Guideline 3-14 Version 2 IN REVIEW

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Bone Health and Bone-Targeted Therapies for Prostate Cancer

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An assessment conducted in January 2025 placed Guideline 3-14 Version 2 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 3-14 Version 2 is comprised of 5 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/31716

Section 1:	**Recommendations**
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Table of Contents

Bone Health and Bone-Targeted Therapies for Prostate Cancer

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVE

To evaluate the effectiveness of therapies targeting bone across all stages of prostate cancer.

TARGET POPULATION

Men with prostate cancer.

INTENDED USERS

Healthcare professionals, health care administrators, medical or radiation oncologists who treat genitourinary cancer, urologists, radiologists, nuclear medicine physicians, geriatricians, primary care physicians, and osteoporosis experts.

Table 1-1. Dosage definitions for denosumab and zoledronic acid.

Drug	Indication	Current recommended dosage
Denosumab	Osteoporosis	60 mg subcutaneous injection every six months
	Bone metastasis	120 mg subcutaneous injection every four weeks
Zoledronic acid	Osteoporosis	5 mg intravenous infusion once per year[a]
	Bone metastasis	4 mg intravenous infusion every three to four weeks[b]

[a]Dosage and frequency used in most of the published studies was a 4 mg intravenous infusion every 3 months. See qualifying statement for Question 1.
[b]Less frequent dosing (every 12 weeks) may be acceptable. See qualifying statement for Question 3.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

QUESTION 1

Can therapeutic interventions reduce osteoporosis-related outcomes in men with prostate cancer receiving androgen deprivation therapy (ADT)?

Recommendation:
1. For men with prostate cancer at high risk of fracture (with or without bone metastases) receiving ADT, denosumab at the osteoporosis-indicated dosage should be considered to reduce the risk of fracture. In situations or jurisdictions where denosumab is contraindicated or not available, a bisphosphonate is a reasonable option.

Qualifying statements:

- Fracture risk can be estimated based on risk prediction tools such as the World Health Organization Fracture Risk Assessment Tool (WHO FRAX) or the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) tool [1,2].
- Baseline bone mineral density (BMD) testing with conventional dual X-ray absorptiometry is encouraged for men prior to starting ADT to help determine the risk of fracture and identify those individuals most likely to benefit from denosumab or bisphosphonates. If a BMD test has been performed in the past one to two years, a repeat BMD test is not likely to be informative prior to starting ADT unless the patient was initiated on denosumab or bisphosphonates.
- The optimum duration of therapy is unknown. Current studies provide results up to 36 months of therapy.
- The dosages used in the studies were:
    - Denosumab, 60 mg subcutaneous injection every six months [3] (See Table 1-1).
    - Alendronate, 70 mg oral dose each week [4,5].
    - Zoledronic acid (ZA), 4 mg intravenous (IV) infusion every three months [6-12], 4 mg IV every six months [13], and 4 mg IV once yearly [14]. Both Health Canada and the U.S. Food and Drug Administration have approved a 5 mg IV infusion dose for the treatment of osteoporosis in men, whereas neither agency has approved the 4 mg dose for the treatment of osteoporosis in men (See Table 1-1).
- Denosumab was shown to reduce fractures in this population. Other agents only improved BMD. However, there is substantial indirect evidence of fracture reduction in other populations with the use of bisphosphonates.
- Toremifene and raloxifene are selective estrogen receptor modulators (SERMs). Although both drugs were associated with increased BMD and toremifene reduced the risk of fracture, SERMs are associated with increased risk of venous thromboembolic events, raising safety concerns in this population.
- Three small trials comparing exercise programs with usual care [15-17] and one small trial comparing group exercise with personal training [18] showed no difference in BMD between groups. One trial showed improvements in quality of life measures with exercise [17]. A more comprehensive review of exercise for people with cancer is available (see Guideline 19-5: Exercise for People with Cancer).
- In patients with metastatic disease, fracture is part of the skeletal-related events (SRE) composite outcome (See question 3).
- Men with castration-sensitive prostate cancer with bone metastasis may derive benefit from starting or continuing denosumab at the osteoporosis-indicated dosage or a bisphosphonate for fracture prevention. However, few trials that were reviewed for this question included such men and analyses, stratified by the presence or absence of bone metastasis, were not performed. Therefore, the evidence of benefit is less compelling in this scenario.

QUESTION 2
Can therapeutic interventions prevent bone metastases in men with prostate cancer?

Recommendations:
2a. In men with high-risk localized prostate cancer, bisphosphonates are not recommended to reduce the risk of first bone metastasis. **2b. In men with nonmetastatic castration-resistant prostate cancer (CRPC), denosumab at the bone metastasis-indicated dosage is not recommended to reduce the risk of first bone metastasis.**
Qualifying statements:
• Denosumab has not been approved in Canada or the United States for this indication (2b). (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs%20/OncologicDrugsAdvisoryCommittee/UCM293709.pdf) • Denosumab, 60 mg subcutaneously every six months, can still be used to prevent osteoporosis-related outcomes (see Recommendation 1).

QUESTION 3
Can bone-targeted therapies reduce the incidence of SREs, reduce pain, or improve quality of life in men with prostate cancer metastatic to bone?

Recommendation:
3a. In men with metastatic CRPC (mCRPC), either ZA (minimally symptomatic or asymptomatic disease) or denosumab (disease independent of symptoms) (both at bone metastasis-indicated dosages) is recommended for preventing or delaying SREs. Insufficient evidence exists to make a recommendation with respect to men with castration-sensitive prostate cancer and bone metastasis.

Recommendation:
3b. In men with symptomatic mCRPC and bone pain, radium (Ra)-223 should be considered for reducing symptomatic skeletal events and improving health-related quality of life.

Recommendation:
3c. In men with mCRPC and bone pain, radiopharmaceuticals or IV bisphosphonates may be considered for pain palliation.

Qualifying statements for Question 3 recommendations:
• See Table 1-1 for dosages. Patients receiving either denosumab or ZA should be taking 1000 mg of elemental calcium (from dietary and/or supplemental sources) and ≥400 IU of vitamin D daily. The dose of ZA should be reduced in cases of renal insufficiency (creatinine clearance [CrCl] <60 mL/min or serum creatinine [SCr]

>132.5 µmol/L). ZA is not recommended below a CrCl of 30 mL/min (or SCr >265 µmol/L). In patients over the age of 65, CrCl (whether estimated or directly measured) should be used rather than SCr. Denosumab and ZA should not be given in combination.

- There is uncertainty regarding the optimum duration of therapy; with respect to ZA, less-intensive therapy (i.e., every 3 months) may be as effective as monthly treatment (CALGB 70604 Alliance study [19]).
- SRE definitions and data reporting pain are not identical across studies.
- Recommendation 3b applies to men with predominantly bony metastases and no evidence of visceral metastases or large nodal metastases.
- Radiopharmaceuticals can permanently reduce bone marrow reserves, and this should be considered if the patient remains a candidate for palliative cytotoxic chemotherapy. The recommended dose for Ra-223 is one IV injection of 55 kBq/kg of body weight every four weeks for a total of six injections (based on the primary standardization revision for Ra-223 in 2015 by the National Institute of Standards and Technology [20]). The optimal sequencing of Ra-223, denosumab, and bisphosphonates is unclear, and recommendations to patients should be done in consultation with a clinician with expertise in CRPC treatment.
- Systemic therapies for the treatment of mCRPC such as abiraterone/prednisone, enzalutamide, docetaxel, and cabazitaxel have been shown to reduce SREs, improve bone pain and health-related quality of life, and/or improve overall survival in mCRPC. Mitoxantrone has also been shown to improve pain and health-related quality of life (see Guideline 3-15: Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer). The optimal sequencing or combination of these therapies with bone targeted agents is unclear, and recommendations to patients should be done in consultation with a clinician with expertise in CRPC treatment.
- Radiotherapy is one of the main therapeutic approaches to palliate pain in men with bone metastasis [21,22].

QUESTION 4
Can bone-targeted therapies improve overall survival in men with established prostate cancer and bone metastases?

Recommendation:
4. In men with symptomatic mCRPC, Ra-223 is recommended to extend overall survival.
Qualifying statements:
• This recommendation applies to men with predominantly bony metastases and no evidence of visceral metastases or large nodal metastases. • Ra-223 appears to be equally effective whether or not patients have received prior docetaxel or are eligible to receive docetaxel. • Other options are available aside from bone-targeted therapies or radiopharmaceuticals for improving outcomes (see Guideline 3-15: Systemic Therapy

in Men with Metastatic Castration-Resistant Prostate Cancer). The optimal sequencing of therapies is unknown.

- There is insufficient evidence to support an improvement in overall survival with bisphosphonates or denosumab in this population.
- Systemic therapies for the treatment of mCRPC such as abiraterone/prednisone, enzalutamide, docetaxel, and cabazitaxel have been shown to reduce SREs, improve bone pain and health-related quality of life, and/or improve overall survival in mCRPC (see Guideline 3-15: Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer). The optimal sequencing or combination of these therapies with bone-targeted agents is unclear, and recommendations to patients should be done in consultation with a clinician with expertise in CRPC treatment.

Bone Health and Bone-Targeted Therapies for Prostate Cancer

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVE

To evaluate the effectiveness of therapies targeting bone across all stages of prostate cancer.

TARGET POPULATION

Men with prostate cancer.

INTENDED USERS

Healthcare professionals, health care administrators, medical or radiation oncologists who treat genitourinary cancer, urologists, radiologists, nuclear medicine physicians, geriatricians, primary care physicians, osteoporosis experts, patients, and media.

Table 2-1. Dosage definitions for denosumab and zoledronic acid.

Drug	Indication	Current recommended dosage
Denosumab	Osteoporosis	60 mg subcutaneous injection every six months
	Bone metastasis	120 mg subcutaneous injection every four weeks
Zoledronic Acid	Osteoporosis	5 mg intravenous infusion once per year[a]
	Bone metastasis	4 mg intravenous infusion every three to four weeks[b]

[a]Dosage and frequency used in most of the published studies was a 4 mg intravenous infusion every 3 months. See qualifying statement for Question 1.
[b]Less frequent dosing (every 12 weeks) may be acceptable. See qualifying statement for Question 3.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

QUESTION 1

Can therapeutic interventions reduce osteoporosis-related outcomes in men with prostate cancer receiving androgen deprivation therapy (ADT)?

Recommendation:
1. For men with prostate cancer at high risk of fracture (with or without bone metastases) receiving ADT, denosumab at the osteoporosis-indicated dosage should be considered to reduce the risk of fracture. In situations or jurisdictions where denosumab is contraindicated or not available, a bisphosphonate is a reasonable option.
Qualifying statements:
• Fracture risk can be estimated based on risk prediction tools such as the World Health Organization Fracture Risk Assessment Tool (WHO FRAX) or the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) tool [1,2].

- Baseline bone mineral density (BMD) testing with conventional dual X-ray absorptiometry is encouraged for men prior to starting ADT to help determine the risk of fracture and identify those individuals most likely to benefit from denosumab or bisphosphonates. If a BMD test has been performed in the past one to two years, a repeat BMD test is not likely to be informative prior to starting ADT unless the patient was initiated on denosumab or bisphosphonates.
- The optimum duration of therapy is unknown. Current studies provide results up to 36 months of therapy.
- The dosages used in the studies were:
    - Denosumab, 60 mg subcutaneous injection every six months [3] (See Table 2-1).
    - Alendronate, 70 mg oral dose each week [4,5].
    - Zoledronic acid (ZA), 4 mg intravenous (IV) infusion every three months [6-12], 4 mg IV every six months [13], and 4 mg IV once yearly [14]. Both Health Canada and the U.S. Food and Drug Administration have approved a 5 mg IV infusion dose for the treatment of osteoporosis in men, whereas neither agency has approved the 4 mg dose for the treatment of osteoporosis in men (See Table 2-1).
- Denosumab was shown to reduce fractures in this population. Other agents only improved BMD. However, there is substantial indirect evidence of fracture reduction in other populations with the use of bisphosphonates.
- Toremifene and raloxifene are selective estrogen receptor modulators (SERMs). Although both drugs were associated with increased BMD and toremifene reduced the risk of fracture, SERMs are associated with increased risk of venous thromboembolic events, raising safety concerns in this population.
- Three small trials comparing exercise programs with usual care [15-17] and one small trial comparing group exercise with personal training [18] showed no difference in BMD between groups. One trial showed improvements in quality of life measures with exercise [17]. A more comprehensive review of exercise for people with cancer is available (see Guideline 19-5: Exercise for People with Cancer).
- In patients with metastatic disease, fracture is part of the skeletal-related events (SRE) composite outcome (See question 3).
- Men with castration-sensitive prostate cancer with bone metastasis may derive benefit from starting or continuing denosumab at the osteoporosis-indicated dosage or a bisphosphonate for fracture prevention. However, few trials that were reviewed for this question included such men and analyses stratified by the presence or absence of bone metastases were not performed. Therefore, the evidence of benefit is less compelling in this scenario.

Key evidence:

For the outcome of fracture, one large randomized controlled trial (RCT) (n=1468) in men with castration-sensitive prostate cancer reported that denosumab (60 mg subcutaneously every 6 months), compared with placebo, reduced new vertebral fractures at 12 (0.3% vs. 1.9%; relative risk [RR], 0.15; p=0.004), 24 (1.0% vs. 3.3%; RR, 0.31; p=0.004), and 36 months (1.5% vs. 3.9%; RR, 0.38; 95% confidence interval [CI], 0.19 to 0.78; p=0.006). Denosumab

improved BMD more than placebo in the lumbar spine, femoral neck, total hip, and one-third distal radius at 24 months ($p \leq 0.001$). No statistically significant differences in adverse effects were observed between the groups [3].

In a meta-analysis of 10 placebo-controlled trials of bisphosphonates (8 IV, 1 intramuscular, 1 oral), no statistically significant difference was observed between bisphosphonates and placebo in the incidence of fractures (4 trials; odds ratio [OR], 1.40; 95% CI, 0.53 to 3.67; p=0.50); BMD was improved in the lumbar spine (10 trials; weighted mean difference [WMD], 6.02; 95% CI, 5.39 to 6.65; p<0.001), femoral neck (7 trials; WMD, 2.91; 95% CI, 2.16 to 3.67; p<0.001), and total hip (8 trials; WMD, 2.82; 95% CI, 2.05 to 3.58; p<0.001). The meta-analysis also showed bisphosphonates were associated with a higher risk of gastrointestinal symptoms (3 trials; OR, 2.89; 95% CI, 1.18 to 7.04; p=0.02) and fever (2 trials; OR, 7.99; 95% CI, 2.08 to 30.61; p=0.002); no difference was observed between bisphosphonates and placebo in 6 trials reporting severe adverse events (17% vs. 18%; OR, 0.88; 95% CI, 0.61 to 1.28; p=0.52) [23].

Only one relevant RCT comparing bisphosphonates with control for the outcome of fracture has been published since the Ding et al. review [13]; therefore, no additional meta-analysis was conducted by the Working Group.

Although the evidence for bisphosphonates on the incidence of fracture in men on ADT is inconclusive at present, there is substantial evidence of efficacy for this class of agents on fracture reduction in women and men with osteoporosis [24-27].

For the outcome of BMD, a meta-analysis performed by the Working Group pooled 14 RCTs including the 10 trials from Ding et al. plus four more recent trials of bisphosphonates (3 trials of oral bisphosphonates and 1 trial of IV bisphosphonates). A statistically significant improvement from baseline was seen in BMD for bisphosphonates compared with control at 12 months: lumbar spine (6.65% difference; p<0.001), femoral neck (2.87% difference; p<0.001), and total hip (2.68% difference; p<0.001). A sensitivity analysis showed statistically significant differences between bisphosphonates and control with oral and IV bisphosphonates analyzed separately for all BMD sites (except total hip with oral bisphosphonates).

Few trials have evaluated the incidence of osteoporosis in men with prostate cancer. One trial (n=94) evaluating IV clodronate (1500 mg infused over 2 hours every 28 days) or ZA (4 mg IV every month) showed a reduction in incidence of osteoporosis with clodronate (17.9%) or ZA (20.8%) compared with control at 36 months (58%) (p<0.001 for both comparisons) [28]. No difference was seen in three other trials of bisphosphonates [7,29,30].

In men with documented prostate cancer and bone metastasis, two small trials showed improvements in BMD with IV bisphosphonates [31,32]. One trial comparing ZA with oral clodronate (n=137) showed greater percent improvement from baseline in lumbar spine BMD with ZA at 36 months (4.5% vs. 2.3%; p=0.03), but no difference in femoral neck or total hip BMD. ZA was associated with a lower incidence of gastrointestinal adverse effects (16% vs. 31%; p=0.01). Other important but nonsignificantly different adverse effects were renal dysfunction (31 [45%] vs. 23 [34%] patients), osteonecrosis of the jaw (1 [1%] vs. 0 patients), and hypocalcemia (6 [9%] vs. 2 [3%] patients) [33].

Interpretation of evidence:

The Working Group members believed that fracture was a critical outcome for recommendation development.

For denosumab, the quality of the evidence was considered to be high according to GRADE criteria*. The Working Group members believed the desirable effects were moderate to large, (i.e., there was a clinically meaningful difference between denosumab and placebo in fracture rates). Furthermore, the undesirable effects were small, (i.e., with no statistically significant difference in adverse effects). Therefore, the benefits of denosumab in fracture reduction outweigh the harms. The evidence is generalizable to the population of interest.

For bisphosphonates, the quality of the evidence was considered to be moderate according to GRADE criteria. Few bisphosphonate trials were designed or powered to detect differences in fracture rates. The Working Group members believed that the desirable effects were likely moderate (i.e., there was no statistically significant difference between bisphosphonates and placebo in fracture rates, but bisphosphonates improved BMD). Furthermore, the undesirable effects were small. Therefore, the benefits of bisphosphonates in improving BMD outweigh the harms. The evidence applies to the population of interest.

*GRADE=Grading of Recommendations Assessment, Development and Evaluation.

QUESTION 2

Can therapeutic interventions prevent bone metastases in men with prostate cancer?

Recommendations:

2a. In men with high-risk localized prostate cancer, bisphosphonates are not recommended to reduce the risk of first bone metastasis.

2b. In men with nonmetastatic castration-resistant prostate cancer (CRPC), denosumab at the bone metastasis-indicated dosage is not recommended to reduce the risk of first bone metastasis.

Qualifying statements:

- Denosumab has not been approved in Canada or the United States for this indication (2b). (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs%20/OncologicDrugsAdvisoryCommittee/UCM293709.pdf)

- Denosumab, 60 mg subcutaneously every six months, can still be used to prevent osteoporosis-related outcomes (see Recommendation 1).

Key evidence:

One trial (n=1433) comparing ZA (4 mg IV every 3 months) with control in men with high-risk localized or locally advanced prostate cancer showed no statistically significant difference between groups in bone metastasis at a median of 4.8 years (14.7% vs. 13.2%; p=0.65). Adverse events were more common in patients receiving ZA than control (79% vs. 74%; p=0.03). Nine patients receiving ZA had osteonecrosis of the jaw compared with one patient in the control group [34].

One trial (n=508) comparing oral sodium clodronate (2080 mg every day) with placebo in men with nonmetastic prostate cancer at high risk of developing bone metastasis showed no difference between groups in symptomatic bone metastasis (24% vs. 19%; hazard ratio [HR], 1.32; 95% CI, 0.91 to 1.93; p=0.15). Clodronate led to more patients having dose-modifying adverse events than placebo (41% vs. 28%; p=0.002) [35].

One trial (n=1432) comparing denosumab (120 mg subcutaneous injection every 4 weeks) with placebo in patients with nonmetastatic CRPC showed that denosumab delayed the median time to first bone metastasis (33.2 vs. 29.5 months; HR, 0.84; 95% CI, 0.71 to 0.98; p=0.032) and reduced the proportion of CRPC patients with symptomatic bone metastases (10% vs. 13%; HR, 0.67; 95% CI, 0.49 to 0.92; p=0.01). Denosumab was associated with an increased risk of osteonecrosis of the jaw (33 [5%] vs. 0 patients) and hypocalcemia (12 [2%] vs. 2 patients [<1%]), and had no effect on overall survival (43.9 vs. 44.8 months; HR, 1.01; 95% CI, 0.85 to 1.20) [36].

Interpretation of evidence:

The Working Group members believed that bone metastasis was an important outcome for recommendation development.

Bisphosphonates did not prevent bone metastases and were associated with increased risk of adverse effects. The quality of the evidence was considered to be high according to GRADE criteria. The Working Group members believed that for this indication, the desirable effects were negligible and undesirable effects were present. Bisphosphonates should not be used to reduce the risk of bone metastasis.

Denosumab at a bone metastasis-indicated dosage delayed the median time to first bone metastasis by four months, but at the risk of developing osteonecrosis of the jaw. The quality of the evidence was considered to be moderate according to GRADE criteria. The Working Group members believed that the desirable effects were moderate, but the adverse effect risk was unacceptable. Bone metastasis-indicated denosumab therapy should not be used to reduce the risk of bone metastasis; however, the osteoporosis-indicated dosage of denosumab may be used to reduce the risk of osteoporosis-related outcomes.

QUESTION 3

Can bone-targeted therapies reduce the incidence of SREs, reduce pain, or improve quality of life in men with prostate cancer metastatic to bone?

Recommendation:

3a. In men with metastatic CRPC (mCRPC), either ZA (minimally symptomatic or asymptomatic disease) or denosumab (disease independent of symptoms) (both at bone metastasis-indicated dosages) is recommended for preventing or delaying SREs. Insufficient evidence exists to make a recommendation with respect to men with castration-sensitive prostate cancer and bone metastasis.

Key evidence:

CRPC and bone metastasis:

One trial (n=1904) comparing denosumab (120 mg subcutaneous injection every 4 weeks) with ZA (4 mg IV infusion every 4 weeks) in men with mCRPC showed prolonged median time to first SRE with denosumab (20.7 vs. 17.1 months; HR, 0.82; 95% CI, 0.71 to 0.95; p=0.0002). Denosumab was associated with greater rates of grade 3 or higher adverse effects than ZA (72% v.s 66%; p=0.01) and unspecified hypocalcemia (13% vs. 6%; p<0.0001). Osteonecrosis of the jaw occurred in 22 (2%) denosumab and 12 ZA patients (1%) and renal impairment occurred in 139 (15%) denosumab and 153 (16%) ZA patients [37].

One network meta-analysis showed a reduction in the risk of first SRE with denosumab compared with placebo (HR, 0.56; 95% CI, 0.40 to 0.77) [38].

Castration-sensitive prostate cancer and bone-metastasis:
One trial (n=59) comparing ZA with control showed a lower incidence of SREs with ZA (HR, 0.38; 95% CI, 0.15 to 0.94; p=0.019). No serious adverse events occurred in either group [39].

One trial (n=645) of early ZA showed no difference between ZA and placebo in median time to first SRE (31.9 vs. 29.8 months, p=0.39). Grade ≥3 osteonecrosis occurred in 10 (3.2%) ZA patients compared with six (1.9%) placebo patients. Grade 3 hypocalcemia occurred in five (2%) versus two (1%) and grade 4 occurred in two (1%) versus one (<1%) ZA and placebo patients, respectively. The study was terminated before the target sample and SREs had been reached [40].

One trial (n=137) comparing ZA with oral clodronate showed no difference in the incidence of SREs (17% vs. 20%; p=0.62). ZA was associated with lower incidence of gastrointestinal adverse effects than clodronate (16% vs. 31%; p=0.01). Other important adverse effects that did not differ to a statistically significant extent between groups were renal dysfunction (31 [45%] vs. 23 [34%] patients), osteonecrosis of the jaw (1 [1%] vs. 0 patients), and hypocalcemia (6 [9%] vs. 2 [3%] patients) [33].

Additional evidence:
One meta-analysis pooled three trials of bisphosphonates (oral clodronate [41], ZA [42], and pamidronate [43]). In all three trials, the men had (evidence of) metastatic disease. One trial included castration-sensitive patients [41] and two trials included patients with CRPC [42,43]. The meta-analysis showed a borderline statistically significant reduction in SREs with bisphosphonates (38% vs. 43%; OR, 0.79; 95% CI, 0.62 to 1.00). Higher rates of nausea were observed with bisphosphonates (2 trials, 39% vs. 30%; OR, 1.35; 95% CI, 1.02 to 1.77; p=0.034), but there were statistically nonsignificant differences between groups for vomiting and anemia [44].

The 24-month results of the placebo-controlled trial by Saad et al. (n=643) showed an 11% reduction in ≥1 SRE with 4 mg of ZA (38% vs. 49%; p=0.028). The rates of mild-to-moderate fatigue, myalgia, and fever that were higher with ZA at the 15-month follow-up were similar between the ZA and placebo groups at 24 months [45].

Interpretation of evidence:

The Working Group members believed that the incidence of SREs in men with mCRPC was an important outcome for recommendation development. For denosumab, the quality of the evidence was considered to be moderate to high according to GRADE criteria. The Working Group members believed the desirable effects were moderate and the undesirable effects were small. Denosumab was associated with a clinically meaningful reduction in SREs compared with placebo and compared with ZA, but was also associated with an increased risk of hypocalcemia and a small but important risk of osteonecrosis of the jaw. Overall, the Working Group members believed that the benefits outweighed the harms.
For ZA, the quality of the evidence was considered to be moderate according to GRADE criteria. The Working Group members believed that the desirable effects were moderate and the undesirable effects were small. ZA was associated with a clinically meaningful reduction in SREs compared with placebo, despite a small increased risk of osteonecrosis of the jaw. Overall, the group believed that the benefits outweighed the harms.
In men with metastatic castration-sensitive prostate cancer, the quality of evidence for ZA was low and the evidence of benefit varied across studies.

Recommendation:

3b. In men with symptomatic mCRPC and bone pain, radium (Ra)-223 should be considered for reducing symptomatic skeletal events and improving health-related quality of life.

Key evidence:

One trial (ALSYMPCA) (n=921) comparing Ra-223 (6 IV injections of 50 kBq/kg of body weight, 1 injection every 4 weeks) with placebo showed Ra-223 prolonged median time to first symptomatic skeletal event (15.6 vs. 9.8 months; HR, 0.66; 95% CI, 0.52 to 0.83; p<0.001) and improved quality of life according to the Functional Assessment of Cancer Therapy-Prostate (FACT-P) instrument (25% vs. 16%; p=0.02). Adverse events were consistently lower in the Ra-223 group than the placebo group but did not differ to a statistically significant extent: all adverse events (93% vs. 96%), grade 3 or 4 adverse events (56% vs. 62%), serious adverse events (47% vs. 60%), and study drug discontinuation due to adverse events (16% vs. 21%). One grade 5 case of thrombocytopenia occurred in the Ra-223 group and one grade 5 case of anemia occurred in the placebo group [46,47]. In a subset of patients in the ALSYMPCA trial, there was a suggestion that combining Ra-223 and bisphosphonates was beneficial in delaying time to first symptomatic skeletal event compared with Ra-223 alone (HR for bisphosphonate use at baseline, 0.49; 95% CI, 0.38 to 0.64; p<0.001); however, the trial was not powered for multiple subset analyses of a secondary endpoint [47].

An earlier phase II trial in similar patients (n=64) comparing Ra-223 (4 IV injections of 50 kBq/kg of body weight, 1 injection every 4 weeks for 16 weeks) with placebo showed a three-week difference in median time to first SRE (14 vs. 11 weeks; HR, 0.57; 95% CI, 0.31 to 1.04; p=0.065). There were no substantial differences between groups in hematological adverse events [48].

Interpretation of evidence:

The Working Group members believed that the incidence of symptomatic skeletal events was an important outcome and quality of life was a critical outcome for recommendation development. For Ra-223, the quality of the evidence was considered to be moderate to high according to GRADE criteria. The Working Group members believed that the desirable effects of Ra-223 were large and clinically meaningful in reducing symptomatic skeletal events and improving quality of life, with few undesirable effects. The benefits of Ra-223 outweigh the harms. The evidence applies to the population of interest.

Recommendation:

3c. In men with mCRPC and bone pain, radiopharmaceuticals or IV bisphosphonates may be considered for pain palliation.

Key evidence:

One meta-analysis comparing radiopharmaceuticals (strontium [Sr]-89, samarium [Sm]-153, Ra-223 [phase II trial], and rhenium [Re]-186) with control showed that more patients receiving radiopharmaceuticals had complete pain relief (100% reduction in pain) (4 trials, 35% vs. 15%; RR, 2.10; 95% CI, 1.32 to 3.35; p=0.0018) or complete/partial pain relief (50% to 100% reduction in pain) (3 trials, 52% vs. 29%; RR, 1.72; 95% CI, 1.13 to 2.63; p=0.0012) than patients not receiving radiopharmaceuticals. The groups did not differ for the outcome of any amount of pain relief (0% to 100% reduction in pain) (5 trials, 55% vs. 42%; RR, 1.36; 95% CI, 0.77 to 2.40; p=0.29). Meta-analysis of five trials showed a 5% increase in grade 3 to 4 side effects (leukopenia, thrombopenia, and anemia) with radiopharmaceuticals (8.8% vs. 3.7%; P<0.001) [49].

Beyond the meta-analysis, three additional trials compared Sr-89 with radiotherapy or chemotherapy [50-52]). None of the trials showed a difference in pain outcomes between groups. In one trial, less nausea, vomiting, and diarrhea but more white blood cell and platelet toxicity were noted after Sr-89 than radiotherapy [50]. Another trial comparing Sr-89 with radiotherapy showed more patients receiving Sr-89 had pain flare (18% vs. 8%) and one patient had a pathologic femoral fracture [51].

One meta-analysis of four trials comparing bisphosphonates (oral and IV) with no bisphosphonates in patients with mCRPC showed no statistically significant difference in the proportion of patients with pain response (28% vs. 21%; OR, 1.54; 95% CI, 0.97 to 2.44; p=0.065) or decreased analgesic consumption (28% vs. 25%; OR, 1.27; 95% CI, 0.82 to 1.98; p=0.28) [44]. In the same systematic review, a meta-analysis of two trials comparing IV bisphosphonates (pamidronate and ZA) with placebo showed a decrease in mean pain favouring bisphosphonates (standardized mean difference −1.58; 95% CI, −1.41 to −1.75; p<0.001). Higher rates of nausea were observed with bisphosphonates (ZA and pamidronate) (2 trials, 39% vs. 30%; OR, 1.35; 95% CI, 1.02 to 1.77; p=0.034); no difference between groups was seen for vomiting (2 trials [ZA and pamidronate], 23% vs. 18%; p=0.22) or anemia (3 trials [ZA, pamidronate, and clodronate], 20% vs. 20%; p=0.83) [44].

One trial evaluating docetaxel with or without ZA in men with mCRPC showed a reduction in bone pain and total discomfort with ZA (p=0.04), and no difference between groups in adverse events [53].

One trial (n=137) comparing ZA with oral clodronate showed greater improvement in mean pain intensity with ZA during the first three months (improvement of ≥2 points on a 10-point [10-cm] visual analogue scale [VAS] 92% vs. 76%; p=0.02) [33].

Interpretation of evidence:

The Working Group members believed that bone pain was an important outcome for recommendation development. For radiopharmaceuticals, the quality of evidence was considered to be moderate according to GRADE criteria. The Working Group members believed that the desirable effects for pain palliation were moderate and clinically meaningful, with few undesirable effects. The benefits of radiopharmaceuticals in improving bone pain outweigh the harms.

For bisphosphonates, the quality of evidence was considered to be low according to GRADE criteria. The Working Group members believed that the desirable effects of IV bisphosphonates for pain palliation were small and clinically equivocal with few undesirable effects. IV bisphosphonates may be of value in selected patients with bone pain due to prostate cancer and limited therapeutic options (e.g., not candidates for radiopharmaceuticals).

Qualifying statements for Question 3 recommendations:

- See Table 2-1 for dosages. Patients receiving either denosumab or ZA should be taking 1000 mg of elemental calcium (from dietary and/or supplemental sources) and ≥400 IU of vitamin D daily. The dose of ZA should be reduced in cases of renal insufficiency (creatinine clearance [CrCl] <60 mL/min or serum creatinine [SCr] >132.5 µmol/L). ZA is not recommended below a CrCl of 30 mL/min (or SCr >265 µmol/L). In patients over the age of 65, CrCl (whether estimated or directly

measured) should be used rather than SCr. Denosumab and ZA should not be given in combination.
- There is uncertainty regarding the optimum duration of therapy; with respect to ZA, less intensive therapy (i.e., every 3 months) may be as effective as monthly treatment (CALGB 70604 Alliance study [19]).
- SRE definitions and data reporting pain are not identical across studies.
- Recommendation 3b applies to men with predominantly bony metastases and no evidence of visceral metastases or large nodal metastases.
- Radiopharmaceuticals can permanently reduce bone marrow reserves, and this should be considered if the patient remains a candidate for palliative cytotoxic chemotherapy. The recommended dose for Ra-223 is one IV injection of 55 kBq/kg of body weight every four weeks for a total of six injections (based on the primary standardization revision for Ra-223 in 2015 by the National Institute of Standards and Technology [20]). The optimal sequencing of Ra-223, denosumab, and bisphosphonates is unclear, and recommendations to patients should be done in consultation with a clinician with expertise in CRPC treatment.
- Systemic therapies for the treatment of mCRPC such as abiraterone/prednisone, enzalutamide, docetaxel, and cabazitaxel have been shown to reduce SREs, improve bone pain and health-related quality of life, and/or improve overall survival in mCRPC. Mitoxantrone has also been shown to improve pain and health-related quality of life (see Guideline 3-15: Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer). The optimal sequencing or combination of these therapies with bone targeted agents is unclear, and recommendations to patients should be done in consultation with a clinician with expertise in CRPC treatment.
- Radiotherapy is one of the main therapeutic approaches to palliate pain in men with bone metastasis [21,22].

QUESTION 4
Can bone-targeted therapies improve overall survival in men with established prostate cancer and bone metastases?

Recommendation:
4. In men with symptomatic mCRPC, Ra-223 is recommended to extend overall survival.
Qualifying statements:

- This recommendation applies to men with predominantly bony metastases and no evidence of visceral metastases or large nodal metastases.
- Ra-223 appeared to be equally effective whether patients received, were not eligible to receive, or declined to receive docetaxel.
- Other options are available aside from bone-targeted therapies or radiopharmaceuticals for improving outcomes (see Guideline 3-15: Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer). The optimal sequencing of therapies is unknown.

- There is insufficient evidence to support an improvement in overall survival with bisphosphonates or denosumab in this population.
- Systemic therapies for the treatment of mCRPC such as abiraterone/prednisone, enzalutamide, docetaxel, and cabazitaxel have been shown to reduce SREs, improve bone pain and health-related quality of life, and/or improve overall survival in mCRPC (see Guideline 3-15: Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer). The optimal sequencing or combination of these therapies with bone-targeted agents is unclear, and recommendations to patients should be done in consultation with a clinician with expertise in CRPC treatment.

Key evidence:

In one placebo-controlled trial (n=921), Ra-223 (1 IV injection of 50 kBq/kg every 4 weeks for a total of 6 months) showed an improvement in median overall survival (14.9 vs. 11.3 months; HR, 0.70; 95% CI, 0.58 to 0.83; p<0.001). Adverse events were consistently lower in the Ra-223 group than the placebo group but did not differ to a statistically significant extent [46].
In one placebo-controlled trial (n=64), Ra-223 (1 IV injection of 50 kBq/kg every 4 weeks for a total of 4 months) improved median overall survival (65.3 vs. 46.6 weeks; HR, 0.476l 95% CI, 0.26 to 0.88; p=0.017). The groups did not differ in hematologic parameters in the 24-month follow-up and no cases of leukemia, myelodysplastic syndrome, or aplastic anemia occurred in either group [54].

