NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Reconsideration

Radium-223 dichloride for treating metastatic hormone relapsed prostate cancer with bone metastases (Cancer Drugs Fund reconsideration of TA376)

The following documents are made available to the consultees and commentators:

1. **CDF committee meeting slides**

2. **Company submission** from Bayer

3. **Patient group, professional group and NHS organisation submission** from:
   - **National Cancer Research Institute – Royal College of Physicians - Association of Cancer Physicians** (joint submission)
   - **Prostate Cancer UK**
   - **Tackle Prostate Cancer**

4. **Expert personal perspectives** from:
   - [redacted] – clinical expert, nominated by the British Uro-oncology Group
   - [redacted] – patient expert, nominated by Tackle Prostate Cancer

5. **Evidence Review Group report** prepared by Aberdeen HTA Group

6. **Company's fact check of the ERG report & ERG's responses**

7. **Erratum to the ERG Report** prepared by Aberdeen HTA Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Radium-223 dichloride for treating metastatic hormone-relapsed prostate cancer with bone metastases Cancer Drug Fund Reconsideration

July 2016

Manchester

Former Committee: D

Single Technology Appraisal

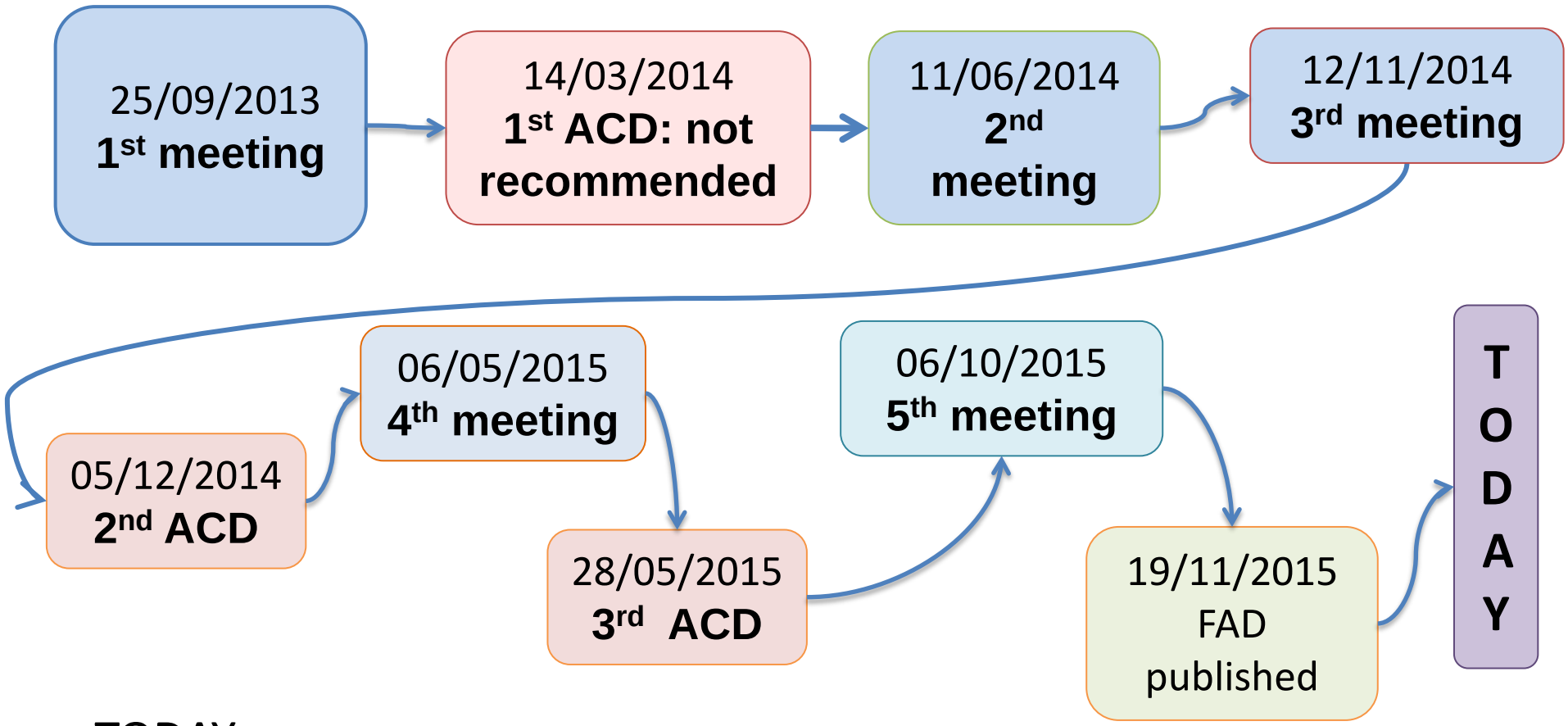
Chair: Amanda Adler

NICE: Nwamaka Umeweni, Helen Knight

Aberdeen HTA Group

Public observer slides

Recap radium 223



TODAY:

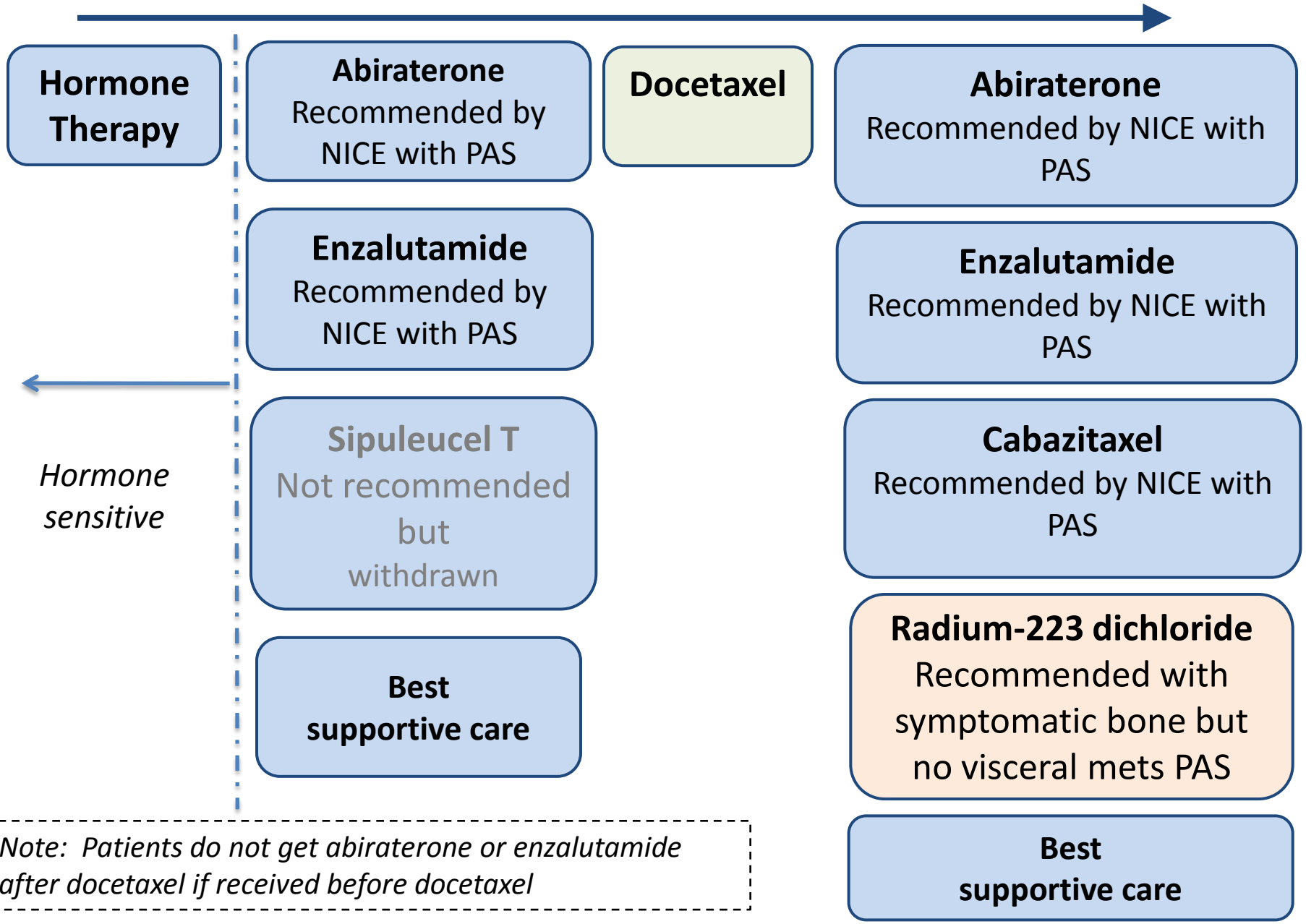
Subset of population, committee preferences addressed

No changes to existing patient access scheme

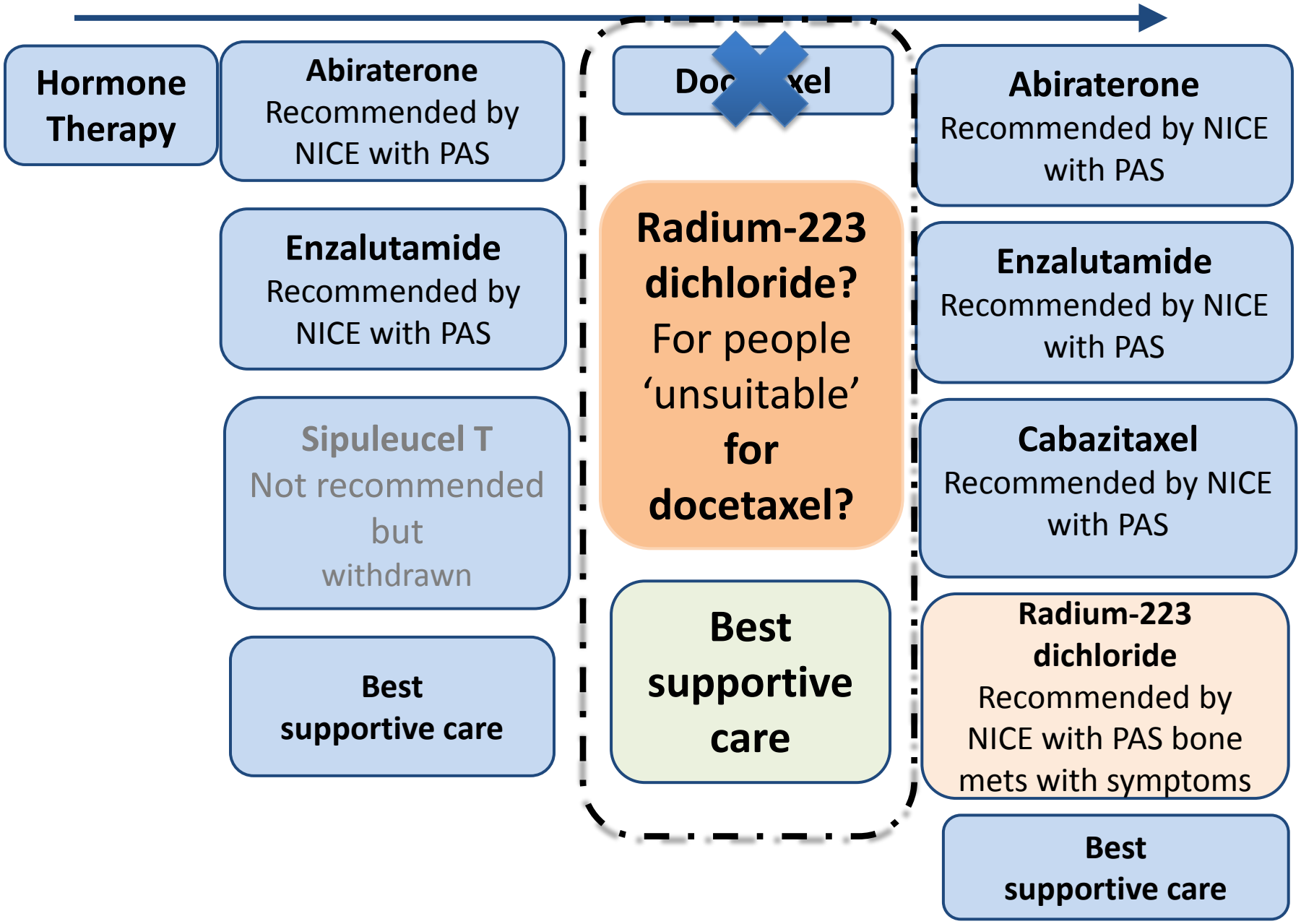
Bone metastases and radium-223 dichloride

- **Bone mets in hormone relapse:** >90% of patients
- **Radium 223**
  - Radiopharmaceutical that selectively binds to areas of increased bone turnover in bone metastases and delivers alpha radiation
  - IV injection every 4 weeks for 6 injections
- **Marketing authorisation**
  - Adults with hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases

Metastatic hormone-relapsed prostate cancer



Reconsideration today



TA376: Original decision problem

2 populations: previous, no previous, docetaxel

NICE scope	Company
Previous docetaxel: • abiraterone • best supportive care No previous docetaxel : • docetaxel (if fit to receive it) • abiraterone • best supportive care	Previous docetaxel: • abiraterone • best supportive care No previous docetaxel: • abiraterone • best supportive care

Committee agreed abiraterone not a comparator for subgroup being addressed today

Key issues for discussion

- What characterises people unsuitable for docetaxel?
- Are patients unsuitable for docetaxel also unsuitable for radium 223?
- Is evidence from trial generalisable to patients unsuitable for docetaxel?
- Which analyses inform patients unsuitable for docetaxel?
- Resource use costs: include them or not?
- Utilities: subgroup specific? Benefit lasts how long?
- Waste: Company still does not accounting for radium waste. Appropriate?

Key evidence for Radium 223

Alpharadin in Symptomatic Prostate Cancer Patients
ALSYMPCA

921 patients who:
- received docetaxel

OR
- not eligible to receive docetaxel
- declined docetaxel
- docetaxel unavailable

Radium 223 + Best supportive care

Placebo + Best supportive care

1° endpoint
Overall Survival

Stratified on randomisation prior docetaxel or not; 42% no prior docetaxel
Study stopped early after pre-specified analysis with 314 events
Updated analysis presented today with 528 events 'before cross-over'
EQ-5D collected

Parker et al. N Engl J Med 2013; 369:213-223

Are patients who have not received docetaxel the same as people not suitable for docetaxel?

- Committee wrote: ‘there is a clinically recognised group for whom radium-223 treatment is suitable, because docetaxel is contraindicated or unsuitable’
- ERG wrote: ‘no prior docetaxel’ participants of the ALSYMPCA trial included people who declined docetaxel or for whom docetaxel was unavailable’. This means the trial results reflect both people who are ‘suitable and unsuitable’
- Company provided a survey from physicians to define who is not suitable to receive docetaxel

Who is ‘unsuitable’ for docetaxel?

Bayer round table of 6 oncologists

excludes ‘refused docetaxel or for whom docetaxel was unavailable’

- Allergic to docetaxel*
- Neutrophil count of <1.5 x 10^9/L*
- Platelets <100 x10^9/L*
- Treatment with immunosuppressant
- Severe liver impairment*
- ECOG 3 or greater
- ECOG 2 and above with the existence of comorbidities

Comorbidities*:

- Charlson comorbidity score ≥ 5
- Severe COPD
- Symptomatic heart failure (NYHA ≥ II)
- Bowel disease
- Peripheral neuropathy
- Tuberculosis
- Recurrent pancreatitis
- Poorly controlled diabetes
- Poor peripheral circulation

Patients with poor cognition or social support – who cannot understand treatment and provide consent*

* Likely excluded from ALSYMPCA

Did trial recruit unsuitable patients?

ALSYMPCA inclusion exclusion criteria

Inclusion

- 'No intention to use cytotoxic chemotherapy in next 6 months'
- 'ECOG Performance status: 0-2'
- 'Life expectancy ≥ 6 months'
- 'Absolute neutrophils ≥ 1.5 x 10^9/L; platelets ≥ 100 x10^9/L; hemoglobin ≥ 10.0 g/dL'
- Adequate renal, liver function

Exclusion

- Patients who are fit enough for docetaxel, willing and where docetaxel is available
- Any other serious illness or medical condition

⊙ Does trial provide results for patients unsuitable for docetaxel?

Did trial include unsuitable patients?

ALSYMPCA baseline characteristics no prior docetaxel

	No prior docetaxel (n=395)
Median age years	73.2
Median Haemoglobin (g/dL)	
ECOG at baseline	0 (27.8%) 1 (57.5%) ≥2 (14.4%)
Extent of disease Grade 1: < 6 metastases Grade 2: 6-20 metastases Grade 3: > 20 metastases Grade 4: superscan	

Who is unsuitable for Radium 223?
Special warnings and precautions for use from summary of patient characteristics

- ‘Before the first administration, the absolute neutrophil count (ANC) should be ≥ 1.5 x 10^9/l, the platelet count ≥ 100 x 10^9/l and haemoglobin ≥ 10.0 g/dl’
- Safety and efficacy in patients with Crohn’s disease and with ulcerative colitis have not been studied
- Hepatic impairment: not studied
- Renal impairment: no dose adjustment
- Adverse events:
  - ‘Common’: Thrombocytopenia

Results clinical-effectiveness

interim vs. updated analysis whole population
n.b. study stopped after interim analysis

	Radium -223		Placebo		Δ med OS	Hazard ratio	95% CI and p value
	N deaths	Median overall survival months	N deaths	Median overall survival months			
Interim	191/541 (35%)	14.0	123/268 (46%)	11.2	2.8	0.695	0.552 – 0.875, p=00185
Follow-up	333/614 (54%)	14.9	195/307	11.3	3.6	0.695	0.581 – 0.832

Question to company: why is the denominator bigger in follow-up analyses?

Ref: From summary of product characteristics

* calculated.

Results clinical effectiveness

All vs. subgroup 'not received prior docetaxel' median overall survival in months

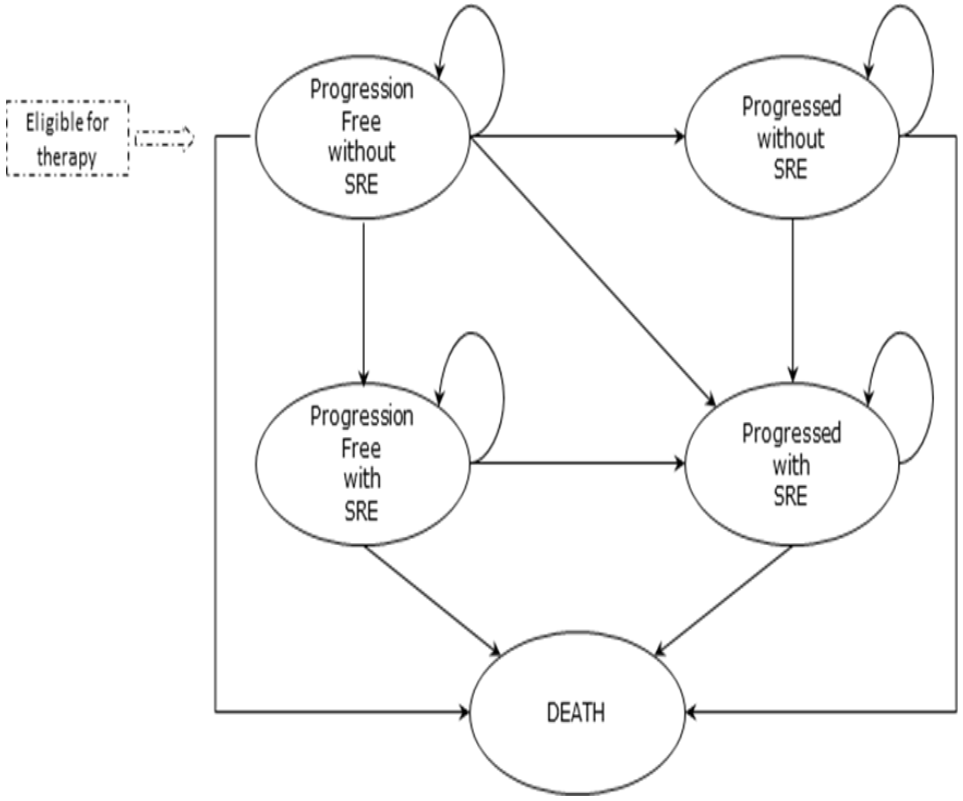
	Radium - 223	**Placebo**	**Δ**	**Hazard ratio**	**95% CI and p value**
All	14.9	11.3	3.6	0.70	0.58 to 0.83 p<0.001)
No docetaxel	16.1	11.5	4.6	0.75	0.56 to 0.99 p=0.004

⊙ Values from updated analysis? Hazard ratio correct? Used in updated modelling? Is radium 223 effective in people who have not received docetaxel?

Company submission from Parker C, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. New England Journal of Medicine 2013;369(3):213-23

TA376: Company's semi-Markov model

- Horizon 5 years
- Skeletal-related events (SREs)
- 3 measures of progression explored:
  1. serum prostate-specific antigen
  2. ECOG deterioration
  3. serum alkaline phosphatase – *preferred by Committee*
- Simple PAS – unchanged



TA376: Committee's conclusions
Decision problem and clinical effectiveness

Decision Problem	
4.2 – 4.3	**Comparators** • People for whom docetaxel is suitable: docetaxel • People for whom docetaxel is contraindicated or unsuitable: best supportive care
Clinical effectiveness	
4.5 - 4.6	**ALSYMPCA** • Radium-223 plus best supportive care more effective than best supportive care alone • Concerned that some patients who did not have prior docetaxel actually refused it or did not have access to it, and not just because it was unsuitable

Committee's conclusions

Economic analysis – Modelling approach and Utilities	
4.12	5–year time horizon not in line with the NICE reference case. A lifetime time horizon more appropriate
4.11	Preferred measure of disease progression - alkaline phosphatase
4.13	• Inconsistent approach to selecting parametric models – should consider both lognormal and Weibull • Weibull in line with clinical experts' expectations • ERG's approach of using log normal then doubling probability of mortality after 2 years more reasonable than company extrapolating beyond 3 years when only 1 person at risk
4.14	Uncertainty about how to calculate cohort flow – affects ICER
4.16	**Utility values:** • Subgroup-specific utility values most appropriate • Quality-of-life with radium 223 compared with best supportive care could extend beyond 24 weeks, but duration is uncertain, would likely diminish over time, and can not assume it lasts lifelong

Committee's conclusions

Economic analysis - Resource use and Costs	
4.18	Committee could not consider additional evidence on medical resource use from ALSYMCA • Little information on patient numbers and outcomes • Company stated 'protocol-driven' costs would not help modelling because they do not represent real life
4.19	Incorporating waste worsens cost effectiveness • No arrangement with the NHS to refund wasted doses
4.20	Potential additional costs of administering radium-223 uncertain • Committee not presented with data

Committee's conclusion for no prior docetaxel: 1. suitable 2. unsuitable

Cost effectiveness and end of life (EoL)	
4.26	**No prior docetaxel, and docetaxel is suitable** Committee unable to make any recommendations because company did not submit evidence - ***Not recommended***
4.22, 4.25, 4.26	**No prior docetaxel, but docetaxel is contraindicated or unsuitable** Using sub-group specific utilities and assuming life-long QoL benefit, ICER is £49,600 • **End of life criteria met** • Most plausible ICER would be >£50,000 per QALY considering uncertainties around duration of QoL benefits, modelling survival, calculating cohort flow, and accounting for treatment waste. - ***Not recommended***

Company's changes to model

⊙ Which are appropriate?

