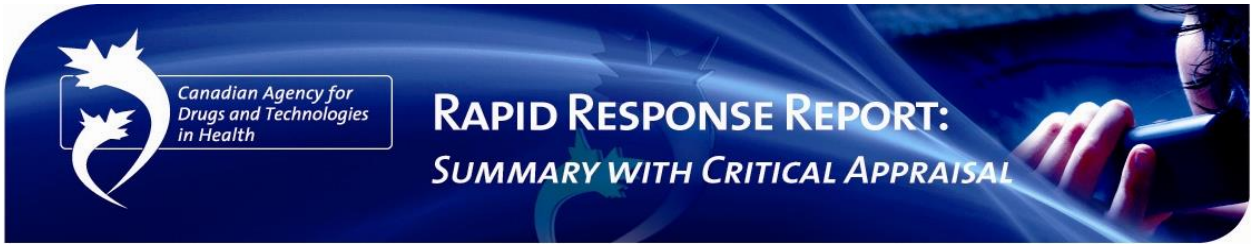

TITLE: Radium-223 for Patients with Castration Resistant Prostate Cancer with Bone Metastases: A Review of Clinical Effectiveness, Cost-effectiveness and Guidelines

DATE: 31-October 2016

CONTEXT AND POLICY ISSUES

Prostate cancer is the most commonly diagnosed than any other cancer in adult male, representing 21.0% of all cancer cases in Canadian men.[1] An estimated about 21,600 new cases diagnosed in 2016,[1] and one in eight males is expected to be diagnosed in their lifetime.[1] An estimated 4,003 men will die from prostate cancer, representing 10% of all cancer death in 2016.[1]

Androgen deprivation therapy, also called hormone therapy or androgen suppression therapy, from surgical castration or use of drugs has been the mainstay of treatment for prostate cancer.[2] Despite an initial response to androgen blockage, the disease can eventually progress within one to three years to an advanced stage called metastatic castration-resistant prostate cancer (mCRPC).[2] In this advanced stage, cancer cells metastasize and preferentially spread to bone, resulting in a significant increase in mortality and morbidity.[3] Bone metastasis leads to an increased risk of fracture, bone pain, and decreased hematopoiesis resulting in anemia.[3]

Bisphosphonates, such as zoledronic acid and human monoclonal antibody denosumab, have been used to prevent skeletal complications in mCRPC.[3] Approved therapeutic options for mCRPC include chemotherapy (i.e., docetaxel, cabazitaxel), CYP17A1 inhibitor (i.e., abariterone), androgen receptor inhibitor (i.e., enzalutamide), immunotherapy (i.e., sipuleucel-T), and bone-targeting radiopharmaceuticles (i.e., strontium-89, samarium-153, radium-223).[3,4]

Radium-223 (Ra-223) is a first-in-class radiopharmaceutical agent proved to have survival benefit.[5] Unlike the β-emitter radionuclides, such as strontium-89 and samarium-153, Ra-223 emits 95.3% of its energy as α-particles with a half-life of 11.4 days.[2] As a calcium mimetic agent, Ra-223 selectively targets high bone turnover and forms complex with hydroxyapatite, highly in the areas of bone metastases.[2] In contrast to β particles, which have low energy radiation with track length of several millimeters, the α-particles emit radiation with higher linear energy transfer and a shorter track length of <0.1 mm (<10 cells diameters), offering the advantage of killing cancer cells with a reduced risk of damage to the bone marrow and consequent effects on hematopoiesis.[2]

The aim of this report is to review the clinical effectiveness, cost-effectiveness, and evidence-based guidelines of Ra-223 in patients with bone mCRPC.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of Ra-223 in patients with castration resistant prostate cancer with bone metastases?
2. What is the cost effectiveness of Ra-223 in patients with castration resistant prostate cancer with bone metastases?
3. What are the evidence-based guidelines associated with the use of Ra-223 in patients with castration resistant prostate cancer with bone metastases?

KEY FINDINGS

The clinical evidence from a Phase III, double-blind, placebo-controlled trial showed that Ra-223 improved overall survival and delayed in time to first symptomatic skeletal event with an acceptable safety profile in men with bone mCRPC. The economic evaluation suggested that Ra-223 therapy was not cost-effective. All the included guidelines recommended that Ra-223 be used in symptomatic bone mCRPC without visceral metastases. One guideline, however, considered costs and recommended Ra-223 if an agreement on a discounted price of the drug was attainable.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and October 3, 2016.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with castration resistant prostate cancer with bone metastases (with or without concomitant therapy)
Intervention	Radium-223 dichloride (Xofigo)
Comparator	Q1 and 2: Chemotherapy, radiation therapy, hormonal therapy or placebo No comparison (only if non-randomized studies are included, e.g. only if there are not enough higher levels of evidence

	[HTAs/SRs/MAs/RCTs]) Q3: No comparator
Outcomes	Clinical effectiveness and clinical benefits and harms, safety Cost-effectiveness Guidelines
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), economic evaluations, guidelines

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, if they were published prior to 2011, conference abstracts or duplicate publications of the same study, or included in a selected HTA or SR.

Critical Appraisal of Individual Studies

The SIGN checklists were used to assess the quality of RCTs,[6] and economic evaluations. [7] The Appraisal of Guidelines Research & Evaluation (AGREE II) instrument was used to evaluate the quality of the included guidelines.[8]

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 294 citations. Upon screening titles and abstracts, 35 potential relevant articles were retrieved for full-text review. Five additional relevant reports were retrieved from other sources. Of the 40 potentially relevant articles, seven reports were included in this review including one RCT,[9] one economic evaluation[10] and five guidelines.[11-15] The study selection process is outlined in a PRISMA flowchart (Appendix 1). Additional references of potential interest including related articles to the included RCT, a single technology appraisal, horizon scanning and advice reports, and a conference abstract of a cost-effectiveness study are listed in Appendix 11.

Summary of Study Characteristics

The characteristics of the clinical and economic studies are summarized below and details are available in Appendix 2 and Appendix 3, respectively. Appendix 4 presents the grading of recommendations and levels of evidence of the included guidelines.

Randomized Controlled Trial

An international, multicentre, Phase III, randomized, double-blind, placebo-controlled trial (ALSYMPCA)[9] published in 2013 was identified that provided the evidence for the clinical efficacy and safety of radium-223 dichloride (Ra-223) in men with CRPC and bone metastasis.

