Single Technology Appraisal

Radium-223 dichloride for treating metastatic hormone relapsed prostate cancer with bone metastases [ID576]

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Rider on responsibility for report

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Contributions of authors

Ewen Cummins reviewed the cost-effectiveness evidence, carried out further sensitivity analyses, and drafted the cost-effectiveness, impact on the ICER and end of life sections. Craig Ramsay and Clare Robertson reviewed the methods of the clinical effectiveness evidence synthesis and drafted the summary, background, manufacturer's decision problem and clinical effectiveness sections. Craig Ramsay drafted the overall conclusions. Thomas Lam provided clinical advice and contributed to the background and the critique of the manufacturer's decision problem sections. Neil Scott critiqued the statistical methods used, checked all the numerical results, tables, and figures of the clinical effectiveness part of the submission, and conducted further statistical analyses. Fiona Stewart critiqued the methods used for identifying relevant studies in the literature. Craig Ramsay supervised the work throughout the project. All authors assisted in preparing the final manuscript and commenting on early drafts.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AIC	Akaike Information Criterion
ALP	Alkaline Phosphatase
BSC	Best Supportive Care
CI	Confidence Interval
CRD	Centre for Reviews and Dissemination
DSU	Decision Support Unit
EBRT	External Beam Radiation Therapy
ECOG	European Cooperative Oncology Group
EQ-5D	EuroQuol 5-Dimension
ERG	Evidence Review Group
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-P	Functional Assessment of Cancer Therapy - Prostate
FAS	Full Analysis Set
FDA	Food and Drug Administration
HR	Hazard Ratio
HRQoL	Health-related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
ITT	Intention To Treat
LHRH	Luteinising Hormone Releasing Hormone
mCRPC	Metastatic Castration Resistant Prostate Cancer
MS	Manufacturer's Submission
OS	Overall Survival
PFS	Progression Free Survival
PSA	Prostate Specific Antigen
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
SAE	Serious Adverse Avent
SEER	Surveillance Epidemiology and End Results
SRE	Skeletal Related Event
TEAE	Treatment Emergent Adverse Event

1 SUMMARY

This report provides a review of the evidence submitted by Bayer in support of radium-223 dichloride (trade name Xofigo) for the treatment of metastatic castration resistant prostate cancer (mCRPC). It considers the original manufacturer's submission (MS) received by the ERG on 28th June 2013 and the manufacturer's responses to clarification requests received on 5th August 2013.

1.1 Critique of the decision problem in the manufacturer's submission

The MS encompasses the clinical and cost-effectiveness of radium-223 dichloride for the treatment of mCRPC patients with bone metastases as a first line treatment if patients are not suitable for docetaxel, and as a second line option following treatment with docetaxel. Comparison was made between placebo and best supportive care. There were a few differences between the scope issued by NICE and that submitted by the manufacturer. These are summarised below.

The NICE scope for this STA stated that abiraterone should be considered as a comparator for radium-223 dichloride for people who had previously received docetaxal. For people who had not received docetaxal NICE requested that abiraterone and docetaxal should be considered as comparators. In their submission, the manufacturer provided an argument against abiraterone and docetaxal being used as comparators. The manufacturer argued that those patients who were eligible for their first course of docetaxel were excluded from the phase III study (ALSYMPCA) and as such, a comparison with docetaxel was inappropriate. The ERG agrees in principle with this change though does note that in the ALSYMPCA trial some patients were categorised as "refused docetaxal" and "docetaxal was not available" and as such may therefore have been eligible for docetaxel. In such cases the comparator should in the opinion of the ERG remain docetaxal.

The MS also argued that a comparison with abiraterone in the second line setting was limited by trial heterogeneity and expert clinical opinion indicated that this (indirect) comparison was not appropriate or likely to be helpful, a view which was endorsed by key opinion leader opinion. Although the ERG accepts that ALSYMPCA provides the main evidence in this submission, it suggests that comparators should have been included based on the inclusion criteria of the scope issued by NICE and not based on similarity to one of the trials (ALSYMPCA) in the review.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The main evidence for the clinical effectiveness of radium-223 dichloride came from an international, multicentre, double-blind phase three randomised controlled trial (RCT) sponsored by the manufacturer, the ALSYMPCA trial. Evidence from a smaller phase-two, international multicentre, double-blind RCT (BC1-02) was presented in a supportive role. Both trials included some centres located in the UK and compared radium-223 dichloride with placebo plus BSC. Unlike BC1-02, however, patients participating in ALSYMPCA were allowed to receive bisphosphonates prior to study entry and as part of BSC therapy during the trial. Patients who were fit enough and willing to receive docetaxel were excluded from the ALSYMPCA trial.

1.2.1 Primary outcome

Overall survival (OS) was the primary outcome in ALSYMPCA. Radium-223 dichloride significantly prolonged median OS by 3.6 months (HR=0.695; 95% confidence interval [CI] 0.581 to 0.832, p=0.00007) representing a 30.5% reduction in the risk of death. These results were consistent across all subgroups (baseline levels of total ALP, current use of bisphosphonates, and ECOG status at baseline),

[redacted]

OS was a secondary outcome in the BC1-02 trial. Radium-223 dichloride improved median overall survival by 4.7 months (65.3 vs 46.4 weeks, HR=0.476; 95% CI 0.258 to 0.877, p=0.017) for the ITT population.

1.2.2 Secondary outcomes

Skeletal-related events

Both ALSYMPCA and BC1-02 reported skeletal-related events (SREs). In both trials, radium-223 dichloride reduced the incidence and frequency of SREs compared with the placebo plus BSC group. Median time to an SRE event was also extended by radium-223 dichloride in comparison with placebo plus BSC, although this difference was only significant in the ALSYMPCA trial. Time to first SRE was 15.6 months for radium-223 dichloride vs 9.8 months for placebo in ALSYMPCA (HR=0.658, 95% CI 0.522to 0.830 p=0.00037). In the ITT BC1-02 population, median time to first SRE was 14 weeks (95% CI 9 to 30) in the radium-223 dichloride arm and 11 weeks (95% CI 5 to 25) in the placebo group (p=0.257 log rank).

Changes and time to PSA progression

Compared with placebo, treatment with radium-223 dichloride led to a higher proportion of patients with a PSA reduction of ≥30% or ≥50% in ALSYMPCA ([redacted]). Radium-223 dichloride was also associated with delayed time to progression in both studies. The ERG notes that for both SRE and PSA regression time to event analyses that death was treated as a censored case not an event and therefore bias due to informative censoring may have been introduced.

Alkaline phosphatase (ALP)

Treatment with radium-223 [redacted]

Change in bone ALP was a primary endpoint in BC1-02 but was not measured in ALSYMPCA. Bone ALP was lowered in the radium-223 dichloride arm compared with the placebo plus BSC arm. [redacted]

1.2.3 Additional effectiveness outcomes

Pain

Pain response was not formally evaluated in ALSYMPCA, although a number of pain-related endpoints provided evidence in support of a positive effect of radium-223 dichloride on bone pain. These included reduction in opioid use and increased time to initial opioid use, increased time to EBRT for skeletal pain, fewer reports of bone pain as an adverse event [redacted].

The effect of pain in BC1-02 is potentially confounded as all patients received EBRT at baseline.

Quality of life

Quality of life was measured by FACT-P and EQ-5D in the ALSYMPCA trial and by the Edmonton Symptom Assessment Scale in BC1-02. Radium-223 dichloride was associated with better quality of life than placebo plus BSC in ALSYMPCA [redacted].

1.2.4 Safety

Radium-223 dichloride had a lower incidence of Grade 3 or 4 adverse events (AEs), serious AEs, AEs leading to discontinuation of treatment and [redacted] compared to placebo plus BSC. [redacted]. There were also slight increases in myelosuppression, mild to moderate (grade 1 and 2) diarrhoea, constipation, nausea and vomiting associated with radium-223 dichloride.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The submission appears complete in that two RCTs comparing radium-223 dichloride with placebo plus BSC were presented. The ERG are satisfied that there are no missing studies from the MS. Both trials provided persuasive evidence that radium-223 dichloride confers a survival advantage, increasing median OS by about 3-4 months. The RCTs provided evidence that radium-223 dichloride has a positive impact on SREs and disease progression and is well-tolerated with a favourable safety profile when compared to BSC. The evidence provided by the manufacturer is weak to support the use of radium-223 for first line use as the 1st line patient population in ALSYMPCA is highly selective and radium-223 has not been compared against all valid comparators.

The methodological quality of ALSYMPCA and BC1-02 was generally good, although the ERG note that the ALSYMPCA trial included a heterogeneous patient population. The ERG notes that Black and other racial groups were under-represented in the trial populations and it cannot be certain that the observed effects are necessarily generalisable to these groups. This may be an important consideration for the decision problem as, although the number of African Caribbean men aged over 40 years is much lower that the number of Caucasians, African Caribbean men are three times more likely to get prostate cancer than white men of the same age.

No attempt was made to meta-analyse the results of the two trials due to the different number of administered doses of radium-223 dichloride (six in ALSYMPCA versus four in BC1-02); difference in inclusion criteria for life expectancy (six months in ALSYMPCA versus 3 months in BC1-02); patients in ALSYMPCA could receive bisphosphonates as part of BSC, whereas bisphosphonate treatment within 3 months prior to study entry was an exclusion criteria for BC1-02; and a requirement for EBRT was an inclusion criterion for BC1-02 but patients could have been treated with regular analgesia or EBRT for bone pain in the previous

12 weeks in ALSYMPCA. The ERG is satisfied that the difference in dosing administration renders the intervention sufficiently different that clinical heterogeneity precludes statistical pooling of results.

The MS contended that only patients who had previously received docetaxel or who were ineligible for docetaxel treatment represented the most appropriate population for the decision problem. This population did not correspond exactly with that outlined in the final NICE scope as discussed in detail in sections 1.1 and 3 of the ERG report.

The manufacturer identified two eligible RCTs, both of which compared abiraterone plus prednisone with placebo plus prednisone, and four single-arm studies of abiraterone. However, the manufacturer stated that comparison with radium-223 was limited due to clinical heterogeneity between the trial populations. Furthermore, the manufacturer stated that clinical key opinion leaders advised that abiraterone is not a valid clinical comparator. While, the ERG accepts that the heterogeneous population included in the ALSYMPCA trial of chemotherapy-naive patients and patients previously treated with chemotherapy, limits direct comparison with the trials of abiraterone, it is the ERG belief that, while problematic, it would have been possible to conduct a meta-analysis by sub-groups of patients by their ECOG performance status and prior use of docetaxel. Indeed, the manufacturer presents sub-group analysis for the economic model.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer developed a de novo model of the cost effectiveness of radium-223 compared to best supportive care, or placebo. It is a cost utility model with a weekly cycle and a five year time horizon. The model estimates the overall survival in each arm up to the end of the five year time horizon. For each cycle, the remaining survivors are divided into those:

- without progression and without an on study SRE;
- with progression and without an on study SRE;
- without progression and with an on study SRE; and
- with progression and with an on study SRE.

Adverse events are included within the modelling, with HRQoL and cost allowances for these being added to the first cycle of the model.

Overall survival is based upon lognormal curves fitted to the Kaplan Meier data of the ALSYMPCA trial. The calculation of the proportions of survivors falling into each of the four health states of the model is also mainly based upon lognormal curves fitted to the Kaplan Meier data for progression free survival data and first on trial SRE.

HRQoL estimates for those with and without progression are based upon the EQ-5D data of the ALSYMPCA trial. These estimates are differentiated by treatment arm. They suggest that [redacted], but that treatment with radium-223 provides a quality of life increment of around [redacted] compared to placebo. This quality of life increment endures for the lifetime of the patient.

HRQoL estimates for the impacts of SREs are estimated separately, and are based upon a weighted average of values taken from the literature. These HRQoL impacts from SREs are applied to patients modelled as having had an on study SRE. They are additional to the radium-223 [redacted] quality of life increment. They are also assumed to endure for the remaining lifetime of the patient.

An average of [redacted] radium-223 administrations is applied within the model. The cost per radium-223 treatment is [redacted], plus an additional £200 cost of administration as drawn from NHS reference costs.

Ongoing resource use is based upon a manufacturer commissioned survey of oncologists and urologists [redacted].

Progression leads to second line treatment at an average cost of [redacted], this being based upon a weighted average drawn from the IMS Oncology Analyser.

Incident SREs are costed at an average of [redacted] within the radium-223 arm and [redacted] within the placebo arm. This is based upon unit costs for the four SREs that are averages of a range of NHS reference costs and some additional GP costs, coupled with arm specific balances between the 1st on trial SREs drawn from the ALSYMPCA trial.

Adverse events are included, with both cost and quality of life impacts, but these have minimal impact upon results.

An end of life cost of £2,087 is applied within the model, based upon values within a paper from the literature.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The model structure is broadly reasonable. The calculation of the cohort flow may require some revision, but this only worsens the cost effectiveness estimate by around 2%.

The key model drivers are:
the cost of radium-223;
the number of radium-223 cycles;
the overall survival curves; and,
the post progression utility increment for radium-223 over placebo.

Uncertainty around the overall survival curve relates to whether the lognormal curve or the loglogistic curve is the most appropriate, and how far to extrapolate beyond the trial data. The manufacturer base case applies the lognormal curve and a 5-year time horizon. There is no obvious reason to prefer the lognormal curve over the loglogistic curve, and the loglogistic curve worsens the cost effectiveness estimates by around 5%. Results are particularly sensitive to the time horizon, with shorter time horizons somewhat worsening the cost effectiveness estimates.

Uncertainty around the post progression utility increment for radium-223 over placebo arises due to the minimal information within the submission about the EQ-5D values collected during the ALSYMPCA trial. No real statistical analysis of this data is presented within the submission. Simple means are used, split by arm and progression, with no consideration of SREs or any other variables within the data. Given the model health states, it is surprising that no analysis of the EQ-5D data was undertaken to estimate quality of life values for the main health states and events within the model, while considering baseline values. The analysis of the ALSYMPCA EQ-5D data as presented within the economics of the submission is exceptionally sparse.

If end of life criteria apply, the appropriate quality of life value for calculating the value of the additional survival is uncertain. Values of 1.00 and 0.78 are candidates, and it seems unlikely that the appropriate value will lie outside this range. The resulting values placed upon the additional survival are insufficient to result in the cost effectiveness estimates being within the NICE cost effectiveness thresholds of £30,000 per QALY and £20,000 per QALY. The end of life adjusted cost effectiveness estimates typically remain above [redacted] per QALY for the 1.00 quality of value, and for the 5-year time horizon are closer to [redacted] per QALY. For the 0.78 quality of life value the end of life adjusted cost effectiveness estimates typically

remain above [redacted] per QALY, and for the 5-year time horizon tend to exceed [redacted] per QALY.

The ERG critique of more specific points of the analysis are given in section 1.6.2 below.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

- Overall, the search strategies used by the manufacturer were highly sensitive and fit for purpose.
- Two good quality, double-blind RCTs demonstrated a clear survival gain from the use of radium-223 dichloride.
- The RCTs provided evidence that radium-223 dichloride has a positive impact on SREs and disease progression.
- Radium-223 dichloride is well-tolerated with a favourable safety profile.
- A clear model structure with the main cohort flow being reasonably implemented.
- The written submission being broadly in line with the electronic model submitted and sufficient to assess most aspects of it.

1.6.2 Weaknesses and areas of uncertainty

- The ERG believes that it was not appropriate to exclude the abiraterone RCTs from the systematic review. The abiraterone studies clearly met the inclusion criteria for the review and included patients with bone metastases (with and without visceral disease).
- The ERG is concerned that there was no clear rationale for applying two different search criteria so that BC1-02 was eligible for a meta-analysis of radium-223 dichloride versus best standard care but not for a wider network meta-analysis.
- The manufacturer's primary analyses of time to progression and time to SRE treat deaths as a censored event. This may introduce bias as this introduces informative censoring.
- The use of the lognormal distribution for overall survival for most analyses. The loglogistic may be equally suitable based upon the Akaike information criterion, and may actually be preferable for the prior docetaxel subgroup.
- The EQ-5D data supplied at clarification does not obviously tally with that supplied in the submission, although this may be a misinterpretation on the part of the ERG.
- The analysis of the ALSYMPCA EQ-5D data is exceptionally bald and weak. It only considers progression and arm, despite SREs being within the data and a defining

element of the model health states. The data supplied at clarification suggests that SREs within ALSYMPCA EQ-5D data may have a considerable impact on quality of life. Controlling for this may somewhat reduce the quality of life increment for radium-223 over placebo for the post progression health states.

- The quality of life increment for radium-223 over placebo for the post progression health states is assumed to apply for the remainder of the patient lifetime.
- The quality of life impacts of SREs may have been double counted, given that these impacts will be within the ALSYMPCA EQ-5D data already. The quality of life decrements of SREs are also assumed to persist for the patient lifetime. Sensitivity analyses excluding these impacts have little effect upon results, but this does not take into account the above criticism of the analysis of the ALSYMPCA EQ-5D data.
- No consideration of the resource use data collected during the ALSYMPCA trial is reported, other than for the proportion of adverse events treated as inpatients.

Weaknesses of lesser importance include:

- There may be some concerns around the reliability of the identification of SREs events beyond six months and the impact this might have upon the estimated SRE curves.
- The possible double counting of some cost impacts of SREs, given the differentiation of the routine care costs by arm and by progression. There is also a possible underestimation of the costs of SREs based upon the MTA review of denosumab for the prevention of SREs.
- Assuming that all pathological fractures were either of the arm, leg or rib.
- A lack of clarity as to the resource use data taken from the [redacted], and why only the Q4 2011 data was used.
- A lack of clarity around the resource use survey of the manufacture and how it gives rise to some differentiation of resource use by arm.
- Adverse event rates within the economics apparently do not correspond with those given in the clinical effectiveness section of the submission.
- SRE and progression costs are based upon Kaplan Meier curves rather than the parametric curves.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG revisions to the manufacturer base case that retain the submission EQ-5D utility values suggest cost effectiveness estimates for radium-223 compared to placebo of [redacted] per QALY, [redacted] per QALY and [redacted] per QALY for all patients, the prior docetaxel subgroup and the no prior docetaxel subgroup respectively. The corresponding estimates

when using the EQ-5D utility values supplied at clarification are [redacted] per QALY, [redacted] per QALY and [redacted] per QALY.

Note that using the EQ-5D utility values supplied at clarification does not address the main concerns of the ERG about the lack of any detailed analysis of the ALSYMPCA EQ-5D data.

The full range of sensitivity analyses undertaken by the ERG are tabulated in section 5.4 of the MS. A summary of these is presented below:

- The main sensitivity regarding quality of life values is to the post progression quality of life increment of a little over [redacted] for radium-223 compared to placebo. Excluding this worsens the cost effectiveness estimates by around 22%. The quality of life impacts of SREs and adverse events have relatively little impact upon the modelling, with the worst case scenarios that exclude them altogether typically changing the cost effectiveness estimates by less than 1%.
- The cost effectiveness estimates are sensitive to the time horizon adopted. A 3-year time horizon increases the cost effectiveness estimate for all patients to around [redacted] per QALY, while a 7-year time horizon reduces it to between [redacted] per QALY. The sensitivity to the time horizon is also non-linear, meaning that even if 5 years is seen as the most reasonable for the base case any uncertainty around it would tend to further increase the ICER.
- There is no obvious reason for preferring the lognormal over the loglogistic for overall survival. Applying the loglogistic curve for overall survival worsens the cost effectiveness estimate by around 5%, though the effect is less marked for the no prior docetaxel subgroup. Applying the Weibull curve for overall survival has a larger impact, worsening the cost effectiveness estimates by around 20% for all patients and the prior docetaxel subgroup, and by around 30% for the no prior docetaxel subgroup. But given the AICs the Weibull is less obviously justified for overall survival.
- The exploration of costs has relatively little impact upon results. Only the application of the denosumab MTA SRE costs has any real effect, but this only worsens the cost effectiveness estimates by a little over 1%.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer's description of prostate cancer in terms of prevalence, symptoms and complications is accurate and appropriate to the decision problem.

