IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Radium-223 dichloride – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Radium-223-dichlorid – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 March 2014). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EOD	extent of disease
EQ-5D	European Quality of Life-5 Dimensions
FACT-P	Functional Assessment of Cancer Therapy-Prostate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
kBq	kilobecquerel
LH-RH	luteinizing hormone-releasing hormone
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
U/L	Unit per litre
WHO	World Health Organization

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug radium-223 dichloride. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 16 December 2013.

Research question

The aim of this report is to assess the added benefit of radium-223 dichloride (hereinafter referred to as "radium-223") in comparison with the appropriate comparator therapy (ACT) in patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

The G-BA specified an ACT for each different patient group:

- for patients with the primary treatment goal of prolongation of life: docetaxel in combination with prednisone or prednisolone
- for patients with the primary treatment goal of symptom control and prevention of late complications and for patients for whom docetaxel treatment is not an option: best supportive care (BSC) (particularly adequate pain therapy, treatment with bisphosphonates and/or radionuclides)

In this benefit assessment, the group of patients with the primary treatment goal of symptom control and prevention of late complications and the group of patients for whom docetaxel treatment is not an option were primarily considered jointly, also because of the identical ACT, and are hereinafter referred to as "BSC population". The group of patients with the primary treatment goal of prolongation of life is hereinafter referred to as "docetaxel population".

Studies that investigated a comparison of radium-223 with or without BSC versus BSC could be considered for the benefit assessment of radium-223 compared with the ACT BSC.

The assessment was based on patient-relevant outcomes. One direct comparative randomized controlled trial (RCT) was included in the assessment.

Results

Docetaxel population

There were no evaluable data for the comparison of radium-223 with docetaxel in patients who are eligible for treatment with docetaxel and whose primary treatment goal is prolongation of life. The comparison on the basis of various RCTs on docetaxel and on one

RCT on radium-223, which was presented and referred to as “qualitative indirect comparison” by the company, was unsuitable to derive an added benefit of radium-223 versus the ACT docetaxel. Hence an added benefit of radium-223 versus the ACT docetaxel is not proven.

BSC population

The BC1-06 study (ALSYMPCA), the approval study of radium-223, was included in the assessment.

Study characteristics

The BC1-06 study included is a randomized, double-blind, multicentre, placebo-controlled phase 3 study. Men with progressive symptomatic castration-resistant prostate cancer with ≥ 2 bone metastases and no known visceral metastases were included in the study. According to the inclusion and exclusion criteria of the study, the patients had either received pretreatment with docetaxel or were not eligible for a first course of docetaxel. Possible reasons for the latter were that the patients were not eligible for docetaxel treatment because of their health status or declined to receive docetaxel, or that docetaxel was not available in the respective country. It can be assumed for patients with docetaxel pretreatment that they were mainly no longer eligible for docetaxel treatment. Docetaxel was available in the vast majority of the countries where the BC1-06 study was conducted. Hence due to the study design, it was assumed for patients without docetaxel pretreatment that they mainly declined docetaxel, a treatment which potentially prolongs life, but is also associated with severe adverse events (AEs), not for medical reasons, but based on their own individual decision. The patient population investigated in the BC1-06 study was therefore considered as sufficient approximation of the populations of patients with the primary treatment goal of symptom control and prevention of late complications and of the patients for whom treatment with docetaxel is not an option. A total of 921 patients were randomly assigned in a ratio of 2:1, 614 patients to the radium-223 arm, and 307 patients to the placebo arm.

The study treatment with radium-223 was administered in compliance with the approval. The patients in the radium-223 arm received 6 slow intravenous injections of radium-223 at a dose of 50 kBq/kg body weight and at intervals of 4 weeks between each administration. The patients in the placebo arm received placebo instead. The patients in both treatment groups additionally received BSC. The study consisted of a screening phase, the treatment phase (24 weeks) and a follow-up phase of up to 3 years after enrolment.

Overall survival and skeletal-related events were followed-up during the total course of the study. AEs were recorded up to 12 weeks after the last injection of the study medication. The outcomes on health-related quality of life were recorded in week 16 and 24 during the treatment phase and once within the follow-up phase (week 44). Primary outcome of the BC1-06 study was overall survival.

Risk of bias

The risk of bias at study level was rated as low for the BC1-06 study. At outcome level, the risk of bias for the combined outcome "time to first symptomatic skeletal-related event" and for the outcome "overall survival" was rated as low. The results based on naive proportions on the outcomes "serious AEs (SAEs)", severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or 4), "discontinuation due to AEs" and "diarrhoea" were rated as potentially highly biased. The risk of bias for the outcome on health-related quality of life measured with the Functional Assessment of Cancer Therapy-Prostate (FACT-P) instrument was rated as high. No evaluable data were available for health-related quality of life measured with the European Quality of Life-5 Dimensions (EQ-5D) questionnaire.

Mortality (overall survival)

Treatment with radium-223 + BSC resulted in a statistically significant prolongation of overall survival in comparison with placebo + BSC for the total population of the BC1-06 study. In addition, there was an indication of an effect modification by the characteristic "age" for the outcome "overall survival". For both age groups, there was an indication of an added benefit of radium-223 + BSC for overall survival compared with the ACT BSC, the extent of which was different, however.

Morbidity (time to first symptomatic skeletal-related event)

The time to first symptomatic skeletal-related event was statistically significantly longer under treatment with radium-223 + BSC than under treatment with placebo + BSC. In addition, there was an indication of an effect modification by the characteristic "concomitant bisphosphonate treatment at baseline" for this outcome. For patients with concomitant bisphosphonate treatment, there was an indication, for patients without concomitant bisphosphonate treatment, there was a hint of an added benefit of radium-223 + BSC compared with BSC for the outcome "time to first symptomatic skeletal-related event".

Health-related quality of life

The dossier contained no evaluable data for health-related quality of life. However, sensitivity analyses on the basis of calculations by the Institute could be conducted for the analysis of the proportion of patients with improvement in health-related quality of life, measured with the FACT-P. These produced non-robust results. An added benefit of radium-223 + BSC in comparison with BSC for this outcome is therefore not proven.

Adverse events

The dossier contained different analyses on the outcomes "SAEs", "severe AEs (CTCAE grade 3 or 4)" and "discontinuation due to AEs". Besides analyses based on all events that occurred in the study during the course of the treatment including the 12-week follow-up, the dossier also contained analyses that excluded events associated with a skeletal-related event and recorded at the same time. These analyses were primarily used for this benefit assessment

because skeletal-related events were considered as separate outcome in this benefit assessment.

In the BC1-06 study, there was a statistically significant difference in favour of radium-223 + BSC with regard to the proportion of patients with at least one SAE. This difference was presumably due to SAEs caused by an increased use of drugs (e.g. analgesics) in the placebo + BSC group. In addition, there was an indication of an effect modification by the subgroup characteristic "opiate treatment at baseline" for the outcome. For patients who had not been treated with opiates at baseline, there was an indication, for patients who already were treated with opiates at baseline, there was a hint of lesser harm from radium-223 + BSC in comparison with BSC.

There was no statistically significant difference between the treatment groups for the outcome "severe AEs (CTCAE grade 3 or 4)". However, there was an indication of an effect modification by the characteristics "opiate treatment at baseline" and "pretreatment with docetaxel" for this outcome. For patients who had not been treated with opiates at baseline, there was a hint of lesser harm from radium-223 + BSC in comparison with the ACT BSC. For patients with docetaxel pretreatment, there was also a hint of lesser harm from radium-223 + BSC in comparison with the ACT BSC. Greater or lesser harm from radium-223 is not proven for patients who already were treated with opiates at baseline or for patients without docetaxel pretreatment.

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs".

There was a statistically significant difference to the disadvantage of radium-223 + BSC compared with placebo + BSC in the BC1-06 study for the outcome "diarrhoea". In addition, in each case, there was an indication of an effect modification by the characteristic "docetaxel pretreatment". For patients without docetaxel pretreatment, there was a hint of greater harm from radium-223 + BSC in comparison with the ACT BSC with regard to diarrhoea.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug radium-233 compared with the ACT is assessed as follows:

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

Docetaxel population

As no relevant data were available for the research question of radium-223 in comparison with docetaxel in patients with the treatment goal "prolongation of life", an added benefit of radium-223 in comparison with the ACT is not proven for this subpopulation.

