menopausal osteoporosis, administered by subcutaneous 60 mg every six months.

On average, one of the major skeletal events occur every three to six months. Skeletal related events resulted in greatest morbidity which includes pain, hypercalcemia and pathological fracture affecting patients' quality of life over the years and may increase healthcare cost. Survival rates for people with bone metastases vary depending on the primary tumour type. In breast cancer, median survival was 24 months with a 5-year survival rate of 20% and in prostate cancer there was a 5-year survival rate of 25% and a median survival of 40 months.[1, 11] In addition, hospitalisation with SREs is associated with high health economic burden. [16, 17]

Evidence showed that among these drugs, Ibandronate, Zoledronic acid and Denosumab were the most effective in preventing SREs.[16] Zoledronic acid with Zometa® trade name was approved by United States Food and drug Administration (US FDA) in 2001 for the treatment of patients with multiple myeloma and documented bone metastases from solid tumours in conjunction with standard therapy. While in United Kingdom (UK), Ibandronic acid is licensed for bone metastases in breast cancer only and Zoledronic acid is the only drug that is licensed for all cancers involving the bone.[16] Denosumab with Xgeva® trade name was

approved on November 18, 2010 by US FDA for the prevention of SREs in patients with bone metastases from solid tumours.[16]

However in Drug Formulary Ministry of Health, Malaysia, Ibandronic acid tablet and Denosumab injection was approved for the treatment of post-menopausal osteoporosis, while Zoledronic acid was approved for prevention of SREs only in patients with multiple myeloma involving multiple bone lesions.[17] Zoledronic acid

might not be convenient among patients as it is delivered IV for 15 minutes compared to Denosumab which is administered by subcutaneously, hence, would be a better option but the cost need to be taken into account.[18-22] As these agents play an important role in preventing SREs, their effectiveness and economic implications need to be assessed. This HTA was requested by Clinical Oncologist, Hospital Kuala Lumpur (HKL).

2. POLICY QUESTION

4 Should Bone Targeting Agents (BTAs) be used in preventing SREs for metastatic cancers of solid tumours?

5 Which BTAs should be used in routine clinical practice?

3. OBJECTIVES

3.1. To conduct a systematic review:

v. To assess and compare the effectiveness of BTAs in preventing SREs for metastatic cancers of solid tumours.

vi. To assess the safety of BTAs in preventing SREs for metastatic cancers of solid tumours.

vii. To assess the cost-effectiveness of BTAs in preventing SREs.

viii. To assess the organisational or societal issues related to the use of BTAs in preventing SREs for metastatic cancers of solid tumours.

3.2. To conduct local economic evaluation of Bisphosphonates and Denosumab.

Research questions

v. What are the short and long term benefits of using BTAs in preventing SREs for metastatic cancers of solid tumours? Is there a subgroup of patients who is more likely to benefit from these agents (e.g. type of cancer, etc.)?

vi. How safe is BTAs in preventing SREs for metastatic cancers of solid tumours?

vii. What is the economic implication of using BTAs in preventing SREs compared to current best practice?

viii. What are organisational or societal issues related to the use of BTAs in preventing SREs for metastatic cancers of solid tumours?

4. METHODS

4.1. Search Strategy

5.1.1 Electronic database will be searched for published literatures pertaining to the use of BTAs in preventing SREs for metastatic cancers of solid tumours.

5.1.2 Databases as follows: MEDLINE, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-DARE, EBM Reviews-NHS Economic Evaluation Database and Embase through the Ovid interface will be searched. Searches will also be conducted in PubMed, Horizon Scanning database, INAHTA database, and FDA database.

5.1.3 Additional literatures will be identified from the references of the retrieved articles.

5.1.4 General search engine will also be used to get additional web-based materials and information.

4.1.5 The detail of the search strategy will be presented as appendix.

4.2. Inclusion and exclusion criteria

4.2.1. Inclusion criteria

d. Population: Adult patients with metastatic cancers or stage IV cancers (breast cancer, prostate cancer, lung cancer and other solid tumours)

e. Intervention: Bisphosphonates or Receptor Activator of Nuclear Factor Kappa B Ligand (RANKL) inhibitor

f. Comparators: Placebo or best supportive care or Bisphosphonates or Chemotherapy

d. Outcome: Effectiveness:

vi. Time to first SREs

vii. Time to first and subsequent SREs

viii. No. of patients with first SREs

ix. No. of events per year

x. Quality of life

Safety:

vi. Hypocalcaemia

vii. Osteonecrosis of the jaw

viii. Adverse events potentially associated with renal

impairment

ix. Patients experiencing acute-phase reactions (acute pain, bone pain)

x. Gastrointestinal toxicity (Bisphosphonates)

Organisational issues (e.g. hospital admission, length of stay, day care)
Social issues (e.g. patient satisfaction, compliance)

e. Study design: HTA reports, Systematic Review, Randomised Controlled Trials (RCT) and studies which include economic evaluation.

f. English full text articles

4.2.2 Exclusion criteria

a. Study design: Non-randomised controlled trials, animal study, laboratory study, observational studies, narrative review, editorials, and letter to the editors.

b. Non English full text article.

Based on the above inclusion and exclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion.

4.3 Critical Appraisal of Literature

The risk of bias (methodology quality) of all retrieved literatures will be assessed using the relevant checklist of Cochrane Collaboration Assessment tools and Critical Appraisal Skill Programme (CASP) by two reviewers depending on the type of the study design.

4.4 Analysis and Synthesis of Evidence

4.4.1 Data extraction strategy

The following data will be extracted:

iv. Details of methods and study population characteristics.

v. Details of intervention and comparators.

vi. Details of individual outcomes for safety, effectiveness, cost implication, organisational and societal issues associated with the use of bone targeting agents.

Data will be extracted from selected studies by two reviewers using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion.

4.4.2 Methods of analysis/synthesis

Data on the effectiveness, safety and cost implication of using BTAs will be presented in tabulated format with narrative summaries. Meta- analysis may be conducted for this Health Technology Assessment.

4.5 Local economic evaluation model

A literature-based decision analytic model will be developed to compare the direct costs and quality adjusted life years (QALY) for hypothetical cohort of patients with metastatic solid cancer (breast cancer or prostate cancer). Three treatment strategies that will be evaluated are:

i. palliative care / best supportive care (without bone targeting therapy)
ii. bisphosphonates
iii. Denosumab

Clinical and cost parameters that will be included in this model are outlined below.

Category	Input parameters
Survival / duration	Median/mean survival (in months)
	Median duration to first SRE (in months)
Rate / proportion	Skeletal morbidity rate (number of SRE divided by time on study)
	Proportion of SREs (pathological fracture, spinal cord compression, bone pain, radiotherapy and surgery)
Probabilities	Probability of first SRE among patients with metastatic cancer
	Probability of subsequent SRE among patients with metastatic cancer
	Probability of death
Utility values	Receiving treatment(s) without SRE
	Receiving treatment(s) with SRE
	Not receiving treatment without SRE
	Not receiving treatment with SRE
Costs	Drug costs (Zoledronic acid, Denosumab)
	IV therapy administration cost
	Palliative care cost / best supportive care cost
	Surgical / Oncology clinic visit cost (for follow-up)
	Cost of treatment for SREs - radiation therapy for SREs - surgery to stabilize pathological bone fracture - decompression and destabilization surgery for spinal cord compression

5. Report Writing

6. REFERENCES

1. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006; 12(20 Suppl):6243s-6249s.

2. Ibrahim A, Scher N, Williams G et al. Approval summary for Zoledronic acid for treatment of multiple myeloma and cancer bone metastases. Clin Cancer Res. 2003; 9: 2394-2399.

3. Onukwugha E, Kwok Y, Ciezki JP, et al. Skeletal-related events and mortality among men diagnosed with advanced prostate cancer: The impact of alternative measures of radiation to the bone. PLoS One. 2017; 12(4):e0175956.