Eligible patients had histologically confirmed progressive CRPC, with at least two bone marrow metastases detected on skeletal scintigraphy and no known visceral metastases, and either received with or without docetaxel prior to treatment. Patients had baseline prostate specific antigen (PSA) level of 5 ng/ml or greater and evidence of progressively increasing PSA values (i.e., two consecutive increases over the previous reference value), an Eastern Co-operative Oncology Group (ECOG) performance status score of 0 to 2 (i.e., on a scale of 0 to 5, with 0 indicating no symptoms, higher scores for increasing functional compromise, and 5 for death),

and a life expectancy of at least six months. Patients also had symptomatic disease with regular use of analgesic medication or treatment with external beam radiation therapy for cancer-related bone pain in the previous 12 weeks.

A total of 921 patients were randomized in a 2:1 ratio to receive six intravenous injections of Ra-223 (50 kBq/kg) (n=614) or matching placebo (n=307); one injection every 4 weeks. Patients were stratified by previous use or nonuse of docetaxel, baseline total alkaline phosphatase (tALP) level (<220 U/L or ≥220 U/L), and current use or nonuse of a bisphosphonate. All patients received best standard of care, defined as the routine care provided at each centre. Chemotherapy, hemibody external radiotherapy, and other systemic radionuclides were not allowed during treatment period. The follow-up period was three years.

The patient characteristics were balanced between groups. The median age was 71 years, ranging from 44 to 94 years. The primary endpoint was overall survival (OS), defined as time from randomization to all-cause death. The main secondary endpoints were time to first symptomatic skeletal event (SSE), time to an increase in tALP level, time to an increase in PSA level, tALP response, and normalization of tALP level. Other secondary end points included quality of life (QoL) and adverse events. Pre-specified subgroups included tALP level at baseline (i.e., <220 U/L, ≥220 U/L), current bisphosphonate use (i.e., yes, no), previous docetaxel use (i.e., yes, no), baseline ECOG performance-status score (i.e., 0 or 1, ≥2), opioid use (yes, no), and extent of disease (i.e., <6 metastases, 6-20, >20, superscan).

The trial was sponsored by Algeta and Bayer HealthCare Pharmaceuticals.

Economic Evaluation

One economic evaluation[10] published in 2015 was identified. The study used the cost-utility analysis approach to estimate the value (i.e., costs per life-year gained [LYG]) of anticancer drugs in the treatment of CRPC. The treatment effects were the overall survival gain (OSg) over control in days and hazard ratio of death, which were obtained from published data. The average whole sale price or third-party payments in United States dollars (US$) were used for costs of drugs. The outcomes were cost/OSg and cost/LYG. The results were expressed in relative value (RV), which was calculated as US$50,000 per cost/outcome according to the UK perspective as per the National Institute for Health and Care Excellence (NICE) recommendations, or as US$100,000 per cost/outcome according to the US perspective. The anticancer drugs belonged to different classes such as chemotherapy (i.e., docetaxel, cabazitaxel), immunotherapy (i.e., sipuleucel-T), androgen receptor signaling targeted therapy (i.e., abiraterone, enzalutamide), and radiopharmacotherapy (i.e., Ra-223). Ancillary costs, such as intravenous administration, oral medications and bone marrow growth factors, were added to the costs of docetaxel and cabazitaxel. The costs associated with professional fees (e.g., doctors, pharmacists, nurses), hospitalizations, and radiology were excluded.

The source of funding of this study was not reported.

Guidelines

Five evidence-based guidelines[11-15], published between 2014 and 2016, were identified. One was from Canada (i.e., Canadian Urological Association – Canadian Urologic Oncology Group [CUA-CUOG], 2015[13]), two from US (i.e., American Urological Association [AUA], 2015;[14] American Society of Clinical Oncology and Cancer Care Ontario [ASCO and CCO], 2014[15]); one from UK (i.e., NICE, 2016[11]), and one from Europe (i.e., European Association of Urology – European Society for Radiotherapy & Oncology – International Society of Geriatric Oncology [EAU-ESTRO-SIOG], 2016.[12]

Summary of Critical Appraisal

The summary of the critical appraisal for the clinical and economic studies are presented below and details are available in Appendix 5 and Appendix 6, respectively. Appendix 7 outlines the results of the critical appraisal for the included guidelines.

The included RCT[9] was of high quality as most of the criteria were fulfilled, including an explicit question, a detailed description of methodology on randomization, blinding, similarity between treatment groups, relevant outcome measures, and an intention-to-treat analysis (Appendix 5). The method of concealment and the results of all clinical centres, however, were not reported in the published article. The percentage of patients dropped out before study completion was 37% for Ra-223 versus 53% for placebo.

The economic evaluation study[10] was of moderate quality as some of the criteria were fulfilled. They include clarity and importance of the study question, inclusion of all costs and appropriate values, use of relevant outcome measures to answer the study question, and providing of relevance information to policy (Appendix 6). The discounting of future costs, assumptions and sensitivity analysis, and comparisons based on incremental costs and outcomes were not applicable to the cost-utility analysis in this study.

The evidence-based guidelines[11-15] were explicit in terms of scope and purpose, clarity of presentation, and editorial independence (Appendix 7). For the stakeholder involvement, it was not clear if the views and preferences of patients were sought.[12-16] For rigour of development, three guidelines[11-13] did not apply systematic methods to search for the evidence. In terms of applicability, the item such as the consideration of potential resource implications of applying the recommendations was addressed in the NICE guidelines.[11]

Summary of Findings

The main findings of the clinical and economic studies are presented below, and the details are found in Appendix 8 and Appendix 9, respectively. The guideline recommendations for the use of Ra-223 for treatment of mCRPC are shown in Appendix 10.

Randomized Controlled Trial

Overall survival (OS):

In the interim analysis (based on 809 enrolled patients), 314 patients died (35% in Ra-223 group and 46% in placebo group). The median OS was significantly longer in the Ra-223 group than that in the placebo group by 2.8 months. In an updated analysis, there were 528 deaths (54% in Ra-223 group and 64% in placebo group. The median OS was significantly longer in the Ra-223 group than that in the placebo group by 3.6 months. The survival benefit of Ra-223 was consistent in all pre-specified subgroup analyses, including previous docetaxel use, tALP level at baseline, current bisphosphonate use, baseline ECOG performance-status score, opioid use, and extent of disease (Appendix 8).