	Committee preference	Original	Revised	ERG Comment
Horizon	Lifetime	5 years	10 years	↑ QALY
Utility for group with no prior docetaxel	Specific to group	Overall population	New, lower values	
Medical resource usage	No	No	Yes	Double-counting?
Costs skeletal events SRE 1. Pathologic Fracture 2. Cord Compression 3. Ext. Beam Radiation 4. Surgery	ERG preferred Ford et al (2013)	 £1,862.79 £3,272.90 £105.46 £4,453.69	Ford et al (2013) £956.43 £7,458.59 £675.36 £7,415.75	
Measure of progression	Alk Phos	Alk Phos + PSA	Alk Phos	
'Cohort flow' through progression, SREs	Censoring issues	Old analysis	Re-analysed	Identified a bug

What company did not change

	Committee preference	Old	Revised	ERG
Waste	Account for it	No	Company refunded hospitals for 2 cases where patients did not receive drug	Hospital may not apply for refund
Utility	Likely diminishes	Life-long	Scenario	
Extrapolating overall survival	Consider log-normal + Weibull	Log-normal	Weibull in scenario	
Doubling risk of mortality after 104 weeks	Preferred	After 156 weeks	Scenario – 104 weeks	Preferred
Subsequent line treatment	Truncate incident progression at 30 weeks		30 weeks for radium and used 99 weeks for BSC	Inconsistent; 99 weeks for both

‘Undocumented’ changes identified by ERG:

	Committee preference	Old	Revised	ERG
Frequency of administering LHRH agonist	No comment	Every 4 weeks	Every 12 weeks - in line with the recommended dosing frequency	Company applied only to radium-223 arm for the stable disease states, resulting in an unjustified difference in LHRH costs between the Radium-223 and BSC arms

Company's revised base case results

	Total costs (£)	Total QALYs	Δ costs (£)	Δ QALYs	ICER (£)
Radium-223	[redacted]	[redacted]	[redacted]	[redacted]	25,963
BSC	[redacted]	[redacted]	-	-	-

Company's scenario analyses

1. Overall survival log normal then doubling risk of mortality after 2 years
2. Waning of QoL benefit after specific periods
3. Loglogistic model for skeletal related events–free survival best model fit to trial
4. Weibull model for all endpoints – discussed by committee as a clinically plausibility and consistent alternative distribution
5. 5-year time horizon
6. Utility values for the overall population
7. Excluding medical resource use data from ALSYMPCA

Company's selected scenario analysis

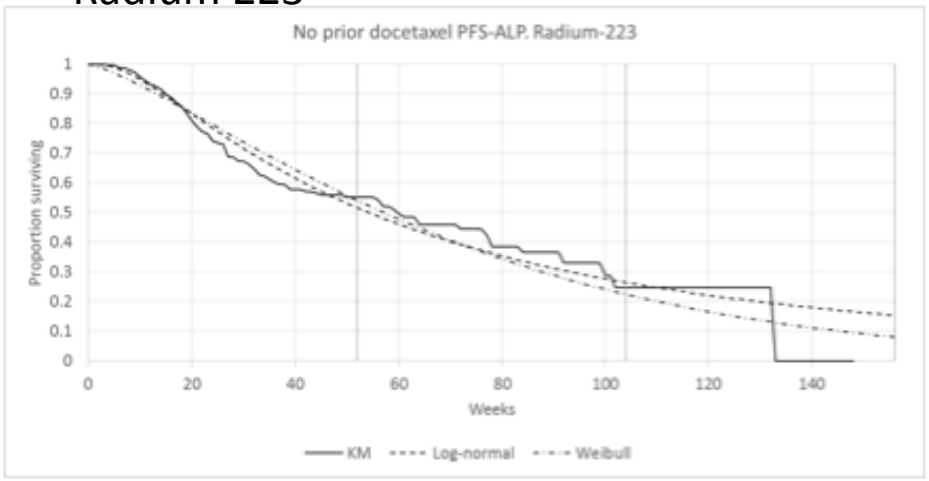
Base-case	**£25,963**
Mortality doubles after 104 weeks	£33,710
Radium utility benefit lasts up to 24 weeks	£32,150
Radium utility benefit lasts up to 52 weeks	£29,357
Radium utility benefit lasts up to 104 weeks	£27,891
Radium utility benefit lasts up to 208 weeks	£26,805
Radium utility benefit lasts up to 416 weeks	£26,101
Weibull curves fitted to OS, PFS and SSE	£39,580
Log-logistic curves fitted to SSE	£25,953
Time horizon of 5 years (260 weeks)	£29,365
Pooled utility point estimates	£28,908
Overall population utilities	£22,690
No medical resource use (MRU) costs	£29,156
Combined: no MRU, mortality doubles after 104 weeks, radium utility benefit lasts to 52 weeks)	£42,319
Combined: no MRU, Weibull all endpoints, radium utility lasts to 52 weeks	£49,114

Other ERG comments

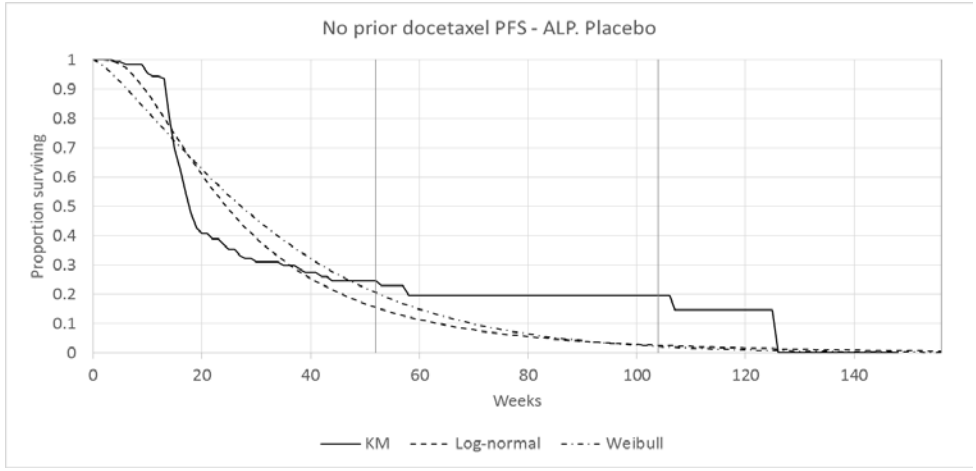
- Lognormal curve provides a better fit for the radium arm than the placebo arm of ALSYMCA
- Medical resource use data from ALSYMPCA
  - Its inclusion is not well justified
- Decrease in the revised ICER results from:
  - increased QALY gain mainly from the longer time horizon
  - reduced incremental costs mainly from correcting a bug in the original medical resource use data

ERG comments: Extrapolating progression free survival based on Alk Phos

Radium 223



Placebo



- Both lognormal (basecase) and Weibull OK for Radium-223 but for placebo, fit appears 'less satisfactory'
- Suggested piece wise,' using KM data up to 20 or 30 weeks, and parametric curves therafter

⊙ Is the modelling of progression appropriate?

ERG exploratory analyses

Revisions to company base case

- Corrected error in dosing LHRH agonist
- Subsequent treatment costs (abiraterone, enzalutamide, docetaxel (?) etc) made same between radium-223 and best supportive care
- Excluded ALSYMPCA medical resource use data
- Corrected cell referencing errors and a bug

Results

	Total costs (£)	Total QALYs	Δ costs	Δ QALYs	ICER (£)
Radium-223	[redacted]	[redacted]	[redacted]	[redacted]	31,172
Best supportive care	[redacted]	[redacted]	-	-	-

- Docetaxel modelled as a subsequent treatment – appropriate?

Summary results ICERs (1)

Scenario	Company ICERs (£)	ERG ICERs (£)
Base-case	***25,963***	***31,172***
Mortality doubles after 104 weeks	33,710	39,337
Radium utility benefit lasts up to 24 weeks	32,150	40,895
Radium utility benefit lasts up to 52 weeks	29,357	37,309
Radium utility benefit lasts up to 104 weeks	27,891	34,438
Radium utility benefit lasts up to 156 weeks	27,217	33,149
Radium utility benefit lasts up to 208 weeks	26,805	32,439
Radium utility benefit lasts up to 260 weeks	26,532	32,000
Radium utility benefit lasts up to 312 weeks	26,341	31,709
Radium utility benefit lasts up to 364 weeks	26,204	31,507
Radium utility benefit lasts up to 416 weeks	26,101	31,362
Radium utility benefit lasts up to 468 weeks	26,023	31,254

Summary results ICERs (2)

Scenario	Bayer	ERG
Base-case	***25,963***	***31,172***
Weibull curves for OS, PFS and SSE instead of lognormal	39,580	46,940
Log-logistic curves fitted to SSE instead of log normal	25,953	31,183
Time horizon of 5 years instead of 10 years	29,365	35,982
Pooled utility point estimates instead of arm specific	28,908	??*
Treatment-specific utilities from overall ALYSMPCA instead of no-prior docetaxel subgroup	22,690	27,630
No medical resource use costs (MRU)	29,156	base case
Assuming that radium 223 does not save resource costs (e.g. hospitalisation) (ERG: Double counting?)	base case	27,968
Implement PFS and SSE free survival per old model informing	-	33,817
Combined: 1. no MRU, 2. radium utility benefit lasts up to 52 weeks, 3. mortality doubles after 104 weeks	42,319	47,870
Combined: 1. no MRU, 2. radium utility benefit lasts up to 52 weeks, 3. Weibull curves fitted to all endpoints	49,114	56,208

?? - not clear to ERG which utility values company chose

Key issues for discussion

Generalisability

- In seeing evidence for people who:
  1. were not eligible to receive docetaxel,
  2. declined docetaxel or
  3. for whom docetaxel was unavailable,

  has committee seen evidence for people ‘unsuitable’ for docetaxel’?
- Does the estimate of effectiveness reflect this population?

Modelling

- Log normal or Weibull?
- Include or exclude new medical resource use data?
- Modelling of progression free survival – appropriate?
- Subgroup specific utilities – appropriate? How long do they last?
- Docetaxel modelled as a subsequent treatment – appropriate?
- Company did not account for radium waste – appropriate?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Submission template for the re-consideration of current CDF technologies under the new proposed CDF criteria

February 2016

Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases *(men who have not received docetaxel and for whom docetaxel is contraindicated or not suitable)*

Bayer plc

Radium-223 dichloride is indicated for men with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases. NICE issued a positive recommendation for the subgroup of the indicated population that had received prior docetaxel. The following submission is made for the sub-group of the indicated population who have not received docetaxel and for whom docetaxel is contraindicated or not suitable. In the appraisal of the full licensed indication for radium-223 (TA 376), the Appraisal Committee concluded that:

- there is a clinically recognised group of men for whom radium-223 treatment is suitable, because docetaxel is contraindicated or unsuitable. It concluded that for this group of men, best supportive care is the most relevant comparator.

- for men who have not had prior docetaxel and for whom docetaxel is contraindicated or unsuitable, the first 3 criteria for end-of-life had been met.

Bayer seeks recommendation from NICE for the use of radium-223 dichloride for the treatment of men with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases among patients who have not received docetaxel and for whom docetaxel is contraindicated or not suitable.

The evidence that we submit as part of the cost-effectiveness analysis will address uncertainties previously identified by the Appraisal Committee.

In this submission, Bayer:

- Presents revised analysis of patient level data from ALSYMPCA, the pivotal Phase III study, which addresses the Appraisal Committee's concerns *(section 4.14 and section 4.26 of technology appraisal TA376)* about the cohort flow as a result of death being treated as a censored event, rather than an event. The updated survival data handles death as an event rather than as censored data and thus addresses this issue that was considered important by the Appraisal Committee:

- Section 4.14 of the published technology appraisal (TA 376) states that *'The Committee agreed that the calculation of the cohort flow was an important issue and while there was uncertainty relating to the most appropriate approach, the Committee noted the significant effect on the ICER when applying the company's formula to model cohort flow'.*

- Applies the Appraisal Committee's preferred assumptions regarding utilities
- Applies the Appraisal Committee's preferred time horizon
- Applies the Appraisal Committee's preferred measure of disease progression
- Explores the impact of including the published medical resource use data in the base case
- Applies the Appraisal Committee's preferred costs for skeletal events
- Updates all relevant cost data
- Presents scenario and sensitivity analysis around these data
- Presents an updated systematic review of the literature for radium-223 dichloride. This was conducted to ensure that all relevant published data was taken into account. Significantly, publications relating to the medical resource usage data collected in ALSYMPCA were identified, with the data being included in the analysis, as noted above. No additional relevant data were identified.

The revised base-case ICER with the confidential patient access scheme is £25,963. When parameters are varied in scenario and sensitivity analyses, the ICER ranges from £22,690 - £49,114, with there being only two values above £40,000 per QALY.

There was also concern expressed by the Appraisal Committee regarding the potential for treatment waste if the patient did not attend for their dose. When a patient is unable to attend because they are too ill or have died, and the hospital is

unable to use the dose of radium-223 for another patient, Bayer refunds the hospital for the 'wasted' dose. Bayer has reviewed the records and can confirm that in 2015, there were 2 cases of hospitals being issued credits for where the patient did not receive the dose, which demonstrates that this is not a widespread issue. Bayer believes that the potential for wastage is small and that the existing process for managing wasted doses should address the Appraisal Committee's concerns about the impact of wastage on uncertainty of the ICER.

Finally, to address the previous discussions by the Appraisal Committee about the definition of the patient population who have castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases and who have not received docetaxel and for whom docetaxel is contraindicated or not suitable, Bayer will undertake a project to provide further clarity around the identification of these patients. The outputs from this project will not be available for 26th February 2016, but it has been agreed by NICE (verbal communication 9th February 2016 with follow up email on the same day) that this could be provided after this deadline to further inform discussions by the Committee.

In summary, Bayer believes that in this submission, it has presented evidence and analyses that address key areas of uncertainty raised by the Appraisal Committee during the original appraisal for the use of radium-223 dichloride in men with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases among patients who have not received docetaxel and for whom docetaxel is contraindicated or not suitable and that the resulting ICER, with the confidential patient access scheme, is £25,963.

1 Details of the patient access scheme/ commercial access agreement

No changes are proposed to the existing patient access scheme.

2 Cost effectiveness

2.1 Please show the changes made to the original company base case to align with the assumptions that determined the most plausible incremental cost effectiveness ratio(s) as determined by the Appraisal Committee and presented in the published guidance. A suggested format is presented in Table 1. Provide sufficient detail about how the Appraisal Committee's preferred assumptions have been implemented in the economic model. Provide sufficient detail to allow the replication of the changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. No other changes should be made to the model.

The table below sets out the changes made to the original Bayer model to align with the assumptions that determined the most plausible ICER as determined by the Appraisal Committee.

Table 2 and Table 3 present the medical resource usage values included in the model further to the publication by Cislo et al (1), identified in the systematic literature review (details of the systematic literature review are in Appendix 3).

Table 12 in Appendix 1 sets out the updated cost parameters and the associated costs used in the economic modelling.

Table 1. Assumptions in the economic model

Assumption	Original company model	Appraisal Committee's preferred assumption	Change	Cell reference	Old value	New value
Measure of progression	Both ALP and PSA used as measures of progression	ALP progression is the most appropriate method for analyses comparing radium-223 with best supportive care (BSC) *(Section 4.11 of TA 376).*	PSA progression removed	"Executive summary" tab, measure of progression list	ALP and PSA progression	ALP progression
Time horizon	5 years	Lifetime horizon was preferred *(Section 4.12 of TA 376).*	10 years (>99% of patients modelled as dead by this point)	"Markov_PBC" and "Markov_Radium_final" tabs, rows 437:577	5 years	10 years
No prior docetaxel utilities	Utilities specific to overall population were used	Utilities specific to no prior docetaxel population were preferred *(Section 4.16 of*	No prior docetaxel utilities included (derived from Bayer utility	"Utility inputs" tab, W18:X25 cells	Progression-free no SSE BSC: [redacted] Progression-free no SSE radium-223: [redacted]	Progression-free no SSE BSC: [redacted] Progression-free no SSE radium-223: [redacted]

Assumption	Original company model	Appraisal Committee's preferred assumption	Change	Cell reference	Old value	New value
		TA 376).	report (2) as referenced in Cislo et al 2015 (3))		[redacted] Progressed no SSE BSC: [redacted] Progressed no SSE radium-223: [redacted] Progression-free SSE BSC: [redacted] Progression-free SSE radium-223: [redacted] Progressed SSE BSC: [redacted] Progressed SSE radium-223: [redacted]	[redacted] Progressed no SSE BSC: 0.5621 [redacted] Progressed no SSE radium-223: [redacted] Progression-free SSE BSC: [redacted] Progression-free SSE radium-223: [redacted] Progressed SSE BSC: [redacted] Progressed SSE radium-223: [redacted]
Medical resource usage (MRU) from ALSYMPCA	Not included	Data as identified by the systematic literature review (SLR). Please see Appendix 3.	MRU data was identified in the SLR and included in the model	"Cost inputs" tab, E172:E208 and E273:E309 cells	Not included	Please see Table 2 and Table 3 for the medical resource usage values included in the model

Assumption	Original company model	Appraisal Committee's preferred assumption	Change	Cell reference	Old value	New value
		(section 4.18 of TA 376)				
SSE costs	SSE costs obtained from NHS reference costs	Ford et al 2013 (4) was the most preferred reference *(Sections 3.38 and 4.17 of TA376)*	SSE costs were obtained from Ford et al 2013 (4) and inflated to 2015	"Cost inputs" tab, G135:G138 cells	Pathologic Bone Fracture: £1,862.79 Spinal Cord Compression: £3,272.90 External Beam Radiation: £105.46 Surgical Intervention £4,453.69	Pathologic Bone Fracture: £956.43 Spinal Cord Compression: £7,458.59 External Beam Radiation: £675.36 Surgical Intervention £7,415.75
Unit costs update	2013 values	NA	2015 values	NA	NA	Please see Table 12

Table 2. Medical resource usage based on ALP progression for the management of stable disease

	No prior docetaxel population		
	Base Case	**SD**	**SE**
Length of stay (days per year) ALP based			
Pre-SSE Radium-223	[redacted]	[redacted]	[redacted]
Pre-SSE BSC	[redacted]	[redacted]	[redacted]
Post-SSE Radium-223	[redacted]	[redacted]	[redacted]
Post-SSE BSC	[redacted]	[redacted]	[redacted]
Nursing Home Use (weeks per year) ALP based			
Pre-SSE Radium-223	[redacted]	[redacted]	[redacted]
Pre-SSE BSC	[redacted]	[redacted]	[redacted]
Post-SSE Radium-223	[redacted]	[redacted]	[redacted]
Post-SSE BSC	[redacted]	[redacted]	[redacted]
Care Centre Use (days per year) ALP based			
Pre-SSE Radium-223	[redacted]	[redacted]	[redacted]
Pre-SSE BSC	[redacted]	[redacted]	[redacted]
Post-SSE Radium-223	[redacted]	[redacted]	[redacted]
Post-SSE BSC	[redacted]	[redacted]	[redacted]
Home Health Care Services Use (hours per year) ALP based			
Pre-SSE Radium-223	[redacted]	[redacted]	[redacted]
Pre-SSE BSC	[redacted]	[redacted]	[redacted]
Post-SSE Radium-223	[redacted]	[redacted]	[redacted]
Post-SSE BSC	[redacted]	[redacted]	[redacted]
Physician Visits (visits per year) ALP based			
Pre-SSE Radium-223	[redacted]	[redacted]	[redacted]
Pre-SSE BSC	[redacted]	[redacted]	[redacted]
Post-SSE Radium-223	[redacted]	[redacted]	[redacted]
Post-SSE BSC	[redacted]	[redacted]	[redacted]

* MRU report (5) as referenced in Cislo et al 2015 (1)

Table 3. Medical resource usage based on ALP progression for the management of progressed disease

	No prior docetaxel population		
	Base Case	**SD**	**SE**
Length of stay (days per year) ALP based			
Pre-SSE Radium-223	[redacted]	[redacted]	[redacted]
Pre-SSE BSC	[redacted]	[redacted]	[redacted]
Post-SSE Radium-223	[redacted]	[redacted]	[redacted]
Post-SSE BSC	[redacted]	[redacted]	[redacted]
Nursing Home Use (weeks per year) ALP based			
Pre-SSE Radium-223	[redacted]	[redacted]	[redacted]
Pre-SSE BSC	[redacted]	[redacted]	[redacted]
Post-SSE Radium-223	[redacted]	[redacted]	[redacted]
Post-SSE BSC	[redacted]	[redacted]	[redacted]
Care Centre Use (days per year) ALP based			
Pre-SSE Radium-223	[redacted]	[redacted]	[redacted]
Pre-SSE BSC	[redacted]	[redacted]	[redacted]
Post-SSE Radium-223	[redacted]	[redacted]	[redacted]
Post-SSE BSC	[redacted]	[redacted]	[redacted]
Home Health Care Services Use (hours per year) ALP based			
Pre-SSE Radium-223	[redacted]	[redacted]	[redacted]
Pre-SSE BSC	[redacted]	[redacted]	[redacted]
Post-SSE Radium-223	[redacted]	[redacted]	[redacted]
Post-SSE BSC	[redacted]	[redacted]	[redacted]
Physician Visits (visits per year) ALP based			
Pre-SSE Radium-223	[redacted]	[redacted]	[redacted]
Pre-SSE BSC	[redacted]	[redacted]	[redacted]
Post-SSE Radium-223	[redacted]	[redacted]	[redacted]
Post-SSE BSC	[redacted]	[redacted]	[redacted]

* MRU report (5) as referenced in Cislo et al 2015 (1)

2.2 If the population to whom the patient access scheme/ commercial access agreement applies (as described in sections 3.4 and 3.5) is not the same as that in the published technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for company submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme/ commercial access agreement. You must also complete the rest of this template.

Radium-223 dichloride is indicated for the treatment of men with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases (6).

The population to whom the patient access scheme applies is the full licensed indication, and this is the same as the population considered in the published technology appraisal (TA 376).

This submission relates to the group of men with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases among patients who have not received docetaxel and for whom docetaxel is contraindicated or not suitable.

In the subgroup of men who had not previously received docetaxel, there was a statistically significant improvement of 4.6 months in median overall survival in the pivotal ALSYMPCA study; this was 16.1 months in the radium-223 group compared with 11.5 months in the placebo group (HR 0.75; 95% CI 0.56 to 0.99; p=0.004) (7). For the overall ALSYMPCA population, there was was a statistically significant improvement of 3.6 months in median overall survival; this was 14.9 months in the radium-223 group compared with 11.3 months in the placebo group (hazard ratio, 0.70; 95% CI, 0.58 to 0.83; P<0.001) (7).

There were discussions by the Appraisal Committee during the initial appraisal about the definition of the patient population who have not received docetaxel and for whom docetaxel is contraindicated or not suitable. Bayer is undertaking a project to provide further clarity on this. The outputs from this project are not available at the time of this submission, but it has been agreed by NICE that this could be provided at a later date to further inform discussions by the Committee.

2.3 Please provide a summary of the clinical effectiveness parameters (resulting from the Committee's preferred evidence synthesis) which are used in the economic model which includes the patient access scheme/ commercial access agreement.

The Appraisal Committee raised concerns *(section 4.14 and section 4.26 of the published technology appraisal TA376)* about the cohort flow as a result of death being treated as a censored event, rather than an event in the determination of progression-free survival.

Bayer has conducted further analysis of the patient level data and the revised progression-free survival data handles death as an event rather than as censored data. This is described below.

For more information about the Kaplan-Meier survival estimates and parameterisation models please refer to Appendix 4. The main endpoints of the revised survival analysis are the following:

- Alkaline phosphatase progression-free survival (ALP-FS)
- Symptomatic skeletal related events-free survival (SSE-FS)

Specifically, ALP progression free-survival is defined as the time from the date of randomisation to the date of first ALP progression or the date of death within 9 weeks of last ALP assessment date due to any cause. Subjects alive without any ALP progression at the data cut-off date were censored at the last ALP assessment date. Subjects who died after 9 weeks of last ALP assessment date without any ALP

progression at the data cut-off date were censored at the last ALP assessment date. A 9 week window (2 assessment cycles plus 1 week) was used so that ALP progression free-survival was not made artificially longer for patients who discontinued ALP assessment follow-up and died without a documented ALP progression.

In addition, SSE-free survival is defined as the time from the date of randomisation to the date of first symptomatic skeletal event (the use of external beam radiotherapy for relief of pain, the occurrence of new pathological fractures, the occurrence of spinal cord compression or tumour-related orthopaedic surgical intervention) or the date of death within 9 weeks of last SSE efficacy assessment date due to any cause. Subjects alive without any SSE at the data cut-off date were censored at the last SSE efficacy assessment date. Subjects who died after 9 weeks of last SSE efficacy assessment date without any SSE at the data cut-off date were censored at the last SSE efficacy assessment date. A 9 week window (2 assessment cycles plus 1 week) was used so that SSE-FS is not made artificially longer to an extensive degree for patients who discontinued SSE follow-up and died without an SSE.

Table 4. Median survival (in months) for each outcome derived from the ALSYMPCA trial for the no prior docetaxel population

Outcomes	Median survival (in months)	
	Radium 223	Placebo
ALP progression free survival	[redacted]	[redacted]
SSE free survival	[redacted]	[redacted]

2.4 Please list any costs associated with the implementation and operation of the patient access scheme/ commercial access agreement (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in Table 5. Please give the reference source of these

costs. Please provide sufficient detail to allow the replication of changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. Please refer to section 6.5 of the 'Specification for company submission of evidence'

Table 5. Costs associated with the implementation and operation of the patient access scheme (PAS)/ commercial access agreement (CAA)

	Calculation of cost	Reference source
Stock management	N/A	N/A
Administration of claim forms	N/A	N/A
Staff training	N/A	N/A
Other costs…	N/A	N/A
…	…	…
…	…	…
Total implementation/ operation costs	N/A	N/A

2.5 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme/ commercial access agreement. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Not applicable to our case, however please refer to Table 12, in Appendix 1 for the most up to date values used in the economic model.

Summary results

New base-case analysis

2.6 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without any (new) patient access scheme/ commercial access agreement; that is with the price for the technology considered in the published guidance.
- the results for the intervention with the patient access scheme/ commercial access agreement.

The results presented below represent the revised base-case analyses using the NHS list price and also the confidential patient access scheme price.

Table 6. New base-case cost-effectiveness results using the NHS list price from the published technology appraisal (no prior docetaxel population)

	Radium-223	Best Supportive care
Drug cost (£)	[redacted]	0
Administration costs (£)	1,196	0
Patient management costs (£)	[redacted]	[redacted]
Total MRU costs(£)	[redacted]	[redacted]
Hospitalisations(£)	[redacted]	[redacted]
Nursing Home Use (£)	[redacted]	[redacted]
Day Care Centre Use (£)	[redacted]	[redacted]
Home Health Care Services Use (£)	[redacted]	[redacted]
Physician Visits (£)	[redacted]	[redacted]
Second & subsequent lines of treatment (£)	[redacted]	[redacted]
End of Life care (£)	[redacted]	[redacted]
SSEs costs (£)	[redacted]	[redacted]
AE Costs (£)	[redacted]	[redacted]
Total costs(£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	-
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	-
ICER (£)	[redacted]	-

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 7. New base-case cost-effectiveness results using the PAS price (no prior docetaxel population)

	Radium-223	Best Supportive care
Drug cost (£)	[redacted]	0
Administration costs (£)	1,196	0
Patient management costs (£)	[redacted]	[redacted]
Total MRU costs(£)	[redacted]	[redacted]
Hospitalisations(£)	[redacted]	[redacted]
Nursing Home Use (£)	[redacted]	[redacted]
Day Care Centre Use (£)	[redacted]	[redacted]
Home Health Care Services Use (£)	[redacted]	[redacted]
Physician Visits (£)	[redacted]	[redacted]
Second & subsequent lines of treatment (£)	[redacted]	[redacted]
End of Life care (£)	[redacted]	[redacted]
SSEs costs (£)	[redacted]	[redacted]
AE Costs (£)	[redacted]	[redacted]
Total costs(£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	**25,963**	**-**

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

2.7 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the (new) patient access scheme/ commercial access agreement, that is with the price for the technology considered in the published appraisal.
- the results for the intervention with the patient access scheme/ commercial access agreement.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance.

[2] For outcome-based schemes, please see section 5.3.9 in appendix 5.3.

The results presented below represent the incremental results for the revised base-case analyses using the NHS list price and also the confidential patient access scheme price.

Table 8. New base-case incremental results using the NHS list price from the published technology appraisal, no prior docetaxel population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Radium-223	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A

Table 9. New base-case incremental results using the PAS price, no prior docetaxel population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Radium-223	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,963	25,963
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A

Sensitivity analyses with the relevant PAS/CAA

2.8 Please refer to the published guidance to identify the key sensitivity and scenario analyses (that is, analyses that were discussed in the 'considerations' section and which alter the ICER). Present the results of these sensitivity and scenario analyses with the patient access scheme/ commercial access agreement.

Scenario analyses were conducted to address factors raised by the Appraisal Committee during the original appraisal (TA 376) as possible sources of uncertainty. These are presented in Table 10.

Mortality in the model

Section 4.13 of the published technology appraisal discusses a sensitivity analysis presented by Bayer which explored the consequences of replacing mortality observed in the trial with a doubled risk of death after week 156. The Appraisal Committee considered that an analysis exploring doubled risk of death after week 104 would be more informative, so this scenario is presented here.