4. Wilkinson AN, Viola R, Brundage MD. Managing skeletal related events resulting from bone metastases. BMJ. 2008 Nov 3;337:a2041. doi: 10.1136/bmj.a2041.

5. Clemons M, Gelmon KA, Pritchard KI, Paterson AHG. Bone-targeted agents and skeletal-related events in breast cancer patients with bone metastases: the state of the art. Current Oncology. 2012;19(5):259-68.

6. National Cancer Registry Department. National Cancer Registry Report 2007-2011, Ministry of Health, Malaysia: 2017.

7. National Institute for Health and Care Excellence (NICE). CG121: The diagnosis and the treatment of lung cancer (update). London: NICE; 2011.

8. National Institute for Health and Care Excellence (NICE). CG175: Prostate Cancer: diagnosis and treatment. London: NICE; 2014.

9. National Institute for Health and Care Excellence (NICE). CG75: Metastatic spinal cord compression: diagnosis and management of patients at risk of or with metastatic spinal cord compression. London: NICE; 2008.

10. National Institute for Health and Care Excellence (NICE). CG81: Advanced breast cancer: diagnosis and treatment. London: NICE; 2009.

11. Berenson JR, Rajdev L, Broder M. Treatment strategies for skeletal complications of cancer. Cancer Biol Ther. 2006; 5(9):1074-1077.

12. Chern B, Joseph D, Joshua D, Pittman K, Richardson G, Schou M, et al. Bisphosphonate infusions: patient preference, safety and clinic use. Support Care Cancer. 2004; 12(6):463-466.

13. Wang Z, Qiao D, Lu Y et al. Systematic literature review and network meta-analysis comparing bone-targeted agents for the prevention of skeletal-related events in cancer patients with bone metastasis. Oncologist. 2015; 20(4):440-449.

14. Chen F and Pu F. Safety of Denosumab versus Zoledronic acid in patients with bone metastases: a meta-analysis of randomized controlled trials. Oncol Res Treat. 2016; 39:1-7.

15. Castellano D, Sepulveda JM, Garcia-Escobar I et al. The role of RANK-ligand inhibition in cancer: the story of Denosumab. Oncologist. 2011; 16(2):136-145.

16. Ford J, Cummins E, Sharma P et al. Systematic review of the clinical effectiveness and cost-effectiveness and economic evaluation of Denosumab for the treatment of bone metastases from solid tumours. Health Technology Assessment.2013; 17(29):1-408.

17. Formulari Ubat Kementerian Kesihatan Malaysia. Available at https://www.pharmacy.gov.my/v2/ms/apps/fukkm. Accessed on 13/2/2018.

18. Carter JA, Joshi AD, Kaura S et al. Pharmacoeconomics of Bisphosphonates for skeletal-related event prevention in metastatic non-breast solid tumours. Pharmacoeconomics. 2012; 30(5):373-386.

19. Reed SD, Radeva JI, Glendenning GS et al. Cost-effectiveness of Zoledronic acid for the prevention of skeletal complications in patients with prostate cancer. J Urol 2004; 171(4): 1537-1542.

20. Carter JA, Joshi A, Kaura S et al. Cost effectiveness of Zoledronic acid in the management of skeletal metastases in hormone-refractory prostate cancer patients in France, Germany, Portugal and the Netherlands. J Med Econ. 2011; 14(3):288-298.

21. Joshi AD, Carter JA, Botteman MF et al. 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. Clin Ther. 2011; 33(3):291-304.

22. Botteman MF, Maijboom M, Foley I at al. 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. Eur J Health Econ. 2011; 12(6):575-588.

Appendix 3

SEARCH STRATEGY

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

---

1 solid tum?r.tw. (9449)

2 solid tumor.mp. (9619)

3 BREAST NEOPLASMS/ (258780)

4 (breast adj1 (cancer or carcinoma* or tumor* or neoplasm*)).tw. (254358)

5 (breast malignant adj2 (neoplasm* or tumor*)).tw. (37)

6 human mammary neoplasm*.tw. (4)

7 mammary cancer*.tw. (3251)

8 ((malignant neoplasm or malignant tumor) adj2 breast).tw. (34)

9 (cancer adj3 breast).tw. (242160)

10 tumor*,breast.tw. (685)

11 cancer*,mammary.tw. (114)

12 carcinoma*,breast.tw. (593)

13 neoplasm*,breast.tw. (34)

14 cancer, breast.tw. (1675)

15 COLORECTAL NEOPLASMS/ (75001)

16 (colorectal adj1 (cancer* or carcinoma* or neoplasm* or tumor*)).tw. (97312)

17 cancer*, colorectal.tw. (855)

18 carcinoma*,colorectal.tw. (127)

19 neoplasm*,colorectal.tw. (19)

20 tumor*,colorectal.tw. (129)

21 STOMACH NEOPLASMS/ (88082)

22 (stomach adj1 (cancer* or neoplasm*)).tw. (6873)

23 (gastric adj1 (cancer* or neoplasm*)).tw. (53412)

24 (cancer* adj3 stomach).tw. (9844)

25 neoplasm*, gastric.tw. (17)

26 neoplasm*, stomach.tw. (2)

27 cancer*,gastric.tw. (767)

28 cancer*,stomach.tw. (251)

29 NEOPLASMS/ (384980)

30 benign neoplasm*.tw. (3196)

31 malignant neoplasm*.tw. (12738)

32 cancer*.tw. (1505049)

33 malignanc*.tw. (212000)

34 neoplas*.tw. (238936)

35 tumor*.tw. (1265021)

36 NEOPLASM METASTASIS/ (96388)

37 metastas*.tw. (307609)

38 neoplasm metastasis.tw. (82)

39 neoplasm metastases.tw. (46)

40 LIVER NEOPLASMS/ (133240)

41 (hepatic adj1 (cancer* or neoplasm*)).tw. (2041)

42 (liver adj1 (cancer* or neoplasm*)).tw. (18439)

43 (cancer adj3 liver).tw. (21359)

44 neoplasm*,hepatic.tw. (15)

45 PROSTATIC NEOPLASMS/ (112237)

46 (prostat* adj1 (cancer* or neoplasm*)).tw. (105544)

47 (cancer adj3 prostate).tw. (101835)

48 cancer*, prostat*.tw. (1627)

49 neoplasm*, prostat*.tw. (21)

50 BONE NEOPLASMS/ (58259)

51 (bone adj1 (cancer or neoplasm*)).tw. (2847)

52 (cancer adj3 bone).tw. (6764)

53 ADENOCARCINOMA/ (144674)

54 adenocarcinoma*.tw. (127357)

55 ((basal or granular) adj2 cell adenocarcinoma*).tw. (173)

56 granular cell carcinoma*.tw. (42)

57 ((cribriform or tubular) adj2 carcinoma*).tw. (810)

58 malignant adenoma*.tw. (142)

59 oxyphilic adenocarcinoma*.tw. (2)

60 tubular adenocarcinoma*.tw. (819)

61 BRAIN NEOPLASMS/ (101168)

62 ((benign or brain) adj2 neoplasm*).tw. (6032)

63 (brain adj2 (cancer* or tumor* or neoplasm*)).tw. (36771)

64 intracranial neoplasm*.tw. (1064)

65 ((brain malignant or malignant brain) adj2 neoplasm*).tw. (32)

66 (cancer adj3 brain).tw. (4694)

67 ((malignant primary or primary malignant) adj3 (brain tumor* or brain neoplasm*)).tw. (760)

68 (primary brain adj2 (tumor* or neoplasm*)).tw. (3583)

69 recurrent brain tumor*.tw. (208)

70 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 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 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51

or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 (2873150)

71 DENOSUMAB/ (1177)

72 amg 162.tw. (33)

73 Denosumab.tw. (1991)

74 prolia.tw. (37)