BSC population

Positive effects were shown in the outcome categories "mortality", "serious/severe late complications" and "serious/severe AEs", each of which depends on different subgroup characteristics. The negative effect was shown in the outcome category "non-serious/non-severe AEs" and only in the subgroup of patients without docetaxel pretreatment.

The balancing of the positive and negative effects below is conducted separately for the 2 age groups considered.

Subgroup characteristic "age" (< 65 years versus ≥ 65 years)

There is an indication of a major added benefit for the outcome "overall survival" for patients < 65 years. This effect is decisive at first for the overall conclusion on added benefit. In the outcome categories "serious/severe late complications" and "serious/severe AEs", there are also at most indications of an added benefit with the extent also being at most major. These effects do not change the overall conclusion. This is offset by a hint of considerably greater harm from radium-223 + BSC. Against the background that this effect was only shown in a subgroup and that the diarrhoea occurred was almost exclusively non-severe, this does not raise doubts about the overall conclusion.

There is an indication of a minor added benefit for patients ≥ 65 years for the outcome "overall survival". Furthermore, there is an additional positive effect for the outcome "time to first symptomatic skeletal-related event". This effect depends on the presence of baseline concomitant bisphosphonate treatment. There is an indication of a major added benefit for this outcome for patients receiving concomitant bisphosphonate treatment. Hence for these patients, this effect is decisive at first for the overall conclusion on added benefit. For patients who do not receive concomitant bisphosphonate treatment, there is a hint of a non-quantifiable (at most considerable) added benefit for the outcome "time to first symptomatic skeletal-related event". Overall, an indication of a minor added benefit remains at first for these patients due to the greater certainty of results for the outcome "overall survival". In the outcome category "serious/severe AEs", there are also at most indications of an added benefit with the extent being at most minor. This does not change the respective overall conclusion. This is offset by a hint of considerably greater harm from radium-223 + BSC in each case. Against the background that this effect was only shown in a subgroup and that the diarrhoea occurred was almost exclusively non-severe, this does not raise doubts about the overall conclusion.

In summary, there is an indication of a major added benefit for patients < 65 years and for patients ≥ 65 years with concomitant bisphosphonate treatment. There is an indication of a minor added benefit for patients ≥ 65 years without concomitant bisphosphonate treatment.

The result of the assessment of the added benefit of radium-223 in comparison with the ACT is summarized in Table 2.

Table 2: Patient groups, ACTs and extent and probability of added benefit of radium-223 in patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases

Patient group	**ACT**[a]	**Subgroup**	**Extent and probability of added benefit**
Patients with the treatment goal of prolongation of life (docetaxel population)	Docetaxel in combination with prednisone or prednisolone	-	Added benefit not proven
Patients with the treatment goal of symptom control and prevention of late complications and patients for whom treatment with docetaxel is not an option (BSC population)	BSC[b]	Age < 65 years	Indication of a major added benefit
		Age ≥ 65 years, concomitant bisphosphonate treatment	Indication of a major added benefit
		Age ≥ 65 years, no concomitant bisphosphonate treatment	Indication of a minor added benefit
a: Presentation of the respective ACT specified by the G-BA. b: BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care			

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of radium-223 in comparison with the ACT in patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

The G-BA specified an ACT for each different patient group:

- for patients with the primary treatment goal of prolongation of life: docetaxel in combination with prednisone or prednisolone
- for patients with the primary treatment goal of symptom control and prevention of late complications and for patients for whom docetaxel treatment is not an option: BSC (particularly adequate pain therapy, treatment with bisphosphonates and/or radionuclides)

BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.

Hence 3 patient groups can be derived from the G-BA's specification. In this benefit assessment, the group of patients with the primary treatment goal of symptom control and prevention of late complications and the group of patients for whom docetaxel treatment is not an option were primarily considered jointly, also because of the identical ACT, and are hereinafter referred to as "BSC population". The group of patients with the primary treatment goal of prolongation of life is hereinafter referred to as "docetaxel population".

In principle, the company followed the G-BA's specification, but deviated from the G-BA in the definition of the patient groups (see Section 2.7.1 and 2.7.2.1 of the full dossier assessment). The ACT specified by the G-BA was used for this benefit assessment.

Studies that investigated a comparison of radium-223 with or without BSC versus BSC could be considered for the benefit assessment of radium-223 compared with the ACT BSC.

The assessment was conducted based on patient-relevant outcomes and on direct comparative RCTs.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on radium-223 (studies completed up to 29 October 2013)
- search in trial registries for studies on radium-223 (last search on 29 October 2013)

- bibliographical literature search on the ACT (last search on 23 July 2013)

The Institute's own search to check the completeness of the study pool:

- search in trial registries for studies on radium-223 (last search on 20 January 2014)

No additional relevant study was identified from the check.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2, 4.2.3, 4.2.5.6 and 4.3.2 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Docetaxel population

No studies were identified from the steps of information retrieval mentioned from which an added benefit of radium-223 could be derived for the comparison of radium-223 with docetaxel in patients who are eligible for treatment with docetaxel and whose treatment goal is prolongation of life (docetaxel population). This assessment deviated from that of the company. The company also identified no RCT that would be suitable for a direct or an adjusted indirect comparison, but it presented a comparison, which it called "qualitative indirect comparison", on the basis of different RCTs on docetaxel and one RCT on radium-223. In this comparison, the company considered the outcome "overall survival" (called "effectiveness" by the company) and the outcomes on AEs (called "tolerability" by the company). It used different approaches in each case. The reasons why this comparison was unsuitable for deriving an added benefit of radium-223 versus the ACT docetaxel are given below.

For the outcome "overall survival", the company used one RCT each on the radium-223 side and on the docetaxel side of the indirect comparison. On the one hand, this was the BC1-06 study, an RCT on the comparison of radium-223 + BSC versus placebo + BSC (see Section 2.3.2) and the three-arm TAX-327 study [3], in which 2 treatment regimens of docetaxel (weekly and every three weeks) and mitoxantrone were compared. The company conducted a qualitative comparison of the treatment effects on overall survival.

For the outcomes on AEs, the company conducted an unadjusted indirect comparison by comparing the results on AEs, SAEs, discontinuation due to AEs and severe AEs (CTCAE grade 3 and 4) and specific AEs from the docetaxel arms of several RCTs [3-12] with those from the radium-223 arm of the BC1-06 study descriptively without effect estimates.

However, a simple comparison of effect estimates as conducted by the company for overall survival does not allow to draw any valid conclusions. The unadjusted indirect comparisons conducted for the outcomes on AEs under consideration of the frequency of events in individual study arms from various studies also represent no valid method of analysis because there was no randomization between the individual study arms and structural equality of the treatment groups was therefore not guaranteed [13-15]. Evidence-based conclusions on added benefit can be derived from an unadjusted comparison only in case of very large differences,

in which it can be excluded that they are caused by systematic bias alone. The company described no methodological approach about whether and how possible very large effects should be identified or interpreted. For the research question of the present benefit assessment, such effects could not be derived for overall survival or for the outcomes on AEs from the comparison presented by the company. For the outcome "overall survival", this assessment concurs with that of the company, which itself only concluded from the comparison it presented that radium-223 was not inferior to the ACT docetaxel, but rather appeared better numerically. Nevertheless, the company derived an added benefit of radium-223 versus the ACT docetaxel for overall survival on the basis of this comparison. Moreover, the company described an advantage of radium-223 on the basis of the data on AEs. It justified this with the differences with respect to the AE outcomes considered, which, from the company's point of view, were consistently and clearly in favour of radium-223 (see Section 2.7.2.3.2 of the full dossier assessment). This was not accepted. Instead, the picture for the outcomes on AEs was very heterogeneous. Hence the data on AEs presented by the company were also unsuitable for deriving greater or lesser harm from radium-223. This assessment deviates from that of the company, which, on the basis of the data on AEs, derived lesser harm from radium-223 compared with the ACT docetaxel.

Additional aspects that partly further increase the uncertainty, but are not decisive for the overall assessment, are commented on in Section 2.7.2.3.2 of the full dossier assessment.

Overall, the comparison presented by the company was unsuitable to draw conclusions on the added benefit of radium-223 versus the ACT docetaxel. The study characteristics and the patient population are therefore not described.