The manufacturer states that prostate cancer cell growth is stimulated by androgens, in particular testosterone and dihydrotestosterone. Treatments in advanced stages of prostate cancer, often referred to as hormone therapy, are aimed at reducing androgen levels and is achieved either surgically by bilateral orchiectomy, or medically, using a combination of luteinising hormone releasing hormone (LHRH) receptor agonists or antagonists, and antiandrogens. Eventually, prostate cancer is no longer controlled by hormone therapy, despite castration levels of testosterone.[1] At this stage, the disease is referred to as castration-resistant prostate cancer.

The majority of patients with castration-resistant prostate cancer have already developed metastatic disease prior to diagnosis; for those without metastases, many surviving patients experience metastases during the course of their disease. The manufacturer states that the most common site of metastases is bone, typical sites of involvement being the spine, pelvis, femur and rib cage.[2-4] The manufacturer states that mCRPC is associated with reduced survival and a poor quality of life.[5,6] In section 2.3 of the submission, the manufacturer provides estimates for life expectancy that are based on data obtained from one Danish cohort study[7] and from U.S. SEER data,[8] which present survival rates for prostate cancer patients with and without bone metastases and with bone metastases plus skeletal related events. While these data are comparable with the UK, it is unclear whether figures for bone metastases also include patients with visceral metastases from the data presented. As radium-223 dichloride is suitable for treating mCRPC with bone metastases only, it is unclear how many men would be eligible for treatment from the data presented.

In addition to reduced survival, the clinical implications of bone metastases include pain, increased analgesic consumption, lack of energy, as well as skeletal related events (SREs), impaired mobility, and haematological consequences of bone marrow involvement such as anaemia. SREs include spinal cord compression and neurologic symptoms (e.g. paraesthesia, lower extremity weakness or paralysis, bladder and bowel dysfunction), requiring emergency neurosurgical decompression or external beam radiotherapy, and pathological bone fracture and the need for orthopaedic surgery or external beam radiotherapy.[6,9] Consequently, the

management of mCRPC is associated with substantial economic burden[6,10] and patients with mCRPC invariably have a decreased quality of life,[6,11,12] and experience significant anxiety and depression.[11]

2.2 Critique of manufacturer's overview of current service provision

Section 2.4 of the manufacturer's submission (MS) presents an overview of current treatment options within the NHS. It is the opinion of the ERG that this description is accurate at the time of submission.

The majority of mCRPC patients have bone metastases, and the main cause of disability and death among those with mCRPC is bone metastases. mCRPC is not curable and so the goals of treatment are palliative in nature (i.e. to improve survival and quality of life, and to control symptoms). At this stage in the disease the control of symptoms and measures that improve quality of life can become as important as treatments that prolong life. The prognosis for mCRPC patients is worsened if the patient has also experienced one or more SRE.[7,8] Treatment decisions are based on the risk of further disease progression, as well as other factors including life expectancy, overall health and acceptability of side effects. Currently available treatments can be aggressive and be associated with significant toxicities.

NICE currently recommends docetaxel as a first line treatment in patients with good performance status (Karnofsky performance of at least 60%) for a maximum of 10 cycles – fewer cycles in case of serious adverse events (AEs) or further disease progression. Repeat cycles are not recommended. NICE Technology Appraisal 259,[13] published in June 2012, recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of mCRPC in adults if their disease has progressed on or after one docetaxel-containing chemotherapy regimen. Crucially, in this second-line setting, the drug is suitable in all mCRPC patients, regardless of site or nature of metastases (e.g. bony, soft tissue or visceral metastases).

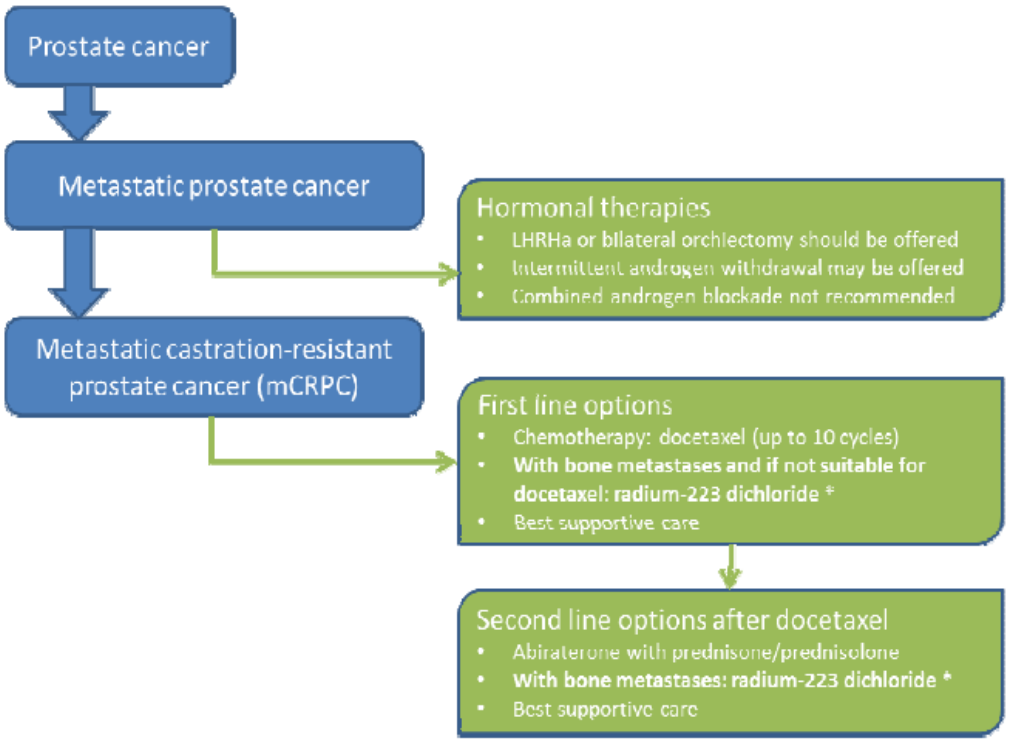
Patients with mCRPC may also receive concomitant best supportive care (BSC) therapies at any point in their management if additional symptomatic relief of bone metastases is required. These may include: external beam radiotherapy, strontium- 89, orthopaedic surgery, analgesics, steroids (e.g. dexamethasone).

Bisphosphonates are not recommended except on failure of analgesics or radiotherapy to control pain. Spinal MRI should be considered in men with extensive bone metastases if they develop spinal related symptoms.[14] Therapies for mCRPC are primarily palliative, to relieve symptoms such as pain, fractures and other SREs. Like radium-223 dichloride,[15,16] both docetaxel and abiraterone treatments have been demonstrated to improve overall survival.[4,17] Other therapies, listed under best supportive care (BSC) and not all approved by NICE, have not been shown to improve survival but some may delay skeletal disease progression or help to alleviate pain.[14,18]

Although not specific to prostate cancer or its treatment, there has been further guidance relating to the prevention of skeletal-related events (SREs) in adults with bone metastases from solid tumours. NICE Technology Appraisal 265,[18] published in October 2012, recommended against the use of denosumab for preventing SREs in adults with bone metastases from prostate cancer. Uses in other settings were however recommended.[18] There is an ongoing appraisal of denosumab for prevention of SREs in a different patient group: people with non-metastatic castration-resistant prostate cancer at high risk of developing bone metastases.[19]

In section 2.5 of the MS, the manufacturer presents Radium-223 dichloride solution for the treatment of mCRPC as a first line treatment if patients are not suitable for docetaxel, and as a second line option following treatment with docetaxel. The clinical pathway is reproduced below (Figure 1).

Figure 1 Clinical pathway, including proposed positioning of radium-223 dichloride



Radium-223 applies to mCRPC patients with bone metastases but without visceral metastases. It is worth noting that this is a subset of patients already incorporated in the full NICE guidance for abiraterone. NICE technology appraisal guidance 259[13] states that 'abiraterone in combination with prednisone or prednisolone is recommended as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed on or after one docetaxel-containing chemotherapy regimen and the manufacturer provides abiraterone at the discount agreed in the NICE patient access scheme'. However, people currently receiving abiraterone in combination with prednisone or prednisolone whose disease does not meet this criterion should be able to continue therapy until they and their clinician consider it appropriate to stop. Abiraterone can therefore be used as a second line treatment in patients with bone and visceral metastases, unlike radium-223 dichloride.

Radium-223 dichloride has no UK or European marketing authorisation. The manufacturer expects European approval to be granted in [redacted]. The U.S Food and Drug Administration (FDA) have granted approval to treat mCRPC patients with metastases of bone but not other organs.[20]

3 CRITIQUE OF THE MANUFACTURER'S DEFINITION OF THE DECISION PROBLEM

3.1 Population

The NICE scope for this STA stated that adults with hormone-relapsed prostate cancer with symptomatic bone metastases should be the considered population. The manufacturer's submission considered mCRPC adult patients with bone metastases. The manufacturer's rationale for altering the considered population is to match the licensed indication, respecting clinical guidance on terminology and defining castrate-resistant populations.[14,21,22] The ERG is in agreement with this change.

The ERG notes that the argument made by the manufacturer on appropriate comparators for second line treatment considers the population of interest to be those with only bone metastases and not bone metastases with any visceral disease. As discussed in the background section 2.1, abiraterone can therefore be used as a second line treatment in patients with bone and visceral metastases, unlike the proposed population for radium-223 dichloride. The ERG believes that the MS scope and the intended NICE final scope populations do differ with the MS population being the subset of adults with castration-resistant prostate cancer with **only** bone metastases.

3.2 Intervention

The submitted technology, Radium-223 dichloride, is a therapeutic alpha-particle emitting pharmaceutical with targeted anti-tumor effect on bone metastases. Radium-223 dichloride is a ready-to-use solution for injection. Each ml of solution contains 1000 kBq radium Ra 223 dichloride (radium-223 dichloride), corresponding to 0.53 ng radium-223 at the reference date. Radium is present in the solution as a free ion. Each vial contains 6 ml of solution (6.0 MBq radium-223 dichloride at the reference date). The dose regimen of Radium-223 dichloride is 50 kBq per kg body weight, given at 4 week intervals for 6 injections. Each single-use vial contains radium-223 dichloride at a concentration of 1,000 kBq/mL (27 microcurie/mL) at the reference date with a total radioactivity of 6,000 kBq/vial (162 microcurie/vial) at the reference date The molecular weight of radium-223 dichloride, 223RaCl2, is 293.9 g/mol.

Radium-223 has a half-life of 11.4 days. The specific activity of radium-223 is 1.9 MBq (51.4 microcurie)/ng. The six-stage-decay of radium-223 to stable lead-207 occurs via short-lived daughters, and is accompanied predominantly by alpha emissions. There are also beta and

gamma emissions with different energies and emission probabilities. The fraction of energy emitted from radium-223 and its daughters as alpha-particles is 95.3% (energy range of 5 -7.5 MeV). The fraction emitted as beta-particles is 3.6% (average energies are 0.445 MeV and 0.492 MeV), and the fraction emitted as gamma-radiation is 1.1% (energy range of 0.01 -1.27 MeV).

3.2.1 Distribution

After intravenous injection, radium-223 is rapidly cleared from the blood and is distributed primarily into bone or is excreted into intestine. Fifteen minutes post-injection, about 20% of the injected radioactivity remained in blood. At four hours, about 4% of the injected radioactivity remained in blood, decreasing to less than 1% at 24 hours after the injection. At 10 minutes post-injection, radioactivity was observed in bone and in intestine. At four hours post-injection, the percentage of the radioactive dose present in bone and intestine was approximately 61% and 49%, respectively.

3.2.2 Metabolism

Radium-223 is an isotope that decays and is not metabolised.

3.2.3 Elimination

The whole body measurements indicated that approximately 63% of the administered radioactivity was excreted from the body within 7 days after injection (after correcting for decay). Faecal excretion is the major route of elimination from the body. At 48 hours after injection, the cumulative faecal excretion was 13% (range 0 -34%), and the cumulative urine excretion was 2% (range 1 -5%). There was no evidence of hepato-biliary excretion based on imaging data.

The rate of elimination of radium-223 dichloride from the gastrointestinal tract is influenced by the high variability in intestinal transit rates across the population. Patients with a slower intestinal transit rate could potentially receive a higher intestinal radiation exposure. It is not known whether this will result in increased gastrointestinal toxicity.

3.2.4 Special populations

Pediatric patients

The safety and effectiveness of Radium-223 dichloride have not been established in children and adolescents below 18 years of age.

Patients with hepatic impairment

No dedicated pharmacokinetic study in patients with hepatic impairment has been conducted. However, since radium-223 is not metabolized and there is no evidence of hepato-biliary excretion based on imaging data, hepatic impairment is not expected to affect the pharmacokinetics of radium-223 dichloride.

Patients with renal impairment

No dedicated pharmacokinetic study in patients with renal impairment has been conducted. However, since excretion in urine is minimal and the major route of elimination is via the faeces, renal impairment is not expected to affect the pharmacokinetics of radium-223 dichloride.

Other indications

Radium-223 is not indicated for use in women. Radium-223 can cause fetal harm when administered to a pregnant woman based on its mechanism of action.

In patients with bone marrow suppression, blood counts should be measured prior to treatment initiation and before every dose of Radium-223 dichloride. Radium-223 dichloride should be discontinued if hematologic values do not recover within 6 to 8 weeks after treatment. Patients with compromised bone marrow reserves should be monitored closely and treatment discontinued in patients who experience life-threatening complications despite supportive care measures.

3.2.5 Drug interactions

No formal clinical drug interaction studies have been performed. Subgroup analyses indicated that the concurrent use of bisphosphonates or calcium channel blockers did not affect the safety and efficacy of Radium-223 dichloride in the randomized clinical trial.

3.2.6 Overdosage

There have been no reports of inadvertent overdosing of radium-223 dichloride during clinical studies at the time of the manufacturer's submission. There is no specific antidote. In the event of an inadvertent overdose of radium-223 dichloride, general supportive measures should be utilised, including monitoring for potential hematological and gastrointestinal toxicity, and consider using medical countermeasures such as aluminum hydroxide, barium sulfate, calcium carbonate, calcium gluconate, calcium phosphate, or sodium alginate.[23]

The manufacturer states that clinical trial data and summary product characteristics support the use of Radium-223 dichloride to be used across the treatment pathway – i.e. mCRPC patients with bone metastases who have not received docetaxel and are not suitable to receive docetaxel (first line); mCRPC patients with bone metastases who have received docetaxel (second line).

Radium-223 dichloride has no UK or European marketing authorisation. The manufacturer submitted Radium-223 dichloride for European approval under the Centralised Procedure in December 2012 and was granted accelerated approval by the Committee for Human Medicinal Products (CHMP) in January 2013. The manufacturer expects approved to be granted in [redacted]. The Food and Drug Administration (FDA) provided regulatory approval of Radium-223 dichloride for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease in the United States on 15th May 2013. Radium-223 dichloride was not subject to any other form of health technology assessment in the UK at the time of the manufacturer's submission.

3.3 Comparator

The comparator considered in this submission is best supportive care (BSC). BSC may involve an extensive mix of treatments for the patient, none of which extend life. When delivered in combination with an active treatment, the quantity of BSC resource required may be reduced due to the effectiveness of that active treatment.

The NICE scope for this STA stated that abiraterone should be considered as a comparator for radium-223 dichloride in patients for people who had previously received docetaxal. For people who had not received docetaxal NICE requested that abiraterone and docetaxal should be considered as comparators. In their submission, the manufacturer provided an argument against abiraterone and docetaxal being used as comparators. They argued that those patients who were eligible for their first course of docetaxel were excluded from the phase III study (ALSYMPCA) and as such, a comparison with docetaxel was inappropriate. The ERG agrees in principle with this change though does note that in the ALSYMPCA trial some patients were categorised as "refused docetaxal" and "docetaxal was not available" and as such may therefore have been eligible for docetaxel. In such cases the comparator should in the opinion of the ERG remain docetaxal.

The MS also argued that a comparison with abiraterone in the second line setting was limited by trial heterogeneity and expert clinical opinion indicated that this (indirect) comparison was not appropriate or likely to be helpful, a view which was endorsed by key opinion leader

opinion. Although the ERG accepts that ALSYMPCA provides the main evidence in this submission, it suggests that comparators should have been included based on the inclusion criteria of the scope issued by NICE and not based on similarity to one of the trials (ALSYMPCA) in the review.

3.4 Outcomes

The outcomes considered by the manufacturer included: overall survival; time to first skeletal related event; incidence of individual skeletal related events; changes and time to PSA progression; changes and time to progression in total-ALP and change in bone-ALP; pain; health-related quality of life and adverse effects of treatment. This is in keeping with the issued scope.

3.5 Other relevant factors

The manufacturer's submission does not include equity considerations. At the time of submission there was no known Patient Access Scheme application by the manufacturer.

Table 1 outlines the differences between the final scope issued by NICE and the decision problem addressed in the manufacturer's submission.

Table 1 Differences between the final scope issued by NICE and the decision problem addressed in the manufacturer's submission

	Final scope issued by NICE	Decision problem addressed in the submission	Manufacturer rationale if different from the scope
Population	Adults with hormone-relapsed prostate cancer with symptomatic bone metastases	Adults with castration-resistant prostate cancer with bone metastases	To match the licensed indication, respecting clinical guidance on terminology and defining castrate-resistant populations.[14,21,22]
Intervention	Radium-223 dichloride	No difference	NA
Comparator(s)	For people who have received previous docetaxel therapy: • abiraterone • best supportive care without radium-223 dichloride (this may include radiotherapy, radiopharmaceuticals (apart from radium-223 dichloride), analgesics, bisphosphonates, further hormonal therapies and corticosteroids)	Best supportive care only	Docetaxel (if fit to receive docetaxel therapy) should not be a comparator because radium-223 dichloride is not proposed to be used in patients who would be suitable for docetaxel. Any comparison with abiraterone is limited by the clinical heterogeneity which exists due to differences in the patient populations of COU-AA-302[24] and ALSYMPCA.[22,25]
	For people who have not received previous		

	docetaxel therapy: • docetaxel (if fit to receive docetaxel therapy) • abiraterone (subject to ongoing NICE appraisal) • best supportive care without radium-223 dichloride (this may include radiotherapy, radiopharmaceuticals (apart from radium-223 dichloride), analgesics, bisphosphonates, further hormonal therapies and corticosteroids)		
Outcomes	The outcome measures to be considered include: • overall survival • time to first skeletal related event • incidence of individual skeletal related events (pathological fracture, spinal cord compression, radiation and surgery to the bone) • pain • adverse effects of treatment • health-related quality of life.	No difference	NA

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	No difference, with the exception of taking account of the availability of patient access schemes in comparator technologies.	It will only be possible to take account of the availability of patient access schemes in comparator technologies if suffficient information on the design of such schemes and the level of any pricing discount is provided to the manufacturer.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time	No difference, with the exception of taking account of the availability of patient access schemes in comparator technologies.	It will only be possible to take account of the availability of patient access schemes in comparator technologies if suffficient information on the

	horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.		design of such schemes and the level of any pricing discount is provided to the manufacturer.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. If evidence allows, consideration will be given to subgroups defined by the performance status at baseline and previous docetaxel exposure	No difference	NA

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Description of manufacturer's search strategies and critique

The manufacturer stated that literature searches were undertaken in February 2013 with no date restrictions imposed on the searches. A wide range of databases were searched including conference proceedings from 2008 – 2013 and reference lists of articles were checked as appropriate. Full details of the search strategies were included in Appendix 10 of the MS.

The searches were designed to identify trials of effectiveness of radium-223 and its comparators but they were not designed to identify studies reporting data relating to adverse events therefore it is possible that relevant information may have been missed.