Utility – duration of benefit

In the ALSYMPCA trial patients treated with radium-223 reported significantly better quality of life than patients on BSC. The trial data were however not sufficient to demonstrate for how long this benefit continued. The published technology appraisal *(TA 376 section 4.16)* states that the Committee had some concerns, about Bayer's assumption that a quality-of-life increment from radium-223 over best supportive care for a given health state, would continue indefinitely. The Committee heard from the clinical experts that it is not implausible for the quality-of-life benefit to extend over a long period of time as a result of suppressing the disease with radium-223. Despite this, the Committee considered that Bayer's assumption of a lifetime benefit was unlikely and that the benefit probably diminished over time. However, it also considered that the ERG's assumption of a 24-week point was arbitrary and may be conservative.

Bayer have conducted further analysis of the full EQ-5D data set from ALSYMPCA which supports a persistent benefit. This was presented as part of the original appraisal process.

The Bayer position is that the evidence demonstrates that radium-223 treatment maintains quality of life better than BSC and the quality of life benefit for the on-treatment period was comparable to the benefit for the off-treatment time period. Given that off-treatment EQ-5D QoL measurements were made up to 132 weeks after baseline and the average time associated with the EQ-5D QoL

measurements was 47.8 weeks after baseline, there is sufficient evidence to believe the QoL benefit extends well into the off-treatment period. Furthermore, the magnitude of benefit in the off-treatment period has been found to be comparable to that observed during the on-treatment period.

Despite the evidence that the differential benefit is maintained over the long-term, Bayer has conducted scenario analysis exploring the impact on the ICER assuming the differential benefit is maintained for 24, 52, 104, 156, 208, 260, 312, 364, 416 and 468 weeks. The base case retains the assumption of a lifetime differential in benefit.

Extrapolation

The Appraisal Committee noted that the lognormal extrapolation provided the best fit to the data (*section 4.13 of TA 376*) but also wished to consider the more conservative Weibull distribution in decision making.

The re-analysis of the patient flow considering death as an event has slightly altered the AIC/BIC criteria. The log normal remains the best fit for OS and ALP progression free survival but the log-logistic form is now the best fit for SSE free survival. Bayer therefore presents the following scenario analyses:

- A base case using lognormal for all curves following logic discussed previously
- A scenario analysis where the log-logistic distribution is applied to SSE-FS since it offers the best fit to the trial data. The impact of this is to change the ICER by less than £20 per QALY gained
- A second scenario analysis where the more conservative Weibull distribution was applied to both arms and all endpoints.

Time horizon

During the original appraisal, the Appraisal Committee *(section 4.9 of TA 376)* concluded that Bayer's choice of a 5–year time horizon was not in line with the NICE

reference case and that a lifetime time horizon would have been more appropriate to capture all relevant costs and benefits. Bayer has used a lifetime (10 year) time horizon in the base case in this submission.

A scenario analysis including the original 5 year time horizon has also been reported as this was discussed in the considerations section of the published technology appraisal and affects the ICER.

Utilities – point estimates

In the original appraisal, the Appraisal Committee noted that in some cases Bayer had used an arm-specific utility, and in other cases it used estimates that were pooled across arms, depending on whether the estimate was statistically significant. The Committee agreed with the ERG's approach to use point estimates, rather than the average between the arms, when there was no statistically significant difference between these. In this submission, Bayer has used the point estimates in the base case analysis and presents a sensitivity analysis with pooled utilities as this was discussed in the considerations section of the published technology appraisal (*section 4.15 of TA376*) and affects the ICER.

Utilities – overall study population vs 'no prior docetaxel' population

In the original appraisal (*section 4.16 of TA376*), the ERG highlighted that Bayer had applied utility values derived from all patients in the ALSYMPCA study rather than those derived specifically from the no-prior-docetaxel group. The Appraisal Committee agreed with the ERG that utility values from the no-prior-docetaxel group were the most appropriate to use. In this submission, Bayer has used utility values from the no-prior-docetaxel group in the base case analysis. Bayer presents a sensitivity analysis with overall population utilities as this was discussed in the considerations section of the published technology appraisal and affects the ICER.

Medical resource use from ALSYMPCA

Medical resource use collected during ALSYMPCA was not presented in the initial company submission leading to TA 376, however, it was raised during the appraisal

process and considered as part of 'additional evidence' submitted by Bayer. The Appraisal Committee decided not to consider this evidence further *(section 4.18 of the published TA)* but whilst Bayer accepts there are limitations including medical resource use data from an international clinical trial, Bayer believes that the important findings of a significant reduction in healthcare resource utilisation, regardless of prior docetaxel use, should be taken into account in the modelling, as it is consistent with the efficacy results and therefore not implausible. This data has been presented as an abstract (1), identified as part of the systematic literature review (see Appendix 3). These data have now been further analysed and estimates of UK cost savings have been presented (8). Bayer has used data from an unpublished report (5) in the base case analysis, providing more information than contained within the published abstract.

Table 10. Scenario analysis (PAS price; no prior docetaxel population)

Scenario	ICER
Base-case	*£25,963*
Mortality doubles after 104 weeks	£33,710
Radium utility benefit lasts up to 24 weeks	£32,150
Radium utility benefit lasts up to 52 weeks	£29,357
Radium utility benefit lasts up to 104 weeks	£27,891
Radium utility benefit lasts up to 156 weeks	£27,217
Radium utility benefit lasts up to 208 weeks	£26,805
Radium utility benefit lasts up to 260 weeks	£26,532
Radium utility benefit lasts up to 312 weeks	£26,341
Radium utility benefit lasts up to 364 weeks	£26,204
Radium utility benefit lasts up to 416 weeks	£26,101
Radium utility benefit lasts up to 468 weeks	£26,023
Weibull curves fitted to OS, PFS and SSE	£39,580
Log-logistic curves fitted to SSE	£25,953
Time horizon of 5 years (260 weeks)	£29,365
Pooled utility point estimates	£28,908
Overall population utilities	£22,690

No medical resource use (MRU) costs	£29,156
Combined scenario (no MRU, mortality doubles after 104 weeks and radium utility benefit lasts up to 52 weeks)	£42,319
Combined scenario (no MRU, Weibull curves fitted to all endpoints and radium utility benefit lasts up to 52 weeks)	£49,114

2.9 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

One way sensitivity analysis (OWSA) was conducted and results are reported in Appendix 2, Figure 3.

Table 11. Probabilistic sensitivity analysis results (PAS price; no prior docetaxel population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Radium-223	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,268	26,268
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A

Figure 1. Cost-effectiveness scatter plot (PAS price; no prior docetaxel population)

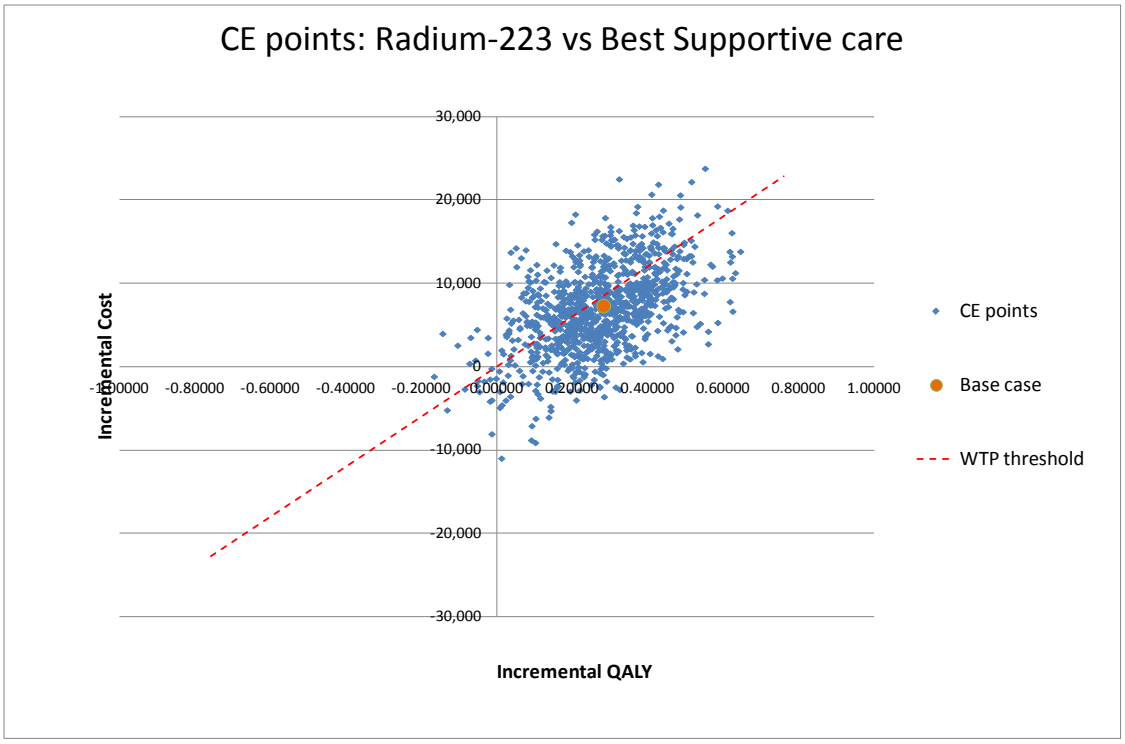
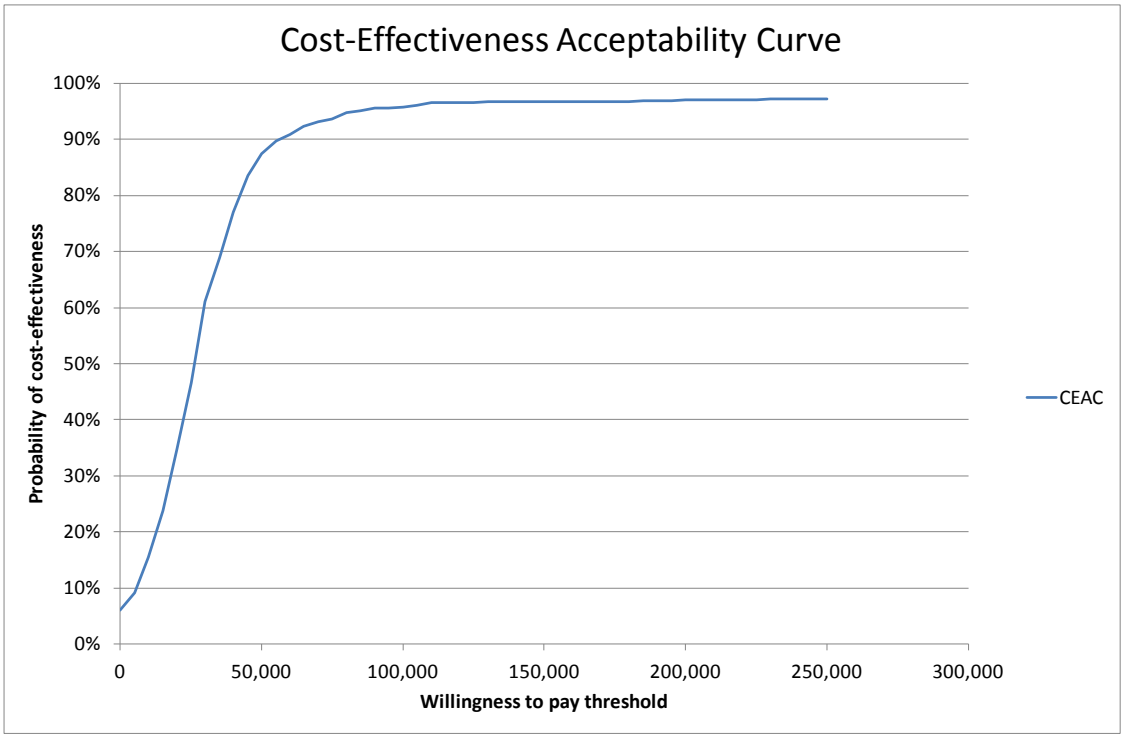


Figure 2. Cost-effectiveness acceptability curve (PAS price; no prior docetaxel population)



2.10 If any of the criteria on which the patient access scheme/ commercial access agreement depends is a clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

The PAS agreement does not depend on alteration of clinical variables.

3 Appendices

APPENDIX 1

Updated costs used in the economic model

Table 12. Updated costs to 2015 values

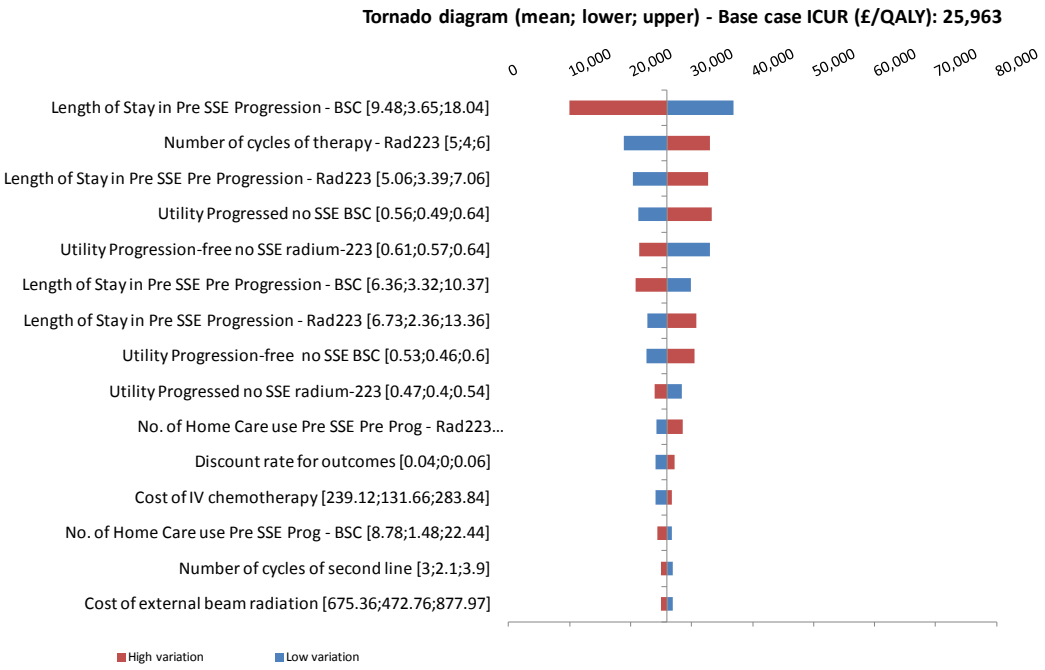
Cost parameter	Unit cost (£)	Reference/comments
Drug costs		
Radium-223	[redacted]	Bayer - PAS price (list price £4040)
Ongoing therapy (stable and progressed costs) costs		
Goserelin (Zoladex) (per mg)	21.76	BNF Jan 2016 (9)
Morphine (per mg)	0.12	BNF Jan 2016 (9)
Zoledronic acid (per mg)	45.92	BNF Jan 2016 (9)
Drugs for adverse events treatment		
Filgrastim (Nivestim 48 Mio E/0.5ml) (per mg)	0.45	BNF Jan 2016 (9)
Meropenem HEXAL 1000mg(per mg)	0.02	BNF Jan 2016 (9)
Cabazitaxel(per mg)	61.60	BNF Jan 2016 (9)
Docetaxel(per mg)	6.74	BNF Jan 2016 (9)
Mitoxantrone (per mg)	3.42	BNF Jan 2016 (9)
Abiraterone (per pack)	2,930	BNF Jan 2016 (9)
Prednisone (per mg)	0.43	BNF Jan 2016 (9)
Estramustine (280 mg po TID for 5 days)	0.01	BNF Jan 2016 (9)
Cyclophophamide (50 mg)	0.02	BNF Jan 2016 (9)
Vinorelbine (20 mg/m2 on day 1 and 3 q 3 weeks)	2.86	BNF Jan 2016 (9)
Cost of administration		
Deliver IV Treatment (per visit)	239.12	NHS reference costs 2014-2015 (10) Currency code(s): SB12Z
Procedure cost		
Imaging CT scan - abdominal	111.61	NHS reference costs 2014-2015 (10) Currency code(s): RD22Z
Imaging CT scan - pelvic	111.61	NHS reference costs 2014-2015 (10) Currency code(s): RD22Z
Imaging MRI - pelvic	181.76	NHS reference costs 2014-2015 (10) Currency code(s): RD03Z
Imaging bone scan	201.12	NHS reference costs 2014-2015 (10) Currency code(s): RN16A
Imaging ultrasound - prostate transrectal ultrasound	54.17	NHS reference costs 2014-2015 (10) Currency code(s): RD41Z
Imaging chest X-ray	201.12	NHS reference costs 2014-2015 (10) Currency code(s): RN16A
Complete blood count	3.01	NHS reference costs 2014-2015 (10) Currency code(s): DAPS05
PSA	1.19	NHS reference costs 2014-2015 (10) Currency code(s): DAPS04
ECG	510.96	NHS reference costs 2014-2015 (10) Currency code(s): EY51Z
Echocardiogram	81.48	NHS reference costs 2014-2015 (10) Currency code(s): RD51A
Home support and assisted living cost		
Day Care Centre Cost (per day)	889.00	PSSRU, Unit Costs of Health and Social Care 2015 (11)

Nursing home cost per week (per week)	110.89	PSSRU, Unit Costs of Health and Social Care 2015 (11)
Home Health Care Services Cost (per hour)	37.00	PSSRU, Unit Costs of Health and Social Care 2015 (11)
Physician visit	67.00	PSSRU, Unit Costs of Health and Social Care 2015 (11)
Hospitalisation (day cost)	624.03	NHS reference costs 2014-2015 (10) Currency code(s): LB06H, LB06J, LB06K, LB06L, LB06M, LB06N, LB06P, LB06Q, LB06R, LB06S
Costs of treating Adverse Events (cost per event)		
Inpatient costs		
Fatigue	389.62	NHS reference costs 2014-2015 (10) Currency code(s): AA31C, AA31D, AA31E
Nausea	449.94	NHS reference costs 2014-2015 (10) Currency code(s): FZ91A, FZ91B, FZ91C, FZ91D, FZ91E, FZ91F, FZ91G, FZ91H, FZ91J, FZ91K, FZ91L, FZ91M
Vomiting	449.94	NHS reference costs 2014-2015 (10) Currency code(s): FZ91A, FZ91B, FZ91C, FZ91D, FZ91E, FZ91F, FZ91G, FZ91H, FZ91J, FZ91K, FZ91L, FZ91M
Anaemia	1,569.57	NHS reference costs 2014-2015 (10) Currency code(s): SA01G, SA01H, SA01J, SA01K
Thrombocytopenia	610.11	NHS reference costs 2014-2015 (10) Currency code(s): SA12G, SA12H, SA12J, SA12K
Hypokalemia	624.03	NHS reference costs 2014-2015 (10) Currency code(s): LB06H, LB06J, LB06K, LB06L, LB06M, LB06N, LB06P, LB06Q, LB06R, LB06S
Bone Pain	893.01	NHS reference costs 2014-2015 (10) Currency code(s): HD26D, HD26E, HD26F, HD26G
Outpatient cost		
Nausea	0.33	WHO DDD for metroclopramide: 30 mg, usual prescription: 10-20 mg q 4-6 h prn and BNF Jan 2016 (9)
Vomiting	0.33	WHO DDD for metroclopramide: 30 mg; Prescription: 10mg x3 daily and BNF Jan 2016 (9)
Anaemia	329.99	Cost of blood + Additional fee for monitoring and supervision - duration >2 hours (12)
Thrombocytopenia	329.99	Cost of platelet + Additional fee for monitoring and supervision - duration >2 hours (12)
Hypokalemia	7.65	Potassium supplement - Slow-K® potassium chloride 600 mg (8 mmol each of K+ and Cl-), net price 100 = £7.65. Assumed one pack is sufficient. BNF Jan 2016 (9)
Bone Pain	16.96	WHO DDD for Hydromorph: 20 mg and BNF Jan 2016 (9)
Neutropenia	385.25	NHS reference costs 2014-2015 (10) Currency code(s): XD25Z
End of life care	2,087.15	Abel et al. 2013 - Assumed cost of last 3 months of life (average hospital/hospice) (13)

APPENDIX 2

One way sensitivity analysis

Figure 3. Tornado graph (PAS price; no prior docetaxel population)



APPENDIX 3

Updated Systematic Literature Review

An update of the clinical systematic literature review was conducted to identify RCTs and non-randomised studies of radium-223 dichloride versus best supportive care in adults with castration resistant prostate cancer (CRPC) who had no prior docetaxel experience, published since the last review in February 2013.

The following databases were searched using the OVID SP platform:

- MEDLINE
- Medline® In-Process
- EMBASE
- The Cochrane Library

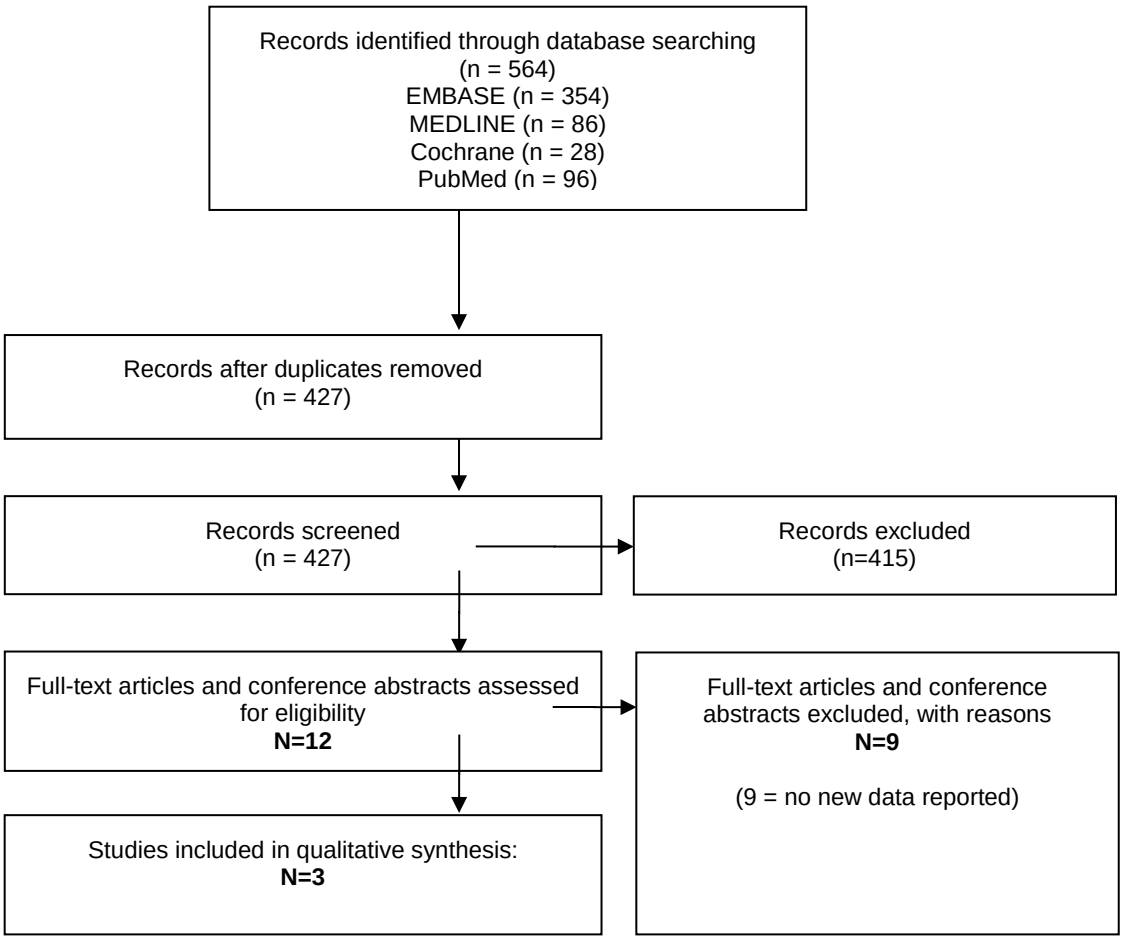
A supplementary search of the PubMed database was also completed for the last six-months in order to identify studies currently only available online as e-publications. This additional search was completed as OVID SP does not list e-publications submitted in the last 3-6 months. Search terms and associated number of hits are presented at the end of this appendix (Table 15-Table 18). To identify relevant clinical trials, the following eligibility criteria were used (Table 13).

Table 13. Eligibility criteria used in search strategy

Criteria	Clinical effectiveness
Inclusion criteria	**Population** • Adults with castration resistant prostate cancer (CRPC) • Docetaxel unsuitable patients only
	Interventions • Radium-223 dichloride
	Comparators • Best supportive care
	Outcomes • 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 events of treatment • Health-related quality of life • Resource use/costs
	Study design • Randomised controlled trials (RCTs) • Non-randomised controlled clinical trials • Single-arm interventional studies/uncontrolled trials • Observational studies • Systematic reviews/meta-analyses
	Language restrictions • Language: English
	Publication timeframe All publications and conference proceedings from 1 Jan 2013 to 19 Jan 2016
Exclusion criteria	**Population** • Non-human, paediatric populations, prostate cancer other than CRPC, docetaxel experienced **Study design** • Editorials • Notes • Comments • Letters • Case studies • Phase I trials • Single centre uncontrolled case series **Language restrictions** • Non-English studies

A flow diagram of the numbers of studies included and excluded at each stage is shown in Figure 4.

Figure 4.Flow Diagram of Included Studies



A number of single centre uncontrolled case series were found, and while these confirm the increasing use of radium-223 dichloride in practice, they do not add materially to our understanding of its benefits and therefore uncontrolled studies were not considered further.

The twelve titles selected for full-text review are outlined in Table 14. Nine of the twelve titles did not report any new data beyond what had been available in the clinical study report. However, three additional conference abstracts were identified which reported analysis that were not available in the clinical study report. Information provided by these conference abstracts is summarised under Table 14 below.

Table 14.List of full-text publications and conference abstracts retained for full-text review and decision on exclusion with reason.