In most trials, neither bisphosphonates nor denosumab prolonged overall survival in men with nonmetastatic prostate cancer [34-36,55].
Bisphosphonates did not extend overall survival in men with newly diagnosed metastatic prostate cancer [40,42,43,56-59]. A survival benefit at 10 years was seen with clodronate (2080 mg/day for 3 years) [55]; however, this result has not been supported by recent evidence from the STAMPEDE trial, which showed no survival benefit from the addition of ZA [60].
A trial evaluating ZA in combination with docetaxel-based chemotherapy in 105 men with mCRPC showed prolonged survival in the ZA arm (19 vs. 15 months; P=0.02) [53].

Interpretation of evidence:

The Working Group members believed that overall survival was a critical outcome for recommendation development. For Ra-223, the quality of evidence was considered to be high according to GRADE criteria. The Working Group members believed that the desirable effects of Ra-223 were medium to large in improving overall survival, with minimal adverse effects. The benefits of Ra-223 outweigh the potential harms. The evidence applies to the population of interest.

IMPLEMENTATION CONSIDERATIONS

The Working Group members consider these recommendations to represent a current standard of care and believe they will be feasible to implement. They believe the outcomes valued by clinicians will align with the outcomes valued by patients and most patients and healthcare providers will view the recommendations as acceptable. The Working Group members also believe that these recommendations will not require additional training for the providers or necessitate a significant change to the current health system.

RELATED GUIDELINES

- Segal R, Zwaal C, Green E, Tomasone J, Loblaw A, Petrella T. Exercise for People with Cancer. Toronto (ON): Cancer Care Ontario; 2015 Jun 30. Program in Evidence-Based Care Guideline No.: 19-5.

- Basch E, Loblaw D, Oliver T, Bennett C, Carducci M, Chen R, et al. Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer. Toronto (ON): Cancer Care Ontario; 2014 Sep 8. Program in Evidence-Based Care Guideline No.: 3-15.

Bone Health and Bone-Targeted Therapies for Prostate Cancer

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

JUSTIFICATION FOR GUIDELINE

Since the last guideline PEBC produced, there have been two major inducements leading to the current update. First, a number of important new studies have been published in both metastatic and nonmetastatic prostate cancer. Second, there is a growing awareness of bone health issues in men with non-metastatic prostate cancer, along with an absence of evidence-based guidelines to guide clinicians in managing this issue in the broader prostate cancer population.

GUIDELINE DEVELOPERS

This guideline was undertaken by the PEBC at the request of the Genitourinary Cancer Disease Site Group (GU DSG). This group was comprised of four medical oncologists, nine radiation oncologists, seven urologist/surgical oncologists, one pathologist, and one PEBC methodologist (see Appendix 1 for membership).

The project was led by a small Working Group, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group members are listed in Appendix 1 and included a geriatrician with expertise in both genitourinary cancer and bone health in men (SA) and a radiologist/nuclear medicine physician with expertise in prostate cancer imaging and targeted radionuclide therapy (KZ). All members contributed to final interpretation of the evidence, refinement of the recommendations, and approval of the final version of the document. Other members of the GU DSG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [61,62]. This process includes a systematic review, interpretation of the evidence by the Working Group, resulting recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the Appraisal of Guidelines for Research and Evaluation (AGREE) framework [63] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this project, the following sources were searched for existing guidelines:

- Practice guideline databases:
  - Inventory of Cancer Guidelines
  - National Guidelines Clearinghouse
- Guideline developer websites:
  - National Institute for Health and Care Excellence (NICE [UK])
  - Scottish Intercollegiate Guidelines Network (SIGN [UK])
  - American Society of Clinical Oncology (ASCO [US])
  - National Comprehensive Cancer Network (NCCN [US])

A search for existing guidelines for adaptation or endorsement was conducted and no comprehensive guidelines that covered all types of targeted therapies for bone health were found. A search of the primary literature was required (see section 4).

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the targeted peer review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through professional consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

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Bone Health and Bone-Targeted Therapies for Prostate Cancer

Section 4: Systematic Review

INTRODUCTION

Prostate cancer is the most common internal malignancy in men and the third most common cause of cancer death. There were an estimated 24,000 new cases and 4100 deaths due to prostate cancer in Canada in 2015 [64]. It predominantly affects older men, with a mean age at diagnosis of 68 to 70 years. Almost 90% of men are diagnosed at an early disease stage, where the 10-year survival is excellent. However, almost one in two of these men will be exposed to ADT at some point after diagnosis, and 30% to 40% will eventually progress to mCRPC. During the past decade, new treatment options for mCRPC have emerged and dramatically altered the management landscape.

The use of these treatments is associated with important improvements in overall survival, which has led to a greater focus on maximizing quality of life and reducing treatment-related toxicity. ADT in particular is widely used and associated with a large number of potential adverse effects ranging from anemia, fatigue, sexual dysfunction, reduced muscle mass, metabolic effects including diabetes, and skeletal side effects. In particular, ADT is associated with significant bone loss and an increased risk of low trauma or fragility fractures that are similar to those seen in people with osteoporosis. ADT is associated with declines of 4% to 6% in BMD in the lumbar spine and femoral neck in the first year of use [65,66]. These changes are associated with a 20% to 30% increased risk of fractures [67-69]. Although ongoing ADT is associated with attenuated losses in BMD in subsequent years, losses continue per year with ongoing use, along with an increased risk of fractures.

Given the relatively advanced age of most men with prostate cancer, it is important to recognize that many men starting ADT are already at risk of osteoporosis due to advanced age, hypogonadism, and other risk factors. Several studies have demonstrated that 20% to 40% of men have osteoporosis at the time of initiating ADT, and another 20% to 40% have osteopenia [70,71]. Among men with normal BMD prior to starting ADT, the risk of developing osteoporosis is less than 5% after five years of ADT. However, among men with osteopenia prior to starting ADT (defined as a T-score between −1.0 and −2.5) without evidence of prior fragility (low trauma) fracture, the risk of developing osteoporosis is as high as 35% after one year of ADT and up to 60% after two years of continuous ADT [72].

Taking cues from the field of osteoporosis in women, experts have called for a systematic approach to the prevention, diagnosis, and treatment of osteoporosis in men with prostate cancer. Important components in this approach include (a) the systematic assessment of BMD with dual x-ray absorptiometry at the time of initiating ADT and periodic monitoring for men who remain on ADT; and (b) counselling about lifestyle management and risk factor modification to reduce the risk of bone loss and falls (e.g., moderating alcohol intake, stopping smoking, optimizing calcium intake, and vitamin D supplementation). Systematic assessment of fracture risk is also recommended by using a validated fracture risk prediction algorithm such as the WHO FRAX or CAROC tools [1,2]). Men who are considered to be at high risk of future fragility fracture (typically >3% risk of hip fracture or >20% risk of major osteoporotic fracture over 10 years) should be considered for pharmacologic therapy to reduce the risk of future fracture. Pharmacologic agents include oral or IV bisphosphonates, denosumab, and other agents. At the same time, multiple studies have demonstrated important gaps in the quality of bone health care for men with prostate cancer, including low rates of BMD testing either before

or while on ADT, low rates of diet and lifestyle counselling, low rates of education about side effects of ADT, and low rates of pharmacologic therapy to reduce fracture risk [70,73-75].

The most common site of metastatic disease in men with advanced prostate cancer is bone [76]. The clinical implications of bone metastases are serious, since progressive disease often affects quality of life through the development of such outcomes as bone pain, pathological fractures, spinal cord compression, use of analgesics, loss of mobility, and depression [77]. Optimal patient management depends on several factors, and the changing landscape of available local and systemic therapy has shown the multidisciplinary approach to be invaluable [78,79]. Although radionuclide therapy has been used for several years to palliate pain associated with prostate cancer bone metastases, one of the innovations in recent times is the advent of Ra-223, a radionuclide therapy that can improve pain and extend life [46]. Although a complete review of the methods currently used to treat pain related to osseous metastatic disease is beyond the scope of this review, taken together, the recent changes in our approach to bone health and bone-targeted therapy suggest the need for guideline development to assist clinicians managing men with prostate cancer.

The Working Group members developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

1. Can therapeutic interventions reduce osteoporosis-related outcomes in men with prostate cancer receiving ADT?
   - Population: Men with prostate cancer receiving ADT, either (neo)adjuvant or palliative
   - Intervention: Drugs, supplements, lifestyle modifications, exercise
   - Comparison: Placebo, other interventions
   - Outcomes: Fracture, BMD, and diagnosis of osteoporosis

2. Can therapeutic interventions prevent bone metastases in men with prostate cancer?
   - Population: Men with advanced/established prostate cancer
   - Intervention: Bone-targeted therapies
   - Comparison: Placebo, other interventions
   - Outcomes: First bone metastasis

3. Can bone-targeted therapies reduce the incidence of SREs, reduce pain, or improve quality of life in men with prostate cancer metastatic to bone?
   - Population: Men with advanced/established prostate cancer and bone metastases
   - Intervention: Bone-targeted therapies
   - Comparison: Placebo, other interventions
   - Outcomes: SREs, pain, quality of life

4. Can bone-targeted therapies improve overall survival in men with prostate cancer?
   - Population: Men with advanced/established prostate cancer and bone metastases
   - Intervention: Bone-targeted therapies
   - Comparison: Placebo, other interventions
   - Outcomes: Overall survival

METHODS

Search for Existing Systematic Reviews

Systematic reviews were identified by searching MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews. The searches for systematic reviews done in MEDLINE and EMBASE were combined with those performed for primary literature.

Identified systematic reviews were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool (http://amstar.ca) [80]. The results of the AMSTAR assessment were used to determine whether or not an existing review could be incorporated as part of the evidentiary base.

Any identified reviews that did not meet the criteria above, whose AMSTAR assessment indicated important deficiencies in quality, or that were otherwise not incorporated as part of the evidence base were reported in the reference list, but not further described or discussed.

Literature Search Strategy

A primary literature search was conducted to ensure the retrieval of the latest studies on bone-targeted therapies. Literature searches were performed in the MEDLINE, EMBASE, and Cochrane Library databases to identify primary studies and existing systematic reviews, and the annual meeting proceedings of ASCO and the American Urological Association were searched for conference abstracts. MEDLINE was searched in Ovid from 1946 to January 2016 (Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® <1946 to Present>). EMBASE was searched in Ovid from 1980 to January 2016 (EMBASE 1996 to 2016 Week 4).

The literature searches in MEDLINE and EMBASE combined methods terms for meta-analyses, systematic reviews, and RCTs with terms describing prostate cancer, bone health, and interventions. The full search strategies are found in Appendix 2.

Study Selection Criteria and Process

Selected studies were required to meet the following inclusion criteria:

- RCTs or systematic reviews (with or without meta-analysis) containing RCTs.
- The study population consisted of men with prostate cancer at any stage. In studies with mixed populations (i.e., including patients with primary cancer sites other than prostate), the data had to be reported separately for prostate cancer patients to be eligible for inclusion.
- The intervention involved therapies directed at improving bone health in nonmetastatic patients or reducing the outcomes associated with prostate cancer metastatic to bone (drug, supplement, or lifestyle modification) alone or in combination and was compared with placebo, no treatment, or other agents.

A review of the titles and abstracts that resulted from the search was conducted by one reviewer (CW). For those items that warranted full-text review, CW reviewed each item and discussed with the lead authors (SA, KZ) to confirm the final study selections. All data were audited by a second, independent auditor.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data extraction was conducted by one Working Group member (CW) with assistance from the two lead authors (SA, KZ). The methodological quality characteristics of the included RCTs were recorded. These included allocation concealment, blinding, intention-to-treat analysis, funding, patient follow-up, statistical power and sample size, baseline characteristics balance, and early termination. ADT status, intervention groups and numbers of patients, dosage schedule, follow-up periods, and outcome measures were recorded for each study.

Synthesizing the Evidence

When clinically homogeneous results from two or more trials were available, a meta-analysis was conducted using the Review Manager software (RevMan 5.3) [81] provided by the

Cochrane Collaboration (http://www.cochrane.org/revman). If the HR or its standard error were not reported, they were derived from other information reported in the study, if possible, using the methods described by Parmar et al. [82]. For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models in RevMan was used.

Statistical heterogeneity would be calculated using the x^2 test for heterogeneity and the I^2 percentage. A probability level for the x^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% would be considered indicative of statistical heterogeneity.

The GRADE method for assessing the quality of aggregate evidence was used for each comparison [83]. The outcomes were rated for their importance for decision-making by the Working Group members. Four factors were assessed for each outcome in each comparison. These included the risk of bias, inconsistency, indirectness, and imprecision. Risk of bias was assessed by the presence/absence of the methodologic quality characterstics described above.

RESULTS

Literature Search Results

The flow diagram depicting the literature search results is shown in Appendix 3. The literature search identified 3642 citations in MEDLINE and EMBASE, and 744 citations were identified through other sources (e.g., conference abstracts).

After the initial review of potential systematic reviews and RCTs for inclusion based on the inclusion criteria, the lead authors reviewed the articles for clinical relevance to the research questions. Conference abstracts were excluded because in most cases they did not provide enough data to be included in any meta-analyses and had insufficient detail to contribute to individual results. Trials that only reported results related to bone turnover markers were considered not clinically relevant and were excluded. Among studies with multiple publications, the most recent or most complete reports were included. The final number of included papers was 93 (15 systematic reviews and 78 reports of 72 RCTs).

Study Design and Quality

Systematic Reviews

Fifteen relevant systematic reviews were identified in the literature search [23,38,44,49,65,84-93]. The AMSTAR tool was applied to each systematic review (Appendix 4). The AMSTAR questions address the methodological quality of systematic reviews including the literature search, study selection, publication bias, data extraction, and meta-analytic techniques. The scores varied across the 11-point spectrum. Higher scores were seen for Cochrane reviews.

Seven of the 12 systematic reviews were not considered further: because all of the studies in the 2002 review by Wong et al. [85] were included in the review by Yuen et al. [44], the Wong review was discarded. The RCTs in the review by Brundage et al. [84] were included in the review by Bauman et al. [86]; therefore, the Brundage review was not considered further.

The reviews by Datta et al., Israeli et al., and Liu et al. contained insufficient detail regarding search methods, study selection, or quality assessment and AMSTAR ratings were 0, 1, and 1, respectively [65,88,93].

In the meta-analysis by Tunio et al., the numbers of events and sample sizes from the individual studies in several instances did not match the numbers we extracted and the inconsistencies could not be explained [92].

We excluded the meta-analysis by Qi et al. because we considered the pooling of studies to be inappropriate [91]. The low-dose and high-dose denosumab trials were not separated in

either in primary or sensitivity analyses and different comparison groups and patient populations were pooled.

Thus, the included trials of these reviews were considered individually and the reviews were not discussed further.

Eight systematic reviews were included in this evidence review [23,38,44,49,86,87,89,90]. Five reviews addressed the role of bisphosphonates [23,44,87,89,90], one evaluated denosumab [38], and two evaluated radiopharmaceuticals [49,86]. Four reviews included mixed populations, but results were available for the subset of prostate cancer patients [38,49,86,90]. The characteristics of the reviews are shown in Appendix 5.

Randomized Controlled Trials

Data Extraction

For each trial, data were extracted on ADT status, intervention groups and numbers of patients, dosage schedule, and outcome measures. The study details are shown in Appendix 6.

Risk of Bias

The methodological quality characteristics of the 72 trials are shown in Appendix 7. Each study was assessed for the presence/absence of allocation concealment, blinding, intention-to-treat analysis, and industry funding; extent of patient follow-up (incomplete outcome data); baseline characteristic balance; adequacy of statistical power and target sample size; and early termination. Allocation concealment was reported in 27 trials. Blinding of investigators, patients, or outcome assessors was present in 44 trials. Thirty-four trials performed an intention-to-treat analysis. Sixty trials had at least 80% follow-up of patients for the primary outcome measure. In three trials, patient follow-up was not ascertainable.

A power statement or sample size calculation was included in 43 trials. Of these, four trials had limited statistical power due to insufficient sample size [9,29,94]) or were not powered for any formal hypothesis testing [95]. Slow accrual caused one trial to extend the patient enrolment period from 18 months to 28 months and included 191 patients instead of the expected 216 [5]. A cross-over trial combined data to obtain adequate sample size [31]. In two trials evaluating pamidronate, neither trial achieved full enrolment and the data were pooled [43]. Ten trials had no power statement but had small sample sizes and were likely under powered [96-105]. Three trials were described as pilot or exploratory analysis [18,32,52]. Eight trials were terminated early [9,13,29,40,46,99,106,107].

Outcomes

The evidence is organized according to treatment of nonmetastatic or metastatic patients and the ADT status of patients. For each study and systematic review, data for the following outcomes were extracted: fracture, BMD, osteoporosis, SREs, bone metastasis, overall survival, pain, patient-reported quality of life, and adverse effects. In addition to common adverse effects related to treatment, any rare but serious adverse effects were specifically recorded, including osteonecrosis of the jaw, hypocalcemia, atypical femoral fractures, renal failure, and atrial fibrillation. The evidence corresponding to the research questions is shown in Table 4-1.

Table 4-1. Research questions and studies.

Question	Systematic reviews	RCTs	Outcomes

1. Can therapeutic interventions reduce osteoporosis-related outcomes in men with prostate cancer receiving ADT?	Serpa Neto 2012 [89], Ding 2013 [23]	NONMETASTATIC Kearns 2010 [29], Choo 2013 [106], Taxel 2010 [96], Greenspan 2007 [4], Greenspan 2008 [30], Morabito 2004 [108], Ryan 2006 [6], Ryan 2007b [107], Israeli 2007 [7], Michaelson 2007 [14], Bhoopalam 2009 [8], Kapoor 2011 [9], Kachnic 2013 [13], Smith 2009 [3], Smith 2004 [109], Smith 2010 [110], Winters-Stone 2014 [15], Nilsen 2015 [16], Cormie 2015 [17], Santa Mina 2012 [18], Smith 2001 [111], Klotz 2013 [5], Rodrigues 2007 [28], Smith 2003 [10], Rao 2008 [11], Casey 2010 [12], Denham 2014 [112] METASTATIC Wang 2013 [33], Diamond 2001 [31], Satoh 2009 [32], Lang 2013 [113]	Fracture Bone mineral density Osteoporosis
2. Can therapeutic interventions prevent bone metastases in men with prostate cancer?		NONMETASTATIC Smith 2012 [36], Mason 2007 [35], Wirth 2014 [34]	First bone metastasis
3. Can bone-targeted therapies reduce the incidence of SREs, reduce pain, or improve quality of life in men with prostate cancer metastatic to bone?	Berry 2006 [87], Serpa Neto 2012 [89], Yuen 2006 [44], Ford 2013 [38], Roque I Figuls 2011 [49], Palmieri 2013 [90]	METASTATIC Smith 1989 [97], Adami 1989 [98], Lipton 1994 [114], Dearnaley 2003 [41], Wang 2013 [33], Ueno 2013 [39], Smith 2014 [40], Strang 1997 [99], Elomaa 1992 [115], Kylmala 1993 [56], Kylmala 1997 [116], Ernst 2003 [57], Meulenbeld 2012 [59], Small 2003 [43], Saad 2002 [42], Pan 2014 [53], Fizazi 2009 [100], Fizazi 2011 [37], Hoskin 2015 [117], Buchali 1988 [101], Lewington 1991 [102], Porter 1993 [118], Quilty 1994 [50], Oosterhof 2003 [51], Nilsson 2005 [52], Baczyk 2007 [119], Palmedo 2003 [120], Han 2002 [103], Sartor 2004 [104], Resche 1997 [121], Tian 1999 [105], Nilsson 2007 [48], Nilsson 2013 [54], Parker 2013 [46], Sartor 2014 [47], Nilsson 2012 [122], Parker 2013b [94]	SREs Patient-reported quality of life Pain Analgesic consumption
4. Can bone-targeted therapies improve overall survival in men with prostate cancer?	Yuen 2006 [44], Roque I Figuls 2011 [49]	NONMETASTATIC Mason 2007 [35], Dearnaley 2009 [55], Wirth 2014 [34], Smith 2012 [36] METASTATIC Dearnaley 2003 [41], Dearnaley 2009 [55], Wang 2013 [33], Ueno 2013 [39], Smith 2014 [40], Kylmala 1993 [56], Ernst 2003 [57], Figg 2005 [58], Meulenbeld 2012 [59], Small 2003 [43], Saad 2002 [42], Pan 2014 [53], Fizazi 2011 [37], Hoskin 2015 [117], Lara 2006 [123], Buchali 1988 [101], Porter 1993 [118], Bilen	Overall survival

		2015 [124], Quilty 1994 [50], Tu 2001 [95], Oosterhof 2003 [51], Palmedo 2003 [120], Han 2002 [103], Resche 1997 [121], Nilsson 2007[48], Nilsson 2013 [54], Parker 2013 [46], Parker 2013b [94]	

ADT=androgen deprivation therapy; RCT=randomized controlled trial; SRE=skeletal-related event.

GRADE

The GRADE tool was used to assess the quality of the aggregate evidence for the outcomes. This information, organized by comparison, is shown in Appendices 8 to 21.

QUESTION 1

Can therapeutic interventions reduce osteoporosis-related outcomes in men with prostate cancer receiving ADT?

Fracture

The incidence of fracture was reported in three comparisons: bisphosphonates versus placebo, denosumab versus placebo, and toremifene versus placebo. The overall certainty of the estimate of effects ranged from moderate (due to serious risk of imprecision) to high (Appendix 8, 12, 14).

Systematic Reviews

Fracture was reported in three systematic reviews [23,44,89]) and 14 RCTs [3-7,10,13,30,37,41-43,110,112]. In one review [44] and four trials [37,41-43], patients had metastases and fracture was one component of the composite outcome of SREs. Fracture results for those trials are discussed with the SRE outcome.

The systematic review and meta-analysis by Serpa Neto et al. sought to determine the effects of bisphosphonates in the treatment of bone loss in prostate cancer patients undergoing ADT. We found that the meta-analysis of fracture incidence had methodological issues that limited its authority. It combined different patient populations and follow-up periods, and in two studies the outcome measure was not limited to fractures but expanded to include all SREs. The results of the meta-analysis were therefore not considered further.

Ding et al. assessed the efficacy of bisphosphonates for osteoporosis in nonmetastatic prostate cancer patients receiving ADT [23]. For the outcome of fracture at 12 months, one trial of alendronate [4] and three trials of ZA [6,7,10] were combined. No details of the meta-analysis were provided; a pooled OR showed a statistically nonsignificant increase in the risk of fracture with bisphosphonates compared with placebo (OR, 1.40; 95% CI, 0.53 to 3.67; p=0.50).

Primary Studies

Additional studies evaluating fracture were 24-month results for the trial of alendronate [30], a 12-month trial of alendronate [5], two trials of ZA [13,112], one trial evaluating denosumab [3], and one trial evaluating toremifene [110]. All trials were placebo controlled and patients were currently receiving or commencing ADT. The trials of ZA [13], denosumab [3], and toremifene [110] were powered to detect a difference in fracture rate.

Fracture rates were low among the trials evaluating oral bisphosphonates or ZA, with no statistical difference between active treatment and placebo. In a trial of continued, withdrawn, or delayed alendronate, clinical fracture occurred in one, two, and one patients, respectively,

at 24 months [30]. In another placebo-controlled trial of alendronate, fracture occurred in one patient receiving alendronate and three patients receiving placebo [5]. In a trial comparing ZA with no ZA, one patient in each group had a fracture [13]. In a factorial trial comparing short- and intermediate-term ADT with or without ZA, there was no reduction in incident vertebral fractures with the use of ZA at three years. The rates of fracture in the short-term ADT, short-term ADT plus ZA, intermediate-term ADT, and intermediate-term ADT plus ZA groups were 19%, 15.1%, 10.1%, and 14.3%, respectively. The odds of three-year vertebral fracture were 0.75 (p=0.26) in the short-term ZA group and 0.69 (p=0.15) in the intermediate-term ZA group compared with short-term ADT alone [112].

Denosumab (compared with placebo) prevented new vertebral fractures at 12 (0.3% vs. 1.9; RR, 0.15; p=0.004), 24 (1.0% vs. 3.3%; RR, 0.31; p=0.004), and 36 months (1.5% vs. 3.9%; RR, 0.38; p=0.006). Fracture at any site occurred in fewer patients receiving denosumab than patients receiving placebo but the difference was not statistically significant (5.2% vs. 7.2%; p=0.10). More than one fracture at any site occurred in fewer denosumab patients (0.7% vs. 2.5%; p=0.006) [3].

Toremifene (compared with placebo) reduced all fractures (6.3% vs. 10.1%; relative risk reduction, 38%; p=0.036) and vertebral fractures (2.5% vs. 4.9%; relative risk reduction, 50%; p<0.05) at 24 months [110]. Toremifene is not approved by the U.S. Food and Drug Administration or Health Canada.

Bone Mineral Density

BMD was reported in eight comparisons: bisphosphonates versus placebo, IV versus oral bisphosphonates, different doses/schedules of bisphosphonates, denosumab versus placebo, toremifene versus placebo, raloxifene versus placebo, exercise versus usual care, and different types of exercise. The overall certainty of the estimate of effects ranged from low (due to serious risk of bias and imprecision) to high (Appendix 8, 9, 11, 12, 14-17).

Systematic Reviews

The systematic review by Serpa Neto et al. included 15 RCTs, including five trials with metastatic patients [89]. The meta-analysis for BMD did not specify which studies were included; thus, insufficient data were available to accept the results with a high degree of certainty. The systematic review by Ding et al. included 10 RCTs comparing bisphosphonates with no bisphosphonates in nonmetastatic patients receiving ADT [23]. Meta-analysis showed significant differences favouring the bisphosphonate group at 12 months for lumbar spine BMD (10 trials, WMD in the percent change from baseline in BMD, 6.02; 95% CI, 5.39 to 6.65; p<0.0001); femoral neck (7 trials, WMD, 2.91; 95% CI, 2.16 to 3.67; p<0.0001), and total hip (8 trials, WMD, 2.82; 95% CI, 2.05 to 3.58; p<0.0001).

Meta-analysis

The Working Group conducted a meta-analysis for BMD at 12 months that included two trials comparing risedronate with placebo [29,106], one trial comparing alendronate with placebo [5], and two trials comparing ZA with placebo [9,11] (in addition to the 10 trials in Ding et al. [4,6-8,10,12,14,107,108,111]. In the Bhoopalam et al. trial, the patients were stratified according to receipt of ADT for less than or greater than one year and then randomized to ZA or placebo. Each stratum was powered to detect a significant difference in BMD at the lumbar spine. The strata were treated as two comparisons [8].

The percent change from baseline and standard deviations for each group were entered into Rev Man 5.3. For seven trials, standard deviations were calculated from standard errors [7,9,10,12,14,106,111] and in three trials standard deviations were calculated from CIs

[4,6,107]. In two trials, the standard deviations were imputed from the data in similar trials [8,108]. In two trials, the percent change from baseline was calculated from the absolute BMD values [29,108]. The therapies included oral risedronate (2 trials), oral alendronate (2 trials), neridronate by intramuscular injection (1 trial), IV pamidronate (1 trial), and IV ZA (9 trials). The BMD sites were lumbar spine (14 trials), femoral neck (11 trials), and total hip (10 trials).

Meta-analysis of all bisphosphonate studies showed a statistically significant difference between bisphosphonates and placebo for change from baseline to 12 months for BMD at the lumbar spine, femoral neck, and total hip favouring bisphosphonates (Figures 4-1 to 4-3).

Figure 4-1. Percent change from baseline in response to bisphosphonate therapy in lumbar spine BMD at 12 months.

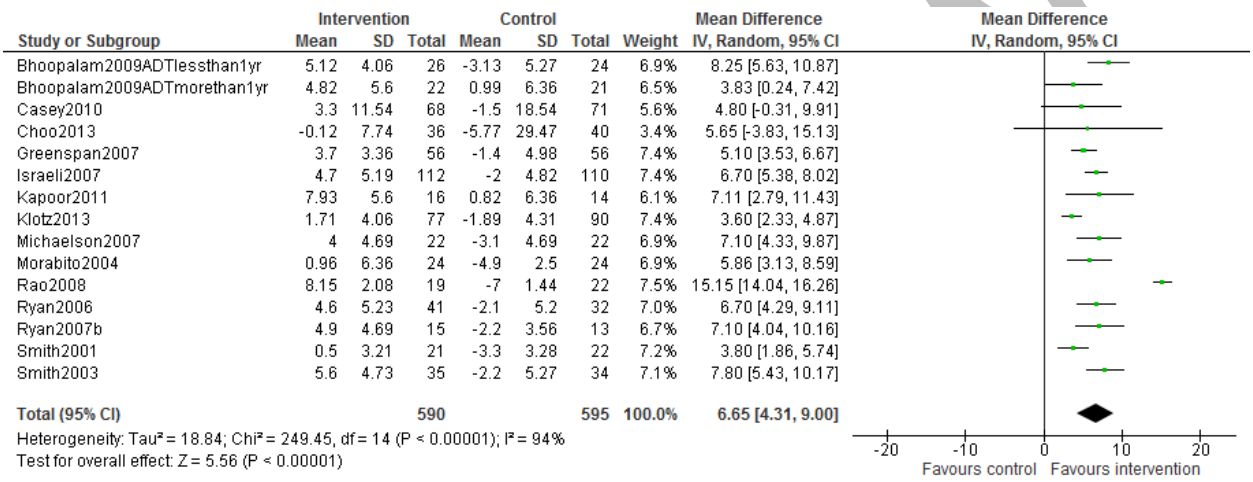


Figure 4-2. Percent change from baseline in response to bisphosphonate therapy in femoral neck BMD at 12 months.

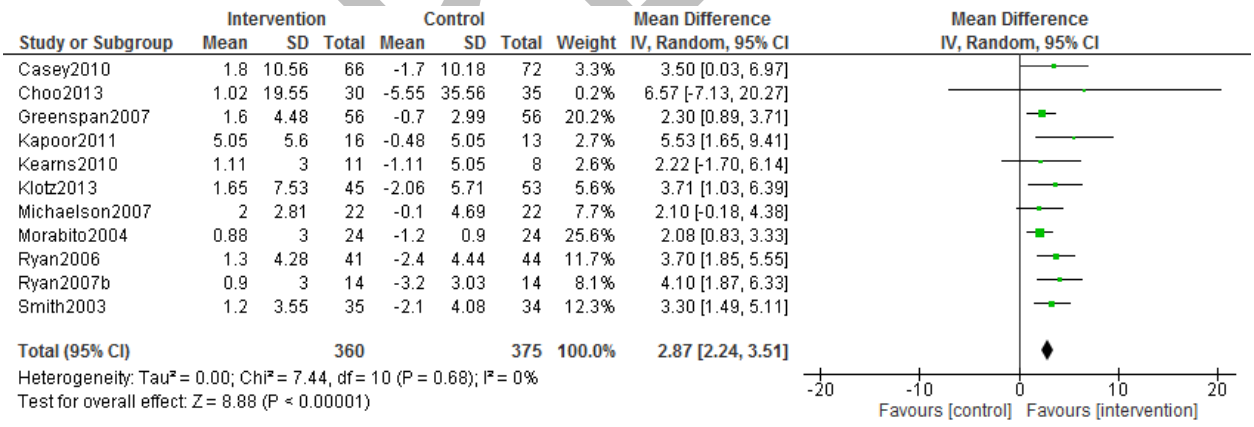
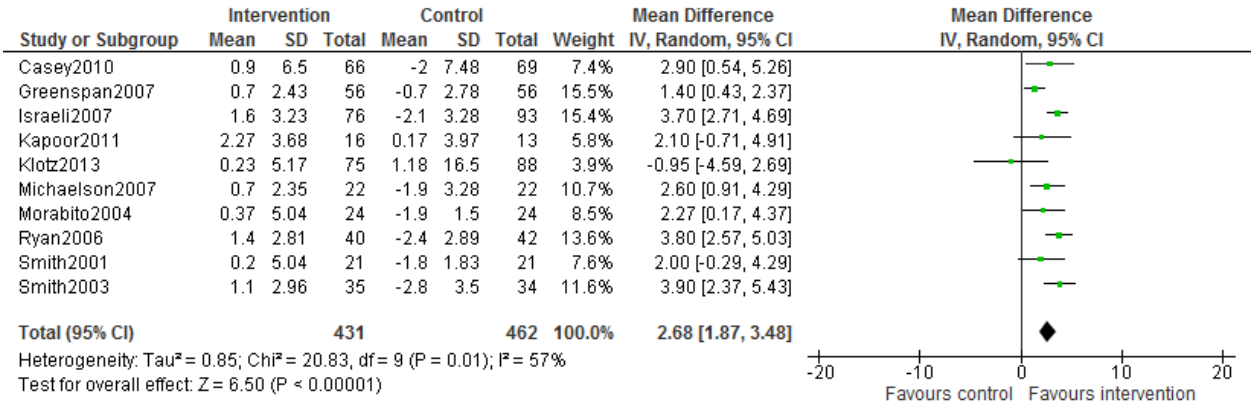


Figure 4-3. Percent change from baseline in response to bisphosphonate therapy in total hip BMD at 12 months.



Sensitivity analyses were performed on trials with no imputed data, trials of oral bisphosphonates alone, and trials of IV bisphosphonates alone. The results showed statistically significant differences between bisphosphonates and no bisphosphonates for all analyses except for that of total hip BMD with oral bisphosphonates (Table 4-2).

Table 4-2. Sensitivity analyses for bisphosphonates vs. no bisphosphonates.

BMD site	Analysis	Number of trials	Mean difference (95% CI)
Lumbar spine	Trials with no imputed data	12	6.80 (4.04 to 9.57)
	Oral bisphosphonates	3	4.24 (3.16 to 5.32)
	IV bisphosphonates	10 (11 comparisons)	7.22 (4.22 to 10.05)
Femoral neck	Trials with no imputed data	9	3.18 (2.43 to 3.93)
	Oral bisphosphonates	4	2.60 (1.41 to 3.79)
	IV bisphosphonates	6	3.49 (2.55 to 4.42)
Total hip	Trials with no imputed data	9	2.70 (1.82 to 3.58)
	Oral bisphosphonates	2	0.91 (-0.97 to 2.78)
	IV bisphosphonates	7	3.39 (2.21 to 3.98)

BMD=bone mineral density; CI=confidence interval; IV=intravenous.

Primary Studies

Insufficient data were available to pool bisphosphonate studies with six-month, 24-month, or 36-month results. At six months, one trial showed a statistically significant difference in BMD at the lumbar spine, femoral neck, and total hip for risedronate compared with placebo favouring risedronate ($p \leq 0.04$) [96]. Improvements in BMD were sustained at 24 months at the proximal femur in one trial of risedronate ($p=0.0096$) [106] and at the lumbar spine, femoral neck, and total hip in one trial of alendronate ($p<0.05$) [30]. One trial showed greater improvement with ZA at 36 months compared with no ZA at the lumbar spine, left femoral neck, and left hip ($p \leq 0.0007$) [13].

A factorial trial evaluated leuprorelin and radiotherapy with or without ZA. In a nested BMD substudy of 222 men, ZA increased total hip BMD at up to four years by 1.8% in patients receiving short-term ADT ($p=0.003$) and by 1.2% in patients receiving medium-term ADT ($p=0.09$) compared with baseline [112].

Three studies reported BMD outcomes in studies investigating other agents [3,109,110]. In one trial evaluating raloxifene at 12 months, a statistically significant difference between raloxifene and no raloxifene was seen in BMD changes at the total hip and trochanter favouring raloxifene ($p<0.001$). Although BMD increased with raloxifene, differences between groups did

not reach statistical significance at the lumbar spine (p=0.07) or femoral neck (p=0.06) [109]. A trial comparing toremifene with placebo showed statistically significant differences favouring toremifene at two years at the lumbar spine, femoral neck, and total hip (p<0.0001 [110]. One trial evaluating denosumab also showed increased BMD at all sites compared with placebo (p≤0.001) [3].