75 xgeva.tw. (18)

76 DIPHOSPHONATES/ (14932)

77 Bisphosphonates.tw. (10200)

78 Diphosphonates.tw. (552)

79 CLODRONIC ACID/ (1552)

80 Bonefos.tw. (23)

81 cl2mdp.tw. (187)

82 clodronate.tw. (1835)

83 clodronic acid.tw. (32)

84 dichloromethane diphosphonate.tw. (19)

85 dichloromethanediphosphonate.tw. (11)

86 dichloromethylene bisphosphonate.tw. (90)

87 dichloromethylene diphosphonate.tw. (297)

88 disodium, clodronate.tw. (42)

89 acid, clodronic.tw. (2)

90 sodium, clodronate.tw. (15)

91 Pamidronate.tw. (2327)

92 Ibandronate.tw. (939)

93 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 (22735)

94 PLACEBO EFFECT/ (4105)

95 effect*, placebo.tw. (86)

96 placebo effect*.tw. (3815)

97 PALLIATIVE CARE/ (48448)

98 (palliative adj1 (care or surgery or therapy or treatment*)).tw. (31877)

99 surgery, palliative.tw. (60)

100 therapy, palliative.tw. (70)

101 treatment, palliative.tw. (91)

102 care, palliative.tw. (219)

103 ANTINEOPLASTIC COMBINED CHEMOTHERAPY PROTOCOLS/ (127223)

104 anticancer drug combination*.tw. (51)

105 antineoplastic chemotherapy protocol*.tw. (1)

106 antineoplastic drug combination*.tw. (4)

107 cancer chemotherapy protocol*.tw. (19)

108 combined antineoplastic agent*.tw. (5)

109 antineoplastic agent*, combined.tw. (3)

110 chemotherapy protocol*, antineoplastic.tw. (0)

111 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 (193410)

112 70 and 93 and 111 (660)

113 limit 112 to humans (620)

114 skeletal related event*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1085)

115 skeletal related event*.tw. (1064)

116 114 or 115 (1085)

117 113 and 116 (67)

EMBASE Search Terms

(('breast neoplasm' OR 'breast tumor'/exp OR 'breast gland tumor' OR 'breast gland tumour' OR 'breast mass' OR 'breast neoplasms' OR 'breast neoplasms, male' OR 'breast tumor' OR 'breast tumour' OR 'female breast neoplasm' OR 'female breast tumor' OR 'female breast tumour' OR 'mamma tumor' OR 'mamma tumour' OR 'mammary gland tumor' OR 'mammary gland tumour' OR 'mammary neoplasms' OR 'mammary tumor' OR 'mammary tumor cell' OR 'mammary tumour' OR 'mammary tumour cell' OR 'unilateral breast neoplasms' OR 'colorectal neoplasm') AND ('colorectal tumor'/exp OR 'colorectal neoplasia' OR 'colorectal neoplasm' OR 'colorectal neoplasms' OR 'colorectal tumor' OR 'colorectal tumour' OR 'tumor, colorectal' OR 'tumour, colorectal') OR 'stomach tumor'/exp OR 'gastric tumor' OR 'gastric tumour' OR 'mucosa tumor, stomach' OR 'mucosa tumour, stomach' OR 'stomach mucosa tumor' OR 'stomach mucosa tumour' OR 'stomach neoplasia' OR 'stomach neoplasm' OR 'stomach neoplasms' OR 'stomach tumor' OR 'stomach tumour' OR 'stomach ulcerated tumor' OR 'stomach ulcerated tumour' OR 'stomach ulcerating tumor' OR 'stomach ulcerating tumour' OR 'tumor, stomach mucosa' OR 'tumour, stomach mucosa' OR 'neoplasm'/exp OR 'acral tumor' OR 'acral tumour' OR 'neoplasia' OR 'neoplasm' OR 'neoplasms' OR 'neoplasms by histologic type' OR 'neoplasms, cystic, mucinous, and serous' OR 'neoplasms, embryonal and mixed' OR 'neoplasms, germ cell and embryonal' OR 'neoplasms, glandular and epithelial' OR 'neoplasms, hormone-dependent' OR 'neoplasms, post-traumatic' OR 'neoplastic disease' OR 'tumor' OR 'tumour' OR 'neoplasm metastasis' OR 'liver tumor'/exp OR 'hepatic tumor' OR 'hepatic tumour' OR 'liver cell tumor' OR 'liver cell tumour' OR 'liver neoplasm' OR 'liver neoplasma' OR 'liver neoplasms' OR 'liver tumor' OR 'liver tumour' OR 'tumor, liver' OR 'tumour, liver' OR 'prostate tumor'/exp OR 'bone tumor'/exp OR 'adenocarcinoma'/exp OR 'adenocancer' OR 'adenocarcinoma' OR 'adenocarcinoma, clear cell' OR 'adenocarcinoma, follicular' OR 'adenocarcinoma, papillary' OR 'adenocarcinoma, scirrhous' OR 'adenocarcinoma, sebaceous' OR 'adenoepidermoid

carcinoma' OR 'adenoid basal carcinoma' OR 'glandular carcinoma' OR 'villous adenocarcinoma' OR 'brain neoplasm') AND ('Denosumab'/exp OR 'amg162' OR 'amgiva' OR 'Denosumab' OR 'prolia' OR 'xgeva' OR 'amg 162' OR prolia OR xgeva OR 'biphosphonates' OR 'bisphosphonate' OR 'bisphosphonate derivative' OR 'bisphosphonates' OR 'bisphosphonic acid derivative' OR 'diphosphonate derivative' OR 'diphosphonate series' OR 'diphosphonates' OR 'diphosphonic acid derivative' OR 'biphosphonate' OR 'bisphosphonic acid derivative'/exp) AND 'skeletal related event'/exp

Ovid-EBM Reviews - Cochrane Central Register of Controlled Trials <March 2018>

---

1 BREAST NEOPLASMS/ (8695)
2 (breast adj1 (cancer or carcinoma* or tumor* or neoplasm*)).tw. (21229)
3 (breast malignant adj2 (neoplasm* or tumor*)).tw. (0)
4 human mammary neoplasm*.tw. (0)
5 mammary cancer*.tw. (43)
6 ((malignant neoplasm or malignant tumor) adj2 breast).tw. (1)
7 (cancer adj3 breast).tw. (21148)
8 tumor*,breast.tw. (76)
9 cancer*,mammary.tw. (2)
10 carcinoma*,breast.tw. (229)
11 neoplasm*,breast.tw. (4)
12 cancer, breast.tw. (266)
13 COLORECTAL NEOPLASMS/ (3061)
14 (colorectal adj1 (cancer* or carcinoma* or neoplasm* or tumor*)).tw. (7462)
15 cancer*, colorectal.tw. (97)
16 carcinoma*,colorectal.tw. (30)
17 neoplasm*,colorectal.tw. (3)
18 tumor*,colorectal.tw. (16)
19 STOMACH NEOPLASMS/ (1693)
20 (stomach adj1 (cancer* or neoplasm*)).tw. (232)
21 (gastric adj1 (cancer* or neoplasm*)).tw. (3219)
22 (cancer* adj3 stomach).tw. (294)
23 neoplasm*, gastric.tw. (0)
24 neoplasm*, stomach.tw. (1)
25 cancer*,gastric.tw. (45)
26 cancer*,stomach.tw. (35)
27 NEOPLASMS/ (4552)
28 benign neoplasm*.tw. (16)
29 malignant neoplasm*.tw. (154)
30 cancer*.tw. (83268)

