16 APPENDICES

APPENDIX 1 SEARCH STRATEGIES

CLINICAL EFFECTIVENESS

Ovid MEDLINE 1948 to March Week 5 2011

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

Ovid MEDLINE In-Process & Other Non-Indexed Citations April 08, 2011

1. (solid tumor or solid tumour* or cancer or carcinoma or myeloma).ti.
2. (bone adj2 metast*).tw.
3. (skeletal related event* or fracture*).tw.
4. or/2-3
5. 1 and 4
6. random*.tw.
7. randomized controlled trial.pt.
8. or/6-7
9. 5 and 8

Ovid Embase 1980 to March Week 5 2011

1. exp *DENOSUMAB/
2. *clodronic acid/ or *ibandronic acid/ or *pamidronic acid/ or *zoledronic acid/
3. (denosumab or bisphosphonate* or ibandron* or clodron* or pamidron* or zoledron*).tw.
4. (radiation or radiotherapy or radionuclide* or hormone therapy or strontium or samarium).ti.
5. or/1-4
6. (solid tumor or solid tumour* or cancer or carcinoma or myeloma).tw.
7. 5 and 6
8. exp *bone cancer/
9. ((bone or osteolytic or lytic) adj lesion*).tw.
10. (bone adj2 metast*).tw.
11. (skeletal or fracture*).tw.
12. or/8-11
13. 7 and 12

14. randomized controlled trial/
15. 13 and 14
16. limit 15 to english language

Cochrane Database of Systematic Reviews Issue 3 of 12, Mar 2011

Cochrane Central Register of ControlLed Trials (Central) Issue 1 of 4, Jan 2011

1. (denosumab or bisphosphonate* or ibandron* or clodron* or pamidron* or zoledron*):ti,ab,kw
2. (radiation or radiotherapy or radionuclide* or hormone therapy or strontium or samarium):ti
3. (solid tumor or solid tumour* or cancer or carcinoma or myeloma):ti,ab,kw
4. (#1 OR #2)
5. (#4 AND #3)
6. (bone or skeletal) near/1 metast*:ti,ab,kw
7. (osteoly* or lesion* or lytic) near/3 bone*:ti,ab,kw
8. (#6 OR #7)
9. (#5 AND #8)

Conference Proceedings

American Society of Clinical Oncology 2011 abstracts
http://abstract.asco.org/

American Urological Association's Annual Meeting 2011
http://www.aua2011.org/

ECONOMICS OR QUALITY OF LIFE OF BONE METASTASES AND SRES

Ovid MEDLINE 1948 to May Week 3 2011

1. "Costs and Cost Analysis"/
2. "cost of illness"/
3. exp Economics/
4. (pharmacoeconomic$ or pharmaco-economic$ or economic$ or cost-effective* or cost-benefit).tw.
5. exp Health Status/
6. exp "Quality of Life"/
7. quality-adjusted life years/
8. (health state* or health status).tw.
9. (qaly$ or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36).tw.
10. (markov or time trade off or standard gamble or hrql or hrqol or disabilit$).tw.
11. (quality adj2 life).tw.
12. (decision adj2 model).tw.
13. (utilit* adj3 (cost* or analys* or score* or health or value* or assessment*)).tw.
14. ((utilit* or preference) adj3 (weight* or score*)).tw.
15. or/1-14
16. ((skeletal or fracture or bone) and (malignan* or metastat* or cancer or carcinoma)).tw.
17. (spinal cord compression or hypercalc* or (surgery adj3 bone)).tw.
18. ((radiation or radiotherapy) adj3 bone).tw.
19. or/16-18
20. 15 and 19
21. limit 20 to english language

Embase 1980 to 2011 Week 21
Ovid MEDLINE In-Process & Other Non-Indexed Citations May 27, 2011
(pharmacoeconomic$ or pharmaco-economic$ or economic$).ti.

1. (health state* or health status).tw.
2. (qaly$ or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36).tw.
3. (markov or time trade off or standard gamble or hrql or hrqol or disabilit$).tw.
4. (quality adj2 life).tw.
5. (decision adj2 model).tw.
6. (utilit* adj3 (cost* or analys* or score* or health or value* or assessment*)).tw.
7. ((utilit* or preference) adj3 (weight* or score*)).tw.
8. (cost or costs).m_titl.
9. ((skeletal or fracture or bone) and (malignan* or metastat* or cancer or carcinoma)).ti
10. spinal cord compression or SRE or hypercalc* or (surgery adj3 bone)).ti.
11. ((radiation or radiotherapy) and bone).ti.
12. or/10-12
13. or/1-9
14. 13 and 14
15. limit 15 to english language

Science Citation Index – 1970 - present
Social Sciences Citation Index – 1970 - present
Conference Proceedings Citation Index – Science – 1990 - present
Conference Proceedings Citation Index – Social Science & Humanities – 1990 - present

1. Title=((skeletal or fracture or bone) and (malignan* or metastat* or cancer or carcinoma)) AND Title=(spinal cord compression or SRE or hypercalc* or surgery or radiation or radiotherapy)
2. Topic=(Pharmacoeconomic* or pharmaco-economic* or economic* or cost or costs or quality of life or health status or health utiliti*)
3. #1 and #2
4. Title=(Pharmacoeconomic* or pharmaco-economic* or economic* or cost or costs or quality of life or health status or health utiliti*) AND Topic=((skeletal or fracture or bone) and (malignan* or metastat* or cancer or carcinoma)) AND Topic=(spinal cord compression or SRE or hypercalc* or surgery or radiation or radiotherapy)
5. #3 or #4 Refined by: Languages=(ENGLISH)

ECONOMICS OF DENOSUMAB AND BISPHOSPHONATES

Ovid MEDLINE 1948 to May Week 3 2011

1. (denosumab or bisphosphonate* or ibandron* or clodron* or pamidron* or zoledron*).tw.
2. ((skeletal or fracture or bone) and (malignan* or metastat* or cancer or carcinoma)).tw.
3. 1 and 2
4. "Costs and Cost Analysis"/
5. "cost of illness"/
6. exp Economics/
7. (pharmacoeconomic$ or pharmaco-economic$ or economic$ or cost-effective* or cost-benefit).tw.
8. exp Health Status/
9. exp "Quality of Life"/
10. exp quality-adjusted life years/
11. health state* or health status).tw.
12. (qaly$ or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36).tw.

13. (markov or time trade off or standard gamble or hrql or hrqol or disabilit$).tw.
14. (quality adj2 life).tw.
15. (decision adj2 model).tw.
16. (utilit* adj3 (cost* or analys* or score* or health or value* or assessment*)).tw.
17. ((utilit* or preference) adj3 (weight* or score*)).tw.
18. or/4-17
19. 3 and 18
20. limit 19 to english language

Embase 1980 to 2011 Week 21
Ovid MEDLINE In-Process & Other Non-Indexed Citations June 02, 2011

1. (denosumab or bisphosphonate* or ibandron* or clodron* or pamidron* or zoledron*).tw.
2. ((skeletal or fracture or bone) and (malignan* or metastat* or cancer or carcinoma)).tw.
3. 1 and 2
4. (pharmacoeconomic$ or pharmaco-economic$ or economic$ or cost-effective* or cost-benefit).tw.
5. (health state* or health status).tw.
6. (qaly$ or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36).tw.
7. (markov or time trade off or standard gamble or hrql or hrqol or disabilit$).tw.
8. (quality adj2 life).tw.
9. (decision adj2 model).tw.
10. (utilit* adj3 (cost* or analys* or score* or health or value* or assessment*)).tw.
11. ((utilit* or preference) adj3 (weight* or score*)).tw.
12. or/4-11
13. 3 and 12
14. limit 13 to English language

NHS Economic Evaluation Database
Centre for Reviews and Dissemination
URL: http://www.york.ac.uk/inst/crd/

1. denosumab or bisphosphonate* or ibandron* or clodron* or pamidron* or zoledron*:TI

Science Citation Index – 1970 - present
Social Sciences Citation Index – 1970 - present
Conference Proceedings Citation Index – Science – 1990 - present
Conference Proceedings Citation Index – Social Science & Humanities – 1990 - present

1. Title=(denosumab or bisphosphonate* or ibandron* or clodron* or pamidron* or zoledron*) AND Title=(pharmacoeconomic* or pharmaco-economic* or economic* or cost* or quality of life or qaly* or EQ5D or EQ-5D or health utilit* or euroqol or euro-qol or SF-36 or SF36) NOT Title=(post-menopaus* or postmenopaus* or osteopor*)

Conference Proceedings

American Society of Clinical Oncology 2010 and 2011 abstracts
http://www.asco.org/ascov2/meetings/abstracts

SAFETY AND ADVERSE EVENTS

Ovid MEDLINE 1996 to June Week 3 2011

1. exp *Diphosphonates/ae [Adverse Effects]
2. exp *RANK Ligand/ae [Adverse Effects]
3. (denosumab or bisphosphonate* or ibandron* or clodron* or pamidron* or zoledron*).ti.
4. (risk or safety or adverse or harm or pharmacovigilance).ti.
5. (side-effect* or precaution* or warning* or contraindication* or contra-indication* or tolerability or toxic* or complication*).ti.
6. (osteonecrosis or ONJ or renal or hypocalc*).ti.
7. or/4-6
8. or/1-2
9. 3 and 8
10. 7 and 9
11. limit 10 to yr="2000 - 2011"

Ovid MEDLINE In-Process & Other Non-Indexed Citations June 28, 2011

1. (denosumab or bisphosphonate* or ibandron* or clodron* or pamidron* or zoledron*).ti.
2. (risk or safety or adverse or harm or pharmacovigilance).ti.
3. (side-effect* or precaution* or warning* or contraindication* or contra-indication* or tolerability or toxic* or complication*).ti.
4. (osteonecrosis or ONJ or renal or hypocalc*).ti.
5. or/2-4
6. 1 and 5

Embase 1996 to 2011 Week 25

1. exp *denosumab/ae [Adverse Drug Reaction]
2. exp *bisphosphonic acid derivative/ae [Adverse Drug Reaction]
3. (denosumab or bisphosphonate* or ibandron* or clodron* or pamidron* or zoledron*).ti.
4. (risk or safety or adverse or harm or pharmacovigilance).ti
5. (side-effect* or precaution* or warning* or contraindication* or contra-indication* or tolerability or toxic* or complication*).ti.
6. (osteonecrosis or ONJ or renal or hypocalc*).ti.
7. or/4-6
8. or/1-2
9. 3 and 8
10. 7 and 9
11. limit 10 to (english language and yr="2005 - 2011")

Science Citation Index – 1970 - present
Social Sciences Citation Index – 1970 - present
Arts & Humanities Citation Index – 1970 - present
Conference Proceedings Citation Index – Science – 1990 - present
Conference Proceedings Citation Index – Social Science & Humanities – 1990 – present

1. Title=(denosumab or bisphosphonate* or ibandron* or clodron* or pamidron* or zoledron*) AND Title=(osteonecrosis or ONJ or renal or hypocalc* or risk or safety or

adverse or side-effect*) AND Title=(cancer or carcinoma or metast* or malignant or complication*)
Refined by: Document Type=(MEETING ABSTRACT)
Timespan=2008-2011 – June 30th.

SYSTEMATIC REVIEWS OF DENOSUMAB AND BISPHOSPONATES FOR BONE METASTASES AND SKELETAL RELATED EVENTS

Ovid MEDLINE 2000 to 11th July 2011

1. (bone and metast*).ti.
2. bisphosphonate*.m_titl.
3. (metast* or cancer).tw.
4. 2 and 3
5. 1 or 4
6. "cochrane database of systematic reviews".jn.
7. (systematic review or meta-analysis).tw.
8. or/6-7
9. 5 and 8
10. limit 9 to english language
11. limit 10 to yr="2000 – 2011

APPENDIX 2 DATA EXTRACTION FORM

STUDY DETAILS

Name of the reviewer			
Study Details			
Name	**Duration of trial**	**Settings**	**Comparisons**
Name and year of the study			Intervention versus Comparators
Study aim:			
Study design:			
Dosing: **Dose of Intervention:** **Dose of Control:** **Dose of any other treatments:** **Intervention in both groups:**			
Definition of skeletal-related event:			
Methods of assessment of skeletal-related events during follow-up:			
Primary outcomes :			
Other outcomes:			
Follow-up:			
Safety data:			
Inclusion criteria:			
Exclusion criteria:			
Previous treatment			

PATIENT CHARACTERISTICS

No. of patients, n (%)	**Intervention (n=)**	**Control (n=)**
Screened		
Excluded		
Enrolled		
Randomised		
Excluded		
Efficacy analysis		
Safety analysis		
Discontinued		
Primary data analysis cutoff date		
Patient characteristics	**Intervention (n=)**	**Control (n=)**
Total patients, n		
Age (years)		
Sex (M/F), n (%)		
Ethnicity, n (%)		
White		
Other		
ECOG performance status 0-1, n (%)		
Time from diagnosis of prostate cancer to randomisation (months/years)		
Time from diagnosis of bone metastases to randomisation (months/years)		
Presence of visceral metastases, n (%)		
Recent chemotherapy, n (%)		
Haemoglobin concentration (g/L), mean (SD)		
Creatinine clearance of ≥1.5 mL/s, n (%)		
PSA at randomisation (µg/L)		
<10, n (%)		
≥10, n (%)		
Gleason score at diagnosis, n (%)		
2 to 6		
7		
8 to 10		
missing		

Bone turnover markers, median (IQR)		
Bone-specific alkaline phosphatase (µg/L)		
Urinary N-telopeptide (nmol/mmol)		
Previous skeletal-related events, n (%)		

QUALITY OF THE STUDY

Quality of the study	Details	Yes/No/Unclear
Adequate sequence generation		
Allocation concealment		
Blinding		
Incomplete outcome data addressed		
Free of selective reporting		
Generalisability		
Sample size calculation		
Conflict of interest		
Source of funding		

OUTCOMES AND SAFETY

	Intervention (n=)	**Control (n=)**	**Difference between groups (95% CI)**	**p value**
Time to first on-study skeletal-related events (in months/years)				
	Intervention (n=)	**Control (n=)**	**Difference between groups (95% CI)**	**p value**
Time to first and subsequent on-study skeletal- related events,				
number of events				
	Intervention (n=)	**Control (n=)**	**Difference between groups**	**p value**
Number of patients with first on-study skeletal-related events, n (%)				

Total confirmed events				
Radiation to bone				
Pathological fracture				
Spinal cord compression				
Surgery to bone				
	Intervention (n=)	**Control (n=)**	**Difference between groups**	**p value**
Overall survival rate				
	Intervention (n=)	**Control (n=)**		
Skeletal morbidity rate (the ratio of the number of skeletal complications to the time on trial)				
	Intervention (n=)	**Control (n=)**	**Difference between groups**	**p value**
Time to disease progression				
	Intervention (n=)	**Control (n=)**	**Difference between groups**	**p value**
Health-related quality of life				
	Intervention (n=)	**Control (n=)**	**Difference between groups**	**p value**
Any adverse events, n (%)				
Acute phase reactions, n (%)				
Adverse events associated with renal impairments, n (%)				
Withdrawals due to adverse events, n (%)				
Reasons for withdrawal				
Death				
Disease progression				
Consent withdrawn				
Adverse events				
Patient request				
Lost to follow up				

Noncompliance				
Administrative decision				
Protocol deviation				
Ineligibility determined				
Other				
	Intervention (n=)	**Control (n=)**	**Difference between groups**	**p value**
CTCAE grade 3 or 4 adverse events				
Adverse events occurring with ≥20% frequency in either treatment group, n (%)				
Back pain				
Pain in extremity				
Bone pain				
Arthralgia				
Asthenia				
Anaemia				
Decreased appetite				
Nausea				
Fatigue				
Constipation				
Peripheral oedema				
Infectious adverse events, n (%)				
Cumulative osteonecrosis of the jaw (total)				
year 1				
year 2				
Hypocalcaemia				
Serious adverse events				
Fatal adverse events				
New primary malignant disease				

APPENDIX 3 THE COCHRANE COLLABORATION'S TOOL FOR ASSESSING RISK OF BIAS

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.

Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

APPENDIX 4 LIST OF INCLUDED STUDIES

Breast cancer

A. Direct evidence reporting denosumab or contributing data to the NMA

Kohno 2005

Kohno N, Aogi K, Minami H, Nakamura S, Asaga T, Iino Y et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. *J Clin Oncol* 2005;**23**:3314-21.

Lipton 2000

Primary report

Lipton A, Theriault RL, Hortobagyi GN, Simeone J, Knight RD, Mellars K et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer* 2000;**88**:1082-90.

Secondary reports

Hortobagyi GN, Theriault RL, Porter L, Blayney D, Lipton A, Sinoff C et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *New England Journal of Medicine* 1996;**335**:1785-91.

Hortobagyi GN, Theriault RL, Lipton A, Porter L, Blayney D, Sinoff C et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. *J Clin Oncol* 1998;**16**:2038-44.

Theriault RL, Lipton A, Hortobagyi GN, Leff R, Gluck S, Stewart JF et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. *J Clin Oncol* 1999;**17**:846-54.

Rosen 2003a

Primary report

Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer* 2003;**98**:1735-44.

Secondary reports

Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer Journal* 2001;**7**:377-87.

Rosen LS, Gordon DH, Dugan W, Jr., Major P, Eisenberg PD, Provencher L et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer* 2004;**100**:36-43.

Stopeck 2010a

Primary report

Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* 2010;**28**:5132-9.

Secondary reports
Clinical study report 20050136

Fallowfield L, Patrick D, Body JJ, Lipton A, Tonkin KS, Qian Y et al. The Effect of Treatment With Denosumab or Zoledronic Acid on Health-Related Quality of Life in Patients With Metastatic Breast Cancer. *33rd Annual San Antiono Breast Cancer Symposium* 2010.

Fallowfield L, Patrick D, Body J, Lipton A, Tonkin KS, Qian Y et al. Effects of denosumab versus zoledronic acid (ZA) on health-related quality of life (HRQL) in metastatic breast cancer: Results from a randomized phase III trial. *J Clin Oncol* 2010;**28(Suppl)**:abstr 1025.

Martin M, Steger G, von Moos R, Stopeck A, de Boer R, Bourgeois H et al. Benefit of denosumab therapy in patients with bone metastases from breast cancer: A number-needed-to-treat (NNT) analysis. *Breast* 2011;**20**:S85.

Stopeck A, Martin M, Ritchie D, Body JJ, Paterson A, Viniegra M et al. Effect of denosumab versus zoledronic acid treatment in patients with breast cancer and bone metastases: Results from the extended blinded treatment phase. *33rd Annual San Antiono Breast Cancer Symposium* 2010.

Stopeck A, Fallowfield L, Patrick D, Cleeland CS, de Boer RH, Steger GG et al. Effects of denosumab versus zoledronic acid (ZA) on pain in patients (pts) with metastatic breast cancer: Results from a phase III clinical trial. *J Clin Oncol* 2010;**28(Suppl)**:abstr 1024.

Stopeck A, Fallowfield L, Patrick D, Cleeland CS, de Boer RH, Steger GG et al. Pain in patients (pts) with metastatic breast cancer: Results from a phase III trial of denosumab versus zoledronic acid (ZA). *33rd Annual San Antiono Breast Cancer Symposium* 2010.

Stopeck A, Lipton AA, Campbell-Baird C, von Moos R, Fan M, Haddock B et al. Acute-phase reactions following treatment with zoledronic acid or denosumab: Results from a randomized, controlled phase 3 study in patients with breast cancer and bone metastases. *33rd Annual San Antiono Breast Cancer Symposium* 2010.

Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH et al. Reply to V. Fusco et al. *J Clin Oncol* 2011;**29**:e523-e524.

B. Meeting inclusion criteria but not included in NMA

Body 2003
Primary report

Body JJ, Diel IJ, Lichinitser MR, Kreuser ED, Dornoff W, Gorbunova VA et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Annals of Oncology* 2003;**14**:1399-405.

Secondary report

Diel IJ, Body JJ, Lichinitser MR, Kreuser ED, Dornoff W, Gorbunova VA et al. Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. *European Journal of Cancer* 2004;**40**:1704-12.

Body JJ, Diel IJ, Lichinitzer M, Lazarev A, Pecherstorfer M, Bell R et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. *British Journal of Cancer* 2004;**90**:1133-7.

Body 2004

Body JJ, Diel IJ, Bell R, Pecherstorfer M, Lichinitser MR, Lazarev AF et al. Oral ibandronate improves bone pain and preserves quality of life in patients with skeletal metastases due to breast cancer. *Pain* 2004;**111**:306-12.

Secondary report

Tripathy D, Lichinitzer M, Lazarev A, MacLachlan SA, Apffelstaedt J, Budde M et al. Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomized, double-blind, placebo-controlled trial. *Annals of Oncology* 2004;**15**:743-50.

Elomaa 1988

Elomaa I, Blomqvist C, Porkka L, Holmström T, Taube T, Lamberg-Allardt C et al. Clodronate for osteolytic metastases due to breast cancer. *Biomedicine & pharmacotherapy = Biomédecine & pharmacothérapie* 1988;**42**:111-6.

Heras 2009

Heras P, Kritikos K, Hatzopoulos A, Georgopoulou AP. Efficacy of ibandronate for the treatment of skeletal events in patients with metastatic breast cancer. *European Journal of Cancer Care* 2009;**18**:653-6.

Kristensen 1999

Kristensen B, Ejlertsen B, Groenvold M, Hein S, Loft H, Mouridsen HT. Oral clodronate in breast cancer patients with bone metastases: a randomized study. *Journal of Internal Medicine* 1999;**246**:67-74.

Paterson 1993

Paterson AH, Powles TJ, Kanis JA, McCloskey E, Hanson J, Ashley S. Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. *J Clin Oncol* 1993;**11**:59-65.

Prostate cancer

A. Direct evidence reporting denosumab or contributing data to the NMA

Fizazi 2011

Primary report

Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L 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**:813-22.

Secondary reports

Brown JE, Cleeland CS, Fallowfield LJ, Patrick DL, Fizazi K, Smith MR et al. Pain Outcomes in Patients with Bone Metastases from Castrate-Resistant Prostate Cancer: Results from A Phase 3 Trial of Denosumab Vs. Zoledronic Acid. *European Urology Supplements* 2011;**10**:336.

Clinical study report 20050103

Miller K, Fizazi K, Smith M, Moroto JP, Klotz L, Brown J et al. Benefit of denosumab therapy in patients with bone metastases from castrate resistant prostate cancer: a number-needed-to-treat (NNT) analysis. *J Urol* 2011;**185**:e262.

Patrick D, Cleeland C, Fallowfield L, Smith MR, Trachtenberg J, Chilingirov P et al. Effects of denosumab and zoledronic acid on pain interference with daily functioning in patients with castrate-resistant prostate cancer. *J Urol* 2011;**185(Suppl)**:e286.

Shore ND, Smith MR, Jievaltas M, Fizazi K, Damiao R, Chin J et al. Effect of denosumab versus zoledronic acid in patients with castrate-resistant prostate cancer and bone metastases: Subgroup analyses by prior SRE and baseline pain. *J Clin Oncol* 2011;**29(Suppl)**:abstr 4533.

Saad 2002

Primary report

Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *Journal of the National Cancer Institute* 2002;**94** :1458-68.

Secondary reports

EMA report for Zoledronic acid

Saad F, Olsson C, Schulman CC. Skeletal morbidity in men with prostate cancer: quality-of-life considerations throughout the continuum of care. *European Urology* 2004;**46**:731-9.

Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *Journal of the National Cancer Institute* 2004;**96**:879-82.

Saad F. Clinical benefit of zoledronic acid for the prevention of skeletal complications in advanced prostate cancer. *Clinical Prostate Cancer* 2005;**4**:31-7.

Saad F, Chen YM, Gleason DM, Chin J. Continuing benefit of zoledronic acid in preventing skeletal complications in patients with bone metastases. *Clinical Genitourinary Cancer* 2007;**5**:390-6.

Saad F, Lipton A, Cook R, Chen YM, Smith M, Coleman R. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. *Cancer* 2007;**110**:1860-7.

Saad F, Eastham J. Zoledronic Acid improves clinical outcomes when administered before onset of bone pain in patients with prostate cancer. *Urology* 2010;**76**:1175-81.

Weinfurt KP, Anstrom KJ, Castel LD, Schulman KA, Saad F. Effect of zoledronic acid on pain associated with bone metastasis in patients with prostate cancer. *Annals of Oncology* 2006;**17**:986-9.

B. Meeting inclusion criteria but not included in NMA

Adami 1989

Primary report

Adami S, Mian M. Clodronate therapy of metastatic bone disease in patients with prostatic carcinoma. *Recent Results in Cancer Research* 1989;**116**:67-72.

Secondary report

Adami S, Salvagno G, Guarrera G. Dichloromethylene-diphosphonate in patients with prostatic carcinoma metastatic to the skeleton. *Journal of Urology* 1985;**134**:1152-4

Buchali 1988

Buchali K, Correns HJ, Schuerer M, Schnorr D, Lips H, Sydow K. Results of a double blind study of 89-strontium therapy of skeletal metastases of prostatic carcinoma. *European Journal of Nuclear Medicine* 1988;**14**:349-51.

Dearnaley2003

Dearnaley DP, Sydes MR, Mason MD, Stott M, Powell CS, Robinson AC et al. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). *Journal of the National Cancer Institute* 2003;**95**:1300-11.

Elomaa 1992

Elomaa I, Kylmala T, Tammela T, Viitanen J, Ottelin J, Ruutu M et al. Effect of oral clodronate on bone pain. A controlled study in patients with metastic prostatic cancer. *International Urology & Nephrology* 1992;**24**:159-66.

Ernst 2003

Ernst DS, Tannock IF, Winquist EW, Venner PM, Reyno L, Moore MJ et al. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. *J Clin Oncol* 2003;**21**:3335-42.

Kylmala 1993

Kylmala T, Tammela T, Risteli L, Risteli J, Taube T, Elomaa I. Evaluation of the effect of oral clodronate on skeletal metastases with type 1 collagen metabolites. A controlled trial of the Finnish Prostate Cancer Group. *European Journal of Cancer* 1993;**29A**:821-5.

Kylmala 1997
Kylmala T, Taube T, Tammela TL, Risteli L, Risteli J, Elomaa I. Concomitant i.v. and oral clodronate in the relief of bone pain--a double-blind placebo-controlled study in patients with prostate cancer. *Br J Cancer* 1997;**76**:939-42.

Nilsson 2005
Nilsson S, Strang P, Ginman C, Zimmermann R, Edgren M, Nordstrom B et al. Palliation of bone pain in prostate cancer using chemotherapy and strontium-89. A randomized phase II study. *Journal of Pain & Symptom Management* 2005;**29**:352-7.

Porter 1993
Porter AT, McEwan AJ, Powe JE, Reid R, McGowan DG, Lukka H et al. Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. *International Journal of Radiation Oncology, Biology, Physics* 1993;**25**:805-13.

Quilty 1994
Quilty PM, Kirk D, Bolger JJ, Dearnaley DP, Lewington VJ, Mason MD et al. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. *Radiotherapy & Oncology* 1994;**31**:33-40.

Small 2003
Small EJ, Smith MR, Seaman JJ, Petrone S, Kowalski MO. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol* 2003;**21**:4277-84.

Smith 1989
Smith JA, Jr. Palliation of painful bone metastases from prostate cancer using sodium etidronate: results of a randomized, prospective, double-blind, placebo-controlled study. *J Urol* 1989;**141**:85-7.

Strang 1997
Strang P, Nilsson S, Brandstedt S, Sehlin J, Borghede G, Varenhorst E et al. The analgesic efficacy of clodronate compared with placebo in patients with painful bone metastases from prostatic cancer. *Anticancer Research* 1997;**17**:4717-21.

Other solid tumours

A. Direct evidence reporting denosumab or contributing data to the NMA

Henry 2011
Primary report
Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J et al. Randomized, double-blind study of denosumab versus zoledronic Acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol* 2011;**29**:1125-32.

Secondary reports
Clinical study report 20050244

Henry DH, von Moos R, Hungria V, Costa L, Woll PJ, Scagliotti G et al. Delaying skeletal-related events in a randomized phase III study of denosumab versus zoledronic acid in patients with advanced cancer. *J Clin Oncol* 2010;**15(Suppl)**:abstr 9133.

von Moos R, Patrick D, Fallowfield L, Cleeland CS, Henry DH, Qian Y et al. Effects of denosumab versus zoledronic acid (ZA) on pain in patients (pts) with advanced cancer (excluding breast and prostate) or multiple myeloma (MM): Results from a randomized phase III clinical trial. *J Clin Oncol* 2010;**28(Suppl)**:abstr 9043.

Rosen 2003b

Primary report

Rosen LS, Gordon D, Tchekmedyian S, Yanagihara R, Hirsh V, Krzakowski M et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial--the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003;**21**:3150-7.

Secondary reports

Rosen LS, Gordon D, Tchekmedyian NS, Yanagihara R, Hirsh V, Krzakowski M et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. *Cancer* 2004;**100**:2613-21.

Schulman CC. Efficacy of zoledronic acid in the treatment of bone metastases secondary to renal cell carcinoma. *European Urology Supplements* 2004;**3**:40-5.

B. Meeting inclusion criteria but not included in NMA

Arican 1999

Arican A, Icli F, Akbulut H, Cakir M, Sencan O, Samur M et al. The effect of two different doses of oral clodronate on pain in patients with bone metastases. *Medical Oncology* 1999;**16**:204-10.

Berensen 2001

Berenson JR, Rosen LS, Howell A, Porter L, Coleman RE, Morley W et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases.[Erratum appears in Cancer 2001 May 15;91(10):1956]. *Cancer* 2001;**91**:1191-200.

Brown 2007

Brown JE, McCloskey EV, Dewar JA, Body JJ, Cameron DA, Harnett AN et al. The use of bone markers in a 6-week study to assess the efficacy of oral clodronate in patients with metastatic bone disease. *Calcified Tissue International* 2007;**81**:341-51.

Heras 2007

Heras R, I, Zubillaga R, I, Castrillo TM, Montalvo Moreno JJ. Osteonecrosis of the jaws and bisphosphonates. Report of fifteen cases. Therapeutic recommendations. *Medicina Oral, Patologia Oral y Cirugia Bucal* 2007;**12**:E267-E271.

Jagdev 2001

Jagdev SP, Purohit P, Heatley S, Herling C, Coleman RE. Comparison of the effects of intravenous pamidronate and oral clodronate on symptoms and bone resorption in patients with metastatic bone disease. *Annals of Oncology* 2001;**12**:1433-8.

Lipton 2003
Lipton A, Zheng M, Seaman J. Zoledronic acid delays the onset of skeletal-related events and progression of skeletal disease in patients with advanced renal cell carcinoma. *Cancer* 2003;**98**:962-9.

Mystakidou 2008
Mystakidou K, Stathopoulou E, Parpa E, Kouloulias V, Kouskouni E, Vlahos L. Oral versus intravenous ibandronic acid: a comparison of treatment options for metastatic bone disease. *Journal of Cancer Research & Clinical Oncology* 2008;**134**:1303-10.

O'Rourke 1995
O'Rourke N, McCloskey E, Houghton F, Huss H, Kanis JA. Double-blind, placebo-controlled, dose-response trial of oral clodronate in patients with bone metastases. *J Clin Oncol* 1995;**13**:929-34.

Piga 1998
Piga A, Bracci R, Ferretti B, Sandri P, Nortilli R, Acito L et al. A double blind randomized study of oral clodronate in the treatment of bone metastases from tumors poorly responsive to chemotherapy. *Journal of Experimental & Clinical Cancer Research* 1998;**17**:213-7.

Robertson 1995
Robertson AG, Reed NS, Ralston SH. Effect of oral clodronate on metastatic bone pain: a double-blind, placebo-controlled study. *J Clin Oncol* 1995;**13**:2427-30.

Zaghloul 2010
Zaghloul MS, Boutrus R, El-Hossieny H, Kader YA, El-Attar I, Nazmy M. A prospective, randomized, placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer. *International Journal of Clinical Oncology* 2010;**15**:382-9.

Zhao 2011
Zhao YY, Xue C, Hou X, Liao H, Li S, Zhao HY et al. Changes of bone resorption marker (NTX) in chemotherapy plus zoledronic acid versus chemotherapy alone for nasopharyngeal cancer patients with bone metastases. *European Journal of Cancer* 2011;**47**:848-53.

APPENDIX 5 LIST OF EXCLUDED STUDIES

Adjuvant use of drug

1. Robertson CN, Paulson DF. Radical surgery versus radiation therapy in early prostatic carcinoma. *Acta Oncologica* 1991;**30**:239-42.

2. Kanis JA, Powles T, Paterson AH, McCloskey EV, Ashley S. Clodronate decreases the frequency of skeletal metastases in women with breast cancer. *Bone* 1996;**19**:663-7.

3. Brincker H, Westin J, Abildgaard N, Gimsing P, Turesson I, Hedenus M et al. Failure of oral pamidronate to reduce skeletal morbidity in multiple myeloma: a double-blind placebo-controlled trial. Danish-Swedish co-operative study group. *British Journal of Haematology* 1998;**101**:280-6.

4. Saarto T, Blomqvist C, Virkkunen P, Elomaa I. Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial. *J Clin Oncol* 2001;**19**:10-7.

5. Powles T, Paterson S, Kanis JA, McCloskey E, Ashley S, Tidy A et al. Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. *J Clin Oncol* 2002;**20**:3219-24.

6. Atula S, Powles T, Paterson A, McCloskey E, Nevalainen J, Kanis J. Extended safety profile of oral clodronate after long-term use in primary breast cancer patients. *Drug Safety* 2003;**26**:661-71.

7. Saarto T, Vehmanen L, Virkkunen P, Blomqvist C. Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients. *Acta Oncologica* 2004;**43**:650-6.

8. Saarto T, Taube T, Blomqvist C, Vehmanen L, Elomaa I. Three-year oral clodronate treatment does not impair mineralization of newly formed bone--a histomorphometric study. *Calcified Tissue International* 2005;**77**:84-90.

9. Mystakidou K, Katsouda E, Parpa E, Kelekis A, Galanos A, Vlahos L. Randomized, open label, prospective study on the effect of zoledronic acid on the prevention of bone metastases in patients with recurrent solid tumors that did not present with bone metastases at baseline. *Medical Oncology* 2005;**22**:195-201.

10. Leppa S, Saarto T, Vehmanen L, Blomqvist C, Elomaa I. Clodronate treatment influences MMP-2 associated outcome in node positive breast cancer. *Breast Cancer Research & Treatment* 2005;**90**:117-25.

11. Powles T, Paterson A, McCloskey E, Schein P, Scheffler B, Tidy A et al. Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [ISRCTN83688026].[Erratum appears in Breast Cancer Res. 2006;8(3):406]. *Breast Cancer Research* 2006;**8**:R13.

12. Ellis GK, Bone HG, Chlebowski R, Paul D, Spadafora S, Smith J et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. *J Clin Oncol* 2008;**26**:4875-82.

13. Kristensen B, Ejlertsen B, Mouridsen HT, Jensen MB, Andersen J, Bjerregaard B et al. Bisphosphonate treatment in primary breast cancer: results from a randomised comparison of oral pamidronate versus no pamidronate in patients with primary breast cancer. *Acta Oncologica* 2008;**47**:740-6.

14. Ellis GK, Bone HG, Chlebowski R, Paul D, Spadafora S, Fan M et al. Effect of denosumab on bone mineral density in women receiving adjuvant aromatase inhibitors for non-metastatic breast cancer: subgroup analyses of a phase 3 study. *Breast Cancer Research & Treatment* 2009;**118**:81-7.

15. Gnant M. The evolving role of zoledronic acid in early breast cancer. *OncoTargets and therapy* 2009;**2**:95-104.

16. Dearnaley DP, Mason MD, Parmar MK, Sanders K, Sydes M. Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer: long-term overall survival results from the MRC PR04 and PR05 randomised controlled trials. *The Lancet Oncology* 2009;**10**:872-6.

17. McCloskey E, Paterson A, Kanis J, Tahtela R, Powles T. Effect of oral clodronate on bone mass, bone turnover and subsequent metastases in women with primary breast cancer. *European Journal of Cancer* 2010;**46**:558-65.