Four trials investigated non-drug interventions [15-18]. The trials evaluated exercise in nonmetastatic men receiving ADT. Three trials compared supervised exercise with usual care [15-17], and one trial compared group-based exercise with personal training [18]. None of the trials showed a significant difference between groups in change from baseline in BMD.

Four trials reported BMD outcomes in men with metastatic disease who were receiving or about to begin ADT [31-33,113]. A cross-over trial comparing IV pamidronate with placebo showed pamidronate increased BMD at the lumbar spine, femoral neck, Ward's triangle, and trochanter compared with placebo (p<0.01) [31]. In one trial comparing ZA with no ZA in 40 men beginning ADT, BMD improved at all sites with ZA at six months (p≤0.0063) and 12 months (p≤0.0393) [32]. A phase II trial evaluated different schedules of ZA, randomizing men to ZA once, one week before ADT; ZA once, six months after ADT; and ZA monthly, six months after ADT. Administering ZA before ADT showed increases in BMD at six months at the proximal femur and trochanter compared with ZA after ADT (p≤0.016) and at six months at the femoral neck (p=0.036) [113]. In a trial comparing ZA with clodronate, statistically significant differences were seen between groups at 36 months favouring ZA at the lumbar spine (p=0.03); the differences were not significant at the femoral neck (p=0.35) or total hip (p=0.62) [33].

Osteoporosis

Primary Studies

Osteoporosis was reported in four trials comparing bisphosphonates with no bisphosphonates in men with nonmetastatic prostate cancer receiving ADT [7,28-30]. Pooling of these trials was not possible because of the different agents and follow-up periods. The overall certainty of the estimate of effects was low due to serious inconsistency and imprecision (Appendix 8).

A trial evaluating risedronate and estrogen, alone and in combination, showed no difference in the incidence of osteoporosis at six or 12 months across the four study arms (25%, 29%, 33%, 29%, p=0.98; and 31%, 35%, 39%, 41%, p=0.96, respectively) [29].

Greenspan et al. compared alendronate with placebo to determine whether oral alendronate could prevent bone loss. After 12 months of follow-up, the study was extended for a second year with additional random assignment for those who initially received alendronate. Thus, 25 patients continued on alendronate (alendronate-alendronate) and 26 patients received placebo (alendronate-placebo). The original placebo group crossed over to alendronate (placebo-alendronate) to assess the effect of delaying treatment by one year. The incidence of osteoporosis in the alendronate-alendronate, alendronate-placebo, and placebo-alendronate groups at 24 months did not significantly differ across the three groups (22%, 36%, 54%, p=0.097) [30].

One trial comparing ZA with placebo reported no cases of osteoporosis in the ZA group and one case in the placebo group at 12 months [7]. A study comparing clodronate or ZA with control showed a statistically significantly lower occurrence of osteoporosis with clodronate or ZA than with control after 12 months (18% vs. 58%, p<0.05; and 21% vs. 58%, p<0.001) [28].

QUESTION 2
Can therapeutic interventions prevent bone metastases in men with prostate cancer?

Bone Metastases

Primary Studies

The incidence of first bone metastasis was assessed in two RCTs evaluating bisphosphonates [34,35] and one evaluating denosumab [36]. For the comparison of bisphosphonates versus placebo, the overall certainty of the estimate of effects was high (Appendix 8). For the comparison of denosumab versus placebo, the overall certainty of the estimate of effects was moderate due to serious imprecision (Appendix 12).

A nonsignificant increase in symptomatic bone metastases or death from prostate cancer occurred with oral clodronate compared with placebo (31% vs. 27%; HR, 1.22; 95% CI, 0.88 to 1.68; p=0.23) [35]. In a study in high-risk nonmetastatic patients, Wirth et al. compared ZA with standard prostate cancer therapy. Fifty-one percent of patients were receiving ADT before baseline. The difference in the proportion of patients with bone metastases after a median follow-up of 4.8 years was not statistically significant (14.7% vs. 13.2%; p=0.65). ZA had no effect on bone metastases in the subgroups of patients with and without prior ADT [34].

Smith et al. compared denosumab with placebo to determine the effect on bone metastasis-free survival in nonmetastatic castration-resistant patients at high risk of bone metastasis who were receiving ADT. Symptomatic bone metastases were reported in fewer patients receiving denosumab than patients receiving placebo (10% vs. 13%; p=0.03). Denosumab extended the time to first bone metastasis by 3.7 months compared with placebo (33.2 vs. 29.5 months; HR, 0.84; 95% CI, 0.71 to 0.98; p=0.032) [36].

QUESTION 3

Can bone-targeted therapies reduce the incidence of skeletal-related events, reduce pain, or improve quality of life in men with prostate cancer metastatic to bone?

Skeletal-related Events

SREs were assessed in patients with metastatic prostate cancer as a composite endpoint that usually included fracture, radiotherapeutic or surgical intervention, and spinal cord compression, but the outcome composition varied across studies. In two studies, SREs included bone pain [39,94].

SREs were reported in six comparisons: bisphosphonates versus placebo, IV versus oral bisphosphonates, denosumab versus placebo, denosumab versus ZA, radiopharmaceuticals versus placebo, and different doses of radiopharmaceuticals. The overall certainty of the estimate of effects ranged from low (due to serious risk of bias and serious imprecision) to high (Appendix 8, 9, 12, 13, 18, 20).

Systematic Reviews

SREs were reported in five systematic reviews [38,44,87,89,90] and 12 RCTs [33,37,39,40-43,45,46,48,53,54,94,100].

The review by Berry et al. was superseded by more recent reviews with more trials combined with meta-analysis [87]. The review by Serpa Neto et al. had unreliable coverage of SREs and was not considered further [89].

The Cochrane review by Yuen et al. [44] included a clodronate-placebo comparison [41], a pamidronate-placebo comparison [43], and a ZA-placebo comparison [42]. These studies varied considerably by follow-up period, with a median of 59 months in the clodronate trial, 27 weeks in the pamidronate trial, and 15 months in the ZA trial. Furthermore, the patients in the

clodronate study were castration-sensitive, while patients in the pamidronate and ZA studies were castration-resistant. Yuen et al. considered the definitions of SREs qualitatively similar enough to combine the three trials in a meta-analysis. The overall OR for the proportion of patients having any SRE was 0.79 (95% CI, 0.62 to 1.00; p=0.05), showing a borderline statistically significant difference favouring bisphosphonates. Including the 4 mg ZA group from the Saad et al. trial in the meta-analysis decreased the risk of any SRE to a statistically significant extent (OR, 0.76; 95% CI 0.59 to 0.98).

Yuen et al. also performed a meta-analysis on the individual components of SREs [44]. For these analyses, the 4 mg and 8/4 mg ZA groups of Saad et al. were collapsed and a placebo-controlled clodronate trial was included [57]. The results are shown in Table 4-3. The differences were not statistically significant. The authors indicated that there was significant heterogeneity on pooling the data for pathological and vertebral fractures and the data should be interpreted cautiously.

Table 4-3. Meta-analyses for individual SRE components with bisphosphonates vs. control [44].

SRE component	References	Total events		Odds ratio (95% CI)
		Treatment	Control	
Pathologic fractures	Small 2003 [43] Saad 2002 [42]	86/617	68/404	0.75 (0.53 to 1.06)
Vertebral fractures	Small 2003 [43] Saad 2002 [42]	27/617	27/404	0.65 (0.38 to 1.13)
Non-vertebral fractures	Small 2003 [43] Saad 2002 [42]	58/617	45/404	0.74 (0.49 to 1.12)
Spinal cord compression	Small 2003 [43] Saad 2002 [42]	25/617	17/404	0.82 (0.44 to 1.55)
Receipt of bone radiotherapy	Ernst 2003 [57] Small 2003 [43] Saad 2002 [42]	145/732	106/516	0.83 (0.62 to 1.11)
Receipt of bone surgery	Small 2003 [43] Saad 2002 [42]	16/617	13/404	0.80 (0.38 to 1.70)

CI=confidence interval; SRE=skeletal-related event.

The systematic review by Palmieri et al. included the same three studies that were included in Yuen et al. and performed a mixed-treatment meta-analysis to determine the annual incidence rate of SREs for each bisphosphonate [90]. The annual incidence rates for ZA, clodronate, and pamidronate were 0.83, 1.11, and 1.41, respectively. The excess SRE rates over ZA for clodronate and pamidronate were 35% and 71%, respectively.

Ford et al. performed a systematic review and network meta-analysis on the effectiveness of denosumab in treating bone metastases in solid tumours [38]. Two prostate cancer trials met the criteria for network meta-analysis: the placebo-controlled RCT of ZA [42] and a trial comparing ZA with denosumab [37]. Patients in both trials were castration-resistant. Denosumab delayed the median time to first SRE more than ZA (20.7 vs. 17.1 months; HR, 0.82; 95% CI, 0.71 to 0.95). Using indirect results from network meta-analysis it appeared that denosumab, compared with placebo, reduced the risk of first SRE (HR, 0.56; 95% CI, 0.40 to 0.77).

Primary Studies

Results for composite and individual SRE outcomes are in Appendix 22. Fifteen-month follow-up of the ZA versus placebo comparison from Saad et al. showed a lower incidence of

composite SRE outcomes in the 4 mg ZA group than placebo (33% vs. 44%; p=0.021), while the difference between ZA 8/4 mg and placebo was not statistically significant (39% vs. 44%; p=0.22) [42].

Three recent trials of ZA in metastatic, castration-sensitive prostate cancer showed varying results. A trial of 60 patients showed a reduction in a composite measure of SREs that included pathological fracture, spinal cord compression, bone pain, radiotherapy to bone, and surgery to bone with ZA compared with no ZA (HR, 0.381; 95% CI, 0.15 to 0.94) [39]. A study comparing ZA with placebo showed no difference between groups in median time to first SRE (31.9 vs. 28.8 months; HR, 0.97; p=0.385). The power of the study may have been affected by early termination, which resulted in 64% of the study target SREs [40]. A study comparing ZA with placebo in 105 men with mCRPC showed no difference between groups in the rate of SREs over two years (12% vs. 15%; p=0.42) [53]. A study comparing ZA with clodronate showed similar rates of SREs in each group (17% vs. 20%; p=0.62) [33].

In a phase II trial of 64 men who were castration-resistant, Ra-223 and placebo did not differ in the median time to first SRE (p=0.065) [48].

The larger phase III ALSYMPCA trial evaluated the time to first symptomatic skeletal event. In this study, there were fewer mandated scans than those of other studies; thus, only symptomatic events were picked up. A statistically significantly longer time to first symptomatic skeletal event occurred with Ra-223 than placebo (15.6 vs. 9.8 months; HR, 0.66; 95% CI, 0.52 to 0.83, p<0.001) [46]. Among the individual SRE components, Ra-223 showed a benefit in time to spinal cord compression (p=0.03) and time to external beam radiotherapy (p=0.001). The groups did not differ for time to pathological bone fracture (p=0.10) or surgery to bone (p=0.48) [47].

A phase II trial comparing three different doses of Ra-223 (25, 50, and 80 kBq/kg) in men with bone metastases and castration-resistant disease showed no difference in the nature or number of SREs [94].

Pain and Palliative Response

Pain was reported in seven comparisons: bisphosphonates versus placebo, IV versus oral bisphosphonates, bisphosphonates versus radiotherapy, different doses of bisphosphonates, radiopharmaceuticals versus placebo, radiopharmaceuticals versus radiopharmaceuticals, and different doses of radiopharmaceuticals. The overall certainty of the estimate of effects ranged from low (due to serious risk of bias, inconsistency, and imprecision) to moderate (due to serious imprecision) (Appendix 8-11, 18-20).

Systematic reviews

Pain and/or analgesic consumption were assessed in four systematic reviews [44,49,86,87] and 37 RCTs of patients with metastatic prostate cancer. There was considerable overlap of studies between Berry et al. and Yuen et al. and between Bauman et al. and Roque I Figuls et al.; therefore, results from the two more recent Cochrane reviews are presented [44,49]).

Yuen et al. included five trials of bisphosphonates that reported pain response [56,57,97,115,116]. Four trials were combined in a meta-analysis [57,97,115,116]. Pain was measured by patients and investigators using numerical and linear analogue scales [97], presence or absence of pain [115], and the WHO grading for intensity of pain graded from 0 (no pain) to 4 (intolerable pain) [116]. The six-point present pain inventory (PPI) was completed by patients in the trial by Ernst et al. [57]. Meta-analysis using data from intention-to-treat analysis showed a statistically nonsignificant trend toward pain relief with bisphosphonates.

The same four trials were combined for the proportion of patients with decreased analgesic consumption, with similar results (Table 4-4).

Table 4-4. Meta-analysis for pain and analgesic consumption with bisphosphonates vs. placebo in metastatic prostate cancer [44].

Outcome	References	Total events		Pooled odds ratio (95% CI)*
		Treatment	Control	
Pain response	Smith 1989 [97] Elomaa 1992 [115] Kylmala 1997 [116] Ernst 2003 [57]	62/222	41/194	1.54 (0.97 to 2.44)
Decreased analgesic consumption	Smith 1989 [97] Elomaa 1992 [115] Kylmala 1997 [116] Ernst 2003 [57]	62/222	49/194	1.27 (0.82 to 1.98)

*A fixed effects model was used. CI=confidence interval.

A 1993 trial by Kylmala, not included in the meta-analysis because the original number of patients was not available, showed no statistically significant difference between clodronate and placebo in the proportion of patients free of pain within one month or in reduction in analgesic consumption (p not significant within and between groups) [56].

Ernst et al. also assessed palliative response, defined as a ≥2 point reduction in PPI without an increase in analgesic consumption or >50% decrease in analgesic score without an increase in PPI. There was no difference between clodronate and placebo in the proportion of patients with palliative response (45% vs. 39%; p=0.54) [57].

Mean pain change was reported by four trials included in Yuen et al. [42,43,98,99]. The data from Saad et al. and Small et al. were adequate for pooling and showed a significant decrease in pain favouring bisphosphonates (standard mean difference, −1.58; 95% CI, −1.75 to −1.41). However, the authors cautioned that a meaningful conclusion was impossible as there was considerable heterogeneity evident in the meta-analysis.

The placebo-controlled study by Adami et al. showed a decrease in mean pain with clodronate at one, two, and four weeks (p<0.01), but it should be noted that this comparison had a small sample size (n=13) and was one of four treatment regimens within the study [98].

The clodronate and placebo groups did not differ for changes in mean pain intensity in Strang et al. (p not reported). This was a small study that was terminated early due to poor accrual [99].

In a trial comparing ZA with placebo in 105 patients with mCRPC, the physicians's assessment of pain relief showed more improvement with ZA (p=0.04). The improvement was detectable after the first two months of treatment [53].

A trial comparing IV ibandronate with local radiotherapy in 470 men with metastatic prostate cancer, most of whom were receiving ADT, showed no difference between groups in pain measures [117].

A Cochrane review by Roque I Figuls et al. examined the efficacy of radiopharmaceuticals to control pain in patients with metastatic bone lesions [49]. The literature search included RCTs published up to 2010 that compared radiopharmaceuticals with

placebo or alternative radiopharmaceutical, or compared different doses of the same radiopharmaceutical in patients with metastatic bone pain caused by any primary tumour. The main outcome measure was pain relief categorized as complete reduction of pain (100% reduction from baseline), complete or partial reduction of pain (≥50% reduction from baseline), and any reduction in pain. Secondary outcomes included reduction in analgesic consumption, rescue medication, complications from bone metastases, disease progression, quality of life, and side effects. Of 15 RCTs (20 reports) included, seven trials pertained specifically to prostate cancer, seven trials included a proportion of patients with prostate cancer, and one trial dealt specifically with breast cancer and is not discussed further.

Assessments of the presence and degree of heterogeneity did not preclude a meta-analysis. Eight of the nine placebo-controlled trials contributed data that could be pooled for the outcome of pain relief. In six trials, all patients had prostate cancer [48,101-104,118]. The proportions of prostate cancer patients in the other two trials were 45% [125] and 67% [126]. All trials were placebo-controlled. The radiopharmaceuticals evaluated were Sr-89 (4 trials), Re-186 (2 trials), Sm-153 (1 trial), and Ra-223 (1 trial). A statistically significant difference was seen favouring radiopharmaceuticals for complete pain relief and complete or partial pain relief; the difference was not significant for the outcome of any amount of pain relief (Table 4-5).

Table 4-5. Meta-analysis for pain relief with radiopharmaceuticals vs. placebo in metastatic prostate cancer [49].

Outcome	References	Total events		Pooled relative risk (95% CI)*
		Treatment	Control	
Complete relief[a]	Lewington 1991 [102] Porter 1993 [118] Sartor 2004 [104] Nilsson 2007 [48]	61/175	18/121	2.10 (1.32 to 3.35)
Complete or partial relief[b]	Lewington 1991 [102] Porter 1993 [118] Nilsson 2007 [48]	33/63	16/56	1.72 (1.13 to 2.63)
Any relief[c]	Lewington 1991 [102] Buchali 1988 [101] Han 2002 [103] Maxon 1991[d] [125] Smeland 2003[e] [126]	64/116	48/113	1.36 (0.77 to 2.40)

*A random effects model was used. CI=confidence interval.
[a]100% reduction in pain from baseline.
[b]≥50% reduction in pain from baseline.
[c]Any reduction in pain from baseline.
[d]Mixed population; 45% had prostate cancer.
[e]Mixed population; 67% had prostate cancer.

Other outcomes assessed in the placebo-controlled trials were conflicting or inconclusive. Of four trials measuring analgesic consumption, three showed no difference between groups for less or equal analgesic consumption: RR, 7.00; 95% CI, 0.90 to 54.38 [118]; RR, 1.67; 95% CI, 0.98 to 2.85 [103]; and RR, 1.01; 95% CI, 0.69 to 1.47 [48]. The fourth trial showed a greater decrease in the analgesia index with radiopharmaceuticals (mean difference, 5.20; 95% CI, 0.85 to 9.55) [125].

Of two trials comparing different radioisotopes, one compared Sr-89 with Sm-153 [119] and one compared Sr-89 with phosphorus-32 [127]. Both of these trials had mixed populations, with approximately one-half of the patients having prostate cancer. Neither trial showed a significant difference between groups for pain relief.

Among three trials that compared different doses of radiopharmaceuticals, few differences were observed. Two trials that compared 1.0 with 0.5 mCi/kg (37 vs. 18.5 MBq/kg) doses of Sm-153 showed no difference in the frequency of pain relief [121,128]. One trial showed a greater reduction from baseline in pain measured on a VAS with the higher dose of Sm-153 (mean difference in men with prostate cancer, 2.24) [121]. One trial comparing a single with a repeated injection of Re-188 showed that more patients who received two injections had greater overall pain relief than patients who received one injection (92% vs 60%, $p<0.01$) [120]. A fourth trial was included in the systematic review but not analyzed due to insufficient information [105]. This trial included 105 patients with various cancer types and randomized them to 18.5 or 37 MBq of Sm-153. Thirteen patients had prostate cancer. Analysis by subgroup of cancer type showed no statistically significant differences in pain score between the different doses.

Primary Studies

A trial of bisphosphonates published more recently than the Yuen review compared docetaxel plus risedronate with docetaxel alone [59]. Pain response was defined as a ≥2 point reduction from baseline median PPI score, without an increase in analgesic consumption, or a decrease in analgesic consumption without an increase in PPI, maintained for two consecutive measurements at least three weeks apart. Response rates were similar between risedronate and no risedronate (31% vs. 28% [p not provided]). The duration of response also did not differ between groups (3.4 vs. 5.5 months; HR, 1.27; 95% CI 0.84 to 1.92).

A dose-ranging trial randomized 58 men with bone metastases from prostate cancer to one of four IV pamidronate regimens to determine the optimal dose for pain relief [114]. All four regimens produced reductions from baseline in pain score with no statistically significant differences among the groups (graph only, p not provided). No differences between groups were observed in narcotic score (p not provided).

A trial in which patients received combined androgen blockade with or without ZA included bone pain as an SRE [39]. As an individual component of SREs, comparative statistics were not reported for pain, but the time to first appearance of bone pain was longer in the ZA group (17.2 vs. 11.7 months).

A trial comparing ZA with clodronate showed improvement in pain intensity by ≥2 points on a 10-point VAS during the first three months in 92% of patients receiving ZA compared with 76% of patients receiving clodronate (p=0.02) [33]. The VAS score reached <1 sooner in the ZA group than the clodronate group (9 vs. 13 months; p=0.03).

Five additional RCTs of radiopharmaceuticals were not included in the Roque I Figuls meta-analysis or were published more recently [50-52,94,122].

Pain response was assessed in two dose-finding trials of Ra-223. Nilsson et al. randomized patients to doses of 5, 25, 50, or 100 kBq/kg of Ra-223. A dose response for pain was seen by week 2 (p=0.035). At week 8, the percentage of responders (reduced pain and stable analgesic consumption) in the 5, 25, 50, and 100 kBq/kg groups were 40%, 63%, 56%, and

71%, respectively [122]. A trial comparing 25, 50, and 80 kBq/kg of Ra-223 showed no statistically significant difference among groups in pain response (average pain in the past week and analgesic consumption) over 24 weeks [94].

Two trials assessing pain compared Sr-89 with radiotherapy. Three hundred five men with prostate cancer and bone metastases were treated with local field or hemibody radiotherapy and within each radiotherapy group patients were randomized to Sr-89 or radiotherapy [50]. At 12 weeks, Sr-89 compared with local radiotherapy resulted in 65.1% vs. 66.7% of patients having some relief of pain and Sr-89 compared with hemibody radiotherapy resulted in 70% vs. 67.4% of patients having some relief of pain. Percentages for some reduction in analgesics for Sr-89 versus local radiotherapy were 39.7% versus 33.3% and for Sr-89 versus hemibody radiotherapy were 28.3% versus 34.8%. The p values were not provided. The occurrence of new pain sites was lower in the Sr-89 groups compared with local and hemibody radiotherapy (63.9% vs. 41.7%, $p<0.05$; and 73.3% vs. 51.1%, $p<0.05$, respectively).

Oosterhof et al. randomized 203 men with bone metastases and prostate cancer to Sr-89 or local field radiotherapy and evaluated subjective response, defined as a reduction in pain score (5-point WHO score) by at least one level and no deterioration in performance status, an unchanged pain level and a reduction in daily analgesic consumption by at least 25%, or improvement in performance status by at least one level without an increase in pain level or analgesic consumption. The Sr-89 and radiotherapy groups did not differ in subjective response (34.7% vs. 33.3%; p=0.84). The median duration of response was 4.6 months after Sr-89 and 4.5 months after radiotherapy (p=0.60) [51].

In an exploratory phase II study, Nilsson et al. compared Sr-89 with chemotherapy (5-fluorouracil, epirubicin, and mitomycin C) in 35 men with prostate cancer and bone metastases. Pain intensity was measured with a five-point verbal rating scale (0=no pain to 4=intractable pain). Both groups had reductions in pain intensity. At 12 weeks, the Sr-89 and chemotherapy groups did not differ (change from baseline 0.090 vs. 0.039; p=0.75) [52].

Quality of Life

Primary Studies

Quality of life outcomes were reported in four bisphosphonate trials [42,57,117,129], two exercise trials [16,17], and two radiopharmaceutical trials [46,118]. For the comparison of bisphosphonates versus placebo in one trial of nonmetastatic patients, the overall certainty of the estimate of effects was low due to serious indirectness and imprecision and moderate in two trials of metastatic patients due to serious imprecision (Appendix 8). For the comparison of bisphosphonates versus radiotherapy in one trial of patients with metastatic disease, the overall certainty of the estimate of effects was moderate due to serious imprecision (Appendix 10). For the comparison of exercise versus usual care in two trials of nonmetastatic patients, the overall certainty of effects was moderate due to serious imprecision (Appendix 16). For the comparison of radiopharmaceuticals versus placebo in two trials, the overall certainty of the estimate of effects was high (Appendix 18).

In a trial comparing clodronate with placebo, patients completed a nine-item quality of life instrument (Prostate Cancer-Specific Quality of Life Instrument) that assessed pain, physical activity, fatigue, appetite, constipation, passing urine, family/marriage relationships, mood, and overall wellbeing [57]. A significant difference between groups in change in the pain domain favoured clodronate (p=0.022). No differences between groups were observed in any other domain.

In a trial comparing ZA with placebo, Saad et al. measured patient-reported quality of life parameters with the FACT – General and EURO Quality of Life EQ-5D questionnaires [42].

No statistically significant difference was observed between groups in change from baseline on either score.

In the factorial RADAR trial, the addition of ZA to six or 18 months of ADT was not associated with any independent effects on patient-reported outcomes from the European Organization for Research and Treatment of Cancer quality of life and prostate-specific quality of life modules [129].

One trial showed no difference between ibandronate and local radiotherapy in overall quality of life at four weeks (p=0.37) or 12 weeks (p=0.84) [117].

One trial comparing strength training with usual care showed no effect of strength training on health-related quality of life after 16 weeks [16]. Another trial comparing supervised aerobic and resistance exercises sessions with usual care showed improvement with exercise in three measures of health-related quality of life (social functioning, p=0.015; mental health, p=0.006; and mental health composite, p=0.022) [17].

In a trial comparing Sr-89 with placebo, patients were assessed using the same nine-item linear analogue scale quality of life questionnaire used in Ernst et al. [118]. Patients receiving Sr-89 had better overall scores than placebo group patients (p=0.006). Among the individual categories, Sr-89 was superior in alleviating pain (p<0.05) and improving physical activity (p<0.05).

In the ALSYMPCA trial, more patients who received Ra-223 than placebo had meaningful improvement on the FACT-P questionnaire (25% vs. 16%; p=0.02). The mean change from baseline to week 16 also favoured the Ra-223 group (−2.7 vs. −6.8; p=0.006) [46].

QUESTION 4
Can bone-targeted therapies improve overall survival in men with prostate cancer?

Overall Survival

Overall survival was reported in eight comparisons: bisphosphonates versus placebo, IV versus oral bisphosphonates, bisphosphonates versus radiotherapy, denosumab versus placebo, denosumab versus ZA, radiopharmaceuticals versus placebo, different doses of radiopharmaceuticals, and different doses of matrix metalloproteinase inhibitor. The overall certainty of the estimate of effects ranged from low (due to serious risk of bias, inconsistency, and imprecision) to high (Appendix 8-10, 12, 13, 18, 20, 21).

Systematic Reviews

Survival outcomes were reported in two systematic reviews [44,49] and 16 individual trials. Most trials were not powered to detect a difference in survival. Five trials that compared bisphosphonates with control in patients with metastatic disease and reported death from prostate cancer were included in Yuen et al. Four could be combined in a meta-analysis and showed a nonsignificant reduction in favour of bisphosphonates [44] (Table 4-6). The fifth trial reported median time of survival and showed no difference between ZA at 4 mg and placebo (546 vs. 464 days; p=0.091) or between ZA at 8/4 mg and placebo (407 vs. 464 days; p=0.386) [42].

Table 4-6. Meta-analysis for death from prostate cancer with bisphosphonates vs. placebo [44].

Outcome	References	Total events		Pooled odds ratio (95% CI)*
		Treatment	Control	

Death from prostate cancer	Dearnaley 2003 [41] Elomaa 1992 [115] Ernst 2003 [57] Small 2003 [43]	209/488	226/503	0.82 (0.61 to 1.11)

*A fixed effects model was used. CI=confidence interval.

A meta-analysis of three trials showed no difference in mortality between radiopharmaceuticals (Sr-89, Re-186, Sm-153) and placebo. A meta-analysis of two trials comparing low and higher doses of Sm-153 showed no difference in survival [49] (Table 4-7).

Table 4-7. Meta-analysis for death with radiopharmaceuticals [49].

Outcome	References	Total events		Pooled relative risk (95% CI)*
Death	Buchali 1988 [101] Han 2002 [103] Serafini 1998 [128]	Treatment 15/138	Placebo 10/99	1.14 (0.27 to 4.77)
	Resche 1997 [121] Serafini 1998 [128]	Lower dose 15/90	Higher dose 12/94	1.27 (0.63 to 2.59)

*A random effects model was used. CI=confidence interval.

Primary Studies

Among nonmetastatic patients, no difference in overall survival was observed with bisphosphonates [34,35,55] or denosumab [36]. For clodronate compared with placebo, overall survival rates were 78% vs. 79% at five years (HR, 1.02; 95% CI, 0.80 to 1.30; p=0.90) and 48% vs. 51% at 10 years (HR, 1.12; 95% CI, 0.89 to 1.42; p=0.94) [35,55]. For ZA compared with no ZA, the rates for death at four years were 16.7% vs. 17.5%; p=0.70 [34]. In the factorial RADAR trial, the addition of ZA to six or 18 months of ADT did not reduce all-cause mortality (p≥0.45) [130].

In men with CRPC at risk of bone metastasis, denosumab did not differ from placebo in overall survival (43.9 vs. 44.8 months; HR, 1.01; 95% CI, 0.85 to 1.20; p=0.91) [36].

Among individual trials evaluating bisphosphonates in metastatic patients not included in Yuen et al., there was no difference between bisphosphonates and control (placebo or no bisphosphonate) in overall or progression-free survival in five trials [39,40,56,58,59]. In one trial comparing clodronate with placebo that showed no difference in five-year overall survival, a benefit was seen with clodronate at 10 years (17% vs. 9%; HR, 0.77; 95% CI, 0.60 to 0.98; p=0.032) [55].

One trial of docetaxel with or without ZA in 105 men with mCRPC showed longer bone progression-free survival (median 9 vs. 6 months; p<0.05) and overall survival with ZA (median 19 vs. 15 months; p=0.02 [53].

A trial comparing IV ibandronate with local radiotherapy showed no difference in overall survival (12.9 vs. 12.2 months; HR, 0.89; 95% CI, 0.73 to 1.09; p=0.29) [117].

Among head-to-head bisphosphonate trials, no difference was observed in three-year overall survival between ZA and clodronate (69.6% vs. 64.2%; p=0.54) [33]. No difference in

survival was observed between denosumab and ZA (median overall survival, 19.4 vs. 19.8 months; HR, 1.03; 95% CI, 0.91 to 1.17; p=0.65) [37].

A phase II trial of 80 patients comparing two doses of a selective matrix metalloproteinase inhibitor (1200 mg once vs. twice daily) showed no statistically significant difference in overall survival between the once-daily and twice-daily regimens (not reached vs. 21 months; p=0.2) [123].

Among individual trials investigating radiopharmaceuticals, a statistically significant survival advantage was seen with Ra-223 [46,48,54]. In a phase II trial comparing Ra-223 with placebo in 64 patients, overall survival favoured Ra-223 (65.3 vs. 46.4 weeks; HR, 0.48; 95% CI, 0.26 to 0.88; p=0.017) [54]. A phase III trial of 921 patients comparing a regimen of six injections of Ra-223 with placebo was powered to detect an HR of 0.76 for the risk of death between Ra-223 and placebo [46]. Ra-223 improved overall survival at both a prespecified interim analysis (14.0 vs. 11.2 months; HR, 0.70; 95% CI, 0.55 to 0.88; p=0.002) and at final analysis (14.9 vs. 11.3 months; HR, 0.70; 95% CI, 0.58 to 0.83; p<0.001).

Five trials evaluating Sr-89 showed mixed results. Longer overall survival was observed in one trial comparing induction chemotherapy plus Sr-89 with no Sr-89 (27.7 vs. 16.8 months; HR, 2.76; 95% CI, 1.44 to 5.29; p=0.0014) [95]. A trial comparing Sr-89 with no Sr-89 in men with castration-sensitive metastatic prostate cancer showed no difference between groups in median overall survival (47.4 vs. 53.5 months; p=0.97) [124]. A trial in which all patients received local field radiotherapy showed no difference in overall survival between Sr-89 and placebo (27 vs. 34 weeks; p=0.6) [118]). A study that stratified patients by suitability to local or hemibody radiotherapy and randomized them to Sr-89 or radiotherapy showed no difference between groups in overall survival (33 vs. 28 weeks; p=0.10) [50]. A trial comparing Sr-89 with local field radiotherapy showed borderline significantly shorter survival with Sr-89 (7.2 vs. 11 months; p=0.0457) [51].

A trial comparing single with repeated injections of Re-188 showed a survival advantage with repeated injections (12.7 vs. 7.0 months; p=0.043) [120]. A dose-finding study found no difference among 25, 50, and 80 kBq/kg dose groups of Ra-223 in the proportion of patients who died (p=0.31) or in time to death (p=0.44) [94].

Adverse Effects (Nonmetastatic)

Systematic Reviews

One systematic review reported adverse effects associated with bisphosphonates in nonmetastatic patients and performed a meta-analysis [23]. The agents studied were ZA (6 trials), alendronate (1 trial), pamidronate (1 trial), and neridronate (1 trial). ZA and pamidronate were given intravenously, neridronate was given as an intramuscular injection, and alendronate was given orally. An increase was seen in gastrointestinal symptoms (3 trials, OR, 2.89; 95% CI, 1.18 to 7.04; p=0.02) and fever (2 trials, OR, 7.99; 95% CI, 2.08 to 30.61; p=0.002) with bisphosphonates compared with placebo. No statistically significant difference was seen between bisphosphonates and placebo in fatigue, anemia, flushing, arthralgia, constipation, musculoskeletal pain, limb pain, hypertension, upper respiratory infection or influenza syndrome, or urinary frequency.

Primary Studies

The adverse effects are summarized for each study in Appendix 23. Adverse effects in trials of bisphosphonates not included in Ding et al. showed no or few serious side effects. No important adverse events or gastrointestinal adverse effects occurred in a placebo-controlled trial of risedronate [96]. Another trial comparing risedronate with placebo reported two

occurrences of gastroenteritis and diarrhea of at least grade 3 in the risedronate group [106]. A trial of alendronate noted more hypertension with alendronate than placebo (2.8% vs. 0; p=0.02), but less nausea (0 vs. 2.8%; p=0.046) [5]. In a trial comparing clodronate with placebo, more patients receiving clodronate reported a dose-modifying adverse event (105 vs. 71 patients; p=0.002). Gastrointestinal problems were responsible for approximately one-half of these events [35]. None of the trials of oral bisphosphonates reported the rare but serious adverse effects of renal failure, atypical femoral fractures, atrial fibrillation, osteonecrosis of the jaw, or hypocalcemia.

Among trials of ZA, adverse effects in renal function were rare. Four trials reported no renal failure associated with ZA [6,10,12,112], and one trial reported no persistent renal failure [11]. Acute renal failure developed in one patient in each group of a placebo-controlled ZA trial [7], and reversible acute renal failure developed in one ZA patient in another placebo-controlled trial [9]. Grade 3 to 4 renal failure occurred in four ZA patients and one placebo patient in one trial [13]. In one placebo-controlled trial, one ZA patient developed atrial fibrillation [9]. The incidence of hypocalcemia in ZA studies was rare. In two trials, one patient in the ZA group in each trial developed hypocalcemia [8,13]. In another trial, fewer than 1% of patients in both the ZA and no ZA groups had hypocalcemia [3] and in another the incidence was four patients versus one patient [34]. In The factorial RADAR trial evaluating leuprorelin and radiotherapy with or without ZA, the frequency of grade 1 hypocalcemia ranged from 2.7% to 8.8% [112]. Two trials comparing ZA with no ZA reported osteonecrosis of the jaw: two patients receiving ZA developed osteonecrosis of the jaw in one trial [112], and in the other the incidence was nine patients versus one patient [34]. No trials of ZA reported any afemoral fractures.