#	Publication	Publication type	Excluded	Reason for Exclusion
1	Cislo et al, 2015. Effect of radium-223 dichloride (Ra-223) on risk for and duration of hospitalization in ALSYMPCA by docetaxel (D) subgroup (1)	Conference abstract	No	N/A
2	Cislo et al, 2015. Effects of radium-223 dichloride (Ra-223) on health-related quality of life (HRQoL) assessed by the EQ-5D utility scores in ALSYMPCA (3)	Conference abstract	No	N/A
3	Donga et al, 2014. Health state utilities among metastatic castrate-resistant prostate cancer patients with and without symptomatic skeletal events (14)	Conference abstract	No	N/A
4	Chalhoub et al, 2015. Treatment of skeletal metastases with ^{223}Ra-chloride (15)	Journal article	Yes	No further trials indentified in this review article
5	Coleman et al, 2013. Time to first symptomatic skeletal-related event (SSE) with radium-223 dichloride (Ra-223) in patients with castration-resistant prostate cancer (CRPC) and bone metastases: ALSYMPCA trial stratification factors analysis (16)	Conference abstract	Yes	No new data reported
6	Gee et al, 2015. Health-related quality of life in men with metastatic castration-resistant prostate cancer (17)	Journal article	Yes	No further trials indentified in this review article
7	Heinrich et al, 2013. Updated analysis of radium-223 dichloride (Ra-223) impact on pain, symptomatic skeletal-related events (SSE), and survival from the phase 3 randomized trial (ALSYMPCA) in patients with castration-resistant prostate cancer (CRPC) and bone metastases (18)	Conference abstract	Yes	No new data reported
8	Hoskin et al, 2014. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial (19)	Journal article	Yes	No new data reported
9	Wedel et al, 2014. Further characterization of the effects on sequential treatment of docetaxel before or after radium-223 dichloride therapy in Castration-Resistant	Conference abstract	Yes	No new data reported

	Prostate Cancer (CRPC) patients with symptomatic bone metastases included in the phase 3 ALSYMPCA trial (20)			
10	Michalski et al, 2013. Radium-223 dichloride (Ra-223) impact on skeletal-related events, external beam radiation therapy (EBRT), and pain in patients with castration-resistant prostate cancer (CRPC) with bone metastases: Updated results from the phase 3 alsympca trial (21)	Conference abstract	Yes	No new data reported
11	Sartor et al, 2015. 3-year follow-up of chemotherapy following radium-223 dichloride (Ra-223) in castration-resistant prostate cancer (CRPC) patients (Pts) with symptomatic bone metastases (Mets) from ALSYMPCA (22)	Conference abstract	Yes	No new data reported
12	Wedel et al, 2013. Updated analysis of radium-223 dichloride (Ra-223) impact on survival, safety, and skeletal-related events in castration-resistant prostate cancer (CRPC) patients with bone metastases from the phase 3 ALSYMPCA trial (23)	Conference abstract	Yes	No new data reported

Summary of studies selected for inclusion in the model

The aim of the study by Cislo *et al*. (1) was to understand whether reduced health care resource utilization associated with radium-223 treatment is consistent regardless of prior exposure to docetaxel. The resource use analysed by the authors included hospitalization, nursing home visits, home health care, physician visits and adult day care services for each patient. To account for variation in the observation time due to differences in survival, resource use was annualized for each patient and mean values in radium-223 versus placebo group compared using t-tests. Results demonstrated that radium-223 treatment resulted in reduced resource use compared to placebo regardless of prior exposure to docetaxel. The effect was more pronounced in patients with prior docetaxel who experienced 8.0 fewer hospital days per patient per year compared to 4.6 in those with no prior docetaxel. Reduced resource utilization was driven by reduction in hospitalizations as well as shorter length of hospital stay.

Another Cislo *et al*. (3) study was a post-hoc analysis of health-related quality of life (HRQoL) data from ALSYMPCA trial which sought to determine the effect of treatment (radium-223 or placebo), disease progression and symptomatic skeletal events (SSE) on EQ-5D-based utility scores for CRPC disease states. Linear regression models were used to estimate least-squares mean utility scores for each disease state. Results showed that patients in radium-223 treatment group had higher utility scores compared to placebo group while in stable disease and prior to an SSE regardless of how disease progression is defined (0.62 vs 0.55, p=0.038 in ALP-stable disease, 0.61 vs 0.45, p=0.0001 in PSA-stable disease). Post-SSE however there was little difference in HRQoL between the two groups. The study highlighted alkaline phosphatase and SSEs as more accurate markers of CRPC progression than prostate-specific antigen.

The objective of the study by Donga *et al.* (14) was to assess differences in utilities between CRPC health states with and without SSEs in US population. Utility data were collected alongside the ALSYMPCA trial using EQ-5D questionnaire and evaluated with the time trade-off method. Assessments administered prior to an SSE were included in the No SSE health state, while those administered on or after an SSE were included in the SSE health state. Results of the study show that CRPC patients who have not experienced an initial SSE have a significantly higher HRQoL than those who have (0.718 vs 0.617, 95% CI: -0.1101, -0.08553, p<0.0001). In addition, mean unadjusted utilities associated with both health states were somewhat higher in the radium-223 group than the placebo group (No SSE: 0.731 vs 0.721, SSE: 0.644 vs 0.616; p>0.05 for both comparisons).

Search terms

Table 15: Search terms - EMBASE

#	Disease Terms - CRPC	Hits
1	prostate cancer/	121328
2	((prostate or prostatic) and (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$ or malignant$)).mp.	192120
3	1 or 2	192120
4	((hormone$ or castrat$ or androgen) and (refract$ or resist$ or independent)).mp.	83914
5	Hormone-refractory.mp.	3489
6	Hormone-resistant.mp.	807
7	Hormone-independent.mp.	1375
8	Androgen-independent.mp.	3943
9	Androgen-resistant.mp.	153
10	Castration-resistant.mp.	7458
11	Castrate-resistant.mp.	1485
12	or/4-11	83914
13	3 and 12	19369
14	exp castration resistant prostate cancer/	5646
15	(CRPC or HRPC or AIPC).mp.	4521
16	Or/13-15	19718
17	radium chloride ra 223/	482
18	alpharadin.mp.	149
19	radium 223.mp.	616
20	xofigo.mp.	88
21	223Ra.mp.	147
22	223Ra chloride.mp.	14
23	radium ra 223 chloride.mp.	0
24	(bay 88 8223 or bay88 8223).mp.	2
25	or/17-24	949
26	randomized controlled trial/	375547
27	exp clinical trial/	1015346

28	double blind procedure/	118246
29	single blind procedure/	21286
30	crossover procedure/	45525
31	randomization/	66511
32	experimental design/	11924
33	control group/	85232
34	placebo/	235969
35	(clin$ adj3 trial$).mp.	1132876
36	randomi?ed controlled trial$.mp.	500036
37	RCT.mp.	20042
38	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).mp.	204707
39	placebo$.mp.	314595
40	(random$ adj2 allocat$).mp.	27754
41	((random$ or control$ or clinical$) adj2 (trial$ or stud$)).mp.	6623609
42	(crossover$ or (cross adj over$)).mp.	79047
43	or/26-42	6820202
44	exp clinical study/	5966819
45	exp case control study/	109042
46	family study/	10615
47	longitudinal study/	81720
48	retrospective study/	430840
49	prospective study/	312579
50	randomized controlled trial/	375547
51	49 not 50	276652
52	cohort analysis/	226820
53	(cohort adj (study or studies)).mp.	154544
54	(Case control adj (study or studies)).tw.	88230
55	(follow up adj (study or studies)).tw.	41280
56	(observational adj (study or studies)).tw.	85224
57	(epidemiologic$ adj (study or studies)).tw.	74578
58	(epidemiologic$ adj (study or studies)).tw.	74578
59	(cross sectional adj (study or studies)).tw.	111418
60	or/44-48,51-59	6197577
61	43 or 60	9434884
62	16 and 25 and 61	502
63	**limit 62 to (english language and yr="2013 -Current")**	**354**

Table 16: Search terms – Medline and Medline (R) In-Process

#	Disease Terms - CRPC	Hits
1	Prostatic Neoplasms/	99558
2	((prostate or prostatic) and (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$ or malignant$)).mp.	135124
3	1 or 2	135124
4	((hormone$ or castrat$ or androgen) and (refract$ or resist$ or independent)).mp.	62415
5	Hormone-refractory.mp.	2628
6	Hormone-resistant.mp.	655
7	Hormone-independent.mp.	1339
8	Androgen-independent.mp.	3134
9	Androgen-resistant.mp.	138
10	Castration-resistant.mp.	3305
11	Castrate-resistant.mp.	593
12	or/4-11	62415
13	3 and 12	11754
14	(CRPC or HRPC or AIPC).mp.	2313
15	or/13-14	11969
16	alpharadin.mp.	47
17	radium 223.mp.	213
18	xofigo.mp.	20
19	223Ra.mp.	51
20	223Ra chloride.mp.	4
21	radium ra 223 chloride.mp.	0
22	(bay 88 8223 or bay88 8223).mp.	0
23	or/16-22	290
24	Randomized Controlled Trial/	403865
25	Randomized Controlled Trials as topic/	99922

26	exp Clinical Trial/	719499
27	exp Clinical Trials as topic/	285860
28	exp Clinical Trial/	719499
29	exp Clinical Trials as topic/	285860
30	Double-Blind Method/	132244
31	Single-Blind Method/	21096
32	Random Allocation/	84919
33	Placebos/	32941
34	Control Groups/	1506
35	clinical trial, phase i.pt.	15428
36	clinical trial, phase ii.pt.	24966
37	clinical trial, phase iii.pt.	10485
38	clinical trial, phase iv.pt.	1092
39	controlled clinical trial.pt.	89971
40	randomized controlled trial.pt.	403865
41	multicenter study.pt.	191798
42	clinical trial.pt.	495854
43	(clin$ adj3 trial$).mp.	844523
44	randomi?ed controlled trial$.mp.	535602
45	RCT.mp.	11370
46	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).mp.	191704
47	placebo$.mp.	184645
48	(random$ adj2 allocat$).mp.	106865
49	((random$ or control$ or clinical$) adj2 (trial$ or stud$)).mp.	1511188
50	(crossover$ or (cross adj over$)).mp.	75763
51	or/24-50	1719404
52	Epidemiologic studies/	6948
53	exp case control studies/	746510

54	exp cohort studies/	1480972
55	Case control.tw.	88090
56	(cohort adj (study or studies)).tw.	107328
57	Cohort analy$.tw.	4472
58	(Follow up adj (study or studies)).tw.	40027
59	(observational adj (study or studies)).tw.	56461
60	Longitudinal.tw.	159951
61	Retrospective.tw.	324541
62	Cross sectional.tw.	205235
63	Cross-sectional studies/	203448
64	or/52-63	2117478
65	51 or 64	3271140
66	15 and 23 and 65	120
67	limit 66 to (english language and yr="2013 -Current")	86

Table 17: Search terms – Cochrane Library

#	Disease Terms - CRPC	Hits
1	Prostatic Neoplasms/	2881
2	((prostate or prostatic) and (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$ or malignant$)).mp.	6146
3	1 or 2	6146
4	((hormone$ or castrat$ or androgen) and (refract$ or resist$ or independent)).mp.	4545
5	Hormone-refractory.mp.	259
6	Hormone-resistant.mp.	71
7	Hormone-independent.mp.	10
8	Androgen-independent.mp.	89
9	Androgen-resistant.mp.	3
10	Castration-resistant.mp.	380

11	Castrate-resistant.mp.	85
12	or/4-11	4545
13	3 and 12	1009
14	(CRPC or HRPC or AIPC).mp.	313
15	or/13-14	1024
16	alpharadin.mp.	6
17	radium 223.mp.	43
18	xofigo.mp.	1
19	223Ra.mp.	0
20	223Ra chloride.mp.	0
21	radium ra 223 chloride.mp.	0
22	(bay 88 8223 or bay88 8223).mp.	0
23	or/16-22	45
24	15 and 23	43
25	limit 24 to english language [Limit not valid in CDSR,CLCMR; records were retained]	43
26	limit 25 to yr="2013 -Current"	28

Table 18 : CRPC Clinical search terms – Supplementary PubMed search

#	Term	Hits
1	(castration resistant prostate cancer OR hormone refractory prostate cancer) AND (abiraterone OR alpharadin OR radium-223) date limits: Aug2015-Jan2016	96

APPENDIX 4

Clinical parameters and variables

Methodology

To capture the long-term cost-utility of radium-223 dichloride for the treatment of metastatic CRPC and bone metastasis, a survival-analysis based on patient-level-data from the ALSYMPCA trial was performed (7).

In line with the model structure, the main endpoints of the revised survival analysis are the following where death is considered an event rather than censored data, as requested by the Appraisal Committee:

- Alkaline phosphatase-free survival (ALP-FS)
- Symptomatic skeletal related events-free survival (SSE-FS)

Extrapolation of the ALSYMPCA trial OS, ALP-FS and SSE-FS data for the duration of the trial period and beyond was evaluated using five different parametric models: Weibull, exponential, log-logistic, Gompertz and log normal. The selection of the most appropriate extrapolation method was based on Akaike's Information Criteria (AIC) and Bayesian Information Criterion (BIC) for each parametric distribution method. The AIC and BIC are criteria for selecting a model based on goodness of fit. Both can be described as a measure of fit, based on the likelihood function, with a complexity penalty. It is this complexity penalty that differs between the two, as well as some underlying assumptions. AIC's complexity penalty is an increasing function of the number of estimated parameters. BIC's complexity penalty is an increasing function of the number of estimated parameters and sample size. Which criterion to choose depends on the context, although both can be reported. When using these criteria for model section, one should choose the model with the lowest value (24). The extrapolations begin from the start of the trial period and continue beyond the end of the trial period.

Overall survival

The overall survival Kaplan-Meier curve from ALSYMPCA trial the no prior docetaxel population is shown in Figure 5. Median OS was 16.1 months with radium 223 compared to 11.5 months with placebo. *Please note that in figures below rtrt=1 refers to radium treatment while rtrt=2 refers to placebo.*

Figure 5. Kaplan Meier estimates of overall survival probability in ALSYMPCA trial (no prior docetaxel population)

Table 19 indicates that the log-logistic model provides the lowest AIC and BIC for Radium 223 OS, and the log normal gives the minimum AIC and BIC for placebo OS. Due to the different shapes of different parametric models, the same parametric model type should be chosen for the two treatment arms (24). In order to use the AIC and BIC whilst keeping the same parametric model in both arms, the sum of the AICs and BICs across the two treatment arms was used to inform the parametric model choice. The sum of the AICs and BICs, respectively, supports the use of the log normal extrapolation. For the base case analysis, the log normal extrapolation of the data was selected for the OS curves for both treatment arms.

Table 19. AICs and BICs for different parametric models for overall survival probability extrapolation (no prior docetaxel population)

	Placebo		Radium		Combination	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[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]

The extrapolations of the ALSYMPCA Kaplan-Meier curves for OS over the full time horizon are shown for radium 223 and placebo for the best fit parametric model. The base case scenario (log normal model) is shown in Figure 6.

Figure 6. Log normal model for overall survival – no prior docetaxel population (compared to the ALSYMPCA Kaplan-Meier data)

ALP Progression Free Survival (ALP-FS)

The ALP progression-free survival KM curves from the ALSYMPCA docetaxel naive population is shown in Figure 7. For the no prior docetaxel population, median ALP FS was [redacted] months in the radium 223 arm and [redacted] months in the placebo arm.

Please note that in figures below rtrt=1 refers to radium treatment while rtrt=2 refers to placebo.

Figure 7. Kaplan Meier estimates of ALP progression free survival in ALSYMPCA trial (no prior docetaxel population)

As seen in Table 20 the log normal model provides the lowest AIC and BIC for Radium 223 ALP-FS, and the log-logistic gives the minimum AIC and BIC for placebo ALP-FS. Due to the different shapes of different parametric models, the same parametric model type should be chosen for the two treatment arms (25). In order to use the AIC and BIC whilst keeping the same parametric model in both arms, the sum of the AICs and BICs across the two treatment arms was used to inform the parametric model choice. The sum of the AICs and BICs, respectively, supports the use of the log normal extrapolation. For the base case analysis, the log normal extrapolation of the data was selected.

Table 20. AICs and BICs for different parametric models for ALP free survival extrapolation (no prior docetaxel)

	Placebo		Radium		Combination	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[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]

The extrapolations of the ALSYMPCA Kaplan-Meier curves for ALP FS over the full time horizon are shown for radium 223 and placebo for the best fit parametric model. The base case scenario (log normal model) is shown in Figure 8.

Figure 8. Log normal model for ALP progression free survival – no prior docetaxel population (compared to the ALSYMPCA Kaplan-Meier data)

SSE Free Survival (SSE-FS)

The SSE free survival KM curves from ALSYMPCA for the docetaxel naive population is shown in Figure 9. The median SSE FS was [redacted] months in the radium 223 arm and [redacted] months in the placebo arm. *Please note that in figures below rtrt=1 refers to radium treatment while rtrt=2 refers to placebo.*

Figure 9. Kaplan Meier estimates of SSE free survival in ALSYMPCA trial (no prior docetaxel population)

As seen in Table 21 the Weibull model provides the lowest AIC and BIC for Radium 223 SSE-FS, and the log-logistic gives the minimum AIC and BIC for placebo SSE-FS. Due to the different shapes of different parametric models, the same parametric model type should be chosen for the two treatment arms (25). In order to use the AIC and BIC whilst keeping the same parametric model in both arms, the sum of the AICs and BICs across the two treatment arms was used to inform the parametric model choice. The sum of the AICs and BICs, respectively, supports the use of the log-logistic extrapolation. However, the base case results include log normal as the best fitted model for extrapolation for both arms and all endpoints. A scenario analysis was carried out using log-logistic extrapolation model for SSE FS for both arms. Results are reported in section 2.9, Table 10.

Table 21. AICs and BICs for different parametric models for SSE free survival extrapolation (no prior docetaxel population)

	Placebo		Radium		Combination	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[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]

The extrapolations of the ALSYMPCA Kaplan-Meier curves for SSE-FS (over the full time horizon are shown for radium-223 and placebo for the best fitted parametric model (i.e. log-logistic) and the base case model (i.e. log-normal) (Figure 10).

Figure 10. Log normal and log-logistic models for SSE free survival – no prior docetaxel population (compared to the ALSYMPCA Kaplan-Meier data)

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Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA376 - Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted] submitting on behalf of:

Name of your organisation: NCRI-ACP-RCP

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA376 - Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The decision to approve radium-223 for men with prior docetaxel is very welcome.

The recommendation to deny radium-223 to men without prior docetaxel is not. The conclusion reached seems extraordinary, given that the pivotal trial of radium-223, ALSYMPCA, included men both with and without prior docetaxel. Furthermore, the efficacy and safety of radium-223 was not different between these two groups.

Around one half of men with CRPC never receive docetaxel because they are considered unfit for it. This is reasonable given that the average age of death from prostate cancer is over 80 years of age. It seems most unfair to deny such men access to radium-223, a drug proven to improve survival and quality of life, when it is available to younger, fitter men.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology

be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA376 - Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA376 - Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission

TA376 - Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]
Name of your organisation: Prostate Cancer UK
Your position in the organisation: Head of Policy, Knowledge and Impact
Brief description of the organisation: Prostate Cancer UK is the UK's leading charity for men with prostate cancer and prostate problems. We support men and provide information, find answers through funding research and lead change to raise awareness and improve care. The charity is committed to ensuring the voice of people affected by prostate disease is at the heart of all we do.

Prostate Cancer UK has a policy that funding from pharmaceutical and medical device companies will not exceed 5% of its total annual income. During the financial year 2014/2015 donations from such organisations, expressed as a percentage of our total annual income, were less than 0.1%. We outline the specifics of this spend in appendix A.

Our submission is focused on the use of radium-223 dichloride for men with advanced hormone-relapsed prostate cancer and symptomatic bone metastases who have *not* had docetaxel chemotherapy. This is because radium-223 dichloride has already been recommended as an option for treating men with this stage of the disease who have had prior docetaxel.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Pain is a common problem for men with advanced prostate cancer, but the most common cause is when the cancer has spread to the bones.

Men tell us the bone pain is a very specific feeling, with some describing it as feeling similar to a toothache but in the bones, or like a dull aching or stabbing.

The pain men experience as a consequence of bone metastases can also be a symptom of a more serious condition called metastatic spinal cord compression (MSCC). This happens when prostate cancer cells spread to the bones of the spine and press on the spinal cord. This can cause problems with how the nerves in the spinal cord carry messages to the rest of the body. This can cause a range of symptoms which can get worse if left untreated. For example, it can make men less able to walk and move around, in some instances leading to paralysis.

It can also cause any of the following symptoms (1,2):

- Pain or soreness in the lower, middle or upper back or neck which is severe or different from usual pain. The pain might get worse when men cough, sneeze, lift or strain, or go to the toilet. It might get worse when they are lying down and it might wake them at night or stop them from sleeping.
- A narrow band of pain around the abdomen or chest which can move towards the lower back, buttocks or legs.
- Pain that moves down the arms or legs.

- Weakness in the arms or legs, or difficulty standing or walking. Men may also feel unsteady on their feet or feel like their legs are giving way. Some men say they feel clumsy.
- Persistent numbness or pins and needles in the legs, arms, fingers, toes, buttocks, stomach area or chest.
- Problems controlling their bladder or bowel. Men might be unable to empty their bladder or bowel, or might become incontinent.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Treatments that can extend life and improve quality of life are of greatest importance to men living with prostate cancer and their loved ones (3).

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

The majority of currently available treatments aim at eradicating or limiting metastases or palliating the side-effects. A number of treatment options for bone metastases are noted in clinical guidelines, including external beam radiotherapy, bisphosphonates and strontium-89 and radium-223 (from April 2013 to September 2015, 1170 men accessed radium-223 dichloride via the Cancer Drugs Fund [CDF] (4–6)). Radium-223 is currently the only radiopharmaceutical that offers a survival benefit for men with hormone-relapsed prostate cancer and symptomatic bone metastases(7,8).

Additionally, as radium-223 dichloride can be used in patients with hormone-relapsed prostate cancer and symptomatic bone metastases irrespective of their previous therapy, we believe it is difficult to identify appropriate, relevant comparators. We believe this lack of comparator also applies because radium-223 dichloride operates differently to all other treatment options available for advanced prostate cancer and therefore should be applicable when a patient becomes resistant to all or any of these.

Published evidence shows that the side-effects associated with radium-223 dichloride are mild and may be more acceptable to patients than the high toxicity that can be associated with chemotherapy (9).

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health

- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

It is unfortunate that evidence of clinical benefit has not been collected from patients who have been accessing radium-223 dichloride before docetaxel via the CDF. This evidence would have addressed the Committee's uncertainties in relation to whether the 4.6 months overall survival gain experienced by patients in the Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial who had prior docetaxel (10) could be generalised for the population in UK clinical practice for whom docetaxel is contraindicated or unsuitable.

To redress the failure to use CDF data in this way this treatment should receive a conditional approval. It would be unacceptable for men who decline to receive docetaxel or are not fit enough to receive it to be denied a treatment whose use prior to docetaxel produces a median overall survival benefit of 4.6 months (16.1 vs 11.5 with placebo) (compared to 3.1 months [14.4 vs 11.3 with placebo] in the subgroup of patients that received previous docetaxel) (10) simply because some of the patients in the ALSYMPCA trial did not have docetaxel because it was not available locally at the time of the trial.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Radium-223 dichloride provides an additional 5.8 months to their first symptomatic skeletal related event in comparison to the best standard care (BSC) available at the time of the trial (9). Delaying the time to a skeletal event can increase the time that a man can remain active and reduce the burden on carers.

Radium-223 dichloride can also reduce the risk of spinal cord compression and pathological fractures, which can result in high morbidity. It also provides an overall survival benefit that other treatments do not.

As mentioned above, published evidence shows that the side-effects associated with radium-223 dichloride are mild and may be more acceptable to patients than the high toxicity that can be associated with chemotherapy (9)

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

None

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)

- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

We have not collected this information and refer instead to the side-effects associated with current treatments, which include:

- Flu-like symptoms, nausea, vomiting, appetite loss, increased pain, jaw and kidney problems (bisphosphonates)
- Effects on bone marrow, which might change the way that blood clots and increase risk of infection and anaemia. Men may also get a fever, chills, bruising, bleeding or tiredness (strontium-89).
- Sickness, diarrhoea, tiredness, skin coloration (external beam therapy)

Please list any concerns patients or carers have about the treatment being appraised.

Radium-223 dichloride does not cause much damage to the surrounding healthy cells, so it doesn't usually cause side effects. If side effects do materialise they are mild and include feeling and being sick, diarrhoea and low levels of blood cells, which means patients might bleed more easily. These side effects are negligible compared to those resulting from chemotherapy.

From our survey of 309 men and family/friends, (11) the following was reported when asked how they felt about the side effects of radium-223 dichloride:

- No concerns: 53 (24%)
- Concerned, but no more than for any other standard treatment: 162 (73%)
- Very concerned, would consider carefully before trying this treatment: 6 (3%)

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

The ALSYMPCA study revealed that men with hormone-resistant prostate cancer and bone metastases who had either chosen not to have chemotherapy, been unsuitable for it or had difficulty accessing it recorded a slightly higher overall survival benefit than men at the same stage of the disease who had received docetaxel (4.6 months and 3.1 months, respectively) (10).

We therefore believe that any man who is unsuitable for or chooses not to have docetaxel should be able to access this treatment. This should not just be limited to patients genuinely unable to have docetaxel (unsuitable or contraindicated). Limiting treatment access in this way removes a valuable treatment option from those men experiencing symptomatic bone metastasis, simply because they prefer to avoid chemotherapy. It leaves them to rely instead on treatments for symptomatic bone metastases that are only eradicating, limiting or palliating their side-effects.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Only those men that do not have hormone-resistant prostate cancer and bone metastases.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☒ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

We do not believe that evidence for the use of radium-223 dichloride in the chemotherapy naïve setting has been fully taken into account.

For some men, chemotherapy is not an option, either because they are too frail, have other conditions that prevent its use, or decline it.

At least 20-40% of patients with incurable, advanced prostate cancer and bone metastases never receive chemotherapy (9). Radium-223 dichloride, therefore, addresses an important unmet need in this population, which is not served by current therapies.

Not only was this indication included in the ALSYMPCA trial, but a pre-specified docetaxel subgroup analysis for the ALSYMPCA trial showed that radium-223 dichloride significantly prolonged overall survival compared with placebo in patients with hormone-relapsed prostate cancer and symptomatic bone metastases, irrespective of previous docetaxel use (10).

Furthermore, the approved indication within the marketing authorisation of radium-223 dichloride is not restricted to use after chemotherapy (12). Neither does the National CDF approved criteria for radium-223 dichloride specify the sequential use of chemotherapy and radium-223 dichloride (13).