2.3.2 BSC population

2.3.2.1 Studies included

The BC1-06 study (ALSYMPCA) listed in Table 3 was included in the benefit assessment.

Table 3: Study pool – RCT, direct comparison: radium-223 + BSC vs. placebo + BSC

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
BC01-06 (ALSYMPCA)	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. BSC: best supportive care; RCT: randomized controlled trial; vs.: versus			

The pool of the studies included for the BSC population deviates from that of the company, which additionally included the BC1-02 study in the assessment, and conducted a meta-analysis using the data from both studies.

Contrary the company's assessment, the BC1-02 study was not included in the present benefit assessment. In this study, radium-223 was only administered 4 times at 4-week intervals. According to the Summary of Product Characteristics (SPC) however, only 6 administrations are approved for radium-223 [16]. On request, this was confirmed by the competent regulatory authority and can also be concluded from the approval documents, from which it can be inferred that exclusively six administrations of radium-223 were considered particularly for the assessment of clinical safety [17].

Section 2.6 contains a reference list for the study included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2.2 Study characteristics

Table 4 and Table 5 describe the BC1-06 study used for the benefit assessment.

Table 4: Characteristics of the study included – RCT, direct comparison: radium-223 + BSC vs. placebo + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
BC1-06 (ALSYMPCA)	RCT, placebo-controlled, double-blind, parallel, phase 3	Adult men with CRPC, symptomatic bone metastases and no known visceral metastases	1) radium-223 + BSC (N = 614) 2) placebo + BSC (N = 307)	Treatment: first injection up to 4 weeks after the last injection (6 injections in total, 24 weeks) follow-up: 3 years for overall survival and skeletal-related events up to 12 weeks after the last injection for AEs (every 2 months from the 4th week until the 52nd week after the last injection, every 4 months from the 53rd week until 3 years after enrolment)	173 centres in 19 countries (recruitment from 136 centres) ongoing study first patient enrolled: 6/2008; last patient enrolled: 2/2011 cut-off date for first interim analysis: 14 Oct 2010 cut-off date for second interim analysis: 15 Jul 2011	Primary outcome: overall survival secondary outcomes: time to first symptomatic skeletal-related event, health-related quality of life (FACT-P, EQ-5D), AEs

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for this benefit assessment.

AE: adverse event; BSC: best supportive care; CRPC: castration-resistant prostate cancer; EQ-5D: European Quality of Life-5 Dimensions FACT-P: Functional Assessment of Cancer Therapy-Prostate; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 5: Characteristics of the interventions – RCT, direct comparison: radium-223 + BSC vs. placebo + BSC

Study	Intervention	Comparison	Concomitant medication
BC01-06 (ALSYMPCA)	Radium-223 50 kBq/kg body weight IV 6 times at 4-week intervals + BSC	Placebo IV 6 times at 4-week intervals + BSC	▪ BSC was defined as the standard treatment at each centre, e.g. external radiotherapy, corticosteroids, oestrogens (stilboestrol), antiandrogens, estramustine or ketoconazole. Any medical treatment that served either the clinical benefit or the supportive treatment of the patient could be administered at the investigator's discretion. ▪ analgesics (including opioids) ▪ treatment of CRPC: LH-RH agonists or polyoestradiol ▪ bisphosphonates
BSC: best supportive care; CRPC: castration-resistant prostate cancer; IV: intravenous; LH-RH: luteinizing hormone-releasing hormone; RCT: randomized controlled trial; vs.: versus			

The BC1-06 study included is a randomized, double-blind, placebo-controlled phase 3 study, the approval study of radium-223. It was of a multicentre design and was carried out in 173 centres in Australia, Europe, Israel, North and South America as well as in Singapore and Hong Kong. Patients were enrolled in only 136 of these study centres. Men with progressive symptomatic castration-resistant prostate cancer with ≥ 2 bone metastases and no known visceral metastases were included in the study. Presence of symptoms was assumed if the patient received regular (not only occasional) treatment with analgesics (at least World Health Organization [WHO] score of 1) or treatment with external radiotherapy because of bone pain, which should have been administered within 12 weeks before randomization. Overall, the criteria of the approved therapeutic indication of radium-223 were regarded as being fulfilled.

According to the inclusion and exclusion criteria of the study, the patients had either received pretreatment with docetaxel or were not eligible for a first course of docetaxel. Possible reasons for the latter were that the patients were not eligible for docetaxel treatment because of their health status or declined to receive docetaxel, or that docetaxel was not available in the respective country. It can be assumed for patients with docetaxel pretreatment that they were mainly no longer eligible for docetaxel treatment (for reasons, see Section 2.7.2.4.1 of the full dossier assessment). For the remaining patients, this could not be finally inferred from the available information. As docetaxel was available in the vast majority of the countries where the BC1-06 study was conducted, this criterion for ineligibility for docetaxel only applied to very few patients. Hence due to the study design, it was assumed for patients without docetaxel pretreatment that they mainly declined docetaxel, a treatment which potentially prolongs life, but is also associated with severe AEs, not for medical reasons, but based on their own individual decision (for reasons, see Section 2.7.2.4.1 of the full dossier

assessment). The patient population investigated in the BC1-06 study was therefore considered as sufficient approximation of the population of patients with the primary treatment goal of symptom control and prevention of late complications and of the patients for whom treatment with docetaxel is not an option. Hence the total population of the BC1-06 study was relevant for this benefit assessment for the comparison of radium-233 and BSC. To still investigate whether the missing eligibility for docetaxel affected the treatment effect, docetaxel pretreatment was considered specifically as subgroup characteristic. There were only individual indications of an effect modification (see Appendix C of the full dossier assessment). For this reason, the total study population of the BC1-06 study was assessed jointly. The observed indications of effect modifications by docetaxel pretreatment were considered in the interpretation of the results.

A total of 921 patients were randomly assigned in a ratio of 2:1, 614 patients to the radium-223 arm, and 307 patients to the placebo arm. The randomization was stratified by the factors "total alkaline phosphatase level" (< 220/≥ 220 U/L), concomitant bisphosphonate treatment (yes/no) and docetaxel pretreatment (yes/no).

The study treatment with radium-223 was administered according to a treatment regimen that corresponded to the description in the SPC [16]. The patients in the radium-223 arm received 6 slow intravenous injections of radium-223 at a dose of 50 kBq/kg body weight and at intervals of 4 weeks between each administration. The patients in the placebo arm received placebo in form of a physiological sodium chloride solution instead. The patients in both treatment groups additionally received BSC. BSC was defined in the study protocol as the routine standard treatment at each study centre, e.g. local external radiotherapy, corticosteroids, antiandrogens, oestrogens (e.g. stilboestrol), estramustine or ketoconazole. Any medical treatment that served either the clinical benefit or the supportive treatment of the patient could be administered at the investigator's discretion. Concomitant treatments allowed during the study were analgesics (including opioids) and luteinizing hormone-releasing hormone (LH-RH) agonists or polyoestradiol for the treatment of patients who had not had bilateral orchiectomy. Patients who had already received bisphosphonates before randomization could continue this treatment during all periods of the study. Treatment with the study medication was to be discontinued when cytotoxic chemotherapy, other systemic radioisotopes, hemibody external radiotherapy or other investigational treatments were regarded as BSC in the treatment phase. A total of 387 (42.0%) of the 921 patients randomized in the BC1-06 study discontinued treatment prematurely, 216 (23.5%) due to AEs or death. It was not clear from the study documents how many of the remaining patients discontinued the study medication because such a treatment as BSC was required. Nevertheless, the BC1-06 study was regarded as relevant for the research question radium-223 + BSC versus BSC.

The study consisted of a screening phase, the treatment phase and a follow-up phase of up to 3 years after enrolment. The treatment phase was defined as period of the first injection of the study medication until 4 weeks after the last injection of the study medication. Due to the

treatment regimen described above, the treatment period was therefore 24 weeks. Follow-up was conducted every 2 months from the 4th week until the 52nd week after the last injection and every 4 months from the 53rd week until 3 years after enrolment.

Overall survival and skeletal-related events were followed-up during the total course of the study. AEs were recorded up to 12 weeks after the last injection of the study medication. Exclusively AEs with an assumed association with the study medication were also recorded in the entire follow-up period, but these were not relevant for this assessment. The outcomes on health-related quality of life were recorded in week 16 and 24 during the treatment phase and once within the follow-up phase (week 44). Primary outcome of the BC1-06 study was overall survival.