Secondary endpoints:

The benefit of Ra-223 over placebo was also observed in all main secondary efficacy endpoints. The median time to first SSE was significantly longer in the Ra-223 groups than that in the placebo group by 5.8 months. Ra-223, as compared to placebo, also significantly prolonged the time to increase in the tALP level and time to increase in PSA level (Appendix 8). A significant

higher proportion of patients in the Ra-223 group than that in the placebo group had tALP response and normalization of tALP level (Appendix 8).

Adverse event:

Adverse events were reported in 93% of patients in Ra-223 group and 96% of patients in the placebo group. They were classified as grade 3 (severe) or 4 (life-threatening) in 56% and 62% of patients in the respective groups, and serious adverse events in 47% and 60% of patients in the respective groups. The main serious adverse events that occurred in at least 5% of patients in the Ra-223 group or the placebo group were disease progression (11% in Ra-223 and 12% in placebo), bone pain (10% and 16%), anemia (8% and 9%), and spinal compression (4% and 5%).

The discontinuation of treatment due to adverse events occurred in 16% of patients in the Ra-223 group and 21% of patients in the placebo group. The main hematologic adverse events with all grades were anemia (31% in Ra-223 and 31% in placebo), thrombocytopenia (12% and 6%), and neutropenia (5% and 1%). There were no differences in frequencies between groups for grade 3 or 4 hematologic adverse events, and for non-hematologic adverse events with all grades, except diarrhea (25% in Ra-223 and 15% in placebo).

Quality of life

Patients in both Ra-223 and placebo groups experienced loss in QoL according to Functional Assessment of Cancer Therapy for Prostate Cancer (FACT-P) total score. However, the loss in QoL in the Ra-223 group was less pronounced than those in the placebo group. The mean changes in the FACT-P total scores from baseline were statistically significant at 16-week follow-up.

Economic Studies

The cost for a complete course of treatment varied from 3,508 US dollars for docetaxel to 93,000 US dollars for sipuleucel-T (Appendix 9). The cost of treatment with Ra-223 was estimated to be 69,000 US dollars. The hazard ratios for OSg among drugs, however, were marginally different. Based on the relative values calculated from the cost per life-year gained from either UK perspective ($50,000) or US perspective ($100,000), it was deemed that docetaxel was the most cost-effective treatment. The remaining drugs, including Ra-223, were considered to be overpriced for their values.

Guidelines

The recommendations of the included guidelines presented in Appendix 10 are summarized in Table 2, and were strongly graded based on high level of evidence.

The guidelines recommended the use of Ra-223 in patients with symptomatic bone mCRPC and without visceral metastases. One guideline, however, considered costs and recommended Ra-223 if an agreement on a discounted price of the drug was attainable.

Table 2: Summary of Guidelines' Recommendations for the Use of Ra-223 in Bone Metastatic Castrate-Resistant Prostate Cancer

Institution	Summary of Recommendation
NICE, 2016[11]	Recommend Ra-223 be a treatment option for patients with symptomatic bone metastases and without visceral metastasis who were previously treated with docetaxel or were deemed unfit for docetaxel. Ra-223 is recommended only when a negotiating discounted price is reached.
EAU-ESTRO-SIOG, 2016[12]	Recommend abiraterone, cabazitaxel, docetaxel, enzalutamide, Ra-223 or sipuleucel-T be first-line treatment of castrate-resistant prostate cancer. The choice should be based on performance status, symptoms, comorbidities and extent of disease.
CUA-CUOG, 2015[13]	Recommend Ra-223 be used in symptomatic bone metastatic castrate-resistant prostate cancer without visceral metastases.
AUA, 2015[14]	Recommend Ra-223 be offered to patients with symptomatic bone metastatic castrate-resistant prostate cancer, without visceral metastases, and with good performance status.
ASCO and CCO, 2014[15]	In addition to androgen-deprivation therapy, Ra-223 is recommended for men with bone metastatic castrate-resistant prostate cancer.

ASCO and CCO = American Society of Clinical Oncology and Cancer Care Ontario; AUA = American Urological Association; CUA-CUOG = Canadian Urological Association – Canadian Urologic Oncology Group; EAU-ESTRO-SIOG = European Association of Urology – European Society for Radiotherapy & Oncology – International Society of Geriatric Oncology; NICE = National Institute for Health and Care Excellence

Limitations

The clinical evidence in this review was based on the results of a Phase III trial sponsored by industry. This trial had several limitations. First, the study population was specific to symptomatic bone mCRPC patients without visceral metastasis and who had or had not received previous docetaxel treatment. Ra-223, therefore, was indicated for use in this population only, so the generalizability of the study to the overall bone metastatic castrate-resistant prostate cancer population was limited. As such, it remains to be determined if Ra-223 can be used to treat asymptomatic patients or even to prevent the development of bone metastasis. Second, the concomitant therapy in the form of best standard care was not standardized across the clinical centres, but this approach was deemed to be appropriate by local physicians in the study. As a result, the outcomes may vary among clinical centres. Third, the study did not compare Ra-223 to other active agents, such as chemotherapy, hormonal therapy or other radiopharmaceutical therapy. Fourth, it did not assess the effect of Ra-223 in combination with other therapies, including docetaxel, abiraterone, and enzalutamide. Trials for combination of bone-targeted agents are currently ongoing.[2,3] Fifth, although the safety profile of Ra-223 in the trial was considered to be acceptable, long-term safety of Ra-223 (e.g., the risk of secondary malignancies) remains to be examined.