The Scottish Medicines Consortium approved radium-223 dichloride for use in patients both before and after chemotherapy in September 2015, finding it both clinically beneficial and cost effective. Restricting access to radium-223 dichloride before chemotherapy in England (and potentially Wales) will create unacceptable treatment access variation across the UK and will also see Scotland's standard of care become more advanced than in England. This

has the potential to limit further clinical trials on treatments for hormone resistant prostate cancer and bone metastases in England.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

The clinical trials have shown radium-223 dichloride to be of clinical benefit to men prior to docetaxel, not simply because it was unsuitable or contraindicated, but because they failed to get access. While access issues may not be as prevalent now, there will still be some men who choose not to have chemotherapy and as such, we believe that they have the potential to equate to men who could not access it.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

No

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☒ Yes ☐ No

If yes, please provide references to the relevant studies.

Prostate Cancer UK-conducted research on patient experience of radium-223 dichloride:

Prostate Cancer UK. A survey of the public's views on Xofigo® (radium-223 dichloride) becoming a treatment option for men with advanced prostate cancer. Total sample size was 308 Scottish adults which included men with prostate cancer and friends/family of men with prostate cancer. Fieldwork was undertaken between 12th and 31st May 2015. The survey was carried out online. 2015.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Radium-223 dichloride could be a significant treatment for black men who have a higher than average risk of developing prostate cancer (1 in 4) than white men (1 in 8) (14).

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment to be innovative?

☒ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Radium-223 dichloride is an innovative mechanism to target cancer cells in more than one area of bone, directly treating those areas and reducing pain. There is no comparator, because there is no other hormone-resistant prostate cancer and bone metastases treatment that is similar to calcium and can be absorbed by active bone cells. This means it can specifically target bone cancer cells which, as cancer cells are more active than normal bone cells, are more likely to pick up the radium-223 dichloride.

Once it is in the bones it releases the radiation. The radiation only travels a short distance, between 2 and 10 cells deep. This is much less than a millimetre. This means that the cancer cells receive a high dose of radiation and some of them die. And healthy cells receive only a low dose or no radiation. So this treatment causes few side effects.

On this basis, we believe that radium-223 dichloride offers a therapeutic advancement, which also provides a survival benefit and has the potential to be used at various stages of the pathway.

Are there any other issues that you would like the Appraisal Committee to consider?

No

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Metastatic prostate cancer that no longer responds to hormone therapy can be an extremely painful and debilitating condition. Men with this condition are often bed-ridden and unable to perform day-to-day activities, which has a knock on effect on their family/carers' abilities to do the same.
- Men with this condition face an extremely limited range of treatment options to extend their lives and ease the symptoms of advanced disease, especially in the chemotherapy naïve setting.

- At least 20% to 40% of men with incurable, advanced prostate cancer and bone metastases never receive chemotherapy. Radium-223 dichloride should be approved in line with the full remit of its licence to allow patients to access before or after chemotherapy, depending on their circumstances
- The ALSYMPCA trial demonstrated an average 3.6 months overall survival benefit with radium-223 dichloride compared to placebo. Life extension is extremely important to patients and their families as is quality of life, which the delay to first skeletal event provided by this treatment provides.
- Men with prostate cancer, and those closest to them, have told us they will find it extremely distressing if NICE rejects radium-223 dichloride. Knowing that they are being denied a medicine via routine NHS funding that could benefit them will add significantly to the distress and uncertainty they are already experiencing as a result of the nature of their, or their loved one's, disease.
- If the Committee remains concerned about evidence of this treatment's efficacy in men with hormone-relapsed prostate cancer and bone metastases who had not previously had docetaxel, then radium-223 dichloride should receive a conditional approval so that the failure to collect data from patients who have been accessing radium-223 dichloride before docetaxel via the CDF can be redressed.

Appendix A: Pharmaceutical Funding in the past three years:

2013
Prostate Cancer UK received £2,700 from Janssen, for employee FR and matched funding; Gift in kind from Astellas of some unwanted benefits from a sponsorship of a Leicester Tigers player, e.g. signed shirt and match programme advertisement, worth £2,000 approx.; £1,000 +VAT from Lilly for an exhibition stand at a PCUK masterclass in March 2013

2014
Prostate Cancer UK received £19,000 +VAT from Lilly for breakfast symposia sponsorship at the 2014-15 health professionals masterclass series; £1,000 + VAT from Ipsen for stand sponsorship at October Dundee health professional masterclass; £400 + VAT from Pajunk for stand sponsorship at Prostate Cancer UK/ College of Radiographers conference; £2,000 approx. value from Astellas for a non cash gift in kind unrequired benefits of their sponsorship of a Leicester Tigers player

2015
Prostate Cancer UK received £50 approx. value from Astellas for a non cash gift in kind of a signed rugby shirt; £500 from Pfizer as unsolicited employee fundraising donation.

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11. Prostate Cancer UK. A survey of the public's views on Xofigo® (radium-223 dichloride) becoming a treatment option for men with advanced prostate cancer. Total sample size was 308 Scottish adults which included men with prostate cancer and friends/family of men with prostate cancer. Fieldwork was undertaken between 12th and 31st May 2015. The survey was carried out online. 2015.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission

TA376 - Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Tackle Prostate Cancer

Your position in the organisation: Trustee, Volunteer

Brief description of the organisation: Tackle is the only national patient led organisation for prostate cancer. It has some 80 groups around the country and represents about 10,000 patients and their families. Tackle strives to improve the treatment and raise awareness of prostate cancer. Tackle acquires funding from fundraising events by our members, grants from Trust Funds and a variety of commercial companies, including Pharmaceutical companies.

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Advanced prostate cancer is a condition where much of the time, the patient can live a normal life. However, there is the permanent worry that the currant treatment regime will fail and what comes next.

When it gets to the stage where Radium 223 is required, the patient will be experiencing considerable bone pain, rising PSA levels and possibly be in some distress.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Quality of life. This means a decrease in bone pain and the ability to live as normal a life as possible.

A longer time to spend with family and friends. This could mean seeing children getting married and grandchildren born. A price cannot be put on this.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

There are new and exciting treatments for advanced prostate cancer, all have their advantages and few disadvantages. What treatment the patient receives is largely governed by where he is in the treatment journey. When first line hormone treatment fails, the preferred option should be Enzalutamide or Abiraterone. After this, Cabazitazel has been shown to be highly successful as has Radium 223

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

A decrease in bone pain and a better QoL

An increase in mobility

slows down disease progression

An extension of life span

The knowledge that even though the disease has become very advanced, the patient has not been abandoned.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

There are no other comparable treatments

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

None to my knowledge

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

None to my knowledge

Please list any concerns patients or carers have about the treatment being appraised.

None to my knowledge

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None to my knowledge

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Patients for whom bone pain has become an inhibiting factor in their life

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Patients who have not yet reached the stage where they need Radium 223

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

✓ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Yes

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Clinical Trials have captured what is important to patients. I am not aware of any limitations in how the treatment has been assessed in clinical trials

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

None that I know of.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ✓ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

No

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence

you think would help the Committee to identify and consider such impacts.

No

9. Other issues

Do you consider the treatment to be innovative?

✓ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

There is comparable treatment so it is impossible to make comparisons

Are there any other issues that you would like the Appraisal Committee to consider?

NICE has passed Radium 223 for use within NHS England, but only for patients who have previously received Docetaxel. There are a significant number of patients who for one reason or another do not, or cannot receive Docetaxel. At the moment, these patients are covered by the CDF where it is allowed without Docetaxel being given. Therefore, Radium 223 should be kept on the new CDF as these patients will still be able to benefit from Radium 223

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- The CDF covers the patients who have not received docetaxel and it should be kept on the new CDF
- Radium 223 is an important new method of controlling debilitating bone pain and should be available to all patients who need it.
- Radium 223 is the only treatment of it's kind
- Radium 223 has been shown to be highly successful in combatting bone pain and reducing SREs
- Radium 223 should be available to all patients who would benefit from it.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Reconsideration

Radium-223 dichloride for treating metastatic hormone relapsed prostate cancer with bone metastases (review of TA376)

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation : Consultant Oncologist, University Hospitals Bristol

Executive Member of British Uro-Oncology Group

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? Executive Committee Member of British Uro-oncology Group
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Metastatic prostate cancer patients are treated initially with androgen deprivation therapy (medical or surgical castration); at progression, an anti-androgen is added. At relapse, more than 90% have evidence of bone metastasis, which are a major cause of pain disability, decreased quality of life and treatment costs death. Unlike most other malignancies, death from prostate cancer is due to bone disease and its complications in the majority of patients. None of the current treatments targeting bone metastasis (palliative radiotherapy, bisphosphonates, existing radioisotope therapy, denosumab) improve survival, but can provide effective palliation.

At relapse after second line hormone therapy,the NICE approved options are either Abiraterone or Enzalutamide for patients with a good performance status and there is also the option of docetaxel chemotherapy, which has been shown to provide a survival advantage (Technology Appraisal No. 101). Patients who have progressed after docetaxel chemotherapy can be offered treatment with abiraterone with prednisolone (NICE technology appraisal guidance 259) or enzalutamide provided they have not had either of these prior to docetaxel chemotherapy. A survival advantage in this group of patients was seen compared to prednisolone and placebo. Second line chemotherapy with Cabazitaxel has also been shown to improve survival in a Phase III trial in a similar (but not identical) group of patients who have progressed despite docetaxel chemotherapy and Cabazitaxel chemotherapy after docetaxel chemotherapy now has NICE approval.

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CDF Rapid Reconsideration

At progression after chemotherapy and novel androgen receptor targeted therapies, or if patients are unfit for chemotherapy, best supportive care (including palliative care), further hormonal therapy, clinical trials, and bone directed therapies are used. The management of these patients is palliative and individualised based on the pattern of disease, symptoms, performance status, co-morbid conditions and wishes.

Bone pain due to progressive bone metastasis is often the main problem and the technology is used in this setting in specialist secondary centres. It is not suitable for patients with visceral metastasis; small volume asymptomatic lymph node metastases are acceptable. Radium 223 chloride requires special arrangements for transport, storage, administration and waste disposal because of radiation protection issues, ARSAC licence requirements and environmental agency regulations. Patients require regular medical review during the treatment phase by a clinician experienced in treating patients with hormone relapsed prostate cancer. The treatment is given by a team with experience in administration of intravenous systemic radioisotopes.

Radium 223 chloride has been used in the UK by centres which took part in the ALSYMCA trial and subsequently by many centres which have implemented the post-docetaxel use of Radium 223 and also the use in the patients in whom chemotherapy is inappropriate through access through CDF.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

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Radium 223 chloride should be considered to be primarily an additional treatment option for men with castrate-refractory metastatic prostate cancer with symptomatic bone metastasis. The pivotal ALSYMCA trial has shown an improvement in overall survival in the initial paper of 3.8 months with Radium 223 chloride compared to the standard therapy (supportive care) only. The mean time to the first skeletal related event was 13.5 months in the Radium 223 chloride group vs. 8.4 months in the placebo group. Only symptomatic bone events were registered as event. Radium 223 chloride is very well tolerated and has very limited toxicity; indeed the patients in the control group had more symptoms side effects and a lower QOL, presumable due to progressive disease compared to the treatment group. Haematological toxicity was similar in both groups. The current radioisotope in use, strontium, has significant haematological side effects, mostly in form of low platelet and white blood counts. The patients require routine blood tests, a bone scan and a CT scan of the chest abdomen and pelvis prior to starting treatment. Monitoring requires monthly blood test during the 6 month treatment phase (1 i.v. injection every 4 weeks). Because of the absence of toxicity, treatment with Radium 223 chloride was very acceptable to both patients and the health care team.

During follow up, monitoring of PSA levels or repeated bone scans are of very limited use as patients can remain well and symptom free despite raising PSA level and bone scans may not show any objective response. The best way to measure the benefit of any bone directed intervention in this patient group would be the time to the next therapeutic intervention or death; if patients are not fit enough for further palliative measures, overall survival is normally very limited.

From the provided evidence, all subgroups are likely to benefit more or less than the group as a whole. We believe that patients recruited into the ALSYMCA broadly represent this patient group. The best symptomatic care allowed any therapy deemed appropriate by the treating clinician, similar to routine clinical practice. We have not observed any additional toxicity in the early access program and other reported data from various centres; because patients have less bone pain, they need fewer analgesics and fewer interventions compared to standard supportive care.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

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Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

There are no such issues and as the number of centres offering this treatment is increasing there should be access for all areas in the country to a nearby centre for delivering this treatment.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

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Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The main difficulties arise from the regulatory requirements for treatment with radioactive isotopes. The ARSAC licence arrangements require the documentation of sufficient training to use the Radium 223 chloride for any team member. The application process is straight forward but requires time.
The Environment Agency application needs to be dealt with by the Radiation Protection experts at each hospital site.
As many centres are already delivering this treatment and more centres in the process of starting this service, it is unlikely that this aspect will be a significant factor.
As per NICE guidelines for use of Radium 223 in the post-docetaxel setting is being delivered, therefore delivering this for the patients in whom chemotherapy is inappropriate should follow the same course of delivery and logistics.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Reconsideration

Radium-223 dichloride for treating metastatic hormone relapsed prostate cancer with bone metastases (review of TA376)

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Tackle Prostate Cancer consequently I will not be submitting a personal statement.

Name: ...[redacted].....

Signed: .....

Date: ....10/6/16.....

Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (men who have not received docetaxel and for whom docetaxel is contraindicated or not suitable)

ERG critique of the company submission for re-consideration of current CDF technologies under the new proposed CDF criteria

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

None

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Rider on responsibility for report

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Contribution of authors

Graham Scotland and Rodolfo Hernandez acted as health economists, critiqued and reviewed the updated cost-effectiveness evidence presented in the submission, checked and re-analysed the economic model, and carried out further sensitivity analyses. Clare Robertson acted as the systematic reviewer and critiqued the company's summary of the decision problem and the updated literature review. Cynthia Fraser acted as information scientist and critiqued the methods used for identifying relevant studies in the literature. Graham Scotland acted as project lead for this appraisal and supervised the work throughout the project. All authors contributed to the writing of the report and approved its final version.

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Key to highlighting; [redacted]; [redacted]

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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) for the sub-group of the indicated population of adult men with symptomatic bone metastases and no known visceral metastases, who have not received docetaxel and for whom docetaxel is contraindicated or not suitable.

1.1 Critique of the decision problem in the company submission

The company submission (CS) encompasses an update of the company's original systematic literature review and presents new cost-effectiveness results based on a revised economic model. The company state that their submission presents evidence that addresses the uncertainties previously identified by the Appraisal Committee.

There have been no overall changes to the population, interventions or outcomes being considered in the decision problem. NICE previously issued a positive recommendation for the subgroup of the indicated population that had received prior docetaxel. The current submission focuses on the sub-group of the indicated population who have not received docetaxel and for whom docetaxel is contraindicated or not suitable. The clinical effectiveness data for radium-223 continues to come solely from the ALSYMPCA trial.

The company have compared radium-223 with best supportive care (BSC). The Appraisal Committee previously accepted that "*there is a clinically recognised group for whom radium-223 treatment is suitable, because docetaxel is contraindicated or unsuitable"* and concluded that best supportive care is the most relevant comparator for this group. While the ERG agrees that BSC is the most appropriate comparator for this submission, it notes that the 'no prior docetaxel' participants of the ALSYMPCA trial included people who declined docetaxel or for whom docetaxel was unavailable. The ERG also notes that the effect estimates from the ALSYMPCA trial were obtained from docetaxel naïve people who were both suitable and unsuitable for docetaxel.

The company undertook a project to provide clarity on the definition of the patient population who have not received docetaxel. A round table of six oncologists reached

a consensus agreement on criteria for patient unsuitability for docetaxel (see section 2.3 below).

The Appraisal Committee previously agreed that abiraterone is not an appropriate comparator for people who have not had docetaxel, because the people who would have radium-223 are distinct from those who would be considered for abiraterone. The ERG agrees that abiraterone is not an appropriate comparator for this submission.

1.2 Summary of the company's updated systematic review

The company updated their original systematic literature review of clinical effectiveness to cover the period from 1st January 2013 to 19th January 2016. The company searched for randomised controlled trials (RCTs) and non-randomised controlled studies (NRS) of radium-223 versus best supportive care in adults with mCRPC who have not previously received docetaxel, and who are unsuitable for docetaxel. The updated review inclusion criteria differ from the original criteria to reflect the current considered population and comparator. The ERG believes this is appropriate for the current submission.

The company re-ran the searches undertaken for their original submission and the strategies were reproduced in Appendix 3 of their current submission. The strategies were considered fit for purpose at the time of the original submission. However, since then both MEDLINE and EMBASE have introduced new subject headings specific to castration resistant prostate cancer: Prostatic Neoplasms, Castration-Resistant/ (MEDLINE) and Castration resistant prostate cancer/ (EMBASE). These new and highly relevant terms have not been incorporated into the new searches. Therefore, the ERG has less confidence in the comprehensiveness of this update.

Three conference abstracts were included in the company's updated review. All three of these abstracts report data for the company sponsored ALSYMPCA trial; however, only one (conducted by Cislo et al 2015)[1] presents results separately for the prior and no prior docetaxel subgroups. The company provides a narrative presentation of the included studies and did not conduct any quantitative data synthesis. The abstracts present data on hospital resource use and health related quality of life (HRQOL) by treatment allocation, progression status, and experience of SSEs, but they do not

provide any new data regarding the clinical effectiveness of radium-223. The company use the identified abstracts to support their economic modelling assumptions.

1.3 Summary of the ERG's critique of the company's updated systematic review

The submission appears complete, although the ERG reiterates the concern regarding the comprehensiveness of the search and, therefore, cannot be certain that no eligible reports are missing from inclusion in the updated review. The ERG believes that the methodological quality of the updated systematic review is generally good. It is not possible for the ERG to comment on the methodological quality of the three abstracts included in the updated review due to the limited amount of information available for presentation in a conference abstract. The ERG previously stated that the methodological quality of the main ALSYMPCA trial was good, although the ERG again notes the heterogeneous nature of the no prior docetaxel population sub-group of the trial. The ERG agrees that the company were correct to not attempt any meta-analyses or quantitative data synthesis for the three abstracts included in the updated review.

1.4 Summary of revised cost effectiveness evidence submitted by the company

The company presented a revised cost-effectiveness analysis based on the same five state model used in their previous submissions for NICE TA376. To address concerns previously raised by the appraisal committee in relation to the cost-effectiveness modelling for TA376, the company have:

1. Updated their analysis of progression free and SSE free survival (to inform cohort flow in the model), treating death as an event rather than censored data
2. Applied the Appraisal Committee's preferred assumptions regarding utilities; i.e. changed from utilities derived from the overall ALSYMPCA population to utilities specific to the no prior docetaxel subgroup.
3. Applied the Appraisal Committee's preferred time horizon; i.e. changed from 5 years to 10 years
4. Applied the Appraisal Committee's preferred measure of disease progression; alkaline phosphatase (ALP) progression

5. Explored the impact of including medical resource use data from the ALSYMPCA trial in the base case analysis; data published in abstract form identified from the updated systematic literature review.
6. Applied the Appraisal Committee's preferred costs for skeletal events; estimates obtained from Ford et al[2] and inflated to 2015 values
7. Updated all other unit cost data to 2015 values
8. Presented updated scenario and sensitivity analyses around the inclusion/exclusion of the ALSYMPCA medical resource use data and further areas of uncertainty.

Based on the above changes, the company presented a new base case ICER of £25,963 (with agreed patient access scheme). This is substantially lower compared to the company's previous base case ICER of £40,721. This is primarily due to a reduced incremental cost associated with radium-223; i.e. [redacted] (at ten years) in the revised model compared to [redacted] (at five years) in the company's previous base case. The revision also result a small increase in the QALY gain with radium-223 ([redacted] at ten tears compared to [redacted] at five years in the previous submission). The revised ICER varied from £22,690 to £49,114 in further scenario analyses presented by the company.

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

The ERG assessed the suitability the company's revisions against the preferences of the committee as outlined in the final guidance for TA376. Most appear to be in line with the appraisal committees stated conclusions, apart from the inclusion of additional medical resource use data derived from the ALSYMPCA trial (point 5 above). Prior to the third AC meeting for TA376, the company submitted an additional exploratory analysis for the no prior docetaxel subgroup, where they factored in data on annual hospitalisation days derived from the ALSYMPCA trial. This had suggested that radium-223 was associated with estimated saving was 4.58 hospital days per year in comparison to BSC, equating to a saving of £2,064 in the no prior docetaxel subgroup. However, the committee previously noted very limited information provided in the published abstracts on this data, and concluded that it could not consider it further (TA376, section 4.18).

In the current submission, the company have formally incorporated additional medical resource use data from ALSYMPCA on hospital days (per year), nursing home use (weeks per year), care centre use (days per year), use of home health care services (hours per year), and physician visits (per year) in their model. In parametrising these estimates, the company refer to an unpublished report on the ALSYMPCA trial, which was not made available to the ERG as part of this revised submission. It is therefore unclear whether incorporation of this data leads to double counting of some cost savings already being captured in the model through delayed progression, prevention of SSEs and prolonged survival. In light of the above, the ERG did not feel that the inclusion of this data in the base case analysis was well justified.

To address concerns the committee previously expressed around the calculation of cohort flow in the model – in relation to the approach used to model progression and SSE free survival - the company presented revised time-to-event analyses for these outcomes. Unlike previous submissions, deaths are treated as events rather than censoring events. The ERG believes this updated analysis is now more consistent with the company's approach to calculating cohort flow in the model, but deaths are still treated as censoring events for participants known to have died at least nine weeks after their last ALP assessment date or their last SSE efficacy assessment date. It was stated that this nine week period was chosen because it equated to two assessment cycles plus one week, and it appears to be used because of [redacted]. Although the ERG accept that it [redacted], there is a lack of clear justification for using this particular time period in the censoring assumptions. [redacted] their remains uncertainty over the most appropriate approach to model progression and SSE free survival.

The committee previously expressed uncertainty in relation to the approach taken to extrapolate overall survival in the company's model and concluded that it should consider extrapolations based on both log-normal and Weibull distributions in its decision making. The committee also considered a scenario analysis useful, whereby

the log-normal distribution was used to extrapolate overall survival but with doubling of mortality from 104 weeks. In their revised submission the company have continued to use the log-normal distribution in the base case analysis, but have assessed the impact of the alternative assumptions through sensitivity analysis.

Whilst the committee previously concluded that it was more plausible that utility increments associated with radium-223 would diminish over time, the company have continued to apply these benefits over the lifetime of patients in their base case analysis. However, they have also explored the impact of removing these health state utility increments from different time points in the revised model.

1.6 ERG commentary on the robustness of company's revised economic analysis

In cross checking the company's reported changes to their economic model, the ERG identified a number of bugs and unjustified/undocumented changes as summarised below:

1. A cell referencing error was identified in the estimation of incident disease progression for the purpose of estimated second and subsequent line treatment costs. This was resulting in the overestimation of incident progression in cycle 1 of the model and the incoherent negative risk of progression in cycle 3 of the model.
2. The LHRH agonist dosing frequency had been revised to once every 12 weeks in the radium-223 arm of the model but remained at once every four weeks in the progression free states of the BSC arm. This was resulting in higher LHRH costs in the BSC arm without any justification given.
3. Second line treatment costs were included up to cycle 99 in the placebo arm of the revised model, but were only included over 30 cycles in the radium-223 arm.
4. Cell referencing errors were identified in the estimation of ALP progression free survival in the "Survival analysis – Placebo" and "Survival analysis – R223" worksheets (cell N75 downwards). This was resulting in the modelled progression free survival probabilities jumping 13 cycles forward from cycle 59 onwards in the model.

Whilst cross checking the updates in the revised model, the ERG also identified a bug in the previous model used to support the decision making for TA376. This was present in the calculation of incident progression in the radium-223 arm of the previous models (for the no prior docetaxel subgroup only), and was resulting in ~[redacted] being inappropriately added to second line treatment costs in cycle 29. This bug appears to have been removed in the revised model, which is a key driver for the substantially reduced ICER.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG corrected and amended the identified bugs and unjustified changes in revised model as detailed above. In addition, given the Committee's previous concerns with respect to the inclusion of the additional medical resource use data from ALSYMPCA, the ERG omitted these added costs from their updated base case analysis.

Following these changes, the ERG estimated a new base case ICER of £31,172 for radium-223 versus BSC; corresponding to an incremental cost of [redacted] for an incremental QALY gain of [redacted].

The main driver for the reduction in the incremental cost in the revised model, compared to the previous modelling for TA376, is the correction of the bug in the calculation of second line treatment costs. Correcting this bug in the previous model reduces the incremental cost of radium-223 by [redacted], and reduces the company's previous base case ICER from 40,721 to £31,166.

The increase in the QALY gain in revised analysis, compared to company's previous base case for TA376, is driven primarily by extension of the time horizon from 5 years to 10 years. Updating of the progression free and SSE free survival modelling which also increases the QALY gain for radium-223. The ERG also identified a bug in the implementation of the revised survival analyses in the company's revised model. This was leading to underestimation of the new QALY gain. Correcting this bug increased the new incremental QALY estimate from [redacted].

From the ERG's new base case, the ICER ranged from £27,630 to £56,208 across the further exploratory scenarios considered.

In conclusion, the updated economic modelling results in a substantially improved ICER for radium-223, which appears justified and is driven primarily by the correction of a bug that was present in the previous model, combined with extension of the time horizon of the model from 5 to 10 years. Key points for further consideration relate to the committee's preferred assumptions with respect to inclusion/exclusion of the additional medical resource use data from ALSYMPCA, the extrapolation approach for overall survival, and the modelled duration of incremental utility benefits for radium-223 over BSC.

2 Critique of the company's definition of the decision problem

As indicated by the company, radium-223 dichloride is indicated for men with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases. NICE previously issued a positive recommendation for the subgroup of the indicated population that had received prior docetaxel (NICE TA376). [3]

The submission for reconsideration is made for the sub-group of the indicated population who have not received docetaxel and for whom docetaxel is contraindicated or not suitable. In the appraisal of the full licensed indication for radium-223 (TA 376), the Appraisal Committee concluded that "…radium 223 could not be recommended in this population as the committee believed the most plausible ICER would be in excess of £50,000, and the magnitude of additional weight that would need to be assigned to the QALY benefits in this patient group would be too great for radium-223 to be considered a cost-effective use of NHS resources" (TA376, section 4.26).[3]

In their resubmission, the company report on an update of their original systematic literature review and present new cost-effectiveness results based on a revised economic model. There have been no overall changes to the population, interventions or outcomes being considered in the decision problem. The clinical effectiveness data for radium-223 continues to come from the ALSYMPCA trial.[4, 5]

2.1 Population

The company seek NICE recommendations for the use of radium-223 dichloride for castration resistant prostate cancer (CRPC) in adult men with symptomatic bone metastases and no known visceral metastases, who have not received docetaxel and for whom docetaxel is contraindicated or unsuitable.