One interim analysis was planned per protocol after approximately 320 deaths. This was conducted after 314 deaths. The data cut-off for this interim analysis was the 14 October 2010. A second analysis was performed at the data cut-off date 15 July 2011, which included the data recorded of all 921 randomized patients at this time point. The reason for the second data cut-off was the recommendation by the independent data monitoring committee (IDMC) to stop the BC1-06 study as the effect for the primary outcome “overall survival” had crossed the prespecified boundaries in the interim analysis. The recommendation to stop the study was followed by the decision to unblind the study. The database of the interim analysis was locked on 30 June 2011 and the study was unblinded on 1 July 2011. An amendment to the study protocol allowed the investigators to offer approval-compliant treatment with radium-223 to those patients from the placebo arm who still participated in the study and fulfilled the inclusion criteria defined in the amendment. Until the second data cut-off date 15 July 2011, no patient from the placebo was treated with radium-223. The data cut-off from 15 July 2011 was decisive for the present benefit assessment because it covered the longest observation period possible. This concurs with the company’s approach, which additionally presented results on the first data cut-off for the outcomes “overall survival” and “time to first symptomatic skeletal-related event”, but only used the results on the second data cut-off for deriving the added benefit.

Table 6 shows the characteristics of the patients in the study included.

Table 6: Characteristics of the study populations – RCT, direct comparison: radium-223 + BSC vs. placebo + BSC

Study characteristic category	**Radium-223 + BSC N[a] = 614**	**Placebo + BSC N[a] = 307**
BC01-06 (ALSYMPCA)		
Age [years], mean (SD)	70 (8)	71 (8)
Baseline ECOG PS, n (%)		
0	165 (26.9)	78 (25.5)
1	371 (60.5)	187 (61.1)
2	76 (12.4)	40 (13.1)
3[b]	1 (0.2)	1 (0.3)
missing	1 (0.2)	1 (0.3)
EOD, n (%)		
EOD 1 (< 6 metastases)	100 (16.4)	38 (12.4)
EOD 2 (6-20 metastases)	262 (42.9)	147 (48.0)
EOD 3 (> 20 metastases, no superscan[c])	195 (31.9)	91 (29.7)
EOD 4 (superscan[c])	54 (8.8)	30 (9.8)
missing	3 (0.5)[d]	1 (0.3)[d]
Use of analgesics [according to WHO ladder], n (%)		
0	12 (2.0)	2 (0.7)
1	257 (41.9)	137 (44.6)
2	151 (24.6)	78 (25.4)
3	194 (31.6)	90 (29.3)
External radiotherapy within 12 weeks before screening visit, n (%)	99 (16.1)	48 (15.6)
Patients with docetaxel pretreatment, n (%)	352 (57.3)	174 (56.7)
Patients with concomitant bisphosphonate treatment at baseline, n (%)	250 (40.7)	124 (40.4)
Time since diagnosis of prostate cancer [months], median (min-max)[e]	58.8 (7.6-312.5)	52.0 (1.2-347.2)
Time since diagnosis of bone metastases [months], median (min-max)[f]	24.8 (0-254.2)	22.0 (0.2-183.2)
Study discontinuations[g]	370 (60.3)	212 (69.1)

(continued)

Table 6: Characteristics of the study populations – RCT, direct comparison: radium-223 + BSC vs. placebo + BSC (continued)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b: 5 patients in the radium-223 group and 1 patient in the BSC group with ECOG PS between 0 and 2 at the screening visit deteriorated to grade 3 at the baseline visit. These were recorded with the screening score.
c: Superscan was defined as diffuse intense skeletal tracer uptake without renal or background activity.
d: Percentages: Institute's calculation.
e: The data refer to the number of patients with existing data on diagnosis (radium-223 group: N = 543; placebo group: N = 271).
f: The data refer to the number of patients with existing data on diagnosis (radium-223 group: N = 526; placebo group: N = 258).
g: During treatment and follow-up (including deaths: 242 in the radium group and 142 in the placebo group).
BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EOD: extent of disease; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation; vs.: versus; WHO: World Health Organization

Patient characteristics were largely comparable in both treatment arms. The mean age of the study population was between 70 and 71 years. The proportion of patients pretreated with docetaxel was approximately 57%. Approximately 40% had concomitant bisphosphonate treatment. A little more than half of the patients already received opiates at baseline (WHO score 2 or 3). The vast majority of the patients (approximately 85%) had at least 6 bone metastases. However, about 87% of the patients in both treatment arms had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 at the start of treatment and only 13% had an ECOG PS of 2. The median time since diagnosis of the prostate cancer was 4.5 years, the time since diagnosis of bone metastases was about 2 years.

Information on the course of the study is provided in Table 7.

Table 7: Information on the course of the study – RCT, direct comparison: radium-223 + BSC vs. placebo + BSC

Study	**Radium-223 + BSC** **N[a] = 597**	**Placebo + BSC** **N[a] = 301**
BC01-06 (ALSYMPCA)		
treatment duration [months]; median (min-max)	141 (1-195)	128 (1-190)
Observation period adverse events	ND	ND

a: Number of patients observed in the safety population.
BSC: best supportive care; ND: no data; RCT: randomized controlled trial; vs.: versus

The median treatment duration was 141 days for the radium-223 arm and 128 days for the placebo arm, and therefore only differed marginally between the treatment groups. No information was available on the actual follow-up period for the individual outcomes including the ones on AEs (follow-up up to 12 weeks after the end of treatment).

Table 8 shows the risk of bias at study level.

Table 8: Risk of bias at study level – RCT, direct comparison: radium-223 + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
BC1-06 (ALSYMPCA)	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus							

The risk of bias at the study level was rated as low for the study. This concurs with the company's assessment.

Further information on study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and in Appendix 4-G of the dossier, and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

2.4.1 Docetaxel population

For the research question on the added benefit of radium-223 compared with docetaxel in patients who are eligible for docetaxel treatment and whose treatment goal is prolongation of life, no data suitable for deriving an added benefit were available. An added benefit of radium-223 versus the ACT docetaxel is therefore not proven for this subpopulation.

2.4.2 BSC population

2.4.2.1 Outcomes included

The following patient-relevant outcomes were considered in this assessment of the added benefit of radium-223 + BSC versus the ACT BSC (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - time to first symptomatic skeletal-related event

- Health-related quality of life
  - FACT-P
  - EQ-5D
- Adverse events
  - SAEs
  - severe AEs (CTCAE grade 3 or 4)
  - discontinuation due to AEs
  - diarrhoea

The outcome "time to first symptomatic skeletal-related event" is a combined outcome consisting of the following components: external radiotherapy to relieve skeletal symptoms, new symptomatic pathological bone fractures (vertebral and non-vertebral), spinal cord compression and tumour-related orthopaedic surgical intervention. All components were considered as patient-relevant and of similar severity. The specific AE "diarrhoea" was chosen based on frequency and differences between the treatment groups in the BC1-06 study under consideration of the patient relevance. The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 9 shows for which outcomes data were available in the study included.

Table 9: Matrix of outcomes – RCT, direct comparison: radium-223 + BSC vs. placebo + BSC

Study	**Outcomes**							
	Overall survival	**Time to first symptomatic skeletal-related event**	**Health-related quality of life (FACT-P)**	**Health-related quality of life (EQ-5D)**	**Serious adverse events**	**Severe adverse events (CTCAE grade 3 or 4)**	**Discontinuation due to adverse events**	**Diarrhoea**
BC1-06 (ALSYMPCA)	Yes	Yes	Yes	No[a]	Yes	Yes	Yes	Yes

a: No evaluable data (see Section 2.7.2.4.3 of the full dossier assessment).
BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate;
RCT: randomized controlled trial; vs.: versus

2.4.2.2 Risk of bias at outcome level

Table 10 shows the risk of bias for the outcomes included.