Among trials of other agents, no serious treatment-related adverse effects were noted with raloxifene other than one case of pulmonary embolism [109]. In a placebo-controlled trial of toremifene, total and serious adverse effects were similar between groups (total: 75% vs. 75%; serious: 21% vs. 20%). Any venous thromboembolic events occurred in more than twice as many toremifene patients as placebo (17 [2.6%] vs. 7 [1.1%]) [110]. Two placebo-controlled trials of denosumab showed similar rates of adverse effects between groups [3,36]. In men receiving ADT, the rates between denosumab and placebo were similar for total adverse effects (87% vs. 87%), grade 3 to 5 effects (37% vs. 34%), serious adverse effects (35% vs. 31%), and serious adverse effects related to infection (5.9% vs. 4.6%). Cardiovascular events occurred in 11% of patients in each group. Hypocalcemia occurred in <1% in each group [3]. In men with nonmetastatic CRPC, the rates between denosumab and placebo were similar for total adverse effects (94% vs. 93%), grade 3 to 5 effects (53% vs. 50%), and serious adverse effects (46% vs. 46%). Hypocalcemia occurred in 12 patients (2%) receiving denosumab compared with two patients (<1%) receiving placebo; in nine patients in the denosumab group, hypocalcemia was grade 3 to 4. One patient had symptomatic hypocalcemia. Osteonecrosis of the jaw developed in 33 denosumab patients (5%) compared with zero placebo patients. The majority of patients had oral risk factors including tooth extraction, poor oral hygiene, and dental appliance use [36]. No patients in either denosumab study had renal failure, atypical femoral fracture, or atrial fibrillation.

Adverse Effects (Metastatic)

Systematic Reviews

One systematic review reported adverse effects associated with bisphosphonates in patients with advanced cancer and performed a meta-analysis [44]. The agents studied were clodronate (4 trials), pamidronate (1 trial), etidronate (1 trial), and ZA (1 trial).

Bisphosphonates were associated with an increase in nausea (2 trials, OR 1.35, 95% CI 1.02 to 1.77, p=0.03). No statistically significant difference between groups was seen in meta-analyses for vomiting (2 trials, OR, 1.22; 95% CI, 0.89 to 1.69; p=0.22), anemia (3 trials, OR, 1.04; 95% CI, 0.76 to 1.41; p=0.83), or bone pain (2 trials, OR, 0.93; 95% CI, 0.72 to 1.21; p=0.58).

One systematic review reported hematological adverse effects associated with radiopharmaceuticals for metastatic bone pain [49]. Meta-analyses for grade 3 to 4 leucopenia, thrombocytopenia, and anemia were performed. The agents included Sr-89 (3 trials) and Sm-153 (2 trials). One trial had a mixed cancer population; however, 68% of patients had prostate cancer [128]. Radiopharmaceuticals were associated with a statistically significant increase in grade 3 to 4 leukopenia (4 trials, RR, 5.90; 95% CI, 1.62 to 21.47) and statistically nonsignificant increases in grade 3 to 4 thrombocytopenia (4 trials, RR, 2.21; 95% CI, 0.98 to 4.99) and anemia (2 trials, RR, 1.09; 95% CI, 0.47 to 2.56).

Primary Studies

Among the individual trials of bisphosphonates not in the meta-analysis, similar rates of adverse events were found between clodronate and placebo in three trials [57,115,116]. In one trial, clodronate was associated with an increased risk of adverse effects (HR, 1.71; 95% CI, 1.21 to 2.41; p=0.002) and an increased risk of dose-modifying adverse events (HR, 2.81; 95% CI, 1.78 to 4.44; p<0.0001) [41]. In a trial comparing alendronate with no alendronate, adverse effects were generally mild and did not differ between groups [58]. A trial comparing risedronate with no risedronate showed no difference between groups in grade 3 or 4 adverse effects [59]. Among serious but rare effects, one patient receiving oral clodronate developed renal failure [115], and in another trial, five clodronate patients developed hypocalcemia [41].

In a trial comparing ZA with placebo in men with castration-sensitive prostate cancer and bone metastases, treatment-related adverse effects of grade 3 or higher were similar between the two groups (14% vs. 12%). The most common grade 3 or higher events were pain, hypophosphatemia, fatigue, and hypocalcemia; the rates were similar in the ZA and placebo groups. One patient in the ZA group had a grade 5 renal failure event. Furthermore, 10 patients receiving ZA and six receiving placebo developed grade 3 osteonecrosis [40]. In a placebo-controlled trial evaluating ZA in castration-resistant patients, four patients each in the 4 mg and 8/4 mg ZA groups experienced grade 3 to 4 hypocalcemia. Deterioration in renal function occurred in 15% of the 4 mg group, 21% of the 8/4 mg group, and 12% of the placebo group [42].

A dose-response trial of pamidronate showed a small number of patients with mild-to moderate adverse effects related to the drug [114]. A small trial allocating patients to ZA once before ADT (n=14), once after ADT (n=15), or monthly after ADT for six months (n=15), showed no grade 3 or 4 adverse effects; however, greater fatigue and myalgia were associated with the six infusions of ZA [113].

Four trials compared two active interventions involving bisphosphonates [33,37,100,117]. In a trial comparing ZA with clodronate, renal dysfunction occurred in 45% of ZA patients and 34% of clodronate patients. Hypocalcemia developed in six ZA patients and two clodronate patients. One patient in the ZA group developed osteonecrosis of the jaw. A statistically significant difference was seen between the ZA and clodronate groups in gastrointestinal disorders (16% vs. 31%; p=0.01) [33]. Two trials comparing denosumab with IV bisphosphonates showed similar rates of adverse effects overall between groups [37,100]. In one trial, higher rates of hypocalcemia occurred with denosumab (13% vs. 6%; p<0.0001); most events were mild to moderate in severity. Osteonecrosis of the jaw occurred in 22 patients on denosumab and 12 patients on ZA (2% vs. 1%; p=0.09). More than 75% of those patients had a history of tooth extraction, poor oral hygiene, or use of a dental appliance. Renal impairment occurred in 15% of denosumab patients and 16% of ZA patients [37]. A trial comparing IV ibandronate with local radiotherapy showed no difference in overall adverse effects, but each

treatment was associated with different events (diarrhea 6% vs. 12%; p=0.014; other [including fever, anorexia] 19% vs. 9%; p=0.001) [117].

Two placebo-controlled trials of Ra-223 showed no difference between groups in hematological adverse effects [46,48]. In one trial, constipation was the only adverse effect to occur to a statistically significant extent more in the Ra-223 group (36% vs. 6.5%; p not reported). One patient in the placebo group developed atrial fibrillation [48]. In another trial, adverse effects were consistently lower in the Ra-223 group than the placebo group: all adverse effects (93% vs. 96%), grade 3 or 4 adverse effects (56% vs. 62%), serious adverse effects (47% vs. 60%), and study drug discontinuation due to adverse effects (16% vs. 21%). One grade 5 case of thrombocytopenia occurred in the Ra-223 group and one grade 5 case of anemia occurred in the placebo group [46].

Ongoing, unpublished, or incomplete studies.

Protocol ID	Title and details of trial	Status
NCT00869206 (CALGB 70604)	**A Randomized, Phase III Study of Standard Dosing Versus Longer Dosing Interval of Zoledronic Acid in Metastatic Cancer.** This randomized phase III trial is studying two different schedules of ZA to compare how well they work in treating patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma with bone involvement. Patients receive ZA IV over ≥15 minutes. Courses repeat every four or 12 weeks for up to two years in the absence of disease progression or unacceptable toxicity. Outcomes of interest: SREs, pain, functional status, osteonecrosis of the jaw, renal dysfunction.	**Ongoing**
NCT00554918 (TRAPEZE)	**A Randomised Phase II Feasibility Study of Docetaxel (Taxotere®) Plus Prednisolone vs. Docetaxel (Taxotere®) Plus Prednisolone Plus Zoledronic Acid (Zometa®) vs. Docetaxel (Taxotere®) Plus Prednisolone Plus Strontium-89 vs. Docetaxel (Taxotere®) Plus Prednisolone Plus Zoledronic Acid (Zometa®) Plus Strontium-89 in Hormone Refractory Prostate Cancer Metastatic to Bone.** This randomized phase II trial is studying the side effects and how well giving docetaxel together with prednisolone works with or without ZA and/or strontium chloride Sr-89 in treating patients with prostate cancer metastatic to bone that has not responded to hormone therapy. Arm I: Patients receive docetaxel IV on day 1 and oral prednisolone once daily. Arm II: Patients receive docetaxel and prednisolone as in arm I and ZA IV over 15 minutes on day 1. Arm III: Patients receive docetaxel and prednisolone as in arm I and a single dose of strontium chloride Sr-89 IV on day 7 of course 2. Arm IV: Patients receive docetaxel and prednisolone as in arm I, ZA as in arm II, and strontium chloride Sr-89 as in arm III. Outcomes of interest: safety, toxicity, BMD, pain, survival, quality of life.	**Completed**

NCT00216060	**A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Ability of Risedronate to Prevent Skeletal Related Events in Patients With Metastatic Prostate Cancer Commencing Hormonal Therapy: Hoosier Oncology Group GU02-41.** The study population will consist of prostate cancer patients with metastatic bone disease for whom ADT is planned. After stratification based on the patient's age, performance status, and severity of metastatic disease, the patients will be randomized at a 1:1 ratio to the following treatment arms: Daily oral risedronate combined with ADT or daily oral placebo combined with ADT. Outcomes of interest: SREs, prostate-specific antigen response, tumour response, survival.	**Unknown**
NCT00459654	**A Phase II Randomised, Placebo-controlled, Multicentre Study in Prostate Cancer Patients with Painful Bone Metastases to Evaluate the Efficacy of Repeated Radium-223 Injections.** Patients receive local field external beam radiotherapy and repeated injections of Ra-223 or saline. Four injections are given at four-weekly intervals starting after the first fraction of external beam radiotherapy. Outcomes of interest: SREs, pain, overall survival, quality of life.	**Completed**
NCT00268476 (STAMPEDE)	**STAMPEDE: Systemic Therapy in Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy - Androgen Suppression-Based Therapy Alone or Combined With Zoledronic Acid, Docetaxel, Prednisolone, Celecoxib, Abiraterone, Enzalutamide and/or Radiotherapy in Treating Patients With Locally Advanced or Metastatic Prostate Cancer.** Patients with high-risk locally advanced or metastatic prostate cancer received other treatments (including ZA) plus long-term ADT compared with ADT alone.	**Recruiting**
NCT00058188	**A Phase III Randomized Study of Zolendronate Bisphosphonate Therapy for the Prevention of Bone Loss in Men With Prostate Cancer Receiving Long-Term Androgen Deprivation**. The purpose is to compare the effectiveness of ZA combined with calcium with that of calcium alone in reventing bone loss in patients with stage III or stage IV prostate cancer who have received long-term androgen deprivation	**Ongoing**
NCT00685646	**A Phase III, Multicenter, Randomized, Controlled Study of Maximum Androgen Blockade With vs. Without Zoledronic Acid in Prostatic Cancer Patients With Metastatic Bone Disease**. ZA may help relieve some of the symptoms caused by bone metastasis. It is not yet known whether androgen-blockade therapy is more effective with or without ZA in treating patients with prostate cancer that has spread to the bone.	**Completed**

NCT00242567	**A Phase III, Parallel Group, Randomized, Open-label, Multi-centre Clinical Trial of Zoledronic Acid in Males Receiving Androgen Deprivation Therapy for Advanced Prostate Cancer.** This study aims to determine whether early treatment with ZA, that is given during the early phase of advanced prostate cancer, will be more efficacious than delayed treatment.	**Completed**
NCT02043678	**A Phase III Randomized, Double-blind, Placebo-controlled Trial of Radium-223 Dichloride in Combination With Abiraterone Acetate and Prednisone/Prednisolone in the Treatment of Asymptomatic or Mildly Symptomatic Chemotherapy-naïve Subjects With Bone Predominant Metastatic Castration-resistant Prostate Cancer(CRPC)**. To determine if the addition of Ra-223 dichloride to standard treatment is able to prolong life and to delay events specific for prostate cancer which has spread to the bone.	**Recruiting**
NCT00365105	**Randomized Phase III Trial to Evaluate Radiopharmaceuticals and Zoledronic Acid in the Palliation of Osteoblastic Metastases From Lung, Breast, and Prostate Cancer**. This randomized phase III trial is studying zoledronate, vitamin D, and calcium to see how well they work compared to zoledronate, vitamin D, calcium, and either Sr-89 or Sm-153 in preventing or delaying bone problems in patients with bone metastases from prostate cancer, lung cancer, or breast cancer.	**Ongoing**
NCT02051218	**Prevention of Symptomatic Skeletal Events With Denosumab Administered Every 4 Weeks Versus Every 12 Weeks - A Non-Inferiority Phase III Trial**. To determine whether the benefit of denosumab is maintained if administered only every 12 weeks compared with every four weeks.	**Recruiting**
NCT02194842 (PEACE III)	**A Randomized Multicenter Phase III Trial Comparing Enzalutamide vs. a Combination of Ra-223 and Enzalutamide in Asymptomatic or Mildly Symptomatic Castration Resistant Prostate Cancer Patients Metastatic to Bone**. To assess whether upfront combination of enzalutamide and Ra-223 improves radiological progression-free survival compared with enzalutamide single agent in asymptomatic or mildly symptomatic castration resistant prostate cancer patients metastatic to bone.	**Recruiting**

DISCUSSION

Bone health is a significant concern in men with prostate cancer across the spectrum of the disease. Prostate cancer typically affects men in their late 60s and beyond; the incidence

of osteoporosis in this age group is 20% to 40%. One of the most widely used treatments in advanced or high-risk prostate cancer, ADT, has deleterious effects on bone that are cumulative with prolonged use. In contradistinction, in recent years, evidence has accumulated demonstrating that multiple agents are effective in reducing bone side effects of prostate cancer treatment as well as reducing SREs in men with advanced prostate cancer. This review sought to evaluate the effectiveness of therapies targeting bone across all stages of prostate cancer.

Almost one in two men with prostate cancer will be exposed to ADT at some point after diagnosis. In the metastatic setting in particular, the duration of ADT is often life long. ADT use is associated with loss of bone density and an increased risk of fractures, particularly low-trauma or osteoporotic fractures. Fractures are the most serious bone complication of ADT use, and are often associated with significant pain, disability, and excess mortality in men with prostate cancer.

Bisphosphonates were found to be effective in increasing BMD, but no benefit has been shown in preventing fractures among nonmetastatic patients [23]. Some evidence indicates that IV bisphosphonates may be more effective than oral bisphosphonates in improving BMD [33]. Trials of bisphosphonates in the nonmetastatic setting have generally been small and not powered to detect differences in fracture outcomes. Denosumab, 60 mg subcutaneously every six months, was shown to improve BMD and reduce the incidence of new vertebral fractures in nonmetastatic men receiving ADT [3].

Beyond improving bone density and reducing the risk of fractures, various trials have attempted to delay the development and reduce the morbidity of metastatic prostate cancer. At present, there is no evidence of effectiveness of denosumab or bisphosphonates in preventing metastasis in men with castration-sensitive disease.

As the disease usually becomes castration-resistant after approximately two years of ADT, investigators have been interested in preventing skeletal morbidity and prolonging survival in this setting. In particular, bone pain and SREs are major causes of morbidity in mCRPC. At present, bisphosphonates have not been shown to be effective in reducing the risk of developing bone metastases [34,35]. Denosumab at a bone metastasis-indicated dosage (120 mg subcutaneously every 4 weeks) delayed the median time to first bone metastasis by four months, but was associated with an increased risk of osteonecrosis of the jaw and hypocalcemia [36].

In men with established mCRPC, more intensive denosumab therapy delays time to development of SREs [37]. Bisphosphonates are somewhat less effective [44]. There is an increased risk of osteonecrosis of the jaw and hypocalcemia with denosumab. In men with mCRPC and bone pain, Ra-223 (an alpha-emitting radiopharmaceutical) delayed symptomatic skeletal events and improved quality of life [46]. Older beta-emitting radiopharmaceuticals show some effectiveness in palliation of bone pain [49].

Finally, an ongoing goal in men with mCRPC is the prolongation of survival. In this setting, Ra-223 has been shown to be effective in prolonging survival with a reasonable side effect profile [46]. No survival benefit has been demonstrated in this setting with either bisphosphonates or denosumab.

Several areas of uncertainty persist in the management of bone health across the spectrum of prostate cancer. In nonmetastatic disease, whether bisphosphonates will reduce the risk of fractures remains to be established. In mCRPC, with the recent approval of potent anti-androgen therapies such as abiraterone and enzalutamide, both of which have been shown to delay the development of bone metastasis, whether treatments such as ZA or denosumab will be equally effective in reducing SREs in patients with stable disease is an area of interest, and whether less intensive regimens than ZA or denosumab every four weeks will prove equally effective is also of significant interest from patient and resource burden perspectives.

CONCLUSIONS

Men with prostate cancer are at risk of skeletal deterioration and other bone-related problems at all stages of the disease. Therapeutic interventions and bone-targeted therapies reduce and/or alleviate bone complications related to prostate cancer.

Bone Health and Bone Targeted Therapies for Prostate Cancer

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel (GU DSG) and the PEBC RAP (Appendix 1). The results of these evaluations and the responses of the Working Group are described below.

Expert Panel Review and Approval

Of the 17 members of the GDG Expert Panel, 15 members cast votes and two abstained, for a total of 88% response in April 2016. Of those that cast votes, 15 approved the document (100%). Of the 15 members, four members had comments for consideration by the Working Group. The main comments from the Expert Panel and the responses of the Working Group are summarized in Table 5-1.

Table 5-1. Summary of the responses of the Working Group to comments from the Expert Panel.

Comments	Responses
1. More detail was requested about the risk level of the men targeted in Recommendation 1. Was it all patients or patients at risk according to baseline BMD or fracture risk?	We changed Recommendation 1 to specify men with prostate cancer at high risk of fracture.
2. More detail was requested about the absolute risk of osteoporosis.	We added a statement about the risk of developing osteoporosis to the introduction of the systematic review.
3. A request was made to elucidate the risk-benefit profile of denosumab compared with ZA in Recommendation 3a.	The quality of the evidence and risks and benefits of denosumab and ZA were more fully described in the Interpretation of Evidence section for Recommendation 3a.
4. A request was made to provide guidance about men with castration-sensitive prostate cancer in Recommendation 3a.	A statement about this population was added to Recommendation 3a.
5. A request was made to be more precise describing the patients in whom Ra-223 is effective in Recommendation 4.	A qualifying statement was amended to accurately describe the patient population.

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document between February and April, 2016. Initially, one RAP member approved (March 3, 2016), and two members conditionally approved (February 25 and 29, 2016) the document. Final approval was given April 19, 2016. The main comments from the RAP and the responses of Working Group are summarized in Table 5-2.

Table 5-2. Summary of the responses of the Working Group to comments from RAP.

Comments	Responses
1. A request was made to make explicit statements about the quality of the evidence in the Recommendations section.	We added statements pertaining to the quality of the evidence from the GRADE assessments for each recommended intervention in the Interpretation of Evidence sections.

2. A query was made as to why the Working Group singled out Sm-153 for bone pain in Recommendation 3c given the weak evidence.	We removed specific mention of Sm-153 from Recommendation 3c.
3. An observation was made that chemotherapy and radiotherapy are options for men with bone pain and mCRPC.	We did not include specific mention of chemotherapy or radiotherapy in the recommendations (beyond scope of the guideline); however, we included mention of these treatment modalities in the qualifying statements for Recommendation 3 with references to other guidelines.

The document was revised according to the actions above and was sent back to the DSG members who had made comments and the RAP members who had conditionally approved. The revised document was approved by all reviewers.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Seventeen targeted peer reviewers from inside and outside Ontario who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group and the GU DSG. Three agreed to be the reviewers (Appendix 1). Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the responses of the Working Group are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (n=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.					3
2. Rate the guideline presentation.				1	2
3. Rate the guideline recommendations.				1	2
4. Rate the completeness of reporting.					3
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?					3
6. Rate the overall quality of the guideline report.					3
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.				1	2
8. I would recommend this guideline for use in practice.				1	2

9. What are the barriers or enablers to the implementation of this guideline report?	The choice of therapy is still left up to the individual clinician and the availability of treament options vary across Canada, which may undermine the recommendations.

Table 5-4. Responses to comments from targeted peer reviewers.

Comments	Responses
1. The availability of treatment options varies across Canada, which may undermine the recommendations.	It is recognized that differences in funding may affect the implementation of these recommendations in different jurisdictions. The purpose of the guideline is to present recommendations based on current evidence. These recommendations primarily focus on the care of patients with prostate cancer in Ontario.
2. Suggest removing mention of patients with bone metastasis from Recommendation 1 since the osteoporosis dosage is being recommended.	There is indirect evidence that denosumab would benefit patients with metastases. We added a qualifying statement about the potential benefit.
3. Suggest clarifying that fracture was not an endpoint in the bisphosphonate trials related to Question 1.	We added to the interpretation of evidence indicating that most of the bisphosphonate trials were not powered to detect differences in fracture rates.
4. More discussion of castration-sensitive prostate cancer is required in Recommendation 3a. ADT and ZA in combination were studied in STAMPEDE, but secondary endpoints such as SREs have not yet been reported.	We added to the interpretation of evidence, referring to the low quality of evidence and varying benefit of ZA for SREs across studies in men with castration-sensitive prostate cancer.
5. Recommendation 3b is somewhat misleading because the primary endpoint of the ALSYMPCA trial was overall survival, with time to symptomatic skeletal events and quality of life as secondary endpoints. Overall survival information should be included here.	The question was posed a priori and focuses on the palliative effects of interventions. While the primary endpoint of ALSYMPCA was overall survival, we should not ignore the significant quality of life benefits. We changed the wording to "should be considered" rather than "is recommended."
6. Recommendation 3b should mention men without visceral metastases in the description of the population.	We added a qualifying statement indicating the recommendation applies to men with predominantly bony metastases and no evidence of visceral metastases or large nodal masses.
7. With respect to the qualifying statement about systemic therapies for the treatment of mCRPC, mitoxantrone shuld be added to the list.	We added a sentence to the qualifying statement indicating that mitoxantrone has been shown to improve pain and health-related qualify of life.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. The following types of clinicians in the PEBC database were contacted: medical oncologists who treat genitourinary cancer or prostate cancer, radiation oncologists who treat genitourinary cancer or prostate cancer, urologists, radiologists, nuclear medicine physicians, family practitioner/primary care physicians, geriatricians, rheumatologists, and osteoporosis experts. We also contacted the following organizations by email to inform them of the survey: International Society of Geriatric Oncology, Osteoporosis Canada, Canadian Association of Nuclear Medicine, and Canadian Society of Endocrinology and Metabolism. In total, 139 clinicians were contacted (111 from within Ontario and 28 outside Ontario), and 17 (12%) responses were received. Ten people stated that they did not have interest in this area or were unavailable to review this guideline

at the time. The results of the survey from 17 people are summarized in Table 5-5. The main comments from the consultation and the responses of the Working Group members are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	n=17 (12%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	1		2	9	5
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.		1		11	5
3. I would recommend this guideline for use in practice.	1		2	9	5
4. What are the barriers or enablers to the implementation of this guideline report?	• Lack of uniform funding for bone-targeted therapies across Canada. • Low-quality evidence supporting the recommendation of bisphosphonates for pain reduction of bone metastases. • In the outpatient setting, denosumab and ZA require an Ontario Drug Benefit Limited Use form, otherwise they may have cost limitations. • Inconclusive evidence to support the use of bisphosphonates for fracture prevention and small numbers of patients in studies of osteoporosis. • The relevance of SRE reduction with denosumab or bisphosphonates is debatable in the absence of a survival benefit, particularly if cost-effectiveness is considered. • The recommended dosage for Ra-223 should be updated. • The use of denosumab must take into consideration high cost, subcutaneous administration, and overall availability.				

Table 5-6. Responses to comments from professional consultants.

Comments	Responses
1. The current recommended ZA dose for osteoporosis is 5 mg IV once per year	Most of the studies that inform our evidence base report 4 mg every 3 months. However, we recognize that a 5 mg IV infusion once per year has been approved in Canada and the United States and thus have changed Tables 1-1 and 2-1 and added to the qualifying statements for Recommendation 1.

2. The current recommended dose for Ra-223 is 55 KBq/kg	We added to the qualifying statement for Recommendation 3 describing the updated Ra-223 dosage.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

References

1. Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, et al.; Scientific Advisory Council of Osteoporosis Canada. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ. 2010 Nov 23;182(17):1864-73.
2. Gralow JR, Biermann JS, Farooki A, Fornier MN, Gagel RF, Kumar RN, et al. NCCN Task Force Report: Bone Health in Cancer Care. J Natl Compr Canc Netw. 2009 Jun;7 Suppl 3:S1-32; quiz S33-5.
3. Smith MR, Egerdie B, Hernandez Toriz N, Feldman R, Tammela TL, Saad F, et al; Denosumab HALT Prostate Cancer Study Group. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med. 2009 Aug 20;361(8):745-55.
4. Greenspan SL, Nelson JB, Trump DL, Resnick NM. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. Ann Intern Med. 2007 Mar 20;146(6):416-24.
5. Klotz LH, McNeill IY, Kebabdjian M, Zhang L, Chin JL; Canadian Urology Research Consortium. A phase 3, double-blind, randomised, parallel-group, placebo-controlled study of oral weekly alendronate for the prevention of androgen deprivation bone loss in nonmetastatic prostate cancer: the Cancer and Osteoporosis Research with Alendronate and Leuprolide (CORAL) study. Eur Urol. 2013 May;63(5):927-35.
6. Ryan CW, Huo D, Demers LM, Beer TM, Lacerna LV. Zoledronic acid initiated during the first year of androgen deprivation therapy increases bone mineral density in patients with prostate cancer. J Urol. 2006 Sep;176(3):972-8.
7. Israeli RS, Rosenberg SJ, Saltzstein DR, Gottesman JE, Goldstein HR, Hull GW, et al. The effect of zoledronic acid on bone mineral density in patients undergoing androgen deprivation therapy. Clin Genitourin Cancer. 2007 Mar;5(4):271-7.
8. Bhoopalam N, Campbell SC, Moritz T, Broderick WR, Iyer P, Arcenas AG, et al. Intravenous zoledronic acid to prevent osteoporosis in a veteran population with multiple risk factors for bone loss on androgen deprivation therapy. J Urol. 2009 Nov;182(5):2257-64.
9. Kapoor A, Gupta A, Desai N, Ahn H. Effect of zoledronic acid on bone mineral density in men with prostate cancer receiving gonadotropin-releasing hormone analog. Prostate Cancer. 2011;2011:176164.
10. Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyian S, Zinner N. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol. 2003 Jun;169(6):2008-12.
11. Rao MP, Kumar A, Goyal NK, Trivedi S, Dwivedi US, Singh PB. Prevention of bone mineral loss by zoledronic acid in men with prostate carcinoma receiving androgen deprivation therapy: a prospective randomized trial in an Indian population. Curr Oncol. 2008;2:79-86.
12. Casey R, Gesztesi Z, Rochford J. Long term zoledronic acid during androgen blockade for prostate cancer. Can J Urol. 2010 Jun;17(3):5170-7.
13. Kachnic LA, Pugh SL, Tai P, Smith M, Gore E, Shah AB, et al. RTOG 0518: randomized phase III trial to evaluate zoledronic acid for prevention of osteoporosis and associated fractures in prostate cancer patients. Prostate Cancer Prostatic Dis. 2013 Dec;16(4):382-6.
14. Michaelson MD, Kaufman DS, Lee H, McGovern FJ, Kantoff PW, Fallon MA, et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing

hormone agonist-induced bone loss in men with prostate cancer. J Clin Oncol. 2007 Mar 20;25(9):1038-42.
15. Winters-Stone KM, Dobek JC, Bennett JA, Maddalozzo GF, Ryan CW, Beer TM. Skeletal response to resistance and impact training in prostate cancer survivors. Med Sci Sports Exerc. 2014 Aug;46(8):1482-8.
16. Nilsen TS, Raastad T, Skovlund E, Courneya KS, Langberg CW, Lilleby W, et al. Effects of strength training on body composition, physical functioning, and quality of life in prostate cancer patients during androgen deprivation therapy. Acta Oncol. 2015 Nov;54(10):1805-13.
17. Cormie P, Galvao DA, Spry N, Joseph D, Chee R, Taaffe DR, et al. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. BJU Int. 2015 Feb;115(2):256-66.
18. Santa Mina D, Ritvo P, Matthew AG, Rampersad A, Stein H, Cheung AM, et al. Group exercise versus personal training for prostate cancer patients: a pilot randomized trial. J Cancer Ther. 2012 Apr;3:146-56.
19. Himelstein AL, Qin R, Novotny PJ, Seisler DK, Khatcheressian JL, Roberts JD, et al. CALGB 70604 (Alliance): A randomized phase III study of standard dosing vs. longer interval dosing of zoledronic acid in metastatic cancer. J Clin Oncol. 2015;33 (suppl; abstr 9501).
20. Zimmerman BE, Bergeron DE, Cessna JT, Fitzgerald R, Pibida L. Revision of the NIST Standard for (223)Ra: New Measurements and Review of 2008 Data. J Res Natl Inst Stand Technol. 2015 Mar 11;120:37-57.
21. Lutz S, Berk L, Chang E, Chow E, Hahn C, Hoskin P, Howell D, Konski A, Kachnic L, Lo S, Sahgal A, Silverman L, von Gunten C, Mendel E, Vassil A, Bruner DW, Hartsell W; American Society for Radiation Oncology (ASTRO). Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys. 2011 Mar 15;79(4):965-76.
22. Saad F, Chi KN, Finelli A, Hotte SJ, Izawa J, Kapoor A, Kassouf W, Loblaw A, North S, Rendon R, So A, Usmani N, Vigneault E, Fleshner NE. The 2015 CUA-CUOG Guidelines for the management of castration-resistant prostate cancer (CRPC). Can Urol Assoc J. 2015 Mar-Apr;9(3-4):90-6.
23. Ding H, Yang L, Du W, Teng Y, Fu SJ, Tao Y, et al. Bisphosphonates for osteoporosis in nonmetastatic prostate cancer patients receiving androgen-deprivation therapy: a systematic review and meta-analysis. Asian Pac J Cancer Prev. 2013;14(5):3337-43.
24. Wells G, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD004523.
25. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD003376.
26. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD001155.
27. Chen L, Wang G, Zheng F, Zhao H, Li H. Efficacy of bisphosphonates against osteoporosis in adult men: a meta-analysis of randomized controlled trials. Osteoporos Int. 2015 Sep;26(9):2355-63.
28. Rodrigues P, Hering FO, Bruna P, Meller A, Afonso Y. Comparative study of the protective effect of different intravenous bisphosphonates on the decrease in bone mineral density in patients submitted to radical prostatectomy undergoing androgen

deprivation therapy. A prospective open-label controlled study. Int J Urol. 2007 Apr;14(4):317-20.
29. Kearns AE, Northfelt DW, Dueck AC, Atherton PJ, Dakhil SR, Rowland KM Jr, et al. Osteoporosis prevention in prostate cancer patients receiving androgen ablation therapy: placebo-controlled double-blind study of estradiol and risedronate: N01C8. Support Care Cancer. 2010 Mar;18(3):321-8.
30. Greenspan SL, Nelson JB, Trump DL, Wagner JM, Miller ME, Perera S, et al. Skeletal health after continuation, withdrawal, or delay of alendronate in men with prostate cancer undergoing androgen-deprivation therapy. J Clin Oncol. 2008 Sep 20;26(27):4426-34.
31. Diamond TH, Winters J, Smith A, De Souza P, Kersley JH, Lynch WJ, et al. The antiosteoporotic efficacy of intravenous pamidronate in men with prostate carcinoma receiving combined androgen blockade: a double blind, randomized, placebo-controlled crossover study. Cancer. 2001 Sep 15;92(6):1444-50.
32. 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 Aug 1;115(15):3468-74.
33. Wang F, Chen W, Chen H, Mo L, Jin H, Yu Z, et al. Comparison between zoledronic acid and clodronate in the treatment of prostate cancer patients with bone metastases. Med Oncol. 2013;30(3):657.
34. Wirth M, Tammela T, Cicalese V, Gomez Veiga F, Delaere K, Miller K, et al. Prevention of Bone Metastases in Patients with High-risk Nonmetastatic Prostate Cancer Treated with Zoledronic Acid: Efficacy and Safety Results of the Zometa European Study (ZEUS). Eur Urol. 2014 Feb 20.
35. Mason MD, Sydes MR, Glaholm J, Langley RE, Huddart RA, Sokal M, et al.; Medical Research Council PR04 Collaborators. Oral sodium clodronate for nonmetastatic prostate cancer--results of a randomized double-blind placebo-controlled trial: Medical Research Council PR04 (ISRCTN61384873). J Natl Cancer Inst. 2007 May 16;99(10):765-76.
36. Smith MR, Saad F, Coleman R, Shore N, Fizazi K, Tombal B, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet. 2012 Jan 7;379(9810):39-46.
37. 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 Mar 5;377(9768):813-22.
38. Ford JA, Jones R, Elders A, Mulatero C, Royle P, Sharma P, et al. Denosumab for treatment of bone metastases secondary to solid tumours: systematic review and network meta-analysis. Eur J Cancer. 2013 Jan;49(2):416-30.
39. Ueno S, Mizokami A, Fukagai T, Fujimoto N, Oh-Oka H, Kondo Y, et al. Efficacy of combined androgen blockade with zoledronic acid treatment in prostate cancer with bone metastasis: the ZABTON-PC (zoledronic acid/androgen blockade trial on prostate cancer) study. Anticancer Res. 2013 Sep;33(9):3837-44.
40. Smith MR, Halabi S, Ryan CJ, Hussain A, Vogelzang N, Stadler W, et al. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). J Clin Oncol. 2014 Apr 10;32(11):1143-50.
41. Dearnaley DP, Sydes MR, Mason MD, Stott M, Powell CS, Robinson AC, et al.; Mrc Pr05 Collaborators. A double-blind, placebo-controlled, randomized trial of oral sodium

clodronate for metastatic prostate cancer (MRC PR05 Trial). J Natl Cancer Inst. 2003 Sep 3;95(17):1300-11.
42. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al.; Zoledronic Acid Prostate Cancer Study Group. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002 Oct 2;94(19):1458-68.
43. 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 Dec 1;21(23):4277-84.
44. Yuen KK, Shelley M, Sze WM, Wilt T, Mason MD. Bisphosphonates for advanced prostate cancer. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD006250.
45. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al.; Zoledronic Acid Prostate Cancer Study Group. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst. 2004 Jun 2;96(11):879-82.
46. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013 Jul 18;369(3):213-23.
47. Sartor O, Coleman R, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. Lancet Oncol. 2014 Jun;15(7):738-46.
48. Nilsson S, Franzen L, Parker C, Tyrrell C, Blom R, Tennvall J, et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. Lancet Oncol. 2007 Jul;8(7):587-94.
49. Roque I Figuls M, Martinez-Zapata MJ, Scott-Brown M, Alonso-Coello P. Radioisotopes for metastatic bone pain. Cochrane Database Syst Rev. 2011 Jul 6;(7):CD003347.
50. 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. Radiother Oncol. 1994 Apr;31(1):33-40.
51. Oosterhof GO, Roberts JT, de Reijke TM, Engelholm SA, Horenblas S, von der Maase H, 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. Eur Urol. 2003 Nov;44(5):519-26.
52. 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. J Pain Symptom Manage. 2005 Apr;29(4):352-7.
53. Pan Y, Jin H, Chen W, Yu Z, Ye T, Zheng Y, et al. Docetaxel with or without zoledronic acid for castration-resistant prostate cancer. Int Urol Nephrol. 2014 Dec;46(12):2319-26.
54. Nilsson S, Franzen L, Parker C, Tyrrell C, Blom R, Tennvall J, et al. Two-year survival follow-up of the randomized, double-blind, placebo-controlled phase II study of radium-223 chloride in patients with castration-resistant prostate cancer and bone metastases. Clin Genitourin Cancer. 2013 Mar;11(1):20-6.
55. Dearnaley DP, Mason MD, Parmar MK, Sanders K, Sydes MR. 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. Lancet Oncol. 2009 Sep;10(9):872-6.