The included economic evaluation was not designed to compare between drugs unless there was a large difference in their values. The limits on costs or outcomes may not be applicable to every scenario; rather it may need to be adjusted according to patients with different prognoses and extent of disease, and jurisdictions of different budgets and pricing systems. Although the costs can be converted to Canadian dollars, it is uncertain if the outcomes can be transferable to a Canadian setting.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Based on the results of a Phase III, randomized, double-blind, placebo controlled trial, Ra-223, as compared with placebo, showed an overall survival benefit and delayed in time to first symptomatic skeletal event, with acceptable safety profile. The indication for Ra-223 was limited to symptomatic bone mCRPC patients without visceral metastasis who had or had not received previous docetaxel treatment. The results from an economic evaluation, which used a simplified drug model weighing on cost and hazard ratio of survival, suggested that Ra-223 was overpriced for its value. According to the study's criteria based on relative values of drugs, costs of Ra-223 should be negotiated from the US perspective (i.e., $100,000) or rejected from the UK perspective (i.e. $50,000). All identified guidelines, including a Canadian one, recommended Ra-223 be used in the treatment of symptomatic bone mCRPC without visceral metastasis. Only the NICE guideline, however, considered costs and recommended Ra-223 if an agreement on a discounted price of the drug can be reached.

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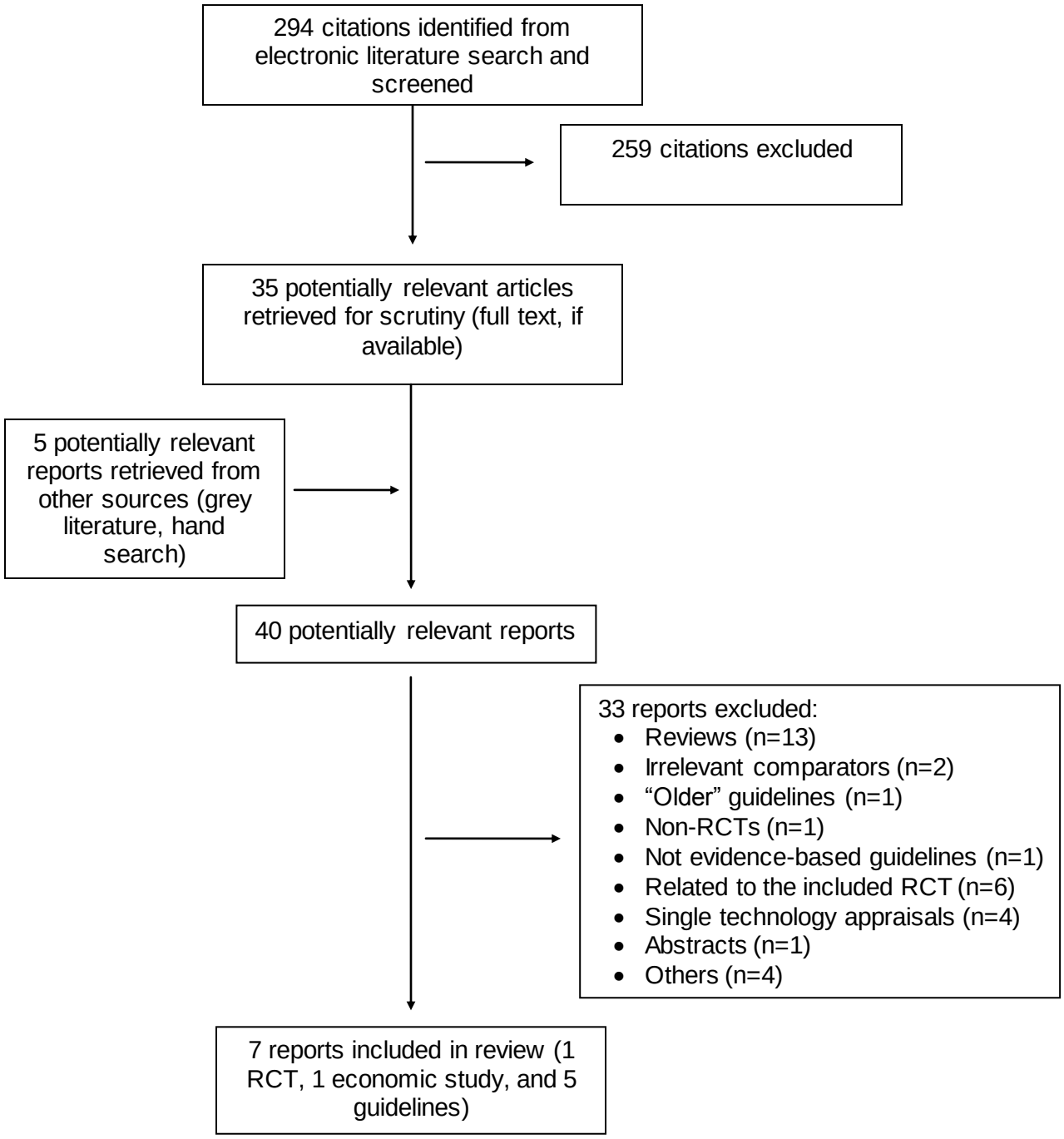
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Randomized Controlled Trial

Study, Year, Country, Design, Funding	Study Characteristics	Patient characteristics	Interventions of interest	Clinical Outcomes
ALSYMPCA trial, Parker et al., 2013[9] Multinational (136 centres in 19 countries) Double-blind, placebo-controlled, phase 3, RCT in a 2:1 ratio Funding: Bayer HealthCare Pharmaceuticals	921 patients enrolled from June 2008 to February 2011 Follow-up: 3 years Cut-off dates for analyses: 14 October 2010 (interim analyses) and 15 July 2011 (updated analysis) Analysis: ITT A formal interim analysis was planned after 50% of the deaths (320 deaths) to assess the effect of Radium on primary end point (OS) A stratified log-rank test was used as the primary analysis for survival Other endpoints were tested at a two-sided significance level of 0.05	• Age – median (range) – yr: Ra 71 (49-90) vs Pla 71 (44-94) • >75 yr – no. (%): Ra 171 (28) vs Pla 90 (29) • tALP – no. (%): - <220 U/L: Ra 348 (57) vs Pla 169 (55) - ≥220 U/L: Ra 266 (43) vs Pla 138 (45) • Current use of bisphosphonates – no. (%): - Yes: Ra 250 (41) vs Pla 124 (40) - No: Ra 364 (59) vs Pla 183 (60) • Previous use of docetaxel – no. (%): - Yes: Ra 352 (57) vs Pla 174 (57) - No: Ra 262 (43) vs Pla 133 (43) • ECOG performance score[a] – no. (%): - 0: Ra 165 (27) vs Pla 78 (25) - 1: Ra 371 (60) vs Pla 187 (61) - ≥2: Ra 77 (13) vs Pla 41 (13) • WHO ladder for cancer pain[b] – no. (%): - 1: Ra 257 (42) vs Pla 137 (45) - 2: Ra 151 (25) vs Pla 78 (25) - 3: Ra 194 (32) vs Pla 90 (29) • Extent of disease – no. (%):	• Ra-223[d] plus best standard of care[e] (n=614) • Matched Pla (saline injection) plus best standard of care (n=307)	<u>Efficacy end points:</u> 1[o] end point: OS[f] 2[o] end points: • Time to first SSE[g] • Time to increase in tALP[h] • Time to increase in PSA[i] • tALP response[j] • Normalization of tALP[k] • QoL[l] <u>Safety</u>Adverse events - Hematologic (i.e., anemia, thrombocytopenia, neutropenia) - Non-hematologic Discontinuation due to adverse events