31 malignanc*.tw. (6776)
32 neoplas*.tw. (3851)
33 tumor*.tw. (30328)
34 NEOPLASM METASTASIS/ (2156)
35 metastas*.tw. (9854)
36 neoplasm metastasis.tw. (2)
37 neoplasm metastases.tw. (1)
38 LIVER NEOPLASMS/ (1885)
39 (hepatic adj1 (cancer* or neoplasm*)).tw. (57)
40 (liver adj1 (cancer* or neoplasm*)).tw. (721)
41 (cancer adj3 liver).tw. (948)
42 neoplasm*,hepatic.tw. (0)
43 PROSTATIC NEOPLASMS/ (3508)
44 (prostat* adj1 (cancer* or neoplasm*)).tw. (7111)
45 (cancer adj3 prostate).tw. (6913)
46 cancer*, prostat*.tw. (281)
47 neoplasm*, prostat*.tw. (1)
48 BONE NEOPLASMS/ (913)
49 (bone adj1 (cancer or neoplasm*)).tw. (233)
50 (cancer adj3 bone).tw. (857)
51 ADENOCARCINOMA/ (2684)
52 adenocarcinoma*.tw. (3642)
53 ((basal or granular) adj2 cell adenocarcinoma*).tw. (1)
54 granular cell carcinoma*.tw. (0)
55 ((cribriform or tubular) adj2 carcinoma*).tw. (26)
56 malignant adenoma*.tw. (0)
57 oxyphilic adenocarcinoma*.tw. (0)
58 tubular adenocarcinoma*.tw. (2)
59 BRAIN NEOPLASMS/ (1164)
60 ((benign or brain) adj2 neoplasm*).tw. (58)
61 (brain adj2 (cancer* or tumor* or neoplasm*)).tw. (893)
62 intracranial neoplasm*.tw. (9)
63 ((brain malignant or malignant brain) adj2 neoplasm*).tw. (1)
64 (cancer adj3 brain).tw. (222)
65 ((malignant primary or primary malignant) adj3 (brain tumor* or brain neoplasm*)).tw. (15)
66 (primary brain adj2 (tumor* or neoplasm*)).tw. (80)
67 recurrent brain tumor*.tw. (13)
68 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 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 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51

or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 (109214)

69 DENOSUMAB/ (129)

70 amg 162.tw. (15)

71 Denosumab.tw. (453)

72 prolia.tw. (0)

73 xgeva.tw. (3)

74 DIPHOSPHONATES/ (918)

75 Bisphosphonates.tw. (796)

76 Diphosphonates.tw. (18)

77 CLODRONIC ACID/ (170)

78 Bonefos.tw. (12)

79 cl2mdp.tw. (13)

80 clodronate.tw. (273)

81 clodronate disodium.tw. (4)

82 clodronic acid.tw. (9)

83 dichloromethane diphosphonate.tw. (0)

84 dichloromethanediphosphonate.tw. (0)

85 dichloromethylene bisphosphonate.tw. (7)

86 dichloromethylene diphosphonate.tw. (19)

87 disodium, clodronate.tw. (7)

88 acid, clodronic.tw. (2)

89 sodium, clodronate.tw. (8)

90 Pamidronate.tw. (422)

91 Ibandronate.tw. (290)

92 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 (2271)

93 PLACEBO EFFECT/ (1287)

94 effect*, placebo.tw. (3092)

95 placebo effect*.tw. (2964)

96 PALLIATIVE CARE/ (1364)

97 (palliative adj1 (care or surgery or therapy or treatment*)).tw. (1715)

98 surgery, palliative.tw. (14)

99 therapy, palliative.tw. (42)

100 treatment, palliative.tw. (32)

101 care, palliative.tw. (26)

102 ANTINEOPLASTIC COMBINED CHEMOTHERAPY PROTOCOLS/ (12305)

103 anticancer drug combination*.tw. (3)

104 antineoplastic chemotherapy protocol*.tw. (0)

105 antineoplastic drug combination*.tw. (0)

106 cancer chemotherapy protocol*.tw. (0)
107 combined antineoplastic agent*.tw. (1)
108 antineoplastic agent*, combined.tw. (19)
109 chemotherapy protocol*, antineoplastic.tw. (0)
110 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 (21599)
111 QUALITY OF LIFE/ (19125)
112 life quality.tw. (1605)
113 (quality adj2 life).tw. (48259)
114 (health related quality adj3 life).tw. (8469)
115 HYPOCALCEMIA/ (101)
116 hypocalcemia*.tw. (358)
117 OSTEONECROSIS/ (64)
118 ((aseptic necrosis or avascular necrosis) adj3 bone).tw. (16)
119 ((bone aseptic or bone avascular) adj2 necrosis).tw. (0)
120 bone necros*.tw. (10)
121 osteonecros*.tw. (383)
122 BISPHOSPHONATE-ASSOCIATED OSTEONECROSIS OF THE JAW/ (14)
123 (bi bisphosphonate associated osteonecrosis adj3 jaw*).tw. (0)
124 (bisphosphonate induced osteonecrosis adj3 jaw*).tw. (2)
125 bisphosphonate osteonecros*.tw. (0)
126 (bisphosphonate related osteonecrosis adj3 jaw).tw. (6)
127 JAW DISEASES/ (29)
128 jaw disease*.tw. (0)
129 RENAL INSUFFICIENCY/ (549)
130 (kidney adj1 (failure* or insuffucienc*)).tw. (296)
131 (renal adj1 (failure* or insufficienc*)).tw. (5201)
132 failure*, kidney.tw. (37)
133 failure*,renal.tw. (162)
134 insufficiency, kidney.tw. (8)
135 ACUTE KIDNEY INJURY/ (836)
136 (acute kidney adj2 (failure* or injur* or insufficienc*)).tw. (1252)
137 acute renal failure*.tw. (873)
138 acute renal injur*.tw. (35)
139 acute renal insufficienc*.tw. (18)
140 kidney failure*,acute.tw. (2)
141 kidney injury*,acute.tw. (7)
142 renal failure*,acute.tw. (14)
143 renal injur*.tw. (326)
144 renal insufficienc*.tw. (1224)

145 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 (59611)

146 68 and 92 and 110 and 145 (22)

Ovid-EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 18, 2018>

---

1 [BREAST NEOPLASMS/] (0)

2 (breast adj1 (cancer or carcinoma* or tumor* or neoplasm*)).tw. (407)

3 (breast malignant adj2 (neoplasm* or tumor*)).tw. (0)

4 human mammary neoplasm*.tw. (1)

5 mammary cancer*.tw. (0)

6 ((malignant neoplasm or malignant tumor) adj2 breast).tw. (0)

7 (cancer adj3 breast).tw. (434)

8 tumor*,breast.tw. (10)

9 cancer*,mammary.tw. (0)

10 carcinoma*,breast.tw. (20)

11 neoplasm*,breast.tw. (29)

12 cancer, breast.tw. (81)

13 [COLORECTAL NEOPLASMS/] (0)

14 (colorectal adj1 (cancer* or carcinoma* or neoplasm* or tumor*)).tw. (278)

15 cancer*, colorectal.tw. (41)

16 carcinoma*,colorectal.tw. (8)

17 neoplasm*,colorectal.tw. (9)

18 tumor*,colorectal.tw. (2)

19 [STOMACH NEOPLASMS/] (0)

20 (stomach adj1 (cancer* or neoplasm*)).tw. (33)

21 (gastric adj1 (cancer* or neoplasm*)).tw. (62)

22 (cancer* adj3 stomach).tw. (49)

23 neoplasm*, gastric.tw. (0)

24 neoplasm*, stomach.tw. (1)

25 cancer*,gastric.tw. (12)

26 cancer*,stomach.tw. (8)

27 [NEOPLASMS/] (0)

28 benign neoplasm*.tw. (5)

29 malignant neoplasm*.tw. (30)

30 cancer*.tw. (2448)

31 malignanc*.tw. (873)

32 neoplas*.tw. (1126)

33 tumor*.tw. (705)

34 [NEOPLASM METASTASIS/] (0)

35 metastas*.tw. (475)

36 neoplasm metastasis.tw. (41)