56. 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. Eur J Cancer. 1993;29A(6):821-5.
57. 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 Sep 1;21(17):3335-42.
58. Figg WD, Liu Y, Arlen P, Gulley J, Steinberg SM, Liewehr DJ, et al. A randomized, phase II trial of ketoconazole plus alendronate versus ketoconazole alone in patients with androgen independent prostate cancer and bone metastases. J Urol. 2005 Mar;173(3):790-6.
59. Meulenbeld HJ, van Werkhoven ED, Coenen JL, Creemers GJ, Loosveld OJ, de Jong PC, et al. Randomised phase II/III study of docetaxel with or without risedronate in patients with metastatic Castration Resistant Prostate Cancer (CRPC), the Netherlands Prostate Study (NePro). Eur J Cancer. 2012 Nov;48(16):2993-3000.
60. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al.; STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016 Mar 19;387(10024):1163-77.
61. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.
62. Browman GP NT, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.
63. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010;182(18):E839-42.
64. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2015. Toronto, ON: Canadian Cancer Society; 2015.
65. Datta M, Schwartz GG. Calcium and vitamin D supplementation during androgen deprivation therapy for prostate cancer: a critical review. Oncologist. 2012;17(9):1171-9.
66. Greenspan SL, Coates P, Sereika SM, Nelson JB, Trump DL, Resnick NM. Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. J Clin Endocrinol Metab. 2005 Dec;90(12):6410-7.
67. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med. 2005 Jan 13;352(2):154-64.
68. Alibhai SM, Duong-Hua M, Sutradhar R, Fleshner NE, Warde P, Cheung AM, et al. Impact of androgen deprivation therapy on cardiovascular disease and diabetes. J Clin Oncol. 2009 Jul 20;27(21):3452-8.
69. Smith MR, Lee WC, Brandman J, Wang Q, Botteman M, Pashos CL. Gonadotropin-releasing hormone agonists and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer. J Clin Oncol. 2005 Nov 1;23(31):7897-903.
70. Panju AH, Breunis H, Cheung AM, Leach M, Fleshner N, Warde P, et al. Management of decreased bone mineral density in men starting androgen-deprivation therapy for prostate cancer. BJU Int. 2009 Mar;103(6):753-7.

71. Morote J, Morin JP, Orsola A, Abascal JM, Salvador C, Trilla E, et al. Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer. Urology. 2007 Mar;69(3):500-4.
72. Wadhwa VK, Weston R, Mistry R, Parr NJ. Long-term changes in bone mineral density and predicted fracture risk in patients receiving androgen-deprivation therapy for prostate cancer, with stratification of treatment based on presenting values. BJU Int. 2009 Sep;104(6):800-5.
73. Tanvetyanon T. Physician practices of bone density testing and drug prescribing to prevent or treat osteoporosis during androgen deprivation therapy. Cancer. 2005 Jan 15;103(2):237-41.
74. Alibhai SM, Yun L, Cheung AM, Paszat L. Screening for osteoporosis in men receiving androgen deprivation therapy. JAMA. 2012 Jan 18;307(3):255-6.
75. Al-Shamsi HO, Lau AN, Malik K, Alamri A, Ioannidis G, Corbett T, et al. The current practice of screening, prevention, and treatment of androgen-deprivation-therapy induced osteoporosis in patients with prostate cancer. J Oncol. 2012;2012:958596.
76. Bubendorf L, Schöpfer A, Wagner U, Sauter G, Moch H, Willi N, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. Hum Pathol. 2000 May;31(5):578-83.
77. Vignani F, Bertaglia V, Buttigliero C, Tucci M, Scagliotti GV, Di Maio M. Skeletal metastases and impact of anticancer and bone-targeted agents in patients with castration-resistant prostate cancer. Cancer Treat Rev. 2016 Mar;44:61-73.
78. Fahey F, Zukotynski K, Capala J, Knight N; Organizing Committee, Contributors, and Participants of NCI/SNMMI Joint Workshop on Targeted Radionuclide Therapy. Targeted radionuclide therapy: proceedings of a joint workshop hosted by the National Cancer Institute and the Society of Nuclear Medicine and Molecular Imaging. J Nucl Med. 2014 Feb;55(2):337-48.
79. Fahey F, Zukotynski K, Jadvar H, Capala J; organizing committee, contributors, and participants of the second NCI–SNMMI Workshop on Targeted Radionuclide Therapy. Proceedings of the Second NCI-SNMMI Workshop on Targeted Radionuclide Therapy. J Nucl Med. 2015 Jul;56(7):1119-29.
80. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007 Feb 15;7:10.
81. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
82. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints.[erratum appears in Stat Med. 2004 Jun 15;23(11):1817]. Stat Med. 1998;17(24):2815-34.
83. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011 Apr;64(4):383-94.
84. Brundage MD, Crook JM, Lukka H. Use of strontium-89 in endocrine-refractory prostate cancer metastatic to bone. Provincial Genitourinary Cancer Disease Site Group. Cancer Prev Control. 1998 Apr;2(2):79-87.
85. Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. Cochrane Database Syst Rev. 2002;(2):CD002068.
86. Bauman G, Charette M, Reid R, Sathya J. Radiopharmaceuticals for the palliation of painful bone metastasis-a systemic review. Radiother Oncol. 2005 Jun;75(3):258-70.

87. 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. Can J Urol. 2006 Aug;13(4):3180-8.
88. Israeli RS, Ryan CW, Jung LL. Managing bone loss in men with locally advanced prostate cancer receiving androgen deprivation therapy. J Urol. 2008 Feb;179(2):414-23.
89. Serpa Neto A, Tobias-Machado M, Esteves MA, Senra MD, Wroclawski ML, Fonseca FL, et al. Bisphosphonate therapy in patients under androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2012 Mar;15(1):36-44.
90. Palmieri C, Fullarton JR, Brown J. Comparative efficacy of bisphosphonates in metastatic breast and prostate cancer and multiple myeloma: a mixed-treatment meta-analysis. Clin Cancer Res. 2013 Dec 15;19(24):6863-72.
91. Qi WX, Tang LN, He AN, Yao Y, Shen Z. Risk of osteonecrosis of the jaw in cancer patients receiving denosumab: a meta-analysis of seven randomized controlled trials. Int J Clin Oncol. 2014 Apr;19(2):403-10.
92. Tunio M, Al Asiri M, Al Hadab A, Bayoumi Y. Comparative efficacy, tolerability, and survival outcomes of various radiopharmaceuticals in castration-resistant prostate cancer with bone metastasis: a meta-analysis of randomized controlled trials. Drug Des Devel Ther. 2015 Sep 21;9:5291-9.
93. Liu J, Huang W, Zhou R, Jia S, Tang W, Luo Y, et al. Bisphosphonates in the treatment of patients with metastatic breast, lung, and prostate cancer: a meta-analysis. Medicine (Baltimore). 2015 Nov;94(46):e2014.
94. Parker CC, Pascoe S, Chodacki A, O'Sullivan JM, Germa JR, O'Bryan-Tear CG, et al. A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium chloride (Ra 223) in patients with bone metastases and castration-resistant prostate cancer. Eur Urol. 2013 Feb;63(2):189-97.
95. Tu SM, Millikan RE, Mengistu B, Delpassand ES, Amato RJ, Pagliaro LC, et al. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomized phase II trial. Lancet. 2001 Feb 3;357(9253):336-41.
96. Taxel P, Dowsett R, Richter L, Fall P, Klepinger A, Albertsen P. Risedronate prevents early bone loss and increased bone turnover in the first 6 months of luteinizing hormone-releasing hormone-agonist therapy for prostate cancer. BJU Int. 2010 Nov;106(10):1473-6.
97. 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 Jan;141(1):85-7.
98. Adami S, Mian M. Clodronate therapy of metastatic bone disease in patients with prostatic carcinoma. Recent Results Cancer Res. 1989;116:67-72.
99. 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 Res. 1997 Nov-Dec;17(6D):4717-21.
100. 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 Aug;182(2):509-15.
101. 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. Eur J Nucl Med. 1988;14(7-8):349-51.
102. 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. Eur J Cancer. 1991;27(8):954-8.
103. Han SH, de Klerk JM, Tan S, van het Schip AD, Derksen BH, van Dijk A, et al. The PLACORHEN study: a double-blind, placebo-controlled, randomized radionuclide study with (186)Re-etidronate in hormone-resistant prostate cancer patients with painful bone metastases. Placebo Controlled Rhenium Study. J Nucl Med. 2002 Sep;43(9):1150-6.
104. Sartor O, Reid RH, Hoskin PJ, Quick DP, Ell PJ, Coleman RE, et al; Quadramet 424Sm10/11 Study Group. Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. Urology. 2004 May;63(5):940-5.
105. 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. Eur J Nucl Med. 1999 Jan;26(1):2-7.
106. Choo R, Lukka H, Cheung P, Corbett T, Briones-Urbina R, Vieth R, et al. Randomized, double-blinded, placebo-controlled, trial of risedronate for the prevention of bone mineral density loss in nonmetastatic prostate cancer patients receiving radiation therapy plus androgen deprivation therapy. Int J Radiat Oncol Biol Phys. 2013 Apr 1;85(5):1239-45.
107. 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 Int. 2007 Jul;100(1):70-5.
108. Morabito N, Gaudio A, Lasco A, Catalano A, Atteritano M, Trifiletti A, et al. Neridronate prevents bone loss in patients receiving androgen deprivation therapy for prostate cancer. J Bone Miner Res. 2004 Nov;19(11):1766-70.
109. Smith MR, Fallon MA, Lee H, Finkelstein JS. Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. J Clin Endocrinol Metab. 2004 Aug;89(8):3841-6.
110. Smith MR, Morton RA, Barnette KG, Sieber PR, Malkowicz SB, Rodriguez D, et al. Toremifene to reduce fracture risk in men receiving androgen deprivation therapy for prostate cancer. J Urol. 2010 Oct;184(4):1316-21.
111. Smith MR, McGovern FJ, Zietman AL, Fallon MA, Hayden DL, Schoenfeld DA, e al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. N Engl J Med. 2001 Sep 27;345(13):948-55.
112. Denham JW, Nowitz M, Joseph D, Duchesne G, Spry NA, Lamb DS, et al. Impact of androgen suppression and zoledronic acid on bone mineral density and fractures in the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomised Androgen Deprivation and Radiotherapy (RADAR) randomized controlled trial for locally advanced prostate cancer. BJU Int. 2014 Sep;114(3):344-53.
113. Lang JM, Wallace M, Becker JT, Eickhoff JC, Buehring B, Binkley N, et al. A randomized phase II trial evaluating different schedules of zoledronic acid on bone mineral density in patients with prostate cancer beginning androgen deprivation therapy. Clin Genitourin Cancer. 2013 Dec;11(4):407-15.
114. 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. Ann Oncol. 1994;5 Suppl 7:S31-5.
115. 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. Int Urol Nephrol. 1992;24(2):159-66.

116. 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(7):939-42.
117. Hoskin P, Sundar S, Reczko K, Forsyth S, Mithal N, Sizer B, et al. A Multicenter Randomized Trial of Ibandronate Compared With Single-Dose Radiotherapy for Localized Metastatic Bone Pain in Prostate Cancer. J Natl Cancer Inst. 2015 Aug 4;107(10).
118. 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. Int J Radiat Oncol Biol Phys. 1993 Apr 2;25(5):805-13.
119. Baczyk M, Czepczyński R, Milecki P, Pisarek M, Oleksa R, Sowinski J. 89Sr versus 153Sm-EDTMP: comparison of treatment efficacy of painful bone metastases in prostate and breast carcinoma. Nucl Med Commun. 2007 Apr;28(4):245-50.
120. Palmedo H, Manka-Waluch A, Albers P, Schmidt-Wolf IG, Reinhardt M, Ezziddin S, et al. Repeated bone-targeted therapy for hormone-refractory prostate carcinoma: tandomized phase II trial with the new, high-energy radiopharmaceutical rhenium-188 hydroxyethylidenediphosphonate. J Clin Oncol. 2003 Aug 1;21(15):2869-75.
121. Resche I, Chatal JF, Pecking A, Ell P, Duchesne G, Rubens R, et al. A dose-controlled study of 153Sm-ethylenediaminetetramethylenephosphonate (EDTMP) in the treatment of patients with painful bone metastases. Eur J Cancer. 1997 Sep;33(10):1583-91.
122. Nilsson S, Strang P, Aksnes AK, Franzen L, Olivier P, Pecking A, et al. A randomized, dose-response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. Eur J Cancer. 2012 Mar;48(5):678-86.
123. Lara PN Jr, Stadler WM, Longmate J, Quinn DI, Wexler J, Van Loan M, et al. A randomized phase II trial of the matrix metalloproteinase inhibitor BMS-275291 in hormone-refractory prostate cancer patients with bone metastases. Clin Cancer Res. 2006 Mar 1;12(5):1556-63.
124. Bilen MA, Johnson MM, Mathew P, Pagliaro LC, Araujo JC, Aparicio A, et al. Randomized phase 2 study of bone-targeted therapy containing strontium-89 in advanced castrate-sensitive prostate cancer. Cancer. 2015 Jan 1;121(1):69-76.
125. Maxon HR 3rd, Schroder LE, Hertzberg VS, Thomas SR, Englaro EE, Samaratunga R, et al. Rhenium-186(Sn)HEDP for treatment of painful osseous metastases: results of a double-blind crossover comparison with placebo. J Nucl Med. 1991 Oct;32(10):1877-81.
126. 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. Int J Radiat Oncol Biol Phys. 2003 Aug 1;56(5):1397-404.
127. Nair N. Relative efficacy of 32P and 89Sr in palliation in skeletal metastases. J Nucl Med. 1999 Feb;40(2):256-61.
128. 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 Apr;16(4):1574-81.
129. Denham JW, Wilcox C, Joseph D, Spry NA, Lamb DS, Tai KH, et al. Quality of life in men with locally advanced prostate cancer treated with leuprorelin and radiotherapy with or without zoledronic acid (TROG 03.04 RADAR): secondary endpoints from a randomised phase 3 factorial trial. Lancet Oncol. 2012 Dec;13(12):1260-70.
130. Denham JW, Joseph D, Lamb DS, Spry NA, Duchesne G, Matthews J, et al. Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced

prostate cancer (TROG 03.04 RADAR): an open-label, randomised, phase 3 factorial trial. Lancet Oncol. 2014 Sep;15(10):1076-89.

Appendix 1. Affiliations and conflict of interest declarations.

Name	Affiliation	Declarations of interest
Working Group		
Shabbir Alibhai Geriatrician	Clinical Lead University of Toronto, Department of Medicine, Division of Geriatric Medicine; Toronto General Hospital, Toronto, Ontario	None declared
Katherine Zukotynski Nuclear Medicine Physician and Radiologist	Clinical Lead McMaster University, Departments of Medicine and Radiology, Hamilton, Ontario	None declared
Urban Emmenegger* Medical Oncologist	University of Toronto, Department of Medicine, Division of Medical Oncology; Odette Cancer Centre, Toronto, Ontario	$5,000 or more in a single year to act in a consulting capacity (Amgen Canada)
Anthony Finelli* Urologist	University of Toronto, Department of Surgery, Division of Urology; Princess Margaret Hospital, Toronto, Ontario	$5,000 or more in a single year to act in a consulting capacity (advisory boards)
Scott Morgan* Radiation Oncologist	University of Ottawa, Department of Radiology, Division of Radiation Oncology; The Ottawa Hospital Cancer Centre, Ottawa, Ontario	$5,000 or more in a single year to act in a consulting capacity (Bayer Canada)
Sebastien Hotte* Co-Chair, Genitourinary Disease Site Group Medical Oncologist	McMaster University, Department of Oncology, Division of Medical Oncology; Juravinski Cancer Centre, Hamilton, Ontario	None declared
Eric Winquist* Medical Oncologist	Western University, Department of Oncology, Division of Medical Oncology; London Health Sciences Centre, London, Ontario	None declared
Cindy Walker-Dilks* Health Research Methodologist	McMaster University, Department of Oncology, Program in Evidence-Based Care, Hamilton, Ontario	None declared
Genitourinary Cancer Disease Site Group		
Andrew Loblaw Co-Chair, Genitourinary Disease Site Group Radiation Oncologist	Sunnybrook Health Sciences Centre, Toronto, Ontario	$5,000 or more in a single year to act in a consulting capacity (Amgen, AstraZeneca, Elekta, GE, Janssen, Paladin, Sanofi, Astellas, Atlas)

		$5,000 or more in a single year as other financial or material support from Janssen and Astellas Grant support from Sanofi and Paladin Principal investigator for several radiation trials Published comment relevant to the objects of study in Lancet Oncology 2014 Provided advice or guidance in multiple news agencies about prostate cancer treatment and side effects
Jack Barkin Urologist	Humber River Regional Hospital, Toronto, Ontario	Principal investigator for a clinical trial for Ferring (luteinizing hormone-releasing hormone antagonist for prostate cancer) and Amgen (Xgeva for bone metastases)
Glenn Bauman Radiation Oncologist	London Health Sciences Centre, London, Ontario	None declared
Rodney Breau Urologist	The Ottawa Hospital/University of Ottawa, Ottawa, Ontario	None declared
Michael Brundage Radiation Oncologist	Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, Ontario	None declared
Christina Canil Medical Oncologist	The Ottawa Hospital/University of Ottawa, Ottawa, Ontario	$5,000 or more in a single year in financial support from Novartis and Sanofi Oncology (combined)as a travel grant
Charles Catton Radiation Oncologist	Princess Margaret Hospital, Toronto, Ontario	None declared
Joseph Chin Urologist	London Health Sciences Centre, London, Ontario	None declared
Andrew Feifer Urologist	Credit Valley Hospital, Mississauga, Ontario	$5,000 or more in a single year to act in a consulting capacity (Astellas Janssen)
Neil Fleshner Urologist	Princess Margaret Hospital, Toronto, Ontario	Principal investigator for a clinical trial: Canadian

		Urology Research Consortium: oral risedronate, 35 mg once per week for the prevention of ADT bone loss in nonmetastatic prostate cancer $5,000 or more in a single year for managerial responsibility for an organization or department from Amgen and Bayer (grants to Canadian Urologic Oncology Group)
Michael Lock Radiation Oncologist	London Regional Cancer Program, Schulich School of Medicine and Dentistry, Western University, London, Ontario	None declared
Aamer Mahmud Radiation Oncologist	Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, Ontario	None declared
Bobby Shayegan Urologist	St. Joseph's Hospital, McMaster University, Hamilton, Ontario	None declared
Tom Short Urologist	Credit Valley Hospital, Mississauga, Ontario	None declared
John Srigley Pathologist	Credit Valley Hospital, Mississauga, Ontario	None declared
Padraig Warde Radiation Oncologist	Princess Margaret Hospital, Toronto, Ontario	None declared
Report Approval Panel		
Melissa Brouwers Director	Program in Evidence-Based Care, McMaster University, Hamilton, Ontario	None declared
Craig Earle	Sunnybrook Health Sciences Centre, Toronto, Ontario	None declared
Shail Verma	The Ottawa Hospital Cancer Centre, Ottawa, Ontario	None declared
Targeted Peer Reviewers		
Fred Saad	Department of Surgery, Chair in Prostate Cancer Research, Université de Montréal Urology	$5,000 or more in a single year to act in a consulting capacity (Amgen) Received grant/research support as a principal or co-investigator (Amgen)

Guila Delouya	Centre Hospitalier, Université de Montréal Radiation Oncology	Received grant/research support as a principal or co-investigator from AbbVie Participated in the CARE Guidance – Treatment Considerations for mCRPC 2015 Consultant honoraria and member of advisory boards regarding Ra-223 and denosumab
Celestia Higano	Department of Medicine and Urology, University of Washington, Fred Hutchinson Cancer Research Center Medical Oncology	$5,000 or more in a single year to act in a consulting capacity (Algeta/Bayer, Bayer, Amgen) Received grant/research support as a principal or co-investigator (Bayer) Been a principal investigator for a clinical trial involving an object of study (Bayer study 16913 Ra-223) Published an abstract regarding an object of study (Radium-223 Alpha Emitter Agent in Non-intervention Safety Study in mCRPC popUlation for Long-teRm Evaluation REASSURE) Had managerial responsibility for an organization or department that has received $5,000 or more in a single year from a relevant business entity (Clinical trials: Bayer 15-396 phase III; Bayer 16-544 phase IIa; Algeta/Bayer BC1-10)

*Members of the Genitourinary Cancer Disease Site Group

Appendix 2. Literature search strategies.

MEDLINE:
1 meta-analysis.af.
2 exp meta analysis/ or exp systematic review/
3 (meta analy$ or metaanaly$ or meta-analy$).tw.
4 (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
5 (systematic adj (review$ or overview?)).tw.
6 exp review/ or review.pt.
7 (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
8 (study adj selection).ab.
9 6 and (7 or 8)
10 1 or 2 or 3 or 4 or 5 or 9
11 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
12 (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
13 exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
14 randomization/ or single blind procedure/ or double blind procedure/
15 ((randomi: adj control: adj trial?) or rct or phase III or phase II or phase 3 or phase 2).tw.
16 or/11-15
17 (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
18 17 and random$.tw.
19 (clinic$ adj trial$1).tw.
20 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
21 ((random: adj allocat:) or (allocated adj randomly)).tw.
22 placebos/ or placebo:.tw.
23 or/18-22
24 exp practice guideline/
25 (practice guideline or practice parameter).tw.
26 [or/35-46]
27 [or/48-71]
28 [or/74-78]
29 meta-analysis.af.
30 exp meta analysis/ or exp systematic review/
31 (meta analy$ or metaanaly$ or meta-analy$).tw.
32 (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
33 (systematic adj (review$ or overview?)).tw.
34 exp review/ or review.pt.
35 (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
36 (study adj selection).ab.
37 34 and (35 or 36)
38 29 or 30 or 31 or 32 or 33 or 37
39 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
40 (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
41 exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
42 randomization/ or single blind procedure/ or double blind procedure/
43 ((randomi: adj control: adj trial?) or rct or phase III or phase II or phase 3 or phase 2).tw.
44 or/39-43
45 (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
46 45 and random$.tw.
47 (clinic$ adj trial$1).tw.
48 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
49 ((random: adj allocat:) or (allocated adj randomly)).tw.
50 placebos/ or placebo:.tw.
51 or/46-50
52 exp practice guideline/

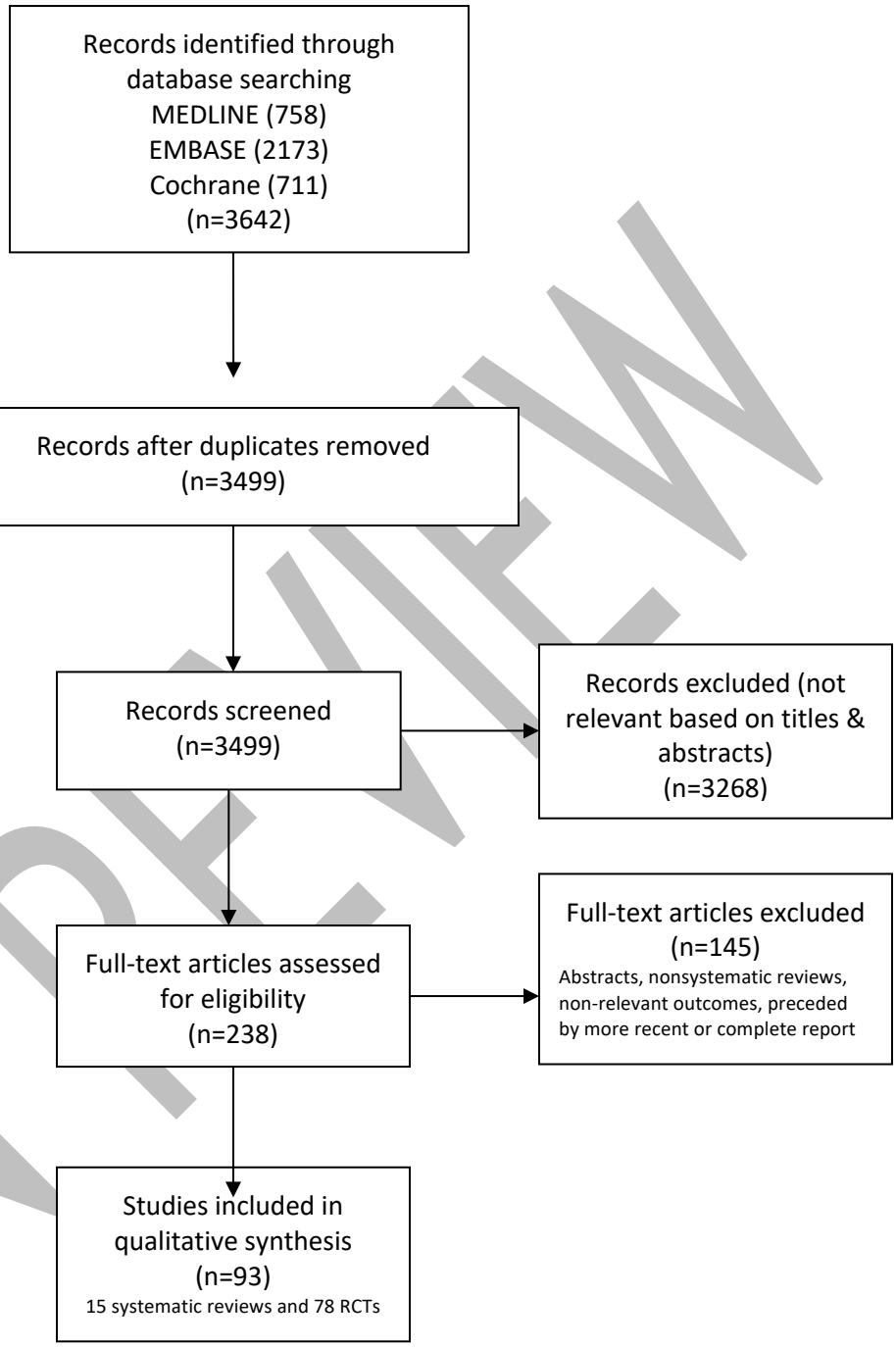
53 (practice guideline or practice parameter).tw.
54 52 or 53
55 38 or 44 or 51 or 54
56 (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
57 55 not 56
58 prostatic neoplasms/
59 prostate:.tw.
60 (cancer or carcinoma or adenocarcinoma or neoplas: or tumo?r:).tw.
61 59 and 60
62 58 or 61
63 exp bone diseases/
64 exp fractures, bone/
65 bone density/
66 BMD.tw.
67 (bone adj loss).tw.
68 (bone adj turnover).tw.
69 spinal cord compression/ or hypercalcemia/
70 (skeletal adj related adj event:).tw.
71 (skeletal adj event:).tw.
72 SRE:.tw.
73 (bone adj metast:).tw.
74 (osteopor: or hypercalcemia).tw.
75 or/63-74
76 bone density conservation agents/
77 exp diphosphonates/
78 (bisphosphonate: or clodron: or pamidron: or ibandron: or risedron: or zoledron: or alendron: or neridron: or opandron:).tw.
79 (bone adj target:).tw.
80 (osteoclast adj target:).tw.
81 denosumab.tw.
82 RANKL.tw.
83 (RANK adj ligand).tw.
84 selective estrogen receptor modulators/
85 SERM.tw.
86 raloxifene/
87 toremifene/
88 (raloxifene or toremifene).tw.
89 exp radioisotopes/
90 radionuclide:.tw.
91 alpharadin:.tw.
92 (radium adj "223").tw.
93 (samarium: or strontium: or rhenium:).tw.
94 exp exercise/
95 exercis:.tw.
96 risk reduction behavior/
97 lifestyle:.tw.
98 (life adj style:).tw.
99 exp dietary supplements/
100 (diet: or nutrition:).tw.
101 (supplement: or agent:).tw.
102 100 and 101
103 calcium/
104 exp vitamin D/
105 (vitamin adj D).tw.
106 (calcium or cholecalciferol).tw.
107 or/76-99
108 or/102-106
109 107 or 108
110 57 and 62 and 75 and 109

EMBASE:

1 exp meta analysis/ or exp systematic review/
2 (meta analy$ or metaanaly$ or meta-analy$).tw.
3 (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
4 (systematic adj (review$ or overview?)).tw.
5 exp review/ or review.pt.
6 (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7 (study adj selection).ab.
8 5 and (6 or 7)
9 1 or 2 or 3 or 4 or 8
10 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11 (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12 exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13 randomization/ or single blind procedure/ or double blind procedure/
14 (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15 or/12-14
16 (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17 16 and random$.tw.
18 (clinic$ adj trial$1).tw.
19 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20 placebo/
21 (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22 (allocated adj2 random).tw.
23 or/18-22
24 exp practice guideline/
25 (practice guideline or practice parameter).tw.
26 9 or 10 or 11 or 15 or 17 or 23 or 24 or 25
27 (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
28 26 not 27
29 exp PROSTATE CARCINOMA/ or exp PROSTATE CANCER/
30 prostate:.tw.
31 (cancer or carcinoma or adenocarcinoma or neoplas: or tumo?r:).tw.
32 30 and 31
33 29 or 32
34 exp bone demineralization/ or exp bone density/ or exp bone disease/ or exp bone erosion/ or exp bone necrosis/ or exp bone metastasis/ or exp bone pain/ or exp bone turnover/
35 exp fracture/
36 exp spinal cord compression/
37 exp osteoporosis/
38 exp hypercalcemia/
39 BMD.tw.
40 (bone adj loss).tw.
41 (bone adj turnover).tw.
42 (skeletal adj related adj event:).tw.
43 (skeletal adj event:).tw.
44 SRE:.tw.
45 (bone adj metast:).tw.
46 (osteopor: or hypercalcemia or fractur:).tw.
47 or/34-46
48 exp bone density conservation agent/
49 exp bisphosphonic acid derivative/
50 (bisphosphon: or diphosphon: or clodron: or pamidron: or ibandron: or risedron: or zoledron: or alendron: or neridron: or olpandron:).tw.
51 (bone adj target:).tw.
52 (osteoclast: adj target:).tw.
53 denosumab/
54 denosumab.tw.
55 RANKL.tw.
56 (RANK adj ligand).tw.
57 selective estrogen receptor modulator/

58 SERM.tw.
59 raloxifene/
60 toremifene/
61 (raloxifene or toremifene).tw.
62 exp radioisotope/
63 (radionuclide: or alpharadin:).tw.
64 radium chloride ra 223/
65 (radium adj "223").tw.
66 (samarium: or strontium: or rhenium:).tw.
67 exp exercise/
68 exercis:.tw.
69 risk reduction/
70 lifestyle modification/
71 (lifestyle: or (life adj style:)).tw.
72 diet supplementation/
73 calcium/
74 (calcium or cholecalciferol).tw.
75 exp vitamin D/
76 (vitamin adj D).tw.
77 (diet: or nutrition:).tw.
78 (supplement: or agent:).tw.
79 77 and 78
80 or/48-76
81 79 or 80
82 28 and 33 and 47 and 81
83 limit 82 to exclude medline journals

Appendix 3. PRISMA Flow Diagram.



Appendix 4. AMSTAR ratings for systematic reviews.

AMSTAR items	Brundage 1998 [84]	Wong 2002 [85]	Bauman 2005 [86]	Berry 2006 [87]	Yuen 2006 [44]	Israeli 2008 [88]	Roque I Figuls 2011 [49]	Serpa Neto 2012 [89]	Datta 2012 [65]	Ford 2013 [38]	Ding 2013 [23]	Palmieri 2013 [90]	Qi 2014 [91]	Tunio 2015 [92]	Liu 2015 [93]
Was an 'a priori' design provided?	No	Yes	No	No	Yes	No	Yes	No	No	Yes	Can't tell	Yes	No	No	No
Was there duplicate study selection & data extraction?	No	Yes	Yes	No	Yes	No	Yes	No	No	Yes	Yes	No	No	No	No
Was a comprehensive literature search performed?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No
Was the status of publication (i.e., grey literature) used as an inclusion criterion?	No	No	Yes	No	No	No	Yes	No	No	Yes	No	No	No	No	No
Was a list of studies (included & excluded) provided?	No	Yes	No	No	Yes	No	Yes	Yes	No	No	No	No	No	No	No
Were the characteristics of the included studies provided?	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Was the scientific quality of the included studies assessed & documented?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No
Were the methods used to combine the findings of studies appropriate?	NA	Yes	NA	NA	Yes	NA	Yes	Yes	NA	Yes	Yes	Yes	No	No	No
Was the likelihood of publication bias assessed?	No	No	No	No	No	No	Yes	Yes	No	No	No	No	Yes	Yes	Yes
Was the conflict of interest stated?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Total AMSTAR points	3	8	5	4	8	0	10	7	1	8	6	5	3	4	1

AMSTAR=Assessment of Multiple Systematic Reviews.
Shaded reviews were not considered in literature results.

Appendix 5. Included systematic reviews.

Study reference	Prostate cancer stage	Objective	Search time period	Study selection	Number of studies	Number of prostate cancer studies	Intervention	Outcomes
Bauman 2005 [86]	Metastatic	To address the role of radiopharmaceuticals in the palliation of metastatic bone pain	Up to 2004	RCTs or meta-analyses that compared radiopharmaceuticals with placebo, another radiopharmaceutical, or another active treatment in patients with bone pain due to metastatic disease	18	15	Strontium-89 (8 trials), samarium-153 (4 trials), rhenium (3 trials)	Pain, analgesic consumption, QOL, adverse effects, overall survival
Berry 2006 [87]	Non-metastatic or metastatic	Should bisphosphonates be used in men with hormone-refractory prostate cancer to: 1. Delay or prevent bone metastases in men without metastases? 2. Reduce skeletal-related events (e.g., bone fracture, spinal cord compression, requirement for radiotherapy or surgery to bone) in men with bone metastases? 3. Reduce pain or analgesic consumption in men with painful bone metastases? 4. Improve survival and quality of life?	Up to 2004	Systematic reviews, clinical practice guidelines, or RCTs that compared treatment with a bisphosphonate to placebo or no treatment (open control) or that compared different bisphosphonates (e.g., different doses, schedules, or routes of administration of the same bisphosphonate), or treatment with a bisphosphonate plus a co-intervention (i.e., hormonal therapy or chemotherapy) to the same treatment without a bisphosphonate.	10		Bisphosphonates (alendronate [1 trial], clodronate [5 trials], etidronate [1 trial], pamidronate [2 trials], ZA [1 trial])	Bone metastases, SREs, bone pain, analgesic consumption, survival, QOL, adverse events
Yuen 2006 [44]	Metastatic	To determine the effectiveness of bisphosphonates in relieving pain in patients with bone metastases from prostate cancer	Up to 2005	RCTs in full peer-reviewed published articles that compared bisphosphonates with placebo, no bisphosphonate treatment, or another bisphosphonate treatment	10 (n=1955)		Bisphosphonates (clodronate [7 trials], pamidronate [1 trial], etidronate [1 trial], ZA [1 trial])	Pain, analgesic consumption, SREs, survival
Roque I Figuls 2011 [49]	Metastatic	To determine the efficacy of radiopharmaceuticals to control pain in patients with metastatic bone lesions	Up to 2010	RCTs that compared radiopharmaceuticals with placebo or alternative radiopharmaceutical, or compared different doses of the same radiopharmaceutical in patients with metastatic bone pain caused by any primary tumour	15	13	Strontium (5 trials), samarium (4 trials), rhenium (3 trials), radium-223 (1 trial)	Pain, analgesic consumption, rescue medication, complications due to bone metastases, disease progression, QOL, side effects

Study reference	Prostate cancer stage	Objective	Search time period	Study selection	Number of studies	Number of prostate cancer studies	Intervention	Outcomes
Serpa Neto 2012 [89]	Non-metastatic or metastatic	To determine the effects of bisphosphonates in the treatment of bone loss in prostate cancer patients undergoing ADT	Up to 2009	RCTs comparing bisphosphonates with placebo in prostate cancer patients receiving ADT	15 (1 trial evaluated 2 bisphosphonates). 11 trials nonmetastatic; 4 trials metastatic		Bisphosphonates (clodronate [2 trials], alendronate [2 trials], neridronate [1 trial], pamidronate [3 trials], ZA [8 trials])	Fracture, osteoporosis, BMD, adverse events
Ford 2013 [38]	Metastatic	To evaluate the effectiveness of denosumab for the treatment of bone metastases in solid tumours. Using network meta-analysis to indirectly compare denosumab with bisphosphonates and best supportive care	Up to 2011	RCTs evaluating denosumab, bisphosphonates, or best supportive care	38 (8 included in network meta-analysis)	16 (2 included in network meta-analysis)	Network meta-analysis: denosumab vs. ZA (1 trial), ZA vs. placebo (1 trial) Not included in network meta-analysis: bisphosphonates (clodronate [7 trials], pamidronate [1 trial], etidronate [1 trial], best supportive care (strontium chloride [4 trials])	SREs, pain, QOL, survival
Ding 2013 [23]	Non-metastatic	To determine the effectiveness and safety of bisphosphonates for osteoporosis in non-metastatic prostate cancer patients receiving androgen-deprivation therapy	Up to 2012	RCTs that compared bisphosphonates with placebo	10 (n=1017)		Bisphosphonates (ZA [7 trials], pamidronate [1 trial], neridronate [1 trial], alendronate [1 trial])	BMD, fracture, adverse events
Palmieri 2013 [90]	Metastatic	To compare the efficacy of ZA, clodronate, pamidronate, and ibandronate in patients with SREs secondary to metastatic breast and prostate cancer and multiple myeloma using a mixed treatment meta-analysis.	1980 to 2012	RCTs comparing a bisphosphonate with placebo or another bisphosphonate in the treatment or prevention of SREs secondary to metastatic breast or prostate cancer or multiple myeloma	17	3	ZA (1 trial) Pamidronate (1 trial) Clodronate (1 trial)	SREs

ADT=androgen deprivation therapy; BMD=bone mineral density; QOL=quality of life; RCT=randomized controlled trial; RT=radiotherapy; SRE=skeletal-related event; ZA=zoledronic acid.