Table 10: Risk of bias at study and outcome level – RCT, direct comparison: radium-223 + BSC vs. placebo + BSC

Study	Study level	Outcomes							
		Overall survival	Time to first symptomatic skeletal-related event	Health-related quality of life (FACT-P)	Health-related quality of life (EQ-5D)	Serious adverse events	Severe adverse events (CTCAE grade 3 or 4)	Discontinuation due to adverse events	Diarrhoea
BC1-06 (ALSYMPCA)	L	L	L	H[a]	-[b]	H	H	H	H

a: A high proportion of patients (> 30%) were not considered in the analysis presented by the company so that this analysis was not evaluable for the present benefit assessment. The Institute's analyses on the basis of all patients randomized have a high risk of bias because they were based on unverifiable assumptions on the proportion of responders among the patients who were not observed.
b: No evaluable data (see Section 2.7.2.4.3 of the full dossier assessment).

BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; H: high; L: low; RCT: randomized controlled trial; vs.: versus

The risk of bias for the combined outcome "time to first symptomatic skeletal-related event" and for the outcome "overall survival" was rated as low. This concurs with the company's assessment. In contrast to the company's assessment, the results based on naive proportions on the outcomes "SAEs", severe AEs (CTCAE grade 3 or 4), "discontinuation due to AEs" and "diarrhoea" were rated as potentially highly biased (see Section 2.7.2.4.2 of the full dossier assessment).

The risk of bias for the outcome on health-related quality of life measured with the FACT-P instrument was rated as high. In principle, this concurs with the company's assessment. However, the company included this outcome on the basis of a deviating operationalization (see Section 2.7.2.4.3 of the full dossier assessment). The Institute conducted its own analyses to assess the outcome, which can also be highly biased because of the assumptions made. No evaluable data were available for health-related quality of life measured with the EQ-5D questionnaire. This contradicts the company's assessment.

The assessment of the risk of bias is justified in Section 2.7.2.4.2 of the full dossier assessment.

Further information about the choice of outcome and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.4.2.3 Results

Table 11, Table 12 and Table 13 summarize the results on the comparison of radium-223 + BSC with placebo + BSC in patients with the primary treatment goal of symptom control and prevention of late complications and of the patients for whom treatment with docetaxel is not an option ("BSC population"). Where necessary, the data from the company's dossier were supplemented by the Institute's own calculations. The Kaplan-Meier curves on the outcome "overall survival", on the combined outcome "time to first symptomatic skeletal-related event" and on the individual component "time to first external radiotherapy to relieve skeletal symptoms" can be found in Appendix B of the full dossier assessment. The results on the event rates for the individual components of the combined outcome "time to first symptomatic skeletal-related event" are presented in Table 29 (Appendix D of the full dossier assessment).

The following descriptions of results only include results from subgroup analyses in cases where these are important for the derivation of conclusions on the added benefit of the respective outcome. See Section 2.4.2.4 for a detailed presentation of the results from subgroup analyses.

Table 11: Results (survival time) – RCT, direct comparison: radium-223 + BSC versus placebo + BSC

Study outcome	Radium-223 + BSC		Placebo + BSC		Radium-223 + BSC versus placebo + BSC	
	N	Median survival time in months [95% CI]	N	Median survival time in months [95% CI]	HR [95% CI][a]	p-value[a,b]
BC1-06 (ALSYMPCA)[c]						
Mortality						
Overall survival	614	14.9 [13.9; 16.1]	307	11.3 [10.4; 12.8]	0.70 [0.58; 0.83]	< 0.001
Morbidity						
Time to first symptomatic skeletal-related event	614	15.6 [13.5; 18.0]	307	9.8 [7.3; 23.7]	0.66 [0.52; 0.83]	< 0.001
Time to first external radiotherapy to relieve skeletal symptoms	614	17.1 [14.1; 19.8]	307	17.5 [7.9; 29.0]	0.67 [0.53; 0.85]	0.001
Time to first symptomatic pathological fracture	614	NA	307	NA	0.62 [0.35; 1.09]	0.095
Time to first tumour-related orthopaedic surgical intervention	614	NA	307	NA	0.72 [0.28; 1.82]	0.479
Time to first spinal cord compression	614	NA	307	NA	0.52 [0.29; 0.93]	0.025

c: Analyses adjusted for total ALP, use of bisphosphonates and docetaxel treatment.
b: Log-rank test.
c: Data cut-off 15 July 2011.

ALP: alkaline phosphatase; BSC: best supportive care; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Table 12: Results health-related quality of life – RCT, direct comparison: radium-223 + BSC versus placebo + BSC

Study outcome	Radium-223 + BSC		Placebo + BSC		Radium-223 + BSC versus placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
BC1-06 (ALSYMPCA)[a]					
Health-related quality of life					
Proportion of patients with improvement[b] (FACT-P)					
Scenario 1[c]	614[d]	106[e] (17.3)	307[d]	30[e] (9.8)	1.77 [1.09; 2.86][f]; p = 0.023[f]
Scenario 2[g]	614[d]	136[e] (22.1)	307[d]	50[e] (16.3)	1.37 [0.94; 1.99][f]; p = 0.099[f]
EQ-5D	No evaluable results				

a: Results are based on data cut-off from 15 July 2011.
b: Patients with an improvement of ≥ 10 points in the FACT-P total score were regarded as responders.
c: All patients with missing values were rated as non-responders (no improvement).
d: Number of randomized patients. Only patients with documentation at baseline and in week 16 or 24 were considered in the analysis presented in the dossier (radium-223: N = 431; placebo: N = 186).
e: Institute's calculation.
f: Institute's calculation with correction of variance according to the dataset resizing approach [18].
g: Patients with missing values in both treatment groups were rated as responders in a proportion that corresponds to the proportion of responders in the control group from the analysis of the available (not missing) data. The remaining patients were rated as non-responders.

BSC: best supportive care; CI: confidence interval; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Table 13: Results (adverse events) – RCT, direct comparison: radium-223 + BSC versus placebo + BSC

Study outcome	Radium-223 + BSC		Placebo + BSC		Radium-223 + BSC versus placebo + BSC
	N	Patients with at least one event n (%)	N	Patients with at least one event n (%)	RR [95% CI][a]; p-value[b]
BC1-06 (ALSYMPCA)[c]					
Adverse events					
Adverse events[d]	600	556 (92.7)	301	285 (94.7)	
Serious adverse events[b]	600	271 (45.2)	301	162 (53.8)	0.84 [0.73; 0.96]; p = 0.014
Discontinuation due to adverse events[d]	600	96 (16.0)	301	58 (19.3)	0.83 [0.62; 1.12]; p = 0.238
Severe adverse events (CTCAE grade 3 or 4)[d]	600	324 (54.0)	301	178 (59.1)	0.91 [0.81; 1.03]; p = 0.146
Diarrhoea[e]	600	151[f] (25.2)	301	45 (15.0)	1.68 [1.24; 2.28]; p < 0.001

a: Institute's calculation, asymptotic.
b: Institute's calculation, unconditional exact test (CSZ method according to [19]).
c: Data cut-off 15 July 2011.
d: All events associated with a skeletal-related event and recorded at the same time were excluded from the analysis.
e: Results based on the Preferred Term "Diarrhea".
f: Contradictory data in Module 4, where 150 patients with event were reported.
BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Mortality

Overall survival

Treatment with radium-223 + BSC resulted in a statistically significant prolongation of overall survival in comparison with placebo + BSC for the total population of the BC1-06 study.

In addition, there was an indication of an effect modification by the characteristic "age" for the outcome "overall survival" (interaction test p = 0.116). It was therefore also necessary to consider the results separately for patients < 65 years and for patients ≥ 65 years. For both age groups, there was an indication of an added benefit of radium-223 + BSC for the outcome "overall survival" compared with the ACT BSC, the extent of which was different, however (see Section 2.4.2.4).

This assessment deviates from that of the company, which, on the basis of the meta-analysis of the BC1-02 study and the BC1-06 study, claimed proof of an added benefit and did not consider the subgroups.

Morbidity

Time to first symptomatic skeletal-related event

The time to first symptomatic skeletal-related event was statistically significantly longer under treatment with radium-223 + BSC than under treatment with placebo + BSC. The result for the combined outcome was largely based on the component "external radiotherapy to relieve skeletal symptoms" (see also Table 29 in Appendix D and Figure 3 in Appendix B of the full dossier assessment).

In addition, there was an indication of an effect modification by the characteristic "concomitant bisphosphonate treatment" for this combined outcome. Hence for patients with concomitant bisphosphonate treatment, there was an indication, for patients without concomitant bisphosphonate treatment, there was a hint of an added benefit of radium-223 + BSC compared with BSC for the outcome "time to first symptomatic skeletal-related event" (see Section 2.4.2.4).