Study, Year, Country, Design, Funding	Study Characteristics	Patient characteristics	Interventions of interest	Clinical Outcomes
		- <6 metastases: Ra 100 (16) vs Pla 38 (12) - 6-20: Ra 262 (43) vs Pla 147 (48) - >20: Ra 195 (32) vs Pla 91 (30) - Superscan[c]: Ra 54 (9) vs Pla 30 (10)		

CI = confidence interval; ECOG = The Eastern Cooperation Oncology Group; HR = hazard ratio; L = liter; mo = months; no. = number; OS = overall survival; Pla = placebo; PSA = prostate specific antigen; Ra = radium; SSE = symptomatic skeletal event; tALP = total alkaline phosphatase; U = unit; vs = versus; yr = year

[a] The Eastern Cooperation Oncology Group (ECOG) scores the performance status of patients with respect to activities of daily living as follows: 0, fully active and able to carry out all pre-disease activities without restrictions; 1, restricted in physical strenuous activity but ambulatory and able to carry out work of a light nature; 2, ambulatory and up and about for more than 50% of waking hours and capable of self-care but unable to carry out work activities; 3, capable of only limited self-care and confined to a bed or chair for more than 50% of waking hours; 4, completely disabled; and 5, dead.

[b] The WHO "ladder" for cancer pain (1, mild pain and no opioid use; 2, moderate pain and occasional opioid use; and 3, severe pain and regular daily opioid use).

[c] Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

[d] At dose of 50 kBq per kg of body weight; one injection administered every 4 weeks for a total of 6 injections plus best standard of care

[e] includes e.g. local external beam radiotherapy, bisphosphonates, corticosteroids, antiandrogens. estrogens, estramustine or ketoconazole.

[f] Median time from randomization to death from any cause

[g] Median time to first use of external beam-radiation therapy to relieve skeletal symptoms; new symptomatic pathologic vertebral or non-vertebral bone fractures; spinal cord compression, or tumor-related orthopedic surgical intervention

[h] Median time to an increase of ≥25% from baseline at week 12 in patients with no decrease from baseline, or as an increase of ≥25% above the nadir, confirmed ≥3 weeks later in patients with an initial decrease from baseline

[i] Median time to relative increase of ≥25% from baseline and an absolute increase of ≥2 ng/ml at ≥12 weeks in patients with no decrease in PSA level from baseline or relative increase of ≥25% from baseline and an absolute increase of ≥2 ng/ml above the nadir confirmed ≥3 weeks later in patients with an initial decrease from baseline

[j] Patients with reduction of ≥30% from baseline value, confirmed ≥4 weeks later

[k] Patients with ALP levels above the upper limit of the normal range at baseline return to a value within the normal range at 12 weeks, confirmed by two consecutive level ≥2 weeks apart, in patients with ALP values

[l] Increase in the score of ≥10 points on a scale of 0 to 156 on the functional Assessment of cancer Therapy-Prostate (FACT-P) instrument

APPENDIX 3: Characteristics of Economic Evaluation

Study, Year, Country, Funding	Study design	Perspective, Time Horizon, Dollar, Discounting	Population, Inclusion criteria	Interventions	Cost included
Guirgis, 2015[10] USA Funding: NR	Cost-utility analysis Outcomes: - cost/OSg - cost/LYG - Relative value[a] Treatment effects: OS gained over control in days and HR of death	Perspective: NICE (UK) and US Time horizon: none Currency: US$ Discount: none	Metastatic castrate-resistant prostate cancer patients	Chemotherapy: - Docetaxel - Cabazitaxel Immunotherapy: - Sipuleucel-T ARST therapy: - Abiraterone - Enzalutamide Radio-pharmacotherapy: - Radium-223	Wholesale prices and/or third-party payments in US$

ARST = androgen receptor signaling targeted; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LYG = life year gain; NICE = National Institute for Health and Care Excellence; NR = not reported; OSg = overall survival gain in days
[a] Relative value was calculated as US$50,000 or $US100,000 per cost/outcome

APPENDIX 4: Grading of Recommendations and Levels of Evidence

Guideline Society or Institute	Grade of Recommendation	Level of Evidence
National Institute for Health and Care Excellence (NICE)[11] 2016 UK	None	None
European Association of Urology – European Society for Radiotherapy & Oncology – International Society of Geriatric Oncology (EAU-ESTRO-SIOG)[12] 2016 Europe	**A** Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial. **B** Based on well-conducted clinical studies, but without randomized trials. **C** Made despite the absence of directly applicable clinical studies of good quality.	**1a** Evidence obtained from meta-analysis of randomized trials. **1b** Evidence obtained from at least one randomized trial. **2a** Evidence obtained from one-well designed controlled studies without randomization. **2b** Evidence obtained from at least one type of well-designed quasi-experimental studies. **3** Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies can case reports. **4** Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.
Canadian Urological Association – Canadian Urologic Oncology Group (CUA-CUOG)[13] 2015 Canada	**A** Usually consistent level 1 evidence **B** Consistent level 2 or 3 evidence or "majority evidence" from RCT's **C** Level 4 evidence, "majority evidence" from level 2 or 3 studies, expert opinion **D** No recommendation possible because of inadequate or conflicting evidence	**1** Meta-analysis of RCTs or good-quality RCT **2** Low-quality RCT or meta-analysis of good-quality prospective cohort studies **3** Good-quality retrospective case-control studies or case series **4** Expert opinion based on "first principles" or bench research, not on evidence
American Urological Association (AUA)[14] 2015 USA	**Standard:** Directive statement that an action should (benefits overweigh risks/burdens) or should not (risks/burdens overweigh benefits) be taken based on Grade A or B evidence **Recommendation:** Directive statement that an action should (benefits overweigh risks/burdens) or	**A** Well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings **B** RCTs with some weaknesses of procedure and generalizability or generally strong observational studies with consistent findings