37 neoplasm metastases.tw. (1)

38 [LIVER NEOPLASMS/] (0)

39 (hepatic adj1 (cancer* or neoplasm*)).tw. (10)

40 (liver adj1 (cancer* or neoplasm*)).tw. (105)

41 (cancer adj3 liver).tw. (117)

42 neoplasm*,hepatic.tw. (0)

43 [PROSTATIC NEOPLASMS/] (0)

44 (prostat* adj1 (cancer* or neoplasm*)).tw. (136)

45 (cancer adj3 prostate).tw. (143)

46 cancer*, prostat*.tw. (30)

47 neoplasm*, prostat*.tw. (3)

48 [BONE NEOPLASMS/] (0)

49 (bone adj1 (cancer or neoplasm*)).tw. (32)

50 (cancer adj3 bone).tw. (54)

51 [ADENOCARCINOMA/] (0)

52 adenocarcinoma*.tw. (282)

53 ((basal or granular) adj2 cell adenocarcinoma*).tw. (0)

54 granular cell carcinoma*.tw. (0)

55 ((cribriform or tubular) adj2 carcinoma*).tw. (0)

56 malignant adenoma*.tw. (2)

57 oxyphilic adenocarcinoma*.tw. (0)

58 tubular adenocarcinoma*.tw. (0)

59 [BRAIN NEOPLASMS/] (0)

60 ((benign or brain) adj2 neoplasm*).tw. (67)

61 (brain adj2 (cancer* or tumor* or neoplasm*)).tw. (67)

62 intracranial neoplasm*.tw. (16)

63 ((brain malignant or malignant brain) adj2 neoplasm*).tw. (0)

64 (cancer adj3 brain).tw. (50)

65 ((malignant primary or primary malignant) adj3 (brain tumor* or brain neoplasm*)).tw. (0)

66 (primary brain adj2 (tumor* or neoplasm*)).tw. (2)

67 recurrent brain tumor*.tw. (0)

68 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 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 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 (2860)

69 [DENOSUMAB/] (0)
70 amg 162.tw. (1)
71 Denosumab.tw. (18)
72 prolia.tw. (4)
73 xgeva.tw. (4)
74 [DIPHOSPHONATES/] (0)
75 Bisphosphonates.tw. (68)
76 Diphosphonates.tw. (24)
77 [CLODRONIC ACID/] (0)
78 Bonefos.tw. (3)
79 cl2mdp.tw. (1)
80 clodronate.tw. (20)
81 clodronate disodium.tw. (2)
82 clodronic acid.tw. (9)
83 dichloromethane diphosphonate.tw. (0)
84 dichloromethanediphosphonate.tw. (0)
85 dichloromethylene bisphosphonate.tw. (0)
86 dichloromethylene diphosphonate.tw. (0)
87 disodium, clodronate.tw. (0)
88 acid, clodronic.tw. (1)
89 sodium, clodronate.tw. (3)
90 Pamidronate.tw. (29)
91 Ibandronate.tw. (20)
92 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 (74)
93 [PLACEBO EFFECT/] (0)
94 effect*, placebo.tw. (572)
95 placebo effect*.tw. (533)
96 [PALLIATIVE CARE/] (0)
97 (palliative adj1 (care or surgery or therapy or treatment*)).tw. (289)
98 surgery, palliative.tw. (7)
99 therapy, palliative.tw. (12)
100 treatment, palliative.tw. (23)
101 care, palliative.tw. (21)
102 [ANTINEOPLASTIC COMBINED CHEMOTHERAPY PROTOCOLS/] (0)
103 anticancer drug combination*.tw. (1)
104 antineoplastic chemotherapy protocol*.tw. (1)
105 antineoplastic drug combination*.tw. (2)
106 cancer chemotherapy protocol*.tw. (1)
107 combined antineoplastic agent*.tw. (1)

108 antineoplastic agent*, combined.tw. (2)

109 chemotherapy protocol*, antineoplastic.tw. (2)

110 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 (1252)

111 [QUALITY OF LIFE/] (0)

112 life quality.tw. (149)

113 (quality adj2 life).tw. (5212)

114 (health related quality adj3 life).tw. (1302)

115 [HYPOCALCEMIA/] (0)

116 hypocalcemia*.tw. (17)

117 [OSTEONECROSIS/] (0)

118 ((aseptic necrosis or avascular necrosis) adj3 bone).tw. (13)

119 ((bone aseptic or bone avascular) adj2 necrosis).tw. (0)

120 bone necros*.tw. (7)

121 osteonecros*.tw. (51)

122 [BISPHOSPHONATE-ASSOCIATED OSTEONECROSIS OF THE JAW/] (0)

123 (bisphosphonate associated osteonecrosis adj3 jaw*).tw. (2)

124 (bisphosphonate induced osteonecrosis adj3 jaw*).tw. (0)

125 bisphosphonate osteonecros*.tw. (0)

126 (bisphosphonate related osteonecrosis adj3 jaw).tw. (2)

127 [JAW DISEASES/] (0)

128 jaw disease*.tw. (4)

129 [RENAL INSUFFICIENCY/] (0)

130 (kidney adj1 (failure* or insuffucienc*)).tw. (197)

131 (renal adj1 (failure* or insufficienc*)).tw. (691)

132 failure*, kidney.tw. (27)

133 failure*,renal.tw. (58)

134 insufficiency, kidney.tw. (4)

135 [ACUTE KIDNEY INJURY/] (0)

136 (acute kidney adj2 (failure* or injur* or insufficienc*)).tw. (101)

137 acute renal failure*.tw. (98)

138 acute renal injur*.tw. (12)

139 acute renal insufficienc*.tw. (4)

140 kidney failure*,acute.tw. (4)

141 kidney injury*,acute.tw. (3)

142 renal failure*,acute.tw. (9)

143 renal injur*.tw. (24)

144 renal insufficienc*.tw. (173)

145 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 (5597)

146 68 and 92 and 110 and 145 (12)

Ovid- EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2018>

---

1 BREAST NEOPLASMS/ (517)

2 (breast adj1 (cancer or carcinoma* or tumor* or neoplasm*)).tw. (590)

3 (breast malignant adj2 (neoplasm* or tumor*)).tw. (0)

4 human mammary neoplasm*.tw. (0)

5 mammary cancer*.tw. (0)

6 ((malignant neoplasm or malignant tumor) adj2 breast).tw. (0)

7 (cancer adj3 breast).tw. (507)

8 tumor*,breast.tw. (0)

9 cancer*,mammary.tw. (0)

10 carcinoma*,breast.tw. (0)

11 neoplasm*,breast.tw. (0)

12 cancer, breast.tw. (3)

13 COLORECTAL NEOPLASMS/ (297)

14 (colorectal adj1 (cancer* or carcinoma* or neoplasm* or tumor*)).tw. (361)

15 cancer*, colorectal.tw. (3)

16 carcinoma*,colorectal.tw. (0)

17 neoplasm*,colorectal.tw. (1)

18 tumor*,colorectal.tw. (0)

19 STOMACH NEOPLASMS/ (72)

20 (stomach adj1 (cancer* or neoplasm*)).tw. (76)

21 (gastric adj1 (cancer* or neoplasm*)).tw. (67)

22 (cancer* adj3 stomach).tw. (7)

23 neoplasm*, gastric.tw. (1)

24 neoplasm*, stomach.tw. (0)

25 cancer*,gastric.tw. (0)

26 cancer*,stomach.tw. (1)

27 NEOPLASMS/ (148)

28 benign neoplasm*.tw. (1)

29 malignant neoplasm*.tw. (8)

30 cancer*.tw. (2185)

31 malignanc*.tw. (243)

32 neoplas*.tw. (2504)

33 tumor*.tw. (218)

34 NEOPLASM METASTASIS/ (76)

35 metastas*.tw. (303)