These assessments deviate from those of the company, which, on the basis of the meta-analysis of the BC1-02 study and the BC1-06 study, claimed proof of an added benefit and did not consider the subgroups.

Health-related quality of life

FACT-P

The dossier contained no evaluable data on health-related quality of life, assessed with the FACT-P, because in each case a proportion of > 30% of the patients were not considered in the analysis because of missing values (see Section 2.7.2.4.3 of the full dossier assessment). Under certain assumptions however, it was possible for the Institute to conduct its own calculations based on all patients randomized for the responder analysis on the proportion of patients with relevant improvement. Two conservative sensitivity analyses were conducted, in which patients who were not included in the company's analysis because of missing values (radium-223 group: 181 patients, placebo group: 121 patients) were considered in the following way:

1) All patients not considered in the company's analysis were included as non-responders (patients without improvement).
2) The patients not considered in the company's analysis were included with a proportion of 16.1% as responders in each of the 2 treatment groups, the remaining ones as non-responders. This proportion corresponds to the rate of responders in the placebo group from the analysis without missing values (30 responders among 186 patients with values at baseline and in week 16 or 24).

The additional consideration of the patients excluded from the company's analysis and the simple addition in the 2x2 table resulted in a more precise effect estimate, which contradicts the existing uncertainty caused by the assumptions made. To correct this increased precision caused by the approach, the confidence intervals were calculated using a correction of variance (dataset resizing approach) proposed by Higgins 2008 [18].

Whereas the first sensitivity analysis (scenario 1 in Table 12) produced a statistically significant difference in favour of radium-223 + BSC, the difference between the treatment groups in the second sensitivity analysis (scenario 2 in Table 12) was not statistically significant. It is unclear which of the 2 sensitivity analyses represents the more realistic scenario. Overall, because of this non-robust result and the outcome-related high risk of bias, an added benefit of radium-223 + BSC compared with the ACT BSC is not proven for the outcome "health-related quality of life", assessed with the FACT-P.

This deviates from the company's assessment, which derived a hint of an added benefit on the basis of the results on the FACT-P it presented.

EQ-5D

The company's dossier contained no evaluable data on health-related quality of life assessed with the EQ-5D. An added benefit of radium-223 + BSC in comparison with BSC for this outcome is therefore not proven.

This deviates from the company's assessment, which derived a hint of an added benefit on the basis of the results on the EQ-5D.

Adverse events

The dossier contained different analyses on the outcomes "SAEs", "severe AEs (CTCAE grade 3 or 4)" and "discontinuation due to AEs". Analyses based on all events occurring in the study during treatment including the 12-week follow-up were planned a priori in the BC1-06 study. However, events associated with a skeletal-related event were also recorded as AEs in the study. The company's dossier contained additional analyses on all outcomes mentioned above as sensitivity analyses, in which all events associated with a skeletal-related event and recorded at the same time were excluded. The sensitivity analysis conducted post hoc by the company was primarily used for this benefit assessment because skeletal-related events were considered as separate outcome in this benefit assessment. The results on the analyses based on all events are presented in Appendix A of the full dossier assessment. There was no difference regarding statistical significance between the analyses with and without events associated with skeletal-related events for any outcome.

Serious adverse events

In the BC1-06 study, there was a statistically significant difference in favour of radium-223 + BSC with regard to the proportion of patients with at least one SAE. This difference was presumably due to AEs caused by an increased use of drugs (e.g. analgesics) in the placebo +

BSC group. There was a high risk of bias for the outcome with known direction of the bias (see Section 2.7.2.4.2 of the full dossier assessment).

In addition, there was an indication of an effect modification by the subgroup characteristic "opiate treatment at baseline" for the outcome (interaction test p = 0.197). It was therefore also necessary to consider the results separately for patients with and without opiate treatment at baseline. For patients who had not been treated with opiates at baseline, there was an indication, for patients who already were treated with opiates at baseline, there was a hint of lesser harm from radium-223 + BSC in comparison with ACT BSC (see Section 2.4.2.4).

This assessment does not concur with that of the company, which, from the meta-analysis of the BC1-02 study and the BC1-06 study, claimed proof of lesser harm and did not consider the subgroups.

Severe adverse events (CTCAE grade 3 or 4)

There was no statistically significant difference between the treatment groups for the outcome "severe AEs (CTCAE grade 3 or 4)". However, there was an indication of an effect modification by the characteristics "opiate treatment at baseline" (interaction test p = 0.112) and "pretreatment with docetaxel" for this outcome (interaction test p = 0.124). It was therefore also necessary to consider the results separately for patients with and without opiate treatment at baseline and for patients with and without docetaxel pretreatment.

For patients who had not been treated with opiates at baseline, there was a hint of lesser harm from radium-223 + BSC in comparison with the ACT BSC. For patients with docetaxel pretreatment, there was also a hint of lesser harm from radium-223 + BSC in comparison with the ACT BSC. Greater or lesser harm from radium-223 is not proven for patients who already were treated with opiates at baseline or for patients without docetaxel pretreatment (see Section 2.4.2.4).

This assessment does not concur with that of the company, which derived proof of lesser harm for patients with docetaxel pretreatment from the meta-analysis of the BC1-02 study and the BC1-06 study and also did not consider the subgroup characteristic "opiate treatment at baseline".

Discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". However, there was an indication of an effect modification by the characteristic "age" (interaction test p = 0.168). Greater or lesser harm from radium-223 + BSC compared with the ACT BSC is not proven for any of the 2 age groups (see Section 2.4.2.4).

This assessment concurs with that of the company, which also derived neither lesser nor greater harm from radium-223 for the outcome "discontinuation due to AEs" on the basis of the meta-analysis of the BC1-02 study and the BC1-06 study.

Diarrhoea

There was a statistically significant difference to the disadvantage of radium-223 + BSC compared with placebo + BSC in the BC1-06 study for the outcome "diarrhoea".

There was also an indication of an effect modification by the characteristic "docetaxel pretreatment" (interaction test $p = 0.152$). It was therefore also necessary to consider the results separately for patients with and without docetaxel pretreatment. For patients without docetaxel pretreatment, this resulted in a hint of greater harm from radium-223 + BSC in comparison with the ACT BSC with regard to diarrhoea (see Section 2.4.2.4).

This assessment deviates from that of the company, which, on the basis of the meta-analysis of the BC1-02 study and the BC1-06 study, claimed proof of greater harm and did not consider the subgroups.

2.4.2.4 Subgroups and other effect modifiers

In order to describe possible effect differences between the patient groups, the following potential effect modifiers were investigated:

- age (< 65/≥ 65 years)
- docetaxel pretreatment (yes/no)
- baseline ECOG PS (0 and 1/≥ 2)
- extent of disease (EOD) according to number of bone metastases (EOD 1 to EOD 4)
- opiate treatment at baseline according to the WHO ladder (yes [WHO score 2 or 3]/no [WHO score 0 or 1])
- concomitant bisphosphonate treatment (yes/no)
- ethnicity (white/others)

Regarding the potential effect modifier "concomitant bisphosphonate treatment" it should be noted that the differentiating characteristic of the patients of the BC1-06 study was whether or not they had bisphosphonate treatment at baseline. The term "concomitant treatment" is used because bisphosphonate treatment that was currently used at baseline could be continued as concomitant medication during the course of the study. This characteristic was also a stratifying factor in the randomization of the BC1-06 study.

Possible effect modification was investigated for all outcomes except health-related quality of life (assessed with the FACT-P). All potential effect modifiers considered except the characteristic "age" were predefined in the BC1-06 study.

The prerequisite for proof of differing effects is a statistically significant homogeneity and/or interaction test ($p < 0.05$). A p-value between 0.05 and 0.2 provides an indication of differing effects.

Table 14 and Table 15 show the results of the subgroup analyses for subgroup characteristics for which an indication of an effect modification was provided. There was no proof ($p < 0.05$) of an effect modification from any of the subgroup analyses.