2.2 Intervention

The intervention remains radium-223 dichloride, hereafter referred to as radium-223, and is unchanged since the company's last submission.

2.3 Comparators

The company have compared radium-223 with best supportive care (BSC) only. The Appraisal Committee previously accepted that "*there is a clinically recognised group for whom radium-223 treatment is suitable, because docetaxel is contraindicated or unsuitable"* and concluded that best supportive care is the most relevant comparator for this group (NICE TA376, section 4.2). The Appraisal Committee also previously agreed that abiraterone is not a suitable comparator for radium-223 in this population. While the ERG agrees that BSC is the most appropriate comparator for this submission, it notes that the 'no prior docetaxel' participants of the ALSYMPCA trial included people who declined docetaxel or for whom docetaxel was unavailable. The Appraisal Committee agreed that docetaxel may be suitable for these people and that docetaxel would be an appropriate comparator for this group. Although the later population group are not considered in the company's submission (CS), effect estimates from the ALSYMPCA trial were obtained from docetaxel naïve people who were both suitable and unsuitable for docetaxel.

The company undertook a project to provide clarity on the definition of the patient population who have not received docetaxel. A round table of six oncologists reached a consensus agreement on criteria for patient unsuitability for docetaxel. The criteria do not cover the ALSYMPCA 'no prior docetaxel' group who either refused docetaxel or for whom docetaxel was unavailable. The agreed criteria for patient unsuitability for docetaxel are as follows:

1. Patients contra indicated for docetaxel
    a. Hypersensitivity to the active substance or to any of the excipients (polysorbate 80, ethanol anhydrous, citric acid)
    b. Patients with baseline neutrophil count of < 1,500 cells/mm3.
    c. Patients with severe liver impairment
2. Patients with poor performance status defined as:
    a. ECOG 3 or greater in isolation (NICE TA101 states docetaxel should be given only if the man is well enough to care for himself with occasional assistance) or;
    b. ECOG 2 and above with the existence of comorbidities

3. Comorbid patients who have:
    a. A Charlson comorbidity index score of 5 or above
    b. Severe chronic obstructive pulmonary disease (COPD):
        i. Defined as severe by GOLD score >2
    c. Symptomatic heart failure:
        i. Symptomatic defined as class II or greater based on the New York Heart Association (NYHA) functional classification
    d. A history of bowel disease:
        i. Significant inflammatory disease
        ii. Resection
        iii. Previous perforation
        iv. Existence/history of fistulas
        v. Sub-acute obstructions
    e. Peripheral neuropathy
        i. Defined as grade 2 or above (WHO, ECOG)
    f. A low white blood cell count (or any increased risk of infection):
        i. Neutrophil <1.5
    g. Platelet <100
    h. Ongoing treatment with immunosuppressant therapy (for any condition)
    i. Recurrent sepsis
    j. Ongoing treatment for tuberculosis
    k. Recurrent pancreatitis
    l. Poor liver function (severe liver function is contraindicated see point 1):
        i. Defined as Child Pugh score 3
    m. Poorly controlled diabetes
    n. Poor peripheral circulation
        i. Evidenced via the existence of skin ulcers
    o. Splenectomy with prophylactic antibiotics
4. Patients whose cognition and or social support will result in:
    a. Non-compliance with the treatment regimen
    b. Inadequate toxicity monitoring
    c. Inability to understand treatment fully and provide informed consent.

The Appraisal Committee previously agreed that abiraterone is not an appropriate comparator for people who have not had docetaxel because the people who would have radium-223 are distinct from those who would be considered for abiraterone. This is because the marketing authorisation for abiraterone in this setting is for people with asymptomatic or mildly symptomatic disease in whom chemotherapy is not yet clinically indicated; the marketing authorisation for radium-223 is for people with symptomatic disease. The ERG agrees that abiraterone is not an appropriate comparator for this submission.

2.4 Outcomes

The outcomes reconsidered by the manufacturer in relation to this new submission include: overall survival; alkaline phosphatase progression-free survival (ALP-FS); symptomatic skeletal related events free survival (SSE-FS); health-related quality of life, health state costs, and medical resource usage based on data from the ALSYMPCA trial.

2.5 Other relevant factors

The company proposes no changes to the existing patient access scheme for radium-223. For the no prior docetaxel subgroup, the committee previously agreed that the end-of-life criteria of short life expectancy, extension to life and small population size had all been met.

3 Critique of the company's updated systematic literature review

3.1 Critique of the methods of review(s)

The company have updated their original systematic literature review of clinical effectiveness to cover the period from 1st January 2013 to 19th January 2016. The company searched for randomised controlled trials (RCTs) and non-randomised controlled studies (NRS) of radium-223 versus best supportive care in adults with CRPC who have not previously received docetaxel, and who are unsuitable for docetaxel.

3.1.1 Searches

The company re-ran their searches which were undertaken for the original submission and the strategies are reproduced in Appendix 3 of their current submission. MEDLINE, MEDLINE In Process, EMBASE and The Cochrane Library were searched from February 2013 using the OIVD platform. A supplementary search of the PubMed database was also completed for the last six-months in order to identify studies currently only available online as e-publications.

The strategies were considered fit for purpose at the time of the original submission. However since then both MEDLINE and EMBASE have introduced new subject headings specific to castration resistant prostate cancer: Prostatic Neoplasms, Castration-Resistant/ (MEDLINE) and Castration resistant prostate cancer/ (EMBASE). These new and highly relevant terms have not been incorporated into the new searches. Therefore, there is less confidence in the comprehensiveness of this update.

3.1.2 Inclusion criteria

The eligibility criteria used in the systematic review of clinical effectiveness were given in Table 13 on page 31 of the CS. The updated inclusion criteria differ from the original criteria to reflect the current considered population and comparator. The ERG believes this is appropriate. The company have also added single centre uncontrolled case series studies to their updated exclusion criteria for study design. The company justifies this by stating that, while a number of single centre uncontrolled case series

were identified, they do not add materially to the understanding of the benefits of radium-223 and were, therefore, not considered in the CS.

3.1.3 Summary of identified studies

After reasonable exclusions, the CS states that three relevant conference abstracts were included in the updated review. All three of these abstracts report data for the company sponsored ALSYMPCA trial. For convenience, Figure 4 from the CS has been reproduced below in Figure 1 to show the number of studies included and excluded at each stage of the updated review. The ERG notes their previous concern regarding the comprehensiveness of the search strategies and, therefore, cannot be certain that no eligible reports are missing from inclusion in the updated review.

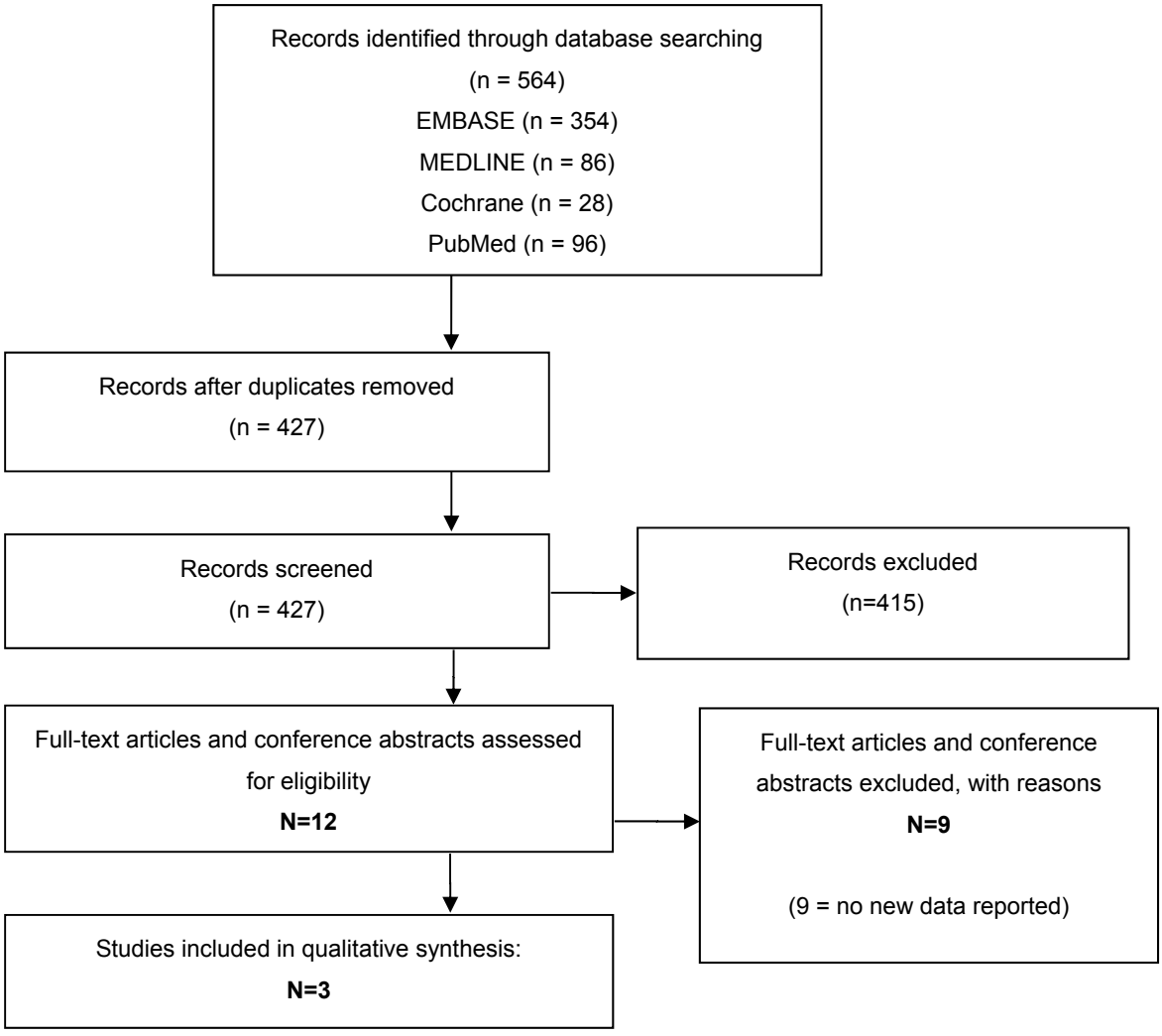

Figure 1 Flow diagram of studies included in the company's updated systematic review

The CS states that "a number of single centre uncontrolled case series were found." The CS also states that these studies, while indicating the increasing use of radium-223 in practice, do not add materially to the understanding of its benefits and were, therefore, not included in the review. The CS does not state how many of these studies were identified.

Of the 12 studies selected for full text assessment, nine were excluded as they did not report any new data since the time of the last clinical effectiveness review. Three conference abstracts were identified as being eligible for inclusion in the updated review.[1, 6 7] The three abstracts all present results for the ALSYMPCA population; however, only one[1] presents results separately for the prior and no prior docetaxel subgroups. The company provided a narrative presentation of the included studies. The company did not conduct any quantitative data synthesis. The abstracts present data on hospital resource use and health related quality of life (HRQOL) but do not provide any new data regarding the clinical effectiveness of radium-223.

The first of two abstracts by Cislo et al[1] evaluated whether health care resource utilisation associated with radium-223 treatment is consistent regardless of prior docetaxel exposure. Results indicated that radium-223 treatment resulted in reduced resource use compared with placebo, regardless of prior docetaxel exposure. Prior docetaxel patients experienced 8.0 fewer hospital days per patient year compared with 4.6 few days per patient year in the no prior docetaxel patient group, driven by a reduction in the number of hospitalisations and shorter length of hospital stay. The abstract does not state how many patients were included in the analysis or the length of outcome follow-up.

The second abstract by Cislo et al[6] describes a post hoc analysis of ALSYMPCA EQ-5D based utility scores, using treatment, disease progression and symptomatic skeletal events (SSEs) as predictors. Linear regression models were used to estimate least-squares mean utility scores for each disease state. Results indicated that the radium-223 treatment group had higher utility scores compared with the placebo group when patients were in a stable disease state and prior to experiencing an SSE, regardless of whether disease progression was defined as alkaline phosphatase (ALP) stable (0.62 v 0.55, p=0.038) or as prostate specific antigen (PSA) stable (0.61 v 0.45, p=0.0001).

There was no statistically significant difference between the radium-223 and placebo treatment groups for patients with stable disease post SSE, or for patients with progressive disease (pre and post SSE).

The final included study is an abstract by Donga et al,[7] which evaluated health state utilities for mCRPC patients with and without SSEs. The EQ-5D data were collected alongside the ALSYMPCA trial and utilities were derived using a published US-population based algorithm based on the time trade-off (TTO) technique. Assessments administered prior to an SSE were included in the 'No SSE health state' and assessments administered on or after an SSE were included in the 'SSE health state.' Results indicated that mCRPC patients who have not experienced an SSE have statistically significant higher HRQOL than patients who have experienced an SSE (0.718 v 0.617, 95% CI: -0.1101, -0.08553, $p<0.0001$). For both health states, mean unadjusted utility scores were higher in the radium-223 group than the placebo group but differences were not statistically significant (No SSE: 0.731 v 0.721, SSE: 0.644 v 0.616; $p>0.05$ for both comparisons).

3.1.4 Quality assessment

The ERG performed a quality assessment of the manufacturer's updated systematic review using the York Centre for Reviews and Dissemination (CRD) criteria (Table 1). The quality of the systematic review was generally good, although the ERG reiterates its concern regarding the comprehensiveness of the search strategies.

Table 1 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 Revised cost-effectiveness analysis

4.1 Summary and critique of the company's revised economic model

The company have submitted a revised economic model and have detailed several changes to inputs and assumptions since the previous assessment (TA376).[3] The focus of the revised modelling is the subgroup in whom radium-223 was not previously recommended; those who had not previously received docetaxel and for whom docetaxel is contraindicated or not suitable.

The five-state model structure is essentially unchanged from the previous assessment, but the model has been stripped of subgroups and measures of progression not relevant to this submission. In addition, the survival analyses at the core of the model have been revised and the corresponding worksheets rebuilt. As a result, some of the cell references have changed in the model. The company have not clearly stated their starting ICER prior to implementing their changes, and have not provided clear documentation and cell references for all changes made to the model. In addition, none of the company's scenario analyses were programmed into the model that the ERG received.

In summary, the company highlight the following key changes to their previous base case analysis, which generated an ICER of £40,721 in the no prior docetaxel subgroup (at five years) when submitted as additional evidence in March 2015 prior to the final AC meeting for TA376:[3]

1. Abiraterone has been excluded as a comparator in this subgroup, and radium-223 is compared only with best supportive care.
2. Disease progression for comparison with BSC is based on alkaline phosphatase (ALP) progression.
3. A 10 y time horizon is adopted to be in line with the NICE reference case, although the approach to extrapolation of overall survival has remained unchanged in the updated base case analysis.
4. Point estimates of the health state utilities, by treatment arm, are taken from the no prior docetaxel subgroup in the ALSYMPCA trial, and applied in the model.

5. The ALP progression free and symptomatic skeletal related events (SSE) free survival analyses have been updated, to inform the cohort flow through the model.
6. The company have updated the source of costs for SSEs, and taken these from the previously published MTA on Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours.[2, 3]
7. All other costs in the model have been updated to 2015 values
8. Additional data on medical resource use, by treatment arm in the ALSYMPCA trial, have been incorporated in the model.

Points 1-4 above directly address the Committee's preferences as stated in the final guidance document for radium-223.[3] Point 5 represents a new analysis to address concerns the Committee had about the cohort flow in the previous model (section 4.14 and section 4.26 of the published guidance TA376), as a result of death being treated as a censored event rather than an event in the determination of progression-free survival. The updated survival analysis is discussed in more detail below (section 4.1.1). Point 6 addresses a comment made by the ERG in the previous assessment, that the costs of pathological fractures applied by the company were substantially lower than those used in the NICE MTA on Denosumb for the prevention of skeletal-related events in adults with bone metastases from solid tumours.[2, 8] In the revised model, the company have updated their costs for all SSEs based on this published report. Point 8 above relates to the incorporation of data, by treatment arm, on medical resource use collected alongside the ALSYMPCA trial.[1, 5] The potential impact of this data on the ICER for radium-223 was previously considered at the third appraisal Committee meeting for TA376, but was not formally incorporated in the economic model. The Committee previously noted very limited information provided in the published abstracts on this data, and concluded that it could not consider it further (TA376, section 4.18).[3] Points 6, 7 and 8 are discussed in more detail in section 4.1.2 below.

Over and above the issues addressed above, the appraisal Committee had previously expressed some further concerns. Whilst these are not reflected in the company's updated base case analysis, the impact of most has been addressed in new scenario analyses:

1. The Committee previously discussed uncertainties relating to the approach for extrapolating overall survival in the model (TA376, section 4.13),[3] and concluded that extrapolations based on both log-normal and Weibull functions should be considered in its decision making. The impact of doubling the mortality risk from 2 years, when using the log-normal distribution for extrapolation, was also considered informative at previous Committee meetings. In response to these concerns the company have continued to use the log-normal distribution to model OS in the base case, but have assessed the impact of the other approaches in sensitivity analysis.
2. The Committee also previously concluded that the utility increments associated with radium-223 over standard care would most likely diminish over time rather than remain over the lifetime of patients, and this has not been included in the company's updated base case analysis (TA376, section 4.16).[3] Its impact has however been assessed through sensitivity analysis.
3. In relation to the costing assumptions applied in the economic model, the Committee previously expressed concerns with respect to the assumption that there would be no wastage of radium-223 (TA376, sections 4.19 and 4.20).[3] Whilst the company has not changed this assumption in the revised economic model, they do provide some further justification for assuming zero wastage. The Committee also previously noted the ERGs point in relation to truncation of incident ALP progression (at 30 weeks) for the purpose of estimating costs of second line treatment in the model used to inform its decision making (TA377, section 4.14).[3] This is discussed in more detail below (section 4.1.2).

4.1.1 Revised survival analysis to inform cohort flow

Summary of key issues previously considered by the Committee

The Committee previously discussed the parametric distributions used by the company to model overall survival. The committee noted that while a log-normal distribution seemed to fit the data best (according to AIC and BIC), 5-year survival predicted by the Weibull function was more in line with the expectations of clinical

experts (TA376, section 4.13).[3] The Committee concluded that log-normal and Weibull distributions should be considered in its decision making. The company had also reported, as an additional analysis prior to the third appraisal Committee meeting, results using the log-normal distribution for extrapolation but with a doubling of the weekly mortality rate from 156 weeks (3 years). The Committee noted that only 1 person remained at risk at 3 years in the trial data, and so concluded that the ERG approach of doubling the risk of mortality after 2 years was more reasonable (TA376, section 4.13).[3]

The Committee also previously discussed the cohort flow calculations in the model in relation to the approach used to assess and model ALP progression free and SSE free survival (TA376, section 4.14).[3] The company disagreed with the ERGs approach to correcting the cohort flow calculations, as per the formulae described in Figure 27 of the company's original submission (June 2013), but accepted that there were missing data that made it difficult to assess disease progression in the trial. Uncertainty regarding the most appropriate cohort flow calculations was exacerbated by the shorter follow-up period for progression compared to OS in the ALSYMPCA trial, and the subsequent treatment of death as a censoring event rather than an event in the company's analysis of progression free and SSE free survival. The ERGs understanding at the time was that death had been treated as a censoring event in the survival analysis and that the company had essentially modelled time to progression conditional on survival rather than progression free survival. However, this was complicated

[redacted]. In response to clarification during the initial appraisal, the company noted that:

[redacted]

[redacted]

The Committee previously agreed that the calculation of the cohort flow was an important issue and "*while there was uncertainty in the most appropriate approach, the Committee noted the significant effect on the ICER when applying the company's formula to model cohort flow*".

The company's revised survival analysis

In the current submission the company have presented revised time-to-event analyses for both ALP progression and symptomatic skeletal-related events (SSE). Unlike previous submissions deaths are treated as events, rather than censoring events, in the primary analyses. The ERG believes this updated analysis is more consistent with the company's approach to calculating the cohort flow in the model, but deaths are still treated as censoring events for participants known to have died at least nine weeks after their last ALP assessment date or their last SSE efficacy assessment date. It was stated that this nine week period was chosen because it equated to two assessment cycles plus one week in duration and it appears to be used because [redacted].

Although the ERG accepted that it may be misleading to treat deaths as events [redacted], there is a lack of clear justification for using this particular time period in the censoring assumptions

As in previous submissions, the company have fitted various curves to the overall survival data and the revised progression-free survival and SSE-free survival data. The sum of the AIC and BIC across the two treatment arms was used to inform the model choice. Based on this the log normal extrapolation was chosen for the overall survival and ALP progression-free survival models. The log-logistic model appeared best for SSE-free survival, but for consistency the log normal was also used in the base case analysis, with log-logistic explored in a scenario analysis. It should be noted that the OS extrapolation model is essentially unchanged from the previous submissions, although it appears to have been updated using time to death measured in days rather than weeks as in the previous model.

Figures 2a) and 2b) below show the updated Kaplan-Meier (KM) data together with Log-normal and Weibull functions fitted to the revised data. Whilst on visual inspection the fitted curves seem reasonable for the Radium-223 arm (Figure 2a), the fit appears somewhat less satisfactory for the placebo arm (Figure 2b). For example, the KM curve in the placebo arm appears to start flattening off beyond 20 weeks after an initial steep decline. The parametric curves then fall below the KM curve towards the tail of the distribution. This could be the result of heterogeneity in the cohort that has not been captured in the approach to survival modelling, with a sub-group of individuals progressing relatively quickly (within the first 20 to 30 weeks) and the remainder progressing more slowly. An alternative piecewise approach to survival analysis could have been considered, with the KM data being used to estimate progression up to 20 or 30 weeks, and parametric curves fitted to the tail ends of the KM data for purposes of extrapolation. However, the observed flattening off the KM data may also be influenced [redacted] in the ALSYMPCA trial. This feature of the trial design remains a problem for estimating PFS, and so any extrapolations based on curves fitted to progression data remain uncertain.

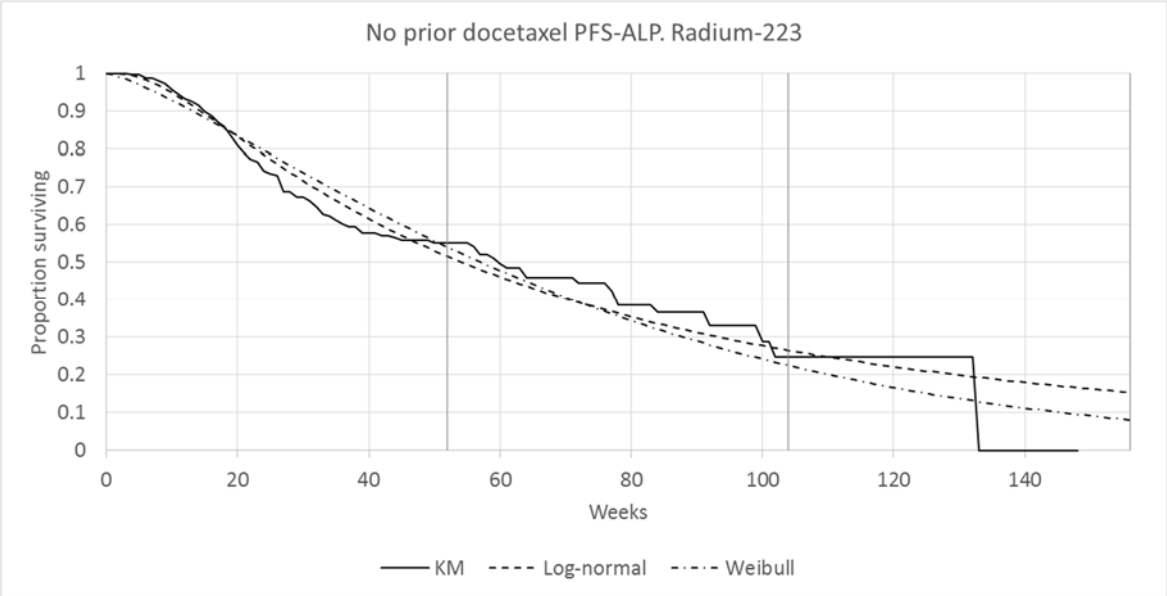

Figure 2a ALP progression free survival (radium-223); Kaplan Maier (KM) estimates and fitted curves

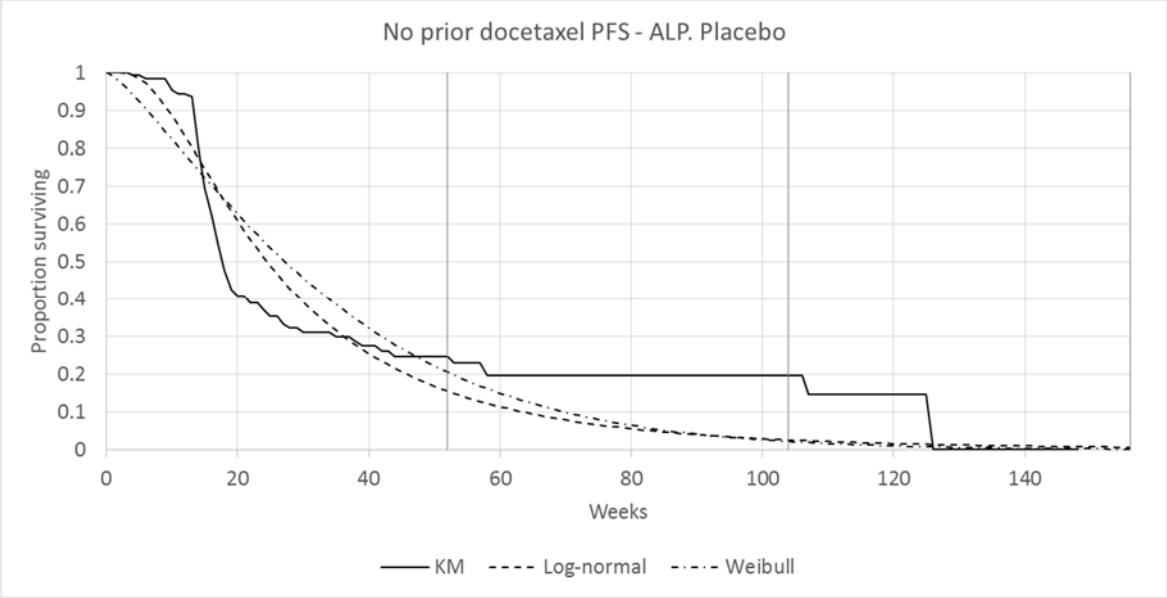

Figure 2b ALP progression free survival (placebo); Kaplan Maier (KM) estimates and fitted curves

It should be noted that when cross checking the implementation of the company's revised survival modelling in the updated model, a cell referencing error was identified in the "Survival analysis – Placebo" and "Survival analysis – R223" worksheets (cell N75 downwards). This was resulting in the modelled progression free survival probabilities jumping 13 cycles forward from cycle 59 onwards in the model.