Guideline Society or Institute	Grade of Recommendation	Level of Evidence
	should not (risks/burdens overweigh benefits) be taken based on Grade C evidence **Option:** Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears equal or appears uncertain based on Grade A, B or C evidence **Clinical Principle:** A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature **Expert Opinion:** A statement achieved by consensus of the panel, that is based on members' clinical training, experience, knowledge, and judgement for which there is no evidence	**C** Observations studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data
American Society of Clinical Oncology and Cancer Care Ontario (ASCO and CCO)[15] 2014 USA and Canada	**Strong:** There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation. **Moderate:** There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation. **Weak:** There is some confidence that	**High:** High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits v harms) and that further research is very unlikely to change either the magnitude or direction of this net effect **Intermediate:** Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect. **Low:** Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect. **Insufficient:** Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

Guideline Society or Institute	Grade of Recommendation	Level of Evidence
	the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.	

RCT = randomized controlled trial

APPENDIX 5: Quality Assessment of Randomized Controlled trials

SIGN Checklist: Randomized Controlled Trials	
Internal Validity	ALSYMPCA, Parker et al., 2013[9]
1. The study addresses an appropriate and clearly focused question.	Yes
2. The assignment of subjects to treatment groups is randomized.	Yes
3. An adequate concealment method is used.	Can't say
4. Subjects and investigators are kept 'blind' about treatment allocation.	Yes
5. The treatment and control groups are similar at the start of trial.	Yes
6. The only difference between groups is the treatment under investigation.	Yes
7. All relevant outcomes are measured in a standard, valid and reliable way.	Yes
8. What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	Radium-223 37% vs Placebo 53%
9. All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Yes
10. Where the study is carried out more than one site, results are comparable for all sites.	Can't say
Overall Assessment of the Study	
High, Moderate, Low	High

For overall assessment of the study: *High* indicated that all or most criteria have been fulfilled; where they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter. *Moderate* indicates that some of the criteria have been fulfilled; those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions. *Low* indicates that few or no criteria fulfilled; the conclusions of the study are thought likely or very likely to alter.

APPENDIX 6: Quality Assessment of Economic Evaluations

SIGN Checklist: Economic Evaluations	
Internal Validity	Guirgis, 2015[10]
1. There is a defined and answerable study question.	Yes
2. The economic importance of the question is clear.	Yes
3. The choice of study design is justified.	Can't say
4. All costs that are relevant from the viewpoint of the study are included and are measured and valued appropriately.	Yes
5. The outcome measures used to answer the study question are relevant to that purpose and are measured and valued appropriately.	Yes
6. If discounting of the future costs and outcomes is necessary, it has been performed correctly.	Not applicable
7. Assumptions are made explicit and a sensitivity analysis performed.	Not applicable
8. The decision rule is made explicit and comparisons are made on the basis of incremental costs and outcomes.	Not applicable
9. The results provide information of relevance to policy.	Yes
Overall Assessment of the Study	
High, Moderate, Low	Moderate

For overall assessment of the study: *High* indicated that all or most criteria have been fulfilled; where they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter. *Moderate* indicates that some of the criteria have been fulfilled; those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions. *Low* indicates that few or no criteria fulfilled; the conclusions of the study are thought likely or very likely to alter.

APPENDIX 7: Quality Assessment of Guidelines

AGREE II checklist: Guidelines						
	NICE 2016[11]	EAU-ESTRO-SIOG 2016[12]	CUA-CUOG 2015[13]	AUA 2015[14]	ASCO and CCO 2014[15]	
Scope and purpose						
Objectives and target patients population were explicit	Yes	Yes	Yes	Yes	Yes	
The health question covered by the guidelines is specifically described	Yes	Yes	Yes	Yes	Yes	
The population to whom the guidelines is meant to apply is specifically described	Yes	Yes	Yes	Yes	Yes	
Stakeholder involvement						
The guideline development group includes individuals from all relevant professional groups	Yes	Yes	Yes	Yes	Yes	
The views and preferences of the target population have been sought	Yes	Not clear	Not clear	Not clear	Not clear	
The target users of the guideline are clearly defined	Yes	Yes	Yes	Yes	Yes	
Rigour of development						
Systematic methods were used to search for evidence	No	No	No	Yes	Yes	
The criteria for selecting the evidence are clearly described	No	No	No	Yes	Yes	
The strengths and limitations of the body of evidence are clearly described	No	Yes	Yes	Yes	Yes	
The methods of formulating the recommendations are clearly described	Not clear	Yes	Yes	Yes	Yes	
The health benefits, side effects, and risks have been considered in formulating the recommendations	Yes	Yes	Yes	Yes	Yes	
There is an explicit link between the recommendations and the supporting evidence	Yes	Yes	Yes	Yes	Yes	
The guideline has been externally reviewed by experts prior to its publication	Not clear	Yes	Yes	Yes	Yes	
A procedure for updating the guideline is provided	Not clear	Yes	Not clear	Yes	Not clear	
Clarity of presentation						
The recommendations are specific and unambiguous	Yes	Yes	Yes	Yes	Yes	
The different options for management of the condition or health issue are clearly	Yes	Yes	Yes	Yes	Yes	

AGREE II checklist: Guidelines						
presented						
Key recommendations are easily identified	Yes	Yes	Yes	Yes	Yes	
Applicability						
The guideline describes facilitators and barriers to its application	Not clear	Yes	Not clear	Yes	Yes	
The guidelines provides advice and/or tools on how the recommendations can be put into practice	Yes	Yes	Not clear	Yes	Yes	
The potential resource (cost) implications of applying the recommendations have been considered	Yes	No	No	No	No	
The guideline presents monitoring and/or auditing criteria	Yes	Yes	Yes	Yes	Yes	
Editorial independence						
The views of the funding body have not influenced the content of the guideline	Yes	Yes	Yes	Yes	Yes	
Competing interests of guideline development group members have been recorded and addressed	Yes	Yes	Yes	Yes	Yes	