The sources used for the identification of studies were appropriate and the search strategies were comprehensive, although the use of the English language limit and of study design filters in MEDLINE and Embase which were designed mainly to identify RCTs may have resulted in the omission of some relevant studies. Furthermore, while there were no date restrictions imposed on the search, the manufacturer has not stated the date ranges of the databases used. However, the ERG replicated the manufacturer's searches and retrieved similar numbers of results. Controlled vocabularies and free text searching were used effectively and included a wide range of synonyms. The facets of the search (castration-resistant prostate cancer; radium-223, abiraterone; clinical trials), and the synonyms within each facet, were combined correctly with Boolean operators. Overall, the search strategies were highly sensitive and fit for purpose and the ERG believes that it is unlikely that any relevant studies have been missed.

4.1.2 Eligibility criteria in the systematic review

The eligibility criteria used in the systematic review of clinical effectiveness were given in Table 8 on page 57 of the MS.

Although one search was conducted, two separate inclusion criteria were applied by the manufacturer for 1) the comparison between radium-223 dichloride and best standard care and 2) the indirect comparison analyses including radium-223, abiraterone and best standard care as potential comparators.

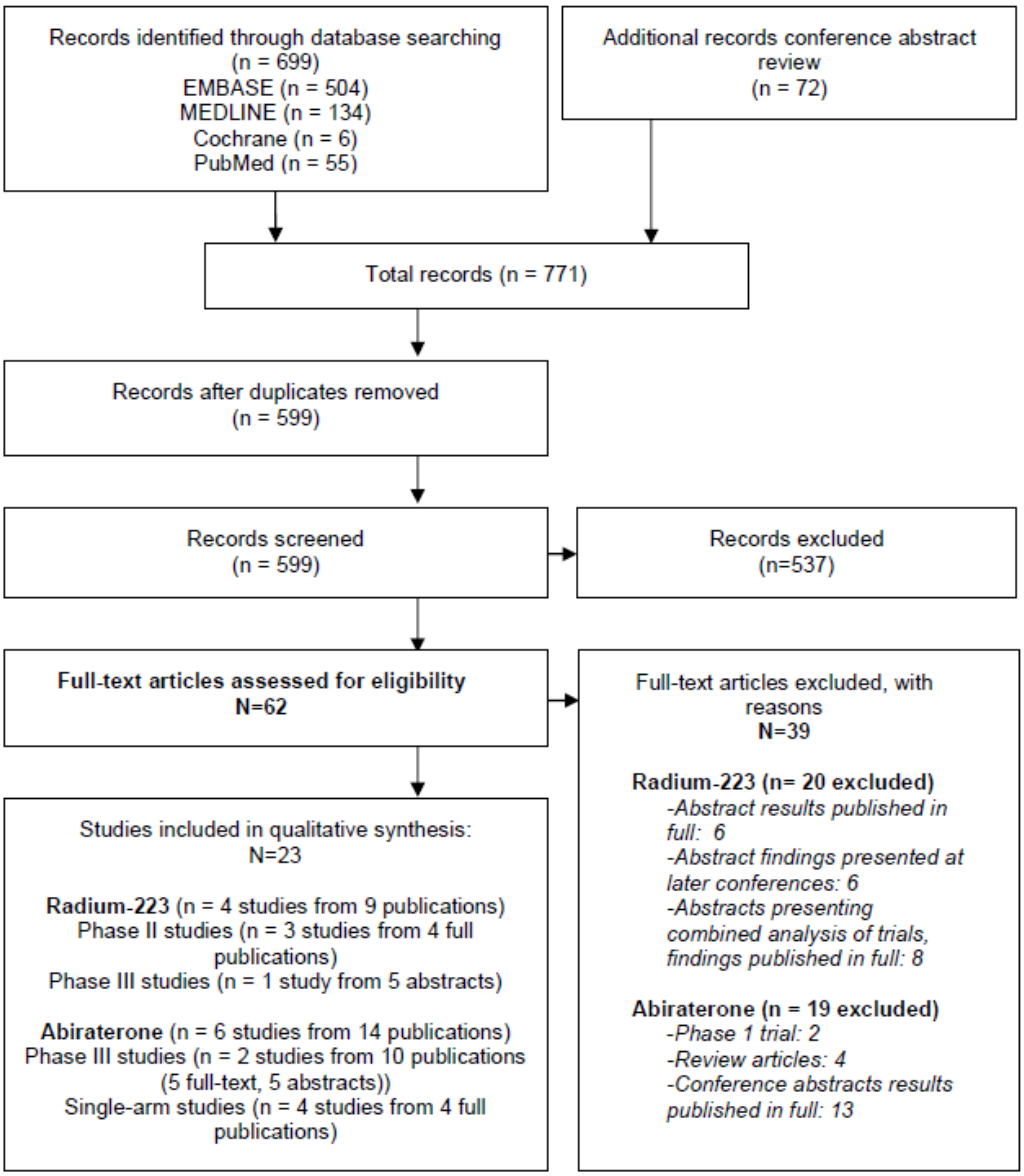
For the network meta-analysis, the manufacturer introduced two further inclusion criteria. To be eligible a study must: 1) use the licensed dosing regimen or the proposed licensed dosing regimen and 2) be available as a full publication (where available). These additional criteria resulted in BC1-02 being excluded from the indirect comparison analyses. In their response to the ERG's clarification questions the manufacturer clarified that BC1-02 was dropped from the indirect comparison because only four injections of 50kBq per kg body weight were administered at four week intervals, whereas the proposed licensed dosing regimen for radium-223 dichloride is six injections of 50kBq per kg body weight at four week intervals. The manufacturer also clarified that the second restriction did allow the inclusion of conference abstracts if no full publication were available. This meant that the ALSYMPCA study, only available as an abstract at the time of submission, was still eligible for inclusion.

The ERG was concerned that there was no clear rationale for applying two different sets of inclusion criteria so that BC1-02 was eligible for a meta-analysis of radium-223 dichloride versus best standard care but not for a wider network meta-analysis.

4.1.3 Studies included in the review

After reasonable exclusions, the MS states that one phase-three RCT and one phase-two RCT of radium-223 dicholoride versus placebo plus best supportive care (BSC); two phase-two dose ranging RCTs of radium-223 dicholride; two phase-three RCTs of abiraterone versus placebo plus prednisone and four single-arm studies of abiraterone were considered eligible for inclusion. For convenience, Figure 2 from the MS has been reproduced below in Figure 2 to show the number of studies included and excluded at each stage of the review.

Figure 2 Flow diagram of included and excluded studies



The manufacturer excluded the two dose ranging RCTs of radium-223 dichloride. The two RCTs and four single-arms studies of abiraterone were excluded due to the manufacturer's claim that patient heterogeneity precluded any meaningful comparison with the ALSYMPCA trial, as previously discussed in section 3.3. The manufacturer's clinical evidence comes from two RCTs of radium-223 dicholoride versus placebo plus BSC (ALSYMPCA and BC1-02) were included in the review.

The ERG believes that it was not appropriate to exclude the abiraterone RCTs from the systematic review. The abiraterone studies clearly met the inclusion criteria for the review.

The ERG performed a quality assessment of the manufacturer's systematic review using the York Centre for Reviews and Dissemination (CRD) criteria (Table 2). Excepting the caveat on the abiraterone studies, the quality of the systematic review was generally good.

Table 2 Quality assessment of the manufacturer's review

CRD quality item	Score
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

4.2 Summary and critique of submitted clinical effectiveness evidence

The evidence provided by the manufacturer on the clinical effectiveness of radium-223 dichloride came from two RCTs (ALSYMPCA and BC1-02).

The phase-three international, multicentre, RCT (ALSYMPCA) was sponsored by the manufacturer and was outlined as the main source of evidence in the manufacturer's submission. Patients were enrolled from 136 centres from 19 countries including: Australia, Belgium, Brazil, Canada, Czech Republic, France, Germany, Hong Kong, Israel, Italy, Netherlands, Norwary, Poland, Singapore, Slovakia, Spain, Sweden, United Kingdom, and the United States of America. Patients were randomised 2:1 to receive 6 intravenous injections of radium-223 dicholride (50kBq/kg per body weight) every 4 weeks along with best supportive care or to receive 6 intravenous injections of a placebo every 4 weeks plus best supportive care. Best supportive care included local external beam radiotherapy, corticosteroids, antiandrongens, oestrogens, estramustine and ketoconazole. Patients could also take bisphosphonates during the study if they were currently using at study entry.

The phase-two, international multicentre, double-blind RCT (BC1-02) was sponsored by Algeta, SSA. Patients were recruited from 11 European centres from Sweden, Norway and the United Kingdom. Patients were randomised to receive four 4-weekly intravenous injections of radium-223 dichloride at the same dose as in the ALSYMPCA trial or to receive a saline placebo administered intravenously at four-week intervals. Dose modifications were

not allowed. Dose administration could be delayed by up to one week in the event of a surgical intervention or grade-3 haematological toxicity.

4.2.1 Approach to quality assessment for included trials

The manufacturer assessed the quality of the BC1-02 and ALSYMPCA trials. Although it is unclear if a specific quality assessment tool was used, the methods used for quality assessment were considered adequate by the ERG. The methodological quality of the trials was good.

4.2.2 Approach to statistical analysis for included trials

Methodology of individual trials

The manufacturer provided the results of the ALSYMPCA trial using the intention-to-treat (ITT) population which included all randomised participants. ALSYMPCA was stopped early due to the recommendation of the independent data monitoring committee and for some outcomes both interim (cut-off October 2010) and updated (cut-off July 2011) analyses are presented, although the main analyses presented appear to be based on the updated results. Selected results are also presented for subgroups by prior docetaxel status.

Results for BC1-02 are presented using the full analysis set (FAS) population, defined as all randomised participants who had received at least one dose of study medication.

For both ALSYMPCA and BC1-02 adverse event results are presented including participants who had used at least one dose of study medication.

The ERG did not identify any major statistical or methodological issues with these results.

Survival (time-to-event) analyses

The main primary and secondary outcomes in both ALSYMPCA and BC1-02 were time-to-event outcomes. For ALSYMPCA the primary endpoint was overall survival; for BC1-02 it was the time to a skeletal-related event (SRE).

For survival outcomes Kaplan-Meier curves were produced showing the proportions event-free at each time point. Hazard ratios were derived comparing radium-223 dichloride and placebo using a Cox proportional hazards model adjusting for baseline characteristics.

In general, the ERG thought these analyses were appropriate. However, the manufacturer's primary analyses of time to progression and time to SRE treat deaths as a censored event.

This may introduce bias as this introduces informative censoring. In the response to the ERG's clarification question B4 the manufacturer also presents results for progression and SRE where deaths are also counted as an event. The manufacturer pointed out that these analyses produced some unexpected results, i.e., the time-to-event curves for mortality and for SRE/death cross for both radium-223 dichloride and placebo. They explained that this effect was a consequence of the study design in that participants in ALSYMPCA were only followed up systematically for SRE and progression endpoints for the period of active treatment (up to six months) and a small number of post-treatment visits. Therefore there are different rates of censoring for the overall survival and SRE-free survival endpoints. The ERG notes that the FDA statistical assessment[26] of the ALSYMPCA trial also raised this issue and performed a sensitivity analysis assuming mortality was an event rather than a censored case on the interim dataset. The FDA analysis reduced the median times to SRE but the effect size remained of a similar magnitude to the primary analysis and was still statistically significant. In the absence of any gold standard approach to handling the censoring issue, the ERG considers the manufacturer's approach satisfactory.

4.2.3 Discussion of the extent to which the included trials represented the patient populations and interventions as defined in the final scope

All patients in the ALSYMPCA trial had confirmed castration resistant prostate cancer with >2 bone metastases, no known visceral metastases and were post-docetaxal, unfit for docetaxal, or had declined docetaxal.

All patients in the BC1-02 trial had either bilateral orchidectomy or continued treatment on a luteinising-hormone-releasing-hormone-agonist throughout the study.

Unlike BC1-02, patients participating in ALSYMPCA were allowed to receive bisphosphonates as part of BSC during the trial. Treatment with bisphosphonates within three months prior to study entry was an exclusion criterion for BC1-02.

The ERG considers the populations in the included studies in general to represent those in the final scope. However, it is less clear to the ERG that the population reflects a first line treatment for cases not suitable for docetaxel. The ERG speculates that patients who had declined docetaxel may have been suitable.

4.2.4 Description and critique of methods of any meta-analysis

No attempt was made to meta-analyse the results of the two trials due to the different number of administered doses of radium-223 dichloride (six in ALSYMPCA versus four in BC1-02);

difference in inclusion criteria for life expectancy (six months in ALSYMPCA versus three months in BC1-02); patients in ALSYMPCA could receive bisphosphonates as part of BSC, whereas bisphosphonate treatment within three months prior to study entry was an exclusion criteria for BC1-02; and a requirement for EBRT was an inclusion criterion for BC1-02 but patients could have been treated with regular analgesia or EBRT for bone pain in the previous 12 weeks in ALSYMPCA. The ERG is satisfied that the difference in dosing administration renders the intervention sufficiently different that clinical heterogeneity precludes statistical pooling of results. The ERG also notes that the BC1-02 trial is a much smaller trial in comparison to ALSYMPCA.

4.2.5 Description and critique of methods of any indirect comparison

Three studies (ALSYMPCA, COU-AA-301 and COU-AA-302) were eligible for inclusion in a possible indirect comparison (network meta-analysis). This would involve a network of three treatments: radium-223 dichloride, abiraterone and best standard care/placebo. However, the manufacturer decided not to conduct such an analysis.

The manufacturer justifies the reason for not performing meta-analyses in either setting by stating that other trials are not similar to ALSYMPCA. These differences include the fact that prednisone was taken by all patients in the abiraterone studies, differences in allowable concomitant medication, differences in rates of bone metastases and ECOG performance status and differences in study outcome measures. In addition, ALSYMPCA included both patients who had previously received docetaxel and those who were unsuitable, unfit or had refused docetaxel. One abiraterone study (COU-AA-301) included patients with prior docetaxel use but the other (COU-AA-302) only recruited patients who had not received docetaxel. The manufacturer states that the decision not to perform a network meta-analysis is supported by the opinion of key opinion leaders. In their response to clarification question A9, the manufacturer states that they had consulted both UK-based oncologists with expertise in the management of prostate cancer and non-UK clinicians.

The ERG believes that in principle a network meta-analysis would have been possible for some outcomes such as overall survival, but the ERG accepts that the populations who have and have not received prior docetaxel are distinct patient groups and agrees that it may not be sensible to combine these studies in a network-meta-analysis. It would have been possible to split ALSYMPCA into two subgroups based on prior docetaxel status and include in separate analyses with the abiraterone studies, although the benefits of a randomised design would be lost and they would have had to be treated as observational studies.

Although the ERG accepts that ALSYMPCA provides the main evidence in this submission, it suggests that studies should have been included based on the inclusion criteria of the scope issued by NICE and not based on similarity to one of the trials in the review. The ERG notes that full results for the COU-AA-301 and COU-AA-302 trials have not been presented in the manufacturer's submission or considered in the cost-effectiveness analyses, even though they have met the search criteria for the review.

The ERG asked at clarification for a baseline characteristics table for the abiraterone COU-AA-301 and COU-AA-302 trials so that the manufacturer argument for not combining based on populations could be assessed. Whilst the manufacturer did not produce such a table, the ERG have produced a baseline characteristics table for the abiraterone COU-AA-301 and COU-AA-302 trials in Appendix 1. The ERG agrees that an important difference in the populations between ALSYMPCA and COU-AA-301 relates to the differing proportion of patients with visceral disease and agrees that clinically the groups are different.

4.2.6 Summary and critique of effectiveness results

This section summarises the main findings as reported in the MS and clarification responses to ERG queries. Where possible, emphasis is placed on the final updated results from ALSYMPCA trial (cut-off July 2011).

Overall survival

ALSYMPCA

Overall survival (OS) was the primary endpoint in ALSYMPCA. Radium-223 dichloride significantly improved OS in mCRPC patients with bone metastases when compared with placebo. Median OS for patients receiving radium-223 dichloride [n=614] was 14.9 months versus median OS of 11.3 months in patients receiving placebo [n=307] (two-sided P=0.00007; HR=0.695; 95% CI, 0.581-0.832)(19).

BC1-02

OS was a secondary endpoint for the BC1-02 study. At 24-months follow-up, patients who had received radium-223 had an improved median overall survival of 65.3 weeks when compared with placebo patients (46.4 weeks) (log-rank P=.056). The hazard ratio (HR) for OS, adjusted for baseline prognostic covariates, was 0.476 (95% confidence interval [CI], 0.258-0.877; Cox regression P=0.017)[ITT analysis] (6). At this time, 10 (30%) patients were alive in the radium-223 dichloride group and 4 (13%) patients were alive in the placebo group. OS for the ALSYMPCA and BC1-02 is presented in Table 3.

Table 3 Overall survival in ALSYMPCA and BC1-02

	Median overall survival (months)*								
	All patients			**Prior docetaxel**			**No prior docetaxel**		
	Radium-223 dichloride n=614	Placebo plus BSC n=307	Hazard Ratio [c] (95% CI) P value [d]	Radium-223 dichloride n=352	Placebo plus BSC n=174	Hazard Ratio [c] (95% CI) P value [d]	Radium-223 dichloride n=262	Placebo plus BSC n=133	Hazard Ratio [c] (95% CI) P value [d]
ALSYMPCA (ITT) [a]									
Updated analysis (4;19) Cut-off July 2011	14.9 [redacted]	11.3 [redacted]	0.695 [0.581-0.832] 0.00007	14.4	**11.3**	0.710 [0.565-0.891] 0.00307	16.1	11.5	0.745 [0.562-0.987] 0.03932
BC1-02 (FAS) [b]									
24-month analysis (6)	15.0 (65.3 weeks)*	10.7 (46.4 weeks)*	0.476 [0.258-0.877] 0.017	Only one patient in BC1-02 had received at least one dose of docetaxel prior to study entry (radium-223 dichloride arm n=1 [3%])					

BSC=Best supportive care; ITT=Intention to treat analysis; FAS = Full analysis set; CI = confidence interval;

*BC1-02 study OS data was reported in weeks. A conversion factor of 0.230769 has been used to convert OS from the weeks to months measure.

a Radium-223 dichloride at a dose of 50Kbq/kg BW or placebo, each given every 4 weeks for 6 total doses

b Radium-223 dichloride at a dose of 50Kbq/kg BW or placebo, each given every 4 weeks for 4 total doses

c Hazard ratios were determined by a Cox proportional hazards model as follows:

ALSYMPCA: Adjusted for total ALP, current use of bisphosphonates, and prior use of docetaxel

BC1-02: Adjusted for haemoglobin, LDH, albumin, total ALP, PSA, ECOG and age

Hazard ratios < 1 favour radium-223 dichloride d P-values were determined as follows:

ALSYMPCA: Log rank test stratified by total ALP, current use of bisphosphonates, and prior use of docetaxel

P-value for updated analysis is exploratory

BC1-02: Cox Proportional Hazards adjusted for baseline prognostic factors

Test for difference between treatment groups (no other stratification)

Subgroup analyses of Overall Survival endpoint

ALSYMPCA

Subgroup survival analysis showed a consistent survival benefit for treatment with radium-223 dichloride, independent of baseline levels of total ALP, current use of bisphosphonates, prior use of docetaxel and ECOG status at baseline.[27] Similar proportions of randomised patients were docetaxel-naïve (43%) and docetaxel-treated (57%) and the results of ALSYMPCA demonstrated a clinically relevant statistically significant survival benefit for both groups.

None of these subgroup analyses was independently powered to detect treatment differences and hence, must be considered exploratory.

BC1-02

No subgroup analysis was planned.