18. Kim SH, Lim SK, Hahn JS. Effect of pamidronate on new vertebral fractures and bone mineral density in patients with malignant lymphoma receiving chemotherapy. *American Journal of Medicine* 2004;**116**:524-8.

19. Gnant MF, Mlineritsch B, Luschin-Ebengreuth G, Grampp S, Kaessmann H, Schmid M et al. Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. *J Clin Oncol* 2007;**25**:820-8.

20. Hershman DL, McMahon DJ, Crew KD, Cremers S, Irani D, Cucchiara G et al. Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol* 2008;**26**:4739-45.

Comparing doses of radiotherapy

1. Roos DE, Turner SL, O'Brien PC, Smith JG, Spry NA, Burmeister BH et al. Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). *Radiotherapy & Oncology* 2005;**75**:54-63.

2. Madsen EL. Painful bone metastasis: efficacy of radiotherapy assessed by the patients: a randomized trial comparing 4 Gy X 6 versus 10 Gy X 2. *International Journal of Radiation Oncology, Biology, Physics* 1983;**9**:1775-9.

3. Jeremic B, Shibamoto Y, Acimovic L, Milicic B, Milisavljevic S, Nikolic N et al. A randomized trial of three single-dose radiation therapy regimens in the treatment of metastatic bone pain. *International Journal of Radiation Oncology, Biology, Physics* 1998;**42**:161-7.

4. Kaasa S, Brenne E, Lund JA, Fayers P, Falkmer U, Holmberg M et al. Prospective randomised multicenter trial on single fraction radiotherapy (8 Gy x 1) versus multiple fractions (3 Gy x 10) in the treatment of painful bone metastases. *Radiotherapy & Oncology* 2006;**79**:278-84.

5. Price P, Hoskin PJ, Easton D, Austin D, Palmer SG, Yarnold JR. Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiotherapy & Oncology* 1986;**6**:247-55.

6. Okawa T, Kita M, Goto M, Nishijima H, Miyaji N. Randomized prospective clinical study of small, large and twice-a-day fraction radiotherapy for painful bone metastases. *Radiotherapy & Oncology* 1988;**13**:99-104.

7. Cole DJ. A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. *Clinical Oncology (Royal College of Radiologists)* 1989;**1**:59-62.

8. Nielsen OS, Bentzen SM, Sandberg E, Gadeberg CC, Timothy AR. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. *Radiotherapy & Oncology* 1998;**47**:233-40.

9. Roos DE, O'Brien PC, Smith JG, Spry NA, Hoskin PJ, Burmeister BH et al. A role for radiotherapy in neuropathic bone pain: preliminary response rates from a prospective trial (Trans-tasman radiation oncology group, TROG 96.05).[Erratum appears in Int J Radiat Oncol Biol Phys 2000 May 1;47(2):545]. *International Journal of Radiation Oncology, Biology, Physics* 2000;**46**:975-81.

10. Ozsaran Z, Yalman D, Anacak Y, Esassolak M, Haydaroglu A. Palliative radiotherapy in bone metastases: Results of a randomized trial comparing three fractionation schedules. *Journal of B* 2001;**6**:43-8.

11. Sarkar SK, Sarkar S, Pahari B, Majumdar D. Multiple and single fraction palliative radiotherapy in bone secondaries - A prospective study. *Indian Journal of Radiology & Imaging* 2002;**12**:281-4.

12. van den Hout WB, van der Linden YM, Steenland E, Wiggenraad RG, Kievit J, de HH et al. Single- versus multiple-fraction radiotherapy in patients with painful bone metastases: cost-utility analysis based on a randomized trial. *Journal of the National Cancer Institute* 2003;**95**:222-9.

13. Badzio A, Senkus-Konefka E, Jereczek-Fossa BA, Adamska K, Fajndt S, Tesmer-Laskowska I et al. 20 Gy in five fractions versus 8 Gy in one fraction in palliative radiotherapy of bone metastases. A multicenter randomized study. *Nowotwory* 2003;**53**:261-4.

14. van der Linden YM, Lok JJ, Steenland E, Martijn H, van HH, Marijnen CA et al. Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. *International Journal of Radiation Oncology, Biology, Physics* 2004;**59**:528-37.

15. van der Linden YM, Steenland E, van Houwelingen HC, Post WJ, Oei B, Marijnen CA et al. Patients with a favourable prognosis are equally palliated with single and multiple

fraction radiotherapy: results on survival in the Dutch Bone Metastasis Study. *Radiotherapy & Oncology* 2006;**78**:245-53.

16. Manas A, Casas F, Ciria JP, Lopez C, Saez J, Palacios A et al. Randomised study of single dose (8 Gy vs. 6 Gy) of analgesic radiotherapy plus zoledronic acid in patients with bone metastases. *Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico* 2008;**10**:281-7.

17. Amouzegar-Hashemi F, Behrouzi H, Kazemian A, Zarpak B, Haddad P. Single versus multiple fractions of palliative radiotherapy for bone metastases: a randomized clinical trial in Iranian patients. *Current Oncology* 2008;**15**:36-9.

18. Maranzano E, Trippa F, Casale M, Costantini S, Lupattelli M, Bellavita R et al. 8Gy single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase III randomized multicentre Italian trial. *Radiotherapy & Oncology* 2009;**93**:174-9.

19. Meeuse JJ, van der Linden YM, van TG, Gans RO, Leer JW, Reyners AK et al. Efficacy of radiotherapy for painful bone metastases during the last 12 weeks of life: results from the Dutch Bone Metastasis Study. *Cancer* 2010;**116**:2716-25.

20. Atahan L, Yildiz F, Cengiz M, Kaplan B, Ozkan M, Yazici G et al. Zoledronic acid concurrent with either high- or reduced-dose palliative radiotherapy in the management of the breast cancer patients with bone metastases: a phase IV randomized clinical study. *Supportive Care in Cancer* 2010;**18**:691-8.

21. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. *Radiotherapy & Oncology* 1999;**52**:111-21.

22. Roos DE, Davis SR, Turner SL, O'Brien PC, Spry NA, Burmeister BH et al. Quality assurance experience with the randomized neuropathic bone pain trial (Trans-Tasman Radiation Oncology Group, 96.05). *Radiotherapy & Oncology* 2003;**67**:207-12.

23. Foro AP, Fontanals AV, Galceran JC, Lynd F, Latiesas XS, de Dios NR et al. Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. *Radiotherapy & Oncology* 2008;**89**:150-5.

Dose ranging study

1. Thurlimann B, Morant R, Jungi WF, Radziwill A. Pamidronate for pain control in patients with malignant osteolytic bone disease: a prospective dose-effect study. *Support Care Cancer* 1994;**2**:61-5.

2. Groff L, Zecca E, De CF, Brunelli C, Boffi R, Panzeri C et al. The role of disodium pamidronate in the management of bone pain due to malignancy. *Palliative Medicine* 2001;**15**:297-307.

3. Zhao X, Xu X, Guo L, Ragaz J, Guo H, Wu J et al. Biomarker alterations with metronomic use of low-dose zoledronic acid for breast cancer patients with bone metastases and potential clinical significance. *Breast Cancer Research & Treatment* 2010;**124**:733-43.

4. Wu JSY, Wong R, Johnston M, Bezjak A, Whelan T. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *International Journal of Radiation Oncology Biology Physics* 2003;**55**:594-605.

5. Daragon A, Peyron R, Serrurier D, Deshayes P. Treatment of hypercalcemia of malignancy with intravenous aminohydroxypropylidene bisphosphonate. Results of a stratified, double-blind, randomized two-month dose-response study. *Current Therapeutic Research - Clinical and Experimental* 1991;**50**:10-21.

6. Gallacher SJ. A comparison of low versus high dose pamidronate in cancer-associated hypercalcaemia. *Bone & Mineral* 1991;**15**:249-56.

7. Nussbaum SR, Younger J, Vandepol CJ, Gagel RF, Zubler MA, Chapman R et al. Single-dose intravenous therapy with pamidronate for the treatment of hypercalcemia of malignancy: comparison of 30-, 60-, and 90-mg dosages. *American Journal of Medicine* 1993;**95**:297-304.

8. Glover D, Lipton A, Keller A, Miller AA, Browning S, Fram RJ et al. Intravenous pamidronate disodium treatment of bone metastases in patients with breast cancer. A dose-seeking study. *Cancer* 1994;**74**:2949-55.

9. Vinholes J, Guo CY, Purohit OP, Eastell R, Coleman RE. Metabolic effects of pamidronate in patients with metastatic bone disease. *British Journal of Cancer* 1996;**73**:1089-95.

10. Coleman RE, Purohit OP, Vinholes JJ, Zekri J. High dose pamidronate: clinical and biochemical effects in metastatic bone disease. *Cancer* 1997;**80**:Suppl-90.

11. Cascinu S, Graziano F, Alessandroni P, Ligi M, Del FE, Rossi D et al. Different doses of pamidronate in patients with painful osteolytic bone metastases. *Supportive Care in Cancer* 1998;**6**:139-43.

12. Coleman RE, Purohit OP, Black C, Vinholes JJ, Schlosser K, Huss H et al. Double-blind, randomised, placebo-controlled, dose-finding study of oral ibandronate in patients with metastatic bone disease. *Annals of Oncology* 1999;**10**:311-6.

13. Koeberle D, Bacchus L, Thuerlimann B, Senn HJ. Pamidronate treatment in patients with malignant osteolytic bone disease and pain: a prospective randomized double-blind trial. *Supportive Care in Cancer* 1999;**7**:21-7.

14. Piffanelli A, Dafermou A, Giganti M, Colamussi P, Pizzocaro C, Bestagno M. Radionuclide therapy for painful bone metastases: An Italian multicentre observational study. *Quarterly Journal of Nuclear Medicine* 2001;**45**:100-7.

15. Lipton A, Steger GG, Figueroa J, Alvarado C, Solal-Celigny P, Body JJ 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**:4431-7.

16. Generali D, Dovio A, Tampellini M, Tucci M, Tedoldi S, Torta M et al. Changes of bone turnover markers and serum PTH after night or morning administration of zoledronic acid in breast cancer patients with bone metastases. *British Journal of Cancer* 2008;**98**:1753-8.

17. Satoh T, Kimura M, Matsumoto K, Tabata K, Okusa H, Bessho H et al. Single infusion of zoledronic acid to prevent androgen deprivation therapy-induced bone loss in men with hormone-naive prostate carcinoma. *Cancer* 2009;**115**:3468-74.

18. Fizazi K, Bosserman L, Gao G, Skacel T, Markus R. Denosumab treatment of prostate cancer with bone metastases and increased urine N-telopeptide levels after therapy with intravenous bisphosphonates: results of a randomized phase II trial. *J Urol* 2009;**182**:509-15.

19. Fizazi K, Lipton A, Mariette X, Body JJ, Rahim Y, Gralow JR 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**:1564-71.

20. Gimsing P, Carlson K, Turesson I, Fayers P, Waage A, Vangsted A et al. Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial. *Lancet Oncology* 2010;**11**:973-82.

21. Campbell-Baird C, Lipton A, Sarkeshik M, Ma H, Jun S. Incidence of acute phase adverse events following denosumab or intravenous bisphosphonates: Results from a randomized, controlled phase II study in patients with breast cancer and bone metastases. *Community Oncology* 2010;**7**:85-9.

Economic study

1. Laakso M, Lahtinen R, Virkkunen P, Elomaa I. Subgroup and cost-benefit analysis of the Finnish multicentre trial of clodronate in multiple myeloma. Finnish Leukaemia Group. *British Journal of Haematology* 1994;**87**:725-9.

2. Gessner U, Koeberle D, Thuerlimann B, Bacchus L, Horisberger B. Economic analysis of terminal care for patients with malignant osteolytic bone disease and pain treated with pamidronate. *Supportive Care in Cancer* 2000;**8**:115-22.

3. Dranitsaris G, Hsu T. Cost utility analysis of prophylactic pamidronate for the prevention of skeletal related events in patients with advanced breast cancer. *Supportive Care in Cancer* 1999; **7**:271-9.

4. Dranitsaris G. Pamidronate for the prevention of skeletal-related events in multiple myeloma. What does the public think it is worth? *International Journal of Technology Assessment in Health Care* 1999;**15**:108-22.

5. Hillner BE, Weeks JC, Desch CE, Smith TJ. Pamidronate in prevention of bone complications in metastatic breast cancer: A cost-effectiveness analysis. *J Clin Oncol* 2000;**18**:72-9.

6. Body J-J. Effectiveness and cost of bisphosphonate therapy in tumor bone disease. *Cancer* 2003;**97**:859-65.

7. Reed SD, Radeva JI, Glendenning GA, Saad F, Schulman KA. Cost-effectiveness of zoledronic acid for the prevention of skeletal complications in patients with prostate cancer. *J Urol* 2004;**171**:1537-42.

8. Reed SD, Radeva JI, Glendenning GA, Coleman RE, Schulman KA. Economic evaluation of zoledronic acid versus pamidronate for the prevention of skeletal-related events in metastatic breast cancer and multiple myeloma. *American Journal of Clinical Oncology: Cancer Clinical Trials* 2005;**28**:8-16.

9. Slof J, Badia X, Lizan L, Bautista FJ, Echarri E, Hurle ADG et al. Zoledronic acid versus pamidronate: Cost minimisation in bone metastasis. *Journal of Medical Economics* 2005;**8** :1-12.

10. Malmberg I, Persson U, Ask A, Tennvall J, Abrahamsson PA. Painful bone metastases in hormone-refractory prostate cancer: economic costs of strontium-89 and/or external radiotherapy. *Urology* 1997;**50**:747-53.

Multiple myeloma patient group

1. Kraj M, Poglod R, Maj S, Pawlikowski J, Sokolowska U, Szczepanik J. Long-term efficacy and safety of zoledronic acid compared with pamidronate in the treatment of myeloma bone disease. *Acta Haematologica Polonica* 2004;**35**:227-41.

2. Delmas PD, Charhon S, Chapuy MC, Vignon E, Briancon D, Edouard C et al. Long-term effects of dichloromethylene diphosphonate (CI2MDP) on skeletal lesions in multiple myeloma. *Metabolic Bone Disease & Related Research* 1982;**4**:163-8.

3. Lahtinen R, Laakso M, Palva I, Virkkunen P, Elomaa I. Randomised, placebo-controlled multicentre trial of clodronate in multiple myeloma. Finnish Leukaemia Group.[Erratum appears in Lancet 1992 Dec 5;340(8832):1420]. *Lancet* 1992;**340**:1049-52.

4. Heim ME, Clemens MR, Queisser W, Pecherstorfer M, Boewer C, Herold M et al. Prospective randomized trial of dichloromethylene bisphosphonate (clodronate) in patients with multiple myeloma requiring treatment. A multicenter study. *Onkologie* 1995;**18**:439-48.

5. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. *New England Journal of Medicine* 1996;**334**:488-93.

6. Berenson JR. Bisphosphonates in multiple myeloma. *Cancer* 1997;**80(Suppl)**:7.

7. McCloskey EV, MacLennan IC, Drayson MT, Chapman C, Dunn J, Kanis JA. A randomized trial of the effect of clodronate on skeletal morbidity in multiple myeloma. MRC Working Party on Leukaemia in Adults. *British Journal of Haematology* 1998;**100**:317-25.

8. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. *J Clin Oncol* 1998;**16**:593-602.

9. Terpos E, Palermos J, Tsionos K, Anargyrou K, Viniou N, Papassavas P et al. Effect of pamidronate administration on markers of bone turnover and disease activity in multiple myeloma. *European Journal of Haematology* 2000;**65**:331-6.

10. Fonseca R, Trendle MC, Leong T, Kyle RA, Oken MM, Kay NE et al. Prognostic value of serum markers of bone metabolism in untreated multiple myeloma patients. *British Journal of Haematology* 2000;**109**:24-9.

11. McCloskey EV, Dunn JA, Kanis JA, MacLennan IC, Drayson MT. Long-term follow-up of a prospective, double-blind, placebo-controlled randomized trial of clodronate in multiple myeloma. *British Journal of Haematology* 2001;**113**:1035-43.
12. Kraj M, Poglod R, Maj S, Pawlikowski J. The effects of 8-year pamidronate treatment on skeletal morbidity in patients with advanced multiple myeloma. *Nowotwory* 2004;**54**:570-7.

13. Aviles A, Nambo MJ, Neri N, Castaneda C, Cleto S, Huerta-Guzman J. Antitumor effect of zoledronic acid in previously untreated patients with multiple myeloma. *Medical Oncology* 2007;**24**:227-30.

14. Terpos E, Berenson J, Cook RJ, Lipton A, Coleman RE. Prognostic variables for survival and skeletal complications in patients with multiple myeloma osteolytic bone disease. *Leukemia* 2010;**24**:1043-9.

No relevant comparators

1. Mystakidou K, Katsouda E, Parpa E, Kouskouni E, Chondros C, Tsiatas ML et al. A prospective randomized controlled clinical trial of zoledronic acid for bone metastases. *American Journal of Hospice & Palliative Medicine* 2006;**23**:41-50.

2. Ausili-Cefaro G, Capirci C, Crivellari D, Fontana V, Mandoliti G, Olmi P et al. Radiation therapy vs radiation therapy + pamidronate (Aredia(™)) in elderly patients with breast cancer and lytic bone metastases: A GROG-GIOGer randomized clinical trial. *Rays* 1999;**24**:49-52.

3. Wang RF, Zhang CL, Zhu SL, Zhu M. A comparative study of samarium-153-ethylenediaminetetramethylene phosphonic acid with pamidronate disodium in the treatment of patients with painful metastatic bone cancer. *Medical Principles & Practice* 2003;**12**:97-101.

4. van der Linden YM, Dijkstra SP, Vonk EJ, Marijnen CA, Leer JW, Dutch Bone Metastasis Study Group. Prediction of survival in patients with metastases in the spinal column: results based on a randomized trial of radiotherapy. *Cancer* 2005;**103**:320-8.

5. Michaelson MD, Kaufman DS, Kantoff P, Oh WK, Smith MR. Randomized phase II study of atrasentan alone or in combination with zoledronic acid in men with metastatic prostate cancer. *Cancer* 2006;**107**:530-5.

6. Lipton A, Cook RJ, Major P, Smith MR, Coleman RE. Zoledronic acid and survival in breast cancer patients with bone metastases and elevated markers of osteoclast activity. *Oncologist* 2007;**12**:1035-43.

7. Lipton A, Steger GG, Figueroa J, Alvarado C, Solal-Celigny P, Body JJ et al. Extended efficacy and safety of denosumab in breast cancer patients with bone metastases not receiving prior bisphosphonate therapy. *Clinical Cancer Research* 2008;**14**:6690-6.

No relevant interventions

1. Lewington VJ, McEwan AJ, Ackery DM, Bayly RJ, Keeling DH, Macleod PM et al. A prospective, randomised double-blind crossover study to examine the efficacy of strontium-89 in pain palliation in patients with advanced prostate cancer metastatic to bone. *European Journal of Cancer* 1991;**27**:954-8.

2. Belch AR, Bergsagel DE, Wilson K, O'Reilly S, Wilson J, Sutton D et al. Effect of daily etidronate on the osteolysis of multiple myeloma. *J Clin Oncol* 1991;**9**:1397-402.
3. Porter AT, McEwan AJ. Strontium-89 as an adjuvant to external beam radiation improves pain relief and delays disease progression in advanced prostate cancer: results of a randomized controlled trial. *Seminars in Oncology* 1993;**20**:38-43.

4. Niewald M, Tkocz HJ, Abel U, Scheib T, Walter K, Nieder C et al. Rapid course radiation therapy vs. more standard treatment: a randomized trial for bone metastases. *International Journal of Radiation Oncology, Biology, Physics* 1996;**36**:1085-9.

5. Serafini AN, Houston SJ, Resche I, Quick DP, Grund FM, Ell PJ et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol* 1998;**16**:1574-81.

6. Pelger RC, Hamdy NA, Zwinderman AH, Nijeholt AA, Papapoulos SE. Effects of the bisphosphonate olpadronate in patients with carcinoma of the prostate metastatic to the skeleton. *Bone* 1998;**22**:403-8.

7. Sciuto R, Festa A, Pasqualoni R, Semprebene A, Rea S, Bergomi S et al. Metastatic bone pain palliation with 89-Sr and 186-Re-HEDP in breast cancer patients. *Breast Cancer Research & Treatment* 2001;**66**:101-9.

8. Oosterhof GO, Roberts JT, de Reijke TM, Engelholm SA, Horenblas S, von der MH et al. Strontium(89) chloride versus palliative local field radiotherapy in patients with hormonal escaped prostate cancer: a phase III study of the European Organisation for Research and Treatment of Cancer, Genitourinary Group. *European Urology* 2003;**44**:519-26.

9. Smeland S, Erikstein B, Aas M, Skovlund E, Hess SL, Fossa SD. Role of strontium-89 as adjuvant to palliative external beam radiotherapy is questionable: results of a double-blind randomized study. *International Journal of Radiation Oncology, Biology, Physics* 2003;**56**:1397-404.

10. Pistevou-Gompaki K, Kouloulias VE, Varveris C, Mystakidou K, Georgakopoulos G, Eleftheriadis N et al. Radiotherapy plus either transdermal fentanyl or paracetamol and codeine for painful bone metastases: a randomised study of pain relief and quality of life. *Current Medical Research & Opinion* 2004;**20**:159-63.

11. Wardley A, Davidson N, Barrett-Lee P, Hong A, Mansi J, Dodwell D et al. Zoledronic acid significantly improves pain scores and quality of life in breast cancer patients with bone metastases: a randomised, crossover study of community vs hospital bisphosphonate administration. *British Journal of Cancer* 2005;**92**:1869-76.

12. Harstell WF, Scott CB, Bruner DW, Scarantino CW, Ivker RA, Roach IM et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *Journal of the National Cancer Institute* 2005;**97**:798-804.

13. Clemons MJ, Dranitsaris G, Ooi WS, Yogendran G, Sukovic T, Wong BYL et al. Phase II trial evaluating the palliative benefit of second-line zoledronic acid in breast cancer

patients with either a skeletal-related event or progressive bone metastases despite first-line bisphosphonate therapy. *J Clin Oncol* 2006;**24**:4895-900.

14. Djabelek-Macias M, niewska I, Ochman M, odziejczyk A, Zebrowski J, Piwkowski P. The effects of radioisotope therapy and radiotherapy in subjects with breast cancer with bone metastases. *Nuclear medicine review Central & Eastern Europe : journal of Bulgarian, Czech, Macedonian, Polish, Romanian, Russian, Slovak, Yugoslav societies of nuclear medicine and Ukrainian Society of Radiology* 2006;**9**:138-43.
15. Hamouda WE, Roshdy W, Teema M. Single versus conventional fractionated radiotherapy in the palliation of painful bone metastases. *The gulf journal of oncology* 2007;**1**:35-41.

16. Elomaa I, Blomqvist C, Grohn P, Porkka L, Kairento AL, Selander K et al. Long-term controlled trial with diphosphonate in patients with osteolytic bone metastases. *Lancet* 1983;**1**:146-9.

17. Tian JH, Zhang JM, Hou QT, Oyang QH, Wang JM, Luan ZS et al. Multicentre trial on the efficacy and toxicity of single-dose samarium-153-ethylene diamine tetramethylene phosphonate as a palliative treatment for painful skeletal metastases in China. *European Journal of Nuclear Medicine* 1999;**26**:2-7.

18. Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood* 2006;**108**:3289-94.

No relevant outcomes

1. Coleman RE. Preliminary results of the use of urinary excretion of pyridinium crosslinks for monitoring metastatic bone disease. *British Journal of Cancer* 1992;**65**:766-8.

2. Pentikainen PJ, Elomaa I, Nurmi A-K, Karkkainen S. Pharmacokinetics of clodronate in patients with metastatic breast cancer. *International Journal of Clinical Pharmacology, Therapy, & Toxicology* 1989;**27**:223-8.

3. Cheung WK, Brunner L, Schoenfeld S, Knight R, Seaman J, Brox A et al. Pharmacokinetics of Pamidronate Disodium in Cancer Patients after a Single Intravenous Infusion of 30-, 60- or 90-mg Dose over 4 or 24 Hours. *Am J Ther* 1994;**1**:228-35.

4. Kylmälä T, Castrén-Kortekangas P, Seppänen J, Ylitalo P, Tammela TL. Effect of concomitant administration of clodronate and estramustine phosphate on their bioavailability in patients with metastasized prostate cancer. *Pharmacology & toxicology* 1996;**79**:157-60.

5. Schlosser K, Scigalla P. Biochemical markers as surrogates in clinical trials in patients with metastatic bone disease and osteoporosis. *Scandinavian Journal of Clinical & Laboratory Investigation Supplement* 1997;**227**:21-8.

6. Ylitalo P, Holli K, Monkkonen J, Elo HA, Juhakoski A, Liukko-Sipi S et al. Comparison of pharmacokinetics of clodronate after single and repeated doses. *International Journal of Clinical Pharmacology & Therapeutics* 1999;**37**:294-300.

7. Kanis JA, McCloskey EV, Powles T, Paterson AH, Ashley S, Spector T. A high incidence of vertebral fracture in women with breast cancer. *British Journal of Cancer* 1999;**79**:1179-81.

8. Chen T, Berenson J, Vescio R, Swift R, Gilchick A, Goodin S et al. Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *Journal of Clinical Pharmacology* 2002;**42**:1228-36.

9. Lyubimova NV, Kushlinsky NE, Lichinitser MR, Schlosser K. Renal safety of intravenous ibandronic Acid in breast cancer patients with metastatic bone disease. *Clinical Drug Investigation* 2003;**23**:707-16.

10. Weinfurt KP, Castel LD, Li Y, Timbie JW, Glendenning GA, Schulman KA. Health-related quality of life among patients with breast cancer receiving zoledronic acid or pamidronate disodium for metastatic bone lesions. *Medical Care* 2004;**42**:164-75.

11. Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA et al. The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. *Annals of Oncology* 2005;**16**:579-84.

12. Pecherstorfer M, Rivkin S, Body JJ, Diel I, Bergstrom B. Long-term safety of intravenous ibandronic acid for up to 4 years in metastatic breast cancer: an open-label trial. *Clinical Drug Investigation* 2006;**26**:315-22.

13. Body JJ, Diel IJ, Tripathy D, Bergstrom B. Intravenous ibandronate does not affect time to renal function deterioration in patients with skeletal metastases from breast cancer: phase III trial results. *European Journal of Cancer Care* 2006;**15**:299-302.

14. Cook RJ, Coleman R, Brown J, Lipton A, Major P, Hei YJ et al. Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. *Clinical Cancer Research* 2006;**12**:t-7.

15. Body JJ, Facon T, Coleman RE, Lipton A, Geurs F, Fan M et al. A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clinical Cancer Research* 2006;**12**:1221-8.

16. von Moos R, Caspar CB, Thurlimann B, Angst R, Inauen R, Greil R et al. Renal safety profiles of ibandronate 6 mg infused over 15 and 60 min: a randomized, open-label study. *Annals of Oncology* 2008;**19**:1266-70.

17. von Moos R, Caspar CB, Steiner R, Angst R, Inauen R, Schmieding K et al. Long-term renal safety profile of ibandronate 6 mg infused over 15 minutes. *Onkologie* 2010;**33**:447-50.

18. Markkula R, Repo H, Leirisalo M, Blomqvist C, Elomaa I. Effect of dichloromethylene diphosphonate (Cl2MDP) on immune function in breast cancer patients with bone metastases. *Cancer immunology, immunotherapy : CII* 1983;**15**:159-61.

19. Elomaa I, Blomqvist C, Porkka L, Lamberg-Allardt C, Borgström GH. Treatment of skeletal disease in breast cancer: a controlled clodronate trial. *Bone* 1987;**8 Suppl 1**:S53-S56.

20. Martinez ME, Pastrana P, Sanchez-Cabezudo MJ, Jariego C, Del Campo MT. Effect of clodronate on calcidiol serum levels in women with breast cancer. *Calcified Tissue International* 1997;**61**:148-50.

21. Smith MR, Cook RJ, Coleman R, Brown J, Lipton A, Major P et al. Predictors of skeletal complications in men with hormone-refractory metastatic prostate cancer. *Urology* 2007;**70**:315-9.

22. Body JJ, Lichinitser M, Tjulandin S, Garnero P, Bergstrom B. Oral ibandronate is as active as intravenous zoledronic acid for reducing bone turnover markers in women with breast cancer and bone metastases.[Erratum appears in Ann Oncol. 2008 Mar;19(3):601]. *Annals of Oncology* 2007;**18**:1165-71.

23. Hirsh V, Major PP, Lipton A, Cook RJ, Langer CJ, Smith MR et al. Zoledronic acid and survival in patients with metastatic bone disease from lung cancer and elevated markers of osteoclast activity. *Journal of Thoracic Oncology* 2008;**3**:228-36.

24. Jung A, Chantraine A, Donath A, van OC, Turnill D, Mermillod B et al. Use of dichloromethylene diphosphonate in metastatic bone disease. *New England Journal of Medicine* 1983;**308** :1499-501.

25. Conte N, Di VR, Da RG, Roiter I, Pavan P, Legovini P et al. Clodronate treatment increases serum osteocalcin in normocalcemic osteolytic bone metastases. *Oncology* 1991;**48**:54-7.

26. Redalieu E, Coleman JM, Chan K, Seaman J, Degen PH, Flesch G et al. Urinary excretion of aminohydroxypropylidene bisphosphonate in cancer patients after single intravenous infusions. *Journal of Pharmaceutical Sciences* 1993;**82**:665-7.

27. Clemens MR, Fessele K, Heim ME. Multiple myeloma: effect of daily dichloromethylene bisphosphonate on skeletal complications. *Annals of Hematology* 1993;**66**:141-6.

28. Vinholes JJ, Purohit OP, Abbey ME, Eastell R, Coleman RE. Relationships between biochemical and symptomatic response in a double-blind randomised trial of pamidronate for metastatic bone disease. *Annals of Oncology* 1997;**8**:1243-50.

29. Vinholes J, Coleman RE, Lacombe D, Rose C, Tubiana-Hulin M, Bastit P et al. Assessment of bone response to systemic therapy in an EORTC trial: Preliminary experience with the use of collagen cross-link excretion. *British Journal of Cancer* 1999;**80**:221-8.

30. Ryan CW, Huo D, Bylow K, Demers LM, Stadler WM, Henderson TO et al. Suppression of bone density loss and bone turnover in patients with hormone-sensitive prostate cancer and receiving zoledronic acid. *BJU International* 2007;**100**:70-5.

Not a relevant patient group

1. McLachlan SA, Cameron D, Murray R, Tripathy D, Bergstrom B. Safety of oral ibandronate in the treatment of bone metastases from breast cancer : long-term follow-up experience. *Clinical Drug Investigation* 2006;**26**:43-8.

2. Taube T, Kylmala T, Lamberg-Allardt C, Tammela TL, Elomaa I. The effect of clodronate on bone in metastatic prostate cancer. Histomorphometric report of a double-blind randomised placebo-controlled study. *European Journal of Cancer* 1994;**30A**:751-8.

3. Neskovi&#263, -Konstantinovi&#263, Z, Mitrovi&#263, L, Petrovi&#263 et al. Treatment of tumour-induced hypercalcaemia in advanced breast cancer patients with three different doses of disodium pamidronate adapted to the initial level of calcaemia. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 1995;**3**:422-4.
4. Teshima T, Inoue T, Inoue T, Ikeda H, Murayama S, Yamazaki H et al. Symptomatic relief for patients with osseous metastasis treated with radiation and methylprednisolone: a prospective randomized study. *Radiation Medicine* 1996;**14**:185-8.

5. Rizzoli R, Forni M, Schaad MA, Slosman DO, Sappino AP, Garcia J et al. Effects of oral clodronate on bone mineral density in patients with relapsing breast cancer. *Bone* 1996;**18**:531-7.

6. Elomaa I, Risteli L, Laakso M, Lahtinen R, Virkkunen P, Risteli J. Monitoring the action of clodronate with type I collagen metabolites in multiple myeloma. *European Journal of Cancer* 1996;**32A**:1166-70.

7. van Holten-Verzantvoort AT, Hermans J, Beex LV, Blijham G, Cleton FJ, van Eck-Smit BC et al. Does supportive pamidronate treatment prevent or delay the first manifestation of bone metastases in breast cancer patients? *European Journal of Cancer* 1996;**32A**:450-4.

8. Vinholes J, Guo CY, Purohit OP, Eastell R, Coleman RE. Evaluation of new bone resorption markers in a randomized comparison of pamidronate or clodronate for hypercalcemia of malignancy. *J Clin Oncol* 1997;**15**:131-8.

9. Diel IJ, Solomayer EF, Costa SD, Gollan C, Goerner R, Wallwiener D et al. Reduction in new metastases in breast cancer with adjuvant clodronate treatment. *New England Journal of Medicine* 1998;**339**:357-63.

10. Mardiak J, Bohunicky L, Chovanec J, Salek T, Koza I. Adjuvant clodronate therapy in patients with locally advanced breast cancer--long term results of a double blind randomized trial. Slovak Clodronate Collaborative Group. *Neoplasma* 2000;**47**:177-80.

11. Musto P, Falcone A, Sanpaolo G, Bodenizza C, Cascavilla N, Melillo L et al. Pamidronate reduces skeletal events but does not improve progression-free survival in early-stage untreated myeloma: results of a randomized trial. *Leukemia & Lymphoma* 2003;**44**:1545-8.

12. Theriault RL. Strategies to prevent chemotherapy-induced bone loss in women with breast cancer. *Clinical Breast Cancer* 2005;**5 Suppl**:S63-S70.

13. Fuleihan GEH, Salamoun M, Mourad YA, Chehal A, Salem Z, Mahfoud Z et al. Pamidronate in the prevention of chemotherapy-induced bone loss in premenopausal women with breast cancer: A randomized controlled trial. *Journal of Clinical Endocrinology and Metabolism* 2005;**90**:3209-14.

14. Mitsiades CS, Bogdanos J, Karamanolakis D, Milathianakis C, Dimopoulos T, Koutsilieris M. Randomized controlled clinical trial of a combination of somatostatin

analog and dexamethasone plus zoledronate vs. zoledronate in patients with androgen ablation-refractory prostate cancer. *Anticancer Research* 2006;**26**:3693-700.

15. Mason MD, Sydes MR, Glaholm J, Langley RE, Huddart RA, Sokal M et al. Oral sodium clodronate for nonmetastatic prostate cancer--results of a randomized double-blind placebo-controlled trial: Medical Research Council PR04 (ISRCTN61384873). *Journal of the National Cancer Institute* 2007;**99**:765-76.

16. Loblaw DA, Wu JS, Kirkbride P, Panzarella T, Smith K, Aslanidis J et al. Pain flare in patients with bone metastases after palliative radiotherapy--a nested randomized control trial. *Supportive Care in Cancer* 2007;**15**:451-5.
17. Brufsky A, Harker WG, Beck JT, Carroll R, Tan-Chiu E, Seidler C et al. Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol* 2007;**25**:829-36.

18. Brufsky AM. Managing bone loss in women with early-stage breast cancer receiving aromatase inhibitors. *Clinical Breast Cancer* 2007;**8**:S22-S34.

19. Diel IJ, Jaschke A, Solomayer EF, Gollan C, Bastert G, Sohn C et al. Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow: a long-term follow-up. *Annals of Oncology* 2008;**19**:2007-11.

20. Lester JE, Dodwell D, Purohit OP, Gutcher SA, Ellis SP, Thorpe R et al. Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer. *Clinical Cancer Research* 2008;**14**:6336-42.

21. Musto P, Petrucci MT, Bringhen S, Guglielmelli T, Caravita T, Bongarzoni V et al. A multicenter, randomized clinical trial comparing zoledronic acid versus observation in patients with asymptomatic myeloma.[Erratum appears in Cancer. 2008 Nov 15;113(10):2835]. *Cancer* 2008;**113**:1588-95.

22. Brufsky A, Bundred N, Coleman R, Lambert-Falls R, Mena R, Hadji P et al. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist* 2008;**13**:503-14.

23. Bundred NJ, Campbell ID, Davidson N, DeBoer RH, Eidtmann H, Monnier A et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results. *Cancer* 2008;**112**:1001-10.