ASCO and CCO = American Society of Clinical Oncology and Cancer Care Ontario; AUA = American Urological Association; CUA-CUOG = Canadian Urological Association – Canadian Urologic Oncology Group; EAU-ESTRO-SIOG = European Association of Urology – European Society for Radiotherapy & Oncology – International Society of Geriatric Oncology; NICE = National Institute for Health and Care Excellence

APPENDIX 8: Main Study Findings and Authors' Conclusions – Clinical

<table>
<tr><th>Study, Year, Country, Design, Funding</th><th>Main Findings</th></tr>
<tr><td>ALSYMPCA, Parker et al., 2013[9]

Multinational

Phase 3, RCT (pivotal)

Funding: Algeta and Bayer HealthCare Pharmaceuticals</td><td>

1. Efficacy:

Outcomes	Ra-223 (N=614)	Pla (N=307)	HR (95% CI); *p*-value
Median OS[a] – mo			
Interim analysis	14.0	11.2	0.70 (0.55 to 0.88); p=0.002
Updated analysis	14.9	11.3	0.70 (0.58 to 0.83); *p*<0.001
Time to first SSE[b] – mo	15.6	9.8	0.66 (0.52 to 0.83); *p*<0.001
Time to increase in tALP[c] – mo	7.4	3.8	0.17 (0.13 to 0.22); *p*<0.001
Time to increase in PSA[d] – mo	3.6	3.4	0.64 (0.54 to 0.77); *p*<0.001
Total ALP response[e] – % (n/N)	47 (233/497)	3 (7/211)	*p*<0.001
Normalization of tALP[f] – % (n/N)	34 (109/321)	1.4 (2/140)	*p*<0.001

CI = confidence interval; HR = hazard ratio; mo = months; OS = overall survival; Pla = placebo; PSA = prostate specific antigen; Ra = radium; SSE = symptomatic skeletal event; tALP = total alkaline phosphatase

[a] Median time from randomization to death from any cause

[b] Median time to first use of external beam-radiation therapy to relieve skeletal symptoms; new symptomatic pathologic vertebral or non-vertebral bone fractures; spinal cord compression, or tumor-related orthopedic surgical intervention

[c] Median time to an increase of ≥25% from baseline at week 12 in patients with no decrease from baseline or as an increase of ≥25% above the nadir, confirmed ≥3 weeks later in patients with an initial decrease from baseline

[d] Median time to relative increase of ≥25% from baseline and an absolute increase of ≥2 ng/ml at ≥12 weeks in patients with no decrease in PSA level from baseline or relative increase of ≥25% from baseline and an absolute increase of ≥2 ng/ml above the nadir confirmed ≥3 weeks later in patients with an initial decrease from baseline

[e] Patients with reduction of ≥30% from baseline value, confirmed ≥4 weeks later

[f] Patients with ALP levels above the upper limit of the normal range at baseline return to a value within the normal range at 12 weeks, confirmed by two consecutive level ≥2 weeks apart)

2. Subgroup analysis of hazard ratio for death:

Subgroups	Ra-223	Pla	HR (95% CI)
Median overall survival (mo)			
Previous docetaxel use			
Yes	14.4	11.3	0.70 (0.56 to 0.88)
No	16.1	11.5	0.69 (0.52 to 0.92)
tALP level at baseline			
<220 U/L	17.0	15.8	0.82 (0.64 to 1.07)
≥220 U/L	11.4	8.1	0.62 (0.49 to 0.79)
Current bisphosphonate use			
Yes	15.3	11.5	0.70 (0.52 to 0.93)
No	14.5	11.0	0.74 (0.59 to 0.92)
Baseline ECOG performance-status score[a]			
0 or 1	15.4	11.9	0.68 (0.56 to 0.82)
≥2	10.0	8.4	0.82 (0.50 to 1.35)
Opioid use			
Yes[b]	13.9	10.4	0.68 (0.54 to 0.86)
No[c]	16.4	12.8	0.70 (0.52 to 0.93)
Extent of disease			
<6 metastases	27.0	NE	0.95 (0.46 to 1.95)
6-20 metastases	13.7	11.6	0.71 (0.54 to 0.92)
>20 metastases	12.5	9.1	0.64 (0.47 to 0.88)
Superscan[d]	11.3	7.1	0.71 (0.40 to 1.27)

CI = confidence interval; HR = hazard ratio; mo = months; NE = not evaluated; OS = overall survival; Pla = placebo; Ra = radium

</td></tr>
</table>

Study, Year, Country, Design, Funding	Main Findings

[a] The Eastern Cooperation Oncology Group (ECOG) scores the performance status of patients with respect to activities of daily living as follows: 0, fully active and able to carry out all pre-disease activities without restrictions; 1, restricted in physical strenuous activity but ambulatory and able to carry out work of a light nature; 2, ambulatory and up and about for more than 50% of waking hours and capable of self-care but unable to carry out work activities; 3, capable of only limited self-care and confined to a bed or chair for more than 50% of waking hours; 4, completely disabled; and 5, dead.
[b] The category for use of opioids includes patients with a score of 2 or 3 on the WHO "ladder" for cancer pain (1, mild pain and no opioid use; 2, moderate pain and occasional opioid use; and 3, severe pain and regular daily opioid use).
[c] The category for non-use of opioid included patients without pain or opioid use at baseline and patients with a score of 1 on WHO ladder for cancer pain.
[d] Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

3. Safety:

Adverse events	Ra-223 (N=600)	Pla (N=301)
All AEs – %	93	96
Grade 3 or 4	56	62
Serious AEs – %	47	60
Disease progression	11	12
Bone pain	10	16
Anemia	8	9
Spinal cord compression	4	5
Discontinuation due to AEs – %	16	21
Hematologic with all grades		
Anemia – %	31	31
Thrombocytopenia – %	12	6
Neutropenia – %	5	1
Hematologic with grade 3 or 4	No differences in frequency between groups	
Non-hematologic with all grades	No differences in frequency between groups	

AEs = adverse events; Pla = placebo; Ra = radium

4. Quality of life (QoL):

Functional Assessment of Cancer Therapy – Prostate (FACT-P) was used to assess QoL.