4.1.2 Revised costs

Summary of key issues previously considered by the Committee

In the previous assessment, the company included Drug costs, administration costs, routine patient management costs, second and subsequent line treatment costs, SSE costs, adverse event costs and end of life costs in their economic model.

Prior to the third AC meeting, the company submitted an additional exploratory analysis for the no prior docetaxel group, where they factored in data on medical resource use collected in the ALSYMPCA trial, which was presented at the annual conference for the American Society of Clinical Oncology 2015.[9] (This suggested that radium-223 was associated with 6.56 fewer hospital days per year, resulting in downstream cost saving of £2,955 (at £450.61 per day). The ERG considered this

evidence and noted that the 6.56 reduction in hospital days related to whole cohort, rather than the no prior docetaxel subgroup where the estimated saving was 4.58 hospital days per year (£2,064). The Committee discussed this additional medical resource use data at the third appraisal Committee meeting, but noted that there was very little information included in the abstract upon which it was based. It also noted that NICE and the ERG had previously requested that the company provide the ALSYMPCA resource-use data and that the company had stated that it would not be helpful for the purposes of economic modelling because the data collected were protocol-driven rather than representing clinical practice. As a result the Committee concluded that "it could not consider these data further" (TA376, section 4.18).[3]

Potential wastage of radium-223 was another costing issue previously discussed by the Committee. The Committee previously established that the company had assumed zero wastage, and the company justified this on the grounds that treatment for each patient would be ordered based on their weight, and prepared in advance. However, the Committee remained concerned that wastage could occur if *"a patient did not attend for treatment, particularly given co-morbidities and potential difficulties in getting to specialist centres"* (TA376, section 4.19).[3] The Committee concluded that "*there was added uncertainty in the assumptions about waste, but it agreed that the true costs of treatment waste were difficult to estimate. It also concluded that incorporating waste into the comparison of radium-223 with best supportive care would worsen the cost-effectiveness estimates for that comparison, although the magnitude of the impact is unknown."*

The company's revised costing assumptions

In their revised submission, the company have now formally incorporated the additional medical resource use data from the ALSYMPCA trial in their base case analysis, and assessed the impact of removing it in scenario analysis. In addition, they have updated all unit cost data to 2015 prices, and updating the costs of SSEs.[2] The ERG have also identified a number of further changes relating to cost-calculations in the updated model that have not been specifically documented or justified in the CS (details below).

Incorporation of MRU data from ALSYMPCA

To support their incorporation of costs associated medical resource use from the ALSYMPCA trial, the company referenced two published abstracts. [1, 5] One which presented costs in the UK setting. However, they refer to a more detailed unpublished report to parameterise the model. The ERG did not have access to this unpublished report, and little descriptive details were provided in the CS or the published abstracts. In parametrising the additional medical resource use in the model, the company have incorporated estimates of hospital days (per year), nursing home use (weeks per year), care centre use (days per year), use of home health care services (hours per year), and physician visits (per year) in their model. Appropriate unit costs are applied to these resource use parameters. Point estimates (with assigned distributions) have been incorporated by treatment arm, SSE status and ALP progression status (see Tables 2 and 3 of the CS). Without having access to the detailed report on the methods for informing these estimates, it is difficult for the ERG to assess potential for double counting of costs already included in the model. It is possible, for example, that reductions in costs observed in the ALSYPMCA data reflect reductions in hospital admissions and end of life care associated with delayed progression, prevention of SSEs and extension of life. These are already being captured in the economic model. It is worth noting that when physician costs based on ALSYMPCA data are included in the updated model, physician visits are correspondingly factored out of the ongoing patient management costs. There do not appear to be any adjustments made to the other cost components (management of SSEs, AEs, end of life care) in the model when the ALSYMPCA resource use data are incorporated. Given the lack of methodological details provided for this data, and the Committee's previous conclusions, the ERG do not feel its incorporation in the base case analysis is well justified.

Updated costs of SSEs

The company have revised the costs applied to SSEs in their updated model, using estimates from the previous report on denosumab for the treatment of bone metastases from solid tumours.[2] The ERG had previously suggested this as a more suitable source of cost data for pathological fractures, which appeared low in the company's previous submissions. The company have now based their costs for all SSEs on this

report. This leads to substantial changes in the costs attached to certain events, in particular spinal cord compression and radiation to the bone (Table 2).

Table 2 Updated costs used for SSEs in the company's economic model, compared with previous values based on single NHS reference costs

Event	CSR equivalent definition	Cost (based on Ford et al., inflated to 2015 prices).[2]	Weighted values used	Previous value based on NHS Ref costs.
Veterbral fracture	Pathological fracture	£299.94	**£956.43**	**£233.00**
Non-vertebral fracture		£1,612.92		
Radiation to the bone	External beam radiation	£675.36	**£675.36**	**£98.05**
Surgery to the bone	Surgical intervention	£7,415.75	**£7,415.75**	**£6,721**
Spinal cord compression	Spinal cord compression	£7,458.59	**£7,458.59**	**£817**

Having reviewed the original NHS reference costs used by the company and the report by Ford et al.,[2] the reasons for the differences are as follows. For pathological fracture, the company previously based their cost for hospital admitted care on the weighted average of reference costs for complex to minor pain procedures - AB02Z to AB06Z (£2,451.70) - but assumed only 7% of pathological fractures would require hospitalisation, with the remainder requiring only an outpatient appointment (£66). Ford et al.[2] estimated overall treatment costs, including follow-up, of £1,581 for non-vertebral fractures and £294 for vertebral fractures using different reference costs (HD39 Pathological fractures) and different proportions requiring hospitalisation. It is these latter two costs that the company have now inflated to 2015 prices, and have then taken the average to estimate the updated cost of a pathological fracture (£956). The substantial changes in the costs applied for radiation to the bone are driven by the inclusion of a preparatory visit, multiple treatment visits and follow-up visits by Ford et al.[2] For spinal cord compression, the large difference is driven by the use of different reference costs that appear to map more appropriately to the condition

(HC02-HC08; Extradural/Intradural Spine Major), and the inclusion of excess bed days and rehabilitation costs in the estimates by Ford et al. Having reviewed the assumptions behind each approach, the ERG believe the estimates of Ford et al. better reflect the full health care resource use associated with these skeletal events. Their combined application in the company's revised model, compared with the old values, serves to reduce the ICER by ~£3,000 in favour of radium-223. However, it should be noted that by combining these changes with the inclusion of further MRU data from ALSYMPCA, there may be increased potential for double counting of hospital and outpatient costs associated with SSEs.

Updating of unit costs to 2015 values

The company has also updated all the model unit cost inputs from 2013 to 2015 values. This was done by resourcing each unit cost input from the updated NHS reference costs, Unit Costs of Health and Social care, or BNF.[10-12] The ERG cross checked the new values with the previous ones and double checked a few values that had changed substantially in the updated model. It is apparent that as well as updating to 2015 unit costs, that the company has revised the currency codes for several of the adverse events without documenting and justifying this in their re-submission. However, substituting in the old for the new values has little impact on the ICER in the revised model. The company also provided updated unit costs for use of day care centres, home health care services, nursing home care, and hospital days for combining with their estimates of medical resource use data collected alongside ALSYMPCA. These unit costs were sourced from the PSSRU and NHS reference costs, and were not in use in the previous model based on ALP progression.

Further justification for assuming zero wastage

The company continues to assume zero wastage of radium-223 in their revised economic model. As justification for this, they note that "*when a patient is unable to attend because they are too ill or have died, and the hospital is unable to use the dose of radium-223 for another patient, Bayer refunds the hospital for the 'wasted' dose.*" They also note that that from their records there were only 2 cases in 2015 of hospitals being issued credits for patients not receiving their dose, and state that this "d*emonstrates that this is not a widespread issue*". However, this data may not capture possible missed doses where hospitals have not applied for rebates.

Further undocumented changes and errors

In addition to changes identified above, the ERG noted a further undocumented change to the frequency of LHRH agonist administration (from once every four weeks to once every 12 weeks), which is included in non-treatment specific management costs for stable and progressed disease in the model. There was a note in the revised model indicating that this change is in line with the recommended dosing frequency for the product in question. However, the update was only applied to the radium-223 arm for the stable disease states, resulting in an unjustified difference in LHRH costs between the Radium-223 and BSC arms.

The ERG also note that for purposes of estimating costs of second line treatments (applied based on cycle specific risks of incident progression), the company have estimated incident progression up to 99 weeks in the BSC arm whilst truncating this at week 30 in the radium-223 arm of the model. This is not justified in the CS, and appears to bias the model in favour of radium-223.

In updating the Kaplan Maier data for ALP progression, the company also appear to have corrected an error (possibly inadvertently) that seems to have gone undetected in the previous versions of the model[1]. The ERG identified this when cross checking the new model against the previous model. In the calculations used to estimate cycle specific incidence of progression in the old model (worksheet "NoDTX - PFS ALP", cells BA44 to BF44), the incorrect row of Kaplan Maier data was being selected from a corresponding lookup table, resulting in an implausible probability of progression (2.53) being generated in cycle 29 in the radium arm of the model. This then resulted in ~[redacted] in second line treatment costs being inappropriately added for radium-223 in the previous analyses for the no prior decetaxel subgroup. The correction of this bug in the new model substantially reduces the incremental cost associated with radium-223 – which in turn contributes to the substantially reduced ICER. That said, in implementing the revised PFS estimates in the new model, a further minor cell referencing error occurred in Cell L107 of the "NoDTX - PFS ALP" worksheet. This

[1] Model "ID576_Radium_223_Company_model_utility_changes_18032015_LF_(ACIC).xlsm" company model submitted prior to the 3rd AC meeting in March 2015, sheet "NoDTX - PFS ALP" cells BA44:BF44.

bug results in overestimation of incident progression in cycle 1 of the model and an incoherent negative risk of progression in cycle 3 of the revised model.

4.1.3 Revised utility weights

Summary of key issues previously considered by the Committee

The discussions around utility weights during the original appraisal focussed on two key issues: the health state utility values used in the Company model and the duration of any utility increment assumed for Radium-223 once treatment has ended.

The Committee noted that in the previous submissions the Company had used treatment arm specific utilities for some states, and estimates pooled across study arms for other states - depending on whether differences between arms were statistically significant or not (TA376, section 4.15).[3] The Committee agreed with the ERG view that the point estimates per trial arm should be used for all states in the base case analysis. In addition, the Committee agreed with the ERG that utility estimates for the no-prior-docetaxel subgroup should correspond to those derived from the same subgroup in the ALSYMPCA trial.

The Committee also considered the company's assumption of a lifetime quality of life benefit from radium-223 unlikely. However, it also considered that the duration of the benefit may extend for longer than the treatment period of 24 weeks. The Committee then concluded that "*although the quality of life benefit with radium-223 compared with best supportive care could extend beyond 24 weeks, the duration of this benefit is uncertain, but would likely diminish over time and could not be assumed to extend over the person's lifetime*" (TA376, section 4.16).[3]

The company's revised utility assumptions

The Company's revised base case analysis has applied utility point estimates according to study arm as requested by the Committee. The utility values used are reported in Table 1 of the CS, and are the same as those previously discussed and preferred by the Committee.

The company's updated base case analysis retains the health state quality of life benefits for radium-223 over BSC for the full 10 year time horizon of the model. As

further justification for assuming lifetime health state utility benefits for radium-223 over standard care, the company reiterate the findings of their utility analysis underpinning the original submission:

"*The Bayer position is that the evidence demonstrates that radium-223 treatment maintains quality of life better than BSC and the quality of life benefit for the on-treatment period was comparable to the benefit for the off-treatment time period. Given that off-treatment EQ-5D QoL measurements were made up to 132 weeks after baseline and the average time associated with the EQ-5D QoL measurements was 47.8 weeks after baseline, there is sufficient evidence to believe the QoL benefit extends well into the off-treatment period. Furthermore, the magnitude of benefit in the off-treatment period has been found to be comparable to that observed during the on-treatment period*."

However, despite their stated position, the company has conducted scenario analysis exploring the impact on the ICER of equalising health state utility weights between arms beyond 24, 52, 104, 156, 208, 260, 312, 364, 416 and 468 weeks.

Of some relevance to this issue is the identified abstract by Cislo et al.[6] which sought to determine the effect of treatment (radium-223 or placebo), disease progression and symptomatic skeletal events (SSE) on EQ-5D-based utility scores for CRPC disease states. As summarised in the CS, Cislo et al used linear regression models to estimate mean utility scores for each disease state by treatment arm. Results showed that patients in radium-223 treatment group had higher utility scores compared to the placebo group while in stable disease and prior to an SSE regardless of how disease progression was defined (0.62 vs 0.55, p=0.038 in ALP-stable disease, 0.61 vs 0.45, p=0.0001 in PSA-stable disease). Post-SSE however there was little difference in HRQoL between the two groups. The study highlighted alkaline phosphatase and SSEs as more accurate markers of CRPC progression than prostate-specific antigen. Whilst this helps to justify a treatment related utility benefit for radium-223, it does not particularly help to inform the likely duration of such a benefit.

4.1.4 The company's revised cost-effectiveness results

The company's revised base case analysis

The company presented the revised results below using the NHS list price (Table 3) and also the confidential patient access scheme price (Table 4).

Table 3 New base-case cost-effectiveness results using the NHS list price from the published technology appraisal (no prior docetaxel population)

	Radium-223	**Best Supportive care**
Drug cost (£)	[redacted]	0
Administration costs (£)	1,196	0
Patient management costs (£)	[redacted]	[redacted]
Total MRU costs(£)	[redacted]	[redacted]
Hospitalisations(£)	[redacted]	[redacted]
Nursing Home Use (£)	[redacted]	[redacted]
Day Care Centre Use (£)	[redacted]	[redacted]
Home Health Care Services Use (£)	[redacted]	[redacted]
Physician Visits (£)	[redacted]	[redacted]
Second & subsequent lines of treatment (£)	[redacted]	[redacted]
End of Life care (£)	[redacted]	[redacted]
SSEs costs (£)	[redacted]	[redacted]
AE Costs (£)	[redacted]	[redacted]
Total costs(£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	-
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	-
ICER (£)	[redacted]	-

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 4 New base-case cost-effectiveness results using the PAS price (no prior docetaxel population)

	Radium-223	Best Supportive care
Drug cost (£)	[redacted]	0
Administration costs (£)	1,196	0
Patient management costs (£)	[redacted]	[redacted]
Total MRU costs(£)	[redacted]	[redacted]
Hospitalisations(£)	[redacted]	[redacted]
Nursing Home Use (£)	[redacted]	[redacted]
Day Care Centre Use (£)	[redacted]	[redacted]
Home Health Care Services Use (£)	[redacted]	[redacted]
Physician Visits (£)	[redacted]	[redacted]
Second & subsequent lines of treatment (£)	[redacted]	[redacted]
End of Life care (£)	[redacted]	[redacted]
SSEs costs (£)	[redacted]	[redacted]
AE Costs (£)	[redacted]	[redacted]
Total costs(£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	**25,963**	**-**

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

The striking feature of the updated results is the substantially reduced incremental cost of redium-223 in comparison with BSC. In the company's previous with PAS base case, the total incremental cost was [redacted] at 5 years. With the described revisions this is reduced to [redacted] at 10 years. The key driver of this is the change in second line treatment costs, which are now [redacted] lower in the radium-223 arm

compared to the output generated by the company's previous model. As outlined above (section 4.1.2), this appears primarily due to the removal of a bug in the calculations of cycle specific incident progression in the radium-223 arm of the model, which was resulting in > being inappropriately added to second line treatment costs in cycle 29 of the previous version of the model. As a consequence of this change, radium-223 is now associated with a net saving in second line treatment costs of , where it was previously associated with an increment of .

A further influence on the reduced incremental cost is the incorporation of additional medical resource use data from ALSYMPCA, which generates an additional net saving of in favour of radium-223. In addition, when incorporating the medical resource use data from ALSYMPCA, physician visit costs are factored out of the patient management costs, which increase the net saving in patient management costs associated with radium-223 to ; the corresponding patient management cost saving is only if the ALSYPCA physician visit data are not included in the updated model.

There is also a small increase in the QALY gains in the company's updated model; at ten years compared with the company's previous base case estimate of at 5 years. The incorporation of utility point estimates specific to the no prior docetaxel group (in accordance with the committee's preferences) actually reduces the QALY gain compared to using the overall population utilities, so the increased QALY gain in the new model is a consequence of the extended time horizon in combination with the updated progression free survival analysis informing the cohort flow.

The Company's revised scenario analyses

To address further concerns previously raised by the Committee, the company have provided updated scenario analyses to assess the impact of: doubling mortality beyond 104 weeks (while using the log-normal distribution to model overall survival); removing the utility benefit for radium-223 from selected time points; fitting Weibull curves to OS PFS and SSE free survival; fitting a log-logistic curve to SSE free survival; reducing the time horizon to 5 years; altering utility inputs; excluding medical resource use costs from ALSYMPCA; and combinations of the above changes. Results are replicated in Table 5 below. The ICER for radium-223 ranged

from £22,690 to £49,144 across the scenarios. The ERG cross checked these and were able to replicated all the results except for those involving the doubling of mortality beyond 104 weeks. The scenario analyses were not switchable in the updated model provided by the company, and when the ERG programmed the doubling of mortality as implemented in the company's previous model ("ID576_Radium_223_Company_model_accelerated_fail_18032015_LF_(ACIC).xlsm), the ICER came to £31,485 rather than £33,710 as reported by the company. For the scenario involving the doubling of mortality combined with the removal of medical resource use costs and removal of the utility benefit for radium-223 beyond 52 weeks, the ERG produced an ICER of £41,759 rather than £42,319.

Table 5 Scenario analysis (PAS price; no prior docetaxel population)

Scenario	**ICER**
Base-case	*£25,963*
Mortality doubles after 104 weeks	£33,710
Radium utility benefit lasts up to 24 weeks	£32,150
Radium utility benefit lasts up to 52 weeks	£29,357
Radium utility benefit lasts up to 104 weeks	£27,891
Radium utility benefit lasts up to 156 weeks	£27,217
Radium utility benefit lasts up to 208 weeks	£26,805
Radium utility benefit lasts up to 260 weeks	£26,532
Radium utility benefit lasts up to 312 weeks	£26,341
Radium utility benefit lasts up to 364 weeks	£26,204
Radium utility benefit lasts up to 416 weeks	£26,101
Radium utility benefit lasts up to 468 weeks	£26,023
Weibull curves fitted to OS, PFS and SSE	£39,580
Log-logistic curves fitted to SSE	£25,953
Time horizon of 5 years (260 weeks)	£29,365
Pooled utility point estimates	£28,908
Overall population utilities	£22,690
No medical resource use (MRU) costs	£29,156
Combined scenario (no MRU, mortality doubles after 104 weeks and radium utility benefit lasts up to 52 weeks)	£42,319

Combined scenario (no MRU, Weibull curves fitted to all endpoints and radium utility benefit lasts up to 52 weeks)	£49,114

The Company's revised probabilistic analyses

The company provided an revised probabilistic analysis based on 1000 iterations, and reported a base case ICER similar to the deterministic result; £26,268 per QALY gained with radium-223 versus BSC. The company also presented the incremental cost-effectiveness scatter plot and CEAC for radium-223 (see Figures 1 and 2 of the company's resubmission). Probabilities of cost-effectiveness at given ceiling ratios were not reported, but from rerunning the company's PSA the ERG found these to be: 36.1%, 60.4%, and 87.2% at thresholds of £20,000, £30,000 and £50,000 per QALY gained respectively.

4.1.5 Validation of the company's revised model

The ERG reviewed the company's described changes and cross checked the new model against the previous models submitted prior to the third appraisal committee meeting for TA376. This highlighted a number of errors in the previous and updated models. When implementing the all described changes to the old model, and correcting the identified bugs during the process, the ERG were able to reconcile the QALY estimates of the two models. The key driver of the increased QALY gain associated with radium-223 in the revised model is the extended time horizon. The updated approach to progression and SSE free survival analysis also modestly increases the QALY gain ([redacted]) in comparison with the survival analysis assumptions used in the previous model; i.e. when applying the committee's preferred utilities specific to the no prior docetaxel subgroup, the updated approach to progression free survival analysis slightly reduces the total QALYs in the BSC arm while slightly increasing total QALYs in the radium-223 arm.

There was insufficient time to fully trace the impact of applying all the cost updates to the old model. However, the key driver of the reduced incremental cost associated radium-223 is the correction of the bug in the calculations of second line treatment costs which was present in the company's previous models for the no prior docetaxel subgroup. Further updates to the cost of SSEs and the incorporation of additional

medical resource use data from the ALSYMPCA trial contribute further to the reduced incremental cost.

4.1.6 Exploratory analysis undertaken by the ERG

Following review of the company's revised economic model, the ERG corrected the identified errors in the company's implementation of their described changes. These were amended as follows:

1. The bug in the formula used to estimate cumulative failures from the radium-223 Kaplan Maier data was corrected in worksheet "NoDTX - PFS ALP", by cutting the formula in cell L108 and then pasting it in cell L107 and copying it down to the end of the data range. This removed the overestimation of incident progression in cycle 1 of the model and the incoherent negative risk of progression in cycle 3 of the model. The impact on the ICER was very minor.
2. The asymmetric updating of the LHRH agonist dosing frequency was corrected by updating the dosing frequency in the BSC arm (to once every 12 weeks) to match the updated dosing frequency in the radium-223 arm. This had a more substantial impact on the ICER, increasing it by ~£5,000.
3. Second line treatment costs were included over 99 cycles in the radium-223 arm as they were in the placebo arm. This was done by changing cell BA10 in the "NoDTX - PFS ALP" worksheet to 99 (to match the value in cell AS10). When implementing this change, the ERG also noted cell referencing errors in the formulae used to estimate the cycle specific incidence of progression from cycle 53 onwards. These errors were corrected in Cells BA68:BE155. For the same calculations, errors in the cycle count were identified and corrected from cycle 92 onwards in both the BSC and radium-223 arms (cells AR107 and AZ107 downwards ("NoDTX - PFS ALP" worksheet)).
4. Cell referencing errors for the ALP PFS lookup in the "Survival analysis – Placebo" and "Survival analysis – R223" worksheets (cell N75 downwards) were corrected, to pick up the correct cycle specific progression free survival probabilities from the "NoDTX – PFS ALP" worksheet.

In addition to the above, and given the Committee's previous concerns with respect to the inclusion of the additional medical resource use data from ALSYMPCA, the ERG omitted these added costs from their updated base case analysis. The impact of adding

them back in was assessed through sensitivity analysis. The results of the ERGs updated base case analysis (with PAS) are provided in Tables 6 and 7. Compared with the company results, the combined ERG updates increase the ICER by £5,209.

Table 6 New base-case cost-effectiveness results using the PAS price (no prior docetaxel population)

	Radium-223	**Best Supportive care**
Drug cost (£)	[redacted]	
Administration costs (£)	1,196	
Patient management costs (£)	[redacted]	[redacted]
Total MRU costs(£)	[redacted]	[redacted]
Hospitalisations(£)	[redacted]	[redacted]
Nursing Home Use (£)	[redacted]	[redacted]
Day Care Centre Use (£)	[redacted]	[redacted]
Home Health Care Services Use (£)	[redacted]	[redacted]
Physician Visits (£)	[redacted]	[redacted]
Second & subsequent lines of treatment (£)	[redacted]	[redacted]
End of Life care (£)	[redacted]	[redacted]
SSEs costs (£)	[redacted]	[redacted]
AE Costs (£)	[redacted]	[redacted]
Total costs(£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	
LYG	[redacted]	[redacted]
LYG difference	[redacted]	
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	
ICER (£)	**31,172**	

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[redacted]Table 7 ERG base-case incremental results using the PAS price, no prior docetaxel population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Radium-223	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**31,172**
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A

[redacted]

The ERG updated scenario analysis results

The ERG reran the company's scenario analyses using their modified model (Table 8). The estimated ICERs for radium-223 ranged from £27,630 to £56,208. In addition, the ERG conducted a further scenario analysis to assess the impact of the change in approach to progression free and SSE free survival modelling. Implementing the previous approach to survival modelling in the revised model has a limited effect on the ICER, increasing it to £33,817.

Table 8 Scenario analysis (PAS price; no prior docetaxel population)

Scenario	ICER (£)
Base-case	***31,172***
Mortality doubles after 104 weeks	39,337*
Radium utility benefit lasts up to 24 weeks	40,895
Radium utility benefit lasts up to 52 weeks	37,309
Radium utility benefit lasts up to 104 weeks	34,438
Radium utility benefit lasts up to 156 weeks	33,149
Radium utility benefit lasts up to 208 weeks	32,439
Radium utility benefit lasts up to 260 weeks	32,000
Radium utility benefit lasts up to 312 weeks	31,709
Radium utility benefit lasts up to 364 weeks	31,507
Radium utility benefit lasts up to 416 weeks	31,362
Radium utility benefit lasts up to 468 weeks	31,254
Weibull curves fitted to OS, PFS and SSE	46,940
Log-logistic curves fitted to SSE	31,183
Time horizon of 5 years (260 weeks)	35,982
Pooled utility point estimates	#
Overall population utilities	27,630
Medical resource use (MRU) costs added	27,968
Combined scenario (no MRU, mortality doubles after 104 weeks and radium utility benefit lasts up to 52 weeks)	47,870*
Combined scenario (no MRU, Weibull curves fitted to all endpoints and radium utility benefit lasts up to 52 weeks)	56,208
Implement PFS and SSE free survival as per the previous model informing TA376 (ERG added scenario)	33,817

Notes; * Increases mortality from 104 weeks as per the formula previously used by the company in TA376 (the company appear to have applied a different unspecified formula in their updated analysis); # it is not clear to the ERG which utility values the company used for this analysis, and so it this scenario analysis has not been updated.