Table 14: Subgroups with indication of interaction (survival time): RCT, direct comparison: radium-223 + BSC vs. placebo + BSC

Study outcome characteristic subgroup	Radium-223 + BSC N	Radium-223 + BSC Median survival time in months [95% CI]	Placebo + BSC N	Placebo + BSC Median survival time in months [95% CI]	Radium-223 + BSC versus placebo + BSC HR [95% CI][a]	Radium-223 + BSC versus placebo + BSC p-value
BC1-06 (ALSYMPCA)[b]						
Mortality						
Overall survival						
age						
< 65 years	158	16.9 [14.8; 25.9]	73	11.4 [8.7; 14.8]	0.57 [0.39; 0.82]	0.003[a, c]
≥ 65 years	456	14.1 [12.5; 15.5]	234	11.3 [9.6; 12.9]	0.78 [0.63; 0.95]	0.014[a, c]
					interaction:	0.116[d]
Morbidity						
Time to first symptomatic skeletal-related event						
baseline EOD[e]						
EOD 1-3[f]	575	ND	276	ND	0.62 [0.48; 0.79]	p < 0.001
EOD 1	*100*	*18.5 [10.5; NA]*	*38*	*17.5 [6.7; 29.0]*	*0.68 [0.39; 1.20]*	*0.184[a, c]*
EOD 2	*262*	*17.1 [12.7; NA]*	*147*	*7.8 [6.2; 11.2]*	*0.52 [0.37; 0.72]*	*< 0.001[a, c]*
EOD 3	*195*	*13.6 [9.7; 16.5]*	*91*	*9.0 [6.1; NA]*	*0.76 [0.50; 1.16]*	*0.200[a, c]*
EOD 4	54	17.0 [14.7; NA]	30	NA	2.03 [0.57; 7.21]	0.274[a, c]
					interaction[g]:	0.074[d]
concomitant bisphosphonate treatment[h]						
yes	250	19.6 [16.5; NA]	124	10.2 [7.8; 29.0]	0.49 [0.33; 0.74]	< 0.001[a]
no	364	11.8 [9.3; 13.6]	183	8.4 [6.4; 19.5]	0.77 [0.58; 1.02]	0.068[a]
					interaction:	0.056

c: Analyses adjusted for total ALP, use of bisphosphonates and use of docetaxel. Presumably also adjusted for age, BMI, body weight, baseline ECOG PS, EOD, baseline pain, opiate treatment and ethnicity.
b: Data cut-off 15 July 2011.
c: Log-rank test.
d: Cochran's Q test.
e: The EOD is determined based on the number of bone metastases. The classes are defined as follows: EOD 1: < 6 metastases; EOD 2: 6 to 20 metastases; EOD 3: > 20 metastases, but no superscan; EOD 4: superscan. (Superscan was defined as diffuse intense skeletal tracer uptake without renal or background activity.)
f: The groups EOD 1 to EOD 3 were summarized because heterogeneity could not be demonstrated (p = 0.352), see following text for more details; Institute's calculation of all values. The original subgroups are presented in italics.
g: Interaction test relating to the original subgroups.
h: Recorded by the presence of bisphosphonate treatment at baseline.

ALP: alkaline phosphatase; BMI: body mass index; BSC: best supportive care; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EOD: extent of disease; HR: hazard ratio; N: number of analysed patients; NA: not achieved; ND: no data; RCT: randomized controlled trial; vs.: versus

Table 15: Subgroups with indication of interaction (adverse events): RCT, direct comparison: radium-223 + BSC vs. placebo + BSC

Study outcome characteristic subgroup	Radium-223 + BSC		Placebo + BSC		Radium-223 + BSC versus placebo + BSC	
	N	Patients with at least one event n (%)	N	Patients with at least one event n (%)	RR [95% CI][b]	p-value
BC1-06 (ALSYMPCA)						
Adverse events						
Serious adverse events[a]						
opiate treatment at baseline						
yes	337	168 (49.9)	163	90 (55.2)	0.90 [0.76; 1.08]	0.299[c]
no	236	103 (39.2)	138	72 (52.2)	0.75 [0.60; 0.93]	0.013[c]
					interaction:	0.197[d]
Discontinuation due to adverse events[a]						
age						
< 65 years	153	25 (16.3)	71	9 (12.7)	1.29 [0.64; 2.62]	0.503[c]
≥ 65 years	447	71 (15.9)	230	49 (21.3)	0.75 [0.54; 1.03]	0.084[c]
					interaction:	0.168[d]
Severe adverse events (CTCAE grade 3 or 4)[a]						
opiate treatment at baseline						
yes	337	195 (57.9)	163	95 (58.3)	0.99 [0.85; 1.16]	0.949[c]
no	263	129 (49.0)	138	83 (60.1)	0.82 [0.68; 0.98]	0.035[c]
					interaction:	0.112[d]
docetaxel pretreatment						
yes	347	192 (55.3)	171	112 (65.5)	0.84 [0.73; 0.98]	0.028[c]
no	253	132 (52.2)	130	66 (50.8)	1.03 [0.84; 1.26]	0.846[c]
					interaction:	0.124[d]

(continued)

Table 15: Subgroups with indication of interaction (adverse events): RCT, direct comparison: radium-223 + BSC vs. placebo + BSC (continued)

Study outcome characteristic subgroup	Radium-223 + BSC		Placebo + BSC		Radium-223 + BSC versus placebo + BSC	
	N	Patients with at least one event n (%)	N	Patients with at least one event n (%)	RR [95% CI][b]	p-value
Diarrhoea						
baseline ECOG PS						
0-1	528	138 (26.1)	260	37 (14.2)	1.84 [1.32; 2.56]	< 0.001[c]
≥ 2	72	12 (16.7)	40	8 (20.0)	0.83 [0.37; 1.87]	0.685[c]
					interaction:	0.075[d]
baseline EOD[e]						
EOD 1	99	37 (37.4)	37	5 (13.5)	2.77 [1.18; 6.50]	0.011[c]
EOD 2	256	65 (25.4)	145	19 (13.1)	1.94 [1.21; 3.10]	0.004[c]
EOD 3	192	38 (19.8)	88	15 (17.0)	1.16 [0.68; 2.00]	0.726[c]
EOD 4	51	9 (17.6)	30	6 (20.0)	0.88 [0.35; 2.23]	0.815[c]
					interaction:	0.158[d]
opiate treatment at baseline						
yes	337	80 (23.7)	163	18 (11.0)	2.15 [1.34; 3.46]	< 0.001[c]
no	263	70 (26.6)	138	27 (19.6)	1.36 [0.92; 2.02]	0.126[c]
					interaction:	0.144[d]
docetaxel pretreatment						
yes	347	85 (24.5)	171	30 (17.5)	1.40 [0.96; 2.03]	0.075[c]
no	253	65 (25.7)	130	15 (11.5)	2.23 [1.32; 3.75]	0.001[c]
					interaction:	0.152[d]

a: All events associated with a skeletal-related event and recorded at the same time were excluded from the analysis.
b: Institute's calculation, asymptotic.
c: Institute's calculation: unconditional exact test (CSZ method according to [19]).
d: Institute's calculation: Cochran's Q test.
e: The EOD is determined based on the number of bone metastases. The classes are defined as follows: EOD 1: < 6 metastases; EOD 2: 6 to 20 metastases; EOD 3: > 20 metastases, but no superscan; EOD 4: superscan. (Superscan was defined as diffuse intense skeletal tracer uptake without renal or background activity.)
BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EOD: extent of disease; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Mortality

Overall survival

There was an indication of an effect modification by age (< 65 years or ≥ 65 years) for the outcome "overall survival".

For both age groups, treatment with radium-223 + BSC produced a statistically significant prolongation in overall survival compared with placebo + BSC. Hence for both age groups, there was an indication of an added benefit of radium-223 + BSC for the outcome "overall survival" compared with the ACT BSC, the extent of which was different, however.

These assessments deviate from those of the company, which did not consider the effect modification by age when deriving the added benefit as it derived the proof of added benefit exclusively on the basis of the total population.

Morbidity

Time to first symptomatic skeletal-related event

For the combined outcome "time to first symptomatic skeletal-related event", there was an indication of an effect modification of the disease at baseline (EOD 1 to EOD 4) as well as by the characteristic "concomitant bisphosphonate treatment (yes or no)".