Appendix 6. Included randomized controlled trials.

Study reference	ADT status	Number of patients randomized (number of patients evaluated)	Study comparisons (patients/group)	Dosage schedule	Outcome measures (main outcomes are in bold)
Nonmetastatic					
Kearns 2010 [29]	Currently receiving ADT	71 (40)	Risdedronate + estrogen (19) Risedronate + placebo (17) Estrogen + placebo (18) Placebo + placebo (17)	Oral risdedronate, 30 mg/wk or estrogen, 0.5 mg/day or both or neither All patients: Androgen ablation therapy Calcium, 600 mg/day & vitamin D, 400 IU/day	**BMD @ 12 mo**, BMD @ 6 mo, 5% difference in BMD from baseline, osteoporosis, fracture
Choo 2013 [106]	Starting ADT	104 (79)	Risedronate (52) Placebo (52)	Oral risedronate, 35 mg/wk or placebo All patients: ADT with LHRH analogues & EBRT Calcium, 1000 mg/day & vitamin D 800 IU/day	**BMD @ 12 & 24 mo**
Taxel 2010 [96]	Starting ADT	47 (40)	Risedronate (20) Placebo (20)	Oral risedronate, 35 mg/wk or placebo All patients: LHRH-agonist therapy Calcium, 600 mg/day & vitamin D, 400 IU/day 1 to 2 wk before baseline visit	**BMD @ 6 mo**
Greenspan 2007 [4]	Currently receiving ADT	112 (112)	Alendronate (56) Placebo (56)	Alendronate, 70 mg/wk or placebo All patients: calcium, 1000 mg/day & vitamin D, 400 U/day	**Posterior-anterior spine BMD @ 12 mo**, lateral spine, TH, FN, 1/3 distal radius, & ultra distal radius BMD @ 12 mo, fracture
Greenspan 2008 [30]	Currently receiving ADT	112 (96)	Alendronate-alendronate (25) Alendronate-placebo (26) Placebo-alendronate (52)	Original alendronate group: Continue on alendronate, 70 mg/wk or placebo Original placebo group: Cross-over to alendronate All patients: calcium, 1000 mg/day & vitamin D, 400 IU/day	**Posterior-anterior spine BMD @ 24 mo**, lateral spine, TH, FN, 1/3 distal radius, & ultra distal radius BMD @ 24 mo, osteoporosis
Morabito 2004 [108]	Currently receiving ADT	48 (48)	Neridronate (24) No neridronate (24)	Neridronate, 25 mg IM every mo or no injection All patients: 3-mo depot triptoreline before randomization Calcium, 500 mg/day & vitamin D, 400 IU/day Bicalutamide, 50 mg/day for 4 wk	**BMD @ 12 mo**
Ryan 2006 [6]	Currently receiving or starting ADT	122 (101)	ZA (61) Placebo (61)	ZA, 4 mg IV infusion every 3 mo for 1 yr or placebo All patients: LHRH agonist or orchiectomy planned or already initiated within the past 12 mo Calcium, 500 mg & vitamin D, 400 to 500 IU/day	**LS & FN BMD @ 6 & 12 mo**, fracture
Ryan 2007 [107]	Currently receiving or starting ADT	42	ZA (22) Placebo (20)	ZA, 4 mg IV infusion every 3 mo for 1 yr or placebo All patients: Planned or current LHRH agonist or orchiectomy for ≤1 yr Calcium supplementation	**LS & FN BMD @ 12 mo**

Israeli 2007 [7]	Currently receiving ADT	222 (215)	ZA (112) Placebo (110)	ZA, 4 mg IV infusion every 3 mo or placebo All patients: LHRH agonist therapy Calcium, 500 mg/day & vitamin D, 400-500 IU/day	**LS BMD @ 12 mo**, total hip BMD, osteoporosis, fracture
Michaelson 2007 [14]	Currently receiving ADT	44 (36)	ZA (22) Placebo (22)	ZA, 4 mg IV infusion on day 1 or placebo All patients: Current GnRH agonist & continued treatment throughout study Calcium, 500 mg/day & vitamin D, 400 U/day	**Posteroanterior LS BMD @ 12 mo**, proximal femur & FN BMD
Bhoopalam 2009 [8]	Currently receiving ADT	93 (84)	ZA (48) Placebo (45)	ZA, 4 mg IV infusion every 3 mo or placebo All patients: Initiating or current LHRH agonist or orchiectomy (stratified by <1 or ≥1 yr ADT)	**Lumbar spine BMD @ 12 mo**, TH & FN BMD
Kapoor 2011 [9]	Currently receiving ADT	41 (31)	ZA (21) Placebo (20)	ZA, 4 mg IV infusion every 3 mo or placebo All patients: GnRH-analogue therapy Calcium, 1000 mg/day & vitamin D, 500 IU/day	**BMD @ 12 mo**
Kachnic 2013 [13]	Currently receiving ADT	109 (96)	ZA (57) No ZA (52)	ZA, 4 mg IV infusion every 6 mo for 36 mo or no ZA All patients: LHRH agonist; RT; calcium, 500 mg/day; vitamin D, 400 IU/day	**Freedom from any bone fracture**, QOL, BMD @ 36 mo
Smith 2009 [3]	Currently receiving ADT	1468 (1468)	Denosumab (734) Placebo (734)	Denosumab, 60 mg SC injection every 6 mo or placebo All patients: ADT Calcium, ≥1 g/day & vitamin D, ≥400 IU/day	**LS BMD @ 24 mo**, LS BMD @ 36 mo, TH & FN @ 24 & 36 mo, fracture
Smith 2012 [36]	Currently receiving ADT	1435 (1432)	Denosumab (718) Placebo (717)	Denosumab, 120 mg SC injection every 4 wk or placebo All patients: Been on ADT for ≥6 mo upon entering study Calcium, ≥500 mg/day & vitamin D, ≥400 IU/day	**Bone metastasis-free survival**, time to first bone metastasis (symptomatic or asymptomatic), overall survival
Smith 2004 [109]	Currently receiving ADT	48 (41)	Raloxifene (24) No raloxifene (24)	Oral raloxifene, 60 mg/day or no raloxifene All patients: Been on ADT for ≥6 mo upon entering study Calcium, 500 mg/day & vitamin D, 400 IU/day	**LS BMD @ 12 mo**; proximal femur, trochanter, TH BMD @ 12 mo
Smith 2010 [110]	Currently receiving ADT	1284	Toremifene (646) Placebo (638)	Oral toremifene, 80 mg/day or placebo All patients: ADT	**New vertebral fractures @ 2 y**, fragility fractures, BMD
Winters-Stone 2014 [15]	Currently receiving ADT	51 (51)	Resistance training (29) Control (flexibility exercises) (22)	Moderate resistance training with free weights, squats, deadlifts, lunges, row, chest press, lateral raise, pushup. Impact exercise with 2-footed jumps. 2 classes & 1 home session per week for 12 mo. Flexibility included whole body stretching, relaxation exercises in seated or lying position.	**LS, TH, FN, trochanter BMD @ 12 mo**
Nilsen 2015 [16]	Currently receiving ADT	58 (58)	Strength training (28) Usual care (30)	9 strength training exercises, 3 session per wk for 16 wk with increasing training volume and duratione Control-group patients were encouraged to maintain their habitual activity level	LS, TH, FN, total body, trochanter BMD; HRQOL

Cormie 2015 [17]	Beginning ADT	63 (64)	Exercise (32) Usual care (31)	60 min of moderate-high intensity aerobic & resistance exercises 2 sessions per wk for 3 mo	LS, FN, total body BMD; HRQOL
Santa Mina 2012 [18]	Currently receiving ADT	13 (10)	Group-based exercise (6) Personal training (7)	Group-based exercise or personal training, 60 min sessions, 3 times/wk for 8 wk All patients: Currently receiving ADT or completed within past 3 mo	**Feasibility**, BMD @ 8 wk, HRQOL
Smith 2001 [111]	Beginning ADT	47 (41)	Pamidronate (21) No pamidronate (22)	Pamidronate, 60 mg IV for 2 hr every 12 wk or no pamidronate All patients: 3-mo depot leuprolide, 22.5 mg IM every 12 wk; bicalutamide, 50 mg/d Calcium, 500 mg/d & vitamin D, 400 IU/d	**BMD @ 48 wk**
Klotz 2013 [5]	Beginning ADT	186 (167)	Alendronate (84) Placebo (102)	Oral alendronate, 70 mg/wk or placebo for 12 mo All patients: Initiated ADT with leuprolide acetate, 30 mg IM every 4 mo Calcium, 500 mg & vitamin D, 400 IU	**LS BMD @ 12 mo**, TH, FN BMD; fracture
Rodrigues 2007 [28]	Currently receiving ADT	94 (94)	Clodronate (39) ZA (24) Control (31)	Clodronate, 1500 mg IV for 2 hr every 28 day or ZA, 4 mg IV every mo or no treatment (control) All patients: LHRH agonist or orchiectomy	**Osteoporosis @ 36 mo**, osteopenia, BMD
Smith 2003 [10]	Beginning ADT	106 (79)	ZA (55) Placebo (51)	ZA, 4 mg IV infusion every 3 mo for 12 mo or placebo All patients: Beginning initial ADT with GRH agonist with or without an antiandrogen. Orchiectomy within the past 2 wk also eligible. Calcium, 500 mg/day & vitamin D, 400 IU/day	**LS BMD @ 12 mo**; TH, FN, trochanter, nondominant forearm BMD; fracture
Rao 2008 [11]	Beginning ADT	50 (41)	ZA (19) Placebo (22)	ZA, 4 mg in 100 mL normal saline or 5% dextrose IV infusion every 3 mo or placebo All patients: Hormonal treatment within 1 to 2 wk of enrolment Calcium, 500 mg twice daily & vitamin D, 400 IU/day	**BMD @ 12 mo**
Casey 2010 [12]	Beginning ADT	187 (155)	Phase I ZA (91) No ZA (96)	ZA, 4 mg IV infusion every 3 mo for 12 mo or no ZA All patients: hormonal treatment with goserelin acetate, 10.8 mg Calcium, 500 mg/day & vitamin D, 400 IU/day	**LS BMD @ 12 mo**, TH, FN BMD, height change
			Phase II ZA (55) No ZA (22) ZA delayed (14)		**BMD @ 24 mo**
Denham 2014 [112] Denham 2012 [129] Denham 2014b [130]	Beginning ADT	1071 (1071)	ZA + short-term ADT (STAS+ZA) (268) ZA + intermed-term ADT (ITAS+ZA) (267) Short-term ADT (STAS) (control) (268)	ADT for 6 mo (short-term) + ZA, 4 mg IV every 3 mo or ADT for 18 mo (intermed-term) + ZA or short-term ADT or intermed-term ADT. All patients: ADT with leuprorelin, 22.5 mg IM every 3 mo beginning at randomization; RT to	**Prostate-cancer specific mortality**, vertebral & nonspinal fracture, BMD @ 2 yr, QOL, all-cause mortality

			Intermed-term ADT (ITAS) (268)	prostate & seminal vesicles beginning 5 mo after randomization.	
Mason 2007 [35] Dearnaley 2009 [55]	Half on long-term ADT	508 (508)	Clodronate (254) Placebo (254)	Sodium clodronate, 2080 mg/day or placebo for maximum 5 yr All patients: conventional management for prostate cancer	**Symptomatic bone metastases-free survival**, disease progression, overall survival
Wirth 2014 [34]	Two-thirds on ADT during study	1433 (1393)	ZA (716) No ZA (717)	ZA, 4 mg IV every 3 mo for ≤4 yr or no ZA All patients: ADT if applicable; calcium, 500 mg/day & vitamin D, 400 to 500 IU/day	**Bone metastases**, overall survival
Metastatic					
Smith 1989 [97]	Previous ADT	57 (51)	IV etidronate + oral etid (14) IV etidronate + oral placebo (14) IV placebo + oral etidronate (15) IV placebo + oral placebo (14)	Sodium etidronate, 7.5 mg/kg IV for 2 hr for 3 days followed by 200 mg sodium etidronate tablets twice daily or IV etidronate followed by oral placebo or IV placebo followed by oral etidronate or IV & oral placebo All patients: previous hormonal therapy	**Pain**
Adami 1989 [98]	Previous ADT	13	IV clodronate (7) Placebo (6)	Clodronate, 300 mg IV for 2 hr for 2 wk or placebo	**Pain**
		23	IM clodronate (12) Oral clodronate (11)	Clodronate, 100 mg IM/day for 2 wk or oral clodronate, 1200 mg/day for 2 wk	**Pain**
Lipton 1994 [114]	Previous ADT	58 (52)	Pamidronate 30 mg/2 wk (12) Pamidronate 60 mg/4 wk (16) Pamidronate 60 mg/2 wk (13) Pamidronate 90 mg/4 wk (17)	Pamidronate, IV 30 mg every 2 wk or 60 mg every 4 wk or 60 mg every 2 wk or 90 mg every 4 wk	**Pain**, analgesic use
Diamond 2001 [31]	Currently receiving ADT	21 (18)	Pamidronate Placebo	Pamidronate, single 90 mg IV infusion or placebo with a crossover at 6 mo All patients: combined androgen blockade with long-acting GnRH and flutamide or bicalutamide for >6 mo	**LS BMD @ 6 mo**, FN, Ward triangle & trochanter BMD
Dearnaley 2003 [41] Dearnaley 2009 [55]	Currently receiving or starting ADT	311 (311)	Clodronate (155) Placebo (156)	Sodium clodronate, 2080 mg/d or placebo for max 3 yr All patients: standard hormone therapy for metastatic prostate cancer	**SREs defined as symptomatic bone progression-free survival,** disease progression, overall survival, pain
Wang 2013 [33]	Currently receiving ADT	137	ZA (69) Clodronate (68)	ZA, 4 mg IV every 4 wk or oral clodronate, 1600 mg/day All patients: calcium, 500 mg/day & vitamin D, 400 IU/day	**Bone progression-free survival, overall survival**, BMD, SREs, pain
Ueno 2013 [39]	Beginning ADT	60	ZA (29) No ZA (31)	ZA, 4 mg IV every 4 wk or no ZA All patients: combined androgen blockade	**PSA progression-free survival**, SREs, pain
Smith 2014 [40]	Currently receiving ADT	645 (645)	ZA (323) Placebo (322)	ZA, 4 mg IV every 4 wk or placebo All patients: standard ADT; calcium, 500 mg/day & vitamin D, 400 to 500 IU/day	**Time to SRE**, overall survival, progression-free survival
Satoh 2009 [32]	Beginning ADT	40	ZA (20) No ZA (20)	ZA, one 4 mg IV infusion or no ZA All patients: ADT	**BMD @ 6 & 12 mo**

Lang 2013 [113]	Beginning ADT	44	ZA once before ADT (14) ZA once after ADT (15) ZA monthly after ADT (15)	ZA, 4 mg once 1 wk before beginning ADT or ZA, 4 mg once 6 mo after beginning ADT or ZA, 4 mg monthly 6 mo after beginning ADT for 6 mo	**BMD @ 6, 12, 18, 24 mo**
Strang 1997 [99]	Hormone refractory	52 (46)	Clodronate (25) Placebo (27)	Clodronate, 300 mg IV for 3 days, followed by 1600 mg orally twice daily for 4 wk or placebo	**Pain**
Elomaa 1992 [115]	Failed hormone therapy	75 (60)	Clodronate (36) Placebo (39)	Clodronate, 3.2 g for 1 mo, then 1.6 g or placebo All patients: estramustine phosphate, 280 mg twice daily	**Pain**
Kylmala 1993 [56]	Failed hormone therapy	99	Clodronate (50) No clodronate (49)	Clodronate, 3.2 g for 1 mo, then 1.6 g for 5 mo or no clodronate All patients: estramustine phosphate, 280 mg twice daily	**Pain**, survival, bone metastases
Kylmala 1997 [116]	Failed hormone therapy	57 (55)	Clodronate (28) Placebo (29)	Clodronate, 300 mg/day IV for 5 days then 1.6 g/d orally for 12 mo or placebo All patients: estramustine phosphate, 280 mg twice daily	**Pain**
Ernst 2003 [57]	Hormone refractory; could continue	227 (209)	Clodronate (115) Placebo (112)	Clodronate, 1500 mg IV infusion or placebo All patients: Continued hormonal therapy permitted, additional androgen ablation not permitted. Prednisone, 5 mg twice daily & mitoxantrone, 12 mg/m^2 IV every 3 wk	**Palliative response** (2-point reduction in 6-point Present Pain Intensity [PPI] scale or >50% decrease in analgesic score without increase in PPI), disease progression; time to symptomatic progression, duration of palliative response, PSA response, HRQOL
Figg 2005 [58]	Hormone refractory; could continue	72	Alendronate (36) No alendronate (36)	Alendronate, 40 mg/day or no alendronate All patients: ketoconazole, 400 mg three times daily & hydrocortisone, 10 mg/day. Prochlorperazine or metoclopramide recommended as antiemetics.	**PSA response (≥50% decrease**), response duration, progression-free survival, overall survival
Meulenbeld 2012 [59]	Hormone refractory; could continue	592 (569)	Risedronate (291) No risdedronate (301)	Oral risedronate, 30 mg/day or no risedronate All patients: Docetaxel, 75 mg/m^2 IV every 3 wk & prednisone, 5 mg twice/day	**Time to progression (composite endpoint: progression by RECIST criteria, PSA progression, or pain progression)**, PSA response, pain response, overall survival
Small 2003 [43]	Hormone refractory; could continue	378 (301)	Pamidronate (182) Placebo (196)	Pamidronate, 90 mg IV in 2-h infusion every 3 wk for 27 wk or placebo All patients: standard radiotherapy including Sr-89 and Sm-153 were allowed as well as hormonal therapy or chemotherapy or corticosteroids	**Pain**, SREs, survival, fracture
Saad 2002 [42] Saad 2004 [45]	Failed hormone therapy	643 (643)	ZA, 4 mg (214) ZA, 8 mg (221) Placebo (208)	15-min IV infusion ZA, 4 or 8 mg every 3 wk for 15 mo or placebo. Protocol amendment switched 8 mg patients to 4 mg for renal safety; All patients: Calcium, 500 mg/day & vitamin D, 400 to 500 IU/day	**≥1 SRE @ 15 mo**, time to first SRE, skeletal morbidity rate, individual SREs, fracture, time to disease progression, objective bone lesion response, QOL (including pain response **[**using Brief Pain Inventory]), bone metastases
Pan 2014 [53]	Castration resistant	105 (105)	ZA (53) Placebo (52)	30-min IV infusion ZA, 4 mg every 3 wk or placebo	Pain, SREs, overall survival

				All patients: Docetaxel, 75 mg/m^2 IV every 3 wk & prednisone, 5 mg twice daily; calcium, 500 mg/day & vitamin D, 400 IU/day	
Fizazi 2009 [100]	Failed hormone therapy	111 (78) Prostate cancer: 50 (49)	Denosumab q 4 wk (17) Denosumab q 12 wk (16) Bisphosphonates (17) *Denosumab arms pooled for analysis*	Denosumab, 180 mg SC injection every 4 wk or every 12 wk or IV bisphosphonates (ZA or pamidronate) every 4 wk All patients: median 6 mo ZA before randomization Calcium, 500 mg/day & vitamin D, ≥400 IU/day	SREs, hypercalcemia
Fizazi 2011 [37]	Failed hormone therapy	1904 (1901)	Denosumab (951) ZA (953)	Denosumab, 120 mg subcutaneous injection (or placebo) every 4 wk or 15-min IV infusion ZA (or placebo) every 4 wk All patients: calcium, ≥500 mg/day & vitamin D, ≥400 IU/day	**Time to 1st on-study SRE** (assessed for noninferiority), time to 1st & subsequent SREs (assessed for superiority), fracture, overall survival, disease progression (exploratory analysis)
Hoskin 2015 [117]	Majority currently on ADT	470 (470)	Ibandronate (235) RT (235)	Ibandronate, single 6 mg IV infusion over 15 min or single dose of EBRT, 8 Gy	**Pain @ 12 wk, pain @ 52 wk, QOL, overall survival**
Lara 2006 [123]	Hormone refractory; could continue	80	Matrix metalloproteinase inhibitor (MMPI) 1200 mg once daily (39) MMPI 1200 mg twice daily (41)	Oral MMPI, 1200 mg once daily or twice daily All patients: ADT	**PFS @ 4 mo**, survival
Buchali 1988 [101]	Not stated	49	Sr-89 (25) Placebo (24)	Sr-89, 3 injections of 75 MBq every mo or placebo	**Pain**, survival
Lewington 1991 [102]	Hormone refractory; could continue	32 (26)	Sr-89 (12) Placebo (14)	Sr-89, 150 MBq or placebo: 1st injection followed by 2nd injection at 6 wk	**Pain**
Porter 1993 [118]	Hormone refractory; could continue	126 (124)	Sr-89 (68) Placebo (58)	Sr-89, 400 MBq or placebo All patients: local field RT	**Pain**, survival, QOL
Bilen 2015 [124]	Castration-sensitive	79 (72)	Sr-89 (39) No Sr-89 (40)	Sr-89, 4 mCi IV or no Sr-89 All patients: LHRH agonist or bilateral orchiectomy; doxorubicin, 20 mg/m^2 IV days 1, 8, 15 every 28 days for 2 cycles; ZA, 4 mg IV over 15 min every 28 d for 6 doses	**Progression-free survival,** overall survival
Quilty 1994 [50]	Failed hormone therapy	305 (284)	Sr-89 (153) EBRT (152)	Sr-89, 200 MBq or EBRT (local field or hemibody)	**Pain**, survival
Tu 2001 [95]	Hormone refractory; could continue	72 (72)	Sr-89 (36) No Sr-89 (36)	Sr-89, 2.035 MBq per kg of body weight or no Sr-89 All patients: Weeks 1,3,5: Doxorubicin, 20 mg/m^2 IV on 1st day of each wk; ketoconazole, 400 mg thrice daily for 7 days	**Time to progression**, survival

				Weeks 2,4,6: Vinblastine, 4 mg/m^2 IV on 1st day of each wk; estramustine, 140 mg thrice daily for 7 days Hydrocorticsone, 30 mg/day	
Oosterhof 2003 [51]	Hormone refractory; could continue	203	Sr-89 (101) RT (102)	Sr-89, 150 MBq IV or local RT	**Pain (time to subjective progression)**, survival
Nilsson 2005 [52]	Failed hormone therapy	35 (32)	Sr-89 (18) FEM (17)	Sr-89, 150 MBq IV or FEM (5-fluorouracil 750 mg/m^2, epirubicin 40 mg/m^2, mytomycin C 0.1 mg/kg) IV administered on 2 consecutive days every 3 wk for 12 wk or progression of pain.	**Pain**
Baczyk 2007 [119]	Not stated	60	Sr-89 (30) Sm-153 (30)	Sr-89, 150 MBq or Sm-153 chelated with ethylene diamine tetramethylene phosphonate, 37 MBq/kg	**Pain**
Palmedo 2003 [120]	Failed hormone therapy	64 (58)	Re-188 1 injection (32) 2 injections (32)	Re-188 ethylene diamine tetramethylene phosphonate, 70 to 90 mCi, 1 injection or 2 injections 2nd injection 8 wk after the first	**Pain**, time to progression, survival
Han 2002 [103]	Failed hormone therapy	131 (79)	Re-186 (66) Placebo (65)	Re-186, 1295 to 2960 MBq or placebo	**Pain**
Sartor 2004 [104]	Failed hormone therapy	152	Sm-153 (101) Placebo (51)	Sm-153-lexidronam, 1 mCi/kg IV or placebo (nonradioactive Sm-152) administered for 1 min	**Pain**
Resche 1997 [121]	Not stated; previous ADT	67 (58)	Sm-153 0.5 mCi/kg (32) Sm-153 1.0 mCi/kg (35)	Sm-153 ethylene diamine tetramethylene phosphonate, 0.5 or 1.0 mCi/kg	**Pain**, survival
Tian 1999 [105]	Not stated; previous ADT	12	Sm-153 37 MBq/kg (n=7) Sm-153 18.5 MBq/kg (n=5)	Sm-153 ethylene diamine tetramethylene phosphonate, 18.5 or 37 MBq (0.5 or 1.0 mCi/kg)	**Pain**
Nilsson 2007 [48] Nilsson 2013 [54]	Previous or ongoing ADT	64 (64)	Ra-223 (33) Placebo (31)	Ra-223, 50 kBq/kg injection every 4 wk for 12 wk or placebo All patients: EBRT	**Time to first SRE,** survival
Parker 2013 [46] Sartor 2014 [47]	Previous or ongoing ADT	921	Ra-223 (614) Placebo (307)	Ra-223, 50 kBq/kg IV every 4 wk or placebo All patients: best standard of care	**Survival**, time to 1st SRE, pain
Nilsson 2012 [122]	mCRPC	100 (83)	Ra-223 5 kBq/kg (26) 25 kBq/kg (25) 50 kBq/kg (25) 100 kBq/kg (24)	Single injection Ra-223 of 5, 25, 50 or 100 kBq/kg	**Pain response**
Parker 2013b [94]	mCRPC	122 Per-protocol population (≥2 Ra-223 injections) for	Ra-223 25 kBq/kg (41) 50 kBq/kg (39) 80 kBq/kg (42)	3 IV injections of Ra-223 of 25, 50, or 80 kBq/kg at 6 wk intervals	**PSA response**, SREs, pain response, survival

		all outcomes except survival 112) Safety population (≥1 Ra-223 injection) for survival 122))			

ADT=androgen deprivation therapy; BMD=bone mineral density; EBRT=external-beam radiotherapy; FN=femoral neck; GnRH=Gonadotropin-releasing hormone; hr=hour; HRQOL=health-related quality of life; IM=intramuscular; IV=intravenous; IU= international units; LHRH=luteinizing hormone-releasing hormone; LS=lumbar spine; mCRPC=metastatic castration-resistant prostate cancer; min=minute; mo=month; PSA=prostate specific antigen; QOL=quality of life; Ra=radium; Re=rhenium; RECIST=response evaluation criteria in solid tumours; RT=radiotherapy; SC=subcutaneous; Sm=samarium; Sr=strontium SRE=skeletal related event; TH=total hip; wk=week; yr=year; ZA=zoledronic acid.

Appendix 7. Methodological quality assessment of randomized controlled trials.

Study reference	Allocation concealment	Blinding	Intention to treat	Industry funding	Patient follow-up – included in analysis	Baseline characteristics balanced	Statistical power and target sample size	Terminated early
Kearns 2010 [29]		•	•	•	40/71 (56%)		•	•[a]
Choo 2013 [106]	•	•	•	•	76/104 (73%)	•	•	•[b]
Taxel 2010 [96]	•	•		•	40/47 (85%)	•		
Greenspan 2007 [4]	•	•	•		112 (100%)	Some differences in BMD	•	
Greenspan 2008 [30]		•	•		96/112 (86%)	Some differences in BMD		
Morabito 2004 [108]					48/48 (100%)	•		
Ryan 2006 [6]		•	•	•	101/122 (83%)	Difference in FN BMD	•	
Ryan 2007 [107]		•	•	•	28 (67%)	•	•	•[c]
Israeli 2007 [7]		•		•	215/222 (97%)	•	•	
Michaelson 2007 [14]	•	•			36/44 (82%)	•	•	
Bhoopalam 2009 [8]		•	•	•	84 (90%)	Difference in smoking status	•	
Kapoor 2011 [9]	•	•		•	31/41 (76%)	•	•	•[a]
Kachnic 2013 [13]			•		96/109 (88%)		•	•[a]
Smith 2009 [3]	•	•	•	•	1468/1468 (100%)	•	•	
Smith 2012 [36]	•	•	•	•	1432/1435 (99.8%)	•	•	
Smith 2004 [109]		•			41/48 (85%)	•	•	
Smith 2010 [110]		•		•	970/1389 (70%) 970/1284 (76%)	•	•	
Winters-Stone 2014 [15]		•	•		51/51 (100%)	•	•	
Nilsen 2015 [16]	•		•		58/58 (100%)		•	
Cormie 2015 [17]	•	•	•	•	63/63 (100%)	•	•	
Santa Mina 2012 [18]	•				10/13 (77%)	•		
Smith 2001 [111]			•		41/47 (87%)	•		
Klotz 2013 [5]		•	•	•	167/186 (90%)		•	
Rodrigues 2007 [28]					94/94 (100%)			
Smith 2003 [10]	•	•		•	79/106 (75%)	•	•	

Study reference	Allocation concealment	Blinding	Intention to treat	Industry funding	Patient follow-up – included in analysis	Baseline characteristics balanced	Statistical power and target sample size	Terminated early
Rao 2008 [11]	•	•			41/50 (82%)	•	•	
Casey 2010 [12]	•			•	155/187 (83%)	•	•	
Denham 2014 [112] Denham 2012 [129] Denham 2014b [130]	•		•	•	1071/1071 (100%)	•	•	
Mason 2007 [35] Dearnaley 2009 [55]	•	•	•	•	508/508 (100%)	•	•	
Wirth 2014 [34]		•	•	•	1393/1433 (97%)	•	•	
Smith 1989 [97]		•			51/57 (89%)			
Adami 1989 [98]					13/13 (100%)			
Lipton 1994 [114]		•			52/58 (90%)	•		
Diamond 2001 [31]		•	•		18/21 (86%)	•	•	
Dearnaley 2003 [41] Dearnaley 2009 [55]	•	•	•	•	311/311 (100%)	•	•	
Wang 2013 [33]			•		137/137 (100%)	•		
Ueno 2013 [39]					60/60 (100%)	•		
Smith 2014 [40]		•	•	•	645/645 (100%)	•	•	•[d]
Satoh 2009 [32]					40/40 (100%)	•		
Lang 2013 [113]	•		•	•	44/44 (100%)	•	•	
Strang 1997 [99]		•		•	46/52 (88%)			•[a]
Elomaa 1992 [115]				•	60/75 (80%)			
Kylmala 1993 [56]				•	99			
Kylmala 1997 [116]		•			55/57 (96%)			
Ernst 2003 [57]		•	•		209/227 (92%)	•	•	
Figg 2005 [58]					72/72 (100%)	•		
Meulenbeld 2012 [59]				•	569/592 (96%)	•	•	
Small 2003 [43]		•	•	•	301/378 (80%)	•	•	
Pan 2014 [53]					105/105 (100%)	•		
Saad 2002 [42] Saad 2004 [45]	•	•	•	•	643/643 (100%)	•	•	
Fizazi 2009 [100]				•	49/50 (98%)	Generally yes but more	•	

Study reference	Allocation concealment	Blinding	Intention to treat	Industry funding	Patient follow-up – included in analysis	Baseline characteristics balanced	Statistical power and target sample size	Terminated early
						patients in denosumab group had ECOG status of 2 and greater extent of bone resorption		
Fizazi 2011 [37]	•	•	•	•	1901/1904 (99.8%)	•	•	
Hoskin 2015 [117]	•		•		470/470 (100%)	•	•	
Lara 2006 [123]					80	•	•	
Buchali 1988 [101]		•			49/49 (100%)	•		
Lewington 1991 [102]	•	•		•	26/32 (81%)			
Porter 1993 [118]	•	•			124/126 (98%)	•		
Bilen 2015 [124]			•		72/79 (91%)		•	
Quilty 1994 [50]	•			•	217/284 (76%)	•		
Tu 2001 [95]			•	•	72/72 (100%)		•	
Oosterhof 2003 [51]			•		188/203 (93%)	•	•	
Nilsson 2005 [52]					32/35 (91%)	•		
Baczyk 2007 [119]					60/60 (100%)	•		
Palmedo 2003 [120]					58/64 (91%)	Yes except more patients had low Gleason score in single injection group; % of high Gleason scores greater in double injection group	•	
Han 2002 [103]	•	•		•	79/131 (60%)	•		
Sartor 2004 [104]	•	•		•	152	•		
Resche 1997 [121]		•		•	58/67 (87%)			
Tian 1999 [105]		•			12/12 (100%)			

Study reference	Allocation concealment	Blinding	Intention to treat	Industry funding	Patient follow-up – included in analysis	Baseline characteristics balanced	Statistical power and target sample size	Terminated early
Nilsson 2007 [48] Nilsson 2013 [54]	•	•	•	•	All 64 patients received at least 1 injection (included in analysis)	•	•	
Parker2013 [46] Sartor2014 [47]	•	•	•	•	921/921 (100%)	•	•	•[e]
Nilsson 2012 [122]		•	•	•	Included in PP analysis 93/100 (93%)	•		
Parker 2013b [94]		•		•	Included in PP analysis 112/122 (92%)	•	•	

BMD=bone mineral density; Diff=difference; ECOG=Eastern Cooperative Oncology Group; PP=per protocol.

[a] Closed early due to slow accrual.

[b] Early termination recommended because smaller studies just published showed significant BMD increase with single dose of zoledronic acid.

[c] Superseded by a larger trial.

[d] Corporate supporter withdrew study drug supply.

[e] Survival advantage at interim analysis.

Appendix 8. Bisphosphonates vs. placebo or no bisphosphonates.