Skeletal-related events (SREs)

ALSYMPCA and BC1-02 used slightly different definitions for SRE, which the manufacturer stated, impeded direct comparison across the two studies. The definitions of SREs for the two trials are presented in Figure 9 on page 85 of the MS. Upon request, the manufacturer provided further clarification for the definition of skeletal related events for ALSYMPCA: a skeletal related event required the use of external beam radiotherapy to relieve skeletal symptoms or the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral) or the occurrence of spinal cord compression or a tumour related orthopaedic surgical intervention. The pathological bone fracture component was always stated as symptomatic. Furthermore, no radiological imaging was included in the protocol, or routinely performed, unless other clinical findings (e.g. symptomatic bone pain) were observed. Additionally, investigators and sites were not paid for any radiological imaging, nor did data capture forms request imaging data as a way of recording an event. Radiological imaging was therefore used to confirm symptoms of a pathological fracture rather than as a method for identifying fractures. The ERG agrees that the direct comparison of SRE across studies is not appropriate.

In both studies, radium-223 reduced the incidences of SREs, delayed the onset of SREs and reduced the frequency of individual components of SREs. Radium-223 was associated with a significant prolongation in time to first spinal cord compression and a reduced incidence of spinal cord compression overall in the ALSYMPCA trial. Time to first SRE was statistically significantly longer in the radium-223 dichloride group compared to placebo in the

ALSYMPCA trial (median number of months = 15.6 for radium-223 dichloride vs 9.8 months for placebo; HR=0.658, 95% CI 0.522-0.830, p=0.00037) and in the BC1-02 trial (Median number of months = 3.2 for radium-223 dichloride vs 2.5 weeks for placebo, 95% CR 9-30, p=0.257).

[redacted]

The ERG notes that no information on subsequent bisphosphonate use by patients during the follow up period of the study was given in the MS therefore the ERG could not assess if the SRE was confounded by bisphosphonate use.

4.2.7 Delayed time to PSA progression

The ALSYMPCA and BC1-02 studies both showed a prolonged time to onset of PSA progression in favour of radium- 223 dichloride. Time to PSA progression was significantly improved on radium- 223 dichloride compared to placebo in the ALSYMPCA trial (HR=0.643 [0.539- 0.768], p<0.00001).[27] Median time to PSA progression in BC1-02 was 26 weeks (95% CI 16-39) versus 8 weeks (95% CI 4-12; p=0.048) for radium-223 dichloride versus placebo, respectively.[28]

4.2.8 Reduced PSA levels

Compared to placebo, treatment with radium-223 dichloride led to a notably higher proportion of patients with a PSA reduction of ≥30% or ≥50%. [redacted]

A confirmed PSA response of more than 50% was seen in 11 of 31 of the BC1-02 patients (35%) assigned radium-223 dichloride and 5 of 28 (18%) assigned placebo (p=0.153 Fisher's exact test).

Alkaline phosphatase levels (ALP)

The effect on total-ALP was a secondary endpoint in ALSYMPCA. Treatment with radium-223 dichloride [redacted]

The proportion of patients achieving a confirmed (value confirmed by a second reading after approximately 4 weeks) total ALP response (≥ 30% or ≥ 50% respectively) at week 12 were 47% and 27% for patients treated with radium-223 dichloride and 3% and <1% for patients receiving placebo; both significantly in favour of radium-223 dichloride (≥ 30% p<0.001 and ≥ 50% p<0.001).[27]

Total ALP normalisation (in patients who had elevated total ALP at baseline) occurred in 109/[redacted] patients ([redacted]) in the radium-223 dichloride treated group and only 2/[redacted] patients ([redacted]) in the group receiving placebo / BSC.[27]

[redacted]

Change in bone-ALP was a primary endpoint in BC1-02 but was not measured in ALSYMPCA. The median relative change in bone-ALP in BC1-02 from baseline to four weeks after last study injection (i.e. week 16) was -65.6% (95% CI -69.5 to -57.7) in the radium-223 dichloride group and +9.3% (95% CI 3.8 to 60.9) in the placebo group (p<0.0001 Wilcoxon ranked-sums test). Bone-ALP remained lower in the radium-223 dichloride treated group compared with the placebo group at 12 months (6). [redacted]

Compared with the placebo group, the radium-223 dichloride group reduced all other measured serum markers of bone i.e. Bone formation: Procollagen I N propeptide (PINP), Bone resorption: C-terminal crosslinking telopeptide of type 1 collagen (S-CTX-1), Type 1 collagen crosslinked C- telopeptide (ICTP) measured in the BC1-02 study are summarised in Table 23 on page 116 of the MS.

Pain

Although ALSYMPCA did not measure pain response as a specific formal endpoint, the following pain-related endpoints provided evidence in support of a positive effect of radium-223 dichloride on bone pain.

4.2.9 Use of opioid analgesics

A post hoc analysis of time to initial opioid use was conducted to evaluate the effect of radium-223 dichloride on pain. Fewer patients in the radium-223 dichloride group (36%) than in the placebo group (50%) received opioids for pain relief. Also, the median time to initial opioid use was significantly longer in the radium-223 dichloride group compared with the placebo group ([redacted]; HR=0.621; 95% CI, 0.456-0.846; P=0.0023).[29]

4.2.10 Time to EBRT

Time to treatment by EBRT for skeletal pain was significantly longer in the radium-223 dichloride group versus placebo (HR=0.670; 95% CI, 0.525-0.854; P=0.00117).[29]

4.2.11 Bone pain

Fewer patients reported bone pain as an adverse event in the radium-223 dichloride group compared to placebo (50% vs. 62%). This is despite the radium-223 dichloride patients living longer.[29]

[redacted]

In BC1-02, the effect of radium-223 dichloride on pain and pain-related endpoints was less clear-cut, due to a limitation of the study design, whereby all patients received EBRT at baseline, and the pain reduction observed in both groups was possibly due to the EBRT.

Health-related quality of life (HRQoL)

The ALSYMPCA assessed quality of life using the Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaire and EuroHRQoL (EQ-5D) questionnaires. Quality of life was assessed at fixed timepoints (baseline, week 16 and 24 [redacted].[16]

[redacted]

[redacted] Relative to placebo, and relative to baseline, visit-specific analysis showed that the decrease from baseline in mean HRQoL was significantly smaller for patients treated with radium-223 at week 16, i.e. there was improvement in HRQoL, in the FACT-P total score (p=0.006), Trial Outcome Index score (p=0.011), FACT-G score (p=0.004), emotional well-being (p<0.001), functional well-being (p=0.011) and prostate cancer subscale (p=0.012). The rate of decrease in score appears to be faster for the placebo group compared with the radium-223 dichloride group.[16]

[redacted]

4.3 Indirect comparison

As discussed in section 4.1 on critique of the methodology of review, the MS did not undertake an indirect comparison.

4.4 Adverse events

4.4.1 Treatment-emergent adverse events and serious adverse events

Treatment-emergent adverse events (TEAEs) were defined as events occurring or worsening after the first injection of study treatment and within 12 weeks after the last injection of study treatment. The safety analysis populations included patients who had received at least one dose of study medication. Safety results presented in the manufacturer's submission for ALSYMPCA relate to the updated analysis time-point for the efficacy data (cut-off date of 15th July 2011). [redacted]

The safety and tolerability of radium-223 dichloride observed in ALSYMPCA was favourable. Important safety risks caused by radium-223 dichloride were not identified.

Overall, the incidence of TEAEs, serious adverse events (SAEs), any TEAE of grade 3 and 4, and any TEAE leading to discontinuation or death was consistently lower in the radium-223 dichloride group than in the placebo group, see table 4 below. [redacted]

Table 4 Summary of safety reports during ALSYMPCA (7;90)

Patients with adverse events (AE), n(%)	**Radium-223 dichloride n=600**	**Placebo plus BSC n=301**
Pre-treatment AE	[redacted]	[redacted]
TEAEs	558 (93%)	290 (96%)
Grade 3 or 4	339 (57%)	188 (63%)
Drug-related AE[a]	[redacted]	[redacted]
Leading to discontinuation of treatment	99 (17%)	62 (21%)
Leading to death[b]	[redacted]	[redacted]
TE-SAEs	281 (47%)	181 (60%)
Drug-related SAE[a]	[redacted]	[redacted]
Post-treatment AE[c]	[redacted]	[redacted]

a. Drug-related AEs were those with a causality of possible, probable or missing

b. [redacted]

c. Those events occurring >12 weeks after the last injection and have a causality of possible, probable or missing

As summarised in Table 29 on page 143 of the MS, bone pain was the most frequently recorded TEAE in both treatment groupsbut was ower in the radium-223 dichloride than placebo group (50% vs 62%). [redacted].

There was a low incidence of myelosuppression, although radium-223 dichloride was associated with a higher incidence than the placebo group for (all grades) in neutropenia (5% vs. 1%) and thrombocytopenia (12% vs.6%) and grades 3 and 4 neutropenia (2% vs. 1%) and thrombocytopenia (6% vs. 2%).

Overall, the frequency of grade 3 and 4 neutropenia and thrombocytopenia was lower in patients that had not previously received docetaxel 0.8% and 2.8% radium-223 dichloride; 0.8% and 0.8%placebo compared to those who had previously received docetaxel (3.2% and 8.9%radium-223 dichloride; 0.6% and 2.9% placebo);

A small increase in the frequency of mild to moderate (grade 1 and 2) diarrhoea, nausea and vomiting was seen in the radium-223 dichloride group. There was no difference in the rate of severe (grade 3 or 4) TEAEs or anaemia between the groups.

AEs and SAEs considered by the ALSYMPCA trial investigator to be related to study treatment occurring more frequently in the radium-223 dichloride group included:

In the BC1-02 study, TEAEs and SAEs were observed in a similar pattern to the ALSYMPCA study; apart from mild to moderate constipation, which occurred more often in the radium-223 dichloride group. Haematological toxic effects did not differ significantly between the two groups.

4.4.2 Injection-related adverse events

4.4.3 Deaths

4.4.4 AEs leading to treatment discontinuation

AEs that led to discontinuation of treatment were lower in the radium-223 dichloride treated group (17%, n=99) than in the placebo group (21%, n=62). The most common of these events are detailed in Table 5.

Table 5 TEAEs leading to discontinuation of study treatment, occurring in ≥1% of patients in either treatment group in ALSYMPCA (safety population) (7;90)

MedDRA system organ class/Preferred term	Radium-223 dichloride n=600	Placebo plus BSC n=301
	N (%)	N (%)
Patients with TEAEs leading to treatment discontinuation	99 (16.5%)	62 (20.6%)
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Malignant neoplasm progression	[redacted]	[redacted]
Spinal cord compression	[redacted]	[redacted]

The manufacturer stated in their clarification document that no patient discontinued radium-223 dichloride because of treatment toxicity in the BC1-02 trial.

[redacted]

4.4.5 Post-treatment follow-up adverse events

[redacted]

[redacted]

4.4.6 Long term toxicity

[redacted]

4.4.7 Cytotoxic mCRPC treatment after participating in ALSYMPCA

[redacted]

4.4.8 Summary of submitted evidence for adverse events

Evidence of the safety and tolerability of radium-223 dichloride was provided by safety analyses and adverse event reporting from the ALSYMPCA trial, with supporting data provided by the BC1-02 trial. Neither trial included any safety outcomes as a basis for primary analysis. [redacted]

Bone pain was the most frequently reported adverse event but was significantly lower in the radium-223 dichloride than BSC plus placebo group. The manufacturer notes that the observed increased frequency of mild to moderate diarrhoea in the ALSYMPCA radium-223 dichloride group is contrary to higher reporting of constipation in the BC1-02 radium-223 dichloride group compared with BSC plus placebo. Although not raised in the manufacturer's submission, the ERG notes concerns raised by the FDA regarding secondary exposure to the patient and/or caregivers through radioactivity present in faeces during the first several days after injection, although this concern was mitigated by the very short path length of the alpha-emission based radioactivity.[30] Evidence for long-term toxicity is unclear due to the limited follow up period. [redacted]

4.5 Additional work carried out by ERG

No additional work was necessary for the ERG.

4.6 Conclusions of the clinical effectiveness section

The ERG believes that there is compelling evidence that radium-223 dichloride significantly prolongs overall survival, reduces skeletal related events and extends time to progression when compared with BSC in second line therapy in this population. The adverse event profile is also of less concern than the comparator, BSC. The ERG is concerned that abiraterone was not considered a comparator in second line therapy, though does accept that clinical heterogeneity in the evidence base may preclude a network meta-analysis as defined by the MS. The evidence provided by the manufacturer is weaker to support the use of radium-223 for first line use as the 1st line patient population in ALSYMPCA is highly selective and radium-223 has not been compared against all valid comparators (in the opinion of the ERG).

5 COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

The manufacturer carried out a full systematic review to identify relevant cost-effectiveness studies. The ERG believes that the MS systematic review was of good quality.

The manufacturer states that three different sets of searches were carried out; firstly, to inform the review of cost-effectiveness, secondly, to identify HRQL data in adults with mCRPC and thirdly, to identify HRQL data in adults with bone metastases or who have experienced SREs.

All searches were undertaken in February 2013 and were restricted to English language publications between 2000 and 2013. MEDLINE, MEDLINE-in-Process, Embase, PubMed, EconLIT and NHS EED were searched. Full details of the search strategies are included in Appendix 10 (cost-effectiveness) and Appendix 12 (HRQL) of the MS and are reproducible.

The sources used for the identification of studies were appropriate and the search strategies were comprehensive, with search filters and date and language restrictions used where appropriate.

5.1.2 Inclusion/exclusion criteria

For all reviews, the considered patient population included adults with castration resistant prostate cancer and/or adults with bone metastases and all lines of therapy. All reviews were also restricted to English language publications published since 2000. Details of the remaining inclusion criteria are presented for each of the reviews in Tables 31, 47 and 58 on pages 161, 197 and 225 of the MS.

5.1.3 Studies included/excluded

After reasonable exclusions, nine articles were included in the cost-effectiveness review. Eight of the nine studies were based on Markov models. The remaining study was based on a decision-analytic model.[31]

Zolendronic acid was the most common comparator, reported in four studies. Patients were mainly elderly with a mean age of at least 65 years old. Five of the studies were set in the USA, one in Europe (France, Germany, Portugal and the Netherlands) and three in the UK.

In the opinion of the ERG the submission to NICE on Abiraterone Acetate for the treatment of metastatic castration resistant prostate cancer following previous cytotoxic therapy was the

most important study.[13] The manufacturer quality assessed the report and found that, although most data were graded high quality when reported, many items had "limited information available due to confidentiality".

5.1.4 Conclusion

The manufacturer has not stated any conclusions from the review. The ERG notes that no included studies fully addressed the decision problem in this appraisal.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

Table 6 NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice. The scope identifies two subgroups: those who have received prior docetaxel; and, those who have not received prior docetaxel. For those who have received prior docetaxel: • abiraterone • BSC For those who have not received prior docetaxel[a]: • docetaxel • BSC	The submission only compares radium-223 with placebo in addition to BSC. The base case presents results for the ALSYMPCA trial patient population. Results are also presented two subgroups: those who have received prior docetaxel; and, those who have not received prior docetaxel due to being contraindicated to it or not wanting to receive it.
Patient group	As per NICE scope. "*Adults with hormone-relapsed prostate cancer with symptomatic bone metastases*"	Yes.
Perspective costs	NHS & Personal Social	Yes.

[a] The scope also identified abiraterone as a comparator subject to NICE appraisal. Assessment ID503 Prostate cancer (metastatic, castrate-resistant, not treated with chemotherapy) - abiraterone acetate (with prednisolone) is currently suspended.

	Services	
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Cost utility analysis.
Time horizon	Sufficient to capture differences in costs and outcomes	The base case employs a 5 year time horizon. Given the lognormal extrapolation of overall survival, at 5 years [redacted] are modelled as surviving in the radium-223 arm compared to [redacted] in the BSC arm.
Synthesis of evidence on outcomes	Systematic review	The economic modelling relies entirely upon the ALSYMPCA trial results for the clinical effectiveness estimates.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes. The quality of life values that drive the analyses are those for progression free survival and survival post progression. These are differentiated by arm. The values are drawn from EQ-5D data collected during the ALSYMPCA trial.
Benefit valuation	Time-trade off or standard gamble	Time trade off.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes. The main EQ-5D utility values use the standard UK social tariff.

Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes. Though there may be an end of life argument which could argue for increasing the quality of life value the additional survival is valued at.
Probabilistic modelling	Probabilistic modelling	Probabilistic modelling was undertaken for the base case for all patients, and for the prior docetaxel subgroup and the no prior docetaxel subgroup.
Sensitivity analysis		A range of sensitivity analyses were performed by the manufacturer.

5.2.2 Model structure

The manufacturer develops a de novo model of the cost effectiveness of radium-223 compared to best supportive care, or placebo. It is a cost utility model with a weekly cycle and a five year time horizon. The model estimates the overall survival in each arm up to the end of the five year time horizon. For each cycle, the remaining survivors are divided into those:

- without progression and without an on study SRE;
- with progression and without an on study SRE;
- without progression and with an on study SRE; and
- with progression and with an on study SRE.

Adverse events are included within the modelling, with HRQoL and cost allowances for these being added to the first cycle of the model.

Overall survival is based upon log-normal curves fitted to the Kaplan Meier data of the ALSYMPCA trial. The calculation of the proportions of survivors falling into each of the four health states of the model is also mainly based upon log-normal curves fitted to the Kaplan Meier data of the ALSYMPCA trial. These curves are estimates from the progression

free survival data and first on trial SRE data, although there are some adjustments made to the resulting curves as outlined in greater detail below.
The model structure does not differentiate the first on study SRE by SRE type, but the quality of life impacts and costs of SREs are weighted averages of the four main types: pathological bone fracture, spinal cord compression, surgical intervention and external beam radiation.

HRQoL estimates for those with and without progression are based upon the EQ-5D data of the ALSYMPCA trial. These estimates are differentiated by treatment arm. They suggest that progression itself has little impact upon HRQoL but that treatment with radium-223 provides a quality of life increment of around [redacted] compared to placebo. This quality of life increment endures for the lifetime of the patient.

HRQoL estimates for the impacts of SREs are estimated separately, and are based upon a weighted average of values taken from a paper within the literature.[32] These HRQoL impacts from SREs are applied to patients modelled as having had an on study SRE. They are additional to the radium-223 [redacted] quality of life increment. They are also assumed to endure for the remaining lifetime of the patient.

An average of [redacted] radium-223 administrations is applied within the model. The cost per radium-223 treatment is [redacted], plus an additional £200 cost of administration as drawn from NHS reference costs.

Ongoing resource use is based upon a manufacturer commissioned survey of oncologists and urologists [redacted].

Progression leads to second line treatment at an average cost of [redacted]. This is based upon a weighted average drawn from the IMS Oncology Analyser.

Incident SREs are costed at an average of [redacted] within the radium-223 arm and [redacted] within the placebo arm. This is based upon unit costs for the four SREs that are averages of a range of NHS reference costs and some additional GP costs, coupled with balances between the first on trial SREs drawn from the ALSYMPCA trial that are specific to the trial arms.

An end of life cost of £2,087 is applied within the model, based upon values within a paper from the literature.[33]

5.2.3 Population

The patient population reflects that of the ALSYMPCA trial with the base case analysing the data for all patients.

Analyses for the subgroup of prior docetaxel and for the subgroup of no prior docetaxel are also presented.

5.2.4 Interventions and comparators

Radium-223 is compared with placebo in addition to BSC.

5.2.5 Perspective, time horizon and discounting

As per NICE guidelines, the patient perspective is adopted for benefits while the NHS and PSS perspective is adopted for costs. A five-year time horizon is adopted, and both costs and benefits are discounted at 3.5%.