36 neoplasm metastasis.tw. (76)

37 neoplasm metastases.tw. (0)

38 LIVER NEOPLASMS/ (108)

39 (hepatic adj1 (cancer* or neoplasm*)).tw. (4)

40 (liver adj1 (cancer* or neoplasm*)).tw. (121)

41 (cancer adj3 liver).tw. (28)

42 neoplasm*,hepatic.tw. (0)

43 PROSTATIC NEOPLASMS/ (137)

44 (prostat* adj1 (cancer* or neoplasm*)).tw. (155)

45 (cancer adj3 prostate).tw. (124)

46 cancer*, prostat*.tw. (1)

47 neoplasm*, prostat*.tw. (1)

48 BONE NEOPLASMS/ (39)

49 (bone adj1 (cancer or neoplasm*)).tw. (39)

50 (cancer adj3 bone).tw. (10)

51 ADENOCARCINOMA/ (67)

52 adenocarcinoma*.tw. (102)

53 ((basal or granular) adj2 cell adenocarcinoma*).tw. (0)

54 granular cell carcinoma*.tw. (0)

55 ((cribriform or tubular) adj2 carcinoma*).tw. (0)

56 malignant adenoma*.tw. (0)

57 oxyphilic adenocarcinoma*.tw. (0)

58 tubular adenocarcinoma*.tw. (0)

59 BRAIN NEOPLASMS/ (34)

60 ((benign or brain) adj2 neoplasm*).tw. (36)

61 (brain adj2 (cancer* or tumor* or neoplasm*)).tw. (36)

62 intracranial neoplasm*.tw. (0)

63 ((brain malignant or malignant brain) adj2 neoplasm*).tw. (0)

64 (cancer adj3 brain).tw. (3)

65 ((malignant primary or primary malignant) adj3 (brain tumor* or brain neoplasm*)).tw. (0)

66 (primary brain adj2 (tumor* or neoplasm*)).tw. (0)

67 recurrent brain tumor*.tw. (0)

68 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 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 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 (3075)

69 DENOSUMAB/ (0)

70 amg 162.tw. (0)
71 Denosumab.tw. (17)
72 prolia.tw. (0)
73 xgeva.tw. (0)
74 DIPHOSPHONATES/ (57)
75 Bisphosphonates.tw. (43)
76 Diphosphonates.tw. (57)
77 CLODRONIC ACID/ (4)
78 Bonefos.tw. (0)
79 cl2mdp.tw. (0)
80 clodronate.tw. (6)
81 clodronate disodium.tw. (0)
82 clodronic acid.tw. (4)
83 dichloromethane diphosphonate.tw. (0)
84 dichloromethanediphosphonate.tw. (0)
85 dichloromethylene bisphosphonate.tw. (0)
86 dichloromethylene diphosphonate.tw. (0)
87 disodium, clodronate.tw. (0)
88 acid, clodronic.tw. (0)
89 sodium, clodronate.tw. (0)
90 Pamidronate.tw. (13)
91 Ibandronate.tw. (9)
92 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 (84)
93 PLACEBO EFFECT/ (3)
94 effect*, placebo.tw. (0)
95 placebo effect*.tw. (22)
96 PALLIATIVE CARE/ (94)
97 (palliative adj1 (care or surgery or therapy or treatment*)).tw. (236)
98 surgery, palliative.tw. (2)
99 therapy, palliative.tw. (2)
100 treatment, palliative.tw. (10)
101 care, palliative.tw. (0)
102 ANTINEOPLASTIC COMBINED CHEMOTHERAPY PROTOCOLS/ (336)
103 anticancer drug combination*.tw. (0)
104 antineoplastic chemotherapy protocol*.tw. (0)
105 antineoplastic drug combination*.tw. (0)
106 cancer chemotherapy protocol*.tw. (0)
107 combined antineoplastic agent*.tw. (0)
108 antineoplastic agent*, combined.tw. (0)

109 chemotherapy protocol*, antineoplastic.tw. (0)

110 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 (565)

111 QUALITY OF LIFE/ (1268)

112 life quality.tw. (35)

113 (quality adj2 life).tw. (6238)

114 (health related quality adj3 life).tw. (401)

115 HYPOCALCEMIA/ (4)

116 hypocalcemia*.tw. (8)

117 OSTEONECROSIS/ (0)

118 ((aseptic necrosis or avascular necrosis) adj3 bone).tw. (0)

119 ((bone aseptic or bone avascular) adj2 necrosis).tw. (0)

120 bone necros*.tw. (0)

121 osteonecros*.tw. (6)

122 BISPHOSPHONATE-ASSOCIATED OSTEONECROSIS OF THE JAW/ (0)

123 (bi bisphosphonate associated osteonecrosis adj3 jaw*).tw. (0)

124 (bisphosphonate induced osteonecrosis adj3 jaw*).tw. (0)

125 bisphosphonate osteonecros*.tw. (0)

126 (bisphosphonate related osteonecrosis adj3 jaw).tw. (0)

127 JAW DISEASES/ (0)

128 jaw disease*.tw. (0)

129 RENAL INSUFFICIENCY/ (10)

130 (kidney adj1 (failure* or insuffucienc*)).tw. (188)

131 (renal adj1 (failure* or insufficienc*)).tw. (232)

132 failure*, kidney.tw. (0)

133 failure*,renal.tw. (6)

134 insufficiency, kidney.tw. (0)

135 ACUTE KIDNEY INJURY/ (15)

136 (acute kidney adj2 (failure* or injur* or insufficienc*)).tw. (16)

137 acute renal failure*.tw. (26)

138 acute renal injur*.tw. (0)

139 acute renal insufficienc*.tw. (1)

140 kidney failure*,acute.tw. (4)

141 kidney injury*,acute.tw. (0)

142 renal failure*,acute.tw. (2)

143 renal injur*.tw. (0)

144 renal insufficienc*.tw. (84)

145 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 (6477)

146 68 and 92 and 110 and 145 (5)

147 limit 146 to humans (8)