24. Brufsky AM, Bosserman LD, Caradonna RR, Haley BB, Jones CM, Moore HC et al. Zoledronic acid effectively prevents aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST study 36-month follow-up results. *Clinical Breast Cancer* 2009;**9**:77-85.

25. Eidtmann H, de BR, Bundred N, Llombart-Cussac A, Davidson N, Neven P et al. Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study. *Annals of Oncology* 2010;**21**:2188-94.

26. Morgan GJ, Davies FE, Gregory WM, Cocks K, Bell SE, Szubert AJ et al. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. *Lancet* 2010;**376**:1989-99.

Not a required dose used

1. van Holten-Verzantvoort AT, Bijvoet OL, Cleton FJ, Hermans J, Kroon HM, Harinck HI et al. Reduced morbidity from skeletal metastases in breast cancer patients during long-term bisphosphonate (APD) treatment. *Lancet* 1987;**2**:983-5.

2. Canfield RE, Siris ES, Jacobs TP. Dichloromethylene diphosphonate action in hematologic and other malignancies. *Bone* 1987;**8 Suppl 1**:S57-S62.

3. Cleton FJ, van Holten-Verzantvoort AT, Bijvoet OL. Effect of long-term bisphosphonate treatment on morbidity due to bone metastases in breast cancer patients. *Recent Results in Cancer Research* 1989;**116**:73-8.

4. Dodwell DJ, Howell A, Ford J. Reduction in calcium excretion in women with breast cancer and bone metastases using the oral bisphosphonate pamidronate. *British Journal of Cancer* 1990;**61**:123-5.

5. van Holten-Verzantvoort AT, Zwinderman AH, Aaronson NK, Hermans J, van EB, van Dam FS et al. The effect of supportive pamidronate treatment on aspects of quality of life of patients with advanced breast cancer. *European Journal of Cancer* 1991;**27**:544-9.

6. Martoni A, Guaraldi M, Camera P, Biagi R, Marri S, Beghe F et al. Controlled clinical study on the use of dichloromethylene diphosphonate in patients with breast carcinoma metastasizing to the skeleton. *Oncology* 1991;**48**:97-101.

7. Francini G, Gonnelli S, Petrioli R, Conti F, Paffetti P, Gennari C. Treatment of bone metastases with dichloromethylene bisphosphonate. *J Clin Oncol* 1992;**10**:591-8.

8. van Holten-Verzantvoort AT, Kroon HM, Bijvoet OL, Cleton FJ, Beex LV, Blijham G et al. Palliative pamidronate treatment in patients with bone metastases from breast cancer. *J Clin Oncol* 1993;**11**:491-8.

9. Conte PF, Giannessi PG, Latreille J, Mauriac L, Koliren L, Calabresi F et al. Delayed progression of bone metastases with pamidronate therapy in breast cancer patients: a randomized, multicenter phase III trial. *Annals of Oncology* 1994;**5**:Suppl-4.

10. Conte PF, Latreille J, Mauriac L, Calabresi F, Santos R, Campos D et al. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. The Aredia Multinational Cooperative Group. *J Clin Oncol* 1996;**14**:2552-9.

11. Giordani S, Sapio A, De PA, Mariano P, Versari R, Romano D. A randomized study on 'prophilactic' use of disodium pamidronate in breast cancer patients (bcps) with bone metastasis at high risk (HR) of complication: The experience of an 'oncological hospital at home' (OHH). *Annals of Oncology* 1996;**7(Suppl 5)**:24.

12. Ernst DS, Brasher P, Hagen N, Paterson AH, MacDonald RN, Bruera E. A randomized, controlled trial of intravenous clodronate in patients with metastatic bone disease and pain. *Journal of Pain & Symptom Management* 1997;**13**:319-26.

13. Coleman RE, Houston S, Purohit OP, Rubens RD, Kandra A, Ford J. A randomised phase II study of oral pamidronate for the treatment of bone metastases from breast cancer. *European Journal of Cancer* 1998;**34**:820-4.

14. Hultborn R, Gundersen S, Ryden S, Holmberg E, Carstensen J, Wallgren UB et al. Efficacy of pamidronate in breast cancer with bone metastases: a randomized, double-blind placebo-controlled multicenter study. *Anticancer Res* 1999;**19**:3383-92.

15. Kraj M, Poglod R, Pawlikowski J, Maj S, Nasilowska B. Effect of pamidronate on skeletal morbidity in myelomatosis. Part 1. The results of the first 12 months of pamidronate therapy. *Acta Poloniae Pharmaceutica* 2000;**57**:113-6.

16. Menssen HD, Sakalova A, Fontana A, Herrmann Z, Boewer C, Facon T et al. Effects of long-term intravenous ibandronate therapy on skeletal-related events, survival, and bone resorption markers in patients with advanced multiple myeloma. *J Clin Oncol* 2002;**20**:2353-9.

17. Terpos E, Viniou N, de la Fuente J, Meletis J, Voskaridou E, Karkantaris C et al. Pamidronate is superior to ibandronate in decreasing bone resorption, interleukin-6 and beta 2-microglobulin in multiple myeloma. *European Journal of Haematology* 2003;**70**:34-42.

Non-RCTs - reviews

1. Awan AM, Weichselbaum RR. Palliative radiotherapy. [Review] [34 refs]. *Hematology - Oncology Clinics of North America* 1990;**4**:1169-81.

2. Delmas PD. The use of clodronate in multiple myeloma. [Review] [14 refs]. *Bone* 1991;**12**:Suppl-4.

3. Paterson AH, Ernst DS, Powles TJ, Ashley S, McCloskey EV, Kanis JA. Treatment of skeletal disease in breast cancer with clodronate. [Review] [32 refs]. *Bone* 1991;**12**:Suppl-30.

4. Clarke NW, McClure J, George NJ. Disodium pamidronate identifies differential osteoclastic bone resorption in metastatic prostate cancer. *British Journal of Urology* 1992;**69**:64-70.

5. Burgers JM. Experience of the EORTC Radiotherapy/Chemotherapy Group in osteosarcoma trials. [Review] [6 refs]. *Cancer Treatment & Research* 1993;**62**:173-5.

6. Porter AT. Strontium-89 (Metastron) in the treatment of prostate cancer metastatic to bone. *European Urology* 1994;**26**:20-5.

7. Bos SD. An overview of current clinical experience with strontium-89 (Metastron). *Prostate* 1994;**24** :23-6.

8. Hoskin PJ. Radiotherapy in the management of bone pain. *Clinical Orthopaedics and Related Research* 1995;105-19.

9. Harvey HA, Lipton A. The role of bisphosphonates in the treatment of bone metastases--the U.S. experience. *Supportive Care in Cancer* 1996;**4**:213-7.

10. Diener KM. Bisphosphonates for controlling pain from metastatic bone disease. *American Journal of Health-System Pharmacy* 1996;**53**:1917-27.

11. Gaze MN, Kelly CG, Kerr GR, Cull A, Cowie VJ, Gregor A et al. Pain relief and quality of life following radiotherapy for bone metastases: a randomised trial of two fractionation schedules. [Review] [19 refs]. *Radiotherapy & Oncology* 1997;**45**:109-16.

12. Adami S. Bisphosphonates in prostate carcinoma. *Cancer* 1997;**80**:1674-9.

13. Lipton A. Bisphosphonates and breast carcinoma. *Cancer* 1997;**80**:1668-73.

14. Berenson JR. The efficacy of pamidronate disodium in the treatment of osteolytic lesions and bone pain in multiple myeloma. *Reviews in Contemporary Pharmacotherapy* 1998;**9**:195-203.
15. Paterson AHG. The emerging role of bisphosphonates in the prevention of bone metastases. *Trends in Endocrinology and Metabolism* 1999;**10**:24-9.

16. Yoneda T, Michigami T, Yi B, Williams PJ, Niewolna M, Hiraga T. Use of bisphosphonates for the treatment of bone metastasis in experimental animal models [Review] [38 refs]. *Cancer Treatment Reviews* 1999;**25**:293-9.

17. Serafini AN. Samarium Sm-153 lexidronam for the palliation of bone pain associated with metastases. [Review] [17 refs]. *Cancer* 2000;**88**:Suppl-9.

18. Ripamonti C, Fulfaro F. Malignant bone pain: pathophysiology and treatments. *Current review of pain* 2000;**4**:187-96.

19. Berenson JR. Myeloma - The therapeutic challenge. *Medizinische Klinik* 2000;**95**:19-21.

20. Major PP, Coleman RE. Zoledronic acid in the treatment of hypercalcemia of malignancy: results of the international clinical development program. [Review] [30 refs]. *Seminars in Oncology* 2001;**28**:Suppl-24.

21. Coleman RE, Seaman JJ. The role of zoledronic acid in cancer: clinical studies in the treatment and prevention of bone metastases. [Review] [36 refs]. *Seminars in Oncology* 2001;**28**:Suppl-6.

22. Djulbegovic B, Wheatley K, Ross J, Clark O, Bos G, Goldschmidt H et al. Bisphosphonates in multiple myeloma. *Cochrane database of systematic reviews (Online)* 2001;CD003188.

23. Gralow JR. The role of bisphosphonates as adjuvant therapy for breast cancer. *Current oncology reports* 2001;**3**:506-15.

24. Jeremic B. Single fraction external beam radiation therapy in the treatment of localized metastatic bone pain. A review. *Journal of Pain and Symptom Management* 2001;**22**:1048-58.

25. Coleman RE. Efficacy of zoledronic acid and pamidronate in breast cancer patients: a comparative analysis of randomized phase III trials. *American Journal of Clinical Oncology* 2002;**25**:Suppl-31.

26. Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane database of systematic reviews (Online)* 2002;CD002068.

27. Pavlakis N, Stockler M. Bisphosphonates for breast cancer. *Cochrane database of systematic reviews (Online)* 2002;CD003474.

28. Saad F. Zoledronic acid significantly reduces pathologic fractures in patients with advanced-stage prostate cancer metastatic to bone. *Clinical Prostate Cancer* 2002;**1**:145-52.

29. Lipton A, Small E, Saad F, Gleason D, Gordon D, Smith M et al. The new bisphosphonate, Zometa (zoledronic acid), decreases skeletal complications in both osteolytic and osteoblastic lesions: A comparison to pamidronate. *Cancer Investigation* 2002;**20**:45-54.

30. Jantunen E. Bisphosphonate therapy in multiple myeloma: Past, present, future. *European Journal of Haematology* 2002;**69**:257-64.
31. Hotte SJ, Webert KE, Major PP. Zoledronic acid: An overview of its current and potential benefits in patients with malignancy. *Today's Therapeutic Trends* 2002;**20**:197-219.

32. Rosen LS. Efficacy and safety of zoledronic acid in the treatment of bone metastases associated with lung cancer and other solid tumors. *Seminars in Oncology* 2002;**29**:28-32.

33. Ibrahim A, Scher N, Williams G, Sridhara R, Li N, Chen G et al. Approval summary for zoledronic acid for treatment of multiple myeloma and cancer bone metastases. *Clinical Cancer Research* 2003;**9**:2394-9.

34. Heffner J, Lonial S. Breakthroughs in the management of multiple myeloma. *Drugs* 2003;**63**:1621-36.

35. Kirby RS. Zoledronic acid: A new advance in managing skeletal events in prostate cancer. *BJU International* 2003;**91**:464-5.

36. Kumar A, Loughran T, Alsina M, Durie BGM, Djulbegovic B. Management of multiple myeloma: A systematic review and critical appraisal of published studies. *Lancet Oncology* 2003;**4**:293-304.

37. Lipton A, Colombo-Berra A, Bukowski RM, Rosen L, Zheng M, Urbanowitz G. Skeletal complications in patients with bone metastases from renal cell carcinoma and therapeutic benefits of zoledronic acid. [Review] [25 refs]. *Clinical Cancer Research* 2004;**10**:6397s-403S.

38. Dando TM, Wiseman LR. Clodronate: A review of its use in the prevention of bone metastases and the management of skeletal complications associated with bone metastases in patients with breast cancer. *Drugs and Aging* 2004;**21**:949-62.

39. Tripathy D. Oral daily ibandronate: An effective and convenient therapy for skeletal complications in metastatic breast cancer. *European Journal of Cancer, Supplement* 2004;**2**:17-20.

40. Diel IJ. Ibandronate: A well-tolerated intravenous and oral treatment for metastatic bone disease. *European Journal of Cancer, Supplement* 2004;**2**:13-6.

41. Saad F, Schulman CC. Role of Bisphosphonates in Prostate Cancer. *European Urology* 2004;**45**:26-34.

42. Gralow J. Evolving role of bisphosphonates in women undergoing treatment for localized and advanced breast cancer. *Clinical Breast Cancer* 2005;**5 Suppl**:S54-S62.

43. Michaelson MD, Smith MR. Bisphosphonates for treatment and prevention of bone metastases. *J Clin Oncol* 2005;**23**:8219-24.

44. Saad F, Lipton A. Zoledronic acid is effective in preventing and delaying skeletal events in patients with bone metastases secondary to genitourinary cancers. *BJU International* 2005;**96**:964-9.

45. Burkinshaw R, Coleman R. Bisphosphonates as adjuvant therapy for breast cancer. *Women's health* 2006;**2**:115-26.

46. Berry S, Waldron T, Winquist E, Lukka H. The use of bisphosphonates in men with hormone-refractory prostate cancer: a systematic review of randomized trials. *The Canadian journal of urology* 2006;**13**:3180-8.

47. Cameron D, Fallon M, Diel I. Ibandronate: its role in metastatic breast cancer. *The oncologist* 2006;**11 Suppl 1**:-33.

48. Yuen KK, Shelley M, Sze WM, Wilt T, Mason MD. Bisphosphonates for advanced prostate cancer. *Cochrane database of systematic reviews (Online)* 2006;CD006250.

49. Body J-J. Bisphosphonates in advanced malignant disease. *Clinical Reviews in Bone and Mineral Metabolism* 2007;**5**:172-7.

50. Burkinshaw R, Thorpe H, Coleman R. Bisphosphonates and prevention of metastases: The AZURE study. *Breast Cancer Online* 2007;**10**:

51. Coleman RE. Emerging Strategies in Bone Health Management for the Adjuvant Patient. *Seminars in Oncology* 2007; **34**:S11-S16.

52. Saad F. Should patients with prostate cancer without bone metastases receive sodium clodronate? Commentary. *Nature Clinical Practice Urology* 2007;**4**:584-5.

53. Wu S, Dahut WL, Gulley JL. The use of bisphosphonates in cancer patients. *Acta Oncologica* 2007;**46**:581-91.

54. Coleman R. Potential use of bisphosphonates in the prevention of metastases in early-stage breast cancer. *Clinical Breast Cancer* 2007;**7**:S29-S35.

55. Lipton A. Efficacy and safety of intravenous bisphosphonates in patients with bone metastases caused by metastatic breast cancer. *Clinical Breast Cancer* 2007;**7**:S14-S20.

56. Luftner D, Henschke P, Possinger K. Clinical value of bisphosphonates in cancer therapy. *Anticancer Research* 2007;**27**:1759-68.

57. Saad F, Sternberg CN. Multidisciplinary management of bone complications in prostate cancer and optimizing outcomes of bisphosphonate therapy. *Nature Clinical Practice Urology* 2007;**4**:S3-S13.

58. Hussein MA. Multiple myeloma: Most common end-organ damage and management. *JNCCN Journal of the National Comprehensive Cancer Network* 2007;**5**:170-8.

59. Lipton A. Treatment of bone metastases and bone pain with bisphosphonates. *Supportive Cancer Therapy* 2007;**4**:92-100.

60. Brandao CMR, Lima MG, Da Silva AL, Silva GD, Guerra J, De Assis AF. Treatment of postmenopausal osteoporosis in women: A systematic review. *Cadernos de Saude Publica* 2008;**24**:S592-S606.

61. Dhillon S, Lyseng-Williamson KA. Zoledronic acid: A review of its use in the management of bone metastases of malignancy. *Drugs* 2008;**68**:507-34.

62. Burkiewicz JS, Scarpace SL, Bruce SP. Denosumab in osteoporosis and oncology. *Annals of Pharmacotherapy* 2009;**43**:1445-55.

63. Husaini D, Wheatley-Price D, Clemons D, Shepherd FA. Prevention and management of bone metastases in lung cancer a review. *Journal of Thoracic Oncology* 2009;**4**:251-9.

64. Miller K, Stenzl A, Tombal B. Advances in the Therapy of Prostate Cancer-Induced Bone Disease: Current Insights and Future Perspectives on the RANK/RANKL Pathways. *European Urology, Supplements* 2009;**8**:747-52.

65. Machado M, Cruz LS, Tannus G, Fonseca M. Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: A meta-analysis of randomized clinical trials. *Clinical Therapeutics* 2009;**31**:962-79.

66. Mhaskar R, Redzepovic J, Wheatley K, Clark OA, Miladinovic B, Glasmacher A et al. Bisphosphonates in multiple myeloma. *Cochrane database of systematic reviews (Online)* 2010;**3**:

67. Diel IJ. Bisphosphonates in breast cancer patients with bone metastases. *Breast Care* 2010;**5**:306-11.

68. Silver DS. Denosumab reduces the incidence of new vertebral fractures in men with prostate cancer. *Current Osteoporosis Reports* 2010;**8**:1-3.

69. Coleman R. The use of bisphosphonates in cancer treatment. *Annals of the New York Academy of Sciences* 2011;**1218**:3-14.

Non-RCTs – other study design

1. Ernst DS, MacDonald RN, Paterson AH, Jensen J, Brasher P, Bruera E. A double-blind, crossover trial of intravenous clodronate in metastatic bone pain. *Journal of Pain & Symptom Management* 1992;**7**:4-11.

2. Lipton A, Glover D, Harvey H, Grabelsky S, Zelenakas K, Macerata R et al. Pamidronate in the treatment of bone metastases: results of 2 dose-ranging trials in patients with breast or prostate cancer. *Annals of Oncology* 1994;**5**:Suppl-5.

3. Bayouth JE, Macey DJ, Kasi LP, Fossella FV. Dosimetry and toxicity of samarium-153-EDTMP administered for bone pain due to skeletal metastases. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 1994;**35**:63-9.

4. Pelliniemi TT, Irjala K, Mattila K, Pulkki K, Rajamaki A, Tienhaara A et al. Immunoreactive interleukin-6 and acute phase proteins as prognostic factors in multiple myeloma. Finnish Leukemia Group. *Blood* 1995;**85**:765-71.

5. Phillips KA, Urch M, Bishop JF. Radiation-recall dermatitis in a patient treated with paclitaxel. *J Clin Oncol* 1995;**13**:305.

6. Seaman E, Goluboff ET, Ross S, Sawczuk IS. Association of radionuclide bone scan and serum alkaline phosphatase in patients with metastatic renal cell carcinoma. *Urology* 1996;**48**:692-5.

7. Fernandez-Conde M, Alcover J, Aaron JE, Ordi J, Carretero P. Skeletal response to clodronate in prostate cancer with bone metastases. *American Journal of Clinical Oncology* 1997;**20**:471-6.

8. Kraj M, Poglod R, Maj S, Pawlikowski J, Sokolowska U, Szczepanik J. Comparative evaluation of safety and efficacy of pamidronate and zoledronic acid in multiple myeloma patients (single center experience). *Acta Poloniae Pharmaceutica* 2002;**59**:478-82.

9. Berenson JR, Hillner BE, Kyle RA, Anderson K, Lipton A, Yee GC et al. American society of clinical oncology clinical practice guidelines: The role of bisphosphonates in multiple myeloma. *J Clin Oncol* 2002;**20**:3719-36.

10. Maxwell C, Swift R, Goode M, Doane L, Rogers M. Advances in supportive care of patients with cancer and bone metastases: nursing implications of zoledronic acid. *Clinical journal of oncology nursing* 2003;**7**:403-8.

11. Plunkett TA, Rubens RD. Bisphosphonate therapy for patients with breast carcinoma: Who to treat and when to stop. *Cancer* 2003;**97**:854-8.

12. Lipton A. Bisphosphonates and metastatic breast carcinoma. *Cancer* 2003;**97**:848-53.

13. Hirsh V, Tchekmedyian NS, Rosen LS, Zheng M, Hei YJ. Clinical benefit of zoledronic acid in patients with lung cancer and other solid tumors: analysis based on history of skeletal complications. *Clinical Lung Cancer* 2004;**6**:170-4.

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

15. Chen BE, Cook RJ. Tests for multivariate recurrent events in the presence of a terminal event. *Biostatistics* 2004;**5**:129-43.

16. Leyland-Jones B. Pharmacokinetic and clinical equivalence of oral and intravenous ibandronate for metastatic bone disease. *European Journal of Cancer, Supplement* 2004;**2**:9-12.

17. Coleman RE, Major P, Lipton A, Brown JE, Lee K-A, Smith M et al. Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. *J Clin Oncol* 2005;**23**:4925-35.

18. Shakespeare TP, Thiagarajan A, Gebski V. Evaluation of the quality of radiotherapy randomized trials for painful bone metastases: Implications for future research design and reporting. *Cancer* 2005;**103**:1976-81.

19. Liepe K, Runge R, Kotzerke J. Systemic radionuclide therapy in pain palliation. *The American journal of hospice & palliative care* 2005;**22**:457-64.

20. Carteni G, Bordonaro R, Giotta F, Lorusso V, Scalone S, Vinaccia V et al. Efficacy and safety of zoledronic acid in patients with breast cancer metastatic to bone: a multicenter clinical trial. *Oncologist* 2006;**11**:841-8.

21. Lein M, Wirth M, Miller K, Eickenberg HU, Weissbach L, Schmidt K et al. Serial markers of bone turnover in men with metastatic prostate cancer treated with zoledronic Acid for detection of bone metastases progression. *European Urology* 2007;**52**:1381-7.

22. Major PP, Cook RJ, Lipton A, Smith MR, Terpos E, Coleman RE. Natural history of malignant bone disease in breast cancer and the use of cumulative mean functions to measure skeletal morbidity. *BMC Cancer* 2009;**9**:272.
23. Sharma K, Mohanti BK, Rath GK, Bhatnagar S. Pattern of palliative care, pain management and referral trends in patients receiving radiotherapy at a tertiary cancer center. *Indian Journal of Palliative Care* 2009;**15**:148-54.

24. Body JJ, Lipton A, Gralow J, Steger GG, Gao G, Yeh H et al. Effects of denosumab in patients with bone metastases with and without previous bisphosphonate exposure. *Journal of Bone & Mineral Research* 2010;**25**:440-6.

Treatment of hypercalcaemia

1. Gucalp R, Ritch P, Wiernik PH, Sarma PR, Keller A, Richman SP et al. Comparative study of pamidronate disodium and etidronate disodium in the treatment of cancer-related hypercalcemia. *J Clin Oncol* 1992;**10**:134-42.

2. Purohit OP, Radstone CR, Anthony C, Kanis JA, Coleman RE. A randomised double-blind comparison of intravenous pamidronate and clodronate in the hypercalcaemia of malignancy. *British Journal of Cancer* 1995;**72**:1289-93.

APPENDIX 6 CHARACTERISTICS OF STUDIES EXCLUDED FROM NETWORK META-ANALYSIS

TABLE A BREAST CANCER STUDIES

Study ID and country	Reason for exclusion	Participants (demographics)	Participants (Cancer details)	Participants (bone mets details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Body 2003, [71](secondary publication- **Diel 2004**[141]**)** Europe, Kuwait, Russia, South Africa, US	Definition of SRE used is not comparable.	Total patients, n: 466 Mean Age (SD): 54.5 -56.1 (10.9-11.5) No of females: 466 Prev SREs: N/R ECOG status: WHO performance - 0=21% 1= 57% 2= 20% 3= 1% 4= <1%	Primary tumour type: breast cancer Time from diagnosis of cancer to bone metastases: mean 46-54.7 (SD 50.2-59.0) months Prescence of other mets: bone metastasis, lung mets, other mets	Time from diagnosis of bone mets to randomisation: mean 15.4-17.4 (SD 19-21.8) months Proportion lytic vs blastic: N/R Prior treatments: chemotheray/hormonal therapy=84% ; radiotherapy= 31%	Bone events were defined as any of: vertebral fractures, pathological non-vertebral fractures; radiotherapy for bone complications (uncontrolled bone pain or impending fractures) or surgery for bone complications (fractures or impending fractures)	Length of intervention: 60 (min) -96 (max) weeks Length of follow-up; N/R	Roche , Switzerland	**A: 2 mg ibandrontae intravenously every 3 or 4 weeks for 96 weeks (max) or 60 weeks (min) (154)** **B: 6 mg ibandronate intravenously every 3 or 4 weeks for 96 weeks (max) or 60 weeks (min) (154)** **C: placebo by intravenously every 3 or 4 weeks for 96 weeks (max) or 60 weeks (min) (158)**

Body 2004, [72]Europe, Australia, US Secondary publication- **Tripathy 2004**[167] USA, Australia, New Zealand, Bulgaria, Russia and South Africa	Definition of SRE used is not comparable. [Definition did not include spinal cord compression.]	Total patients, n: 564 (Body 2004); 435 (Tripathy 2004) Median Age (range): 56 (26-87) ; 57 (27-92) No of females: 100% Prev SREs:95 ECOG status: WHO grade 0 or 1=169 WHO grade 2=31	Primary tumour type: breast cancer Time from diagnosis of cancer to first drug intake: median 3.44 to 3.87 years Prescence of other mets: N/R	Time from diagnosis of bone mets to randomisation: median 0.46 to 0.48 years Proportion lytic vs blastic: 16%-23%/ 8%-14% (Tripathy 2004) Prior treatments : 32.2-39.2% with cytotoxic drugs (Tripathy 2004)	Skeletal complications included vertebral fractures, pathological nonvertebral fractures, radiotherapy for bone complications (uncontrolled bone pain or impending fractures) and surgery for bone complications (fractures or impending fractures]	Length of intervention: 96 weeks (outcomes assessed at 4 weekly clinic visits) Length of follow-up: N/R	by Roche	**A: 20 mg oral ibandronate once daily for 96 weeks (NR)** **B: 50 mg oral ibandronate once daily for 96 weeks (287)** **C: placebo once daily for 96 weeks (277)**

Elomaa 1988,[73] Finland	Definition of SRE used is not comparable. [Measured new bone metastases, fractures and hypercalcaemia]	Total patients, n: 34 Median Age (range): N/R No of females:34 Prev SREs: N/R ECOG status: N/R	Primary tumour type: breast cancer Time from diagnosis of cancer to randomisation: N/R Presence of other mets: multiple osteolytic bone metastases due to breast cancer	Time from diagnosis of bone mets to randomisation: N/R Proportion lytic vs blastic: all lytic Prior treatments: hormonal and cytotoxic therapy	measured new bone metastases, pathologic bone fracture and hypercalcaemia.	Length of intervention: 12 months Length of follow-up: 24 months	N/R	**A: 1.6g clodronate once daily for 12 months (17)** **B: placebo (17)**
Heras 2009,[74] Greece	Definition of SRE used is not comparable. [Definition of SREs included 'change in anti-neoplastic therapy']	Total patients, n: 150 Mean Age (SD):58(5) years old No of females: 148 (2 males) Prev SREs: N/R ECOG status: N/R	Primary tumour type: breast cancer Time from diagnosis of cancer to randomisation: N/R Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation:N/R Proportion lytic vs blastic: N/R Prior treatments: N/R	Skeletal related events included pathologic bone fracture, spinal cord compression, radiation therapy to bone, change in anti-neoplastic therapy and surgery to bone.	Length of intervention: 24 months Length of follow-up: N/R	N/R	**A: 6 mg ibandronate intravenoously every 4 weeks for 24 months (N/R)** **B: placebo (N/R)**

Kristensen 1999,[75] Denmark	Definition of SRE used is not comparable. [Skeletal events were defined as hypercalcaemia, fractures and radiotherapy].	Total patients, n: 100 Median Age (range): 53.1-53.4 (34.0-73.8) No of females: 100 Prev SREs: N/R ECOG status: WHO performance- 0=39 1= 32 2= 22 3= 4 4= 3	Primary tumour type: adenocarcinoma of the breast and recurrence in bone either histologically or on x-ray Time from diagnosis of cancer to randomization: N/R Presence of other mets: N/R	Time from diagnosis of bone mets to randomization: N/R Proportion lytic/mixed/sclerotic/unknown: 33%/44%/22%/1% Prior treatments: 30%	"Events related to the skeleton were defined as hypercalcaemia with S-Ca2+ >1.40mmol/L, a new fracture or radiotherapy to a bone metastasis"	Length of intervention: 24 months Length of follow-up: N/R	N/R	**A: 400 mg of clodronate twice daily (49)** **B: no clodronate in addition to chemotherapy and/or endocrine therapy (51)**
Paterson 1993,[76] UK and Canada	Definition of SRE used is not comparable. [Measured hypercalcaemia, vertebral and non-vertebral fractures and requirement for radiotherapy for bone pain.]	Total patients, n: 173 Median Age (range): 58-61(26-77) No of females: N/R Prev SREs: N/R ECOG status: N/R	Primary tumour type: breast cancer Time from diagnosis of cancer to mets: 30-31 months Prescence of other mets: metastatic skeletal disease	Time from diagnosis of bone mets to randomisation: 12-15 months Proportion lytic vs blastic: N/R Prior treatments: 66% (endocrine) 43% (chemotherapy)	Measured hypercalcaemia, vertebral and non-vertebral fractures and requirement for radiotherapy for bone pain	Length of intervention: 18 months Length of follow-up:median 14 range (4-37) months for pts still alive	medical research programme grant from the breast cancer research trust	**A: 1600 mg of clodronate once daily (or 800 mg twice daily for GI intolerance) for 18 months (extended till 3 years (85)** **B: placebo (88)**

TABLE B PROSTATE CANCER STUDIES

Study ID and country	Reason for exclusion	Participants (demographics)	Participants (Cancer details)	Participants (bone mets details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Adami 1985[210] + 1989[77] Italy	Only painful metastases, IV clodronate	Total patients, n: 64 Mean Age: 64 (42-79) Prev SREs: N/R ECOG status: N/R	Primary tumour type: prostate cancer Time from diagnosis of cancer to randomisation: N/R Prescence of other mets: N/R	Time from diagnosis of bone mets to randomisation: N/R Proportion lytic vs blastic: N/R Prior treatments: 18 orchidectomy and 16 estramustine	N/A	Length of intervention: 2-11 weeks Length of follow-up: 42 patient years	N/R	**A: 300mg IV clodronate daily for 2 weeks (n=13)** **B:100mg IM clodronate daily for 2 weeks (n=12)** **C: 1200mg oral clodronate for 2 weeks (n=11)** **D: Placebo (n=6)** **E: Maintenance therapy -IV clodronate (300mg) followed by oral for 6 weeks (1200mg) (n=18)**

Buchali 1988[78] Germany	SRE definition not reported	Total patients, n: 49 Mean Age 67.4 - 66.5 Prev SREs: N/R ECOG status: N/R	Primary tumour type: bioptically proven prostatic carcinoma with multiple skeletal metastases Time from diagnosis of cancer to randomisation: 1.82-2.19 years Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation: N/R Proportion lytic vs. blastic: N/R Prior treatments: N/R Pain: 84%	N/R	Length of intervention: 12 months Length of follow-up: 12months	N/R	**A: Three injections of 75 MBq ^{89} SR chloride at monthly intervals (n=25)** **B: Placebo (n=24)**
Dearnaley 2003[79] UK and NZ	Hormone sensitive prostate cancer	Total patients, n=311 Mean Age: 71 (47-88) Prev SREs: N/R ECOG status: 0 - 65-66%, 1 - 30-27% and 2 - 5-7%	Primary tumour type: patients with prostate cancer who were commencing or sowing positive response to first line therapy Time from diagnosis of cancer to randomisation: 5-5.5 months Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation: 2.5-3 months Proportion lytic vs. blastic: N/R Prior treatments; N/R Pain: N/R	"similar to the "SRE" endpoint that has been used in other studies of Bps, except this definition includes evidence of asymptomatic disease progression"	Length of intervention: median 16.1-17.1months Length of follow-up: median 59 months	MRC and Boehringer Mannheim	**A: Oral clodronate 2080mg daily (n=155)** **B: Placebo (n=156)**
Elomma 1992[80] Finland	Only painful metastases	Total patients, n= 75 Mean Age: 72-73 (60-83) Prev SREs: N/R ECOG status; N/R	Primary tumour type: castration resistant prostate cancer Time from diagnosis of cancer to randomisation: 37-38 months Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation: N/R Proportion lytic vs. blastic: N/R Prior treatments: N/R Pain: 100%	N/R	Length of intervention: 6 months Length of follow-up: 12 months	Finnish Cancer foundation and Leiras Pharmaceutical company	**A: Clodronate 3.2g for 4 weeks then 1.6g (n=36** **B: Placebo (n=39)**

Ernst 2003[81] Canada	Only painful metastases, unlicensed administration of clodronate	Total patients, n= 209 Median Age - 70.1-70.6 years Prev SREs: N/R ECOG status: 0 - 9%-13%, 1 - 58-62%, 2 - 29-20%, 3 - 5%	Primary tumour type: hormone resistant prostate cancer Time from diagnosis of cancer to randomisation: N/R Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation: N/R Proportion lytic vs. blastic: N/R Prior treatments: N/R Pain: 100%	hypercalaemia, pathological fractures and palliative radiotherapy	Length of intervention: N/R Length of follow-up: N/R	Immunex corporation	**A: Clodronate 150mg IV every 3 weeks plus mitoxantrone and prednisolone (n=104)** **B: Placebo plus mitoxantrone and prednisolone (n=105)**
Kylmala 1993[82] Finland (Similar data set to Elomma)	Only painful metastases	Total patients, n= 99 Mean Age: 71-72 (47-90) Prev SREs: N/R ECOG status: N/R	Primary tumour type: castration resistant prostate Time from diagnosis of cancer to randomisation: 37-38 months Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation: N/R Proportion lytic vs. blastic: N/R Prior treatments: N/R Pain: 100%	N/R	Length of intervention: 6 months Length of follow-up: 6 months	Finnish Cancer foundation and Leiras Pharmaceutical Company	**A: Clodronate (3.2g for 4 weeks the 1.6g for 5mths) plus estramustine (280mg twice daily) (n=50)** **B: Estramustine alone (280mg twice daily) (n=49)**
Kylama 1997[83] Finland	Only painful metastases and unlicensed dose of clodronate	Total patients, n= 57 Mean Age: 74 (52-86) Prev SREs: N/R ECOG status: N/R	Primary tumour type: prostate cancer Time from diagnosis of cancer to randomisation: N/A Presence of other mets: N?A	Time from diagnosis of bone mets to randomisation: Clod - 6 mths, placebo 5 mths (median) Proportion lytic vs.	N/R	Length of intervention: 12 months Length of follow-up: 12 months	Finnish Cancer Foundation, Finnish Medical Society Duodecim, Reino Lahtikari	**A: Clodronate 300mg IV for 5 days followed by 1.6g oral for 12 months plus estramustine 280mg twice daily (n=28)**

				blastic: N/A Prior treatments: 74% orchiectomy, 21% oestrogen, 11% LHRH-agonist, 7% antiandrogens Pain: 100%			Foundation and Leiras Clinical Research	**B: Placebo plus estramustine 280mg twice daily (n=29)**
Nilsson 2005[84] Sweden	Only painful metastases and unlicensed dose of clodronate	Total patients, n= 35 Mean Age: N/R Prev SREs: N/R ECOG status: N/R	Primary tumour type: prostate cancer with persistent bone pain Time from diagnosis of cancer to randomisation: N/R Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation: N/R Proportion lytic vs. blastic: N/R Prior treatments: N/R Pain: 100%	N/R	Length of intervention: single dose Length of follow-up: 12 weeks	N/R	**A: Strontium-89 chloride 150MBq single dose at day 0 (n=18)** **B: FEM (5-fluorouracil, epirubicin and mitomycin-C) two doses at day 0 and 1 (n=17)**
Porter 1992[85] Canada	Study investigating strontium	Total patients, n= 126 Mean Age: 71.5/71.0 years Prev SREs: N/R ECOG status: N/R	Primary tumour type: Castration resistant prostate cancer Time from diagnosis of cancer to randomisation: 21.5months/ 25 months (median) Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation: 11.0 months/ 11.5 months (median) Proportion lytic vs. blastic; N/R Prior treatments: All pts had prev surgical orchiectomy or hormonal treatment Pain: patients receiving strong analgesics 56.3%/43.9%	N/R	Length of intervention: single dose Length of follow-up: N/R	Amersham International	**A: Strontium-89 chloride 10.8mCi single dose plus local radiotherapy** **B: Placebo plus local radiotherapy**