5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness

The clinical effectiveness estimates are drawn from the ALSYMPCA trial, the main inputs being the time to event curves for overall survival (OS), progression free survival (PFS) and the first on trial SRE. The time to event curves for PFS and SRE treat death as a censoring event. Given this, the proportions of patients in each of the five health states of the model are derived by multiplying the proportions in the three time to event curves together:

- $P(\text{PFS no SRE})_t = P(\text{Alive})_t * P(\text{PFS})_t * P(\text{SRE})_t$
- $P(\text{PFS with SRE})_t = P(\text{Alive})_t * P(\text{PFS})_t * (1- P(\text{SRE})_t)$
- $P(\text{Prog. no SRE})_t = P(\text{Alive})_t * (1- P(\text{PFS})_t) * P(\text{SRE})_t$
- $P(\text{Prog. with SRE})_t = P(\text{Alive})_t * (1- P(\text{PFS})_t) * (1- P(\text{SRE})_t)$
- $P(\text{Dead})_t = 1 - P(\text{Alive})_t$

The above assumes that the time to event curves for PFS and SRE are independent; i.e. an SRE is equally likely among patients who have not progressed as it is among patients who have progressed. Note that the base case uses PSA as the measure of progression. A scenario analysis using ALP as the measure of progression is also presented by the manufacturer. The ERG assumption is that the utility values of the model relate to the PSA measure of progression.

The time to event curves are estimated across all patients (n=614+307=921), and also for the subgroups of prior docetaxel therapy (n=352+174=526) and no prior docetaxel therapy (n=262+133=395). The Akaike information criterion (AIC) are presented for the range of

curves estimated, as summarised in Tables 7-9 below, the parameter values also being available within the submission.

Table 7 TTE curves' AICs: All patients

	OS		PFS-PSA		SRE	
	Radium	**BSC**	**Radium**	**BSC**	**Radium**	**BSC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The curves' parameter values are in table 35 page180 and table 36 and 37 page 182 of the submission						

Table 8 TTE curves' AICs: Prior docetaxel subgroup

	OS		PFS-PSA		SRE	
	Radium	**BSC**	**Radium**	**BSC**	**Radium**	**BSC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The curves' parameter values are in table 38, 39 and 40 page183 of the submission						

Table 9 TTE curves' AICs: No prior docetaxel subgroup

	OS		PFS-PSA		SRE	
	Radium	**BSC**	**Radium**	**BSC**	**Radium**	**BSC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The curves' parameter values are in tables 41, 42 and 43 page 184 of the submission						

To calculate the cohort flow for quality of life purposes, the model applies the log-normal curves throughout. The overall survival curves are the main determinants of the cost

effectiveness estimates. These are presented alongside the Kaplan Meier curves and the number at risk curves in Figure 3 below, based upon the data supplied within the manufacturer's electronic model.

Figure 3 OS parametric, OS Kaplan Meir and OS N at risk curves: All patients

The curves for PSA progression and first on study SRE are presented in Figure 4 below, again based upon the data supplied within the manufacturer's electronic model.

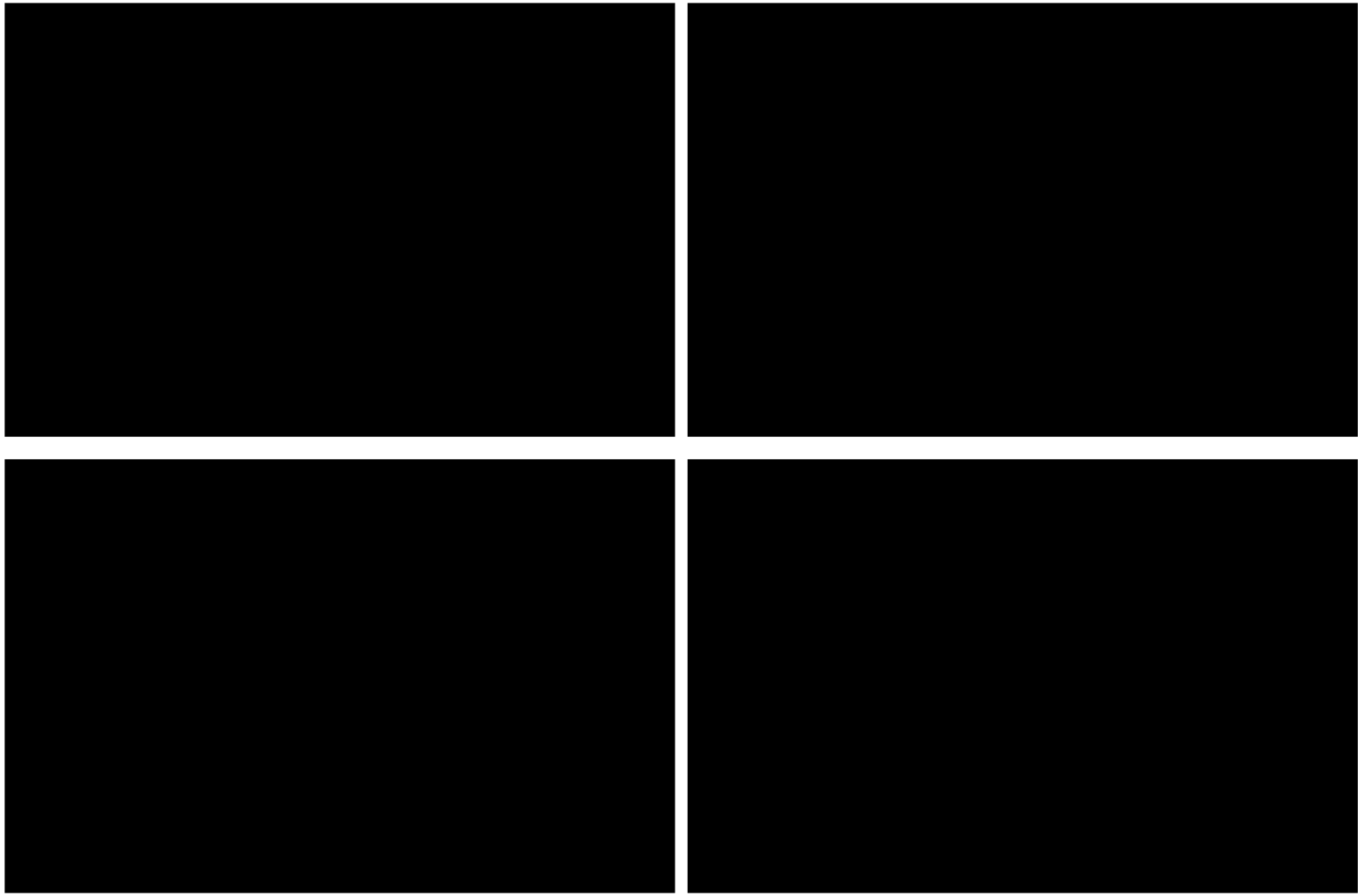
Figure 4 PSA PFS parametric, PSA PFS Kaplan Meier and PSA PFS Number at risk curves: All patients

Figure 5 SRE parametric, SRE Kaplan Meier and SRE Number at risk curves: All patients

Given the parameter values, the curves for PFS and SRE may be modelled as crossing the OS curve. For the PFS curve this is dealt with by limiting the PFS curve to be less than or equal to the OS curve, although this constraint is not actually required for the base case so has no impact. For the SRE curve, this is dealt with by examining the week [redacted] Kaplan Meier data to estimate an adjustment factor: the proportion of surviving patients at week [redacted] who had not had an SRE. This treatment arm specific adjustment factor is applied to the OS curve from the week [redacted] cycle, regardless of the plot of the parameterised SRE curve: [redacted] for radium-223 and [redacted] for placebo.

Applying this adjustment factor results in the following curves for the all patient modelling, as shown in Figure 6 below.

Figure 6 Parameterised curves and adjusted curves: All patients



The above curves are used to determine the quality of life aspects and the ongoing state costs within the model. An estimate of the incidence of these events in each cycle is, however, required to cost the events of progression leading to second line therapy and first on study SRE. For SREs, this incidence is arrived at by calculating the risk of an SRE in each cycle and multiplying it by the proportion of patients alive in that cycle. Regardless of the functional forms outlined above, the risk of an SRE is derived from the Kaplan Meier curve. Note that in effect this models the risk of an SRE falling to zero once the Kaplan Meier data comes to an end, regardless of the parametric curve extrapolation being used for the calculation of the QALY impacts.

Similarly, the cost of progression and second line therapy requires an estimate of the incidence of progression in each cycle, much as for the costing of SREs. The risk of progression for SREs is derived from the Kaplan Meier curve. It is also curtailed but for the risk of progression it is not curtailed once the Kaplan Meier data comes to an end, but is rather set to zero from cycle [redacted] onwards.

Extrapolation

The parameterised curves are used to extrapolate to the five-year time horizon. The quality of life increment for radium-223 dichloride over placebo estimated from the trial is retained for the five-year time horizon.

5.2.7 Health related quality of life

Progression free and with progression survival and HRQoL

EQ-5D data was collected during the ALSYMPCA trial. The manufacturer uses the UK social tariff to estimate the average values for progression free survival and post progression survival. The ERG assumption is that PSA is used for the measure of progression in this analysis, but this was not confirmed at clarification. Estimates for the impact of progression free and with progression survival on HRQOL are presented in Table 10 below.

Table 10 Estimate of progression free and with progression survival on HRQoL

	Radium-223	**Placebo**	**Net**
Progression free	[redacted]	[redacted]	[redacted]
With progression	[redacted]	[redacted]	[redacted]
Net	[redacted]	[redacted]	

[redacted]. The main impact is between the treatment arms, with a HRQoL increment of [redacted] to [redacted] anticipated for those being treated with radium-223 dichloride compared to those being treated with placebo.

SREs and HRQoL

The HRQoL impact of SREs is estimated as a weighted average of values taken from a paper within the literature.[32] Where more than one value is drawn from the literature for SRE subtypes, the subtypes are assumed to be equally likely. The weights for each of the four main types of SREs are drawn from the ALSYMPCA trial, differentiated by treatment arm, as presented in Table 11 below.

Table 11 Impact of SREs on HRQoL

Utility loss per SRE	**Decrement**	**Radium-223**	**Placebo**
Fracture of the leg	0.0500		
Fracture of the rib	0.0300		
Fracture of the arm	0.0300		
Pathological fracture average	0.0367	[redacted]	[redacted]
SCC no paralysis	0.2200		
SCC with paralysis	0.3400		
SCC average	0.2800	[redacted]	[redacted]
Radiation 2 wk 5 appts	0.0500		
Radiation 2 appts	0.0200		
Radiation average	0.0350	[redacted]	[redacted]
Surgery	0.0700	[redacted]	[redacted]
		[redacted]	[redacted]

This results in an average HRQoL decrement of [redacted] in the radium-223 dichloride arm and of [redacted] in the placebo arm. It is assumed that incident SREs have a lifetime HRQoL impact, and the SRE decrements are applied over the model time horizon to all those modelled as having had an on study SRE.

AEs and HRQoL

A one off QALY decrement is applied for AEs based upon the number of AEs recorded during the ALSYMPCA trial, coupled with values from the literature. These are presented in Table 12 below.

Table 12 QALY decrement applied to AEs

Adverse events	Decrement	Radium-223	Placebo
Fatigue	0.0942	[redacted]	[redacted]
Nausea	0.0480	[redacted]	[redacted]
Vomiting	0.0480	[redacted]	[redacted]
Anaemia	0.1250	[redacted]	[redacted]
Thrombocytopenia	0.0897	[redacted]	[redacted]
Hypokalemia	0.0000	[redacted]	[redacted]
Bone Pain	0.0690	[redacted]	[redacted]
Weighted decrement		[redacted]	[redacted]
Total QALY loss		[redacted]	[redacted]

This results in an average decrement per adverse event of [redacted] in the radium-223 dichloride arm and of [redacted] in the placebo arm. These are further conditioned by an average duration per adverse event of three weeks, and are assumed to have a multiplicative impact upon the PFS HRQoL values, resulting in a total QALY loss of [redacted] in the radium-223 arm and [redacted] in the placebo arm.

5.2.8 Resources and costs

Radium-223 drug and administration cost

An average of [redacted] radium-223 administrations is applied within the model. The cost per radium-223 dichloride treatment is [redacted]. There is an additional £200 cost of administration, drawn from the weighted average of NHS reference costs SB12Z for delivering simple parenteral chemotherapy at first attendance. This results in a total average drug cost of [redacted], and a total drug and administration cost of [redacted].

Progression and the costs of second line therapies

The manufacturer uses data from the IMS oncology analyser from the fourth quarter of 2011. The manufacturer appears to suggest that this data is specific to those progressing within the IMS oncology analyser dataset:

> "*…it is already adjusted for the proportion of progressed patients who require vs. do not require subsequent therapy (as per IMS Oncology Analyser data)*"

The means of identification of mCRPC patients' progression within the IMS oncology analyser is not known by the ERG. Presumably, because the number of cycles of treatment is

not recorded within the IMS oncology analyser, the manufacturer assumes an average of three cycles of each treatment subsequent to progression. The costs of second line therapies for the treatment of progression are presented in Table 13 below.

Table 13 Progression and the costs of second line therapies

	Cost	Proportion
[redacted]	[redacted]	[redacted]
Average cost per cycle		[redacted]
Average total cost		[redacted]

The main elements of the [redacted] cost are the costs of cabazitaxel and the costs of abiraterone. Removing cabazitaxel and increasing the other treatments pro-rata would result in the average total cost falling from [redacted] to [redacted], retaining the assumption of an average of three cycles.

It is unclear from the submission whether the data analysed relates only to the UK subset of 124 mCRPC patients, or to the mCRPC patients of the eleven countries of the IMS oncology analyser. It is also unclear why the manufacturer chose to only use the data from the fourth quarter of 2011. The ERG did not enquire about any of these aspects during clarification.

SRE costs

Seven percent of pathological fractures are assumed to be treated as inpatients, with the remainder being treated at a cost of £63 per patient: cost of a GP appointment of 17 minutes taken from the PSSRU Unit costs of health and social care. All other SREs are assumed to be treated as inpatients. The unit costs for these are taken from a variety of NHS reference costs, and weighted by the distribution of 1st on trial SREs recorded in the ALSYMPCA trial. Treatment costs by SRE type are presented in Table 14 below.

Table 14 SRE costs

	IP cost	GP cost	% IP	Unit Cost	Radium-223	Placebo
Pathologic Bone Fracture	£1,863	£63	7%	£189	[redacted]	[redacted]
Spinal Cord Compression	£3,273		100%	£3,273	[redacted]	[redacted]
External Beam Radiation	£105		100%	£105	[redacted]	[redacted]
Surgical Intervention	£4,454		100%	£4,454	[redacted]	[redacted]
Weighted average cost					[redacted]	[redacted]

This results in a weighted average cost per first on study SRE of [redacted] in the radium-223 arm and of [redacted] in the placebo arm. The higher cost in the placebo arm is due to the relatively low cost per fracture, coupled with the higher rate of spinal cord compression in the placebo arm.

Adverse event costs

The proportions experiencing adverse events are coupled with the proportion of adverse events requiring inpatient treatment, this data being drawn from the ALSYMPCA trial. A range of NHS reference costs and drug costs supply the unit costs applied to this. Those not being treated as an inpatient have medication costs plus the £63 cost of a 17 minute GP appointment, as drawn from the PSSRU Unit costs of health and social care. Treatment costs for adverse events are shown in Table 15 below.

Table 15 Adverse event costs

	IP cost	GP cost	% IP	Unit Cost	Radium-223	Placebo
Fatigue	£490.37	£63.00	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	£414.54	£65.43	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	£414.54	£65.43	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	£1,664.64	£392.55	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	£741.00	£392.55	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalemia	£502.59	£64.90	[redacted]	[redacted]	[redacted]	[redacted]
Bone Pain	£2,454.69	£81.24	[redacted]	[redacted]	[redacted]	[redacted]
Total AE cost					[redacted]	[redacted]

This results in an average AE cost for radium-223 of [redacted] compared to an average cost of [redacted] for placebo[b]. The difference mainly arises from the higher rate of bone pain in the placebo arm.

Other ongoing costs

The manufacturer undertook a survey of oncologists and urologists to estimate much of the resource use. When coupled with various NHS reference costs, this results in an average weekly cost for tests and imaging of [redacted] for those whose disease had not progressed and [redacted] for those who had progressed. The rates of concomitant medications were also estimated in the survey for those without disease progression who receive radium-223 dichloride, for those without progression who received placebo and for those who had progressed. Coupled with the weekly drug costs of these, this results in the following weekly costs as presented in Table 16 below.

Table 16 Other ongoing costs

		Progression Free		
	Weekly cost	**Radium-223**	**Placebo**	**Progressed**
Analgesics	[redacted]	[redacted]	[redacted]	[redacted]
Steroids	[redacted]	[redacted]	[redacted]	[redacted]
Biphosphonate	[redacted]	[redacted]	[redacted]	[redacted]
LHRH agonist	[redacted]	[redacted]	[redacted]	[redacted]
Palliative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Medications total		[redacted]	[redacted]	[redacted]
Tests and imaging		[redacted]	[redacted]	[redacted]
Total ongoing		[redacted]	[redacted]	[redacted]

This results in an average weekly cost of [redacted] for those without progression in the radium-223 dichloride arm, of [redacted] for those without progression in the placebo arm and of [redacted] for those who have progressed: annual costs of [redacted], [redacted] and [redacted] respectively.

End of life costs

The average end of life costs of are drawn from the study be Abel and colleagues[33] of the costs of care for the last year of life among 969 UK patients dying in hospital and in non-

[b] The manufacturer in response to ERG clarification question B14 supplies the inpatient and outpatient data for the ALSYMPCA UK subgroup. Applying this within the model has minimal impact upon the ICER.

hospital settings. The average of £8,349 of Abel and colleagues[33] is reduced to a quarter of this to reflect the costs of the three months immediately preceding death: £2,087.

5.2.9 Cost effectiveness results

The deterministic base case results are presented in Table 17 below.

Table 17 Deterministic base case results

	All patients			Prior Docetaxel			No Prior Docetaxel		
	Radium	**BSC**	**Net**	**Radium**	**BSC**	**Net**	**Radium**	**BSC**	**Net**
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Admin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Management	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of life	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SREs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS (undisc)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			[redacted]			[redacted]			[redacted]

The central estimates from the probabilistic modelling run over 10,000 iterations and the likelihood of radium-223 being cost effective at a various willingness to pay thresholds are presented in Table 18 below.

Table 18 Probabilistic base case results

	All Patients			Prior Docetaxel			No Prior Docetaxel		
	Radium	**BSC**	**Net**	**Radium**	**BSC**	**Net**	**Radium**	**BSC**	**Net**
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			[redacted]			[redacted]			[redacted]
Probability of radium-223 being cost effective at WTP per QALY thresholds of:									
£0k	[redacted]			[redacted]			[redacted]		
£20k	[redacted]			[redacted]			[redacted]		
£30k	[redacted]			[redacted]			[redacted]		
£50k	[redacted]			[redacted]			[redacted]		
£100k	[redacted]			[redacted]			[redacted]		

5.2.10 Sensitivity analyses

A range of one-way sensitivity analyses were presented, with the submission concentrating upon the sensitivity analyses that had the largest impact upon the ICER. These are presented in Table 19 below.

Table 19 One-way sensitivity analyses

				All Patients		Prior Docetaxel		No Prior Docetaxel	
	Base	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**
2nd Line cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Outpatient cost	63.0	44.1	81.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycles of 2nd line	3.0	2.1	3.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost DR	3.5%	1.5%	6.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Benefit DR	3.5%	1.5%	6.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% of pts surgery - Radium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% of pts surgery - BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of administration	£200	£128	£241	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radium – Utility PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo – Utility PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radium – Utility WPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo – Utility WPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radium cycles	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radium median OS									
	64.57	60.43	69.86	[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]					[redacted]	[redacted]
Monthly price radium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As would be anticipated, results are sensitive to the cost of radium-223 dichloride, the number of radium-223 dichloride cycles, the overall survival experienced with radium-223 dichloride, the utility estimates for progression free survival and the utility estimates for the with disease progression survival. The sensitivity analyses for the higher values of median overall survival for radium-223 dichloride are not available due to the model inputs underlying these estimates not being presented by the manufacturer within the model. There may also be an error in the implementation of these sensitivity analyses for the median overall survival for BSC. It would be anticipated that results would be similarly sensitive to the median overall survival for BSC.