Pubmed Search Terms

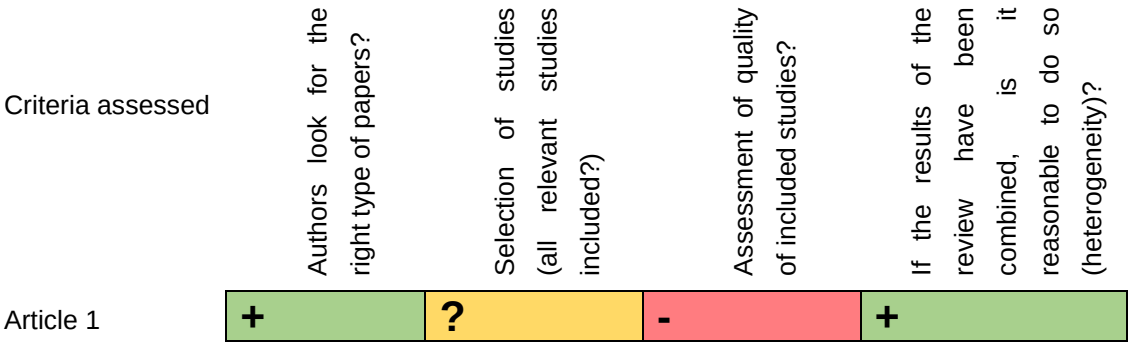
((((((((((((((((((((((((((((((((((((Solid tumor*[Title/Abstract]) OR Solid Tumour*[Title/Abstract]) OR NEOPLASMS[MeSH Terms]) OR Neoplas*[Title/Abstract]) OR Tumor*[Title/Abstract]) OR Benign Neoplasm*[Title/Abstract]) OR Malignanc*[Title/Abstract]) OR Cancer*[Title/Abstract]) OR HEMATOLOGIC NEOPLASMS[MeSH Terms]) OR Hematologic* neoplasm*[Title/Abstract]) OR Hematologic* malignanc*[Title/Abstract]) OR Hematopoietic Malignancies*[Title/Abstract]) OR Hematopoietic Neoplasm*[Title/Abstract]) OR Hematopoietic Malignancies*[Title/Abstract]) OR MELANOMA[MeSH Terms]) OR Melanomas*[Title/Abstract]) OR Malignant melanoma*[Title/Abstract]) OR BREAST NEOPLASMS[MeSH Terms]) OR Breast Tumor*[Title/Abstract]) OR Breast Cancer[Title/Abstract]) OR Breast Carcinoma[Title/Abstract]) OR Breast Neoplasm[Title/Abstract]) OR Mammary Cancer*[Title/Abstract]) OR Breast Malignant Neoplasm*[Title/Abstract]) OR Breast Malignant Tumor[Title/Abstract]) OR Human Mammary Carcinoma*[Title/Abstract]) OR Human Mammary Neoplasm*[Title/Abstract]) OR Malignant Neoplasm of Breast[Title/Abstract]) OR LIVER NEOPLASMS[MeSH Terms]) OR Hepatic Neoplasm*) OR Hepatocellular Cancer*[MeSH Terms]) OR Hepatic Cancer*[Title/Abstract]) OR Liver Cancer*[Title/Abstract]) OR Cancer of Liver[Title/Abstract]) OR Cancer of the Liver[Title/Abstract]) OR Liver Neoplasm[Title/Abstract])) AND (((((Diphosphonates[MeSH Terms]) OR Bisphosphonates[Title/Abstract]) OR RANK ligand inhibitor[Title/Abstract])) AND ((((((((((Skeletal related event[MeSH Terms]) OR pain[Title/Abstract]) OR Splitting Pain*[Title/Abstract]) OR Ache*[Title/Abstract]) OR Burning pain*[Title/Abstract]) OR Crushing Pain*[Title/Abstract]) OR Radiating Pain*[Title/Abstract]) OR Migratory Pain*[Title/Abstract]) OR Physical Suffering*[Title/Abstract]) OR Radiating Pain*[Title/Abstract]))

Appendix 4

ASSESSMENT OF RISK OF BIAS

+	Indicates YES (low risk of bias)
?	indicates UNKNOWN risk of bias
-	Indicates NO (high risk of bias)

Assessment of risk of bias of systematic review (CASP)



Assessment of risk of bias of RCT (Cochrane)

Assessment of risk of bias of economic evaluation (CASP)

Criteria assessed				
A well-define question posed?	+	+	+	+
Comprehensive description of competing alternative given?	?	?	?	?
Effectiveness established?	-	-	-	-
Effects of intervention identified, measured and valued appropriately?	+	+	+	+
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	?	?	?	?
Costs and consequences adjusted for different times at which they occurred (discounting)?	-	-	-	-
Results of the evaluation?	+	+	+	+
Incremental analysis of the consequences and costs of alternatives performed?	?	?	?	?
Sensitivity analysis performed?	-	-	-	-

Appendix 5

Total number of Stage IV patients in 13 solid tumour cancers

Type of cancer	Total number of patients (5 years)	Total number of Stage IV patients (5 years)
Breast	18,343	2,411
Prostate	3,132	658
Trachea, bronchus, lung	10,608	4,028
Colorectal	13,693	2,639
Nasopharynx	5,090	908
Cervix uteri	4,352	514
Liver	4,128	1,061
Ovary	3,472	560
Stomach	3,460	743
Thyroid	2,272	273
Brain / Nervous system	2,236	300
Kidney	1,335	372
Corpus uteri	2,181	204
Total Stage IV solid tumour patients (2007-2011)		**14,671**
Average Stage IV solid tumour patients per year		**2,934**

Source: Zainal Ariffin, O., and I. T. Nor Saleha. "National cancer registry report 2007." Malaysia: Ministry of Health (2011).

Appendix 6

Evidence table can be downloaded from:

- **MOH website:-**

  http://www.moh.gov.my/index.php/pages/view/1691

- **MyMaHTAS mobile apps (android and IOS):-**

  HTA: BONE TARGETING AGENT (BTA) IN PREVENTION OF SREs FOR METASTATIC CANCERS OF SOLID TUMOURS

Appendix 7

LIST OF EXCLUDED STUDIES

1. Scagliotti GV, Kosmidis P, De Marinis F, et al. Zoledronic acid in patients with stage IIIA/B NSCLC: Results of a randomized, phase III study. Annals of Oncology. 2012;23(8):2082-2087.

2. Mhaskar R, Redzepovic J, Wheatley K, et al. Bisphosphonates in multiple myeloma: a network meta-analysis. Cochrane Database of Systematic Reviews. 2012(8).

3. Minton O, Richardson A, Sharpe M, et al. Drug therapy for the management of cancer-related fatigue. Cochrane Database of Systematic Reviews. 2010(9).

4. Palmieri C, Fullarton JR, Brown J. Comparative efficacy of bisphosphonates in metastatic breast and prostate cancer and multiple myeloma: a mixed-treatment meta-analysis. Clin Cancer Res. 2013;19(24):6863-6872.

5. Pruksakorn D, Phanphaisarn A, Settakorn J, et al. Prognostic score for life expectancy evaluation of lung cancer patients after bone metastasis. Journal of bone oncology. 2018;10:1-5.

6. Raje NS, Terpos E, Durie BG, et al. A randomized, double-blind, multinational trial comparing Denosumab with Zoledronic acid for treatment of bone disease in adults with newly diagnosed multiple myeloma. Journal of clinical oncology. 2014;32(15 Suppl.1).

7. Raje NS, Terpos E, Durie BG, et al. Denosumab compared with Zoledronic acid for the treatment of bone disease in adults with newly diagnosed multiple myeloma: An international, randomized, double-blind trial. Journal of clinical oncology. 2015;33(15 Suppl.1).

8. Sze MW, Shelley M, Held I, et al. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy. Cochrane Database of Systematic Reviews. 2011(5).

9. Yuen KK, Shelley M, Sze MW, et al. Bisphosphonates for advanced prostate cancer. Cochrane Database of Systematic Reviews. 2010(2)

10. Spencer S, Marini BL, Figg WD. Novel approaches in the pharmacotherapy of skeletal-related events in metastatic castrate-resistant prostate cancer. Anticancer research. 2012;32(7):2391-2398.

11. Gramza A, Kebebew E. Cancer: thyroid cancer bone metastases and high morbidity rates. Nature Reviews Endocrinology. 2012;8(8):454.

12. Van Poznak C, Somerfield MR, Barlow WE, et al. Role of bone-modifying agents in metastatic breast cancer: an American Society of Clinical

Oncology–Cancer Care Ontario focused guideline update. Journal of Clinical Oncology. 2017;35(35):3978-3986.

13. Gül G, Sendur MAN, Aksoy S, et al. A comprehensive review of Denosumab for bone metastasis in patients with solid tumors. Current medical research and opinion. 2016;32(1):133-145.

14. Raje N, Vadhan-Raj S, Willenbacher W, et al. Evaluating results from the multiple myeloma patient subset treated with Denosumab or Zoledronic acid in a randomized phase 3 trial. Blood Cancer Journal. 2016;6.

15. Raje N, Roodman GD, Willenbacher W, et al. A cost-effectiveness analysis of Denosumab for the prevention of skeletal-related events in patients with multiple myeloma in the United States of America. Journal of medical economics. 2018;21(5):525-536.

16. Yokomoto-Umakoshi M, Umakoshi H, Tsuiki M, et al. Paraganglioma as a risk factor for bone metastasis. Endocrine journal. 2018;65(3):253-260.

17. Xu JY, Murphy Jr WA, Milton DR, et al. Bone metastases and skeletal-related events in medullary thyroid carcinoma. The Journal of Clinical Endocrinology & Metabolism. 2016;101(12):4871-4877.