Quilty 1994[86] UK	Only painful metastases	Total patients, n= 305 Mean Age: 69, 68, 69, 70 years Prev SREs: N/R ECOG status: N/R	Primary tumour type: castration resistant prostate cancer Time from diagnosis of cancer to randomisation: 10, 9, 10, 13 months Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation: 10, 10, 12, 11 months Proportion lytic vs. blastic Prior treatments: orchiectomy or hormonal therapy Pain: 100%	N/R	Length of intervention: 12 weeks Length of follow-up: 12 weeks	Amersham International	**A: Strontium-89 200 MBq IV and local field radiotherapy (n=76)** **B: eternal beam radiotherapy and local field radiotherapy (n=72)** **C: Strontium-89 200 MBq IV and hemibody radiotherapy (n=77)** **D: eternal beam radiotherapy and hemibody radiotherapy (n=80)**
Strang 1997[89] Sweden	Only painful metastases and unlicensed dose of clodronate	Total patients, n= 52 Mean Age: N/R Prev SREs: N/R ECOG status: N/R	Primary tumour type: hormone refractory prostate cancer Time from diagnosis of cancer to randomisation: N/R Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation: N/R Proportion lytic vs. blastic: N/R Prior treatments Pain	N/R	Length of intervention: 4 weeks Length of follow-up: 4 weeks	Leiras OY anf ASTRA Lakemedel	**A: Clodronate 300mg IV for 3 days followed by 3.2g for 4 weeks (n=25)** **B: Placebo (n=27)**

Smith 1989,[88] USA	Only painful metastases	Total patients, n= 57 Mean Age: N/R Prev SREs: N/R ECOG status: N/R	Primary tumour type: prostate cancer Time from diagnosis of cancer to randomisation: N/R Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation Proportion lytic vs. blastic Prior treatments: all patients had undergone hormonal treatment Pain: 100%	N/R	Length of intervention: "at least 1 month" then those who failed to respond crossed over for 6 months Length of follow-up: N/R	N/R	**A: 7.5mg/kg etidronate IV for 3 days followed by etidronate 200mg twice daily (n=14)** **B: 7.5mg/kg etidronate IV for 3 days followed by placebo (n=14)** **C: IV placebo followed by etidronate 200mg twice daily (n=15)** **D: Placebo (n=14)**
Small 2003[87] USA and international (pooled results of two RCTs)	Only painful metastases	Total patients, n= 378 Median Age: 72, 71 Prev SREs: 48%, 49% ECOG status: N/R	Primary tumour type: castration resistant prostate cancer Time from diagnosis of cancer to randomisation: median 3.5, 4.3 years Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation: 1.1, 1.6 years Proportion lytic vs. blastic: N/R Prior treatments: 40%, 43% previous chemo Pain: 100%	hypercalcaemia, a pathologic fracture, requirement of radiation therapy to bone, surgery to bone, spinal cord compression, or need for a spinal orthotic brace	Length of intervention: 27 weeks Length of follow-up: 27 weeks	Aredia	**A: Pamidronate disodium 90mg IV every 3 weeks (n=182)** **B: Placebo IV every 3 weeks (n=196)**

TABLE C OTHER SOLID TUMOURS STUDIES

Study ID and country	Participants (demographics)	Participants (Cancer details)	Participants (bone mets details)	SRE definition	Duration of study	Funding source	Study arms (including number randomised)
Arican 1999,[90] Turkey	Total patients, n: 50 Median Age: 52-59 (range 27-70) No. of females:40 Prev SREs: all with bone pain ECOG status: 1=56% 2=44%	Primary tumour type: bresat cancer (68%); non small cell lung cancer(22%); stomach cancer(6%); colorectal cancer(4%) Time from diagnosis of cancer to randomization: N/R Prescence of other mets: N/R	Time from diagnosis of bone mets to randomisation: N/R Proportion lytic/mixed: 48%/52% Prior treatments: chemotherapy (58%); hormonal therapy (42%)	skeletal morbidities including hypercalcemia, radiotherapy need, pathological fracture, spinal cord compression were measured	Length of intervention: 3 months Length of follow-up: N/R	N/R	**A: 800 mg of clodronate once daily for 3 months (16)** **B: 1600 mg of oral clodronate once daily for 3 months (17)** **C: placebo (17)**

Berenson 2001,[91] US and UK	Total patients, n: 280 Mean Age: 56.5 (SD 13.6) - 59.9 (SD 11.3) years No. of females: 213 Prev SREs: 82% ECOG status: 0= 25% 1= 56% 2= 18% >2= 1%	Primary tumour type: multiple myeloma (39%) breast carcinoma (61%) Time from diagnosis of cancer to randomisation: mean 63.6 (SD 67.8) - 71.2 (SD 81.9) Prescence of other mets: osteolytic lesion	Time from diagnosis of bone mets to randomization: N/R Proportion lytic vs blastic: N/R Prior treatments: N/R	skeletal events were defined as radiation to bone, pathologic fracture, surgery to bone, spinal cord compression, or hypercalcemia	Length of intervention; 10 months Length of follow-up: N/R	Novartis	**A: 0.4 mg zolendronic acid intravenously (as 2 hr infusion) every 4 weeks for up to 10 months (68)** **B: 2.0 mg zolendronic acid intravenously (as 2 hr infusion) every 4 weeks for up to 10 months (72)** **C: 4.0 mg zolendronic acid intravenously (as 2 hr infusion) every 4 weeks for up to 10 months (67)** **D: 90 mg pamidronate intravenously (as 2 hr infusion) every 4 weeks for up to 10 months (73)**

Brown 2007,[92] Europe (six centres)	Total patients:125 Median Age (range): 64 (28-81) years No. of females:87 Prev SREs: radiation therapy=82% ECOG status: Zubrod 0=26% Zubrod 1=58% Zubrod 2=16% (Zubrod is equivalent to ECOG status)	Primary tumour type: breast (70%); prostate (26%); other (4%) Time from diagnosis of cancer to randomization: N/R Prescence of other mets: bone metastases=107(86 %) liver mets=11 (9%) lung mets=12 (10%) other mets=19 (15%)	Median duration of bone mets: 10.9 months Proportion of bone mets type: lytic/mixed=58%; sclerotic=39%; missing=3% Prior treatments: biphosphonates=10%	N/R	Length of intervention: 6 weeks Length of follow-up: N/R	N/R	**A: 800 mg, 1600 mg, 2400 mg or 3200 mg oral clodronate for 6 weeks (27)** **B: placebo for 6 weeks (24)**
Heras 2007[93]	Total patients: 73 Age: >=21 years No of females: N/R Pre SREs: N/R ECOG status: N/R	Primary tumour type: colorectal cancer Time from diagnosis of cancer to randomization: N/R Presence of other mets: N/R	Time from diagnosis of bone mets to randomization: N/R Proportion lytic vs blastic: N/R Prior treatments: N/R	Skeletal related events were defined as pathologic fracture, spinal cord compression, radiation therapy to bone, change in antineoplastic therapy and surgery to bone.	Length of intervention:9 months Length of follow up: N/R	N/R	**A: 6 mg intravenous ibandronate every 4 weeks for 9 months** **B: placebo**

Jagdev 2001,[94] UK	Total patients:51 Median Age (range): 63 (46-79); 58.5 (38-72); 66.5 (38-78) No. of females: 30 Prev SREs: N/R ECOG status: 0=6% 1=51% 2=43%	Primary tumour type: breast (43%); prostate (31%); renal (2%); lung (10%); thyroid (2%); other (12%) Time from diagnosis of cancer to randomization: N/R Prescence of other mets: N/R	Time from diagnosis of bone mets to randomization: N/R Proportion lytic vs blastic: N/R Prior treatments: N/R	N/R	Length of intervention: 3 months Length of follow-up	N/R	**A: 1600 mg of oral clodronate once daily in two divided dose (18)** **B: 1500 mg of single intravenous clodronate + 1600 mg of oral clodronate once daily thereafter (15)** **C: 90 mg pamidronate intravenously as a monthly infusion (18)**
Lipton 2003,[101] US (retrospective subgroup analysis from RCT)	Total randomised patients: 766; **subset analysed: 74** Median Age: 64 years; 65 years No. of males:59 Prev SREs: 85% ECOG status: <=1: 85% >=2: 15%	Primary tumour type: lung carcinoma(381); renal cell carcinoma(74); unknown primary (43); head and neck (17); thyroid (11); other (240) Time from diagnosis of cancer to randomisation: median 25.5; 22.7; 21.2 months Prescence of other mets: N/R	Time from diagnosis of bone mets to randomization: N/R Proportion lytic vs blastic: N/R Prior treatments: immunotherapy=58% hormonal therapy= 4%	SREs were defined as pathological fracture, spinal cord compression; surgery to bone; or radiation therapy to bone	Length of intervention: 9 months Length of follow-up: N/R	Novartis Pharmaceuticals	**A: 4 mg zoledronic acid infusion every three weeks for 9 months (27)** **B: 8/4 mg zolendronic acid 8 mg reduced to 4 mg) every three weeks for 9 months (28)** **C: placebo every three weeks for 9 months (19)**

Mystakidou 2008,[95] Greece	Total patients: 52 Mean Age (SD): 66.9 (10.7), 65.8 (10.7) No. of males/ females: 24/28 Prev SREs: N/R ECOG status: N/R	Primary tumour type: breast (27%); lung (23%); urogenital (13%); colon (13%); prostate (10%); other (13%) Time from diagnosis of cancer to randomisation: N/R Prescence of other mets: only bone metastases	Time from diagnosis of bone mets to randomisation: N/R Proportion lytic vs blastic: N/R Prior treatments: surgery (42%); radiotherapy (85%);	N/R	Length of intervention: 6 months Length of follow-up: N/R	No funding source	**A: 50 mg oral ibandronic acid once daily every 28 days(26)** **B: 6 mg IV ibandronic acid infused over15 min every 28 days (26)**
O'Rourke 1995,[96] UK	Total patients: 84 Median Age (range): 57 (28 to 80) No of male/female: 12/72 Prev SREs: N/R ECOG status: N/R	Primary tumour type: breast (82%); prostate (7%); lung (4%); kideny (2%); other (6%) Time from diagnosis of cancer to randomization: N/R Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation: N/R Proportion lytic vs. blastic: N/R Prior treatments: N/R	N/R	Length of intervention: 4 weeks Length of follow-up	part funded by Boehringer Mannheim	**A: 400 mg oral sodium clodronate once daily for 4 weeks (20)** **B: 1600 mg oral sodium clodronate once daily for 4 weeks (19)** **C: 3200 mg oral sodium clodronate once daily for 4 weeks (20)** **D: placebo for 4 weeks (21)**

Piga 1998,[97] Italy	Total patients: 50 Median Age: 65, 63 Prev SREs: N/R ECOG status; N/R	Primary tumour type: lung (34%); colon (20%); kidney (2%); melanoma (6%); unknown (6%); stomach (12%); others (12%) Time from diagnosis of cancer to randomisation; N/R Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation: N/R Proportion lytic vs. blastic: N/R Prior treatments: N/R	bone responses measured	Length of intervention: 12 months Length of follow-up: N/R	N/R	**A: 1600 mg oral clodronate once daily for 12 months (27)** **B: Placebo once daily for 12 months (23)**
Robertson 1995,[98] UK	Total patients, n: 55 Mean Age (SEM): 60 (4.6); 65 (3.8) Prev SREs: N/R ECOG status: N/R WHO grade; 0 = 7% 1= 43 to 48% 2 = 18 to 19% 3 = 7 to 14%	Primary tumour type: breast (48% to 53%); lung (7%); prostate (7%); myeloma/lymphoma (7%); other cancers (25% to 26%) Time from diagnosis of cancer to randomisation: N/R Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation: N/R Proportion lytic vs. blastic:N/R Prior treatments: tamoxifen 22 to 29%; progestogen 14 to 17%; other hormonal 11 to 14%; chemotherapy 11 to 17% Bone pain (VAS score, median (range): 3.2 (1.6-7.5); 4.8 (2.1-6.9)	changes in severity of bone pain measured; outcomes on chemotherapy/radiotherapy, fracture, hypercalcemia,cord compression reported	Length of intervention, median (range), days: 56 (28-135); 57 (25-171) Length of follow-up: N/R	Boehringer Mannheim	**A: 1600 mg oral clodronate disodium (400mg capsules) once daily in divided doses (n=27)** **B: placebo (n=28)**

Zaghloul 2010,[99] Egypt	Total patients: 40 Median Age:53 (42-70); 55 (41-66) No of male: 31 Prev SREs: radiotherapy- 2 fractions (65%); 5 fractions (35%) ECOG status: N/R	Primary tumour type: bladder cancer Time from diagnosis of cancer to randomisation: N/R Presence of other mets: 25%	Time from diagnosis of bone mets to randomisation: 1-6 months (57%); >=7 months(25%) Proportion lytic vs. Blastic: N/R Prior treatments: palliative radiotherapy given to all patients; analgesics	SREs defined as pathologic fractures, spinal cord compression, hypercalcemia of malignancy, and the need for radiation or bone surgery.	Length of intervention: 6 months Length of follow-up: 12 month; median 24 (range 8-65) weeks	N/R	**A: 4mg IV Zolendronic acid monthly for six months (20) + radiotherapy** **B: placebo (20) + radiotherapy**
Zhao 2011,[100] China	Total patients: 60 Mean Age: 47 (30-70); 45 (20-63) no of male: 52 Prev SREs: N/R ECOG status: 1-2: 7% 3: 38% 4: 47% other: 10%	Primary tumour type: nasopharygeal carcinoma Time from diagnosis of cancer to randomisation: N/R Presence of other mets: N/R	Time from diagnosis of bone mets to randomisation: N/R Proportion lytic vs. Blastic: N/R Prior treatments: chemotherapy 77%	radiation to the bone (n=7) and spinal cord compression reported (n=1)	Length of intervention: 3 months Length of follow-up: median 17 months	N/R	**A: 4mg IV Zolendronic acid 3 times in 4 weeks + chemotherapy and (30)** **B: Chemotherapy (29)**

APPENDIX 7 RESULTS FROM STUDIES EXCLUDED FROM NMA

TABLE A BREAST CANCER

Study ID and country	Study arms (including number randomised)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Body 2003, [71](secondary publication- **Diel 2004[141])** Europe, Kuwait, Russia, South Africa, US * only reported in the study by Diel and colleagues[141]	**2 mg ibandrontae intravenously every 3 or 4 weeks for 96 weeks (max) or 60 weeks (min) (154)**	**Time to first SRE**: median 44.6 weeks Time to first and subsequent SRE (MEA): N/R Incidence of SREs: 4.24 events per patient **SMPR (**events per patient year)**:** All new bone events:1.31 (p=0.152) Proportion with SRE: 62.3%	Hypercalcaemia: N/R ***Pain**: mean change in the bone pain score between baseline and last assessment= 0.21(SD 0.09) mean change in analgesic score = 0.89(SD N/R) ***QoL**(139): mean overall score bw baseline and last assessment (functioning)=-18.1 ***Overall survival**: median 116.4 (95%CI 104-133) weeks	Renal impairment:0.7% ONJ, acute phase reaction, hypocalcaemia or any other significant AE: NR
	6 mg ibandronate intravenously every 3 or 4 weeks for 96 weeks (max) or 60 weeks (min) (154)	**Time to first SRE:**50.6 weeks Time to first and subsequent SRE (MEA): N/R Incidence of SREs: 2.65 events per patient **SMPR** (events per patient year)**:** All new bone events:1.19 (p=0.004) Vertebral fractures: 0.71 (p=0.023) Non-vertebral fractures: 0.72 (p=0.396) Events requiring radiotherapy: 0.91 (p=0.011) Events requiring surgery: 0.56 (p=0.075) Proportion with SRE: 50.6%	Hypercalcaemia: N/R ***Pain:** mean change in the bone pain score between baseline and last assessment= -0.28 (SD 1.11) mean change in analgesic score = 0.51(SD 1.54) ***QoL**(137): mean overall score between baseline and last assessment (functioning)=-10.3 ***Overall survival**: median 113.3 (95%CI 97-129) weeks	Renal impairment: 2.6% ONJ, acute phase reaction, hypocalcaemia or any other significant AE: NR

	placebo by intravenously every 3 or 4 weeks for 96 weeks (max) or 60 weeks (min) (158)	Time to first SRE:33.1 weeks Time to first and subsequent (MEA): N/R Incidence of SREs: 3.64 events per patient **SMPR** (events per patient year): All new bone events:1.48 Vertebral fractures: 0.82 Non-vertebral fractures: 0.81 Events requiring radiotherapy: 1.09 Events requiring surgery: 0.62 Proportion with SRE: 62.0%	Hypercalcaemia: N/R ***Pain**: mean change in the bone pain score between baseline and last assessment=0.19 (SD0.11) mean change in analgesic score = 1.90(SD 1.64) ***QoL**(143): mean overall score bw baseline and last assessment (functioning)= -45.4 ***Overall survival**: median 106.7 (95%CI 95-124) weeks	Renal impairment:1.3% ONJ, acute phase reaction, hypocalcaemia or any other significant AE: NR
Body 2004,[72] (Secondary report- **Tripathy 2004**[167]) Europe , Australia, US * only reported in the study by Tripathy and colleagues[167]	**20 mg oral ibandronate once daily for 96 weeks (NR)**	*Time to first SRE: 76 weeks Time to first and subsequent SRE (MEA): N/R Incidence of SREs: N/R **SMPR** (no of 12 weeks period with new skeletal complications/total observation time): -All new bone events: 0.99 (p=0.041) *Proportion with SRE: 46.5	Hypercalcaemia: N/R *Pain (LOCF bone pain score: change from from baseline to study end point): -0.06 QoL: N/R Overall survival: N/R	*Renal impairment: 3.5% *Hypocalcaemia: 9 ONJ, acute phase reaction, or any other significant AE: NR

	50 mg oral ibandronate once daily for 96 weeks (287)	Time to first SRE: median 90.3 weeks (p=0.089) Time to first and subsequent SRE (MEA): N/R Incidence of SREs: No of events per patient=1.15 (p=0.008) No of 12-week periods with events per patient=0.71 (p=0.015) **SMPR:** -All new bone events=0.99 (p=0.041) -Vertebral fractures=0.49 (p=0.145) -Non-vertebral fractures=0.51 (p=0.330) -Need for radiotherapy=0.80 (p<0.004) -Need for surgery=0.40 (p=0.098) Proportion with SRE: 45.3% (p=0.122)	Hypercalcaemia: N/R *Pain:0.03 QoL: N/R Overall survival: 20% died within 96 weeks	Renal impairment: 5.2% Hypocalcaemia: 9.4% ONJ, acute phase reaction or any other significant AE: NR
	placebo once daily for 96 weeks (277)	Time to first SRE: median 64.9 weeks Time to first and subsequent (MEA): N/R Incidence of SREs: No of events per patient= 1.85 No. of 12 week periods with events per patient= 0.99 **SMPR**: -All new bone events=1.15 -Vertebral fractures=0.52 -Non-vertebral fractures=0.52 -Need for radiotherapy=0.98 -Need for surgery=0.44 Proportion with SRE: 52.2%	Hypercalcaemia: N/R *Pain:0.21 QoL:N/R Overall survival: 15% died within 96 weeks	Renal impairment: 4.7% Hypocalcaemia: 5.1% ONJ, acute phase reaction, or any other significant AE: NR

Elomaa 1988,[73] Finland	**1.6g clodronate once daily for 12 months (17)**	Time to first SRE: N/R Time to first and subsequent SRE (MEA): N/R Incidence of SREs: 3/17- during treatment; 11/17 after treatment SMR: N/R Proportion of each SRE: 1- during treatment; 1 - after treatment	Hypercalcaemia: 1 Pain: N/R QoL: N/R Overall survival: 11 patients	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
	placebo (17)	Time to first SRE: N/R Time to first and subsequent (MEA) Incidence of SREs: 11/17- during treatment; 9/17 after treatment SMR: N/R Proportion of each SRE: 4- during treatment; 9- after treatment	Hypercalcaemia: 4 Pain: N/R QoL: N/R Overall survival: 4 patients	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
Heras 2009,[74] Greece	**6 mg ibandronate intravenoously every 4 weeks for 24 months (150)**	Time to first SRE: median 457 days Time to first and subsequent SRE (MEA): N/R Incidence of SREs: N/R SMR:N/R **Proportion with SRE**: 36% Risk of developing SRE, MEA: HR=0.69; (95%CI 0.42-0.79)	Hypercalcaemia: N/R Pain: N/R QoL: N/R Overall survival: N/R	ONJ: none Renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
	placebo	Time to first SRE: median 304 days Time to first and subsequent SRE (MEA): N/R Incidence of SREs: N/R SMR: N/R **Proportion with SRE**: 48%	Hypercalcaemia: N/R Pain: N/R QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR

Kristensen 1999,[75] Denmark	**400 mg of clodronate twice daily (49)**	Time to first SRE: 15-20 months Time to first and subsequent SRE (MEA): N/R Incidence of SREs: N/R SMR: N/R **Proportion with SRE**: Fracture-6%; radiotherapy-16%; hypercalcaemia-6%; total-29%	Hypercalcaemia: 6% Pain: N/R QoL: N/R Overall survival: N/R	Hypocalcaemia: none ONJ, renal impairment, acute phase reaction or any other significant AE: NR
	no clodronate in addition to chemotherapy and/or endocrine therapy (51)	Time to first SRE: 3-5 months Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR: N/R **Proportion with SRE**: fracture-25%; radiotherapy-8%; hypercalcaemia-8%; total=41%	Hypercalcaemia: 8% Pain: N/R QoL: N/R Overall survival: N/R	Hypocalcaemia: 2 patients ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
Paterson 1993,[76] UK and Canada	**1600 mg of clodronate once daily (or 800 mg twice daily for GI intolerance) for 18 months (extended till 3 years (85)**	Time to first SRE: N/R Time to first and subsequent SRE (MEA): N/R **Incidence of SREs (events/100 pt-yrs)** -hypercalcemic events: 27.9 -nonvertebral fractures: 31.9 -vertebral fractures:84 -vertebral deformity rate: 168 -No of courses of radiotherapy: 74.8 SMR: 218.6/100 pt-yrs Proportion with SRE: -patient requiring radiotherapy: 40% Total no of hypercalcemic episodes: 28 Total no of vertebral fractures: 58	**Hypercalcaemia:** 24% Pain: N/R QoL: N/R Overall survival: at 1 year 62%; at 2 years 35%	Hypocalcaemia: 3 patients ONJ, renal impairment, acute phase reaction, or any other significant AE: NR

	placebo (88)	Time to first SRE: N/R Time to first and subsequent (MEA): N/R **Incidence of SREs (events/100 pt-yrs)** -hypercalcemic events: 51.8 -nonvertebral fractures: 39.8 -vertebral fractures: 124.1 -vertebral deformity rate: 252 -No of courses of radiotherapy:42 SMR: 304.8/100 pt-yrs Proportion of each SRE -patients requiring radiotherapy: 48% Total no of hypercalcemic episodes: 52 Total no of vertebral fractures:90	**Hypercalcaemia:**35% Pain: N/R QoL: N/R Overall survival: at 1 year 54%; at 2 years 14%	Hypocalcaemia: 2 patients ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR

TABLE B PROSTATE CANCER

Study ID and country	Study arms (including number 318andomized)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Adami 1985[210] + 1989[77] Italy	**300mg IV clodronate daily for 2 weeks (n=13)**	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: "most had bone pain relapse fairly soon" QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
	100mg IM clodronate daily for 2 weeks (n=12)	Time to first SRE: N/R Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: "significant fall in analagesic consumption but not [VAS] pain" QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
	1200mg oral clodronate for 2 weeks (n=11)	Time to first SRE: N/R Time to first and subsequent SRE (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: "completely ineffective" QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo (n=6)	Time to first SRE: N/R Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: "stopped early because of ethical reasons" QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR

	Maintenance therapy –IV clodronate (300mg) followed by oral for 6 weeks (1200mg) (n=18)	Time to first SRE: N/R Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain "relapse prevented" QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
Buchali 1988[78] Germany	**Three injections of 75 MBq ^{89} SR chloride at monthly intervals (n=25)**	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain:** 7/19 had relief QoL: N/R Overall survival: Survival rate after 2 years 0.46	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo (n=24)	Time to first SRE: N/R Time to first and subsequent: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain:** 11/22 had relief (p = N.S) QoL: N/R Overall survival: Survival rate after 2 years 0.04 (p<0.05)	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
Dearnaley 2003[79] UK and NZ	**Oral clodronate 2080mg daily (n=155)**	Time to first SRE: median 23.6 months Time to first and subsequent SRE (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Analgesic consumption: Increased HR 1.12 (95% CI 0.86, 1.45) compared to placebo QoL: N/R Overall survival: 37.1 months. HR 0.80 (95%CI 0.62, 1.03) compared to placebo BPFS: 49.3% at 2 years. HR 0.79 (95%CI 0.61, 1.02) compared with placebo	Hypocalcaemia: 4% ONJ, renal impairment, acute phase reaction or any other significant AE: NR
	Placebo (n=156)	Time to first SRE: 19.3 months Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: See above QoL: N/R Overall survival: 28.4 months BPFS: 41% at 2 years	Hypocalcaemia: 0% ONJ, renal impairment, acute phase reaction or any other significant AE: NR

Elomaa 1992[80] Finland	**Clodronate 3.2g for 4 weeks then 1.6g (n=36**	Time to first SRE: N/R Time to first and subsequent SRE : N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: 18% pain free and 18% required no analgesics QoL: N/R Overall survival: No difference: N/R	Renal impairment: 1/36 ONJ, acute phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo (n=39)	Time to first SRE: N/R Time to first and subsequent: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain:** 15% pain free and 23% required no analgesics QoL: N/R Overall survival: No difference	Renal impairment: 0/39 ONJ, acute phase reaction, hypocalcaemia or any other significant AE: NR
Ernst 2003[81] Canada	**Clodronate 150mg IV every 3 weeks plus mitoxantrone and prednisolone (n=104)**	Time to first SRE: N/R Time to first and subsequent SRE (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain:** 46% achieved palliative response to pain (NS), 31% no longer needed analgesics QoL: No over difference in PROSQOLI Overall survival: 10.8 months. HR 0.95 (95%CI 0.71, 1.28) compared to placebo	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo plus mitoxantrone and prednisolone (n=105)	Time to first SRE: N/R Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: 39% achieved palliative response to pain, 25% no longer needed analgesics QoL: No over difference in PROSQOLI Overall survival: 11.5 months	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR

Kylmala 1993[82] Finland (Similar data set to Elomma)	**Clodronate (3.2g for 4 weeks the 1.6g for 5mths) plus estramustine (280mg twice daily) (n=50)**	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain:** "pain relief within 1 month and reduction in analgesics more accentuated in the Clodronate group but NS" QoL: N/R Overall survival: median 10 months (NS difference)	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
	Estramustine alone (280mg twice daily) (n=49)	Time to first SRE: N/R Time to first and subsequent : N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: "pain relief within 1 month and reduction in analgesics more accentuated in the Clodronate group but NS" QoL: N/R Overall survival: median 12 months	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
Kylmala 1997[83] Finland	**Clodronate 300mg IV for 5 days followed by 1.6g oral for 12 months plus estramustine 280mg twice daily (n=28)**	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain:** No statistically significant difference QoL: N/R Overall survival: N/R	Renal impairment: 0 ONJ, acute phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo plus estramustine 280mg twice daily (n=29)	Time to first SRE: N/R Time to first and subsequent : N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain:** No statistically significant difference QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR

Nilsson 2005[84] Sweden	**Strontium-89 chloride 150MBq single dose at day 0 (n=18)**	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain:** Significantly lower than baseline (p = 0.010). No difference compared to FEM. QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia: NR Any other significant 2/14 hospitalized due to side effects
	FEM (5-fluorouracil, epirubicin and mitomycin-C) two doses at day 0 and 1 (n=17)	Time to first SRE: N/R Time to first and subsequent : N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain:** Significantly lower than baseline (p = 0.039). No difference compared to strontium. QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia: NR Any other significant: 7 were hospitalized due to side effects
Porter 1993[85] Canada	**Strontium-89 chloride 10.8mCi single dose plus local radiotherapy**	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain:** No significant difference between arms at 6 months. However strontium significantly delayed onset of pain in asymptomatic pts. QoL: Overall Strontium significantly improved QoL Overall survival: 27 weeks (median) NS	ONJ, renal impairment, acute phase reaction, hypocalcaemia: NR Any other significant: higher incidence of thrombocytopenia in Strontium group. Two deaths because of haemorrhage.

	Placebo plus local radiotherapy	Time to first SRE: N/R Time to first and subsequent: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain:** No significant difference between arms at 6 months QoL: Overall Strontium significantly improved QoL Overall survival: 34 weeks (median) NS	ONJ, renal impairment, acute phase reaction, hypocalcaemia: NR Any other significant: One death due to heamorrhage
Quilty 1994[86] UK	**Strontium-89 200 MBq IV and local field radiotherapy (n=76)**	Time to first SRE: N/R Time to first and subsequent: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: 65.1% had some pain relief, 39.7% reduced analgesic intake (NS) QoL: N/R Overall survival: No statistical difference (p= 0.1)	Renal impairment: 1 pt ONJ, acute phase reaction, hypocalcaemia: NR Any other significant: lower incidence of N+V
	eternal beam radiotherapy and local field radiotherapy (n=72)	Time to first SRE: N/R Time to first and subsequent: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: 66.7% had some pain relief, 33.3% reduced analgesic intake (NS) QoL: N/R Overall survival: No statistical difference (p= 0.1)	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR

	Strontium-89 200 MBq IV and hemibody radiotherapy (n=77)	Time to first SRE: N/R Time to first and subsequent: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: 70% had some pain relief, 28.3% reduced analgesic intake (NS) QoL: N/R Overall survival: No statistical difference (p= 0.1)	ONJ, renal impairment, acute phase reaction, hypocalcaemia: NR Any other significant: lower incidence of N+V
	eternal beam radiotherapy and hemibody radiotherapy (n=80)	Time to first SRE: N/R Time to first and subsequent: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: 67.4% had some pain relief, 34.8% reduced analgesic intake (NS) QoL: N/R Overall survival: No statistical difference (p= 0.1)	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
Small 2003[87] USA and international (pooled results of two RCTs)	**Pamidronate disodium 90mg IV every 3 weeks (n=182)**	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: "similar between groups" Proportion of each SRE: no significant difference between intervention arms (25% vs. 25%)	Hypercalcaemia: <1% Pain: no significant difference between intervention arms QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo IV every 3 weeks (n=196)	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: "similar between groups" Proportion of each SRE: no significant difference between intervention arms (25% vs. 25%)	Hypercalcaemia: 1% Pain: no significant difference between intervention arms QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia: NR Any other significant: None

Smith 1989,[88] USA	**7.5mg/kg etidronate IV for 3 days followed by etidronate 200mg twice daily (n=14)**	Time to first SRE: N/R Time to first and subsequent: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: 2 pts had minor improvement, 0 had major improvement QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
	7.5mg/kg etidronate IV for 3 days followed by placebo (n=14)	Time to first SRE: N/R Time to first and subsequent: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: 2 pts had minor improvement, 2 had major improvement QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
	IV placebo followed by etidronate 200mg twice daily (n=15)	Time to first SRE: N/R Time to first and subsequent: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: 1 pts had minor improvement, 1 had major improvement QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
Strang 1997[89] Sweden	**Clodronate 300mg IV for 3 days followed by 3.2g for 4 weeks (n=25)**	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain:** No significant difference between groups QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR
	Placebo (n=27)	Time to first SRE: N/R Time to first and subsequent: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain:** No significant difference between groups QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR

	Placebo (n=14)	Time to first SRE: N/R Time to first and subsequent: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: 1 pts had minor improvement, 1 had major improvement, 3 recorded decrease in analgesic use QoL: N/R Overall survival: N/R	ONJ, renal impairment, acute phase reaction, hypocalcaemia or any other significant AE: NR

TABLE C OTHER SOLID TUMOURS

Study ID and country	Study arms (including number 327andomized)	SRE outcomes (primary outcome highlighted)	Other outcomes (primary outcome highlighted)	Adverse events
Arican 1999,[90] Turkey	**800 mg of clodronate once daily for 3 months (16)**	Time to first SRE: N/R Time to first and subsequent SRE (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion with SRE: -Radiotherapy = 2 patients -fracture = 0	Hypercalcaemia: 0 **Pain score** (% change 0 vs 3 months): -6.25 P**erformance status** (% change 0 vs 3 months): -6.25 QoL: N/R Overall survival: N/R	Hypocalcaemia:1 ONJ, renal impairment, acute phase reaction, or any other significant AE: NR
	1600 mg of oral clodronate once daily for 3 months (17)	Time to first SRE: N/R Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion with SRE: -Radiotherapy =1patient -fracture = 0	Hypercalcaemia: 0 **Pain score** (% change 0 vs 3 months): -15.29 **Performance status** (% change 0 vs 3 months): -13.23 QoL: N/R Overall survival: N/R	Hypocalcaemia:2 ONJ, renal impairment, acute phase reaction, or any other significant AE: NR
	placebo (17)	Time to first SRE: N/R Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion with SRE: -Radiotherapy = 5 patients -fracture = 0	Hypercalcaemia:1 **Pain score** (% change 0 vs 3 months): 0.6 **Performance status** (% change 0 vs 3 months): 0.0 QoL: N/R Overall survival: N/R	ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR

Berenson 2001,[91] US and UK	**0.4 mg zolendronic acid intravenously (as 2 hr infusion) every 4 weeks for up to 10 months (68)**	Time to first SRE: N/R Time to first and subsequent SRE (MEA): N/R Incidence of SREs: N/R SMR: N/R **Proportion with SRE:** Radiation to bone: 24% Any skeletal event + hypercalcemia=46% any skeletal event - hypercalcaemia= 44% pathologic fractures:28% spinal cord compression:1% surgery to bone: 7%	Hypercalcaemia: 7% Pain score (mean change from 0 to 18 months): -0.3 (SD 3.23) QoL: N/R Overall survival: N/R	ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR
	2.0 mg zolendronic acid intravenously (as 2 hr infusion) every 4 weeks for up to 10 months (72)	Time to first SRE: N/R Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR: N/R **Proportion with SRE** Radiation to bone: 19% any skeletal event + hypercalcemia= 35% any skeletal event - hypercalcaemia= 32% pathologic fractures: 22% spinal cord compression: 0 surgery to bone: 3%	Hypercalcaemia: 3% Pain score (mean change from 0 to 18 months): -0.6 (SD 2.19) QoL: N/R Overall survival: N/R	ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR

	4.0 mg zolendronic acid intravenously (as 2 hr infusion) every 4 weeks for up to 10 months (67)	Time to first SRE: N/R Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR: N/R **Proportion with SRE** Radiation to bone: 21% any skeletal event + hypercalcemia= 33% any skeletal event - hypercalcaemia= 33% pathologic fractures: 21% spinal cord compression: 3 surgery to bone: 3	Hypercalcaemia:0 score (mean change from 0 to 18 months):-0.7 (SD 3.33) QoL: N/R Overall survival: N/R	ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR
	90 mg pamidronate intravenously (as 2 hr infusion) every 4 weeks for up to 10 months (73)	Time to first SRE: N/R Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR: N/R **Proportion with SRE:** Radiation to bone: 18 any skeletal event + hypercalcemia=30 any skeletal event - hypercalcaemia= 30 pathologic fractures: 21 spinal cord compression: 3 surgery to bone: 4	Hypercalcaemia: 3% score (mean change from 0 to 18 months):-0.1 (SD 3.28) QoL: N/R Overall survival: N/R	ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR
Brown 2007,[92] Europe (six centres)	**800 mg, 1600 mg, 2400 mg or 3200 mg oral clodronate for 6 weeks (27)**	Time to first SRE: N/R Time to first and subsequent SRE (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemi: N/R Pain: 8 in 800 mg grp; 9 in 1600 mg grp; 8 in 2400 mg grp; 7 in 3200 mg grp; VAS studied but data not reported QoL: N/R Overall survival: N/R	Renal impairment: 1 (urinary retention in 3200 mg group) Hypocalcaemia: 1 (in 3200 mg group) ONJ, acute phase reaction, or any other significant AE: NR

	placebo for 6 weeks (24)	Time to first SRE: N/R Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: 7; VAS studied but data not reported QoL: N/R Overall survival: N/R	ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR
Heras 2007,[93] Greece	**6 mg intravenous ibandronate every 4 weeks for 9 months**	Time to first SRE: median 279 days (p=0.009) Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR (events/year): mean 2.36 (p=0.018) **Proportion with SRE**: 39% (p=0.019)	Hypercalcaemia: N/R Pain: N/R QoL: N/R Overall survival: N/R	"The incidence of renal adverse events was comparable to placebo" ONJ, hypocalcaemia, acute phase reaction, or any other significant AE: NR
	Placebo	Time to first SRE: median 93 days Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR (events/year): mean 3.14 **Proportion with SRE**: 78%	Hypercalcaemia: N/R Pain: N/R QoL: N/R Overall survival: N/R	Renal adverse events see above ONJ, hypocalcaemia, acute phase reaction, or any other significant AE: NR
Jagdev 2001,[94] UK	**1600 mg of oral clodronate once daily in two divided dose (18)**	Time to first SRE: N/R Time to first and subsequent SRE (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain:4/16 showed improvement in clinical score in 3 months** QoL: N/R Overall survival: N/R	ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR
	1500 mg of single intravenous clodronate + 1600 mg of oral clodronate once daily thereafter (15)	Time to first SRE: N/R Time to first and subsequent SRE (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain : 2/11 showed improvement in clinical score in 3 months** QoL: N/R Overall survival: N/R	ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR

	90 mg pamidronate intravenously as a monthly infusion (18)	Time to first SRE: N/R Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain:9/16 showed improvement in clinical score in 3 months (p<0.01 as compared to combination of above group)** QoL: N/R Overall survival: N/R	ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR
Lipton 2003,[101] US (retrospective subgroup analysis from RCT)	**4 mg zoledronic acid infusion every three weeks for 9 months (27)**	Time to first SRE: not reached, p=0.006; time to first pathologic fracture=not reached, p=0.003 Time to first and subsequent SRE (MEA): HR=0.394, p=0.008 Incidence of SREs: 37% (p=0.015) SMR: mean 2.68 events per year, p=0.014 **Proportion of each SRE**: <u>with 21-day window:</u> Any SRE=15 Radiation to bone=8 Vertebral pathologic fracture= 1 Nonvertebral pathologic fracture= 3 Surgery to bone=3 Spinal cord compression=1 <u>without 21-day window:</u> Any SRE=20 Radiation to bone=11 Vertebral pathologic fracture=1 Nonvertebral pathologic fracture= 3 Surgery to bone=3 Spinal cord compression=2	Hypercalcaemia: N/R Pain(bone): 14 QoL: N/R Overall survival: median 295 days, p=0.179	Renal impairment: 2/18 Hypocalcaemia:5 ONJ, acute phase reaction, or any other significant AE: NR

	8/4 mg zolendronic acid 8 mg reduced to 4 mg) every three weeks for 9 months (28)	Time to first SRE: mean 140 days, p=0.016; time to first pathologic fracture=not reached, p=0.027 Time to first and subsequent (MEA) Incidence of SREs: 50% (p=0.108) SMR: mean 1.67 events per year, p=0.026 Proportion of each SRE	Hypercalcaemia: N/R Pain (bone): 11 QoL: N/R Overall survival: N/R	Renal impairment: 4/21 Acute phase reaction Hypocalcaemia: 0 ONJ, acute phase reaction, or any other significant AE: NR
	placebo every three weeks for 9 months (19)	Time to first SRE: mean 72 days; time to first pathologic fracture=mean 168 days Time to first and subsequent (MEA) Incidence of SREs: 74% SMR: mean 3.38 per year **Proportion of each SRE** with 21-day window: Any SRE=20 Radiation to bone=9 Vertebral pathologic fracture= 4 Nonvertebral pathologic fracture= 9 Surgery to bone=4 Spinal cord compression=3 without 21-day window: Any SRE=35 Radiation to bone=12 Vertebral pathologic fracture=5 Nonvertebral pathologic fracture= 11 Surgery to bone=4 Spinal cord compression=3	Hypercalcaemia: N/R Pain (bone): 12 QoL: N/R Overall survival: median 216 days	Renal impairment: 3/15 Acute phase reaction Hypocalcaemia: 0 ONJ, acute phase reaction, or any other significant AE: NR

Mystakidou 2008,[95] Greece	**50 mg oral ibandronic acid once daily every 28 days(26)**	Time to first SRE: N/R Time to first and subsequent SRE (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: "bone pain scores decreased"; pain in general activity decreased by 65%; interference of pain in enjoyment of life was decreased by 75% QoL (mean increase from baseline at 6 months): physical score- 7.5; functional score- 6.5; physical 8 & functional 8 scores decreased Overall survival: 7 deaths in 6 months ("not related to drug")	ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR
	6 mg IV ibandronic acid infused over15 min every 28 days (26)	Time to first SRE: N/R Time to first and subsequent (MEA): N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain: "bone pain scores decreased"; pain in gneral activity decreased by 66%; interference of pain in enjoyment of life was decreased by 80% QoL (mean increase from baseline at 6 months): physical score - 6.0; functional score- 6.5; physical 8 & functional 8 scores decreased Overall survival: 2 deaths in 6 months ("not related to drug")	ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR

O'Rourke 1995,[96] UK	**400 mg oral sodium clodronate once daily for 4 weeks (20)**	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain score (mean change): 0.1 QoL: N/R Overall survival: N/R	ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR
	1600 mg oral sodium clodronate once daily for 4 weeks (19)	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain score (mean change): -0.7 QoL: N/R Overall survival: N/R	ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR
	3200 mg oral sodium clodronate once daily for 4 weeks (20)	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R Pain score (mean change): -0.5 QoL: N/R Overall survival: N/R	Hypocalcaemia: 1 Any other significant: flatulence=3 ONJ, renal impairment, acute phase reaction: NR
	placebo for 4 weeks (21)	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: 2 Pain score (mean change): -1.5 QoL: N/R Overall survival: N/R	Any other significant: N/R flatulence=0 ONJ, hypocalcaemia, renal impairment, acute phase reaction: NR

Piga 1998,[97] Italy	**1600 mg oral clodronate once daily for 12 months (27)**	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: "no difference in bone responses and rate of skeletal complications was detectable between the two groups" SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain score** (change from baseline & at 3 months): -1.1 (p=0.424) QoL: N/R Overall survival: N/R Karnofsky performance status: inrease 20%= 4.2% (p=0.323) decrease 20%=20.8% stable or minor change=75%	ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR
	Placebo once daily for 12 months (23)	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs:"no difference in bone responses and rate of skeletal complications was detectable between the two groups" SMR: N/R Proportion of each SRE: N/R	Hypercalcaemia: N/R **Pain score** (change from baseline & at 3 months): 1.3 QoL: N/R Overall survival: N/R Karnofsky performance status: inrease 20%= 0.0% decrease 20%=38.1% stable or minor change=61.9%	ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR
Robertson 1995,[98] UK	**1600 mg oral clodronate disodium (400mg capsules) once daily in divided doses (n=27)**	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: chemotherapy/radiotherapy=30% fracture= 15% spinal cord compression=N/R	Hypercalcaemia: N/R **Pain** (change in bone pain from entry to the average score on subsequent visits) median (range): -0.9 (-2.6 to -0.4), p=0.03 **QoL** (change in well being from entry), median (range): 0.3 (-1.0 to 1.2) Overall survival, median (range) days: 240 (25-518)	Hypocalcaemia: 2 ONJ, renal impairment, acute phase reaction, or any other significant AE: NR

	placebo (n=28)	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: chemotherapy/radiotherapy= 32% fracture= 7% spinal cord compression=11%	Hypercalcaemia: 7% **Pain** (change in bone pain from entry to the average score on subsequent visits) median (range): : 0.4 (-1.0 to 4.0) **QoL** (change in well being from entry), median (range): 0.0 (-1.2 to 0.8) Overall survival, median (range) days: 240 (20-486)	Hypocalcaemia: 0 ONJ, hypocalcaemia, renal impairment, acute phase reaction, or any other significant AE: NR
Zaghloul 2010,[99] Egypt	**4mg IV Zolendronic acid monthly for six months (20) + radiotherapy**	Time to first SRE, median weeks: 16 (4-65), p=0.0001 Time to first and subsequent SRE: HR 0.413 , p=0.008 Incidence of SREs ,mean (SD): 0.95 (0.9) per person year, p=0.001 SMR: N/R **Proportion with >= 1 SRE: 60%, p=0.010; 1 SRE=35%; 2 SRE=15%; 3 SREs= 10%**	Hypercalcaemia: N/R Pain score, mean (SD): 2.95 (0.3), p=0.015 QoL Overall survival : 36.3 (11.2), p=0.004; 1-year SRE free survival rate: 27.8 (10.4),p=0.001	ONJ: 0 Renal impairment (elevated Scr):7 Acute phase reaction: N/R Hypocalcaemia: N/R Any other significant: N/R
	placebo (20) + radiotherapy	Time to first SRE, median weeks: 8 (4-16) Time to first and subsequent SRE: see intervention group Incidence of SREs, mean (SD): 2.05 (1.0) per person year SMR: N/R **Proportion with >=1SRE: 90%; 1 SRE=20%; 2 SREs: 30%; 3 SREs=35%; 4 SREs:5%**	Hypercalcaemia: N/R Pain score,mean (SD): 4.37 (0.7) QoL: N/R Overall survival: 0; 1-year SRE free survival rate: 0	ONJ: 0 Renal impairment (elevated Scr): 5 Acute phase reaction: N/R Hypocalcaemia: N/R Any other significant: N/R

Zhao 2011,[211] China	**4mg IV Zolendronic acid 3 times in 4 weeks + chemotherapy and (30)**	Time to first SRE: N/R Time to first and subsequent SRE: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: 4	Hypercalcaemia: N/R Pain: N/R QoL: N/R Overall survival: median 20 months , p=0.27	ONJ: 0 Renal impairment: 0 Acute phase reaction: N/R Hypocalcaemia: N/R Any other significant: vomotting=16.7% anemia=13.3% thrombocytopenia=6.7%
	Chemotherapy (29)	Time to first SRE: N/R Time to first and subsequent: N/R Incidence of SREs: N/R SMR: N/R Proportion of each SRE: 4	Hypercalcaemia: N/R Pain: N/R QoL: N/R Overall survival: median 30 months	ONJ: 0 Renal impairment: 0 Acute phase reaction: N/R Hypocalcaemia: N/R Any other significant: vomotting=10.3% anemia=17.2% thrombocytopenia=3.4%

APPENDIX 8 CHARACTERISTICS OF STUDIES INCLUDED IN INDIRECT COMPARISON

Study Details	Participants	Cancer details	Intervention	Outcomes
BONE METASTASES FROM BREAST CANCER				
Author, year: **Kohno 2005[102]** **Country:** Japan **Duration of study:** 12 months **Funding source:** Novartis Pharmaceuticals	**Primary solid tumour: Breast cancer** **SRE definition:** pathologic fracture, spinal cord compression, surgery to bone, radiation therapy to bone, and HCM (secondary efficacy analyses only)New vertebral compression fractures were diagnosed if there was a decrease in total, anterior, or posterior vertebral height of ≥25% from baseline. **Demographics** **A** **B** Total n 228 Randomised, n 114 113 Age, mean, years 54.3 53.5 ECOG status, n (%) 0 76 (66.7) 74 (65.5) 1 25 (22) 27 (23.9) 2 8 (7.0) 6 (5.3) 3 5 (4.4) 6 (5.3) Pre SREs (excluding	**Primary cancer details** **A** **B** Time from initial diagnosis of cancer to study treatment, (1 month=28 days) Median, months 41.3 44.0 **Bone metastases details** **A** **B** Time from diagnosis of bone metastases to study treatment (1 month=28 days) Median, months 3.9 3.9 Prior treatment, n (%) Hormonal 29 (25.4) 41 (36.3) Chemotherapy 30 (26.3) 38 (33.7) Chemotherapy + hormonal 43 (37.7) 26 (23.0) None 12 (10.5) 8 (7.0)	**Intervention (A):** **Zoledronic acid 4 mg** (n=114) **Comparator (B):** **Placebo** (n=113) Both administered via 15-minute infusion. Infusions were administered every 4 weeks for 12 months	**SRE outcomes** *Ratio of SRE rate* (defined as the total number of SREs divided by the total years on study) for patients treated with zoledronic acid divided by the SRE rate for the placebo group (excluding HCM in definition) Proportion of patients experiencing at least one SRE Time to first SRE Multiple-event analysis by the Andersen-Gill method Risk ratio for developing SREs **Other outcomes** Change from baseline BPI composite pain scores and bone resorption markers **Adverse events of interest (AEs) or significant AEs** Hypocalcemia Renal adverse events Hypophosphatemia Bone pain Pyrexia Fatigue Upper abdominal pain

	HCM), n (%)				
	Pre pathologic fractures, n (%)	28 (24.6)	33 (29.2)		

Author, year: 2000[103] (Aredia trial), Long term follow up of two RCTs (Hortobagi 1996,[22] 1998[108] and Theriault 1998[116]) **Country**: US **Duration of study**: 24 months (24 cycles) **Funding**: Novartis Pharmaceuticals	**Primary solid tumour: breast cancer** **SRE definition:** Pathologic fracture, irradiation of or surgery on bone, spinal cord compression, or hypercalcaemia. **Demographics** Total, n: 754 Randomised, n: A 367, B 384 Age, n (%): A / B <50 years: 92 (25.1) / 110 (28.6) 51-65 years: 154 (42.0) / 145 (37.8) >65 years: 121 (33.0) / 129 (33.6) ECOG status, n (%): A / B 0: 77 (21) / 87 (22.7) 1: 188 (51.2) / 180 (46.9) 2: 72 (19.7) / 85 (22.1) 3: 30 (8.2) / 32 (8.3)	**Primary cancer details** A / B Presence of other metastases, n (%) Lung: 47 (12.8) / 49 (19.3) Liver: 49 (13.4) / 43 (11.2) Brain: 9 (2.5) / 3 (<1) Other: 41 (11.2) / 47 (12.2) None: 236 (64.3) / 254 (66.2) **Bone metastases details** A / B Time from diagnosis of bone metastases to randomisation, n (%) <2 years: 130 (35.4) / 151 (39.3) >=2 years: 237 (64.6) / 233 (60.7) Prior treatment, n (%) Hormonal: 98 (26.7) / 99 (25.8) Chemotherapy: 32 (8.8) / 45 (11.7) Chemotherapy + hormonal: 236 (64.3) / 239 (62.2) None: 1 (<1) / 1 (<1)	**Intervention (A): Pamidronate 90 mg** (n=367) **Comparator (B): Placebo** (n=384) Both administered in 250 mL of 5% dextrose in water given as a 2-hour intravenous infusion every 3-4 weeks for 24 cycles.	**SRE outcomes** *SMR* (number of skeletal complications per time on trial for each patient (events/year); the overall SMR was calculated with and without hypercalcemia counted as a skeletal complication *Proportion of patient with skeletal complications* Time from randomisation to first SRE **Other outcomes** Bone pain score, analgesic use, ECOG performance status and quality of life measured as mean change from baseline to 24 months or last visit (any time during study); Overall survival **Adverse events of interest (AEs) or significant AEs:** Hypocalcaemia Allergic reaction in the left eye Interstitial pulmonary infiltrate Dyspnea

Author, year:
Rosen 2003a[104]
Secondary reports:
Rosen 2001,[109]
Rosen 2004, [110]

Rosen 2003[104]-extension phased - 25 month safety and efficacy of Rosen 2001.[109]
Includes breast and myeloma patients but some breast cancer data reported separately

Country:
Multinational

Duration of study:
25 months [Rosen 2003[104]], 12 months [Rosen 2004[110]]

Funding source:
Novartis Pharmaceuticals

Primary solid tumour: Breast cancer

SRE definition: pathologic fracture, spinal cord compression, radiation therapy, or surgery to bone. Hypercalcemia of malignancy (HCM) was not included in the definition of SREs, because zoledronic acid already has demonstrated efficacy in treating HCM.) HCM was included as an SRE in some secondary analyses.

Demographics

	A	B
Total, n	1130^	
Randomised, n	378	388
Age, median, years	58	56
ECOG status, n (%)		
0-1	328 (86.8)	316 (81.4
>=2	49 (13.0)	70 (18.0)
Pre SREs, n (%)	232 (61.4)	244 (62.9)

^In June 2000, as a result of concerns over renal safety at the higher dose level, required patients originally randomized to receive 8 mg of zoledronic acid to receive 4 mg of zoledronic acid instead; this arm is referred to hereafter as the 8/4-mg arm. For all efficacy variables analyzed, only the 4-mg zoledronic acid arm was used to assess the effectiveness

Primary cancer details

	A	B
Time since diagnosis, mean(SD), months	78(67)	71(62)

Bone metastases details

	A	B
Lesion type, n (%)		
Lytic lesion	190 (50.3)	162 (41.6)
Nonlytic lesion	188 (49.5)	226 (58.3)
Primary therapy, n (%)		
Chemotherapy	178 (47.1)	181 (46.7)
Hormone therapy	200 (53.0)	207 (53.4)

Intervention (A):
Zoledronic acid 4 mg or 8 mg
(n=378)

Comparator (B):
Pamidronate 90 mg
(n=388)

Both administered as an intravenous infusion depending on the scheduling of other antineoplastic treatments every 3–4 weeks for 24 months

Zoledronic acid was initially infused over 5 mins in 50 ml hydration solution; however, because of safety concernsover renal safety a protocol amendment in June 1999 changed the infusion time to 15 minutes and increased infusion volume to 100 ml

SRE outcomes
Proportion of patients who experienced at least 1 SRE during 25 month study period (HCM not included).
Proportion of patients experiencing any SRE (including HCM)
Time to first SRE
SMR
Multiple-event analysis.

(For SMR and multiple event analysis, a 21-day event window was used for counting SREs, such that any event occurring within 21 days of a previous event was not counted. Analyses were performed using the SRE endpoint with and without inclusion of HCM.) Efficacy analysis, n= A 377; B 389

Other outcomes
None reported

Adverse events of interest (AEs) or significant AEs:
Bone pain
Renal impairment (a change from baseline)

	of treatment with zoledronic acid versus pamidronate (because the 8/4-mg dose group was not homogeneous with regard to the dose delivered). **There were 364 patients in 8/4 mg group.**			

Author, year: **Stopeck 2010**[31] (secondary reports-??? Fallowfield 2010a,[107] Fallowfield 2010b,[106] Martin 2011,[117] Stopeck 2010b-f[111-115]

Country: Europe, North America, South America, Japan, Australia, India, and South Africa

Duration of study: From first patient enrollment to primary analysis ~ 34 months

Funding source: Amgen and Daiichi Sankyo

Primary solid tumour: Breast cancer

SRE definition: pathologic fracture, radiation or surgery to bone, or spinal cord compression

Demographics

	A	B
Randomised, n	1026	1020
Age, mean, years	57	56
No of females (%)	1018 (99.2)	1011 (99.1)
No. of postmenopausal women (%)	839 (82.3)	831 (81.8)
ECOG status, n (%)		
0	504 (49.1)	488 (47.8)
1	451 (44.0)	444 (43.5)
2	68 (6.7)	82 (8.0)
Missing or other	3 (<1)	6 (<1)
Pre SREs, n (%)	378 (36.8)	373 (36.6)

Primary cancer details

	A	B
Time from cancer diagnosis to initial diagnosis of bone metastases, median, months	32.8	35.4
Presence of other metastases, n (%)		
Lung	216 (21.1)	210 (20.6)
Liver	211 (20.6)	182 (17.8)
Other	369 (36.0)	369 (36.2)

Bone metastases details

	A	B
Time from initial diagnosis of bone metastases to random assignment, median, months	2.1	2.0
More than two metastases bone lesions, n (%)	242 (23.6)	240 (23.5)
Prior treatment, n (%)		
Hormonal	755 (73.6)	728 (71.4)

Intervention (A): **Denosumab 120 mg** (subcutaneous injection) + **placebo** (intravenous infusion) (n=1026)

Comparator (B): **Zoledronic acid 4 mg** (intravenous infusion, lasting no less than 15 minutes) + **placebo** (subcutaneous injection) (n=1020)

All administered every 4 weeks

Intravenous products (placebo or zoledronic acid) were dose-adjusted on the basis of baseline creatinine clearance 60 mL/min and were held for renal function deterioration on-study (until serum creatinine returned to within 10% of baseline values), per zoledronic acid prescribing information

SRE outcomes

Time to first on-study SRE (non-inferiority test)

Time to first on-study SRE (superiority test)

Time to first and subsequent on-study SREs (multiple event analysis).

[Subsequent events must have occurred at least 21 days apart from the most recent event to ensure that linked events (eg, surgery to repair a fracture or multiple doses of radiation during a course of treatment) were not counted as separate SREs.]

Other outcomes

Overall survival

Disease progression

Skeletal morbidity rate (allowing one event per assessing period [3 weeks])

Percent change from baseline to week 13 in uNTx and BSAP levels.

Adverse events of interest (AEs) or significant AEs:

Incidence of antidenosumab antibodies

Osteonecrosis of the jaw

Acute phase reaction

Renal impairment

Bone pain

		Chemotherapy	A 831 (81)	825 (80.9		
		Recent chemotherapy	410 (40.0)	410 (40.2)		
		Oral biphosphonates	42 (4.1)	38(3.8)		

BONE METASTASES FROM PROSTATE CANCER

Author, year:
Fizazi 2011[29]

Country: 39 countries (multinational)

Duration of study: between May, 2006, and October, 2009; from enrolment to discontinuation for individual patients, or until the primary analysis cut off date (27 months), whichever occurred first.

Funding source: Amgen

Primary solid tumor: Prostate cancer
SRE definition: Pathological fracture (excluding fractures from severe trauma), radiation therapy to bone (including use of radioisotopes), surgery to bone, or spinal cord compression. New bone metastases (symptomatic or asymptomatic were not included)

Demographics

	A	**B**
Randomised, n	950	951
Age , median (IQR), years	71 (64-77)	71 (66-77)
Age>=65 yeras, n(%)	697 (73)	735 (77)
Ethnicity, n (%)		
White	829 (87)	810 (85)
Other	121 (13)	141 (15)
No. of females (%)	1018 (99.2)	1011 (99.1)
ECOG status, n (%)		
0-1	882 (93)	886 (93)
Pre SREs, n (%):	232 (24)	231 (24)
Gleason score at diagnosis, n (%)		
2-6	175 (18)	180 (19)

Primary cancer details

	A	**B**
Time from diagnosis to randomisation		
median(IQR), months	37.5 (18.1-75.4)	41.2 (18.3-82.0)
Presence of visceral metastates, n (%)	161 (17)	181 (19)

Bone metastases details

	A	**B**
Time from diagnosis of bone metastases to randomisation		
median(IQR), months	3.94 (1.22-15.67)	5.19 (1.31-16.10)
Prior treatment, n (%)		
recent chemotherapy	132 (14)	132 (14)

Intervention (A):
Denosumab 120 mg (subcutaneous) + **placebo** (intravenous for at least 15 mins)
(n=950)

Comparator (B):
Zoledronic acid 4 mg (intravenousfor at least 15 mins) + **placebo** (subcutaneous)
(n=951)

For every 4 weeks until the primary analysis cut off date

Intravenous products (placebo or zoledronic acid) were dose-adjusted on the basis of baseline creatinine clearance 60 mL/min and were held for renal function deterioration on-study (until serum creatinine returned to within 10% of baseline values), per zoledronic acid prescribing information

SRE outcomes
Time to first on-study skeletal-related event; assessed for noninferiorit
If testing of the primary endpoint showed non-inferiority, then the same outcome was further tested as a secondary endpoint, together with the secondary endpoint of time to first and subsequent on-study skeletal-related events (multiple events), for superiority
Other outcomes
Overall survival
Overall disease progression (encompassing visceral distant metastatic disease, locoregional progression, and biochemical progression, and excluding skeletal-related events);
Prostate-specific antigen concentration during the study (assesed every 12 weeks)
Change in bone turnover markers from baseline (assessed every 13weeks)
Pain
Adverse events of interest (AEs) or significant AEs
Hypocalcemia,
ONJ,
infectious adverse events,
new primary malignant disease

	7	273 (29)	280 (29)		
	8-10	394 (41)	408 (43)		
	missing	108 (11)	83 (9)		

Author, year:
Saad 2002[118]
Secondary reports: Saad 2004a,[124] Saad 2004b,[122] Saad 2005,[121] Saad 2007a,[19] Saad 2007b,[212] Saad 2010,[119] Weinfurt 2006[129]
Country: US, Europe, S. America and Australasia

Duration of study: Treatment exposure: 15 months; **A-** mean (SD) 8.8 (5.3) to 9.4 (5.8) months; B- 9.0 (5.4) months.

Follow-up bone scans were done 6 and 15 months after enrolment. (Saad 2004 report 24 months outcome)
Extension phase: 24months (from months 15 to 24) (i.e., the extension phase only)

Funding: Novartis Pharmaceuticals

Primary solid tumour: Prostate cancer

SRE definition: pathologic bone fractures (vertebral or nonvertebral), spinal cord compression, surgery to bone, radiation therapy to bone (including the use of radioisotopes) or a change of antineoplastic therapy to treat bone pain

Demographics

	A	B
Total, n	643	
Randomised, n	214	208
Age, mean (SD), years	71.8 (7.9)	72.2 (8.0)
Ethnicity, n (%)		
White	178 (38)	173 (83)
Black	24 (11)	19 ( )
Other	12 (6)	17 (8)
ECOG performance status, n (%)		
0	85 (39.7)	93 (44.7)
1	112 (52.3)	97 (46.6)
>2	17 (7.9)	18 (8.7)
missing	0	0
Pre SREs, n		7

Primary cancer details

	A	B
Time since diagnosis, mean (SD	62.2 (43.5)	66.6 (46.9)
Presence of metastases, n (%)		
Bone	212 (99.1)	205 (98.6)
Distant lymph nodes	29 (13.6)	15 (7.2)
Lung	6 (2.8)	5 (2.4)
Liver	1 (0.5)	1 (0.5)

Bone metastases details

	A	B
Time since first bone metastases diagnosis		
mean (SD), months	23.8 (26.1)	28.4 (30.7)
Median months	16.1	17.8

Intervention (A):
Zolendronic acid 4mg (n=214)

Comparator (B):
Placebo
(n=208)

Administered every 3 weeks for 15 months (20 cycles). Initially 5 min infusion (in 50ml), changed to 15 min infusion (in 100ml) in 1999

SRE outcomes
The proportion of patients having at least one skeletal-related event
Time to the first skeletal- related event
Skeletal morbidity rate Proportion of patients with individual skeletal-related events

Other outcomes
Time to disease progression
Objective bone lesion response
Bone biochemical markers
Quality-of-life parameters (Quality-of-life parameters included a pain score assessed with the Brief Pain Inventory (BPI) (26), analgesic scores, ECOG performance status, and two quality-of-life questionnaires: Functional Assessment of Cancer Therapy-General (FACT-G), version 4 (27) and EURO Quality of Life EQ-5D (EURO QOL))
Adverse events of interest (AEs) or significant AEs:
Bone pain
ONJ
Hypocalcemia
Renal impairment

	(%) 66 (30.8) 8 (37.5)			

BONE METASTASES FROM OTHER SOLID TUMOURS

Author, year:
Henry 2011[30]
(Henry 2010 abstract,[133] von Moos 2010 abstract[135])

Country: multi-centred and multinational

Duration of study: Patients were observed for survival for 2 years after the last dose of blinded investigational product, primary analysis was conducted 34 months after enrolment initiated

Patients were evaluated on study day 1 and Q4W thereafter. Oral examinations were conducted at baseline and every 6 months thereafter

Median time on-study (months)= 7

Primary solid tumour: Other solid tumors

SRE definition: Pathologic fracture, radiation or surgery to bone, spinal cord compression. A subsequent SRE was defined as an event occurring 21 days after the previous SRE.

Demographics

	A	B
Total, n	1779	
Randomised, n	890	886
Age, median (range) years	61 (22-87)	60 (19-89)
Sex, male, n (%)	552 (62)	588 (66)
ECOG status, n (%)		
0	236 (27)	240 (27)
1	492 (55)	508 (57)
2	157 (18)	136 (15)
missing	5 (<1)	2 (<1)
Primary tumor type, n (%)		
NSCLC	352 (40)	350 (39)
Multiple	93 (10)	87 (10)

Primary cancer details

	A	B
Presence of other metastases, n (%)		
Liver	167 (19)	171 (19)
Lung	162 (18)	239 (27)
Other	340 (38)	319 (36)
Total	448 (50)	474 (54)

Bone metastases details

	A	B
Time from diagnosis of bone metastases to randomisation, median (range)	2 (0-130)	2 (0-152)
Prior treatment, n (%)		
Anti-neoplastic treatment	855 (96)	845 (95)
Systemic anti-cancer therapy	770 (87)	767 (87)
Radiotherapy	353 (40)	324 (37)
Surgery	406 (46)	409 (46)

Intervention (A):
Denosumab 120 mg (n=890)

Denosumab administered sub-cutaneously monthly with intravenous placebo

Comparator (B):
Zoledronic acid 4 mg (n=886)

Zoledronic acid administered intravenously monthly with subcutaneous placebo.

Co- intervention: calcium (>500mg) and Vitamin D (>400 U) strongly recommended in each group.

SRE outcomes
Time to first on-study SRE (non-inferiority)
Time to first on-study SRE (superiority tests)
Time to first-and-subsequent SRE (multiple-event analysis).

Other outcomes
Exploratory end points included bone turnover markers (measured at baseline and week 13), overall survival, and overall disease progression.

Adverse events of interest (AEs) or significant AEs:
Acute phase reactions, hypocalcaemia, renal adverse events, adjudicated positive ONJ, serious adverse events reported.

Funding: Amgen	myeloma other 455 (50) 449 (51) Prior SRE 446 (50) 440 (50)		Other 20 (2) 15 (2) Prior BP use 24 (3) 28 (3)		

Author, year:
Rosen 2003b[131]
(Rosen 2004b[134], Schulman 2004[136])

Country: USA, Canada, Australia, Poland

Duration of study: 9 months

Funding: Novartis

Primary solid tumour: Other solid tumors

SRE definition: Pathologic fracture, radiation therapy to bone, surgery to bone and spinal cord compression. For secondary analyses hypercalcaemia was included in the definition.

Demographics

	A	**B**
Randomised, n	257	250
Age, median (range) years	64	64
Sex, male, n (%)	158 ()	159 ()
ECOG status, n (%)		
1or less	211 (83)	215(87)
2 or more	42 (17)	32 (13)
missing	5 (<1)	2 (<1)
Primary tumor type, n (%)		
NSCLC	124 (49)	120 (49)
SCLC	17 (7)	19 (8)
Renal cell carcinoma	27 (11)	19 (8)
Unknown	18 (7)	17 (7)

Primary cancer details

	A	**B**
Median time from initial diagnosis, months	3.8	2.5

Bone metastases details

	A	**B**
Prior treatment, n (%)		
Chemotherapy	207 (82)	197 (80)
Hormonal therapy	3 (1)	2(1)

Patients were also excluded if they had more than a single exposure to a bisphosphonate within 30 days

Intervention (A): Zoledronic acid 4 mg (n=257)

Administered intravenously every 3 weeks for 9 months (initially over 5 minutes in 50 ml but changed to over 15 minutes in 100 mls.

Comparator (B): Placebo (n=250)

Administered intravenously for every 3 weeks for 9 months.

Co- intervention: calcium (500mg) and a multivitamin tablet containing vitamin D (400 to 500 U) to all patients throughout the study.

SRE outcomes
Proportion of patients with at least one SRE
Time to first SRE
SMR (defined as the number of SREs per year) Multiple event analysis

Other outcomes
Change from baseline in BPI composite pain score, analgesic use, ECOG performance status, best bone lesion response, time to progression of bone lesions, changes from baseline in biochemical markers of bone resorption, time to progression of overall disease, and survival. Quality of life was measured using the Function Assessment of Cancer Therapy – General (FACT-G) instrument, and analyzed using a random effect pattern mixture model.

Adverse events of interest (AEs) or significant AEs:
Bone pain reported.

	primary				
	Head and neck	6 (2)	4 (2)		
	Thyroid	2 (1)	4 (2)		
	Other	60 (24)	64 (26)		
	Prior SRE	166 (65)	179 (73)		

APPENDIX 9 QUALITY ASSESSMENT RESULTS FOR THE INDIVIDUAL STUDIES

Study id	Q1 Adequate sequence generation?	Q2 Adequate allocation concealment?	Q3 Blinding?	Q4 Incomplete outcome data addressed?	Q5 Free of selective reporting?
Breast cancer					
Lipton 2000[103]	Yes	Yes	Yes	Unclear	Unclear
Kohno 2005[102]	Yes	Yes	Yes	No	Yes
Stopeck 2010[31]	Unclear	Unclear	Yes	Yes	Yes
Rosen 2003a[104]	Yes	Yes	Yes	Yes	Yes
Prostate cancer					
Fizazi 2011[29]	Yes	Yes	Yes	Yes	Yes
Saad 2002[118]	Yes	Yes	Yes	Yes	Yes
Other solid tumours					
Henry 2011[30]	Yes	Yes	Yes	Yes	Yes
Rosen 2003b[131]	Unclear	Unclear	Yes	No	Yes

APPENDIX 10 BREAST ADVERSE EVENTS

	Study																				
	CSR Stopeck		**Rosen 04[110]**		**Lipton 2000[103 22]**		**Kohno 05[102] (only grade 4 hypocal)**		**Body 04[72]**		**Diel 04[141] Jackson 05[151] (renal) Pecherstorfer 06[155] (extension)**		**Paterson 93[76]**		**Kirsten sen 99[75]**		**Carteni 06[166] (pooled)**	**Coleman 11[140] (AZURE abstract)**		**Houston 10[β149]**	
Intervention	D	Z	Z	P	P	PL	Z	PL	I*	PL	I**	PL	C	PL	C	NT	Z[§]	Z	NT	Z	I*
Time (years)	1.31	1.32	1.08	1.08	1.65	1.48	114	113	1.5	1.33	1.51 (0.87)	1.09 (1.37)	1.17	1.21	1.53	1.5	1.08	3	3	98	91
Number analysis	1013	1020	378	388	367	386	1	1	287	277	154 (46)	158 (16)	85	88	49	51	177	1665	1675	N/R	N/R
Adverse event	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ONJ	20 (2.0)	14 (1.4)																11 (0.7)	0		
Renal toxicity	2 (0.2)	15 (1.5)	29 (7.7)	23 (5.9)			0	1 (0.9)	15 (5.2)	13 (4.7)	6 (3.9)	7 (4.4)					1 (0.6)	2 (0.1)	1 (0.1)	2 (2.0)	2 (2.2)
Hypercalcaemia	2 (0.2)	11 (1.1)			21 (5.7)	49 (12.7)	3 (2.6)	10 (8.8)					28 (32.0)	52 (59.1)	5 (10.2)	5 (9.8)					
Hypocalcaemia	6 (0.6)	4 (0.4)			3 (0.8)	3 (0.8)	1 (0.9)	1 (0.9)	27 (9.4)	14 (5.1)					13 (26.5)	2 (3.9)	28 (15.8)				
Skin Infection	9 (0.9)	5 (0.5)																10 (0.6)	8 (0.5)		
Abdominal	19	16					19	8 (7.1)	6	2											

	Study																					
	CSR Stopeck		**Rosen 04[110]**		**Lipton 2000[103 22]**		**Kohno 05[102] (only grade 4 hypocal)**		**Body 04[72]**		**Diel 04[141] Jackson 05[151] (renal) Pecherstorfer 06[155] (extension)**		**Paterson 93[76]**		**Kirstensen 99[75]**		**Carteni 06[166] (pooled)**		**Coleman 11[140] (AZURE abstract)**		**Houston 10[β149]**	
pain	(1.9)	(1.6)					(16.7)		(2.1)	(0.7)												
Alopecia			67 (17.7)	57 (14.7)			15 (13.2)	22 (19.5)														
Anaemia	34 (3.4)	39 (3.9)	96 (25.4)	91 (23.5)																		
Arthralgia			90 (23.8)	76 (19.6)			24 (21.1)	18 (15.9)														
Asthenia	12 (1.2)	16 (1.6)	77 (20.4)	64 (16.5)													8 (4.5)					
Bone pain	11 (1.1)	14 (1.4)	228 (60.3)	223 (57.5)			36 (31.6)	51 (45.1)									32 (18.1)					
Constipation			92 (24.3)	100 (25.8)			33 (28.9)	37 (32.7)					4 (4.7)	5 (5.7)								
Cough			87 (23.0)	77 (19.8)																		
Dehydration	13 (1.3)	26 (2.5)																				
Diarrhoea	19 (1.9)	16 (1.6)	89 (23.5)	94 (24.2)			29 (25.4)	29 (25.7)					5 (5.9)	2 (2.3)								
Dizziness							17 (14.9)	25 (22.1)														

	Study																			
	CSR Stopeck		Rosen 04[110]		Lipton 2000[103 22]		Kohno 05[102] (only grade 4 hypocal)		Body 04[72]		Diel 04[141] Jackson 05[151] (renal) Pecherstorfer 06[155] (extension)		Paterson 93[76]		Kirsten sen 99[75]		Carteni 06[166] (pooled)	Coleman 11[140] (AZURE abstract)		Houston 10[β149]	
Dyspepsia									20 (7.0)	13 (4.7)										
Dyspnoea	67 (6.6)	47 (4.6)	98 (25.9)	94 (24.2)			21 (18.4)	15 (13.3)												
Esophagitis									6 (2.1)	2 (0.7)										
Fatigue	18 (1.8)	5 (0.5)	152 (40.2)	159 (41.0)	147 (40.1)	107 (27.7)	51 (44.7)	36 (31.9)												
Flu-like symptoms											10 (6.5)	3 (1.9)							4 (4.1)	0
GI symptoms													2 (2.4)	1 (1.1)					12 (12.2)	12 (13.2)
General physical health deterioration	22 (2.2)	16 (1.6)																		
Headache	16 (1.6)	9 (0.9)	70 (18.5)	94 (24.2)			34 (29.8)	32 (28.3)			6 (13.0)	1 (6.3)	1 (1.2)	0			7 (4.0)			
Hepatic failure	32 (3.2)	20 (2.0)																		
Metastases to liver	23 (2.3)	32 (3.1)																		
Myalgia			106 (28.	95 (24.																