5.2.11 Model validation and face validity check

Table 88 on page 267 of the MS presents some validation data. By construction, the modelled adverse events are simply the model inputs. The median progression free survival and median overall survival are also presented by treatment arm. Validation data are presented in Table 20 below.

Table 20 Validation data

	Radium-223		**Placebo**	
	Trial	**Model**	**Trial**	**Model**
Median PFS (mths)	2.31	[redacted]	2.08	[redacted]
Median OS (mths)	14.90	[redacted]	11.30	[redacted]

[redacted]

5.3 ERG cross check and critique

5.3.1 Base case results

The base case results that are reported cross check with those of the manufacturer model.

5.3.2 Data inputs: Correspondence between written submission and the literature

SRE QoL decrements

The quality of life decrements of the model cross check with those reported in Matza and colleagues.[32,c] It should be noted that this data was from a survey among 126 UK members of the general public and was not data relating to patients with mCRPC. Respondents were presented with a hypothetical 2-year lifespan as the result of cancer, with hypothetical health vignettes being assessed by time trade off to yield the estimates for the quality of life decrements associated with SREs.

The SRE quality of life decrements within the Ford and colleagues[34] MTA of denosumab for prevention of SREs are unfortunately redacted.

Excluding the SRE quality of life decrements entirely from the manufacturer base case for all patients revises the cost effectiveness estimate from [redacted] per QALY to [redacted] per QALY.

AE QoL decrements

The ERG has not reviewed the quality of life decrements associated with adverse events. Excluding them entirely from the manufacturer base case for all patients revises the cost effectiveness estimate from [redacted] per QALY to [redacted] per QALY.

SRE costs

The title of Table 75 of the submission is "*Aggregate per model cycle costs for SREs by therapy line per patient*". This could be read as suggesting that SREs are assumed to be associated with ongoing costs of [redacted] per cycle in the radium-223 dichloride arm and [redacted] per cycle in the placebo arm. Within the model these costs are one off costs, however, and are only applied at the incidence of SREs.

The SRE costs of the submission are largely based upon averages of NHS reference costs. The submission assumes that all pathological fractures are non-vertebral leg, arm or rib fractures. This results in an average inpatient cost of £1,863, an average of various NHS reference costs, and an average outpatient cost of £63 as drawn from the PSSRU costing for a GP appointment of 17 minutes. Given the manufacturer assumption that pathological fractures are either leg, arm or rib, it does not seem reasonable to cost non-inpatient treatment of these at the cost of a single GP visit. The balance between inpatient treatment and non-inpatient treatment for pathological fractures of 7% to 93% is apparently drawn from Botteman et al (2011), resulting in an average cost per pathological fracture of £189.

[c] Sponsored by Amgen

Botteman et al (2011) is only referenced within the electronic model, and there is no citation within the submission references for this paper. The written submission gives the inpatient cost of £1,863, but makes no reference to the £63 cost that is assumed for 93% of pathological fractures. Applying only the £1,863 of the submission for pathological fractures would increase the average cost per SRE from [redacted] to [redacted] in the radium-223 dichloride arm and from [redacted] to [redacted] in the placebo arm. This narrows the difference between the arms in the average cost per SRE from [redacted] to [redacted].

Ford and colleagues[34] in the HTA monograph of denosumab for prevention of SREs estimated the following costs for SREs and adverse events, these again being largely based upon NHS reference costs but allowing for treatment follow-up. The cost estimated by Ford and colleagues[34] compared against the MS are presented in Table 21 below.

Table 21 SRE Costs: Ford and colleagues[34] compared to submission

SRE	Ford and Colleagues[34]	Submission
Vertebral fracture	£294	..
Non-vertebral fracture	£1,581	£189
Radiation to the bone	£662	£105
Surgery to the bone	£7,269	£4,454
Spinal cord compression	£7,311	£3,273

It seems likely that pathological fractures recorded within ALSYMPCA will not have been solely leg, arm or rib fractures. This assumption also applies to the quality of life values. Consequently, a sensitivity analysis applying the costs of Ford and colleagues[34] for non-vertebral fractures, radiation to the bone, surgery to the bone and spinal cord compression seems appropriate. To the extent that vertebral fractures were recorded as pathological fractures within the ALSYMPCA trial, applying Ford and colleagues'[34] cost of non-vertebral fracture will be an overestimation, but this is likely to be balanced on the quality of life side of the equation to some extent.

AE costs

The ERG has not reviewed the costs associated with adverse events. Excluding them entirely from the manufacturer base case for all patients as a worst case scenario revises the cost-effectiveness estimate from [redacted] per QALY to [redacted] per QALY.

Costs of progression and second line therapies

The ERG has not reviewed the costs of progression and second line therapies. Given the speed of disease progression in both treatment arms of the ALSYPMCA trial, the costs of the second line therapies are quite similar in both arms. Excluding them entirely from the manufacturer base case for all patients as a worst case scenario revises the cost effectiveness estimate from [redacted] per QALY to [redacted] per QALY.

5.3.3 Data inputs: Correspondence between written submission and electronic model

Number of radium-223 doses

The base case assumes a mean number of [redacted] radium-223 dichloride treatments. Figure 11 of the submission suggests that a total of [redacted] injections of radium-223 dichloride were given during the ALSYMPCA trial. 614 patients were randomised to the radium-223 dichloride arm, with 599 being treated with radium-223 dichloride. This suggests a mean of [redacted] radium-223 dichloride treatments per patient randomised to the radium-223 dichloride arm and a mean of [redacted] radium-223 dichloride treatments per patient treated with radium-223 dichloride during the ALSYMPCA trial. It appears from the electronic model that the parametric curves for the radium-223 dichloride arm were estimated from the data relating to the 614 patients randomised to radium-223. Log-normal and Kaplan Meier estimates for overall survival are presented in Table 22 below.

Table 22 Overall survival log-normal and Kaplan Meier estimates

Week	**0**	**4**	**8**	**12**	**16**	**24**	**Total**
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan Meier	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Within the modelling, the overall survival curve is assumed to follow the log-normal curve. If all surviving patients were assumed to be treated with radium-223 dichloride this would suggest a mean of [redacted] radium-223 dichloride treatments as outlined below. The Kaplan Meier curve for overall survival in the radium-223 dichloride arm shows quite similar percentages surviving, however, and a similar total of [redacted]. As a consequence, for the log-normal modelling of overall survival it may be reasonable to assume that the mean number of doses reported in ALSYMPCA is applicable.

SRE rates

The numbers of patients experiencing at least one SRE by type given in Table 20 of the submission corresponds with the numbers given in Table 1 of the manufacturer response to ERG clarification question A1.

There is no obvious similarity between the MS and the numbers of first on trial SREs given in Table 1 of the manufacturer response to ERG clarification question A1. This is the data that is used within the model, but it is not included in the clinical effectiveness section of the manufacturer submission.

AE rates

The grade 3/4 adverse events rates used within the model do not appear to correspond with either the adverse event rates or the serious adverse event rates given in Table 29 and page 144 of the MS. This is most clearly seen for the adverse events of bone pain, anaemia and thrombocytopenia. Event rates for AEs, SAEs and modelled AEs are shown in Table 23 below.

Table 23 Adverse events rates, serious adverse event rates and the modelled adverse event rates

	AEs		**SAEs**		**Model**	
	Radium-223	**Placebo**	**Radium-223**	**Placebo**	**Radium-223**	**Placebo**
Bone pain	50%	62%	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	31%	31%	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	12%	6%	[redacted]	[redacted]	[redacted]	[redacted]

The serious adverse event rates drawn from page 144 of the MS may relate to the pooled ALSYMPCA and BC1-02 trial, which could account for some of the discrepancies.

5.3.4 ERG commentary on model structure, assumptions and data inputs

The ERG has rebuilt the deterministic model structure retaining the manufacturer assumptions, with almost identical results to those of the manufacturer model, and shown in Table 24 below.

Table 24 ERG cross check rebuild of manufacturer model

	All Patients			Prior Docetaxel			No Prior Docetaxel		
	Radium	**BSC**	**Net**	**Radium**	**BSC**	**Net**	**Radium**	**BSC**	**Net**
Manufacturer model deterministic base case results									
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			[redacted]			[redacted]			[redacted]
ERG cross check model rebuild									
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			[redacted]			[redacted]			[redacted]

Calculation of the distribution between health states among those remaining alive

Figure 27 on page 186 of the MS suggests that the formulae should be of the form:

- $P(\text{PFS no SRE})_t = P(\text{Alive})_t * P(\text{PFS})_t * P(\text{SRE})_t$
- $P(\text{PFS with SRE})_t = P(\text{Alive})_t * P(\text{PFS})_t * (1- P(\text{SRE})_t)$
- $P(\text{Prog. no SRE})_t = P(\text{Alive})_t * (1- P(\text{PFS})_t) * P(\text{SRE})_t$
- $P(\text{Prog. with SRE})_t = P(\text{Alive})_t * (1- P(\text{PFS})_t) * (1- P(\text{SRE})_t)$

The model divides both $(PFS)_t$ and $P(SRE)_t$ by $P(Alive)_t$., however. No justification for this division is presented by the manufacturer. The manufacturer response to ERG clarification question B4 only notes that removing the division by $P(Alive)_t$ revises the cost effectiveness estimate for all patients from [redacted] per QALY to [redacted] per QALY.

The ERG remains unclear as to why division by $P(Alive)_t$ was introduced within the model. As outlined in greater detail in appendix 73, it appears that for the corollary of Kaplan Meier data the formulae of Figure 27 are appropriate. The calculation based upon the formulae of Figure 27 of the submission also suggests that the SRE curve crossing the overall survival curve is no longer problematic and that this adjustment can be removed from the model.

Choice of fitted curve

The model uses the lognormal curves throughout, citing the DSU technical support document in support of this. The DSU technical support document does argue that modelling should not fit one type of curve for one arm and another type of curve for the other arm. But it is not clear that it argues that the same type of curve should be fitted to all relationships within a model; e.g. using loglogistic for overall survival and log-normal for progression could be acceptable provided that these are applied equally to both arms.

This could argue for applying the loglogistic curves for SREs, and possibly also for overall survival, while retaining log-normal curves for progression. Applying loglogistic curves for overall survival worsens the cost effectiveness estimate across all patients from [redacted] per QALY to [redacted] per QALY. The manufacturer model structure is not readily amended to apply the loglogistic curves for the SREs. Applying loglogistic curves for the SREs within the ERG cross check model rebuild has little impact upon the cost effectiveness estimate.

SRE identification

The ERG had been concerned that SREs might have been identified through radiological examination and therefore have had little or no patient impact when identified. The manufacturer in response to ERG clarification question A2 notes, however, that:

> "*An SRE was defined in the protocol as "A skeletal related event is the use of external beam radiotherapy to relieve skeletal symptoms or the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral) or the occurrence of spinal cord compression or a tumour related orthopaedic surgical intervention". The pathological bone fracture component is always stated as "symptomatic". No information was contained in the protocol on how to identify or*

diagnose any of the SRE components, as this is considered common knowledge in the prostate cancer medical community.

Furthermore, and very importantly, no radiological imaging was included in the protocol, nor was it routinely performed unless another clinical finding, e.g. symptomatic bone pain, was observed. Moreover, investigators and sites were not paid for any radiological imaging.

Hence, radiological imaging would not trigger the identification of a pathological fracture, but rather would be used to confirm symptoms. Lastly, the way data was captured during the study (CRF and AE forms) did not request imaging data as a way of recording an event, e.g. SRE."

The effects of symptomatic fractures within the model

The model assumes that all pathological fractures were either fracture of the arm, fracture of the rib or fracture of the leg and that there was an equal balance between these. The ERG in clarification question A1 asked for "*a list of all the separate skeletal-related event types identified within the ALSYMPCA trial, and the number of each SRE experienced*". This was perhaps naïve phrasing by the ERG, as the SREs reported by the manufacturer in its response were limited by type to external beam radiotherapy, surgical intervention, spinal cord compression and pathological bone fracture. As a consequence, it remains unclear whether all pathological fractures were either fracture of the arm, rib or leg and that there was an equal balance between these during the ALSYMPCA trial as is assumed by the model. If lesser fractures were included in pathological bone fractures identified during the ALSYPMCA trial this would tend to lessen their impact to below that assumed within the model. It seems likely that at a minimum there was a split between vertebral and non-vertebral fractures, and that as a consequence not all fractures were fractures of the arm, rib or leg.

Follow up and censoring within the SRE and PFS curves

There are some concerns about the reliability of the Kaplan Meier data for the SRE events, and possibly also for the PFS events.

Firstly, as highlighted in the manufacturer response to ERG clarification question B4:

[redacted]

[redacted]

This is given as justification for not estimating a model for SREs and for PFS, where rather than treating death as a censoring event it would be treated as an event, thereby giving a joint model. This may also raise questions around the use of SRE and PFS data [redacted] for the estimation of the parametric curves. Structural scenario analyses of using only [redacted] for the estimation of the SRE and PFS parametric curves might have been appropriate. This would mainly affect the SRE curves.

Secondly, there may be some concerns about censoring at the start of the ALSYMPCA trial in the SRE and PFS curves, based upon data taken from the electronic model and presented in Table 25 below.

Table 25 ALSYMPCA censoring at day 1: SRE and PFS

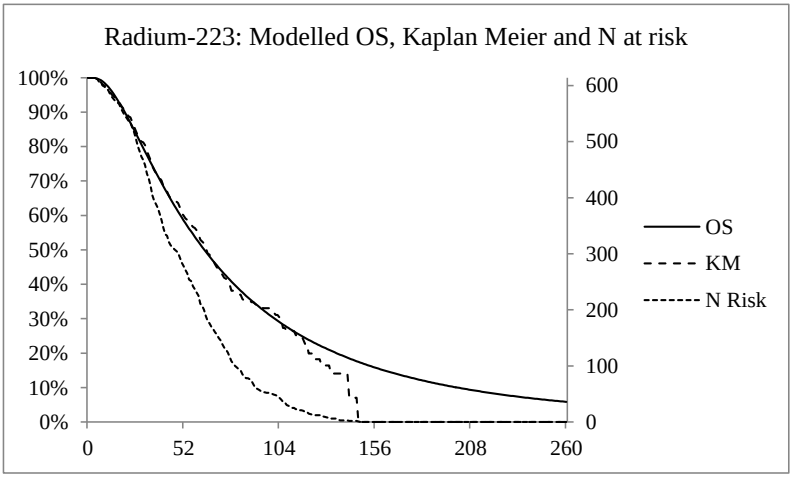
	SRE Censoring Day 1				**PFS-PSA Censoring Day 1**			
	Radium-223		**Placebo**		**Radium-223**		**Placebo**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
All patients	[redacted]							
Prior docetaxel	[redacted]							
No prior docetaxel	[redacted]							

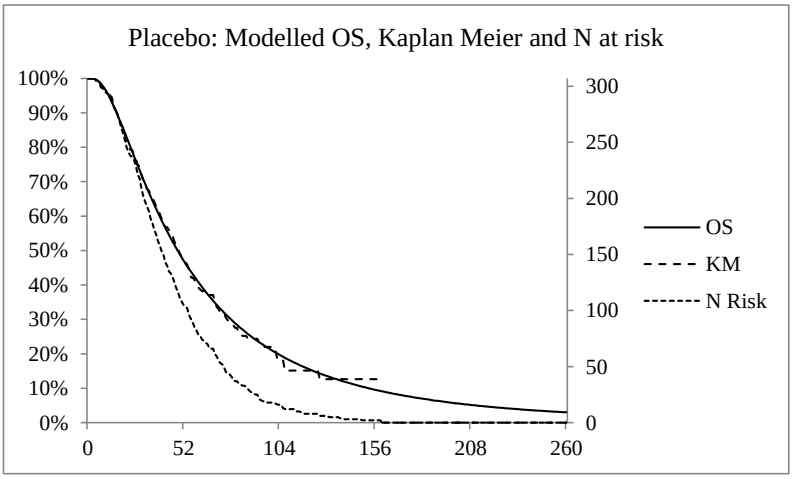
The definition of censoring events is the same for the SRE and PFS curves; death, lost to follow up and trial end. As noted previously, identification of SREs was due to standard clinical practise and was not due to protocol driven radiological examination. There is no obvious reason why patient consent might have led to the large differences in censoring at day 1 that occur between the SRE curves and the PFS curves. Not only is there higher censoring at day 1 for the SRE curves, it is higher in the placebo arm by around [redacted], though the absolute differences are only around [redacted]. No explanation of the day 1 censoring for SREs is presented, and it was not raised by the ERG at clarification. But it may raise some further questions about the reliability of the SRE data.

The appropriate time horizon

Log-normal curves, as used for the base case, have a long tail. This may result in unrealistic extrapolations if taken too far beyond the trial data that the curves are estimated from, and is presumably the reason for the manufacturer limiting the time horizon to 5 years. The ALSYMPCA Kaplan Meier curves and the numbers at risk for overall survival are graphed in Figure 7 below, overlaid with the log-normal overall survival curves[d].

Figure 7 ALSYMPCA OS curves, numbers at risk and log-normal OS curves





[redacted]

[d] This data is drawn from the electronic copy of the model

In the light of the shape of the Kaplan Meier curves, the degree to which it is reasonable to extrapolate beyond 3 years and up to the 5 year time horizon of the base case is open to question. Sensitivity analyses around the time horizon are consequently desirable.

Time horizon and quality of life impacts

As already noted, the quality of life increments of [redacted] for radium-223 dichloride over placebo calculated from the ALSYMPCA trial are assumed to last for the remaining patient lifetime. This extrapolation of effect may be optimistic if patient quality of life tends to continue to fall over time.

Time horizon and end of life costs

Given the 5-year time horizon, the log-normal OS curves are truncated: [redacted] are modelled as surviving in the radium-223 dichloride arm compared to [redacted] in the BSC arm. This suggests a net additional survival at 5 years of [redacted] As a consequence, there is a net reduction in the undiscounted end of life costs of [redacted] While restricting the time horizon and truncating the lognormal OS curves is reasonable due to their long tails, it is not reasonable for this to give rise to the reduction in the undiscounted end of life costs. The expectation is that all patients will die of their disease. Consequently, the model should assume that the OS curve falls to zero at the end of the time horizon.

EQ-5D data supplied within the submission and at clarification

The submission supplied minimal information about the ALSYMPCA EQ-5D data that was used for the modelling. This was apparently simply split by treatment arm and PSA progression to give four mean values. This is despite the health states of the modelling being split by both PSA progression and SRE experience, with the ALSYMPCA EQ-5D data covering this.

The ERG clarification question B3 asked for the trial EQ-5D data mean values, sample standard deviations and patient numbers separately at baseline, week 16, week 24 and any data additional to these time points. On this basis, the baseline data should not include any of the last visit data supplied at clarification. For the baseline, week 16 and week 24 values the patient numbers tally between the various classifications. But for the last visit values the patient numbers do not tally between the various classifications. Details of the last visit patient numbers underlying the EQ-5D data supplied by the manufacturer at clarification are presented in Table 26 below.

Table 26 Last visit patient numbers underlying EQ-5D data supplied at clarification

	Radium-223	Placebo
No PSA prog.	[redacted]	[redacted]
No PSA prog. and no SRE	[redacted]	[redacted]
No PSA prog. and with SRE	[redacted]	[redacted]
Subgroup totals	[redacted]	[redacted]
With PSA prog.	[redacted]	[redacted]
With PSA prog. and no SRE	[redacted]	[redacted]
With PSA prog. and with SRE	[redacted]	[redacted]
Subgroup totals	[redacted]	[redacted]

For the last visit values, the patient numbers for both the aggregate no PSA progression and the aggregate with PSA progression are less than the sum of the relevant subgroups. The HRQoL values for aggregate groups also differ from the weighted average HRQoL values of the relevant subgroups. Given this, there is a lack of clarity about the data for the last visit values supplied at clarification.

In the light of the above, the HRQoL weighted averages can be calculated based upon only the baseline, week 16 and week 24 data and also based upon baseline, week 16, week 24 and last visit data as presented in Table 27 below.