18. Yaldo A, Wen L, Ogbonnaya A, et al. Opioid Use Among Metastatic Prostate Cancer Patients With Skeletal-related Events. Clinical therapeutics. 2016;38(8):1880-1889.

19. Acquavella J, Ehrenstein V, Schiødt M, et al. Design and methods for a Scandinavian pharmacovigilance study of osteonecrosis of the jaw and serious infections among cancer patients treated with antiresorptive agents for the prevention of skeletal-related events. Clinical epidemiology. 2016;8:267.

20. Tanaka R, Yonemori K, Hirakawa A, et al. Risk factors for developing skeletal-related events in breast cancer patients with bone metastases undergoing treatment with bone-modifying agents. The oncologist. 2016;21(4):508-513.

21. El-Amm J, Aragon-Ching JB. Targeting bone metastases in metastatic castration-resistant prostate cancer. Clinical Medicine Insights: Oncology. 2016;10:CMO. Ss30751.

22. Ulas A, Bilici A, Durnali A, et al. Risk factors for skeletal-related events (SREs) and factors affecting SRE-free survival for nonsmall cell lung cancer patients with bone metastases. Tumor Biology. 2016;37(1):1131-1140.

23. Tombal B. Assessing the benefit of bone-targeted therapies in prostate cancer, is the devil in the end point's definition? : European Society for Medical Oncology; 2014.

24. Dahiya N, Khadka A, Sharma A, et al. Denosumab: A bone antiresorptive drug. Medical Journal Armed Forces India. 2015;71(1):71-75.

25. Smith MR, Coleman RE, Klotz L, et al. Denosumab for the prevention of skeletal complications in metastatic castration-resistant prostate cancer: comparison of skeletal-related events and symptomatic skeletal events. Annals of Oncology. 2015;26(2):368-374.

26. Santini D, Pantano F, Riccardi F, et al. Natural history of malignant bone disease in hepatocellular carcinoma: final results of a multicenter bone metastasis survey. PLoS ONE. 2014;9(8):e105268.

27. Vassiliou V. Management of metastatic bone disease in the elderly with bisphosphonates and receptor activator of NF-kB ligand inhibitors: effectiveness and safety. Clinical Oncology (Royal College of Radiologists). 2013;25(5):290-297.

28. Gartrell BA, Saad F. Managing bone metastases and reducing skeletal related events in prostate cancer. Nature reviews Clinical oncology. 2014;11(6):335.

29. Zustovich F, Fabiani F. Therapeutic opportunities for castration-resistant prostate cancer patients with bone metastases. Critical reviews in oncology/hematology. 2014;91(2):197-209.

30. Jacobs C, Kuchuk I, Bouganim N, et al. A randomized, double-blind, phase II, exploratory trial evaluating the palliative benefit of either continuing pamidronate or switching to Zoledronic acid in patients with high-risk bone metastases from breast cancer. Breast Cancer Research and Treatment. 2016;155(1):77-84.

31. Nozawa M, Inagaki T, Nagao K, et al. Phase II trial of Zoledronic acid combined with androgen-deprivation therapy for treatment-naive prostate cancer with bone metastasis. International Journal of Clinical Oncology. 2014;19(4):693-701.

32. Hoefeler H, Duran I, Hechmati G, et al. Health resource utilization associated with skeletal-related events in patients with bone metastases: results from a multinational retrospective–prospective observational study–a cohort from 4 European countries. Journal of bone oncology. 2014;3(2):40-48.

33. Terpos E, Dimopoulos MA, Berenson J. Established role of bisphosphonate therapy for prevention of skeletal complications from myeloma bone disease. Critical Reviews in Oncology-Hematology. 2011;77 Suppl 1:S13-23.

34. Santini D, Tampellini M, Vincenzi B, et al. Natural history of bone metastasis in colorectal cancer: final results of a large Italian bone metastases study. Annals of Oncology. 2012;23(8):2072-2077.

35. Paterson AHG, Anderson SJ, Lembersky BC, et al. Oral clodronate for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and Bowel Project protocol B-34): A multicentre, placebo-controlled, randomised trial. The Lancet Oncology. 2012;13(7):734-742.

36. McKay RR, Taplin M-E, Choueiri TK. Optimizing bone health and minimizing skeletal morbidity in men with prostate cancer. Hematology/Oncology Clinics. 2013;27(6):1261-1283.

37. Oster G, Lamerato L, Glass AG, et al. Natural history of skeletal-related events in patients with breast, lung, or prostate cancer and metastases to bone: a 15-year study in two large US health systems. Support Care Cancer. 2013;21(12):3279-3286.

38. Van den Wyngaert T, Delforge M, Doyen C, et al. Prospective observational study of treatment pattern, effectiveness and safety of Zoledronic acid therapy beyond 24 months in patients with multiple myeloma or bone metastases from solid tumors. Supportive Care in Cancer. 2013;21(12):3483-3490.

39. Huang WW, Huang C, Liu J, et al. Zoledronic acid as an adjuvant therapy in patients with breast cancer: a systematic review and meta-analysis. PLoS ONE [Electronic Resource]. 2012;7(7):e40783.

40. Razaq W. Bone targeted therapies for bone metastasis in breast cancer. Journal of clinical medicine. 2013;2(4):176-187.

41. Hageman K, Patel KC, Mace K, et al. The role of Denosumab for prevention of skeletal-related complications in multiple myeloma. Annals of Pharmacotherapy. 2013;47(7-8):1069-1074.

42. Reed SD, Radeva JI, Glendenning GA, et al. Cost-effectiveness of Zoledronic acid for the prevention of skeletal complications in patients with prostate cancer. The Journal of urology. 2004;171(4):1537-1542.

43. McDougall JA, Bansal A, Goulart BH, et al. The clinical and economic impacts of skeletal-related events among medicare enrollees with prostate cancer metastatic to bone. The oncologist. 2016;21(3):320-326.

44. Cristino J, Finek J, Jandova P, et al. Cost-effectiveness of Denosumab versus Zoledronic acid for preventing skeletal-related events in the Czech Republic. Journal of medical economics. 2017;20(8):799-812.

45. Qian Y, Arellano J, Hauber AB, et al. Patient, caregiver, and nurse preferences for treatments for bone metastases from solid tumors. The Patient-Patient-Centered Outcomes Research. 2016;9(4):323-333.

46. Gatta F, Gonzalez JM, Ertugrul G, et al. Patients' and physicians' preferences for approaches to bone metastases treatment in Turkey. International Journal of Hematology and Oncology. 2015;27(4):118-129.

47. von Moos R, Body JJ, Egerdie B, et al. Pain and analgesic use associated with skeletal-related events in patients with advanced cancer and bone metastases. Supportive Care in Cancer. 2016;24(3):1327-1337.

48. Hadji P, Aapro M, Costa L, et al. Antiresorptive treatment options and bone health in cancer patients—safety profiles and clinical considerations. Cancer treatment reviews. 2012;38(6):815-824.

49. Clemons M, Dranitsaris G, Ooi W, et al. A Phase II trial evaluating the palliative benefit of second-line oral ibandronate in breast cancer patients with either a skeletal related event (SRE) or progressive bone metastases (BM) despite standard bisphosphonate (BP) therapy. Breast Cancer Research & Treatment. 2008;108(1):79-85.

50. Lewiecki E, Bilezikian J. Denosumab for the treatment of osteoporosis and cancer-related conditions. Clinical Pharmacology & Therapeutics. 2012;91(1):123-133.

51. Aapro MS, Coleman RE. Bone health management in patients with breast cancer: current standards and emerging strategies. The Breast. 2012;21(1):8-19.

52. von Moos R, Costa L, Ripamonti CI, et al. Improving quality of life in patients with advanced cancer: Targeting metastatic bone pain. European Journal of Cancer. 2017;71:80-94.