	Study																			
	CSR Stopeck		**Rosen 04[110]**		**Lipton 2000[103 22]**		**Kohno 05[102] (only grade 4 hypocal)**		**Body 04[72]**		**Diel 04[141] Jackson 05[151] (renal) Pecherstorfer 06[155] (extension)**		**Paterson 93[76]**		**Kirsten sen 99[75]**		**Carteni 06[166] (pooled)**	**Coleman 11[140] (AZURE abstract)**		**Houston 10[β149]**	
			0)	5)																	
Nausea	26 (2.6)	26 (2.5)	180 (47.6)	179 (46.1)			57 (50.0)	60 (53.1)	10 (3.5)	4 (1.4)			18 (21.2)	19 (20.5)			9 (5.1)				
Neutropenia	18 (1.8)	25 (2.5)					18 (15.8)	19 (16.8)										8 (0.5)	10 (0.6)		
Oedema peripheral			58 (15.3)	73 (18.8)																	
Pleural effusion	31 (3.1	32 (3.1)																			
Pulmonary embolism	11 (1.1)	21 (2.1)																			
Pyrexia	22 (2.2)	20 (2.9)	118 (31.2)	103 (26.5)	51 (13.9)	19 (4.9)	63 (55.3)	37 (32.7)									67 (37.()	4 (0.2)	3 (0.2)		
Respiratory failure	24 (2.4)	20 (2.0)																			
Thrombocytopenia	14 (1.4)	15 (1.5)																			
Vomiting	40 (3.9)	36 (3.5)	119 (31.5)	120 (30.9)			37 (32.5)	44 (38.9					7 (8.2)	10 (11.4)			10 (5.6)				

D = denosumab 120mg 4 weekly, Z = zoledronic acid 4mg 4 weekly, I* = ibandronic acid 50mg orally, I** = ibandronic acid 6mg IV, C* = 1.6g daily, Z[§] = 4mg and 3mg combined, PL = placebo and NT = no treatement

[β] = observational study

APPENDIX 11 PROSTATE ADVERSE EVENTS

	Study															
	CSR Fizazzi		**Saad 2002[118]**		**Dearnaley 03[79]**		**Elomaa 92[80]**		**Kylmala 97[83]**		**Small 03[87]**		**Walter 08[¥161]**	**Garcia - Saenz 07[¥145]**	**Oh 07[¥153]**	**Bamias 05[¥62]**
Intervention	D	Z	Z	PL	C*	PL	C**	PL	C**	PL	P	PL	VB	VB	Z	VB
Time	1.10	1.04	0.78	0.75	1.43	1.34	0.5	0.5	1	1	0.52	0.52	NR	NR	0.817	1.2
Number	943	945	214	208	155	156	36	39	28	29	180	194	43	104	122	46
Adverse event	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ONJ	22 (2.3)	12 (1.3)											8 (18.6)	3 (2.9)		3 (6.5)
Renal toxicity	52 (5.5)	52 (5.5)	7 (3.3)	2 (1.0)					0		0	0			29 (23.8)	
Hypercalcaemia	0	0									1 (0.6)	2 (1.0)				
Hypocalcaemia	42 (4.5)	8 (0.8)	4 (1.9)	0	5 (3.2)	0										
Skin infection	11 (1.2)	9 (1.0)														
Anaemia	167 (17.7)	120 (13.7)	57 (26.6)	37 (17.8)							3 (1.7)	8 (4.1)				
Anorexia			43 (20.1)	36 (17.3)							1 (0.6)	3 (1.5)				
Arthralgia	12 (1.3)	9 (1.0)			11 (7.1)	10 (6.4)										
Asthenia	43 (4.6)	33 (3.5)	45 (21.0)	40 (19.2)							3 (1.7)	8 (4.1)				
Blood creatinine increased	10 (1.1)	0														

	Study															
	CSR Fizazzi		**Saad 2002[118]**		**Dearnaley 03[79]**		**Elomaa 92[80]**		**Kylmala 97[83]**		**Small 03[87]**		**Walter 08[¥161]**	**Garcia - Saenz 07[¥145]**	**Oh 07[¥153]**	**Bamias 05[¥62]**
Bone pain	29 (3.1)	41 (4.3)	108 (50.5)	127 (61.1)	1 (0.6)	3 (1.9)					10 (5.5)	4 (2.1)				
Cardiovascular problems					12 (7.7)	11 (7.1)										
Cerebrovascular accident	16 (1.7)	5 (0.5)														
Chest pain	9 (1.0)	13 (1.4)														
Confusional state	13 (1.4)	12 (1.3)			0	1 (0.6)										
Constipation	7 (0.7)	10 (1.1)	72 (33.6)	72 (34.6)							0	3 (1.5)				
Dehydration	43 (4.6)	20 (2.1)														
Diarrhoea	15 (1.6)	13 (1.4)	36 (16.8)	32 (15.4)							3 (1.7)	2 (1.0)				
Dizziness			38 (17.8)	24 (11.5)	1 (0.6)	2 (1.3)					0	0				
Dyspnoea	43 (4.6)	32 (3.4)			4 (2.6)	4 (2.6)					5 (2.8)	2 (1.0)				
Fatigue	21 (2.2)	11 (1.2)	70 (32.7)	53 (25.5)							3 (1.7)	0				
Gastrointestinal problems					31 (20)	21 (13.5)										
General physical health deterioration	33 (3.5)	36 (3.8)			2 (1.3)	4 (2.6)										
Haematuria	32 (3.4)	50 (5.3)														
Hepatic failure	13 (1.4)	6 (0.6)			1 (0.6)	0										

	Study															
	CSR Fizazzi		Saad 2002[118]		Dearnaley 03[79]		Elomaa 92[80]		Kylmala 97[83]		Small 03[87]		Walter 08[¥161]	Garcia - Saenz 07[¥145]	Oh 07[¥153]	Bamias 05[¥62]
Hydronephrosis	22 (2.3)	15 (1.6)														
Increased LDH					25 (16.1)	0										
Muscular weakness	10 (1.1)	4 (0.4)														
Myalgia			53 (24.8)	37 (17.8)												
Myocardial infarction	10 (1.1)	13 (1.4)														
Nausea	12 (1.3)	16 (1.7)	77 (36.0)	77 (37.0)			3 (8.3)	7 (17.9)	9 (32.1)	12 (41.4)	5 (2.8)	3 (1.5)				
Oedema peripheral	13 (1.4)	8 (0.8)	41 (19.2)	27 (13.0)												
Performance status decreased	10 (1.1)	2 (0.2)														
Pleural effusion	16 (1.7)	12 (1.3)														
Pneumonia	47 (5.0)	26 (2.8)														
Pulmonary embolism	24 (2.5)	17 (1.8)														
Pyrexia	21 (2.2)	26 (2.8)	43 (20.1)	27 (13.0)							3 (1.7)	1 (0.5)				
Respiratory failure	25 (2.7)	14 (1.5)														
Sepsis	13 (1.4)	11 (1.2)														
Thrombocytopenia	12 (1.3)	5 (0.5)														
Urinary tract infection	33 (3.5)	40 (4.2)									1 (0.6)	3 (1.5				

	Study															
	CSR Fizazzi		**Saad 2002[118]**		**Dearnaley 03[79]**		**Elomaa 92[80]**		**Kylmala 97[83]**		**Small 03[87]**		**Walter 08[¥161]**	**Garcia - Saenz 07[¥145]**	**Oh 07[¥153]**	**Bamias 05[¥62]**
												)				
Vomiting	27 (2.9)	26 (2.8)	46 (21.5)	43 (20.7)							5 (2.8)	3 (1.5)				
Weight decrease			36 (16.8)	26 (12.5)							0	0				

D= denosumab 120mg 4 weekly, P = pamidronate 90mg IV 4 weekyl, PL = placebo, Clod* = clodronate 2.08g per day orally, Clod **= Clod** = clodronate 3.2g initially then 1.6g, VB = various bisphosphonates [¥] = observational studies

APPENDIX 12 OTHER SOLID TUMOURS ADVERSE EVENTS

TABLE A

	CSR Henry		**Arican 99[90]**		**Berenson 01[91]**		**Body 10[165]**		**Brown 07[92]**		**O'Rourke 95[96]**		**Rosen 03+04[131,134]**		**Tralongo 04[¥159]**	**Zuradelli 09[¥162]**
Tumour types	**All, including MM, excl breast and prostate**		**All**		**Breast and MM**		**All**		**All**		**All**		**All, excl breast and prostate**		**Breast, prostate and MM**	**All**
Intervention	D	Z	C	CL	Z	P	VB	D*	PL	C	PL	C	Z	PL	P	Z
Time (years)	0.8	0.8	0.25	0.25	0.83	0.83	1.10	1.10	0.12	0.12	0.08	0.08	1.75	1.75	1.58	NR
Number	878	878	17	17	66	73	78	284	24	25	21	19	254	247	22	240
															(>70 y.o)	
Adverse event																
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abdominal pain	20 (2.3)	17 (1.9)			10 (15, 2)	13 (17.8)										
Anaemia	31 (3.5)	66 (7.5)			16 (24.2)	15 (20.5)	10 (12.8)	40 (14.1)					97 (38.2)	86 (34.8)		
Anorexia	9 (1.0)	8 (0.9)			18 (27.3)	8 (11.0)							62 (24.4)	66 (26.7)		
Arthralgia					15	12	14	30					37	42		

	CSR Henry		Arican 99[90]		Berenson 01[91]		Body 10[165]		Brown 07[92]		O'Rourke 95[96]		Rosen 03+04[131,134]		Tralongo 04[¥159]	Zuradelli 09[¥162]
Tumour types	**All, including MM, excl breast and prostate**		**All**		**Breast and MM**		**All**		**All**		**All**		**All, excl breast and prostate**		**Breast, prostate and MM**	**All**
					(22.7)	(16.4)	(17.9)	(10.6)					(14.6)	(17.0)		
Asthenia	25 (2.8)	17 (1.9)					19 (24.4)	49 (17.3)					74 (29.1)	70 (28.3)		
Cachexia	4 (0.5)	12 (1.4)														
Cardiac failure	12 (1.4)	6 (0.7)														
Confusional state	5 (0.6)	11 (1.3)	1 (5.9)	0												
Constipation	4 (0.5)	9 (1.0)			16 (24.2)	15 (20.5)	13 (16.7)	42 (14.8)					91 (35.8)	94 (38.1)		
Cough					15 (22.7)	19 (26.0)	11 (14.1)	23 (8.1)					52 (20.5)	43 (17.4)		
Dehydration	36 (4.1)	41 (4.7)											43 (16.9)	43 (17.4)		
Diarrhoea	16 (1.8)	13 (1.5)			18 (27.3)	18 (24.7)	11 (14.1)	45 (15.8)	6 (25.0)	8 (32.0)	1 (4.8)	3 (15.8)	44 (17.3)	47 (19.0)	3 (13.6)	
Dyspepsia					14	12			1	2						

	CSR Henry		Arican 99[90]		Berenson 01[91]		Body 10[165]		Brown 07[92]		O'Rourke 95[96]		Rosen 03+04[131,134]		Tralongo 04[¥159]	Zuradelli 09[¥162]
Tumour types	**All, including MM, excl breast and prostate**		**All**		**Breast and MM**		**All**		**All**		**All**		**All, excl breast and prostate**		**Breast, prostate and MM**	**All**
					(21.2)	(16.4)			(4.2)	(8.0)						
Dyspnoea	62 (7.1)	66 (7.5)			18 (27.3)	12 (16.4)	9 (11.5)	19 (6.7)					90 (35.4)	74 (30.0)		
Fatigue	11 (1.3)	6 (0.7)			27 (40.9)	24 (32.9)	9 (11.5)	36 (12.7)					82 (32.3)	74 (30.0)		
Febrile neutropenia	24 (2.7)	36 (4.1)														
General physical health deterioration	26 (3.0)	40 (4.6)														
Headache					21 (31.8)	21 (28.8)	9 (11.5)	33 (11.6)					43 (16.9)	27 (10.9)		
Insomnia					9 (13.6)	12 (16.4)							44 (17.3)	34 (13.8)		
Intestinal obstruction	10 (1.1)	5 (0.6)														
Musculoskeletal pain	6 (0.7)	7 (0.8)											30 (11.8)	32 (13.0)		
Nausea	16 (1.8)	20 (2.3)			26 (39.	37 (50.	17 (21.	64 (22.	7 (29.	6 (24.	6 (28.	3 (15.	124 (48.8)	90 (36.4)	3 (13.6)	2 (0.8)

	CSR Henry		Arican 99[90]		Berenson 01[91]		Body 10[165]		Brown 07[92]		O'Rourke 95[96]		Rosen 03+04[131,134]		Tralongo 04[¥159]	Zuradelli 09[¥162]
Tumour types	**All, including MM, excl breast and prostate**		**All**		**Breast and MM**		**All**		**All**		**All**		**All, excl breast and prostate**		**Breast, prostate and MM**	**All**
					4)	7)	8)	5)	2)	0)	6)	8)				
Oedema peripheral	5 (0.6)	8 (0.9)			8 (12.1)	10 (13.7)	7 (9.0)	25 (8.8)					60 (23.6)	52 (21.1)		
Parasthesia							7 (9.0)	21 (7.4)								
Pleural effusion	39 (4.4)	39 (4.4)														
Pneumonia	64 (7.3)	52 (5.9)														
Pulmonary embolism	19 (2.2)	19 (2.2)														
Pyrexia	27 (3.1)	23 (2.6)			17 (25.8)	14 (19.2)	10 (12.8)	25 (8.8)					69 (27.2)	58 (23.5)	5 (22.7)	23 (3.6)
Respiratory tract infection	4 (0.5)	10 (1.1)														
Thrombocytopenia	20 (2.3)	26 (3.0)														
Urinary tract infection	10 (1.1)	10 (1.1)			6 (9.1)	11 (15.1)										
Vomiting	21 (2.4)	31 (3.5)			24 (36.4)	25 (34.2)	14 (17.9)	43 (15.1)	3 (12.5)	6 (24.0)			96 (37.8)	75 (30.4)		4 (1.7)

D= denosumab 120mg 4 weekly, Z = zoledronic acid 4mg 4 weekly, C = Clodronate 1.6 g, CL =control, P = pamidronate 90mg 4 weekly, D**= denosumab 30mg/120mg/180mg, VB = various bps, PL = placebo, ¥= observational study

TABLE B OTHER SOLID TUMOURS ADVERSE EVENTS

Study	Intervention	Time (years)	Number analyses	Tumour types	Adverse event			
					ONJ	Renal toxicity	Hypercalcaemia	Hypocalcaemia
CSR Henry (includes MM)	D	0.8	878	All excl breast and prostate	10 (1.1)	22 (2.5)	3 (0.3)	22 (2.5)
	Z	0.8	878		11 (1.3)	36 (4.1)	3 (0.3)	8 (0.9)
CSR Henry (excludes MM)	D	0.8	878	All excl breast and prostate	3 (0.3)	11 (1.3)	3 (0.3)	12 (1.4)
	Z	0.8	878		2 (0.2)	23 (2.6)	0	8 (0.9)
Arican 99[90]	C	0.25	17	All			0	2 (11.8)
	CL	0.25	17				1 (5.9)	
Berenson 01[91]	Z	0.83	66	Breast and MM		1 (1.5)	0	2 (3.0)
	P	0.83	73			2 (2.7)	2 (2.7)	1 (1.4)
Body 10[165]	Various Bps	1.096	78	All	0	0		
	Denosumab (30/120/180)	1.096	284		0	0		
O'Rourke 95[96]	PL	0.077	21	All			2 (9.5)	0
	C	0.077	19				0	0
Robertson 95[98]	C	0.153	27	All			0	2 (7.4)
	PL	0.156	28				7 (25.0)	0
Rosen 03+04[131,134]	Z	1.75	254	All, excl breast and prostate		5 (2.0)	0	
	PL	1.75	247			5 (2.0)	9 (3.6)	

Pandey 09 [154]	Z	1.5	120	All	0			10 (8.3)
	I	1.5	120		0			3 (2.5)
Estilo 08[¥143]	P or Z	1.46	310	Breast, prostate and MM	28 (9.0)			
Francini 11[¥144]	Z	1.57	59	Breast and lung	0			
Haidar 09[¥147]	Various Bps	1.17	53	prostate and renal	2 (3.8)			
Hoff 08[¥148]	Z and/or P	1.77	3994	All	29 (0.7)			
Ibrahim 08[¥150]	Various Bps	0.9	539	All	8 (1.5)			
La Verde 08[¥152]	Z and P	NR	186	All	16 (8.6)			
Stumpe 09[¥158]	Various IV Bp	0.76	638	All	6 (0.9)			
Vahtsevanos 09[¥160]	Various Bps	1.7	1621	All	80 (4.9)			
Anguiar Bunjanda 07[¥137]	Z	1.83	67	All	9 (13.4)	0		
Bonomi 10[¥138]	Various Bps	2	398	All	10 (2.5)	16 (4.0)		
McDermott 06[¥61]	Z	2.08(?)	466	All		42 (9.0)		
Ripamonti 09[¥156]	Various Bps	0.8	966	All		28 (2.9)		
Shah 11[¥157]	Z	NR	220 (184 normal RF and 36 abnormal)	All		45 (20.5)		
Diel 2009[¥142]	I	0.91	109	All		14 (12.8)		

	Z	1.36	256			48 (18.8)		
Chennuru 08[¥139]	Z	2	120	All				10 (8.3)
Guarneri 05[¥146]	Z and/or P	2.83	57	Breast, MM, prostate and renal	3 (5.3)	7 (12.3)	1 (1.8)	
Tralongo 04[¥159]	P	1.58	22 (all >70 y.o)	Breast, prostate and MM		2 (9.1)		3 (13.6)
Zuradelli 09[¥162]	Z	NR	240	All	4 (1.7)	3 (1.3)	0	11 (4.6)
Kotteas 08[¥213]	Z	1.5	222	Lung only		0	0	

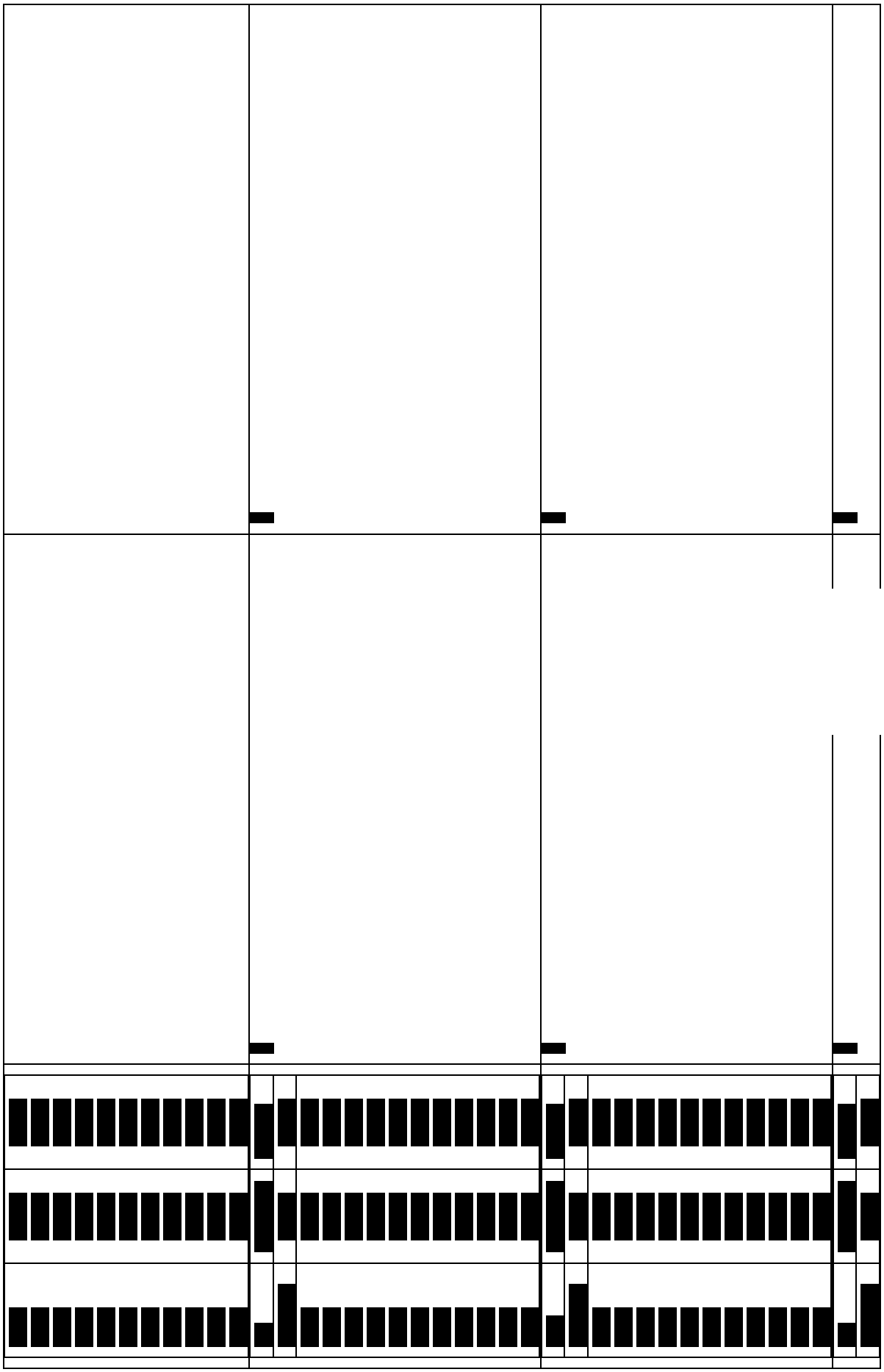
D = denosumab 120mg 4 weekly, Z = zoledronic acid 4mg 4 weekly, P = pamodronate 90mg 4 weekly, C = clodronate 1.6mg orally each day, I= ibandronat, CL = control, PL= placebo, MM = multiple myeloma

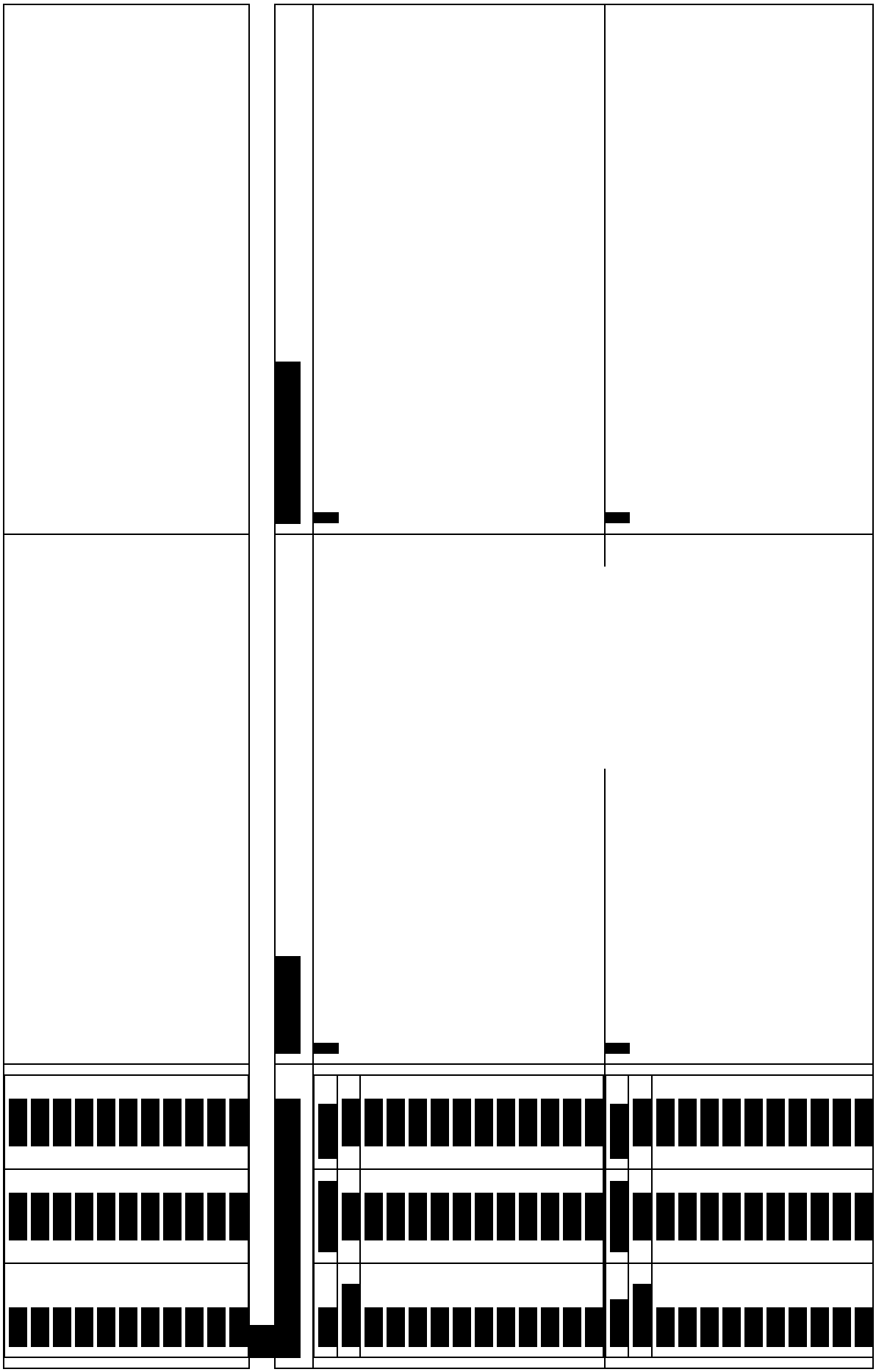
[¥]= observational study

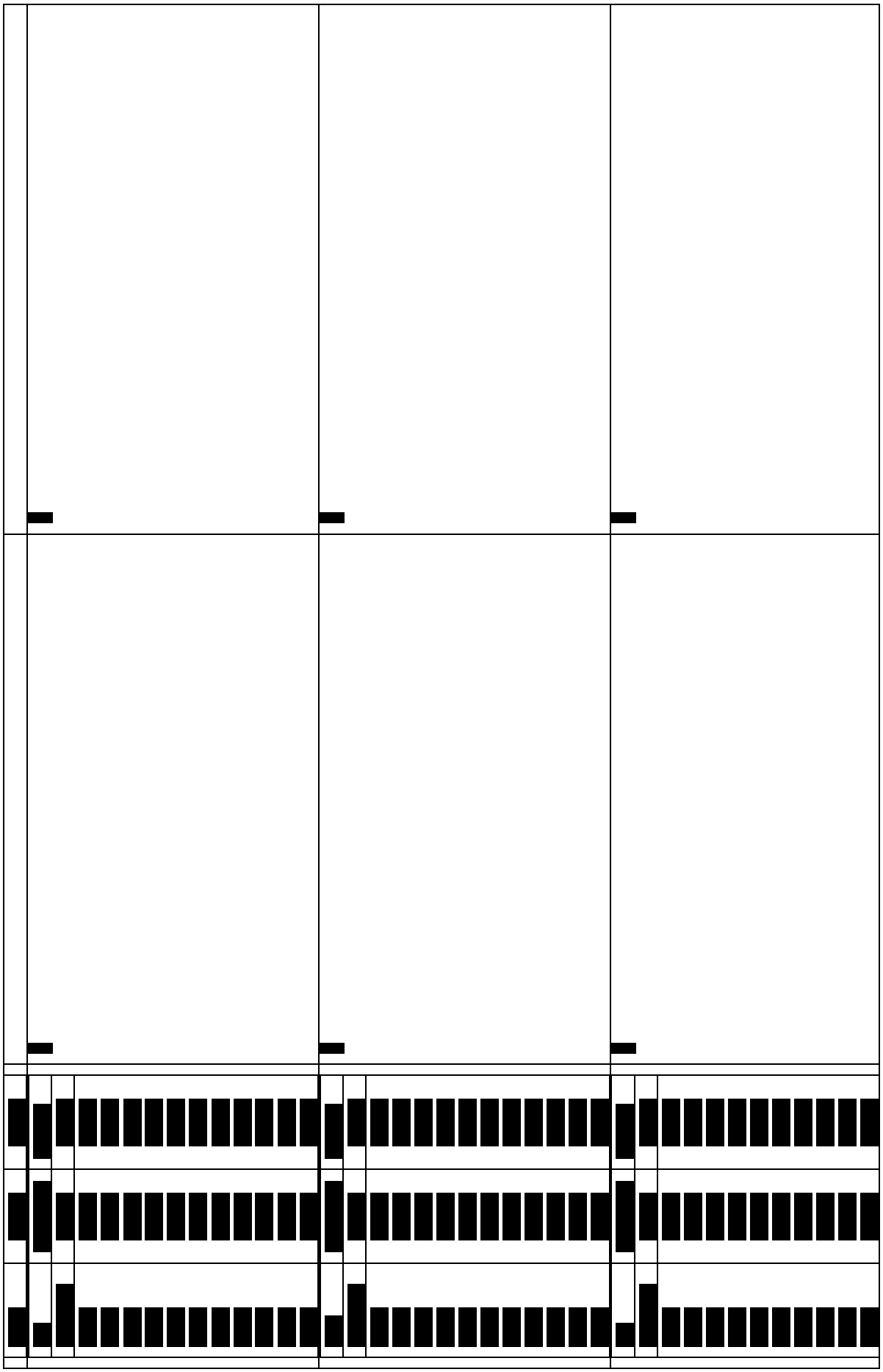
APPENDIX 13 EQ-5D HRQoL ESTIMATES PRESENTED BY THE MANUFACTURER

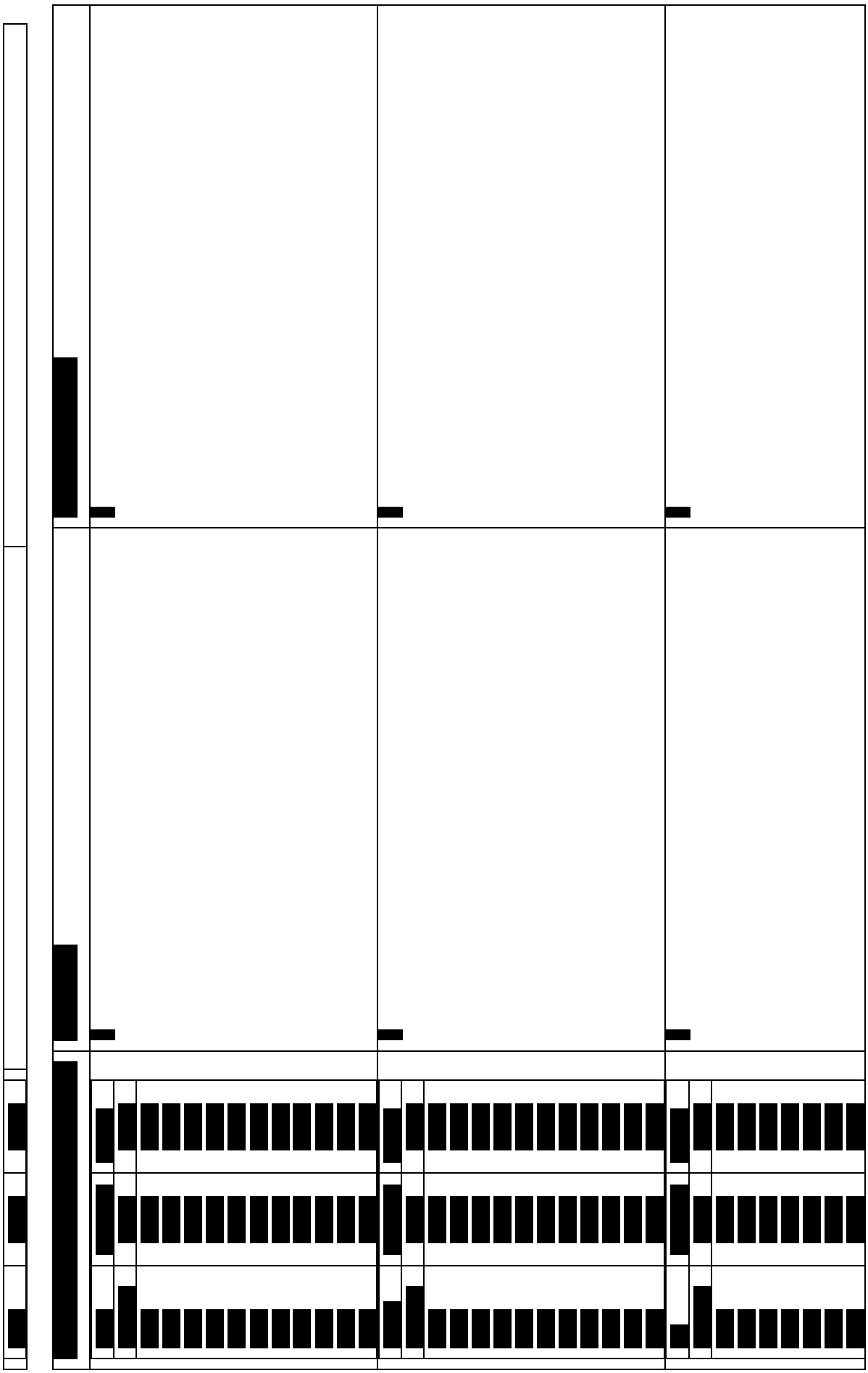
[redacted]