Quality assessment							Number of patients Intervention/Control	Summary of findings	Quality	Importance
Number of studies	Patient population	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision				
FRACTURE										
1 (4 trials) Ding 2013 [23]	Nonmet on ADT	Meta-analysis[a]	No	No	No	Serious	284/276 Events: 10/7	OR 1.40, 95% CI 0.53 to 3.67, p=0.50	⊕⊕⊕◯ MODERATE	CRITICAL
BONE MINERAL DENSITY										
1 (14 trials)	Nonmet on ADT	Meta-analysis	No	No	No	No	590/595	Difference in % change from baseline at 12 mo[b] LS: 6.65%, 95% CI 4.31 to 9.00 FN 2.87%, 95% CI 2.24 to 3.51 TH 2.68%, 95% CI 1.87 to 3.48	⊕⊕⊕⊕ HIGH	IMPORTANT
2 Diamond 2001 [31] Satoh 2009 [32]	Met on ADT	RCT	Serious	No	No	Serious	41/41	Diamond 2001: Difference in % change from baseline at 6 mo for LS 7.8 vs. -5.7, p<0.001 (also stat sig for FN, Ward triangle, and trochanter) Satoh2009: Difference in % change from baseline at 12 mo for LS 3.5 vs. -8.2, p=0.0004 (also stat sig for FN, TH)	⊕⊕◯◯ LOW	IMPORTANT
OSTEOPOROSIS										
4 Kearns 2010 [29] Greenspan 2008 [30] Israeli 2007 [7] Rodrigues 2007 [28]	Nonmet on ADT	RCT	No	Serious	No	Serious	236/202 Events: 30 vs. 40	Rodrigues 2007: Osteoporosis at 12 mo Clodronate vs. control 18% vs. 58%, p<0.001; ZA vs. control 21% vs. 58%, p<0.001 3 trials showed no difference between groups	⊕⊕◯◯ LOW	IMPORTANT
BONE METASTASES										
2 Mason 2007 [35] Wirth 2014 [34]	Nonmet on ADT	RCT	No	No	No	No	970/971 Events: 165 vs. 142	Mason 2007: Symptomatic bone metastases 24% vs. 19%, HR 1.32, 95% CI 0.91 to 1.93, p=0.15 Wirth 2014: Bone metastases at median 4.8 yr 15% vs. 13%, p=0.65	⊕⊕⊕⊕ HIGH	IMPORTANT
SKELETAL-RELATED EVENTS										
1 (3 trials) Yuen 2006 [44]	Met	Meta-analysis	No	Serious	No	No	772/560 Events: 292 vs. 241	OR 0.79, 95% CI 0.62 to 1.00, p=0.05[c] Using 4 mg ZA group from Saad 2002: OR 0.76, 95% CI 0.59 to 0.98	⊕⊕⊕◯ MODERATE	IMPORTANT
PAIN										
1 (4 trials) Yuen 2006 [44]	Met CRPC	Meta-analysis	No	Serious	No	Serious	222/194 Events: 62 vs. 41	Pain relief: OR 1.54, 95% CI 0.97 to 2.44 Decreased analgesic consumption: OR 1.27, 95% CI 0.82 to 1.98	⊕⊕◯◯ LOW	IMPORTANT
1 (2 trials) Yuen 2006 [44]	Met CRPC	Meta-analysis	No	Serious	No	Serious	361/362	Standard mean difference in pain: -1.58, 95% CI -1.75 to -1.41[d]	⊕⊕◯◯ LOW	IMPORTANT
OVERALL SURVIVAL										
2 Mason 2007 [35]	Nonmet on ADT	RCT	No	No	No	No	970/971	Mason 2007: 5-yr OS 78% vs. 79%, HR 1.02, 95% CI 0.80 to 1.30, p=0.90; 10-yr OS 48% vs. 51%, HR 1.12, 95% CI 0.89 to 1.42, p=0.94	⊕⊕⊕⊕ HIGH	CRITICAL

Wirth 2014 [34]								Wirth 2014: Death at 4 yr 16.7% vs. 17.5%, p=0.71[e]		
1 (4 trials) Yuen 2006 [44]	Met CRPC	Meta-analysis	No	No	No	Serious	488/503 Events 209 vs. 226	Death: OR 0.82, 95% CI 0.61 to 1.11[f]	⊕⊕⊕◯ MODERATE	CRITICAL
QUALITY OF LIFE										
1 Denham 2012 [129]	Nonmet on ADT	RCT	No	No	Serious	Serious	n=1071	Changes in patient reported outcome scores did not differ between groups	⊕⊕◯◯ LOW	CRITICAL
2 Ernst 2003 [57] Saad 2002 [42]	Met CRPC	RCT	No	No	No	Serious	n=852	Ernst 2003: improvement with clodronate in 1 domain (pain) of the 9-item Prostate Cancer-Specific Quality of Life Instrument (p=0.022) Saad 2002: No difference between groups in ECOG, FACT-G or EURO-QOL scores	⊕⊕⊕◯ MODERATE	CRITICAL

ADT=androgen deprivation therapy; CI=confidence interval; CRPC=castration-resistant prostate cancer; ECOG=Eastern Cooperative Oncology Group; EURO-QOL=EURO Quality of Life EQ-5D; FACT-G=Functional Assessment of Cancer Therapy-General; FN=femoral neck; HR=hazard ratio; LS=lumbar spine; Met=metastatic; mo=month; Nonmet=nonmetastatic; OR=odds ratio; OS=overall survival; RCT=randomized controlled trial; stat sig=statistically significant; TH=total hip; yr=year; ZA=zoledronic acid.

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a] 4 additional trials showed similar results [5,13,30,112].

[b] Improvements in bone mineral density were sustained at 24 mo in 2 trials [106,30] and 1 trial at 36 mo [13].

[c] 4 additional trials showed fewer skeletal-related events with bisphosphonates in 2 trials [39,45] and no difference in 2 trials [40,53].

[d] 6 additional trials showed no difference between groups in 4 trials [41,56,59,99]; decrease in mean pain and analgesic consumption in 1 trial [98], and a perceptible reduction in bone pain and discomfort in 1 trial [53].

[e] 1 additional trial showed similar results [130].

[f] 6 additional trials measuring overall survival showed no difference between groups in in 4 trials [40,56,58,59]; 1 trial with 10-yr follow-up showed an OS benefit with clodronate: HR 0.77, 95% CI 0.60 to 0.98, p=0.032 [55]; 1 trial showed an OS benefit of 4 months with ZA and docetaxel compared with docetaxel alone (p=0.02) [53].

Appendix 9. Intravenous vs. oral bisphosphonates.

Quality assessment							Number of patients Intervention/Control	Summary of findings	Quality	Importance
Number of studies	Patient population	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision				
BONE MINERAL DENSITY										
1 Wang 2013 [33]	Met on ADT	RCT	Serious	No	No	Serious	69/68	Difference in percent change from baseline at 36 mo LS: 4.5% vs. 2.3, p=0.03 No difference between groups for FN or TH BMD	⊕⊕◯◯ LOW	IMPORTANT
SKELETAL-RELATED EVENTS										
1 Wang 2013 [33]	Met on ADT	RCT	Serious	No	No	Serious	69/68 Events: 12 vs. 14	Incidence of SREs at 3 yr: 17% vs. 20%, p=0.62	⊕⊕◯◯ LOW	IMPORTANT
PAIN										
1 Wang 2013 [33]	Met on ADT	RCT	Serious	No	No	Serious	69/68	Improvement in pain intensity by 2 points in first 3 mo 92% vs. 76%, p=0.02 Pain intensity <1 point reached in 9 vs. 13 mo, p=0.03 No difference in VAS scores at 36 mo	⊕⊕◯◯ LOW	IMPORTANT
OVERALL SURVIVAL										
1 Wang 2013 [33]	Met on ADT	RCT	Serious	No	No	Serious	69/68	3-yr OS 69.6% vs. 64.2%, p=0.54	⊕⊕◯◯ LOW	CRITICAL

ADT=androgen deprivation therapy; BMD=bone mineral density; FN=femoral neck; LS=lumbar spine; Met=metastatic; mo=month; OS=overall survival; RCT=randomized controlled trial; SRE=skeletal-related event; TH=total hip; VAS=visual analogue scale; yr=year.

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Appendix 10. Bisphosphonates vs. radiotherapy.

Quality assessment							Number of patients Intervention/Control	Summary of findings	Quality	Importance
Number of studies	Patient population	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision				
PAIN										
1 Hoskin 2015 [117]	Met on ADT	RCT	No	No	No	Serious	235/235	Worst pain at 4 wk (WHO criteria): 50% vs. 53%, 90% CI -12.4 to 5.0, p=0.49; (EAS criteria): 53% vs. 60%, 90% CI -16 to 0.7, p=0.14	⊕⊕⊕◯ MODERATE	IMPORTANT
OVERALL SURVIVAL										
1 Hoskin 2015 [117]	Met on ADT	RCT	No	No	No	Serious	235/235 Events: 200 vs. 195	Median OS 12.9 vs. 12.2 mo, HR 0.89, 95% CI 0.73 to 1.09, p=0.25	⊕⊕⊕◯ MODERATE	CRITICAL
QUALITY OF LIFE										
1 Hoskin 2015 [117]	Met on ADT	RCT	No	No	No	Serious	235/235	No difference between groups in any QOL measures at 4 wk. Mean change in overall QOL -0.9 vs. 0.3, difference -0.1, 99% CI -4.0 to 2.0, p=0.37	⊕⊕⊕◯ MODERATE	CRITICAL

ADT=androgen deprivation therapy; CI=confidence interval; EAS=Effective Analgesic Score; HR=hazard ratio; Met=metastatic; mo=month; OS=overall survival; QOL=quality of life; RCT=randomized controlled trial; WHO=World Health Organization; wk=week.

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Appendix 11. Different doses/schedules of bisphosphonates.

Quality assessment							Number of patients	Summary of findings	Quality	Importance
Number of studies	Patient population	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision				
BONE MINERAL DENSITY										
1 Lang 2013 [113]	Met on ADT	RCT	Serious	No	No	Serious	n=44	ZA before ADT vs. ZA monthly 6 mo after ADT: % change from baseline Proximal femur: 1.1 vs. -0.5, p=0.008 Trochanter: 1.4 vs. 0.5, p=0.016 FN: 0.7 vs. 1.0, p=0.036	⊕⊕◯◯ LOW	IMPORTANT
PAIN										
1 Lipton 1994 [114]	Met on ADT	RCT	Serious	No	No	Serious	n=58	No difference in change in pain or narcotic score between 4 different doses of pamidronate	⊕⊕◯◯ LOW	IMPORTANT

ADT=androgen deprivation therapy; FN=femoral neck; Met=metastatic; mo=month; RCT=randomized controlled trial; ZA=zoledronic acid.

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Appendix 12. Denosumab vs. placebo.

Quality assessment							Number of patients (Intervention/Control)	Summary of findings	Quality	Importance
Number of studies	Patient population	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision				
FRACTURE										
1 Smith 2009 [3]	Nonmet on ADT	RCT	No	No	No	No	734/734	New vertebral fracture 12 mo 0.3% vs. 1.9%, RR 0.15, p=0.004 36 mo 1.5% vs. 3.9%, RR 0.38, 95% CI 0.19 to 0.78, p=0.006	⊕⊕⊕⊕ HIGH	CRITICAL
BONE MINERAL DENSITY										
1 Smith 2009 [3]	Nonmet on ADT	RCT	No	No	No	No	734/734	Difference in percent change from baseline at 24 mo LS: 6.7%, p≤0.001 FN: 3.9%, p≤0.001 TH: 4.8%, p≤0.001 One-third distal radius: 5.5%, p≤0.001	⊕⊕⊕⊕ HIGH	IMPORTANT
BONE METASTASES										
1 Smith 2012 [36]	Nonmet on ADT	RCT	No	No	No	Serious	716/716	Median time to 1st bone metastasis: 33.2 vs. 29.5 mo, HR 0.84, 95% CI 0.71 to 0.98, p=0.032 Proportion of patients with symptomatic bone metastases: 10% vs. 13%, HR 0.67, 95% CI 0.49 to 0.92, p=0.01	⊕⊕⊕◯ MODERATE	IMPORTANT
SKELETAL-RELATED EVENTS										
1 (2 trials) Ford 2013 [38]	mCRPC	Network meta-analysis	No	No	Serious	No	1386/1161	HR 0.56, 95% CI 0.40 to 0.77	⊕⊕⊕◯ MODERATE	IMPORTANT
OVERALL SURVIVAL										
1 Smith 2012 [36]	Nonmet on ADT	RCT	No	No	No	Serious	716/716	Median 43.9 vs. 44.8 mo, HR 1.01, 95% CI 0.85 to 1.20, p=0.91	⊕⊕⊕◯ MODERATE	CRITICAL

ADT=androgen deprivation therapy; CI=confidence interval; FN=femoral neck; HR=hazard ratio; LS=lumbar spine; mCRPC=metastatic castration-resistant prostate cancer; Met=metastatic; mo=month; Nonmet=nonmetastatic; RCT=randomized controlled trial; RR=relative risk; TH=total hip.

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Appendix 13. Denosumab vs. zoledronic acid.

Quality assessment							Number of patients (Intervention/Control)	Summary of findings	Quality	Importance
Number of studies	Patient population	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision				
SKELETAL-RELATED EVENTS										
2 Fizazi 2009 [100] Fizazi 2011 [37]	mCRPC	RCT	No	No	No	No	984/969 Events: 342 vs. 389	Fizazi 2011: Median time to 1st SRE 20.7 vs. 17.1 mo, HR 0.82, 95% CI 0.71 to 0.95, p=0.008 Fizazi 2009: 1 vs. 3 patients (low event rates)	⊕⊕⊕⊕ HIGH	IMPORTANT
OVERALL SURVIVAL										
1 Fizazi 2011 [37]	mCRPC	RCT	No	No	No	Serious	951/953	Median OS: 19.4 vs. 19.8 mo, HR 1.03, 95% CI 0.91 to 1.17, p=0.65	⊕⊕⊕◯ MODERATE	CRITICAL

CI=confidence interval; CRPC=castration-resistant prostate cancer; HR=hazard ratio; mCRPC=metastatic castration-resistant prostate cancer; mo=month; RCT=randomized controlled trial; OS=overall survival; SRE=skeletal-related event.

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Appendix 14. Toremifene vs. placebo.

Quality assessment							Number of patients (Intervention/Control)	Summary of findings	Quality	Importance
Number of studies	Patient population	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision				
FRACTURE										
1 Smith 2010 [110]	Nonmet on ADT	RCT	No	No	No	Serious	646/638 Events: 28 vs. 47	All fracture: 24 mo 6.3% vs. 10.1%, RRR 38%, 95% CI 2.2 to 60.2, p=0.036 Vertebral fracture: 24 mo 2.5% vs. 4.9%, RRR 50%, 95% CI 1.5 to 75, p<0.05	⊕⊕⊕◯ MODERATE	CRITICAL
BONE MINERAL DENSITY										
1 Smith 2010 [110]	Nonmet on ADT	RCT	No	No	No	No	646/638	Difference in percent change from baseline at 24 mo LS: 2.3%, 95% CI 1.6 to 3.1, p<0.0001 FN 1.9%, 95% CI 1.2 to 2.7, p<0.0001 TH 1.9%, 95% CI 1.3 to 2.4, p<0.0001	⊕⊕⊕⊕ HIGH	IMPORTANT

ADT=androgen deprivation therapy; CI=confidence interval; FN=femoral neck; LS=lumbar spine; mo=month; Nonmet=nonmetastatic; RCT=randomized controlled trial; RRR=relative risk reduction; TH=total hip.

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Appendix 15. Raloxifene vs. no raloxifene.

Quality assessment							Number of patients (Intervention/Control)	Summary of findings	Quality	Importance
Number of studies	Patient population	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision				
BONE MINERAL DENSITY										
1 Smith 2004 [109]	Nonmet on ADT	RCT	Serious	No	No	Serious	24/24	Difference in percent change from baseline at 12 mo LS: 2.0%, 95% CI -0.2 to 4.0, p=0.07 FN 2.0%, 95% CI -0.1 to 4.0, p=0.06 TH 3.7%, 95% CI 2.0 to 5.4, p<0.001 Trochanter: 3.9%, 95% CI 1.9 to 5.9, p<0.001	⊕⊕◯◯ LOW	IMPORTANT

ADT=androgen deprivation therapy; CI=confidence interval; FN=femoral neck; LS=lumbar spine; mo=month; nonmet=nonmetastatic; RCT=randomized controlled trial; TH=total hip.

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Appendix 16. Exercise vs. usual care.

Quality assessment							Number of patients (Intervention/Control)	Summary of findings	Quality	Importance
Number of studies	Patient population	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision				
BONE MINERAL DENSITY										
3 Winters-Stone 2014 [15] Nilsen 2015 [16] Cormie 2015 [17]	Nonmet on ADT	RCT	No	No	No	Serious	35/29	Winters-Stone 2014: No difference in percent change from baseline at 12 mo (resistance training vs. flexibility exercises) in LS, FN, or TH BMD (p≥0.37) Nilsen 2015: No difference in change from baseline at 4 mo in LS, FN, TH, or trochanter BMD (p≥0.22) Cormie 2015: No difference in change from baseline at 3 mo in whole body, LS, TH, or tibia BMD (p≥0.22)	⊕⊕⊕◯ MODERATE	IMPORTANT
QUALITY OF LIFE										
2 Nilsen 2015 [16] Cormie 2015 [17]	Nonmet on ADT	RCT	No	No	No	Serious	60/61	Nilsen 2015: No difference between groups in HRQOL measures Cormie 2015: Improvement with exercise in some patient-reported outcomes on the SF-36 Difference in mean change over 3 mo: Social functioning: 3.8, 95% CI 0.8 to 6.9, p=0.015 Mental health: 3.8, 95% CI 1.1 to 6.5, p=0.006 Mental health composite: 3.6, 95% CI 0.5 to 6.6, p=0.022 No differences in 7 other measures	⊕⊕⊕◯ MODERATE	CRITICAL

ADT=androgen deprivation therapy; BMD=bone mineral density; CI=confidence interval; FN=femoral neck; HRQOL=health-related quality of life; LS=lumbar spine; mo=month; nonmet=nonmetastatic; RCT=randomized controlled trial; SF-36=36-Item Short Form Health Survey; TH=total hip.

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Appendix 17. Different types of exercise.

Quality assessment							Number of patients (Intervention/Control)	Summary of findings	Quality	Importance
Number of studies	Patient population	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision				
BONE MINERAL DENSITY										
1 SantaMina 2012 [18]	Nonmet on ADT	RCT	No	No	No	Serious	6/7	Santa Mina 2012: Difference in change in absolute BMD (group exercise vs. personal training) Calcaneus: 0.01 g/cm^2, p=0.928	⊕⊕⊕◯ MODERATE	IMPORTANT

ADT=androgen deprivation therapy; BMD=bone mineral density; nonmet=nonmetastatic; RCT=randomized controlled trial.

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Appendix 18. Radiopharmaceuticals vs. placebo or no radiopharmaceuticals.

Quality assessment							Number of patients (Intervention/Control)	Summary of findings	Quality	Importance
Number of studies	Patient population	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision				
SKELETAL-RELATED EVENTS										
2 Nilsson 2007 [48] Parker 2013 [46] Sartor 2014 [47]	mCRPC	RCT	No	No	Serious	No	Nilsson 2007 33/31 Parker 2013 614/307	Nilsson 2007: Median time to 1st SRE 14 vs. 11 wk, HR 0.57, 95% CI 0.31 to 1.04, p=0.065[a] Parker 2013: Median time to 1st symptomatic skeletal event 15.6 vs. 9.8 mo, HR 0.66, 95% CI 0.52 to 0.83, p<0.001	⊕⊕⊕◯ MODERATE	IMPORTANT
PAIN										
1 (8 trials) Roque I Figuls 2011 [49]	mCRPC	Meta-analysis	No	No	No	Serious	279/220	Complete pain relief: RR 2.10, 95% CI 1.32 to 3.35 Complete or partial pain relief: RR 1.72, 95% CI 1.13 to 2.63 Any pain relief: RR 1.36, 95% CI 0.77 to 2.40[b]	⊕⊕⊕◯ MODERATE	IMPORTANT
OVERALL SURVIVAL										
1 (3 trials) Roque I Figuls 2011 [49]	mCRPC	Meta-analysis	No	Serious	No	Serious	138/99 Events: 15 vs. 10	Death: RR 1.14, 95% CI 0.27 to 4.77	⊕⊕◯◯ LOW	CRITICAL
7 Nilsson 2007 [48] Nilsson 2013 [54] Parker 2013 [46] Porter 1993 [118] Quilty1994 Tu 2001 [95] Oosterhof 2003 [51] Bilen 2015 [124]	mCRPC	RCT	No	Serious	No	Serious	1044/726	Ra-223 vs. placebo Nilsson 2013: Median OS 65.3 vs. 46.4 mo, HR 0.48, 95% CI 0.26 to 0.88, p=0.017 Parker 2013: Median OS 14.9 vs. 11.3 mo, HR 0.70, 95% CI 0.58 to 0.83, p<0.001 Sr-89 vs. placebo/no Sr-89 Tu 2001 Median OS 27.7 vs. 16.8 mo, HR 2.76, 95% CI 1.44 to 5.29, p<0.0001 Oosterhof 2003: Median OS 7.2 vs. 11.0 mo, HR 1.34, 95% CI 1.01 to 1.75, p=0.046 Porter 1993: Median OS 27 vs. 34 wk, p=0.6 Quilty 1994: Median OS 33 vs. 28 wk, p=0.10 Bilen 2015: Median OS 47.4 vs. 53.5 mo, p=0.97	⊕⊕◯◯ LOW	CRITICAL
QUALITY OF LIFE										
1 Porter 1993 [118] Parker 2013 [46]	mCRPC	RCT	No	No	No	No	682/365	Porter 1993: Improvement with Sr-89 in domains of pain and physical activity of the 9-item Quality of Life Instrument (p<0.05) Parker 2013: Improvement with Ra-223 in the FACT-P total score 25% vs. 16%, p=0.02	⊕⊕⊕⊕ HIGH	CRITICAL

CI=confidence interval; FACT-P=Functional Assessment of Cancer Therapy-Prostate; HR=hazard ratio; mCRPC= metastatic castration-resistant prostate cancer; mo=month; OS=overall survival; Ra=radium; RCT=randomized controlled trial; RR=relative risk; Sr=strontium; SRE=skeletal-related event; wk=week.

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a] To make the HRs of Nilsson 2007 [48] and Parker 2013 [46] comparable, the reciprocal of the HR and CI in Nilsson 2007 [48] was calculated.

[b] 3 additional trials showed a lower occurrence of new pain sites with Sr-89 compared with local or hemibody radiotherapy [50] and no difference in pain measures for Sr-89 compared with chemotherapy [52] or compared with radiotherapy [51].

Appendix 19. Radiopharmaceutical vs. radiopharmaceutical.

Quality assessment							Number of patients	Summary of findings	Quality	Importance
Number of studies	Patient population	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision				
PAIN										
1 Baczyk 2007 [119]	mCRPC	RCT	Serious	No	No	Serious	30/30	Sr-89 vs. Sm-153 Mean change in pain intensity at 2 mo (VAS scale 0 to 10): -4 vs. -4 Mean change in analgesic consumption at 2 mo: -55% vs. -45%	⊕⊕◯◯ LOW	IMPORTANT

CRPC=castration-resistant prostate cancer; mCRPC=metastatic castration-resistant prostate cancer; mo=month; RCT=randomized controlled trial; Sm=samarium; Sr=strontium; VAS=visual analogue scale.

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Appendix 20. Different doses of radiopharmaceuticals.

Quality assessment							Number of patients	Summary of findings	Quality	Importance
Number of studies	Patient population	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision				
SKELETAL-RELATED EVENTS										
1 Parker 2013b [94]	mCRPC	RCT	No	No	No	Serious	n=122	≥1 SRE no stat sign difference between groups 25 kBq/kg: 41% 50 kBq/kg: 50% 80 kBq/kg: 44%	⊕⊕⊕◯ MODERATE	IMPORTANT
PAIN										
5 Resche 1997 [121] Palmedo 2003 [120] Tian 1999 [105] Nilsson 2012 [122] Parker 2013b [94]	mCRPC	RCT	No	Serious	No	Serious	n=359	Resche 1997: Higher vs. lower dose Sm-153: Greater change in pain at 4 wk, p=0.048 Palmedo 2003: Higher vs. lower dose Re-188: Greater pain relief, 92% vs. 60%, p<0.01 Tian 1999: Higher vs. lower dose Sm-153: No statistically significant difference between groups Nilsson 2012: 4 doses of Ra-223: Dose response seen at wk 2 Parker 2013b: 3 doses of Ra-223: No statistically significant difference in pain response	⊕⊕◯◯ LOW	IMPORTANT
OVERALL SURVIVAL										
1 (2 trials) Roque I Figuls 2011 [49]	mCRPC	Meta-analysis	No	No	No	Serious	90/94 Events: 15 vs. 12	Lower vs. higher dose Death: RR 1.27, 95% CI 0.63 to 2.59[a]	⊕⊕⊕◯ MODERATE	CRITICAL

CI=confidence interval; mCRPC=metastatic castration-resistant prostate cancer; mo=month; OS=overall survival; RCT=randomized controlled trial; Ra=radium; Re=rhenium; RR=relative risk; Sm=samarium; SRE=skeletal-related event; wk=week.

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a] 1 additional trial (n=64) showed an OS benefit with a repeated injection of Re-188 compared with a single injection: 12.7 vs. 7.0 mo, p=0.043 [120]; 1 dose-finding trial of 3 doses of Ra-223 showed no difference between groups in death or time to death [94].

Appendix 21. Once vs. twice per day of 1200 mg matrix metalloproteinase inhibitor.

Quality assessment							Number of patients	Summary of findings	Quality	Importance
Number of studies	Patient population	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision				
OVERALL SURVIVAL										
1 Lara 2006 [123]	mCRPC	RCT	Serious	No	No	Serious	39/41	Median OS: not reached vs. 21 mo, p=0.2 PFS at 4 mo: 22% vs. 10%, p=0.008	⊕⊕◯◯ LOW	CRITICAL

mCRPC=metastatic castration-resistant prostate cancer; mo=month; OS=overall survival; PFS=progression-free survival; RCT=randomized controlled trial.
GRADE Working Group grades of evidence:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Appendix 22. Skeletal-related events.

Ref	Comparison	Follow-up period	Composite SRE results	Individual SRE results		SRE definition
Dearnaley 2003 [41]	Clodronate (155) Placebo (156)	Median 59 mo	Symptomatic bone progression Number of events: Clodronate 94 patients Placebo 103 patients HR 0.80, 95% CI 0.60 to 1.06	Radiotherapy	Clodronate 71 patients Placebo 75 patients	Symptomatic bone progression (osseous disease requiring an increase in regular analgesic use, treatment with radiotherapy, or change in hormone therapy, or that was associated with a pathological fracture or spinal cord compression)
				Pathological fracture	Clodronate 8 patients Placebo 11 patients	
				Spinal cord compression	Clodronate 15 patients Placebo 19 patients	
				Treatment with additional bisphosphonates	Clodronate 15 patients Placebo 9 patients	
Wang 2013 [33]	ZA (69) Clodronate (68)	3 yr	SREs ZA 12/69 (17%) Clodronate 14/68 (20%) p=0.62	Fracture	ZA 3 patients (4%) Clodronate 4 patients (6%)	Fracture, radiation to bone, spinal cord compression, surgery to bone, hypercalcemia
				Spinal cord compression	ZA 1 patient (1%) Clodronate 1 patient (1%)	
				Radiotherapy to bone	ZA 6 patients (9%) Clodronate 7 patients (10%)	
				Surgery to bone	ZA 1 patient (1%) Clodronate 0 patients	
				Hypercalcemia	ZA 1 patient (1%) Clodronate 2 patients (3%)	
Ueno 2013 [39]	ZA (29) No ZA (31)	Mean observation period 27.4 to 32.1 mo	Fewer SREs in ZA than no ZA group HR 0.3812, 95% CI 0.154 to 0.943	Pathological fracture	ZA 0 patients No ZA 1 patient	Pathological fracture, spinal cord compression, radiation to bone, surgery to bone, hypercalcemia, bone pain
				Spinal cord compression	ZA 0 patients No ZA 2 patients	
				Bone pain	ZA 7 patients No ZA 11 patients	
				Radiotherapy to bone	ZA 0 patients No ZA 2 patients	
				Surgery to bone	ZA 0 patients No ZA 1 patient	
Smith 2014 [40]	ZA (323) Placebo (322)		Median time to 1st SRE: ZA 31.9 mo Placebo 28.8 mo HR 0.97, 95% CI 0 to 1.17, p=0.385			Radiation to bone, clinical fracture, surgery to bone, or death due to prostate cancer
Small 2003 [43]	Pamidronate (182) Placebo (196)	9 wk	Pamidronate 20/169 patients (12%) Placebo 20/181 patients (11%)			Hypercalcemia (corrected serum calcium ≥12.0 mg/dL), a pathologic fracture (vertebral or nonvertebral), requirement of radiation to bone for pain relief or to treat or prevent fractures or spinal cord compression, surgery to bone to treat or prevent fractures, spinal cord compression, or need for a spinal orthotic brace
		27 wk	Pamidronate 42/169 patients (25%) Placebo 46/181 patients (25%)	Radiotherapy to bone for pain relief	Pamidronate 25 patients (15%) Placebo 29 patients (16%)	
				Radiotherapy to bone to prevent fracture	Pamidronate 8 patients (5%) Placebo 7 patients (4%)	

				Nonvertebral fracture	Pamidronate 14 patients (8%) Placebo 12 patients (7%)	
				Vertebral fracture	Pamidronate 11 patients (7%) Placebo 10 patients (6%)	
				Spinal cord compression	Pamidronate 5 patients (3%) Placebo 3 patients (2%)	
				Surgery to bone	Pamidronate 5 patients (3%) Placebo 6 patients (3%)	
				Hypercalcemia	Pamidronate 1 patient (<1%) Placebo 2 patients (1%)	
Pan 2014 [53]	ZA (53) Placebo (52)	2 yr	ZA 6/53 patients (11%) Placebo 8/52 patients (15%) p=0.42	Fracture	ZA 1 patient (2%) Placebo 3 patients (6%)	Fracture, spinal cord compression, radiation therapy to bone, surgery to bone, hypercalcemia
				Spinal cord compression	ZA 1 patient (2%) Placebo 0 patients	
				Radiotherapy to bone	ZA 3 patients (6%) Placebo 4 patients (10%)	
				Surgery to bone	ZA 0 patients Placebo 0 patients	
				Hypercalcemia	ZA 1 patient (2%) Placebo 1 patient (2%)	
Saad 2002 [42] Saad 2004 [45]	ZA, 4 mg (214) ZA, 8 mg (221) Placebo (208)	15 mo	≥1 SRE ZA 8/4 mg 85 patients (38.5%) ZA 4 mg 71 patients (33.2%) Placebo 92 patients (44.2%) ZA 8/4 mg vs. placebo absolute difference 5.8%, 95% -3.6 to 15.1, p=0.222 ZA 4 mg vs. placebo absolute difference 11.1%, 95% CI 1.8 to 20.3, p=0.021	Pathological fracture	ZA 8/4 mg 33 patients (15%) ZA 4 mg 28 patients (13%) Placebo 46 patients (22%) ZA 8/4 mg vs. placebo, p=0.054	Pathologic bone fractures (vertebral or nonvertebral), spinal cord compression, surgery to bone, radiation to bone (including use of radioisotopes), or change of antineoplastic therapy to treat bone pain
			Median time to 1st SRE ZA 8/4 mg 363 day ZA 4 mg 488 day Placebo 321 day ZA 8/4 mg vs. placebo, HR 0.89, 95% CI 0.67 to 1.19, p=0.434 ZA 4 mg vs. placebo, HR 0.68, 95% CI 0.51 to 0.91, p=0.009	Nonvertebral fracture	ZA 8/4 mg 22 patients (10%) ZA 4 mg 22 patients (10%) Placebo 33 patients (16%) ZA 8/4 mg vs. placebo, p=0.065	
				Vertebral fracture	ZA 8/4 mg 17 patients (8%) ZA 4 mg 8 patients (4%) Placebo 17 patients (8.2%)	

					ZA 8/4 mg vs. placebo, p=0.852	
				Spinal cord compression	ZA 8/4 mg 11 patients (5%) ZA 4 mg 9 patients (4%) Placebo 14 patients (7%) ZA 8/4 mg vs. placebo, p=0.434	
				Radiotherapy to bone	ZA 8/4 mg 53 patients (24%) ZA 4 mg 49 patients (23%) Placebo 61 patients (29%) ZA 8/4 mg vs. placebo, p=0.201	
				Surgery to bone	ZA 8/4 mg 6 patients (3%) ZA 4 mg 5 patients (2%) Placebo 7 (3%) ZA 8/4 mg vs. placebo, p=0.770	
				Change in antineoplastic treatment	ZA 8/4 mg 18 (8%) ZA 4 mg 10 (5%) Placebo 14 (7%) ZA 8/4 mg vs. placebo, p=0.570	
		24 mo	≥1 SRE ZA 8/4 mg 91 patients (41%) ZA 4 mg 81 patients (38%) Placebo 101 patients (49%) ZA 8/4 mg vs. placebo absolute difference -8.0%, 95% CI -16.8 to 2.0, p=0.129 ZA 4 mg vs. placebo absolute difference -11.0%, 95% CI -20.2 to -1.3, p=0.028			
Fizazi 2009 [100]	Denosumab q 4 wk (17) Denosumab q 12 wk (16) Bisphosphonates (17) *Denosumab arms pooled for analysis*	25 wk	Denosumab 1/33 patients (3.0%) Bisphosphonate 3/16 patients (18.8%)			Pathological bone fracture, spinal cord compression, or surgery or radiation to bone
Fizazi 2011 [37]	Denosumab (951) ZA (953)	41 mo	Denosumab 341 patients (36%) ZA 386 patients (41%)	Pathological fracture	Denosumab 137 (14%) ZA 143 (15%)	Pathological fracture (excluding fractures from severe trauma), radiation to bone (including use of radioisotopes), surgery to bone, or spinal cord compression
			Median time to 1st SRE Denosumab 20.7 mo ZA 17.1 mo HR 0.82, 95% CI 0.71 to 0.95, p=0.0002 (noninferiority); p=0.008 (superiority)	Spinal cord compression	Denosumab 26 (3%) ZA 36 (4%)	
				Radiotherapy to bone	Denosumab 177 (19%)	

					ZA 203 (21%)	
				Surgery to bone	Denosumab 1 (<1%) ZA 4 (<1%)	
Nilsson 2007 [48]	Ra-223 (33) Placebo (31)		Median time to 1st SRE Ra-223 14 wk Placebo 11 wk HR 1.75, 95% CI 0.96 to 3.19, p=0.065			25% increase in pain severity index compared with baseline after day 15; increased analgesic consumption; neurological symptoms secondary to skeletal manifestations of prostate cancer; new pathological bone fractures; tumour-related orthopedic surgical intervention; subsequent EBRT to relieve skeletal pain; use of radioisotopes to relieve new skeletal-related symptoms; use of corticosteroids for skeletal pain palliation; use of chemotherapy, bisphosphonates, or hormones to treat progression of skeletal disease
		16 wk	SRE incidence Ra-223 17 patients had 34 SREs Placebo 18 patients had 44 SREs p=0.625			
		52 wk	Ra-223 26 patients had ≥1 SRE Placebo 26 patients had ≥1 SRE			
Parker 2013 [46] Sartor 2014 [47]	Ra-223 (614) Placebo (307)		Median time to 1st SRE Ra-223 15.6 mo Placebo 9.8 mo HR 0.66, 95% CI 0.52 to 0.83, p<0.001	Pathological fracture	Ra-223 32 patients (5%) Placebo 20 patients (7%) p=0.10	Symptomatic skeletal event: 1st use of EBRT to relieve skeletal symptoms, new symptomatic pathologic vertebral or nonvertebral bone fracture, spinal cord compression, or tumour-related orthopedic surgical intervention
				Spinal cord compression	Ra-223 25 patients (4%) Placebo 21 patients (7%) p=0.03	
				Radiotherapy	Ra-223 186 patients (30%) Placebo 105 patients (34%) p=0.001	
				Surgery to bone	Ra-223 12 patients (2%) Placebo 7 patients (2%) p=0.48	
Parker 2013b [94]	Ra-223 25 kBq/kg (41) 50 kBq/kg (39) 80 kBq/kg (42)	24 wk	≥1 SREs 25 kBq/kg 15 (41%) 50 kBq/kg 18 (50%) 80 kBq/kg 17 (44%)	Pathological fracture	25 kBq/kg 1 patient (3%) 50 kBq/kg 0 patients 80 kBq/kg 0 patients	Increase in average pain or analgesic consumption, presence of neurologic symptoms, new pathologic bone fractures, tumour-related orthopedic surgery, EBRT or corticosteroids to relieve pain, radioisotopes to relieve new SRE symptoms, chemo or hormones for disease progression in the skeleton, or bisphosphonates for pain or skeletal disease progression
				Radiotherapy	25 kBq/kg 1 patients(3%) 50 kBq/kg 7 patients (19%) 80 kBq/kg 4 patients (10%)	
				Surgery to bone	25 kBq/kg 0 patients 50 kBq/kg 0 patients 80 kBq/kg 0 patients	

CI=confidence interval; EBRT=external beam radiotherapy; HR=hazard ratio; mo=month; Ra=radium; SRE=skeletal-related event; yr=year; ZA=zoledronic acid.