The ERG revised probabilistic analysis

The results of the probabilistic analysis, with the ERG's implemented changes, are presented in Table 9 and Figures 3 and 4. Based on 1000 probabilistic iteration, radium-223 has a 13.4%, 45.7% and 79.7% chance of being considered cost-effective at willingness to pay thresholds of £20,000, £30,000 and £50,000 per QALY gained respectively.

Table 9 ERG base-case probabilistic results using the PAS price, no prior docetaxel population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Radium-223	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,553
Best supportive care	[redacted]	[redacted]	[redacted]	-	-	-	-

[redacted]

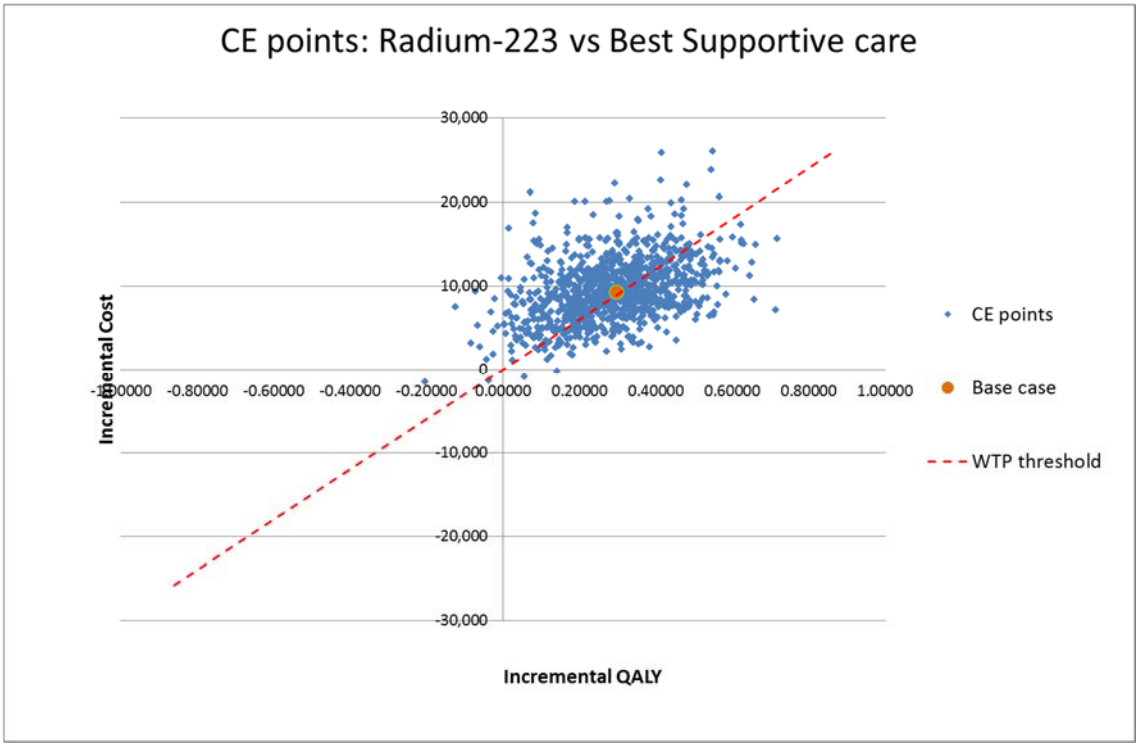

Figure 3 Incremental cost-effectiveness scatter plot (PAS price; no prior docetaxel population)

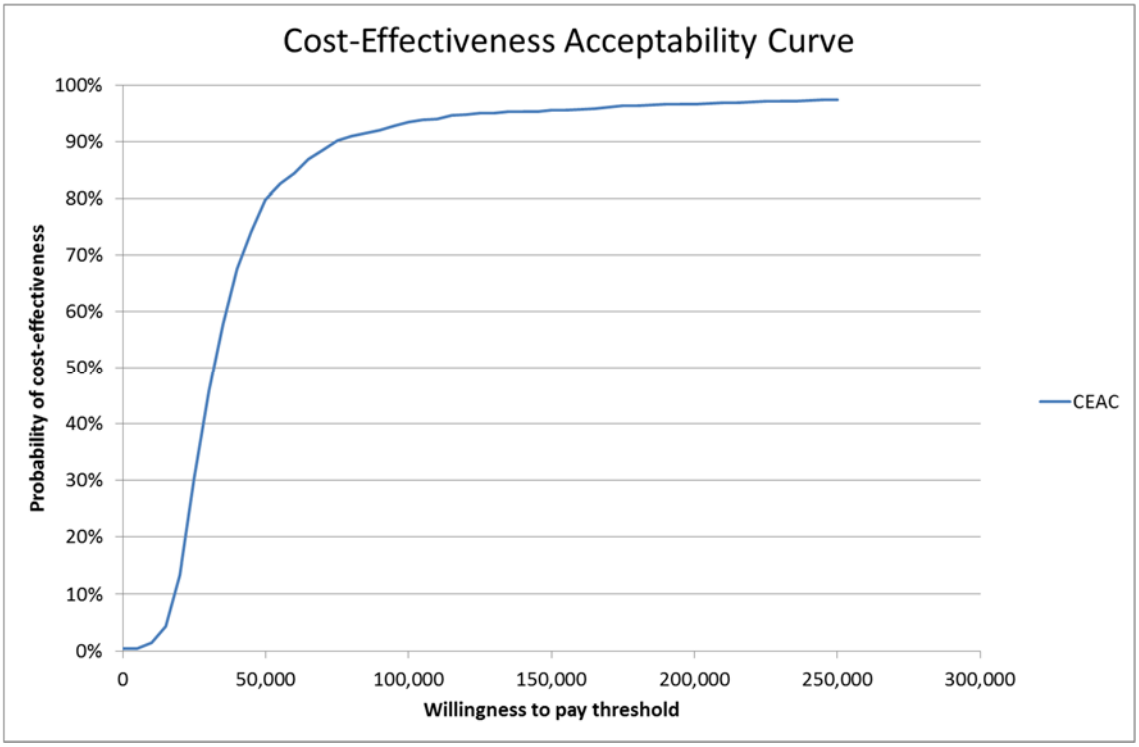

Figure 4 Cost-effectiveness acceptability curve (PAS price; no prior docetaxel population)

5 Conclusions

The company have provided a revised submission, detailing an update to their systematic literature review and several revisions to their cost-effectiveness model. The searches and update of the literature review seem generally appropriate, although the ERG were unable to conduct new searches to cross check the company's findings in the time available.

The updated cost-effectiveness modelling results in a substantially reduced ICER of £25,963 in comparison with the company's previous base case estimate of £40,721 and the committee's most plausible estimate (>£50,000). The reduced ICER compared to the previous assessment is driven by a reduction in the incremental cost associated with radium-223 (from [redacted] under the company's previous base case (at five years), to [redacted] (at ten years) in the revised submission), and a small increase in the QALY gain (from [redacted]). The main drivers for the reduction in the incremental cost are:

- Correction of a bug in the calculations of second line treatment costs that appears to have been present in the modelling conducted for TA376; correcting this bug in the previous model reduces the incremental cost of radium-223 by [redacted], which reduces the company's previous base case ICER by ~£9,555 (£40,721 to £31,166).
- Incorporation of additional medical resource use data from the ALSYMPCA trial, which generates a further net saving of [redacted] for radium-223, plus an accompanying increase in patient management cost savings of [redacted] (total net saving [redacted]).
- Asymmetric updating of the dosing frequency for LHRH agonists in the patient management costs, which increases the patient management cost savings associated with radium-223 by a further [redacted].
- Asymmetric updating of the number of cycles at risk of incident progression in the revised model (for the purpose of estimating second line treatment costs). This also serves to increase the second line treatment cost savings for radium-223 – by [redacted] (compared to equalising the cycles at risk to 99 in each treatment arm).

The small increase in the QALY gain in the company's revised analysis, compared to their previous base case, is the result of combined changes that to an extent cancel each other: 1) application of the committee's preferred utility point estimates which reduce the QALY gain for radium-223; 2) extension of the time horizon from 5 years to 10 years, which increases the estimated QALY gain; and 3) updating of the progression free and SSE free survival modelling which also increases the QALY gain for radium-223. The ERG also identified a bug in the implementation of the revised survival analyses in the new model, which was leading to underestimation of the QALY gain. Correcting this increased the new incremental QALY estimate from [redacted].

Following the correction of all identified bugs and the removal of unjustified changes in the company's revised analysis, the ERG estimated a new base case ICER of £31,172 for radium-223 versus BSC; corresponding to an incremental cost of [redacted] for an incremental QALY gain of [redacted].

From this new base case, the impact of various scenarios was assessed including reducing the duration of treatment specific utility benefits associated radium-223, and the application of alternative extrapolation assumptions for overall and progression and SSE free survival. Applying less optimistic assumptions with respect to extrapolation of survival in combination with the removal of the incremental utility benefits for radium-223 from week 104 onwards, the ICER for radium-223 approached or breached £50,000 per QALY gained. Substituting the new progression and SSE free survival analysis assumptions for the old had a limited impact on the base case ICER (£33,817 versus £31,172).

In conclusion, the updated economic modelling results in a substantially improved ICER for radium-223, which appears to be justified and is driven primarily by the correction of a bug that was present in the previous model. Extension of the time horizon of the model from 5 to 10 years has also increased the QALY gain. Key points for further consideration relate to the committee's preferred assumptions with respect to inclusion/exclusion of the additional medical resource use data from ALSYMPCA, the extrapolation approach for overall survival, and the modelled duration of the incremental utility benefits for radium-223 over BSC.

6 References.

1. Cislo P, Reuning-Scherer JD. Effect of radium-223 dichloride (Ra-223) on risk for and duration of hospitalization in ALSYMPCA by docetaxel (D) subgroup. J Clin Oncol 2015;33(7 Suppl 1).

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Radium-223 dichloride for treating metastatic hormone relapsed prostate cancer with bone metastases (review of TA376) [ID1007]

You are asked to check the ERG report from Aberdeen HTA Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 06 July 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Contains AIC

Issue 1 Docetaxel naïve population in ALSYMPCA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 2 The ERG report states: 'The ERG also notes that the effect estimates from the ALSYMPCA trial were obtained from docetaxel naïve people who were both suitable and unsuitable for docetaxel.' This is not strictly correct. **Page 11** The ERG report states: '…effect estimates from the ALSYMPCA trial were obtained from docetaxel naïve people who were both suitable and unsuitable for docetaxel.' This is not strictly correct. **Page 11** The ERG report states: 'A	**Page 2** Please amend the wording as follows: 'The ERG also notes that the effect estimates from the ALSYMPCA trial were obtained from a heterogeneous group of docetaxel naïve people not eligible for their first course of docetaxel.' **Page 11** Please amend the wording as follows: '…effect estimates from the ALSYMPCA trial were obtained from a heterogeneous group of docetaxel naïve people not eligible for their first course of docetaxel.' **Page 11** Please delete the following text from this	The statements are misleading and not representative of the docetaxel naïve population in the ALSYMPCA study. Further explanation is set out below, which is not new information, but has been provided earlier in the overall appraisal process for radium-223 dichloride prior to the publication of TA376. **<u>Trial eligibility</u>** If subjects were eligible for their first course of docetaxel, they were excluded from the ALSYMPCA study. As such, only patients unsuitable for their first course of docetaxel were included. Whilst the exclusion criteria in relation to being eligible for the 1st course of docetaxel treatment potentially led to a	The ERG does not believe that this is a factual error but will amend the wording to: ''…….. effect estimates from the ALSYMPCA trial were obtained from a docetaxel naïve subgroup that could include both people who were unsuitable for docetaxel and people who were suitable but refused docetaxel or people for whom docetaxel was unavailable.' The ERG refers to Section 4.5 of the previous Appraisal Consultation Document, indicating that the Committee previously decided that some of the

round table of six oncologists reached a consensus agreement on criteria for patient unsuitability for docetaxel. The criteria do not cover the ALSYMPCA 'no prior docetaxel' group who either refused docetaxel or for whom docetaxel was unavailable.' This is not strictly correct.	statement: 'The criteria do not cover the ALSYMPCA 'no prior docetaxel' group who either refused docetaxel or for whom docetaxel was unavailable.'	heterogeneous group of docetaxel naïve patients (patients suitable, willing and where docetaxel is available), Bayer believes that there would be very few patients in ALSYMPCA who would not have been able to access docetaxel. We have re-analysed data for all of the countries who participated in ALSYMPCA and have discovered that in all countries, there were some patients with prior docetaxel exposure. This suggests that 'non-availability' of docetaxel, whilst a valid reason for patients not having prior docetaxel in the ALSYMPCA protocol, was not applicable in practice during the study. As such, patients are most likely to have fallen into the category of being contraindicated or unsuitable for docetaxel. **<u>Biological plausibility for the generalisability of the data</u>**	ALSYMPCA trial population would now be eligible to receive docetaxel in practice. "The Committee noted that patients in the ALSYMPCA trial comprised people who had previously had docetaxel and people who had not. It further noted that the group who had not had docetaxel included people who had refused docetaxel or who had not had access to it, in addition to patients for whom docetaxel was unsuitable. It was aware that approximately 87% of people in the trial had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, indicating that they would have been fit enough to have docetaxel. The Committee heard from

		There is no biologically plausible reason why we would expect the population in the trial that had not had prior docetaxel, for whatever reason, to respond differently to the population of patients in UK clinical practice for whom docetaxel is contraindicated or unsuitable. It is therefore reasonable to assume that the 4.6 months overall survival gain estimated from ALSYMPCA could be generalised to the population in UK clinical practice for whom docetaxel is contraindicated or unsuitable. Further to this, to support the appraisal, Bayer convened a group of clinical experts to define a consensus statement identifying the patients who would fall into the category of docetaxel unsuitability i.e. the group for which Bayer is seeking approval.	clinical experts that assessment of ECOG status was subjective and that there were people in the trial for whom docetaxel was not suitable regardless of their performance status. The Committee heard from the clinical experts that uptake of docetaxel at the time of ALSYMPCA was variable and that clinical practice has changed in the last 5 years. The clinical experts explained that most people in ALSYMPCA had docetaxel because it was one of the few treatments available at the time, and that some of those people would not have docetaxel in clinical practice now. They also explained that patients who were not treated with docetaxel at that time may now be able to have docetaxel in clinical practice. The Committee

		Bayer therefore suggests that the ERG have not taken into account the totality of the evidence from TA376 when making the statements identified in Issue 1.	considered that a significant proportion of the patients in the group who did not have docetaxel would now be eligible for docetaxel in clinical practice, and thus docetaxel is a relevant comparator." The ERG have deleted the following sentence from page 11: 'The criteria do not cover the ALSYMPCA 'no prior docetaxel' group who either refused docetaxel or for whom docetaxel was unavailable.'

Issue 2 OS extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P22. The ERG report states:	This statement should be deleted.	OS is unchanged from previous submissions.	The OS does appear to have been rerun using time in days, leading to coefficients

'It should be noted that the OS extrapolation model is essentially unchanged from the previous submissions, although it appears to have been updated using time to death measured in days rather than weeks as in the previous model.' This is not correct		OS was not a source of uncertainty in previous submissions and is unchanged The comment implies uncertainty - "essentially unchanged"; "appears to be updated" when OS has not changed	on a different scale and revised formulae in the "Overall – OS" worksheet of the economic model. Hence the comment in our original report. However, there is no effect on the extrapolations. To avoid any confusion, we accept the company's concerns and delete this statement on page 22 of our report.

Issue 3 QALY gain or loss

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P36 - The ERG report states: 'The updated approach to progression and SSE free survival analysis also modestly increases the QALY gain (by ~[redacted]) in comparison with the survival analysis assumptions used in the previous model; i.e. when applying the committee's preferred utilities specific to	Please amend the wording as follows: 'The updated approach to progression and SSE free survival analysis also modestly increases the QALY gain (by ~[redacted]) in comparison with the survival analysis assumptions used in the previous model. When applying the committee's preferred utilities specific to the no prior docetaxel subgroup, the updated approach to progression free survival analysis slightly	The ERG has not provided either the updated model or specified which model they are comparing to. However when trying to replicate their results we found that QALYs increased in both arms.	This analysis was based on comparison of the two models that the ERG uploaded with our original report, comparing the new and old approaches to PFS and SSE free survival in the company's revised model, but prior to identifying and correcting the bugs in the model.

the no prior docetaxel subgroup, the updated approach to progression free survival analysis slightly reduces the total QALYs in the BSC arm while slightly increasing total QALYs in the radium-223 arm.' Bayer is unable to replicate this finding.	increases the total QALYs in both arms.'		The two models show the same pattern of results after correcting the bugs (although the change in the incremental QALY is ~[redacted] after correction of the bugs). Implementing the old approach to PFS and SSE free survival, the ERG find the total QALYs in the BSC arm increase very slightly compared to using the new survival analysis assumptions ([redacted]). To clarify this point we have changed the text on page 36 to: 'The updated approach to progression and SSE free survival analysis also modestly increases the QALY gain ([redacted]) in comparison with the survival analysis assumptions used in the previous model; i.e.

			applying the old survival analysis assumptions in the revised model, the ERG found that the total discounted QALYs in the BSC arm increased slightly, whilst total discounted QALYs in the radium-223 arm decreased slightly.’

Aberdeen HTA Group

Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (men who have not received docetaxel and for whom docetaxel is contraindicated or not suitable)

ERG critique of the company submission for re-consideration of current CDF technologies under the new proposed CDF criteria

Erratum

Completed 14 July, 2014

This report was commissioned by
the NIHR HTA Programme as
project number 12/57.

Contains CIC/AIC

This document is intended to replace pages 2, 11, 22 and 36 of the original ERG report critiquing the company submission for re-consideration of radium 223 for treating hormone-relapsed prostate cancer with bone metastases (men who have not received docetaxel and for whom docetaxel is contraindicated or not suitable), under the new proposed Cancer Drugs Fund criteria.

The main issues relate to the rephrasing of several sentences which the company believe may be misleading.

Page 2

The following sentence:

'The ERG also notes that the effect estimates from the ALSYMPCA trial were obtained from docetaxel naïve people who were both suitable and unsuitable for docetaxel.'

has been amended to:

'The ERG also notes that the effect estimates from the ALSYMPCA trial were obtained from a docetaxel naïve subgroup that could include both people who were unsuitable for docetaxel and people who were suitable but refused docetaxel or people for whom docetaxel was unavailable.'

Page 11

The following sentence:

'…. effect estimates from the ALSYMPCA trial were obtained from docetaxel naïve people who were both suitable and unsuitable for docetaxel.'

has been amended to:

'….. effect estimates from the ALSYMPCA trial were obtained from a docetaxel naïve subgroup that could include both people who were unsuitable for docetaxel and people who were suitable but refused docetaxel or people for whom docetaxel was unavailable.'

Page 11

The following sentence has been deleted:

‘The criteria do not cover the ALSYMPCA ‘no prior docetaxel’ group who either refused docetaxel or for whom docetaxel was unavailable.’

Page 22

The following sentence has been deleted:

‘It should be noted that the OS extrapolation model is essentially unchanged from the previous submissions, although it appears to have been updated using time to death measured in days rather than weeks as in the previous model.’

Page 36

The following sentence:

‘The updated approach to progression and SSE free survival analysis also modestly increases the QALY gain ([redacted]) in comparison with the survival analysis assumptions used in the previous model; i.e. when applying the committee’s preferred utilities specific to the no prior docetaxel subgroup, the updated approach to progression free survival analysis slightly reduces the total QALYs in the BSC arm while slightly increasing total QALYs in the radium-223 arm.’

have been amended to:

‘The updated approach to progression and SSE free survival analysis also modestly increases the QALY gain ([redacted]) in comparison with the survival analysis assumptions used in the previous model; i.e. applying the old survival analysis assumptions in the revised model, the ERG found that the total discounted QALYs in the BSC arm increased slightly, whilst total discounted QALYs in the radium-223 arm decreased slightly.’

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) for the sub-group of the indicated population of adult men with symptomatic bone metastases and no known visceral metastases, who have not received docetaxel and for whom docetaxel is contraindicated or not suitable.

1.1 Critique of the decision problem in the company submission

The company submission (CS) encompasses an update of the company's original systematic literature review and presents new cost-effectiveness results based on a revised economic model. The company state that their submission presents evidence that addresses the uncertainties previously identified by the Appraisal Committee.

There have been no overall changes to the population, interventions or outcomes being considered in the decision problem. NICE previously issued a positive recommendation for the subgroup of the indicated population that had received prior docetaxel. The current submission focuses on the sub-group of the indicated population who have not received docetaxel and for whom docetaxel is contraindicated or not suitable. The clinical effectiveness data for radium-223 continues to come solely from the ALSYMPCA trial.

The company have compared radium-223 with best supportive care (BSC). The Appraisal Committee previously accepted that "*there is a clinically recognised group for whom radium-223 treatment is suitable, because docetaxel is contraindicated or unsuitable"* and concluded that best supportive care is the most relevant comparator for this group. While the ERG agrees that BSC is the most appropriate comparator for this submission, it notes that the 'no prior docetaxel' participants of the ALSYMPCA trial included people who declined docetaxel or for whom docetaxel was unavailable. The ERG also notes that the effect estimates from the ALSYMPCA trial were obtained from a docetaxel naïve subgroup that could include both people who were unsuitable for docetaxel and people who were suitable but refused docetaxel or people for whom docetaxel was unavailable.

The company undertook a project to provide clarity on the definition of the patient population who have not received docetaxel. A round table of six oncologists reached

2.3 Comparators

The company have compared radium-223 with best supportive care (BSC) only. The Appraisal Committee previously accepted that "*there is a clinically recognised group for whom radium-223 treatment is suitable, because docetaxel is contraindicated or unsuitable"* and concluded that best supportive care is the most relevant comparator for this group (NICE TA376, section 4.2). The Appraisal Committee also previously agreed that abiraterone is not a suitable comparator for radium-223 in this population. While the ERG agrees that BSC is the most appropriate comparator for this submission, it notes that the 'no prior docetaxel' participants of the ALSYMPCA trial included people who declined docetaxel or for whom docetaxel was unavailable. The Appraisal Committee agreed that docetaxel may be suitable for these people and that docetaxel would be an appropriate comparator for this group. Although the later population group are not considered in the company's submission (CS), effect estimates from the ALSYMPCA trial were obtained from a docetaxel naïve subgroup that could include both people who were unsuitable for docetaxel and people who were suitable but refused docetaxel or people for whom docetaxel was unavailable.

The company undertook a project to provide clarity on the definition of the patient population who have not received docetaxel. A round table of six oncologists reached a consensus agreement on criteria for patient unsuitability for docetaxel. The agreed criteria for patient unsuitability for docetaxel are as follows:

1. Patients contra indicated for docetaxel
    a. Hypersensitivity to the active substance or to any of the excipients (polysorbate 80, ethanol anhydrous, citric acid)
    b. Patients with baseline neutrophil count of < 1,500 cells/mm3.
    c. Patients with severe liver impairment
2. Patients with poor performance status defined as:
    a. ECOG 3 or greater in isolation (NICE TA101 states docetaxel should be given only if the man is well enough to care for himself with occasional assistance) or;
    b. ECOG 2 and above with the existence of comorbidities

The Committee previously agreed that the calculation of the cohort flow was an important issue and "*while there was uncertainty in the most appropriate approach, the Committee noted the significant effect on the ICER when applying the company's formula to model cohort flow*".

The company's revised survival analysis

In the current submission the company have presented revised time-to-event analyses for both ALP progression and symptomatic skeletal-related events (SSE). Unlike previous submissions deaths are treated as events, rather than censoring events, in the primary analyses. The ERG believes this updated analysis is more consistent with the company's approach to calculating the cohort flow in the model, but deaths are still treated as censoring events for participants known to have died at least nine weeks after their last ALP assessment date or their last SSE efficacy assessment date. It was stated that this nine week period was chosen because it equated to two assessment cycles plus one week in duration and it appears to be used because [redacted]. Although the ERG accepted that it may be misleading to treat deaths as events [redacted], there is a lack of clear justification for using this particular time period in the censoring assumptions

As in previous submissions, the company have fitted various curves to the overall survival data and the revised progression-free survival and SSE-free survival data. The sum of the AIC and BIC across the two treatment arms was used to inform the model choice. Based on this the log normal extrapolation was chosen for the overall survival and ALP progression-free survival models. The log-logistic model appeared best for SSE-free survival, but for consistency the log normal was also used in the base case analysis, with log-logistic explored in a scenario analysis.

Figures 2a) and 2b) below show the updated Kaplan-Meier (KM) data together with Log-normal and Weibull functions fitted to the revised data. Whilst on visual inspection the fitted curves seem reasonable for the Radium-223 arm (Figure 2a), the

Combined scenario (no MRU, Weibull curves fitted to all endpoints and radium utility benefit lasts up to 52 weeks)	£49,114

The Company's revised probabilistic analyses

The company provided an revised probabilistic analysis based on 1000 iterations, and reported a base case ICER similar to the deterministic result; £26,268 per QALY gained with radium-223 versus BSC. The company also presented the incremental cost-effectiveness scatter plot and CEAC for radium-223 (see Figures 1 and 2 of the company's resubmission). Probabilities of cost-effectiveness at given ceiling ratios were not reported, but from rerunning the company's PSA the ERG found these to be: 36.1%, 60.4%, and 87.2% at thresholds of £20,000, £30,000 and £50,000 per QALY gained respectively.

4.1.5 Validation of the company's revised model

The ERG reviewed the company's described changes and cross checked the new model against the previous models submitted prior to the third appraisal committee meeting for TA376. This highlighted a number of errors in the previous and updated models. When implementing all the described changes to the old model, and correcting the identified bugs during the process, the ERG were able to reconcile the QALY estimates of the two models. The key driver of the increased QALY gain associated with radium-223 in the revised model is the extended time horizon. The updated approach to progression and SSE free survival analysis also modestly increases the QALY gain ([redacted]) in comparison with the survival analysis assumptions used in the previous model; i.e. applying the old survival analysis assumptions in the revised model, the ERG found that the total discounted QALYs in the BSC arm increased slightly, whilst total discounted QALYs in the radium-223 arm decreased slightly.

There was insufficient time to fully trace the impact of applying all the cost updates to the old model. However, the key driver of the reduced incremental cost associated radium-223 is the correction of the bug in the calculations of second line treatment costs which was present in the company's previous models for the no prior docetaxel subgroup. Further updates to the cost of SSEs and the incorporation of additional