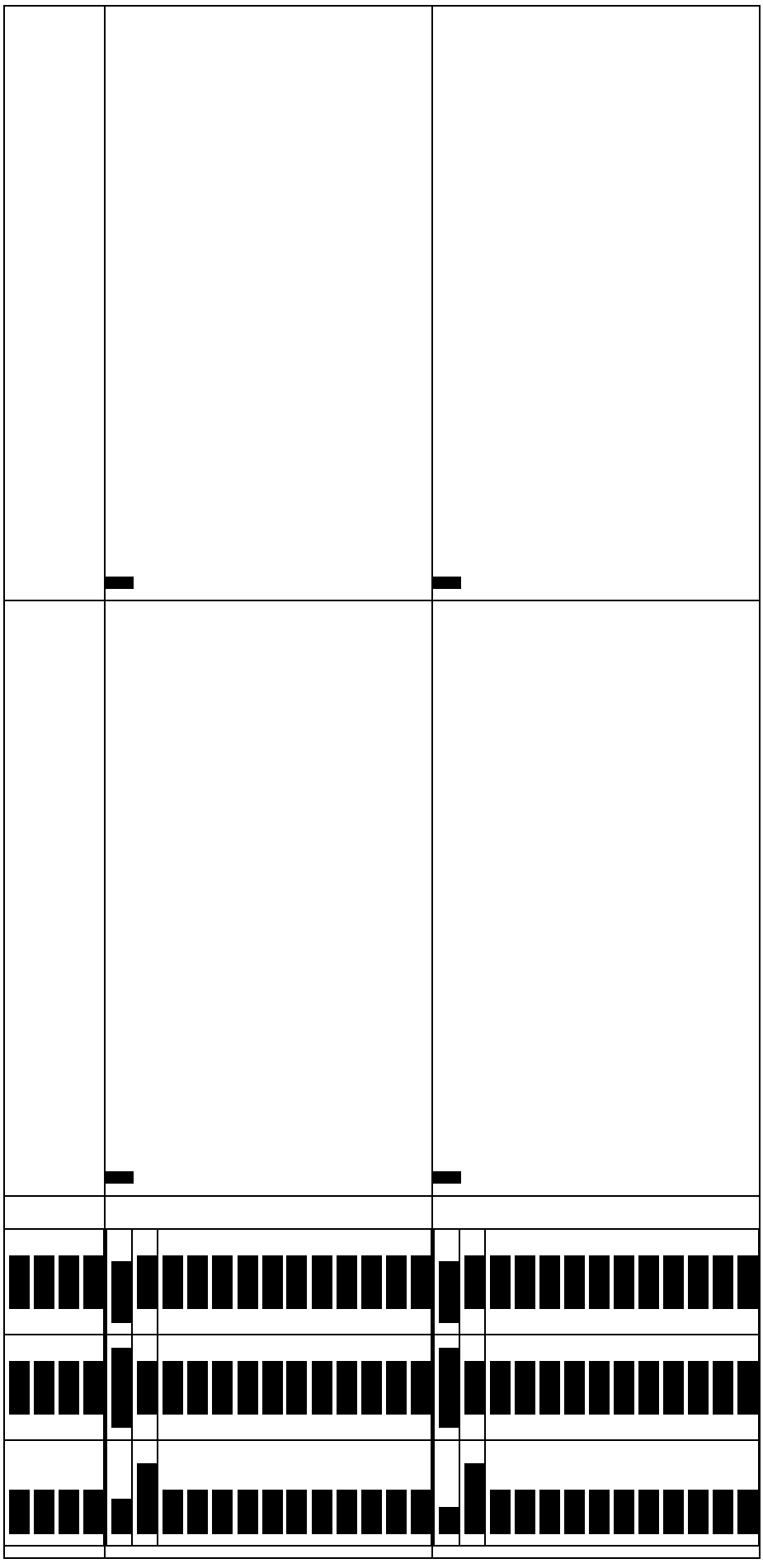
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]











APPENDIX 14 SENSITIVITY ANALYSES PRESENTED BY THE MANUFACTURER

Table A Scenario analyses: breast cancer with PAS

Description		Incremental costs for denosumab with comparator (£)			Incremental QALYs for denosumab with comparator			ICERs for denosumab with comparator (ΔCost (£)/ΔQALY)		
		ZOL	PAM	IBA	ZOL	PAM	IBA	ZOL	PAM	IBA
Base-case		-483	-3,453	-1,895	0.007	0.013	0.005	Dmab Domt	Dmab Domt	Dmab Domt
Time horizon	Time horizon = 2 years	-320	-2,001	-820	0.004	0.009	0.004	Dmab Domt	Dmab Domt	Dmab Domt
	Time horizon = 5 years	-460	-3,192	-1,656	0.007	0.013	0.005	Dmab Domt	Dmab Domt	Dmab Domt
21-day window	Without 21 day-window	-573	-3,600	-1,974	0.009	0.016	0.006	Dmab Domt	Dmab Domt	Dmab Domt
Asymptomatic events	Include costs for trial-defined asymptomatic events	-530	-3,529	-1,935	0.007	0.013	0.005	Dmab Domt	Dmab Domt	Dmab Domt
SRE costs	Based on NHS reference costs	-447	-3,395	-1,864	0.007	0.013	0.005	Dmab Domt	Dmab Domt	Dmab Domt
SRE utilities	Based on TTO	-483	-3,453	-1,895	0.009	0.017	0.007	Dmab Domt	Dmab Domt	Dmab Domt
	Based on Weinfurt 2005	-483	-3,453	-1,895	0.006	0.011	0.004	Dmab Domt	Dmab Domt	Dmab Domt
AE utilities	Normal model	-483	-3,453	-1,895	0.008	0.014	0.005	Dmab Domt	Dmab Domt	Dmab Domt
Starting age	Starting age = 50	-485	-3,468	-1,905	0.007	0.013	0.005	Dmab Domt	Dmab Domt	Dmab Domt
	Starting age = 65	-479	-3,416	-1,868	0.007	0.013	0.005	Dmab Domt	Dmab Domt	Dmab Domt
IV dosing frequency	Based on UK treatment patterns of Q3-4W dosing	-786	-3,895	-2,281	0.007	0.013	0.005	Dmab Domt	Dmab Domt	Dmab Domt
Ibandronic acid	Ibandronic acid administered orally	-483	-3,453	49	0.007	0.013	0.005	Dmab Domt	Dmab Domt	9,354
Denosumab setting	Community (district nurse)	[redacted]	[redacted]	[redacted]	0.007	0.013	0.005	Dmab Domt	Dmab Domt	Dmab Domt
Discontinuation	Zero for all treatments	[redacted]	[redacted]	[redacted]	0.013	0.027	0.016	Dmab Domt	Dmab Domt	Dmab Domt
	0.025 per cycle for all treatments	[redacted]	[redacted]	[redacted]	0.007	0.015	0.009	Dmab Domt	Dmab Domt	Dmab Domt
Discounting	0% for costs and benefits	-515	-3,724	-2,087	0.008	0.014	0.005	Dmab Domt	Dmab Domt	Dmab Domt
	0% for costs and 6% benefits	-515	-3,724	-2,087	0.007	0.013	0.005	Dmab Domt	Dmab Domt	Dmab Domt

Note: Dmab Domt, denosumab dominant. Abbreviations: ZOL, zoledronic acid; PAM, disodium pamidronate; IBA, ibandronic acid; TTO, time trade-off; SRE, skeletal-related event; AE, adverse event; NHS, National Health Service; ICER, incremental cost-effectiveness ratio

Table B Prostate cancer, pain and history of a prior SRE with PAS

Description		Incremental costs for denosumab with comparator (£)	Incremental QALYs for denosumab with comparator	ICERs for denosumab with comparator (ΔCost (£)/ΔQALY)
		ZOL	ZOL	ZOL
Base-case		-281	0.006	Dmab Domt
Time horizon	Time = 2 years	-240	0.005	Dmab Domt
	Time = 5 years	-279	0.006	Dmab Domt
21-day window	Without 21 day-window	-350	0.010	Dmab Domt
Asymptomatic events	Include costs for trial-defined asymptomatic events	-307	0.006	Dmab Domt
SRE costs	Based on NHS reference costs	-215	0.006	Dmab Domt
SRE utilities	SRE utilities based on TTO	-281	0.006	Dmab Domt
	SRE utilities based on Weinfurt 2005	-281	0.002	Dmab Domt
AE utilities	Normal model	-281	0.006	Dmab Domt
Starting age	Starting age = 50	-288	0.006	Dmab Domt
	Starting age = 80	-269	0.006	Dmab Domt
IV dosing frequency	Based on UK treatment patterns of Q3-4W dosing	-469	0.006	Dmab Domt
Denosumab setting	[redacted]	[redacted]	0.006	Dmab Domt
Discontinuation	[redacted]	[redacted]	0.011	Dmab Domt
	[redacted]	[redacted]	0.007	Dmab Domt
Discounting	0% for costs and benefits	-292	0.006	Dmab Domt
	0% for costs and 6% benefits	-292	0.006	Dmab Domt

Abbreviations: ZOL, zoledronic acid; TTO, time trade-off; SRE, skeletal-related event; AE, adverse event; NHS, National Health Service; ICER, incremental cost-effectiveness ratio

Table C Prostate cancer, no pain or pain and no history of a prior SRE [with PAS]

Description		Incremental costs for denosumab with comparator (£)	Incremental QALYs for denosumab with comparator	ICERs for denosumab with comparator (ΔCost (£)/ΔQALY)
		BSC	BSC	BSC
Base-case		2,790	0.039	71,320
Time horizon	Time = 2 years	2,562	0.030	84,079
	Time = 5 years	2,788	0.038	72,496
21-day window	Without 21 day-window	2,584	0.051	51,153
Asymptomatic events	Include costs for trial-defined asymptomatic events	2,693	0.039	68,826
SRE costs	Based on NHS reference costs	3,044	0.039	77,796
SRE utilities	Based on TTO	2,790	0.023	120,262
	Based on Weinfurt 2005	2,790	0.008	355,201
AE utilities	Normal model	2,790	0.039	71,415
Starting age	Starting age = 50	2,838	0.040	70,233
	Starting age = 80	2,702	0.037	73,343
Denosumab setting	Community (district nurse)	[redacted]	0.039	[redacted]
Discontinuation	Zero for all treatments	[redacted]	0.069	[redacted]
	0.025 per cycle for all treatments	[redacted]	0.047	[redacted]
Discounting	0% for costs and benefits	2,874	0.041	69,835
	0% for costs and 6% benefits	2,874	0.038	75,997

Abbreviations: BSC, best supportive care; TTO, time trade-off; SRE, skeletal-related event; AE, adverse event; NHS, National Health Service; ICER, incremental cost-effectiveness ratio

Table D Other solid tumours, pain and history of a prior SRE with PAS

Description		Incremental costs for denosumab with comparator (£)		Incremental QALYs for denosumab with comparator		ICERs for denosumab with comparator (ΔCost (£)/ΔQALY)	
		ZOL	PAM	ZOL	PAM	ZOL	PAM
Base-case		-43	-2,918	0.004	0.006	Dmab Domt	Dmab Domt
Time horizon	Time = 2 years	-63	-2,002	0.003	0.006	Dmab Domt	Dmab Domt
	Time = 5 years	-44	-2,726	0.004	0.006	Dmab Domt	Dmab Domt
21-day window	Without 21 day-window	-78	-2,961	0.005	0.007	Dmab Domt	Dmab Domt
Asymptomatic events	Include costs for trial-defined asymptomatic events	-56	-2,934	0.004	0.006	Dmab Domt	Dmab Domt
SRE costs	Based on NHS reference costs	-8	-2,874	0.004	0.006	Dmab Domt	Dmab Domt
SRE utilities	Based on TTO	-43	-2,918	0.004	0.006	Dmab Domt	Dmab Domt
	Based on Weinfurt 2005	-43	-2,918	0.002	0.003	Dmab Domt	Dmab Domt
AE utilities	Normal model	-43	-2,918	0.004	0.006	Dmab Domt	Dmab Domt
Starting age	Starting age = 50	-43	-2,935	0.004	0.006	Dmab Domt	Dmab Domt
	Starting age = 70	-44	-2,863	0.004	0.006	Dmab Domt	Dmab Domt
IV dosing frequency	Based on UK treatment patterns of Q3-4W dosing	-157	-3,176	0.004	0.006	Dmab Domt	Dmab Domt
Denosumab setting	Community (district nurse)	[redacted]	[redacted]	0.004	0.006	Dmab Domt	Dmab Domt
Disodium pamidronate efficacy	No efficacy (placebo treatment effect)	-43	-3,181	0.004	0.011	Dmab Domt	Dmab Domt
Discontinuation	Zero for all treatments	[redacted]	[redacted]	0.008	0.018	Dmab Domt	Dmab Domt
	0.025 per cycle for all treatments	[redacted]	[redacted]	0.005	0.011	Dmab Domt	Dmab Domt
Discounting	0% for costs and benefits	-40	-3,112	0.004	0.006	Dmab Domt	Dmab Domt
	0% for costs and 6% benefits	-40	-3,112	0.004	0.006	Dmab Domt	Dmab Domt

Note: Dmab Domt, denosumab dominant. Abbreviations: ZOL, zoledronic acid; PAM, disodium pamidronate; TTO, time trade-off; SRE, skeletal-related event; AE, adverse event; NHS, National Health Service; ICER, incremental cost-effectiveness ratio

Table E Other solid tumours, no pain or pain and no history of a prior SRE [with PAS]

Description		Incremental costs for denosumab with comparator (£)	Incremental QALYs for denosumab with comparator	ICERs for denosumab with comparator (ΔCost (£)/ΔQALY)
		BSC	BSC	BSC
Base-case		1,730	0.021	83,763
Time horizon	Time = 2 years	1,683	0.018	93,698
	Time = 5 years	1,735	0.020	85,522
21-day window	Without 21 day-window	1,642	0.024	68,020
Asymptomatic events	Include costs for trial-defined asymptomatic events	1,683	0.021	81,497
SRE costs	Based on NHS reference costs	1,859	0.021	90,036
SRE utilities	Based on TTO	1,730	0.013	128,757
	Based on Weinfurt 2005	1,730	0.005	319,401
AE utilities	Normal model	1,730	0.021	83,439
Starting age	Starting age = 50	1,732	0.021	83,606
	Starting age = 70	1,721	0.020	84,263
Denosumab setting	Community (district nurse)	[redacted]	0.021	[redacted]
Discontinuation	Zero for all treatments	[redacted]	0.042	[redacted]
	0.025 per cycle for all treatments	[redacted]	0.029	[redacted]
Discounting	0% for costs and benefits	1,765	0.021	82,207
	0% for costs and 6% benefits	1,765	0.020	87,728

Abbreviations: BSC, best supportive care; TTO, time trade-off; SRE, skeletal-related event; AE, adverse event; NHS, National Health Service; ICER, incremental cost-effectiveness ratio

APPENDIX 15 UNIVARIATE AND PROBABILISTIC SENSITIVITY ANALYSES

A range of univariate sensitivity analyses have been explored:

	Description	**Abbreviated**
SA01	Base Case	Base Case
SA02	Amgen STARs costing	Amgen STARs
SA03	Amgen NMA results	Amgen NMA
SA04	Amgen STARs costings and NMA results	Amgen STARs+NMA
SA05	No HRQoL step change for naive to experienced	No Naive util step
SA06	SCC permanent utility effect of the average P1-P5 decrement	SCC ongoing mean
SA07	SCC permanent utility effect of the maximum P1-P5 decrement	SCC ongoing max
SA08	No general mortality	No gen. mortality
SA09	5 year horizon	5 yeat horizon
SA10	2 year horizon	2 year horizon
SA11	vdHOUT utility multipliers	vd Hout utility
SA12	Excluding ONJ and renal toxicity utility impact beyond trial average	No SAE P1+
SA13	Excluding SAEs	No SAE
SA14	No general discontinuations	No gen. discs.
SA15	No discontinuations	No discs.
SA16	AG TTF functional form from NAIVE for breast and prostate	TTF form AG naive
SA17	AG TTF functional form all patients for breast, prostate and OSTL	TTF form AG all patients

These are presented for the four cancer groupings: breast (BRST), prostate (PROS), other solid tumour including lung (OSTL) and lung (LUNG). They are also presented for the three patient groups of all, naïve and experiences, coupled with the split between applying the pooled HRs and RRs and the SRE specific HRs and RRs for breast (BRST), prostate (PROS), other solid tumour including lung (OSTL). The summaries that follow all show the net impact of denosumab on total amounts. The costs reported are the total costs including SRE costs and SAE costs: e.g. the cost associated with BSC ex PAS is the additional cost of using denosumab compared to BSC. These sensitivity analyses are only presented for the analyses that apply the pooled HRs and RRs. The parallel sensitivity analyses that present them for the analyses that apply the SRE experience subgroup specific HRs and RRs are available on demand from the AG. Due to zoledronic acid shortly coming off patent, a range of sensitivity analyses around the zoledronic acid price are then presented.

ALL PATIENTS	BRST BSC	BRST BSC	BRST BSC	BRST BSC	BRST BSC	BRST BSC	BRST ZOL	BRST ZOL	BRST ZOL	BRST ZOL	BRST ZOL	BRST ZOL
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£6,114	£4,165	-1.085	0.027	£224,411	£152,847	£1,680	-£270	-0.233	0.013	£126,821	Dominant
Amgen STARs	£5,954	£4,004	-1.085	0.027	£218,523	£146,959	£1,635	-£315	-0.233	0.013	£123,422	Dominant
Amgen NMA	£6,324	£4,374	-0.922	0.023	£274,187	£189,650	£1,705	-£245	-0.213	0.013	£133,556	Dominant
Amgen STARs+NMA	£6,194	£4,245	-0.922	0.023	£268,562	£184,025	£1,664	-£286	-0.213	0.013	£130,322	Dominant
No Naive util step	£6,114	£4,165	-1.085	0.017	£357,529	£243,514	£1,680	-£270	-0.233	0.011	£155,331	Dominant
SCC ongoing mean	£6,114	£4,165	-1.085	0.034	£181,786	£123,815	£1,680	-£270	-0.233	0.015	£115,025	Dominant
SCC ongoing max	£6,114	£4,165	-1.085	0.036	£171,330	£116,693	£1,680	-£270	-0.233	0.015	£111,687	Dominant
No gen. mortality	£6,114	£4,165	-1.085	0.027	£224,411	£152,847	£1,680	-£270	-0.233	0.013	£126,821	Dominant
5 yeat horizon	£5,981	£4,083	-1.027	0.026	£231,901	£158,314	£1,644	-£254	-0.219	0.011	£145,347	Dominant
2 year horizon	£4,699	£3,237	-0.714	0.017	£276,331	£190,380	£1,291	-£170	-0.152	0.006	£216,260	Dominant
vd Hout utility	£6,114	£4,165	-1.085	0.025	£243,706	£165,988	£1,680	-£270	-0.233	0.012	£137,104	Dominant
No SAE P1+	£6,114	£4,165	-1.085	0.029	£212,685	£144,860	£1,680	-£270	-0.233	0.008	£223,916	Dominant
No SAE	£6,147	£4,171	-1.100	0.030	£208,299	£141,339	£1,745	-£230	-0.236	0.007	£263,627	Dominant
No gen. discs.	£11,249	£7,668	-2.034	0.046	£243,696	£166,117	£3,120	-£461	-0.438	0.023	£136,300	Dominant
No discs.	£11,494	£7,835	-2.080	0.047	£244,441	£166,630	£3,189	-£470	-0.448	0.023	£136,702	Dominant
TTF form AG naive	£6,109	£4,159	-1.090	0.028	£221,055	£150,496	£1,680	-£270	-0.232	0.013	£126,523	Dominant
TTF form AG all	£6,012	£4,062	-1.163	0.030	£200,010	£135,139	£1,658	-£292	-0.250	0.014	£118,941	Dominant

ALL PATIENTS	PROS	PROS	PROS	PROS	PROS	PROS	PROS	PROS	PROS	PROS	PROS	PROS
	BSC	BSC	BSC	BSC	BSC	BSC	ZOL	ZOL	ZOL	ZOL	ZOL	ZOL
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£3,880	£2,695	-0.601	0.030	£130,674	£90,788	£941	-£243	-0.228	0.020	£46,976	Dominant
Amgen STARs	£3,798	£2,613	-0.601	0.030	£127,910	£88,023	£885	-£300	-0.228	0.020	£44,137	Dominant
Amgen NMA	£3,947	£2,763	-0.546	0.021	£186,418	£130,489	£1,060	-£124	-0.129	0.010	£107,657	Dominant
Amgen STARs+NMA	£3,882	£2,698	-0.546	0.021	£183,356	£127,427	£1,032	-£152	-0.129	0.010	£104,877	Dominant
No Naive util step	£3,880	£2,695	-0.601	0.015	£251,022	£174,401	£941	-£243	-0.228	0.013	£73,900	Dominant
SCC ongoing mean	£3,880	£2,695	-0.601	0.042	£92,143	£64,018	£941	-£243	-0.228	0.025	£38,060	Dominant
SCC ongoing max	£3,880	£2,695	-0.601	0.051	£76,619	£53,232	£941	-£243	-0.228	0.028	£33,669	Dominant
No gen. mortality	£3,880	£2,695	-0.601	0.030	£130,674	£90,788	£941	-£243	-0.228	0.020	£46,976	Dominant
5 yeat horizon	£3,872	£2,692	-0.593	0.031	£126,231	£87,756	£942	-£238	-0.224	0.020	£48,202	Dominant
2 year horizon	£3,529	£2,463	-0.503	0.029	£122,806	£85,707	£875	-£191	-0.189	0.015	£57,317	Dominant
vd Hout utility	£3,880	£2,695	-0.601	0.026	£150,272	£104,403	£941	-£243	-0.228	0.017	£53,886	Dominant
No SAE P1+	£3,880	£2,695	-0.601	0.044	£88,639	£61,583	£941	-£243	-0.228	0.020	£48,128	Dominant
No SAE	£3,892	£2,683	-0.614	0.047	£83,007	£57,212	£962	-£247	-0.236	0.020	£47,217	Dominant
No gen. discs.	£7,459	£5,200	-1.127	0.049	£151,088	£105,338	£1,831	-£428	-0.398	0.034	£53,545	Dominant
No discs.	£7,763	£5,413	-1.171	0.051	£152,700	£106,489	£2,016	-£333	-0.426	0.035	£56,871	Dominant
TTF form AG naive	£3,906	£2,722	-0.577	0.028	£139,779	£97,405	£956	-£228	-0.215	0.019	£50,127	Dominant
TTF form AG all	£3,866	£2,682	-0.612	0.031	£126,112	£87,481	£935	-£249	-0.233	0.021	£45,548	Dominant

ALL PATIENTS	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL
	BSC	BSC	BSC	BSC	BSC	BSC	ZOL	ZOL	ZOL	ZOL	ZOL	ZOL
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£2,573	£1,791	-0.274	0.013	£197,550	£137,535	£880	£99	-0.064	0.008	£115,741	£12,969
Amgen STARs	£2,523	£1,741	-0.274	0.013	£193,703	£133,688	£850	£68	-0.064	0.008	£111,764	£8,992
Amgen NMA	£2,564	£1,782	-0.279	0.013	£197,562	£137,330	£837	£55	-0.092	0.010	£87,285	£5,737
Amgen STARs+NMA	£2,512	£1,731	-0.279	0.013	£193,597	£133,365	£799	£17	-0.092	0.010	£83,365	£1,818
No Naive util step	£2,573	£1,791	-0.274	0.010	£255,982	£178,216	£880	£99	-0.064	0.007	£122,556	£13,733
SCC ongoing mean	£2,573	£1,791	-0.274	0.016	£164,404	£114,459	£880	£99	-0.064	0.008	£106,513	£11,935
SCC ongoing max	£2,573	£1,791	-0.274	0.018	£144,184	£100,382	£880	£99	-0.064	0.009	£99,858	£11,190
No gen. mortality	£2,573	£1,791	-0.274	0.013	£197,550	£137,535	£880	£99	-0.064	0.008	£115,741	£12,969
5 yeat horizon	£2,572	£1,791	-0.272	0.014	£187,794	£130,790	£878	£98	-0.064	0.007	£128,150	£14,271
2 year horizon	£2,463	£1,717	-0.256	0.014	£178,318	£124,340	£821	£76	-0.058	0.005	£159,951	£14,802
vd Hout utility	£2,573	£1,791	-0.274	0.011	£238,819	£166,267	£880	£99	-0.064	0.006	£140,020	£15,690
No SAE P1+	£2,573	£1,791	-0.274	0.017	£152,847	£106,413	£880	£99	-0.064	0.004	£218,555	£24,490
No SAE	£2,560	£1,772	-0.276	0.018	£144,574	£100,085	£879	£91	-0.065	0.004	£228,318	£23,603
No gen. discs.	£6,080	£4,250	-0.629	0.025	£241,722	£168,954	£1,706	-£124	-0.127	0.020	£84,671	Dominant
No discs.	£6,229	£4,354	-0.644	0.026	£243,284	£170,070	£1,775	-£100	-0.133	0.021	£85,891	Dominant
TTF form AG all	£2,572	£1,790	-0.273	0.013	£195,676	£136,211	£882	£100	-0.063	0.008	£117,172	£13,338

ALL PATIENTS	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG
	BSC	BSC	BSC	BSC	BSC	BSC	ZOL	ZOL	ZOL	ZOL	ZOL	ZOL
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£2,317	£1,637	-0.187	0.009	£263,132	£185,966	£738	£58	-0.059	0.006	£127,599	£10,099
Amgen STARs	£2,287	£1,607	-0.187	0.009	£259,717	£182,551	£710	£31	-0.059	0.006	£122,849	£5,349
No Naive util step	£2,317	£1,637	-0.187	0.007	£316,151	£223,436	£738	£58	-0.059	0.005	£150,393	£11,903
SCC ongoing mean	£2,317	£1,637	-0.187	0.010	£243,374	£172,002	£738	£58	-0.059	0.006	£122,986	£9,734
SCC ongoing max	£2,317	£1,637	-0.187	0.010	£229,002	£161,845	£738	£58	-0.059	0.006	£119,379	£9,448
No gen. mortality	£2,317	£1,637	-0.187	0.009	£263,132	£185,966	£738	£58	-0.059	0.006	£127,599	£10,099
5 yeat horizon	£2,317	£1,637	-0.187	0.009	£263,012	£185,885	£738	£58	-0.059	0.006	£127,925	£10,133
2 year horizon	£2,280	£1,613	-0.181	0.009	£261,304	£184,837	£721	£53	-0.056	0.005	£139,140	£10,311
vd Hout utility	£2,317	£1,637	-0.187	0.007	£340,899	£240,927	£738	£58	-0.059	0.004	£165,191	£13,074
No SAE P1+	£2,317	£1,637	-0.187	0.010	£224,051	£158,346	£738	£58	-0.059	0.004	£174,003	£13,772
No SAE	£2,303	£1,619	-0.188	0.011	£208,567	£146,644	£735	£51	-0.060	0.004	£181,686	£12,632
No gen. discs.	£3,947	£2,799	-0.298	0.013	£301,840	£214,078	£1,103	-£45	-0.066	0.008	£135,554	Dominant
No discs.	£3,988	£2,829	-0.301	0.013	£302,597	£214,628	£1,122	-£37	-0.067	0.008	£136,757	Dominant

NAIVE	BRST	BRST	BRST	BRST	BRST	BRST	BRST	BRST	BRST	BRST	BRST	BRST
	BSC	BSC	BSC	BSC	BSC	BSC	ZOL	ZOL	ZOL	ZOL	ZOL	ZOL
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£6,223	£4,273	-1.028	0.034	£181,007	£124,291	£1,725	-£225	-0.204	0.015	£117,186	Dominant
Amgen STARs	£6,076	£4,126	-1.028	0.034	£176,729	£120,012	£1,686	-£264	-0.204	0.015	£114,532	Dominant
Amgen NMA	£6,432	£4,482	-0.863	0.029	£221,188	£154,136	£1,744	-£205	-0.189	0.014	£122,829	Dominant
Amgen STARs+NMA	£6,316	£4,366	-0.863	0.029	£217,192	£150,140	£1,708	-£242	-0.189	0.014	£120,282	Dominant
No Naive util step	£6,223	£4,273	-1.028	0.017	£362,111	£248,648	£1,725	-£225	-0.204	0.011	£162,740	Dominant
SCC ongoing mean	£6,223	£4,273	-1.028	0.040	£155,543	£106,805	£1,725	-£225	-0.204	0.016	£109,148	Dominant
SCC ongoing max	£6,223	£4,273	-1.028	0.042	£148,816	£102,187	£1,725	-£225	-0.204	0.016	£106,795	Dominant
No gen. mortality	£6,223	£4,273	-1.028	0.034	£181,007	£124,291	£1,725	-£225	-0.204	0.015	£117,186	Dominant
5 yeat horizon	£6,107	£4,209	-0.955	0.032	£190,785	£131,496	£1,693	-£205	-0.188	0.013	£134,988	Dominant
2 year horizon	£4,860	£3,399	-0.616	0.020	£247,598	£173,147	£1,344	-£118	-0.118	0.006	£211,104	Dominant
vd Hout utility	£6,223	£4,273	-1.028	0.032	£196,964	£135,248	£1,725	-£225	-0.204	0.014	£126,916	Dominant
No SAE P1+	£6,223	£4,273	-1.028	0.036	£173,429	£119,087	£1,725	-£225	-0.204	0.009	£192,162	Dominant
No SAE	£6,257	£4,281	-1.042	0.037	£170,535	£116,682	£1,791	-£184	-0.207	0.008	£220,988	Dominant
No gen. discs.	£11,486	£7,905	-1.887	0.056	£206,867	£142,372	£3,216	-£365	-0.373	0.025	£129,511	Dominant
No discs.	£11,738	£8,079	-1.929	0.056	£207,887	£143,084	£3,287	-£372	-0.381	0.025	£130,027	Dominant
TTF form AG naive	£6,213	£4,263	-1.037	0.035	£177,336	£121,684	£1,725	-£225	-0.204	0.015	£116,767	Dominant
TTF form AG all	£6,049	£4,099	-1.160	0.039	£154,533	£104,719	£1,687	-£262	-0.233	0.015	£106,184	Dominant

NAIVE	PROS	PROS	PROS	PROS	PROS	PROS	PROS	PROS	PROS	PROS	PROS	PROS
	BSC	BSC	BSC	BSC	BSC	BSC	ZOL	ZOL	ZOL	ZOL	ZOL	ZOL
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£3,832	£2,648	-0.641	0.038	£100,601	£69,510	£897	-£287	-0.265	0.025	£35,732	Dominant
Amgen STARs	£3,737	£2,553	-0.641	0.038	£98,116	£67,026	£829	-£355	-0.265	0.025	£33,020	Dominant
Amgen NMA	£3,965	£2,780	-0.532	0.025	£159,682	£111,985	£1,062	-£122	-0.128	0.011	£96,168	Dominant
Amgen STARs+NMA	£3,903	£2,719	-0.532	0.025	£157,215	£109,518	£1,035	-£149	-0.128	0.011	£93,720	Dominant
No Naive util step	£3,832	£2,648	-0.641	0.019	£206,119	£142,418	£897	-£287	-0.265	0.015	£59,388	Dominant
SCC ongoing mean	£3,832	£2,648	-0.641	0.051	£74,759	£51,655	£897	-£287	-0.265	0.031	£29,381	Dominant
SCC ongoing max	£3,832	£2,648	-0.641	0.060	£63,543	£43,905	£897	-£287	-0.265	0.034	£26,182	Dominant
No gen. mortality	£3,832	£2,648	-0.641	0.038	£100,601	£69,510	£897	-£287	-0.265	0.025	£35,732	Dominant
5 yeat horizon	£3,826	£2,646	-0.631	0.039	£98,575	£68,171	£899	-£281	-0.259	0.024	£36,753	Dominant
2 year horizon	£3,499	£2,433	-0.526	0.035	£101,245	£70,399	£842	-£224	-0.216	0.019	£44,550	Dominant
vd Hout utility	£3,832	£2,648	-0.641	0.033	£115,708	£79,948	£897	-£287	-0.265	0.022	£41,004	Dominant
No SAE P1+	£3,832	£2,648	-0.641	0.052	£73,450	£50,750	£897	-£287	-0.265	0.025	£36,428	Dominant
No SAE	£3,844	£2,634	-0.654	0.055	£69,360	£47,533	£918	-£292	-0.274	0.026	£35,904	Dominant
No gen. discs.	£7,397	£5,139	-1.179	0.062	£119,273	£82,856	£1,768	-£491	-0.451	0.042	£41,896	Dominant
No discs.	£7,700	£5,351	-1.223	0.064	£120,768	£83,926	£1,952	-£397	-0.479	0.044	£44,688	Dominant
TTF form AG naive	£3,868	£2,684	-0.608	0.036	£108,353	£75,184	£917	-£267	-0.247	0.024	£38,567	Dominant
TTF form AG all	£3,813	£2,629	-0.657	0.039	£96,748	£66,701	£889	-£295	-0.272	0.026	£34,469	Dominant

NAIVE	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL
	BSC	BSC	BSC	BSC	BSC	BSC	ZOL	ZOL	ZOL	ZOL	ZOL	ZOL
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£2,482	£1,700	-0.336	0.020	£125,301	£85,843	£892	£110	-0.059	0.008	£113,054	£13,931
Amgen STARs	£2,416	£1,634	-0.336	0.020	£121,955	£82,497	£863	£81	-0.059	0.008	£109,422	£10,300
Amgen NMA	£2,509	£1,727	-0.320	0.018	£136,091	£93,688	£825	£43	-0.102	0.011	£73,784	£3,878
Amgen STARs+NMA	£2,447	£1,665	-0.320	0.018	£132,743	£90,340	£785	£3	-0.102	0.011	£70,216	£310
No Naive util step	£2,482	£1,700	-0.336	0.014	£176,138	£120,670	£892	£110	-0.059	0.007	£126,056	£15,533
SCC ongoing mean	£2,482	£1,700	-0.336	0.023	£108,030	£74,010	£892	£110	-0.059	0.008	£104,948	£12,932
SCC ongoing max	£2,482	£1,700	-0.336	0.026	£96,870	£66,365	£892	£110	-0.059	0.009	£99,014	£12,201
No gen. mortality	£2,482	£1,700	-0.336	0.020	£125,301	£85,843	£892	£110	-0.059	0.008	£113,054	£13,931
5 yeat horizon	£2,483	£1,702	-0.333	0.020	£122,056	£83,682	£890	£110	-0.059	0.007	£125,318	£15,418
2 year horizon	£2,384	£1,639	-0.311	0.020	£121,313	£83,382	£835	£89	-0.052	0.005	£159,646	£17,095
vd Hout utility	£2,482	£1,700	-0.336	0.016	£151,135	£103,541	£892	£110	-0.059	0.007	£136,322	£16,798
No SAE P1+	£2,482	£1,700	-0.336	0.024	£105,093	£71,998	£892	£110	-0.059	0.004	£206,954	£25,502
No SAE	£2,468	£1,681	-0.339	0.025	£100,630	£68,518	£890	£102	-0.061	0.004	£214,856	£24,620
No gen. discs.	£5,940	£4,110	-0.729	0.036	£163,359	£113,021	£1,738	-£92	-0.110	0.020	£87,158	Dominant
No discs.	£6,087	£4,213	-0.744	0.037	£164,845	£114,086	£1,806	-£68	-0.116	0.020	£88,214	Dominant
TTF form AG all	£2,481	£1,699	-0.334	0.020	£123,772	£84,770	£895	£113	-0.057	0.008	£115,681	£14,640