Appendix 23. Adverse effects.

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
Nonmetastatic											
Vs. placebo or no treatment											
Risedronate + estrogen (19) Risedronate + placebo (17) Estrogen + placebo (18) Placebo + placebo (17)	Kearns 2010 [29]			No serious AEs							
Risedronate (52) Placebo (52)	Choo 2013 [106]	135 vs. 120 events				Grade 1 30 vs. 31 events Grade 2 9 vs. 0 Grade 3 2 vs. 0	0 vs. 0 events				Pain Grade 1 48 vs. 43 events Grade 2 12 vs. 6 Grade 3 0 vs. 0
Risedronate (20) Placebo (20)	Taxel 2010 [96]			No serious AEs leading to discontinuation of treatment							
Clodronate (oral) (254) Placebo (254)	Mason 2007 [35]	132 (52%) vs 117 (46%) (p=0.18) HR for time to 1st reported AE 1.22 (95% CI 0.95 to 1.56, p=0.12)			**105 (41%) vs. 71 (28%), p=0.002 HR for time to 1st dose-modifying AE 1.63 (95% CI 1.21 to 2.19, p=0.0013)**	Gastrointestinal problems 86 vs. 68 events			Cardiovascular problems 12 vs. 15 events		
Alendronate (56) Placebo (56)	Greenspan 2007 [4]	43 (77%) vs. 46 (82%) No difference in any specific symptom		11 (20%) vs. 15 (27%)		Gastric symptoms 3 (5%) vs. 3 (5%) Esophageal symptoms 1 (2%) vs. 2 (4%) Constipation 5 (9%) vs. 8 (14%)			Hypertension 2 (4%) vs. 4 (7%) Cardiac catheterization or coronary bypass 1 (2%) vs. 4 (7%)		Arthralgia 19 (34%) vs. 11 (20%) Myalgia 2 (4%) vs. 8 (14%) Fatigue 3 (5%) vs. 4 (7%)

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
Alendronate-alendronate (25) Alendronate-placebo (26) Placebo-alendronate (52)	Greenspan 2008[a] [30]	23 (92%) vs. 23 (89%) vs. 50 (96%) No difference in any specific symptom		11 (44%) vs. 7 (27%) vs. 18 (35%)		Gastric 1 (4%) vs. 2 (8%) vs. 4 (8%) Esophageal 1 (4%) vs. 1 (4%) vs. 2 (4%) Constipation 2 (8%) vs. 2 (8%) vs. 8 (15%)					Arthralgia 15 (60%) vs. 5 (19%) vs. 18 (35%) Myalgia 6 (24%) vs. 1 (4%) vs. 10 (19%)
Alendronate (77) Placebo (90)	Klotz 2013 [5]	Similar between groups				**Nausea 0 vs. 5 (3%) (p=0.046)** Constipation 3 (2%) vs. 3 (1.6%) Diarrhea 2 (1.4%) vs. 4 (2.2%)			**Hypertension 4 (3%) vs. 0 (p=0.024)** Cardiac AEs 4 (3%) vs. 3 (2%)		Fatigue 9 (6%) vs. 8 (4%)
Neridronate (24) No neridronate (24)	Morabito 2004 [108]	No relevant AEs									
Pamidronate (21) No pamidronate (22)	Smith 2001 [111]			5 (24%) vs. 3 (14%)						Anemia 19 (90%) vs. 20 (91%)	Fatigue 7 (33%) vs. 8 (36%) Arthralgia or fever 3 (14%) vs. 0
ZA (61) Placebo (61)	Ryan 2006 [6]			13 (21%) vs. 18 (30%)		Nausea 6 (9.8%) vs. 0 (p=0.028) Diarrhea 3 (5%) vs. 2 (3%) Constipation 0 vs. 4 (7%)	0 vs. 0	0 vs. 0			Fatigue 11 (18%) vs. 8 (14%) Arthralgia 8 (13%) vs. 6 (10%) Myalgia 3 (5%) vs. 4 (7%) Fever 7 (12%) vs. 2 (3%) Bone pain 10 (16%) vs. 6 (10%)

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
ZA (22) Placebo (20)	Ryan 2007 [107]	Similar between groups		All reported AEs were mild or moderate except for 1 placebo patient with severe pain and neurological events		Nausea 0 vs. 3 (19%) Vomiting 0 vs. 2 (13%) Diarrhea 1 (5%) vs. 4 (25%) Constipation 2 (11%) vs. 1 (6%)					Fatigue 11 (58%) vs. 8 (50%) Fever 2 (11%) vs. 2 (13%) Bone pain/Arthralgia 10 (53%) vs. 6 (38%) Pain 12 (63%) vs. 8 (50%)
ZA (112) Placebo (110)	Israeli 2007 [7]	Similar between groups	Musculoskeletal 4% vs. 3% Administration site disorders 4% vs. 1% Nervous system disorders 1% vs. 4%	24 (21%) vs. 22 (20%)	Treatment discontinuation similar between groups 7% vs. 6%		0 vs. 0	Acute renal failure 1 vs. 1			
ZA (22) Placebo (22)	Michaelson 2007 [14]			No serious AEs							
ZA (48) Placebo (45)	Bhoopalam 2009 [8]	Well tolerated	4 (8%) vs. 1 (2%)			Grade 1 to 2 constipation 1 (2%) vs. 4 (9%)	0 vs. 0		Grade 1 to 2 hypertension 1 (2%) vs. 1 (2%)	Grade 1 to 2 anemia 2 (4%) vs. 2 (4%) Symptomatic hypocalcemia (grade 3 to 4) 1 (2%) vs. 0	Grade 1 to 2 fatigue 1 (2%) vs. 1 (2%) Grade 1 to 2 musculoskeletal pain 5 (10%) vs. 4 (9%); grade 3 to 4 1 (2%) vs. 0
ZA (21) Placebo (20)	Kapoor 2011 [9]	Well tolerated					0 vs. 0	Acute renal failure 1 (5%) vs. 0	Atrial fibrillation 1 (5%) vs. 0		
ZA (57) No ZA (52)	Kachnic 2013 [13]					Gastrointestinal (general) Grade 1 to 2 11 (22%) vs. 12 (26%) Grade 3 to 4	0 vs. 0	Renal/genitourinary (general) Grade 1 to 2 13 (26%) vs. 13 (28%) Grade 3 to 4	Cardiac (general) Grade 1 to 2 1 (2%) vs. 0 Grade 3 to 4 0 vs. 1 (2%) Grade 5	Metabolic (general) Grade 1 to 2 8 (16%) vs. 4 (9%)	Arthralgia 8 vs. 2 Myalgia 3 vs. 1 Pain (general) Grade 1 to 2 17 (34%) vs. 4 (9%)

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
						1 (2%) vs. 2 (4%)		4 (8%) vs. 1 (2%)	1 (2%) vs. 0	Grade 1 hypocalcemia 1 (2%) vs. 0	Grade 3 to 4 (3 (6%) vs. 1 (2%) Bone pain Grade 1 to 2 1 (2%) vs. 0 Grade 3 to 4 1 (2%) vs. 0
ZA (55) Placebo (51)	Smith 2003 [10]		24% vs. 39%		Treatment discontinuation 2 vs. 3	Constipation 9 (16%) vs. 8 (16%)		No renal failure, increased serum creatinine, or renal impairment			Fatigue 21 (38%) vs. 18 (35%) Arthralgia 12 (22%) vs. 7 (14%) Limb pain 7 (13%) vs. 4 (8%)
ZA (19) Placebo (22)	Rao 2008 [11]	Well tolerated with minimal complications						No persistent renal failure	Thrombophlebitis 1 (5%) vs. 1 (4.5%)		Arthralgia 2 (11%) vs. 1 (4.5%)
ZA (91) No ZA (96)	Casey 2010 [12]	Well tolerated		11 (12%) vs. 11 (12%)		Nausea 3 (3%) vs. 2 (2%)	0 vs. 0	Renal failure 0 vs. 1 (1%)			Flu-like symptoms common to bisphosphonates mild to moderate. Bone/joint pain 3 (3%) vs. 5 (5%)
ZA + short-term ADT (268) ZA + intermed-term ADT (267) Short-term ADT (268) Intermed-term ADT (268)	Denham 2014[b] [112]						2 patients receiving ZA in each of the androgen suppression groups	No decline in renal function		Grade 1 hypocalcemia Frequency range 2.7% to 8.8%	
ZA (716) No ZA (717)	Wirth 2014 [34]	554 (79%) vs. 512 (74%) (p=0.03)		315 (45%) vs. 355 (51%)	97 vs. 16 events led to withdrawal		9 vs. 1			Unspecified hypocalcemia 4 vs. 1	More general and musculoskeletal disorders

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
											associated with ZA
Denosumab (734) Placebo (734)	Smith 2009 [3]	638 (87%) vs. 627 (87%)	269 (37%) vs. 244 (34%)	253 (35%) vs. 222 (31%)		Diarrhea 40 (6%) vs. 39 (4%) Constipation 73 (10%) vs. 75 (10%)	0 vs. 0		Hypertension 57 (8%) vs. 51 (7%) Serious cardiovascular events 80 (11%) vs. 80 (11%) Including: Cardiovascular death 19 (2.6%) vs. 21 (2.9%) Acute coronary syndrome 18 (2.5%) vs. 27 (3.7%) Stroke or transient ischemic attack 21 (2.9%) vs. 17 (2.3%) Congestive heart failure 8 (1.1%) vs. 11 (1.5%) Arrhythmia 19 (2.6%) vs. 15 (2.1%)	Grade 2 hypocalcemia 1 (<1%) vs. 0	Fatigue 44 (6%) vs. 45 (6%) Arthralgia 92 (13%) vs. 80 (11%) Musculoskeletal pain 41 (5.6%) vs. 26 (3.6%)
Denosumab (718) Placebo (717)	Smith 2012 [36]	676 (94%) vs. 655 (93%)	381 (53%) vs. 353 (50%)	329 (46%) vs. 323 (46%)		Constipation 127 (18%) vs. 119 (17%) Diarrhea 111 (15%) vs. 102 (14%)	33 (5%) vs. 0			Hypocalcemia Overall 12 (2%) vs. 2 (<1%) Grade 3 to 4 9 (1%) vs. 0	Arthralgia 123 (17%) vs. 112 (16%)

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
										Symptomatic hypocalcemia 1 (<1%) vs. 0	
Raloxifene (24) No raloxifene (24)	Smith 2004 [109]			No serious treatment-related AEs					Pulmonary embolism 1 (4%) vs. 0		
Toremifene (646) Placebo (638)	Smith 2010 [110]	482 (75%) vs. 481 (75%)		136 (21%) vs. 128 (20%)	Discontinuation due to an AE 127 (20%) vs. 110 (17%)	Diarrhea 20 (3%) vs. 33 (5%)			Venous thromboembolism 17 (2.6%) vs. 7 (1.1%) Myocardial infarction 6 (0.9%) vs. 8 (1.3%) Stroke 4 (0.7%) vs. 4 (0.7%)		Fatigue 24 (4%) vs. 32 (5%) Arthralgia 47 (7%) vs. 75 (12%)
Strength training (28) Usual care (30)	Nilsen 2015 [16]				Discontinuation due to knee pain (2 vs. 0) and back pain (1 vs. 0)						
Exercise (32) Usual care (30)	Cormie 2015 [17]	No AEs related to the intervention									
2 active interventions											
Group-based exercise (6) Personal training (7)	Santa Mina 2012 [18]	No AEs related to the interventions									
Metastatic											
Bisphosphonates											
Vs. placebo or no treatment											
IV etidronate + oral etid (14) IV etid + oral placebo (14) IV placebo + oral etid (15)	Smith 1989 [97]			No serious AEs							

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
IV placebo + oral placebo (14)											
Clodronate (oral) (155) Placebo (156)	Dearnaley 2003 [41]	**78 vs. 53** **HR for time to 1st AE 1.71 (95% CI 1.21 to 2.41, p=0.002)**			**54 vs. 20 (HR 2.81, 95% CI 1.73 to 4.44, p<0.0001)**	Gastrointestinal problems 31 vs. 21 events			Cardiovascular problems 12 vs. 11 events	Unspecified hypocalcemia 5 vs. 0 events	Fatigue 2 vs. 4 events Headache 2 vs. 1 event Joint pain 11 vs. 10 events Bone pain/fracture 1 vs. 3 events
Clodronate (oral) (36) Placebo (39)	Elomaa 1992 [115]	Adverse effects were rare				Nausea or diarrhea 3 (8%) vs. 7 (18%)		Renal failure 1 (2.8%) vs. 0	Myocardial infarction 1 (2.8%) vs. 3 (8%) Pulmonary embolism 1 (2.8%) vs. 0		Spinal cord compression 1 (2.8%) vs. 0
Clodronate (IV & oral) (28) Placebo (29)	Kylmala 1997 [116]				Treatment discontinuation due to nausea 2 vs. 1	Nausea 33% vs. 40%		0 vs. 0			
Clodronate (IV) (115) Placebo (112)	Ernst 2003 [57]			Similar between groups	Treatment discontinuation because of toxicity 3 (2.9%) vs. 2 (1.9%)	Nausea/vomiting 9 vs. 7 events			Grade ≥3 0 vs. 3 events	Grade ≥3 Granulocytopenia 14 vs. 14 events Anemia 8 vs. 5 events Thrombocytopenia 2 vs. 4 events	Grade ≥3 Headache 4 vs. 1 events Shortness of breath 4 vs. 7 events Infection 7 vs. 3 events
Risedronate (291) No risedronate (301)	Meulenbeld 2012 [59]	284 (98%) vs. 289 (96%)	161 (55%) vs. 163 (54%) Most frequent were neurotoxicity, diarrhea, and nausea			All grades diarrhea 96 (33%) vs. 86 (29%) Grade ≥3 diarrhea 6 (2%) vs. 9 (3%) All grades nausea 112	0 vs. 0			Grade 3 febrile neutropenia 23 (8%) vs. 15 (5%) Hypocalcemia All grades 3 (1%) vs. 0 Grade ≥3 1 (0.3%) vs. 0	Neurotoxicity All grades 149 (51%) vs. 139 (46%) Grade ≥3 10 (3%) vs. 11 (4%)

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
						(38%) vs. 101 (34%) Grade ≥3 nausea 3 (1%) vs. 3 (1%)					
Alendronate (36) No alendronate (36)	Figg 2005 [58]	Overall AEs mild; similar between groups	5 vs. 3			Grade 3 duodenal ulcer with bleeding 1 (3%) vs. 0 Grade 1 to 2 nausea/vomiting 12 (33%) vs. 16 (44%) Grade 1 to 2 diarrhea 9 (25%) vs. 7 (19%) Grade 1 to 2 constipation 9 (25%) vs. 7 (19%)					Fatigue Grade 1 to 2 16 (44%) vs. 21 (58%) Grade 3 2 (6%) vs. 1 (3%) Grade 1 to 2 headache 6 (17%) vs. 3 (8%)
Pamidronate (IV) (182) Placebo (196)	Small 2003 [43]	Overall well tolerated; similar between groups		Similar between groups	Treatment discontinuation similar between groups (because of toxicity 6.6% vs. 6.6%)	Nausea Overall 50 (28%) vs. 43 (22%) Grade 3 to 4 5 (3%) vs. 3 (2%) Vomiting Overall 31 (17%) vs. 31 (16%) Grade 3 to 4 5 (3%) vs. 3 (2%) Diarrhea Overall 22 (12%) vs. 18 (9%) Grade 3 to 4 3 92%) vs. 2 (1%)				Overall anemia 38 (21%) vs. 39 (20%) Grade 3 to 4 anemia 3 (2%) vs. 8 (4%)	Bone pain Overall 77 (43%) vs. 75 (739%) Grade 3-4 10 (6%) vs. 4 (2%) Fatigue Overall 42 (23%) vs. 36 (19%) Grade 3-4 1 (<1%) vs. 0 Fever Overall 33 (18%) vs. 16 (8%) Grade 3-4

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
						Constipation Overall 39 (22%) vs. 40 (21%) Grade 3 to 4 0 vs. 3 (2%)					3 (2%) vs. 1 (<1%)
ZA (29) No ZA (31)	Ueno 2013 [39]			No serious AEs			0 vs. 0			Unspecified hypocalcemia 0 vs. 0	
ZA (323) Placebo (322)	Smith 2014 [40]		14% vs. 12%		Treatment discontinuation 65 vs. 38		Grade≥ 3 osteonecrosis 10 (3.2%) vs. 6 (1.9%)	Grade 5 1 vs. 0		Hypocalcemia Grade 1 35 (11%) vs. 42 (14%) Grade 2 6 (2%) vs. 9 (3%) Grade 3 5 (2%) vs. 2 (1%) Grade 4 2 (1%) vs. 1 (<1%)	Grade ≥3 Fatigue 3% vs. 2% Pain 3% vs. 3% Hypophosphatemia 3% vs. 2%
ZA (20) No ZA (20)	Satoh 2009 [32]		Grade >3 0 vs. 0				0 vs. 0				
ZA 4 mg (214) ZA 8/4 mg (221) Placebo (208)	Saad 2002[c] [42]				Treatment discontinuation because of serious AE 10%, 12%, 10%	Nausea 77 (36%), 115 (53%), 77 (37%) Vomiting 46 (22%), 64 (29%), 43 (21%) Constipation 72 (34%), 85 (39%), 72 (35%) Diarrhea 36 (17%), 35 (16%), 32 (15%)		Decline in renal function 15%, 21%, 12% Time to 1st renal function deterioration: 4 mg vs. placebo RR 1.07 (95% CI 0.46 to 2.47, p=0.882) 8/4 mg vs. placebo RR 1.76 (95% CI 0.79 to 3.93, p=0.165) 4 mg vs. 8/4 mg RR 1.63 (95% CI 0.80 to 3.30, p=0.176)		Hypocalcemia (Grade 3 to 4) 4 (2%), 4 (1.9%), 0 Hemoglobin decrease (grade ≥3) 9 (5%), 20 (10%), 9 (5%) Anemia 57 (27%), 60 (28%), 37 (18%)	Bone pain 108 (51%), 133 (61%), 127 (61%) Fatigue 70 (33%), 67 (31%), 53 (26%) Fever 43 (20%), 48 (22%), 27 (13%) Myalgia 53 (25%), 53 (24%), 37 (18%)

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
ZA (53) Placebo (52)	Pan 2014 [53]					Grade 3 to 4 nausea, vomiting, diarrhea 13 (25%) vs. 11 (21%) (p=0.37)	0 vs. 0	Renal failure 0 vs. 0		Bone marrow suppression (Grade 3 to 4) (thrombocytopenia, leukopenia, anemia) 37 (70%) vs. 31 (60%) (p=0.45)	Fatigue 22 (42%) vs. 25 (48%) Fever 16 (30%) vs. 15 (29%) Dizziness 10 (19%) vs. 11 (21%) Anorexia 5 (9%) vs. 4 (8%) Myalgia 5 (9%) vs. 3 (6%)
Dose response											
Pamidronate 30 mg q 2 wk (12) 60 mg q 4 wk (16) 60 mg q 2 wk (13) 90 mg q 4 wk (17)	Lipton 1994 [114]	4 (7%) patients with AEs mild to moderate in severity								No cases of hypocalcemia	
ZA Once before ADT (14) Once after ADT (15) Monthly after ADT (15)	Lang 2013 [113]		No grade 3 or 4 events								Greater grade 1 fatigue & arthralgia with monthly dose
2 active interventions											
ZA (IV) (69) Clodronate (oral) (68)	Wang 2013 [33]					**11 (16%) vs. 21 (31%) (p=0.01)**	1 (1%) vs. 0	Renal dysfunction 31 (45%) vs. 23 (34%)		Unspecified hypocalcemia 6 (9%) vs. 2 (3%)	Fever 2 (3%) vs. 1 (1%)
Denosumab (33) ZA (17)	Fizazi 2009[d] [100]	31 (94%) vs. 16 (100%)	2 (6%) vs. 0			Nausea 11 (33%) vs. 3 (19%) Constipation 8 (24%) vs. 3 (19%)	0 vs. 0	Denosumab had no effect on renal or hepatic function		Anemia 12 (6%) vs. 8 (50%) Unspecified hypocalcemia	Arthralgia 5 (15%) vs. 0 Bone pain 14 (42%) vs. 8 (50%)

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
						Diarrhea 5 (15%) vs. 1 (6%)				6 (18%) vs. 1 (6%) Grade 3 hypocalcemia 1 vs. 1 Thrombocytopenia 4 (12%) vs. 1 (6%)	Pyrexia 4 (12%) vs. 1 (6%)
Denosumab (951) ZA (953)	Fizazi 2011 [37]	916 (97%) vs. 918 (97%)	**678 (72%) vs. 628 (66%) (p=0.01)**	594 (63%) vs. 568 (60%)	Treatment discontinuation 164 (17%) vs. 138 (15%)	Nausea 272 (29%) vs. 245 (26%) Constipation 236 (25%) vs. 251 (27%)	22 (2%) vs. 12 (1%)	Renal impairment 139 (15%) vs. 153 (16%)		Anemia 337 (36%) vs. 341 (36%) **Unspecified hypocalcemia 121 (13%) vs. 55 (6%) (p<0.0001)** Mild-to-moderate hypocalcemia 70 (58%) vs. 38 (69%)	Bone pain 235 (25%) vs. 245 (26%) Fatigue 257 (27%) vs. 222 (23%) Arthralgia 194 (21%) vs. 202 (21%)
Ibandronate (235) RT (235)	Hoskin 2015 [117]	Any toxicity 91 (39%) vs. 97 (41%)				**Diarrhea 13 (6%) vs. 28 (12%) (p=0.014)** Nausea 43 (18%) vs. 60 (26%) Vomiting 5 (2%) vs. 10 (4%) Constipation 10 (4%) vs. 14 (6%)			Thrombotic event 6 (3%) vs. 2 (1%)		Fatigue 11 (5%) vs. 14 (6%) Fever/anorexia 17 (7%) vs. 6 (3%) **Other 44 (19%) vs. 6 (3%) (p=0.001)**
Other intervention (dose response)											
MMPI 1200 mg/d (39)	Lara 2006 [123]	Treatment generally well tolerated	Grade 3 5 (13%) vs. 9 (22%)								

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
2400 mg/d (41)			Grade 4 0 vs. 4% (thrombosis, fatigue, motor neuropathy)								
Radiopharmaceuticals											
Vs. placebo or no treatment											
Sr-89 (25) Placebo (24)	Buchali 1988 [101]									Thrombopenia 11 (50%) vs. 4 (24%) Leukopenia 3 (14%) vs. 1 (6%)	
Sr-89 (12) Placebo (14)	Lewington 1991 [102]	No substantial toxicity after the first injection								Sr-89 mean 75% decrease from baseline in platelet count vs. no significant change after placebo	
Sr-89 (68) Placebo (58)	Porter 1993 [118]									Hematologic toxicity was more common in the Sr-89 group. Differences between Sr-89 and placebo for white cell and platelet levels were statistically significant throughout. Hemorrhage 10 (15%) vs. 3 (5%)	

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
										Infection 9 (13%) vs. 7 (12%)	
Sr-89 (39) No Sr-89 (40)	Bilen 2015 [124]	19 vs. 13 events	19 (grade 3) vs. 12 (grade 3) and 1 (grade 4)								
Sr-89 (36) No Sr-89 (36)	Tu 2001 [95]					Nausea 1 (3%) vs. 3 (8%) Vomiting 2 (5.6%) vs. 3 (8%) Dyspepsia, esophagitis, gastritis 9 (25%) vs. 0			Cardiovascular complication 0 vs. 1 (3%) Deep venous thrombosis 2 (5.6%) vs. 4 (11%)	Neutropenia 10 (28%) vs. 7 (19%) Thrombocytopenia 1 (3%) vs. 1 (3%) Anemia 1 (3%) vs. 3 (8%)	Fatigue 10 (28%) vs. 6 (17%) Febrile neutropenia 0 vs. 2 (5.6%) Pain flare 0 vs. 0
Sm-153 (101) Placebo (51)	Sartor 2004 [104]			Mild transient myelosuppression the only clinically significant AE associated with Sm-153						Hemoglobin toxicity Grade 0 to 2 82 (88%) vs. 41 (87%) Grade 3 10 (11%) vs. 5 (11%) Grade 4 1 (1%) vs. 1 (2%) Platelet toxicity Grade 0 to 2 90 (97%) vs. 47 (100%) Grade 3 3 (3%) vs. 0 Grade 4 0 vs. 0 White blood cell toxicity Grade 0 to 2 87 (95%) vs. 47 (100%) Grade 3 5 (5%) vs. 0 Grade 4 0 vs. 0	Pain flare 6% vs. 6% Spinal cord compression 6% vs. 6%

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
Ra-223 (33) Placebo (31)	Nilsson 2007 [48]			12 serious events in 8 (24%) patients vs. 19 events in 14 (45%) patients (all but 4 [vomiting, sepsis x 2, tumour flare] not considered treatment related)	No Ra-223 discontinuation because of AEs	Diarrhea 9 (27%) vs. 10 (32%) Constipation 12 (36%) vs. 2 (6%) Vomiting 8 (24%) vs. 6 (19%) Nausea 9 (27%) vs. 10 (32%)			Myocardial infarction 1 vs. 0 Atrial fibrillation 0 vs. 1 Deep venous thrombosis 0 vs. 1	No substantial differences in hematological AEs. Hemoglobin toxicity Grade 1 to 2 30 (91%) vs. 25 (83%) Grade 3 1 (3%) vs. 0 Grade 4 0 vs. 1 (3%) Platelet toxicity Grade 1 to 2 6 (18%) vs. 4 (13%) Grade 3 0 vs. 1 (3%) Grade 4 0 vs. 0 White blood cell toxicity Grade 1 to 2 10 (30%) vs. 3 (10%) Grade 3 1 (3%) vs. 0 Grade 4 0 vs. 0 Anemia 5 (15%) vs. 7 (23%) Moderate hypocalcemia 0 vs. 1	Fatigue 8 (24%) vs. 7 (23%) Myalgia 5 (15%) vs. 4 (13%) Tumour flare 6 (18%) vs. 7 (23%) Bone pain 10 (30%) vs. 16 (52%) Pyrexia 0 vs. 1
Ra-223 (614) Placebo (307)	Parker 2013 [46]	558 (93%) vs. 290 (96%)	339 (56%) vs. 188 (62%)	281 (47%) vs. 181 (60%) Disease progression 11% vs. 12%	Discontinuation because of AEs 99 (16%) vs. 62 (21%)	Constipation All grades 108 (18%) vs. 64 (21%) Grade 3 6 (1%) vs. 4 (1%)				Anemia All grades 187 (31%) vs. 92 (31%)	Fatigue All grades 154 (26%) vs. 77 (26%)

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
				Bone pain 10% vs. 16% Anemia 8% vs. 9% Spinal cord compression 4% vs. 5%		Grade 4 to 5 0 vs. 0 Diarrhea All grades 151 (25%) vs. 45 (15%) Grade 3 9 (2%) vs. 5 (2%) Grade 4 to 5 0 vs. 0 Nausea All grades 213 (36%) vs. 104 (35%) Grade 3 10 (2%) vs. 5 (2%) Grade 4 to 5 0 vs. 0 Vomiting All grades 111 (18%) vs. 41 (14%) Grade 3 10 (2%) vs. 7 (2%) Grade 4 to 5 0 vs. 0				Grade 3 65 (11%) vs. 37 (12%) Grade 4 11 (2%) vs. 2 (1%) Grade 5 0 vs. 1 (<1%) Thrombocytopenia All grades 69 (12%) vs. 17 (6%) Grade 3 20 (3%) vs. 5 (2%) Grade 4 18 (3%) vs. 1 (<1%) Grade 5 1 (<1%) vs. 0 Neutropenia All grades 30 (5%) vs. 3 (1%) Grade 3 9 (2%) vs. 2 (1%) Grade 4 4 (1%) vs. 0 Grade 5 0 vs. 0	Grade 3 21 (4%) vs. 16 (5%) Grade 4 3 (1%) vs. 2 (1%) Grade 5 0 vs. 0 Pyrexia All grades 38 (6%) vs. 19 (6%) Grade 3 3 (1%) vs. 3 (1%) Grade 4-5 0 vs. 0 Bone pain All grades 300 (50%) vs. 187 (62%) Grade 3 120 (20%) vs. 74 (25%) Grade 4 5 (1%) vs. 3 (1%) Grade 5 0 vs. 0 Pathologic fracture All grades 22 (4%) vs. 15 (5%) Grade 3 13 (2%) vs. 8 (3%) Grade 4 0 vs. 1 (<1%) Grade 5 0 vs. 0 Spinal cord compression All grades 25 (4%) vs. 23 (8%)

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
											Grade 3 14 (2%) vs. 16 (5%) Grade 4 6 (1%) vs. 1 (<1%) Grade 5 1 (<1%) vs. 0
Dose response											
Re-188 1 injection (32) 2 injections (32)	Palmedo 2003 [120]		No grade 3 or 4 toxicities							Moderate toxic effects were related to changes in blood counts Grade 1 to 2 thrombocytes 3 vs. 5 Grade 1 to 2 leukocytes 5 vs. 3	Pain flare 3 (10%) vs. 2 (7%)
Sm-153 0.5 mCi/kg (32) 1.0 mCi/kg (35)	Resche 1997[e] 121]									Platelet toxicity Grade 0 to 2 44 (88%) vs. 49 (86%) Grade 3 3 (6%) vs. 6 (11%) Grade 4 3 (6%) vs. 2 (4%) White blood cell toxicity Grade 0 to 2 46 (92%) vs. 52 (91%) Grade 3 4 (8%) vs. 5 (9%) Grade 4 0 vs. 0	Pain flare 6 (11%) vs. 5 (8%) Infection 9 (16%) vs. 4 (7%) Spinal cord compression 4 (7%) vs. 2 (3%) Pathologic fracture 3 (5%) vs. 3 (5%)
Sm-153 0.5 mCi/kg (7) 1.0 mCi/kg (5)	Tian 1999[f] [105]									White blood cell reduction below normal 13 (37%) vs. 31 (44%)	

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
										Platelet reduction below normal 10 (29%) vs. 24 (34%)	
Ra-223 5 kBq/kg (26) 25 kBq/kg (25) 50 kBq/kg (25) 100 kBq/kg (24)	Nilsson 2012 [122]	97% of patients reported ≥1 AE. No differences between dose groups. No trend in number, nature, or seriousness of AEs with increasing dose.		49% of patients reported ≥1 serious AE	1 patient in the 25 kBq group had an AE leading to withdrawal	Nausea 13 (50%), 9 (36%), 9 (36%), 12 (50%) Vomiting 6 (23%), 9 (36%), 4 (16%), 5 (21%) Diarrhea 4 (15%), 7 (28%), 6 (24%), 5 (20%) Constipation 6 (23%), 5 (20%), 7 (28%), 2 (8%)				Most frequent AEs were anemia (11%) and hemoglobin decrease (15%) with no difference between dose group	Fatigue 8 (31%), 6 (24%), 4 (16%), 8 (33%) Bone pain 2 (8%), 5 (20%), 2 (8%), 2 (8%)
Ra-223 25 kBq/kg (41) 50 kBq/kg (39) 80 kBq/kg (42)	Parker 2013b [94]	92% of patients reported ≥1 AE. Minimal dose response effect		24% of patients reported ≥1 serious AE (40 events). 4 events were attributed to Ra-223: bone pain (50 kBq/kg); muscle weakness, bone pain, constipation (80 kBq/kg)		Slight trend toward increase in gastrointestinal AEs with increasing dose				No difference between groups in hematologic parameters.	
2 active interventions											
Sr-89 (153) EBRT (local field or	Quilty 1994 [50]	AEs infrequent				Less nausea, vomiting, diarrhea after Sr-89 (10%) vs.		1 vs. 0		White cell toxicity grade 3 5 (3.1%) vs. 0	

Comparison groups (n)	Study	Total AEs	≥Grade 3 AEs	Serious/severe AEs	AEs leading to dose-modification or discontinuation	Gastrointestinal	Osteonecrosis of the jaw	Renal	Cardiovascular	Hematologic or endocrine	Other
hemibody) (152)						local RT (27%) or hemibody RT (43%)				Platelet toxicity grade 3 or 4 11 (7%) vs. 5 (3%)	
Sr-89 (101) RT (102)	Oosterhof 2003 [51]					Grade 3 to 4 nausea/vomiting 4% vs. 1% Diarrhea 2% vs. 8%				Grade 3-4 hematologic toxicity 0 vs. 2%. 1 Sr-89 patient had grade 3 thrombocytopenia. No grade 3 or 4 leucopenia.	Pain flare 18% vs. 8% 1 patient randomized to Sr-89 had a pathologic femoral fracture after randomization and received RT
Sr-89 (18) Chemotherapy (17)	Nilsson 2005 [52]			**Hospitalization for AEs 2 vs. 7 (p<0.05)**							
Sr-89 (30) Sm-153 (30)	Baczyk 2007[g] [119]									Severe pancytopenia 3 vs. 2 Moderate granulocytopenia and/or thrombocytopenia 8 vs. 12 Hypercalcemia 5 vs. 5	

ADT=androgen deprivation therapy; AE=adverse effect; CI=confidence interval; d=day; EBRT=external beam radiotherapy; HR=hazard ratio; IV=intravenous; MMPI=matrix metalloproteinase inhibitor; Ra=radium; Re=rhenium; RR=relative risk; RT=radiotherapy; Sr=strontium; Sm=samarium; wk=week; ZA=zoledronic acid.
Data are numbers and proportions of patients unless otherwise stated. Statistically significant differences are in **bold**.
[a] Alendronate-alendronate vs. alendronate-placebo vs. placebo-alendronate.
[b] 2×2 factorial design; patients were allocated to short-term androgen suppression (STAS), intermediate-term androgen suppression (ITAS), STAS+ZA, ITAS+ZA.
[c] Comparison groups are ZA 4 mg vs. placebo and ZA 8/4 mg vs. placebo.
[d] Patients were allocated to continue on IV bisphosphonates (all were using ZA) or to discontinue IV bisphosphonates and switch to denosumab, 180 mg every 4 wk or denosumab 180 mg every 12 wk. The two denosumab arms were pooled for analysis.
[e] Mixed population; 59% of patients had prostate cancer.
[f] Mixed population; 11% of patients had prostate cancer.
[g] Mixed population; 60% of patients had prostate cancer.