Table 27 **EQ-5D HRQoL data supplied at clarification and model values: Radium-223**

	Excluding Last Visit				Including Last Visit		
	Baseline	**Week 16**	**Week 24**	**Mean**	**Last visit**	**Mean**	**Model**
No PSA prog.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n observations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
With PSA prog.		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n observations		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
No PSA prog., no SRE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
n observations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
No PSA prog., with SRE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
n observations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
With PSA prog., no SRE		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
n observations		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
With PSA prog., with SRE		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
n observations		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Table 28 EQ-5D HRQoL data supplied at clarification and model values: Placebo

	Excluding Last Visit				Including Last Visit		
	Baseline	**Week 16**	**Week 24**	**Mean**	**Last visit**	**Mean**	**Model**
No PSA prog.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n observations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
With PSA prog.		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n observations		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
No PSA prog., no SRE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
n observations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
No PSA prog., with SRE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
n observations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
With PSA prog., no SRE		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
n observations		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
With PSA prog., with SRE		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
n observations		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

There is no obvious similarity between the HRQoL data supplied at clarification and the HRQoL data used within the model. The net effects between the treatment arms also differ. For the health state of no PSA progression the differences between the arms' mean HRQoL values are:

- for the clarification data excluding the last visit: [redacted]
- for the clarification data including the last visit: [redacted]
- as applied within the model: [redacted]

For the health state of with PSA progression the differences between the mean HRQoL values are:

- for the clarification data excluding the last visit: [redacted]
- for the clarification data including the last visit: [redacted]
- as applied within the model: [redacted]

Further excluding the baseline values does not cause the data to tally. Note that the ERG is not advocating that the baseline values should be excluded.

It can also be noted that from the data supplied at clarification that the mean baseline HRQoL value is [redacted]

The mean values and their error bars, based upon the sampled standard deviations and patient numbers and assuming symmetric confidence intervals are graphed in Figure 8 below. The week 16 mean value for no progression in the placebo arm immediately looks odd in comparison with the week 16 mean value for with progression in the placebo arm.

Figure 8 Baseline, week 16 and week 24 EQ-5D data supplied at clarification

[redacted]

[redacted]

Within the radium-223 dichloride arm, reading down the columns of the tables the sign of the differences between the various HRQoL values is broadly as would be expected, though the mean week 16 HRQoL value

[redacted] But the picture is further clouded by what appears to be some possibly peculiar values within the placebo arm, possibly due in part to the smaller patient numbers. These may be more serious.

[redacted]

The data supplied at clarification, excluding the last visit data, can be summarised not only by those with and without progression but also by those with and without an SRE. Table 29 presents the EQ-5D data supplied by the manufacturer at clarification, split by progression and SRE: excluding last visit.

Table 29 EQ-5D data supplied at clarification split by progression and SRE: excluding last visit

Radium	No SRE	With SRE	Net
no progression	[redacted]	[redacted]	[redacted]
n observations	[redacted]	[redacted]	
with progression	[redacted]	[redacted]	[redacted]
n observations	[redacted]	[redacted]	
net	[redacted]	[redacted]	
Placebo	No SRE	With SRE	net
no progression	[redacted]	[redacted]	[redacted]
n observations	[redacted]	[redacted]	
with progression	[redacted]	[redacted]	[redacted]
n observations	[redacted]	[redacted]	
net	[redacted]	[redacted]	
Between the arms	No SRE	With SRE	
no progression	[redacted]	[redacted]	
with progression	[redacted]	[redacted]	

The picture is somewhat more complicated when the data is split not only by progression but also by the with SRE and without SRE distinction. A mean net decrement for those having experienced an on trial SRE of between [redacted] and [redacted] is predicted with reasonable consistency. These are somewhat larger than the values drawn from the literature, that average to decrements of [redacted] in the radium-223 arm and [redacted] in the placebo arm. The net effects of progression are also reasonably consistently predicted as being quite small, though there is the outlier value for the with progression and with SRE of [redacted] in the placebo arm. This outlier does have a reasonable [redacted] observations underlying it, however.

[redacted]. The ERG is not arguing that this is a credible result but it does seem that the EQ-5D data of the trial is somewhat more complicated than the manufacturer submission would initially suggest, and that this may call into question the quality of life values for post-progression of [redacted] for radium-223 dichlorideand of [redacted] for placebo. The resulting [redacted] decrement for placebo is a key variable within the modelling.

In the light of the above and the modelled health states, it seems particularly surprising that the manufacturer did not attempt to estimate, from the ALSYMPCA EQ-5D data, a unified model of HRQoL or changes in HRQoL as a function of:

- baseline values;
- with and without PSA progression;
- with and without a first on trial SRE;
- on or off treatment in the radium-223 arm, or pre and post 6 months from baseline;
- trial arm, possibly conditioned by the two bullets above for the without progression and without first on trial SRE states; and,
- a possible time trend.

There is of course the possibility that this option was explored by the manufacturer but not reported, with the submission relying instead upon the much simpler split by treatment arm and by PSA progression.

SRE HRQoL impacts

As noted above, the ALSYMPCA EQ-5D data incorporates the effects of both PSA progression and SRE experience, despite the data only being split by PSA progression. Estimating additional SRE effects from data within the literature seems likely to double count the effects of SREs to some degree. Removing these additional SRE effects from the analysis for either the base case or for a sensitivity analysis would seem desirable.

SRE rates between the treatment arms

The model assumes that the first SRE has a quality of life impact that endures for the remaining lifetime of the patient. This may be more likely for some SREs, such as spinal cord compression, than for others, such as pathological fracture. As a consequence, the model may overestimate the impact of SREs upon quality of life. This is to some extent counterbalanced by the model only taking into account the first SRE, as per the data supplied in response to ERG clarification question A1. Data for first SREs and all SREs by treatment arm are shown in Table 30 below.

Table 30 First SREs and all SREs

	Model:1st SRE		All SREs	
	Radium	**Placebo**	**Radium**	**Placebo**
External Beam Radiation	[redacted]	[redacted]	[redacted]	[redacted]
Pathologic Bone Fracture	[redacted]	[redacted]	[redacted]	[redacted]
Surgical Intervention	[redacted]	[redacted]	[redacted]	[redacted]
Spinal Cord Compression	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

It can be argued that for a given SRE duration, taking into account the subsequent SREs would tend to increase the proportion of time subsequent to the incidence of the first SRE spent that would be spent with an SRE. This might make it more reasonable to assume that the first SRE has a lifetime HRQoL impact.

The total number of SREs was [redacted] higher than the number of first SREs in the radium-223 arm and was [redacted] higher in the placebo arm. This might suggest that the impact of subsequent SREs might be larger in the placebo arm than in the radium-223 arm. But this is highly speculative given the incomplete KM survival curves and the manufacturer acknowledged difficulties in recording SREs beyond the 6 month point.

The model differentiates the SRE proportions being experienced between the arms. This is based upon the first SRE experienced. Despite using the time to 1st SRE curve within the model, it could be argued that for costing purposes the balance between all SREs might be a better reflection of the average cost per SRE. It could also be argued that this might also affect the quality of life impacts, though this is more tenuous given assumptions around costs being up front while quality of life impacts are for the period from first SRE to death. Possible impacts upon costs and quality of life for first and all SREs are presented in Table 31 below.

Table 31 First SREs and all SREs possibly impacts upon costs and quality of life

			Model: 1st SRE		All SREs	
	Unit Cost	**HRQoL**	**Radium**	**Placebo**	**Radium**	**Placebo**
External Beam Radiation	£105	0.0350	[redacted]	[redacted]	[redacted]	[redacted]
Pathologic Bone Fracture	£189	0.0367	[redacted]	[redacted]	[redacted]	[redacted]
Surgical Intervention	£4,454	0.0700	[redacted]	[redacted]	[redacted]	[redacted]
Spinal Cord Compression	£3,273	0.2800	[redacted]	[redacted]	[redacted]	[redacted]
Weighted average cost			[redacted]	[redacted]	[redacted]	[redacted]
HRQoL decrement			[redacted]	[redacted]	[redacted]	[redacted]

The above data suggests that only taking into account the first SRE for costing purposes may be conservative. The differences in the weighted average cost between the arms is smaller when using only the balance between the first SREs than when using the balance between all SREs. This is mainly due to the increase in the proportion requiring surgical intervention in the placebo arm compared to the radium-223 arm.

It is less clear whether the quality of life decrements applied within each cycle subsequent to the first SRE are conservatively estimated using the balance between 1st SREs compared to the balance between all SREs. The reverse may be the case.

A sensitivity analysis applying the balances between all SREs would seem to be reasonable.

ALSYPMCA Resource use data

The ERG clarification question B13 asked that the ALSYMPCA resource use questionnaire be presented alongside some further explanation of it, coupled with the resulting data for with and without PSA progression and with and without a 1st on trial SRE. The ERG also asked that the data be presented for the UK subgroup of the ALSYMPCA trial. The manufacturer response was:

> "*Whilst we could present this data, Bayer do not feel that it is helpful for the purposes of economic modelling as data collected was protocol driven rather than representing clinical practice. As such, Bayer used data sourced from the literature*."

This seems a peculiar and weak justification for not presenting any analysis of the resource use data collected during the trial. It begs the question why the resource use data was collected during the trial. It sits uneasily with the proportion of AEs that are treated as an inpatient being drawn from the ALSYMPCA trial data. It is also unclear why the additional resource use associated with patients progressing or experiencing an SRE would be driven by the trial protocol, particularly in the light of the manufacturer response to ERG clarification question A2 as summarised at the start of this section.

But the response may suggest that the additional resource use associated with patients progressing or experiencing an SRE would not have been captured by the ALSYMPCA resource use questionnaire. This would have been clearer had the manufacturer supplied an example of the ALSYMPCA resource use questionnaire, as requested in ERG clarification question B13.

Costs of ongoing procedures and medicines by state and by arm

There is a lack of clarity within the submission about the resource use survey commissioned by the manufacturer among oncologists and urologists. In particular, it is not clear whether respondents were informed that this was for modelling purposes, and that the model would separately identify the resource use associated with SREs and adverse events. It seems possible that respondents may have been taking these into account within their responses. This might be the source of the anticipated higher pre-progression rate of analgesics and LHRH agonists within the placebo arm compared to the radium-223 dichloride arm, and the higher post progression rate of palliative radiotherapy.

Similarly, the costs of SREs within the model may to some extent reflect the costs of medication identified in the resource use survey and differentiated by arm: [redacted] per week in the radium-223 dichloride arm and [redacted] per week in the placebo arm.

There may be a misinterpretation by the ERG. Page 235 of the submission states that "*No conflict of interest statement was taken as neither the manufacturer nor the product was disclosed to the participants*". If this is the case, it is unclear to the ERG how ongoing resource use was differentiated by treatment arm, as occurs for the ongoing pre-progression medication of Table 65 on page 240 of the submission.

Drawing resource use for ongoing routine care, SREs and adverse events from disparate sources may have tended to double count. Sensitivity analyses equalising the routine ongoing costs between the arms for pre-progression health states, and equalising the routine ongoing costs across all health states can be performed to explore this.

Incidence of second line therapies and resulting costs

The costing of second line therapies requires the incidence of progression to be calculated for each cycle in both arms. Rather than base this upon the parametric curves the manufacturer estimates this from the Kaplan Meier curves, curtailing this at [redacted] weeks: i.e. after [redacted] weeks the incidence of PSA progression for costing purposes is set to zero in both arms. The manufacturer response to ERG clarification question B10 states that "[redacted]". This is true in the placebo arm with the number at risk having fallen to zero, but it is not true in the radium-223 dichloride arm where the number at risk falls to zero shortly after week [redacted]. This additional incidence has not been taken into account within the model.

But the rationale for using the Kaplan Meier curves for calculating the incidence of progression seems peculiar in the context of a model populated using the parametric curves. It would seem more natural to calculate the incidence of progression from the parametric curves of the model.

End of life costs

The last year end of life costs may be concentrated towards the end of the year, and perhaps the last quarter rather than being spread equally over the last year. There is also no obvious rationale for only applying the last quarter costs. It can be argued that the last year end of life cost drawn from the literature should have the other costs within the model subtracted from it. Subtracting the costs of SREs in the last year of life is problematic within the model, but the last year of life routine care costs based upon the post progression figure amount to £4,639. This might argue for increasing the end of life cost from the quarterly cost of £2,087 to an annual cost of £3,708, but as this does not take into account the costs of SREs within the model it may be an overestimate.

As already noted, end of life costs are not applied within the model to those still surviving at the end of the time horizon. This slightly favours radium-223. Having corrected for this, applying an end of life cost of £3,708 instead of £2,087 has virtually no impact upon results. For instance, the cost effectiveness estimate for all patients using the submission utilities of [redacted] per QALY falls very slightly to [redacted] per QALY. The end of life costs have minimal impact upon results, once the model is corrected to apply them eventually to all patients.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

The ERG has altered the manufacturer model along the following lines:

- Revise the calculation of the cohort flows to remove the division of the proportion with progression free survival and not having had a 1st on study SRE by the proportion surviving[e].
- Remove the time point at which the SRE curves are assumed to become a constant proportion of the overall survival curves[f].
- Revise the costs of second line care to include all data within the radium-223 arm[g].
- Include end of life costs for those modelled as surviving at the end of the time horizon[h].

Note that within the manufacturer model it is not possible to easily revise the model structure to permit the incidences of progression and SREs that are required for costing purposes to be based upon the relevant parametric curves. The ERG cross check model rebuild does permit this. As an indication, for the analysis that uses the lognormal curve for overall survival this revises the cost effectiveness estimate for all patients from [redacted] per QALY to [redacted] per QALY.

The results of the model are presented for two sets of analyses, given the uncertainty around the ALSYMPCA EQ-5D utility values supplied within the submission and at clarification. These apply the pre and post progression utility estimates of the submission, or those supplied at clarification but excluding the last visit values[i]. The ERG notes that this retains the manufacturer distinction of the data being only split by arm and progression status: in the radium-223 arm [redacted] for pre-progression and [redacted] for with progression and in the placebo arm [redacted] for pre-progression and [redacted] for the with progression. This does not address any of the wider concerns of the ERG around the treatment of the ALSYMPCA EQ-5D data as outlined in Table 29 above and the surrounding text and which might have a much greater impact upon results.

[e] Implemented within the *Survival_Analysis-R223* and *Survival_Analysis-Placebo* worksheets by revising cells Z17:Z536 to be of the form V*X*P, cells AA17:AA536 to be of the form (1-V)*X*P, cells AB17:AB536 to be of the form V*(1-X)*P and cells AC17:AC536 to be of the form (1-V)*(1-X)*P.

[f] Implemented within the *Survival_Analysis-R223* worksheet and the *Survival_Analysis-Placebo* worksheet by revising cells V17:V315 to be equal to S17:S315.

[g] Implemented within the *Overall_PFS_PSA* worksheet by setting AQ10=35 and AY10=35.

[h] Calculated within the *Markov_Radium_final* and the *Markov_PCB* worksheets as OFFSET(V36,time_horizon,0)*OFFSET(C36,time_horizon,0)*TransitionCost_EndOfLife.

[i] Implemented within the *Utility_Inputs* worksheet by setting cells E19:E22 to the relevant values.

These analyses retain the manufacturer time horizon of 5 years, but sensitivity analyses of time horizons of 3 to 7 years are undertaken. Additional sensitivity analyses are undertaken that:

- SA05: Apply loglogistic overall survival curves.
- SA06: Apply Weibull overall survival curves.
- SA07: Derive the balance between SREs from all recorded SREs rather than from the 1st on trial SREs[j].
- SA08: Remove the pre-progression quality of life decrement associated with placebo.
- SA09: Remove the post-progression quality of life decrement associated with placebo.
- SA10: Exclude the HRQoL impact of SREs[k].
- SA11: Exclude the HRQoL impact of adverse events[l].
- SA12: Set the costs of pre-progression routine care in the placebo arm to be that in the radium-223 arm[m].
- SA13: Set the costs of routine care costs to equal those in the pre-progression radium-223 arm[n].
- SA14: Set the costs of SREs to be in line with those suggested by the denosumab MTA[o].

The ERG conducted additional analysis of EQ-5D utilities and these are presented in Tables 32 and 33 below.

[j] Implemented within the *Clinical_Inputs* worksheet by setting cells E51:54 and E57:60 to the relevant values.

[k] Implemented within the *Data_Summary* worksheet by setting cells E120:E121 to zero.

[l] Implemented within the *Data_Summary* worksheet by setting cells E113:E114 to zero.

[m] Implemented within the *Data_Summary* worksheet by setting O22=H22.

[n] Implemented within the *Data_Summary* worksheet by setting O22=H22 and H36=H22.

[o] Implemented within the *Cost_Inputs* worksheet by setting cells E108:E111 to the relevant values and E179=1.

Table 32 ERG additional analyses: Submission EQ-5D utilities

	ΔCost	ΔQALYs	ICER	ΔCost	ΔQALYs	ICER	ΔCost	ΔQALYs	ICER
Base case	[redacted]								
Sensitivity analyses									
01: 3yr horizon	[redacted]								
02: 4yr horizon	[redacted]								
03: 6yr horizon	[redacted]								
04: 7yr horizon	[redacted]								
05: LogLog OS	[redacted]								
06: Weibull OS	[redacted]								
06: SRE balance	[redacted]								
07: PreProg QoL	[redacted]								
08: Prog QoL	[redacted]								
09: No SRE QoL	[redacted]								
10: No AE QoL	[redacted]								
11: Pre-prog cost	[redacted]								
12: Routine costs	[redacted]								
13: SRE costs	[redacted]								

Table 33 ERG additional analyses: Clarification EQ-5D utilities

	ΔCost	ΔQALYs	ICER	ΔCost	ΔQALYs	ICER	ΔCost	ΔQALYs	ICER
Base case	[redacted]								
Sensitivity analyses									
01: 3yr horizon	[redacted]								
02: 4yr horizon	[redacted]								
03: 6yr horizon	[redacted]								
04: 7yr horizon	[redacted]								
05: LogLog OS	[redacted]								
06: Weibull OS	[redacted]								
06: SRE balance	[redacted]								
07: PreProg QoL	[redacted]								
08: Prog QoL	[redacted]								
09: No SRE QoL	[redacted]								
10: No AE QoL	[redacted]								
11: Pre-prog cost	[redacted]								
12: Routine costs	[redacted]								
13: SRE costs	[redacted]								

5.5 Conclusions of the cost effectiveness section

The submission is reasonably complete in terms of the data described within it, with the exceptions of:

- The lack of any real analysis of the ALSYMPCA EQ-5D data, with little attempt to relate it to the model structure and health states.
- No consideration of the ALSYMPCA resource use data beyond that used for the estimates of adverse events treated as inpatients.

The main uncertainties relate to:

- Whether the lognormal curve or the loglogistic curve is the most appropriate for overall survival, and how far these should be extrapolated beyond the trial data.
- The appropriateness of the pre and post progression utility increments for radium-223 over placebo.

Given the uncertainties it is difficult to conclude whether the submission contains an unbiased estimate of the cost effectiveness of radium-223 dichloride.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG revisions to the manufacturer base case that retain the submission EQ-5D utility values suggest cost-effectiveness estimates for radium-223 compared to placebo of [redacted] per QALY, [redacted] per QALY and [redacted] per QALY for all patients, the prior docetaxel subgroup and the no prior docetaxel subgroup respectively. The corresponding estimates when using the EQ-5D utility values supplied at clarification are [redacted] per QALY, [redacted] per QALY and [redacted] per QALY.

Note that using the EQ-5D utility values supplied at clarification does not address the main concerns of the ERG about the lack of any real analysis of the ALSYMPCA EQ-5D data.