NAIVE	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG
	BSC	BSC	BSC	BSC	BSC	BSC	ZOL	ZOL	ZOL	ZOL	ZOL	ZOL
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£2,292	£1,613	-0.207	0.012	£198,073	£139,364	£683	£3	-0.095	0.009	£79,694	£382
Amgen STARs	£2,257	£1,578	-0.207	0.012	£195,059	£136,350	£646	-£34	-0.095	0.009	£75,384	Dominant
No Naive util step	£2,292	£1,613	-0.207	0.009	£262,474	£184,677	£683	£3	-0.095	0.007	£99,213	£476
SCC ongoing mean	£2,292	£1,613	-0.207	0.012	£185,758	£130,700	£683	£3	-0.095	0.009	£76,624	£368
SCC ongoing max	£2,292	£1,613	-0.207	0.013	£176,583	£124,244	£683	£3	-0.095	0.009	£74,235	£356
No gen. mortality	£2,292	£1,613	-0.207	0.012	£198,073	£139,364	£683	£3	-0.095	0.009	£79,694	£382
5 yeat horizon	£2,292	£1,613	-0.207	0.012	£198,129	£139,410	£683	£3	-0.094	0.009	£79,880	£398
2 year horizon	£2,261	£1,594	-0.197	0.011	£201,933	£142,328	£669	£2	-0.089	0.008	£86,055	£199
vd Hout utility	£2,292	£1,613	-0.207	0.009	£256,735	£180,639	£683	£3	-0.095	0.007	£103,186	£495
No SAE P1+	£2,292	£1,613	-0.207	0.013	£174,867	£123,037	£683	£3	-0.095	0.007	£97,189	£466
No SAE	£2,278	£1,595	-0.208	0.014	£164,993	£115,483	£680	-£4	-0.095	0.007	£99,457	Dominant
No gen. discs.	£3,949	£2,802	-0.304	0.016	£252,990	£179,472	£1,034	-£114	-0.111	0.012	£88,984	Dominant
No discs.	£3,991	£2,831	-0.307	0.016	£254,158	£180,325	£1,053	-£106	-0.112	0.012	£90,065	Dominant

EXPER	BRST BSC	BRST BSC	BRST BSC	BRST BSC	BRST BSC	BRST BSC	BRST ZOL	BRST ZOL	BRST ZOL	BRST ZOL	BRST ZOL	BRST ZOL
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£5,958	£4,008	-1.167	0.017	£350,856	£236,037	£1,615	-£335	-0.273	0.011	£145,171	Dominant
Amgen STARs	£5,779	£3,829	-1.167	0.017	£340,279	£225,459	£1,561	-£389	-0.273	0.011	£140,353	Dominant
Amgen NMA	£6,169	£4,219	-1.008	0.014	£428,102	£292,786	£1,649	-£301	-0.247	0.011	£154,035	Dominant
Amgen STARs+NMA	£6,020	£4,070	-1.008	0.014	£417,746	£282,429	£1,600	-£350	-0.247	0.011	£149,490	Dominant
No naïve util step	£5,958	£4,008	-1.167	0.017	£350,856	£236,037	£1,615	-£335	-0.273	0.011	£145,171	Dominant
SCC ongoing mean	£5,958	£4,008	-1.167	0.024	£243,540	£163,841	£1,615	-£335	-0.273	0.013	£125,405	Dominant
SCC ongoing max	£5,958	£4,008	-1.167	0.027	£221,748	£149,180	£1,615	-£335	-0.273	0.013	£120,149	Dominant
No gen. mortality	£5,958	£4,008	-1.167	0.017	£350,856	£236,037	£1,615	-£335	-0.273	0.011	£145,171	Dominant
5 yeat horizon	£5,799	£3,902	-1.130	0.017	£344,361	£231,668	£1,573	-£325	-0.265	0.010	£164,960	Dominant
2 year horizon	£4,466	£3,004	-0.855	0.013	£337,708	£227,192	£1,215	-£246	-0.201	0.005	£225,004	Dominant
vd Hout utility	£5,958	£4,008	-1.167	0.016	£378,813	£254,845	£1,615	-£335	-0.273	0.010	£156,405	Dominant
No SAE P1+	£5,958	£4,008	-1.167	0.018	£322,342	£216,854	£1,615	-£335	-0.273	0.005	£300,170	Dominant
No SAE	£5,988	£4,012	-1.184	0.019	£312,295	£209,240	£1,679	-£297	-0.277	0.004	£374,577	Dominant
No gen. discs.	£10,908	£7,327	-2.245	0.033	£333,721	£224,162	£2,982	-£599	-0.531	0.020	£148,366	Dominant
No discs.	£11,144	£7,485	-2.298	0.033	£333,255	£223,840	£3,048	-£611	-0.544	0.021	£148,539	Dominant
TTF form AG naive	£5,958	£4,008	-1.167	0.017	£350,856	£236,037	£1,615	-£335	-0.273	0.011	£145,171	Dominant
TTF form AG all	£5,958	£4,008	-1.167	0.017	£350,856	£236,037	£1,615	-£335	-0.273	0.011	£145,171	Dominant

EXPER	PROS	PROS	PROS	PROS	PROS	PROS	PROS	PROS	PROS	PROS	PROS	PROS
	BSC	BSC	BSC	BSC	BSC	BSC	ZOL	ZOL	ZOL	ZOL	ZOL	ZOL
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£4,009	£2,825	-0.493	0.007	£574,364	£404,707	£1,061	-£123	-0.128	0.006	£167,503	Dominant
Amgen STARs	£3,961	£2,777	-0.493	0.007	£567,473	£397,816	£1,034	-£150	-0.128	0.006	£163,303	Dominant
Amgen NMA	£3,900	£2,716	-0.584	0.011	£345,332	£240,474	£1,054	-£130	-0.134	0.007	£159,601	Dominant
Amgen STARs+NMA	£3,826	£2,641	-0.584	0.011	£338,733	£233,875	£1,026	-£159	-0.134	0.007	£155,319	Dominant
No naive util step	£4,009	£2,825	-0.493	0.007	£574,364	£404,707	£1,061	-£123	-0.128	0.006	£167,503	Dominant
SCC ongoing mean	£4,009	£2,825	-0.493	0.017	£230,878	£162,681	£1,061	-£123	-0.128	0.009	£117,299	Dominant
SCC ongoing max	£4,009	£2,825	-0.493	0.025	£163,635	£115,300	£1,061	-£123	-0.128	0.011	£97,267	Dominant
No gen. mortality	£4,009	£2,825	-0.493	0.007	£574,364	£404,707	£1,061	-£123	-0.128	0.006	£167,503	Dominant
5 yeat horizon	£3,995	£2,815	-0.491	0.009	£461,456	£325,150	£1,058	-£122	-0.128	0.006	£169,582	Dominant
2 year horizon	£3,609	£2,543	-0.440	0.013	£278,005	£195,888	£966	-£100	-0.116	0.005	£176,496	Dominant
vd Hout utility	£4,009	£2,825	-0.493	0.006	£658,895	£464,270	£1,061	-£123	-0.128	0.006	£191,385	Dominant
No SAE P1+	£4,009	£2,825	-0.493	0.021	£190,367	£134,136	£1,061	-£123	-0.128	0.006	£181,229	Dominant
No SAE	£4,023	£2,814	-0.504	0.024	£168,805	£118,054	£1,084	-£126	-0.135	0.006	£169,539	Dominant
No gen. discs.	£7,626	£5,367	-0.988	0.015	£502,900	£353,952	£2,002	-£257	-0.255	0.013	£159,370	Dominant
No discs.	£7,931	£5,581	-1.031	0.016	£499,237	£351,357	£2,189	-£161	-0.281	0.013	£166,078	Dominant
TTF form AG naive	£4,009	£2,825	-0.493	0.007	£574,364	£404,707	£1,061	-£123	-0.128	0.006	£167,503	Dominant
TTF form AG all	£4,009	£2,825	-0.493	0.007	£574,364	£404,707	£1,061	-£123	-0.128	0.006	£167,503	Dominant

EXPER	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL	OSTL
	BSC	BSC	BSC	BSC	BSC	BSC	ZOL	ZOL	ZOL	ZOL	ZOL	ZOL
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£2,671	£1,890	-0.206	0.006	£470,820	£333,055	£868	£86	-0.070	0.007	£118,884	£11,844
Amgen STARs	£2,639	£1,857	-0.206	0.006	£465,078	£327,313	£836	£54	-0.070	0.007	£114,502	£7,462
Amgen NMA	£2,624	£1,842	-0.234	0.007	£371,282	£260,665	£849	£68	-0.081	0.008	£108,102	£8,605
Amgen STARs+NMA	£2,583	£1,802	-0.234	0.007	£365,575	£254,957	£814	£33	-0.081	0.008	£103,640	£4,142
No naive util step	£2,671	£1,890	-0.206	0.006	£470,820	£333,055	£868	£86	-0.070	0.007	£118,884	£11,844
SCC ongoing mean	£2,671	£1,890	-0.206	0.008	£346,321	£244,985	£868	£86	-0.070	0.008	£108,309	£10,790
SCC ongoing max	£2,671	£1,890	-0.206	0.009	£283,635	£200,642	£868	£86	-0.070	0.009	£100,815	£10,044
No gen. mortality	£2,671	£1,890	-0.206	0.006	£470,820	£333,055	£868	£86	-0.070	0.007	£118,884	£11,844
5 yeat horizon	£2,668	£1,887	-0.205	0.006	£410,955	£290,707	£866	£85	-0.070	0.007	£131,459	£12,931
2 year horizon	£2,548	£1,802	-0.195	0.007	£340,556	£240,907	£807	£62	-0.065	0.005	£160,294	£12,223
vd Hout utility	£2,671	£1,890	-0.206	0.005	£574,100	£406,114	£868	£86	-0.070	0.006	£144,378	£14,384
No SAE P1+	£2,671	£1,890	-0.206	0.009	£281,699	£199,272	£868	£86	-0.070	0.004	£233,090	£23,221
No SAE	£2,659	£1,871	-0.207	0.010	£257,816	£181,430	£866	£79	-0.071	0.004	£245,422	£22,310
No gen. discs.	£6,232	£4,402	-0.522	0.013	£478,966	£338,290	£1,672	-£158	-0.145	0.020	£82,035	Dominant
No discs.	£6,382	£4,507	-0.536	0.013	£478,641	£338,053	£1,740	-£134	-0.152	0.021	£83,420	Dominant
TTF form AG all	£2,671	£1,890	-0.206	0.006	£470,820	£333,055	£868	£86	-0.070	0.007	£118,884	£11,844

EXPER	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG	LUNG
	BSC	BSC	BSC	BSC	BSC	BSC	ZOL	ZOL	ZOL	ZOL	ZOL	ZOL
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£2,343	£1,664	-0.165	0.006	£403,622	£286,598	£798	£118	-0.021	0.003	£288,320	£42,698
Amgen STARs	£2,318	£1,639	-0.165	0.006	£399,342	£282,318	£780	£101	-0.021	0.003	£282,094	£36,472
No naive util step	£2,343	£1,664	-0.165	0.006	£403,622	£286,598	£798	£118	-0.021	0.003	£288,320	£42,698
SCC ongoing mean	£2,343	£1,664	-0.165	0.006	£362,531	£257,421	£798	£118	-0.021	0.003	£280,207	£41,496
SCC ongoing max	£2,343	£1,664	-0.165	0.007	£334,103	£237,235	£798	£118	-0.021	0.003	£273,769	£40,543
No gen. mortality	£2,343	£1,664	-0.165	0.006	£403,622	£286,598	£798	£118	-0.021	0.003	£288,320	£42,698
5 yeat horizon	£2,343	£1,664	-0.165	0.006	£402,817	£286,026	£797	£118	-0.021	0.003	£289,355	£42,842
2 year horizon	£2,302	£1,634	-0.162	0.006	£380,278	£270,022	£777	£110	-0.020	0.002	£327,636	£46,221
vd Hout utility	£2,343	£1,664	-0.165	0.004	£522,368	£370,915	£798	£118	-0.021	0.002	£373,106	£55,254
No SAE P1+	£2,343	£1,664	-0.165	0.007	£319,188	£226,644	£798	£118	-0.021	0.001	£651,537	£96,487
No SAE	£2,329	£1,645	-0.167	0.008	£289,629	£204,611	£794	£111	-0.021	0.001	£776,986	£108,380
No gen. discs.	£3,945	£2,797	-0.292	0.010	£381,797	£270,720	£1,177	£30	-0.018	0.004	£270,020	£6,782
No discs.	£3,985	£2,825	-0.295	0.010	£381,481	£270,491	£1,196	£37	-0.019	0.004	£270,522	£8,387

The following tables present the sensitivity of the estimates for the cost effectiveness for denosumab versus zoledronic acid to the price of zoledronic acid. For the more complicated cost utility modeling these are only presented for the modeling that applies the pooled HRs and RRs for SREs. These sensitivity analyses for the modeling that applies the SRE naïve and SRE experienced specific HRs and RRs for SREs are available from the assessment group upon request.

Trial based assessment

Table A Breast cancer trial based annual analysis sensitivity to zoledronic acid price

	Average event assessment		Individual event assessment	
Zol Acid Price	**Ex PAS**	**Inc PAS**	**Ex PAS**	**Inc PAS**
100%	[redacted]	[redacted]	[redacted]	[redacted]
95%	[redacted]	[redacted]	[redacted]	[redacted]
90%	[redacted]	[redacted]	[redacted]	[redacted]
85%	[redacted]	[redacted]	[redacted]	[redacted]
80%	[redacted]	[redacted]	[redacted]	[redacted]
75%	[redacted]	[redacted]	[redacted]	[redacted]
70%	[redacted]	[redacted]	[redacted]	[redacted]

Table B **Prostate cancer trial based annual analysis sensitivity to zoledronic acid price**

	Average event assessment		Individual event assessment	
Zol Acid Price	**Ex PAS**	**Inc PAS**	**Ex PAS**	**Inc PAS**
100%	[redacted]	[redacted]	[redacted]	[redacted]
95%	[redacted]	[redacted]	[redacted]	[redacted]
90%	[redacted]	[redacted]	[redacted]	[redacted]
85%	[redacted]	[redacted]	[redacted]	[redacted]
80%	[redacted]	[redacted]	[redacted]	[redacted]
75%	[redacted]	[redacted]	[redacted]	[redacted]
70%	[redacted]	[redacted]	[redacted]	[redacted]

Lifetime cost utility modeling

Table A **Breast cancer c/e sensitivity to zoledronic acid price**

	ICER: All patients		ICER: SRE Naive		ICER: SRE Exper.	
Zol.A. price	**ex PAS**	**inc PAS**	**ex PAS**	**inc PAS**	**ex PAS**	**inc PAS**
100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
85%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

75%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table B Prostate cancer c/e sensitivity to zoledronic acid price

	ICER: All patients		ICER: SRE Naive		ICER: SRE Exper.	
Zol.A. price	**ex PAS**	**inc PAS**	**ex PAS**	**inc PAS**	**ex PAS**	**inc PAS**
100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
85%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
75%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table C OST including lung c/e sensitivity to zoledronic acid price

	ICER: All patients		ICER: SRE Naive		ICER: SRE Exper.	
Zol.A. price	**ex PAS**	**inc PAS**	**ex PAS**	**inc PAS**	**ex PAS**	**inc PAS**
100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
85%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

75%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table D Lung cancer c/e sensitivity to zoledronic acid price

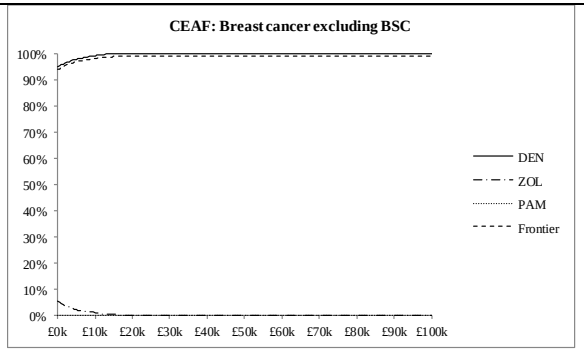
	ICER: All patients		ICER: SRE Naive		ICER: SRE Exper.	
Zol.A. price	**ex PAS**	**inc PAS**	**ex PAS**	**inc PAS**	**ex PAS**	**inc PAS**
100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
85%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
75%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

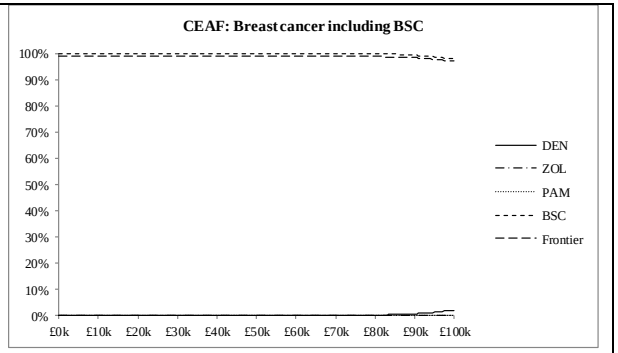
Probabilistic modelling: All patients pooled HRs and RRs across SRE naïve and SRE experienced with PAS

BRST	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	1.817	[redacted]	0.027	£4,163	£151,778
ZOL	1.832		0.013	-£267	Dominant
DEN	1.845		..	..	..
PAM	1.831		0.014	-£3,326	Dominant

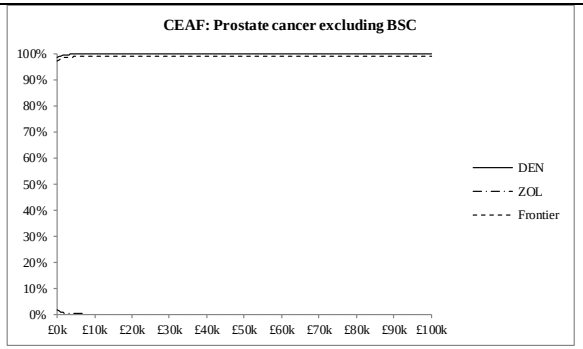
WTP/Q	DEN	ZOL	PAM
£0k	95%	5%	0%
£20k	100%	0%	0%
£30k	100%	0%	0%
£40k	100%	0%	0%
£100k	100%	0%	0%

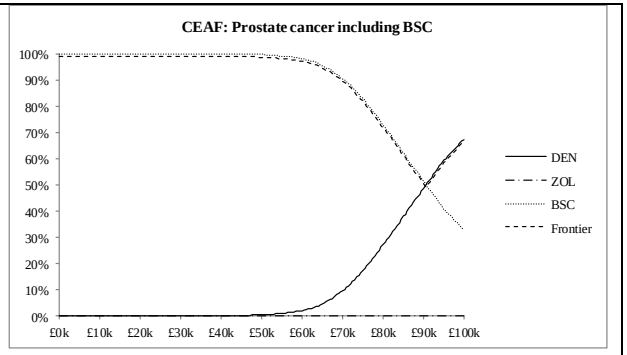
WTP/Q	DEN	ZOL	PAM	BSC
£0k	0%	0%	0%	100%
£20k	0%	0%	0%	100%
£30k	0%	0%	0%	100%
£40k	0%	0%	0%	100%
£100k	2%	0%	0%	98%



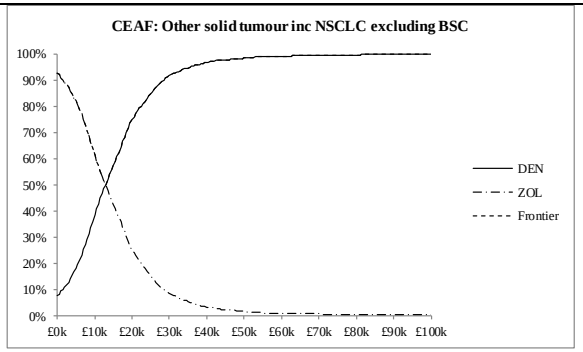


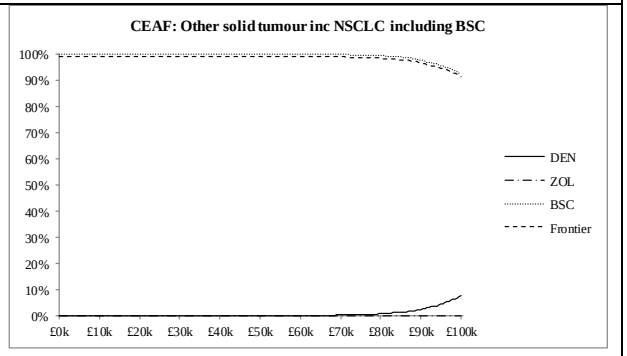
PROS	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	1.069	[redacted]	0.030	£2,694	£90,067
ZOL	1.079		0.020	-£244	Dominant
DEN	1.099		..	..	..
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	98%	2%	0%	0%	100%
£20k	100%	0%	0%	0%	100%
£30k	100%	0%	0%	0%	100%
£40k	100%	0%	0%	0%	100%
£100k	100%	0%	67%	0%	33%



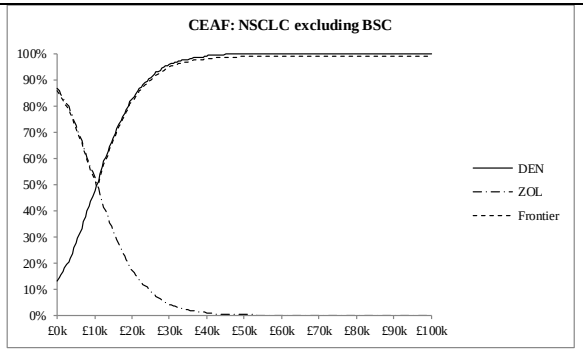


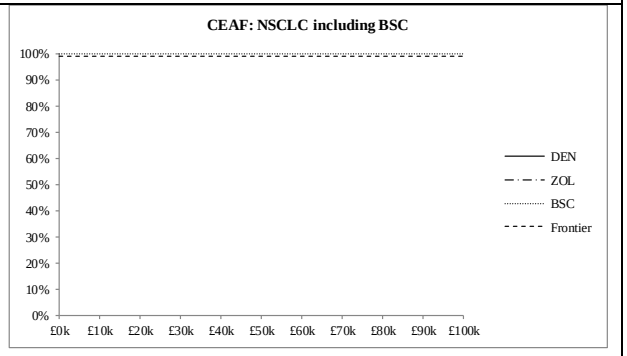
OSTL	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	0.700	[redacted]	0.013	£1,791	£134,912
ZOL	0.706		0.008	£101	£13,200
DEN	0.714		..	..	..
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	7%	93%	0%	0%	100%
£20k	75%	25%	0%	0%	100%
£30k	92%	8%	0%	0%	100%
£40k	97%	3%	0%	0%	100%
£100k	100%	0%	8%	0%	92%





LUNG	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	0.442	[redacted]	0.009	£1,640	£183,922
ZOL	0.445		0.006	£61	£10,597
DEN	0.451		..	..	..
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	13%	87%	0%	0%	100%
£20k	83%	17%	0%	0%	100%
£30k	96%	4%	0%	0%	100%
£40k	99%	1%	0%	0%	100%
£100k	100%	0%	0%	0%	100%



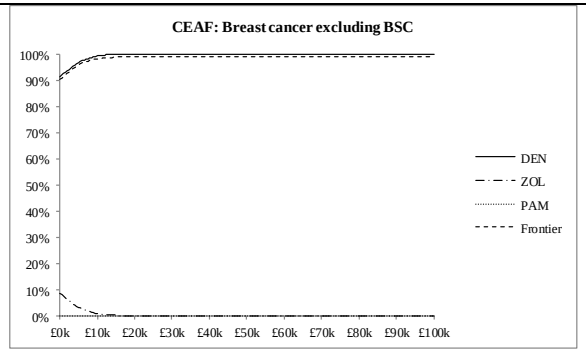


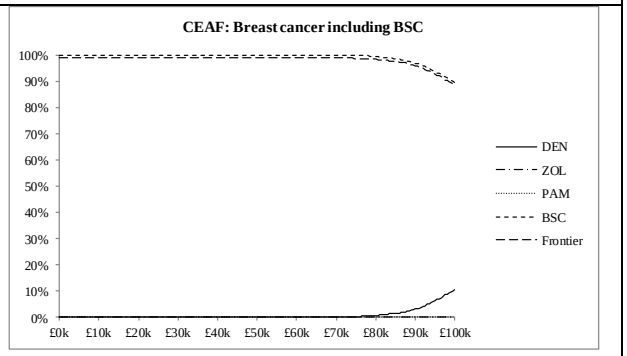
SRE Naive patients

BRST	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	1.849	[redacted]	0.034	£4,290	£124,608
ZOL	1.868		0.015	-£224	Dominant
DEN	1.883		..	..	..
PAM	1.871		0.013	-£3,109	Dominant

WTP/Q	DEN	ZOL	PAM
£0k	92%	9%	0%
£20k	100%	0%	0%
£30k	100%	0%	0%
£40k	100%	0%	0%
£100k	100%	0%	0%

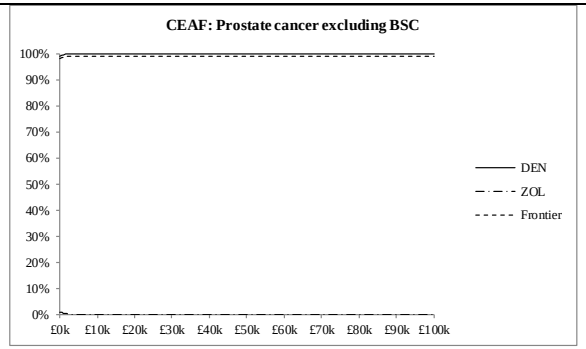
WTP/Q	DEN	ZOL	PAM	BSC
£0k	0%	0%	0%	100%
£20k	0%	0%	0%	100%
£30k	0%	0%	0%	100%
£40k	0%	0%	0%	100%
£100k	10%	0%	0%	90%

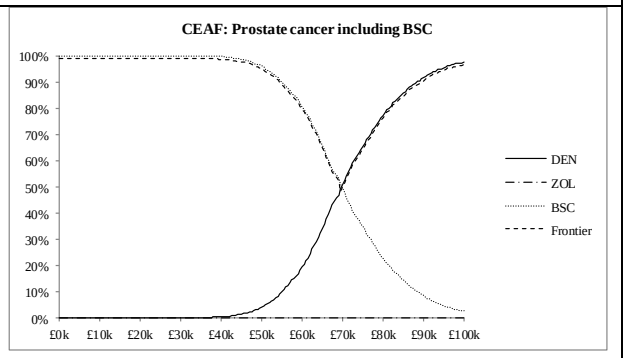




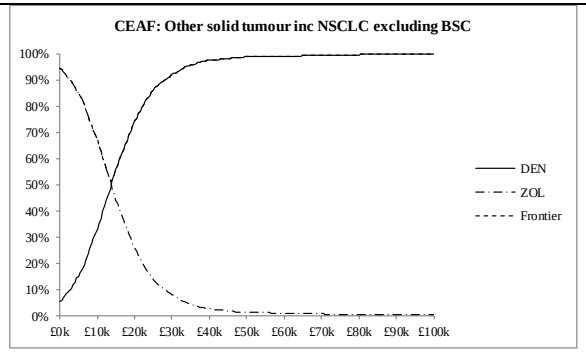
PROS	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	1.090	[redacted]	0.038	£2,652	£69,172
ZOL	1.103		0.025	-£288	Dominant
DEN	1.128		..	..	..

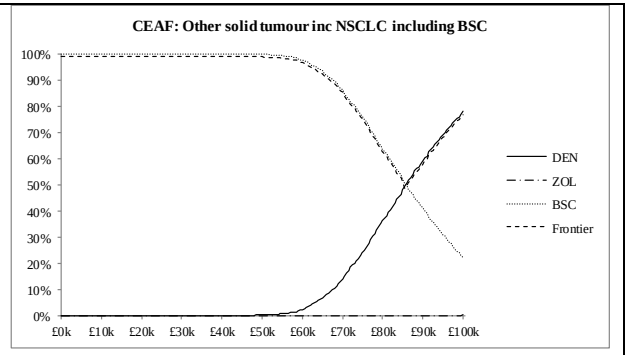
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	99%	1%	0%	0%	100%
£20k	100%	0%	0%	0%	100%
£30k	100%	0%	0%	0%	100%
£40k	100%	0%	0%	0%	100%
£100k	100%	0%	98%	0%	2%



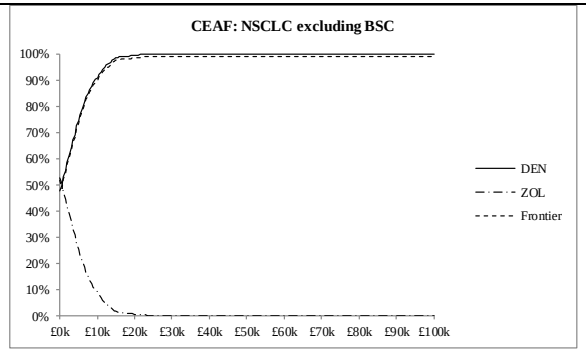


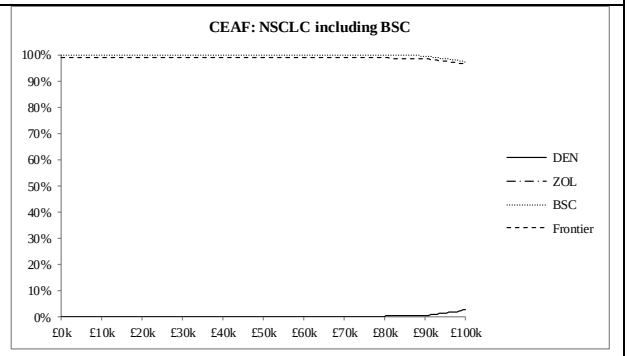
OSTL	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	0.710	[redacted]	0.020	£1,707	£85,435
ZOL	0.722		0.008	£109	£13,701
DEN	0.730		..	..	..
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	5%	95%	0%	0%	100%
£20k	74%	26%	0%	0%	100%
£30k	92%	8%	0%	0%	100%
£40k	98%	2%	0%	0%	100%
£100k	100	0%	78%	0%	22%





LUNG	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	0.456	[redacted]	0.012	£1,613	£138,485
ZOL	0.459		0.009	£2	£264
DEN	0.468		..	..	..
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	48%	53%	0%	0%	100%
£20k	100%	0%	0%	0%	100%
£30k	100%	0%	0%	0%	0%
£40k	100%	0%	0%	0%	100%
£100k	100%	0%	3%	0%	97%



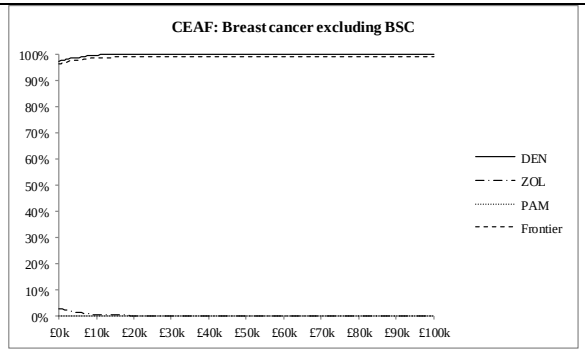


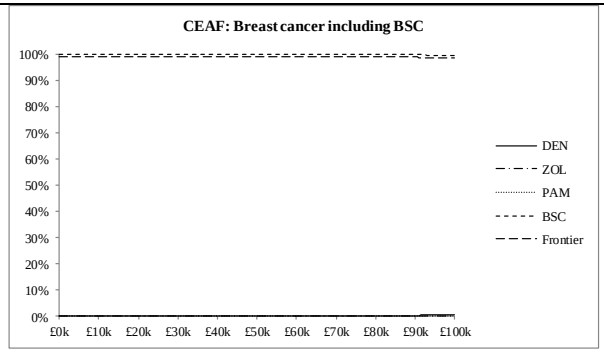
SRE Experienced patients

BRST	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	1.777	[redacted]	0.017	£4,020	£231,476
ZOL	1.783		0.011	-£324	Dominant
DEN	1.794		..	..	..
PAM	1.777		0.017	-£3,610	Dominant

WTP/Q	DEN	ZOL	PAM
£0k	97%	3%	0%
£20k	100%	0%	0%
£30k	100%	0%	0%
£40k	100%	0%	0%
£100k	100%	0%	0%

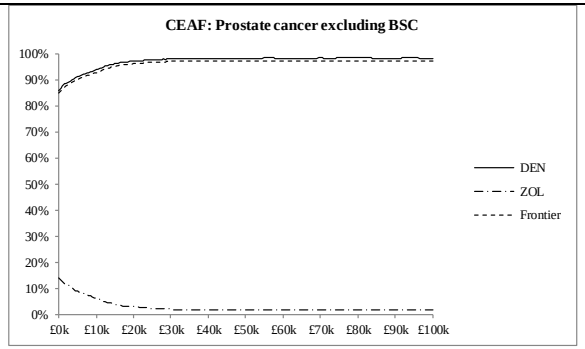
WTP/Q	DEN	ZOL	PAM	BSC
£0k	0%	0%	0%	100%
£20k	0%	0%	0%	100%
£30k	0%	0%	0%	100%
£40k	0%	0%	0%	100%
£100k	0%	0%	0%	100%

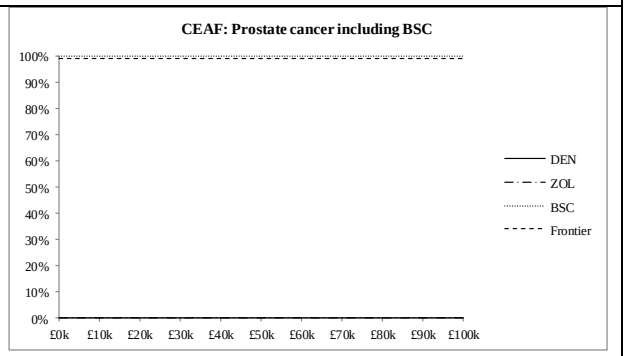




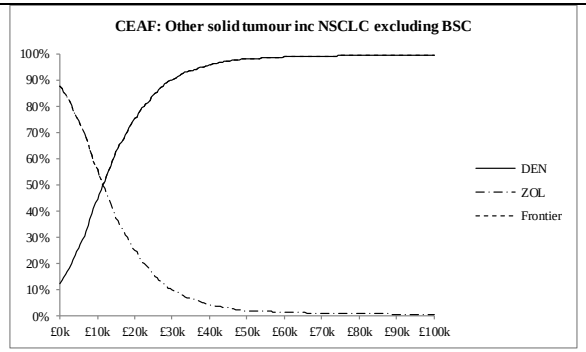
PROS	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	1.007	[redacted]	0.007	£2,830	£401,027
ZOL	1.008		0.006	-£125	Dominant
DEN	1.014		..	..	..

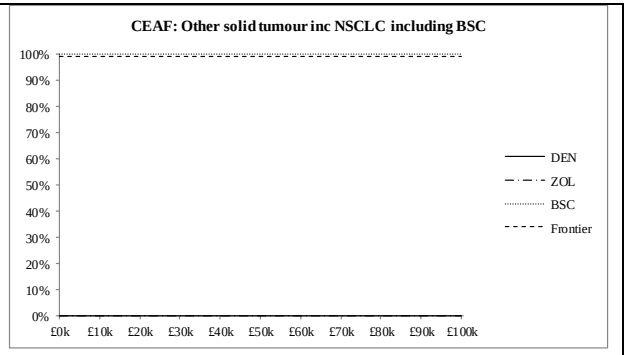
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	86%	14%	0%	0%	100%
£20k	97%	3%	0%	0%	100%
£30k	98%	2%	0%	0%	100%
£40k	98%	2%	0%	0%	100%
£100k	98%	2%	0%	0%	100%





OSTL	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	0.693	[redacted]	0.006	£1,889	£325,996
ZOL	0.691		0.007	£86	£11,667
DEN	0.699		..	..	..
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	12%	88%	0%	0%	100%
£20k	75%	25%	0%	0%	100%
£30k	90%	10%	0%	0%	100%
£40k	96%	4%	0%	0%	100%
£100k	100%	0%	0%	0%	100%





LUNG	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	0.427	[redacted]	0.006	£1,665	£284,084
ZOL	0.430		0.003	£118	£42,891
DEN	0.433		..	..	..
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	1%	99%	0%	0%	100%
£20k	12%	88%	0%	0%	100%
£30k	28%	72%	0%	0%	100%
£40k	45%	55%	0%	0%	100%
£100k	92%	8%	0%	0%	100%