Patients in both Ra-223 and placebo groups experienced loss in QoL according to FACT-P total score. However, the loss in QoL in the Ra-223 group was less pronounced than those in the placebo group (from baseline to week 16: -2.7 versus -6.8, p=0.0006)

Authors' conclusions: "*In this phase 3 study, radium-223 significantly prolonged overall survival in patients who had castration-resistant prostate cancer and bone metastases, with a 30% reduction in the risk of death, as compared with placebo.*"[9] p.220

APPENDIX 9: Main Study Findings and Authors' Conclusions – Economic

<table>
<tr><th>Study, Year, Country, Design, Funding</th><th>Main Findings</th></tr>
<tr><td>Guirgis, 2015[10]

Cost-utility

USA

Not reported</td><td>
Costs and outcomes in chemo-treated patients with mCRPC
<table>
<tr><th>Drug</th><th>OSg (HR), CI</th><th>Cost, US$</th><th>Cost/OSg, US$</th><th>Cost/LYG, US$</th><th>RV</th><th>RV</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>$50,000</td><td>$100,000</td></tr>
<tr><td>Docetaxel</td><td>72 (0.76), not given</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>x10 cy</td><td></td><td>3,508</td><td>49</td><td>17,540</td><td>2.85</td><td>5.70</td></tr>
<tr><td>x10 cy + ancillary costs</td><td></td><td>5,266</td><td>73</td><td>26,330</td><td>1.90</td><td>3.80</td></tr>
<tr><td>Cabazitaxel</td><td>72 (0.70), 0.59 to 0.83</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>x6 cy</td><td></td><td>34,350</td><td>477</td><td>171,750</td><td>0.29</td><td>0.58</td></tr>
<tr><td>x6 cy + ancillary costs</td><td></td><td>41,448</td><td>576</td><td>207,240</td><td>0.24</td><td>0.48</td></tr>
<tr><td>x10 cy + ancillary costs</td><td></td><td>46,180</td><td>641</td><td>230,900</td><td>0.22</td><td>0.44</td></tr>
<tr><td>Sipuleucel-T</td><td>123 (0.78), 0.61 to 0.98</td><td>93,000</td><td>756</td><td>272,195</td><td>0.18</td><td>0.37</td></tr>
<tr><td>Enzalutamide (PREVAIL trial)</td><td>66 (0.70), 0.59 to 0.83</td><td>89,400</td><td>1355</td><td>487,636</td><td>0.10</td><td>0.21</td></tr>
<tr><td>Enzalutamide (AFFIRM trial)</td><td>144 (0.63), 0.53 to 0.75</td><td>89,400</td><td>621</td><td>223,500</td><td>0.22</td><td>0.45</td></tr>
<tr><td>Abiraterone (COU-AA-302 trial)</td><td>132 (0.80), 0.69 to 0.93</td><td>74,400</td><td>536</td><td>202,910</td><td>0.25</td><td>0.49</td></tr>
<tr><td>Abiraterone (COU-AA-301 trial)</td><td>138 (0.74), 0.64 to 0.86</td><td>74,400</td><td>539</td><td>194,087</td><td>0.26</td><td>0.52</td></tr>
<tr><td>Radium-223</td><td>108 (0.695), 0.55 to 0.88</td><td>69,000</td><td>639</td><td>230,000</td><td>0.22</td><td>0.43</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Authors' conclusions: Based on relative values, the authors suggested that radium-223, cabazitaxel, sipuleucel-T, enzalutamide and abiraterone were overpriced for their values in the treatment of mCRPC. Generic docetaxel had the lowest costs, cost/outcome and highest relative values. "Drugs with RVs of <0.5 should be scrutinized, their costs negotiated, or other drugs considered, and those with RVs of <0.25 should be rejected."[10] p.365</td></tr>
</table>

CI = confidence interval; HR = hazard ratio; LYG = life-year gained; mCRPC = metastatic castrate-resistant prostate cancer; OSg = overall survival gain over control in days; QALY = quality adjusted life-year

[a] RV was calculated as US$ 50,000 or US$ 100,000 per cost/LYG

APPENDIX 10: Guidelines and Recommendations for Radium-223 for Treatment of Patients with Bone Metastatic CRPC

Guideline Society or Institute	Recommendations
National Institute for Health and Care Excellence (NICE)[11] 2016 UK	"*1.1 Radium-223 dichloride is recommended as an option for treating hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases in adults, only if:* • *they have already had docetaxel or* • *docetaxel is contraindicated or is not suitable for them.* *The drug is only recommended if the company provides radium-223 dichloride with the discount agreed in the patient access scheme.* *1.2 This guidance is not intended to affect the position of patients whose treatment with radium-223 dichloride was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.*"[11] p.4
European Association of Urology – European Society for Radiotherapy & Oncology – International Society of Geriatric Oncology (EAU-ESTRO-SIOG)[12] 2016 Europe	"*Treat patients with mCRPC with life-prolonging agents. Base the choice of first-line treatment on the performance status, symptoms, comorbidities, and extent of disease (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, radium 223, sipuleucel-T).*"[12] **[Grade A; Level 1b]** p.7
Canadian Urological Association – Canadian Urologic Oncology Group (CUA-CUOG)[13] 2015 Canada	"*Radium-223 every 4 weeks for 6 cycles is recommended in patients with pain due to bone metastases and who do not have visceral metastases.*"[13] **[Grade A; Level 1]** p.92
American Urological Association (AUA)[14] 2015	"*Clinicians should offer radium-223 to patients with symptomatic, cCRPC with good performance status and no prior docetaxel chemotherapy with symptomatic bone metastases and without known visceral disease.*"[14] **[Standard; Evidence strength: Grade B]** p.495

Guideline Society or Institute	Recommendations
USA	
American Society of Clinical Oncology and Cancer Care Ontario (ASCO and CCO)[15] 2014 USA and Canada	"*Therapies in Addition to Androgen-Deprivation Therapy:* *Therapies with demonstrated survival and quality-of-life benefits:* • *Radium-223 should be offered to men with bone metastases.*"[15] **[Recommendation strength: strong; evidence quality: high]** p.3437

mCRPC = metastatic castration-resistant prostate cancer

APPENDIX 11: Additional References of Interest

Related Studies to ALSYMPCA Trial

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