The full range of sensitivity analyses undertaken by the ERG are tabulated in section 5.4 above. A summary of these is presented below:

- The main sensitivity with regards the quality of life values is to the post progression quality of life increment of a little over [redacted] for radium-223 compared to placebo. Excluding this worsens the cost effectiveness estimates by around 22%. The quality of life impacts of SREs and adverse events have relatively little impact upon the modelling, with the worst case scenarios that exclude them altogether typically changing the cost effectiveness estimates by less than 1%.
- The cost effectiveness estimates are sensitive to the time horizon adopted. A 3 year time horizon increases the cost effectiveness estimate for all patients to around [redacted] per QALY, while a 7 year time horizon reduces it to between [redacted] per QALY. The sensitivity to the time horizon is also non-linear, meaning that even if 5 years is seen as the most reasonable for the base case any uncertainty around it would tend to further increase the ICER.
- There is no obvious reason for preferring the lognormal over the loglogistic for overall survival. Applying the loglogistic curve for overall survival worsens the cost effectiveness estimate by around 5%, though the effect is less marked for the no prior docetaxel subgroup. Applying the Weibull curve for overall survival has a larger impact, worsening the cost effectiveness estimates by around 20% for all patients and the prior docetaxel subgroup, and by around 30% for the no prior docetaxel subgroup. But given the AICs the Weibull is less obviously justified for overall survival.

- The exploration of costs has relatively little impact upon results. Only the application of the denosumab MTA SRE costs has any real effect, but this only worsens the cost effectiveness estimates by a little over 1%.

In terms of the unquantifiables, it is surprising that a more sophisticated analysis of the ALSYMPCA EQ-5D data has not been undertaken. Nothing is presented within the submission other than the simple EQ-5D means split by arm and progression. It seems possible to relate the ALSYMPCA EQ-5D data to SREs. Given the NICE methods guide this could be much preferable to the time trade-off study among 126 members of the UK public with no experience of SREs who were presented with hypothetical health state vignettes. The ERG cannot sensibly speculate what impact a more detailed consideration of the ALSYMPCA EQ-5D data might have upon the cost effectiveness estimates.

7 End of life

The MS has not commented on whether NICE end of life conditions are met. The ERG performed additional analyses to investigate the consequences if end of life criteria were met.

Retaining the changes made by the ERG to the manufacturer model as outlined in section 5.4, the modelled life expectancies and net gain from radium-223 over placebo can be presented for model time horizons of 3 to 7 years. These are presented in Tables 34 - 36 below for analyses which apply the lognormal curves for overall survival and for analyses which apply the loglogistic curves for overall survival.

Table 34 Modelled years undiscounted life expectancy: All patients

Time Horizon	3 years	4 years	5 years	6 years	7 years
Lognormal OS					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net: undiscounted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net: discounted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic OS					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net: discounted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 35 Modelled years undiscounted life expectancy: Prior docetaxel subgroup

Time Horizon	3 years	4 years	5 years	6 years	7 years
Lognormal OS					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net: undiscounted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net: discounted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic OS					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net: undiscounted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net: discounted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 36 Modelled years undiscounted life expectancy: No prior docetaxel subgroup

Time Horizon	3 years	4 years	5 years	6 years	7 years
Lognormal OS					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net: undiscounted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net: discounted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic OS					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net: undiscounted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net: discounted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The above suggests that the end of life conditions regarding anticipated survival of less than 24 months and a net gain compared to placebo of over 3 months are met, though the latter is in the balance for a time horizon of 3 years.

Within the model the net gains in survival have been evaluated at the radium-223 dichloride arm specific post progression utility.

Section 2.2.1 of the NICE end of life guidance suggests valuing the additional survival "*using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age*". But it is unclear what value should be applied. Kind and colleagues[35] use the same data set as that used for the UK social tariff to evaluate UK population norms, with an average EQ-5D index value of 0.78 for men aged between 65 and 74. But these figures are for self-reported health states, and so will include both healthy and unhealthy individuals. There is a clear downward trend in the Kind and colleagues[35] EQ-5D index value by age, with this declining steadily from a peak of 0.94 among those aged between 25 and 34. It could be argued that by definition a healthy individual is in full health with an EQ-5D response across the five dimensions of 11111, and so has an EQ-5D index of 1.00 regardless of age.

For the purposes of section 2.2.1 of the NICE end of life guidance, HRQoL values for the evaluation of the extra survival of 0.78 and 1.00 consequently suggest themselves. Applying these to the model outputs derived from the lognormal overall survival curves results in the following values as presented in Tables 37-40 below.

Table 37 End of Life analyses: Submission EQ-5D utilities: 0.78 QoL for additional survival

Time Horizon	3 years	4 years	5 years	6 years	7 years
All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior docetaxel subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No prior docetaxel subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 38 End of Life analyses: Submission EQ-5D utilities: 1.00 QoL for additional survival

Time Horizon	3 years	4 years	5 years	6 years	7 years
All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior docetaxel subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No prior docetaxel subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 39 End of Life analyses: Clarification EQ-5D utilities: 0.78 QoL for additional survival

Time Horizon	3 years	4 years	5 years	6 years	7 years
All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior docetaxel subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No prior docetaxel subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 40 End of Life analyses: Clarification EQ-5D utilities: 1.00 QoL for additional survival

Time Horizon	3 years	4 years	5 years	6 years	7 years
All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior docetaxel subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No prior docetaxel subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Section 2.2.2 of the NICE end of life guidance, suggests that the HRQoL value[ee] that result in the additional discounted survival yielding sufficient QALY gains to reach the NICE £20,000 per QALY and £30,000 per QALY thresholds should be calculated. Since setting the quality of life value equal to 1.00 does not result in any of the cost effectiveness estimates falling

[ee] The additional QALY gains are calculated as the discounted additional survival multiplied by the net HRQoL gain; i.e. the threshold value minus the radium-223 progression HRQoL estimate.

below £30,000 per QALY, no feasible quality of life value can result in the cost effectiveness estimates falling within the NICE thresholds.

Obviously, the above estimates rely upon the other assumptions feeding into the model. Applying the estimates from the loglogistic overall survival curves would worsen the cost effectiveness estimates, as this reduces both the original ICER and the impact of the end of life calculation. The estimates will also be affected in the predictable direction were the sensitivity analyses of section 5.4 applied to the above.

8 OVERALL CONCLUSIONS

The phase-three international, multicentre, RCT (ALSYMPCA), sponsored by the manufacturer, was outlined as the main source of evidence in the manufacturer's submission. Patients were randomised to receive six intravenous injections of radium-223 dichloride (50kBq/kg per body weight) every four weeks along with best supportive care or to receive six intravenous injections of a placebo every four weeks plus best supportive care. Best supportive care included local external beam radiotherapy, corticosteroids, antiandrongens, oestrogens, estramustine and ketoconazole. Further evidence was provided on a smaller trial in a supporting role BC1-02. No standard meta-analyses or indirect mixed treatment comparisons are presented in the current submission. Data from the ALSYMPCA phase III trial are used in the economic model.

8.1 Clinical effectiveness

The ERG believes that there is compelling evidence that radium-223 dichloride significantly prolongs overall survival, reduces skeletal related events and extends time to progression when compared with BSC in second line therapy in this population. The adverse event profile is also of less concern than the comparator BSC.

The main concerns of the ERG are:

- the exclusion of patients with visceral metastatic disease could be problematic for generalising results to the wider treatment population in the NICE final scope;
- the lack of consideration of abiraterone as a comparator in the decision problem.

8.2 Cost effectiveness

The ERG revisions to the manufacturer base case that retain the submission EQ-5D utility values suggest cost effectiveness estimates for radium-223 compared to placebo of [redacted] per QALY, [redacted] per QALY and [redacted] per QALY for all patients, the prior docetaxel subgroup and the no prior docetaxel subgroup respectively. The corresponding estimates when using the EQ-5D utility values supplied at clarification are [redacted] per QALY, [redacted] per QALY and [redacted] per QALY.

The two key uncertainties or weaknesses are:

- Whether the lognormal curve or the loglogistic curve is the most appropriate for overall survival, and how far to extrapolate beyond the trial data. The manufacturer base case applies the lognormal curve and a 5 year time horizon. There is no obvious reason to prefer the lognormal curve over the loglogistic curve, and the loglogistic

curve worsens the cost effectiveness estimates by around 5%. Results are particularly sensitive to the time horizon, shorter time horizons somewhat worsening the cost effectiveness estimates.

- The reasonableness of the pre and post progression utility increment for radium-223 over placebo, due to there being minimal information within the submission about the EQ-5D values collected during the ALSYMPCA trial, and no real statistical analysis of this data being presented within the submission. Simple means are used, split by arm and progression with no consideration of SREs or any other variables within the data. Given the model health states it is surprising that no analysis of the EQ-5D data was undertaken that tried to estimate quality of life values for the main health states and events within the model, with a consideration to baseline values. The analysis of the ALSYMPCA EQ-5D data as presented within the economics of the submission is sparse and limited.

Other uncertainties and weaknesses of the analysis include:

- The EQ-5D data supplied at clarification does not obviously tally with that supplied in the submission, though this may be a misinterpretation on the part of the ERG.
- The quality of life increment for radium-223 over placebo for the post progression health states is assumed to apply for the remainder of the patient lifetime.
- The quality of life impacts of SREs may have been double counted, given that these impacts will be within the ALSYMPCA EQ-5D data already. The quality of life decrements of SREs are also assumed to persist for the patient lifetime. Sensitivity analyses excluding these impacts have little effect upon results, but this does not take into account the above criticism of the analysis of the ALSYMPCA EQ-5D data.
- No consideration of the resource use data collected during the ALSYMPCA trial, other than for the proportion of adverse events treated as inpatients.

Weaknesses of lesser importance include:

- There may be some concerns around the reliability of the identification of SREs events beyond six months, and the impact this might have upon the estimated SRE curves.
- The possible double counting of the some cost impacts of SREs, given the differentiation of the routine care costs by arm and by progression. But also a possible underestimation of the costs of SREs, based upon the MTA review of denosumab for the prevention of SREs.
- Assuming that all pathological fractures were either of the arm, leg or rib.

If end of life criteria apply, the appropriate quality of life value for calculating the value of the additional survival is uncertain. Values of 1.00 and 0.78 are candidates, and it seems unlikely that the appropriate value will lie outside this range.

[redacted] The end of life adjusted cost effectiveness estimates typically remain above [redacted] per QALY for the 1.00 quality of value, and for the 5 year time horizon are closer to [redacted] per QALY. For the 0.78 quality of life value the end of life adjusted cost effectiveness estimates typically remain above [redacted] per QALY, and for the 5 year time horizon tend to exceed [redacted] per QALY.

8.3 Implications for research

There is a need to evaluate the use of radium-223 dicholride in a population of patients with bone metastic disease, with and without visceral metastatic disease.

It would be useful to assess abiraterone versus radium-223 dicholride in a large head to head well-designed randomised trial, with particular attention to cost-effectiveness and adverse events.

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10 APPENDICES

Appendix 1 Tables of participant baseline characteristics

Table 1 Baseline characteristics of patients in the BC1-02 and ALSYMPCA studies (ITT population) (17;19;90)

	BC1-02		**ALSYMPCA (updated analysis)**	
	Radium-223	**Placebo**	**Radium-223**	**Placebo**
ITT patients	N=33	N=31	N=614	N=307
Mean, median (range)				
Age	73, 73 (57-88)	72, 72 (60-84)	70, [redacted]	71, [redacted]
Race. Caucasian, n(%)	[redacted]	[redacted]	575 (94%)	290 (95%)
Weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]
Body Mass Index (kg/m^2)	[redacted]	[redacted]	Not reported	Not reported
Haemoglobin, g/dL	12.5, 12.6 (10.0-15.3)	12.6, 12.9 (9.9-14.9)	[redacted], 12.2 98.5-15.7)	[redacted], 12.1 (8.5-16.4)
PSA, ng/ml (µg/L)	511, 167 (10-6000)	480, 233 (1-4002)	430, 146 (3.8-6026)	[redacted], 173 (1.5-14500)
Bone-ALP ng/mL	121, 57 (13-1145)	132, 68 (11-706)	Not reported	Not reported
TOTAL ALP, U/L	437, 228 (80-3047)	501, 279 (51-2280)	[redacted], 211 (32-6431)	[redacted], 223 (29-4805)
<220 U/L n(%)	Not reported	Not reported	[redacted]	[redacted]
≥220 U/L n(%)	Not reported	Not reported	[redacted]	[redacted]
Albumin, g/L	39, 40 (28-46)	39, 38 (30-47)	[redacted], 40 (24-53)	[redacted], 40 (23-50)
Lactate dehydrongenase U/L	351, 348 (154-750)	426, 345 (144-1284)	[redacted], 315 (76-2171)	[redacted], 336 (132-3856)
ECOG performance status n(%)	9 (27%)	6 (19%)	[redacted]	[redacted]

0 1 2	18 (55%) 6 (18%)	20 (65%) 5 (16%)	76 (12%)	40 (13%)
Extent of disease [a] n(%) Grade 1: <6 metastases Grade2: 6-20 metastases Grade 3: >20 metastases Grade 4: superscan	 12 (36%) 10 (30%) 10 (30%) 1 (3%)	 7 (23%) 13 (42%) 10 (32%) 1 (3%)	 100 (16%) 262 (43%) [redacted]	 38 (12%) 147 (48%) [redacted]
Concurrent bisphosphonates, yes n(%)	Patients receiving bisphosphonates within 3 months of study entry were excluded from study entry		250 (40.7)	124 (40.4)
Prior docetaxel, yes, n(%)	[redacted]	[redacted]	352 (57.3)	174 (56.7)
EBRT within 12 weeks of screening, yes, n(%)	Patients were to receive EBRT at study start		[redacted]	[redacted]
Pain severity index [b]	[redacted]	3.78, 4.00 (0.75-7.75)	Not measured	
WHO ladder cancer pain index ≥2, n(%)	Not measured		345 (56%)	168 (55%)

a. Extent of disease graded using the number of metastatic deposits identified on bone scan b Pain severity index: values are from a maximum of 10
ALP=alkaline phosphatise; ECOG=European Cooperative Oncology Group; no.=number; PSA=prostate specific antigen

Table 2 Baseline characteristics of patients in the abiraterone trials

	COU-AA-301		COU-AA-302	
	Abiraterone + prednisone n=797	Placebo + prednisone n=398	Abiraterone + prednisone n=546	Placebo + prednisone n=542
Age Median (range)	69 (42-95)	69 (39-90)	71 (44-95)	70 (44-90)
Gleason score n/N (%)				
≤7	341/697 (48.9%)	161/350 (46.0%)	225/488 (46%)	254/508 (50%)
≥8	356/697 (51.1%)	189/350 (54.0%)	263/488 (54%)	254/508 (50%)
PSA ng/mL Median (range)	N=792 128.8 (0.4-9253.0)	N=393 137.7 (0.6-10114.0)	N=546 42.0 (0.0-3927.4	n=539 37.7 (0.7-6606.4
PSA at initial diagnosis, ng/mL Median (range)	N=619 27.0 (0.1-16065.9)	N=311 35.5 (1.1-7378.0)	N=470 22.3 (0.4-5036.0)	N=454 21.0 (0.3-9726.3)
Baseline alkaline phosphatase Median (range)			N=546 93.0 (32-1927)	N=536 184.0 (87-781)
Previous cancer therapy n (%)				
Surgery	429/797 (54%)	193/398 (49%)	256/544 (47%)	244/542 (45%)
Radiotherapy	570/797 (72%)	285/398 (72%)	283/544 (52%)	303/542 (556%)
Hormonal	796/797 (99.9%)	396/398 (100%)	544/544 (100%)	542/542 (100%)
Other	797/797 (100%)	398/398 (100%)	82/544 (15%)	63 (12%)
Haemoglobin, g/dL Median (range)	N=779 11.8 (7.3-16.1)	N=389 11.8 (7.2-16.5)		

LDH Median (range)	N=783 223.0 (84-3373)	N=386 237.5 (123-5125)		
ECOG performance status n(%) 0 or 1 2	 715/797 (90%) 82/797 (10%)	 353/398 (89%) 45/398 (11%)		
Extent of disease n(%) a				
Bone	709/797 (89%)	357/397 (90%)	274/542 (51%)	267/540 (49%)
Node	361/797 (45%)	164/397 (41%)		
Soft tissue or node			267/542 (49%)	271/540 (50%)
Liver	90/797 (11%)	30/397 (8%)		
Other			4/542 (0.7%)	7/540 (1.3%)

PSA=prostate specific antigen; ECOG=European Cooperative Oncology Group a: extent of disease graded using the number of metastatic deposits identified on bone scan

Appendix 2 Calculation of the distribution between the health states

The manufacturer submission uses the parameterised curves to derive the proportions feeding into the distribution of the cohort between health states. But a similar logic would appear to apply had the manufacturer used the proportions from the Kaplan Meier curves. Assuming this to be the case, a simple example can be constructed over three time periods for a baseline cohort of N=100, with 10 deaths in period 1, 20 SREs in period 2, 10 progressions in period 3 and no lost to follow up (LFU) throughout, as presented in Tables 1-8 below

Table 1 Events

Time	Deaths	SREs	Progs.	LFU
0	0	0	0	0
1	10	0	0	0
2	0	20	0	0
3	0	0	10	0
T=3 totals	10	20	10	0

Table 2 Resulting actual patient distribution at T=3

	Dead Total	Alive Total	Alive NoSRE	Alive SRE	Alive NoProg	Alive Prog
N at T=3	10	90	70	20	80	10
Dist. at T=3	10.0%	90.0%	70.0%	20.0%	80.0%	10.0%

This results in the following Kaplan Meier curves.

Table 3 Kaplan Meier for overall survival

Time	Deaths (dt)	Censored	At Risk (nt)	dt/nt	1-dt/nt	S(t)
0	0	0	100			100.0%
1	10	0	90	10.0%	90.0%	90.0%
2	0	0	90	0.0%	100.0%	90.0%
3	0	0	90	0.0%	100.0%	90.0%

Table 4 Kaplan Meier for SREs

Time	SREs (dt)	Censored	At Risk (nt)	dt/nt	1-dt/nt	S(t)
0	0	0	100			100.0%
1	0	10	90	0.0%	100.0%	100.0%
2	20	0	70	22.2%	77.8%	77.8%
3	0	0	70	0.0%	100.0%	77.8%

Table 5 Kaplan Meier for Progression

Time	Progs. (dt)	Censored	At Risk (nt)	dt/nt	1-dt/nt	S(t)
0	0	0	100			100.0%
1	0	10	90	0.0%	100.0%	100.0%
2	0	0	90	0.0%	100.0%	100.0%
3	10	0	80	11.1%	88.9%	88.9%

And the following Kaplan Meier proportions at T=3.

Table 6 Kaplan Meier Proportions at T=3

	OS_S(t)	SRE_S(t)	PFS_S(t)
T=3	90.0%	77.8%	88.9%

For the calculation of the patient distribution, the manufacturer model divides the SRE_S(t) and PFS_S(t) proportions by the OS_S(t) proportion; e.g. for progression without an SRE the formula is (1-(PFS_S(t)/OS_S(t))*(SRE_S(t)/OS_S(t))*OS_S(t).

The alternative approach is to adopt the formulae of figure 27 of the manufacturer submission, and to not divide by the OS_S(t) proportion; e.g. (1-PFS_S(t))*SRE_S(t)*OS_S(t).

The alternative methods result in the following estimates as shown in Tables 7 and 8.

Table 7 **Calculated patient distribution at T=3: By model health states**

	Dead Total	Alive Total	Alive No Prog No SRE	Alive No Prog SRE	Alive Prog No SRE	Alive Prog SRE
Model	10%	90%	77%	12%	1%	0%
Figure 27	10%	90%	62%	18%	8%	2%

Table 8 **Resulting patient distribution at T=3: By original data health states**

	Dead Total	Alive Total	Alive No SRE	Alive SRE	Alive No Prog	Alive Prog
Model	10%	90%	78%	12%	89%	1%
Figure 27	10%	90%	70%	20%	80%	10%

The model approach appears to tend to under predict the number of SRE events and progression events, while the approach of figure 27 of the submission results in estimates which are in line with those of the original data.