Characteristic "extent of disease"

When considering the results on the individual subgroups according to the characteristic "baseline EOD", there was a homogeneous picture for the subgroups of patients with EOD 1 to EOD 3. When considering these 3 subgroups alone, there was neither proof nor indication of effect modification (interaction test p = 0.352). Hence the effect modification was only caused by the subgroup of patients with EOD = 4. This subgroup with only approximately 9% of the patients was by far the smallest subgroup. Accordingly, the estimation of the treatment effect was very imprecise. Overall, the subgroup analysis was therefore regarded to be not interpretable and was not considered further.

Characteristic "concomitant bisphosphonate treatment"

For patients with concomitant bisphosphonate treatment, treatment with radium-223 + BSC produced a statistically significant prolongation in time to first symptomatic skeletal-related event compared with placebo + BSC. This provides an indication of an added benefit of radium-223 + BSC compared with BSC for these patients for the outcome "time to first symptomatic skeletal-related event".

In contrast, there was no statistically significant difference between the treatment groups for patients who did not receive concomitant bisphosphonates. Since merely an indication of an effect modification by concomitant bisphosphonate treatment was present, the statistically significant result in favour of radium-223 + BSC in the total population should be considered when interpreting the results for these patients. However, there is an increased uncertainty due

to the lack of a statistically significant effect in the subgroup. Because of this, there is a hint of an added benefit of radium-223 + BSC compared with the ACT BSC in patients without concomitant bisphosphonate treatment.

This assessment does not concur with that of the company, which, from the meta-analysis of the BC1-02 study and the BC1-06 study, claimed proof of added benefit and did not consider the subgroup analyses.

Adverse events

Serious adverse events

There was an indication of an effect modification by the characteristic "opiate treatment at baseline (yes or no)" for the outcome "SAEs".

For patients who had not been treated with opiates at baseline, there was a statistically significant difference in favour of radium-223 + BSC compared with placebo + BSC. There was a high risk of bias for the outcome. This difference was presumably due to AEs caused by an increased use of drugs (e.g. analgesics) in the placebo + BSC group. Due to the known direction of bias, this results in an indication of lesser harm from radium-223 + BSC compared with the ACT BSC with regard to SAEs for these patients.

There was no statistically significant difference between the treatment groups for patients who were already treated with opiates at baseline. Since merely an indication of an effect modification by the characteristic "opiate treatment at baseline" was present, the statistically significant result in favour of radium-223 + BSC in the total population should be considered when interpreting the results for these patients. However, there is an increased uncertainty due to the lack of a statistically significant effect in the subgroup. Because of this, there is a hint of lesser harm from radium-223 + BSC compared with the ACT BSC with regard to SAEs for these patients.

This assessment does not concur with that of the company, which, from the meta-analysis of the BC1-02 study and the BC1-06 study, claimed proof of lesser harm and did not consider the subgroup analyses.

Severe adverse events (CTCAE grade 3 or 4)

There was an indication of an effect modification by the characteristics "opiate treatment at baseline (yes or no)" and "docetaxel pretreatment (yes or no)" for the outcome "severe AEs (CTCAE grade 3 or 4)".

For patients who had not been treated with opiates at baseline and for patients with docetaxel pretreatment, there was, in each case, a statistically significant difference in favour of radium-223 + BSC compared with placebo + BSC. This difference was presumably due to AEs caused by an increased use of drugs (e.g. analgesics) in the placebo + BSC group. Due to the fact that there was no statistically significant difference between the treatment groups in the

total population and that there was only an indication of effect modification by each of the characteristics "opiate treatment at baseline" and "docetaxel pretreatment", the results are subject to increased uncertainty. Overall, in each case, there is a hint of lesser harm from radium-223 + BSC compared with the ACT BSC with regard to severe AEs for these patients.

There was no statistically significant difference between the treatment groups both for patients who were already treated with opiates at baseline and for patients without docetaxel pretreatment. Greater or lesser harm of radium-223 + BSC compared with BSC is therefore not proven for these patients.

This assessment does not concur with that of the company, which derived proof of lesser harm for patients with docetaxel pretreatment from the meta-analysis of the BC1-02 study and the BC1-06 study and also did not consider the subgroup characteristic "opiate treatment at baseline".

Discontinuation due to adverse events

There was an indication of an effect modification by age (< 65 years or ≥ 65 years) for the outcome "discontinuation due to AEs".

There was no statistically significant difference between the treatment groups for the total population or for the age subgroups. Hence, greater or lesser harm of radium-223 + BSC compared with the ACT BSC for the outcome "treatment discontinuation due to AEs" is not proven.

This concurs with the company's assessment.

Diarrhoea

For the outcome "diarrhoea", there was a hint of effect modification by the characteristics "baseline ECOG PS (0 and 1/≥ 2)", "baseline EOD (EOD 1 to EOD 4)", "opiate treatment at baseline (yes/no)" and "docetaxel pretreatment (yes/no)".

The picture was heterogeneous in the consideration of the individual subgroups. Each of the subgroup characteristics "ECOG PS", "EOD" and "opiate treatment" is to be regarded as dimension of the severity grade or stage of the disease. For each of the characteristics "baseline ECOG PS" and "baseline EOD", there was a statistically significant difference to the disadvantage of radium-223 + BSC compared with placebo + BSC only in the lower severity grades (ECOG PS 0 or 1 and EOD 1 and EOD 2). In contrast, for the characteristic "opiate treatment", this was the case only in patients who had already received opiates for pain therapy at baseline. Because of these contradictory results, these subgroup analyses for the outcome "diarrhoea" were regarded as not interpretable and not considered further.

The characteristic "docetaxel pretreatment" is different from the other characteristics. This characteristic is not only to be regarded as dimension of a disease stage, but also represents the previous stress the patient was subjected to by the docetaxel treatment. There was a statistically

significant difference to the disadvantage of radium-223 + BSC compared with placebo + BSC for patients without docetaxel pretreatment. For the outcome that was based on the proportion of patients with at least one event, there was a high risk of bias because it was unclear whether the observation period was relevantly different between the treatment groups (see Section 2.7.2.4.2 of the full dossier assessment). It cannot be excluded that the observed effect was solely caused by systematic bias. This is due to the effect to the disadvantage of radium-223 + BSC and the concurrent known direction of the bias in direction of an effect to the disadvantage of radium-223 + BSC. Hence overall, there is a hint of greater harm from radium-223 + BSC compared with the ACT BSC with regard to diarrhoea for these patients. There was no statistically significant difference between the treatment groups for patients with docetaxel pretreatment. Because of this and because of the uncertainty resulting from the high risk of bias, greater or lesser harm from radium-223 + BSC compared with the ACT BSC with regard to diarrhoea is not proven in these patients.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit for each subpopulation is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Docetaxel population

As no relevant data were available for the research question of radium-223 in comparison with docetaxel in patients with the treatment goal “prolongation of life”, an added benefit of radium-223 in comparison with the ACT is not proven for this subpopulation.

2.5.2 BSC population

2.5.2.1 Assessment of added benefit at outcome level

The data presented in Section 2.4.2 resulted in indications or hints of an added benefit of radium-233 + BSC compared with BSC for the outcomes “overall survival”, “time to first skeletal-related event” and “health-related quality of life”. Both greater and lesser harm from radium-233 + BSC versus BSC were observed for the AE outcomes.

Moreover, there were indications of effect modifications for the following subgroup characteristics: age, concomitant bisphosphonate treatment, opiate treatment at baseline and docetaxel pretreatment.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 16). In the overall assessment, it was then investigated whether different conclusions on the extent of added benefit arise for the individual patient groups.

Table 16: Extent of added benefit at outcome level: radium-223 + BSC vs. BSC

Outcome category **outcome** effect modifier subgroup	**Radium-223 + BSC vs. BSC** **quantile of time to event or proportion of events/** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: 14.9 vs. 11.3 months HR: 0.70 [0.58; 0.83] p < 0.001	
Age (years)		
< 65	Median: 16.9 vs. 11.4 months HR: 0.57 [0.39; 0.82] p = 0.003 probability: "indication"	Outcome category: survival time $CI_u < 0.85$ added benefit, extent: "major"
≥ 65	Median: 14.1 vs. 11.3 months HR: 0.78 [0.63; 0.95] p = 0.014 probability: "indication"	Outcome category: survival time $0.95 \leq CI_u < 1.00$ added benefit, extent: "minor"
Morbidity		
Time to first symptomatic skeletal-related event	Median: 15.6 vs. 9.8 months HR: 0.66 [0.52; 0.83] p < 0.001	
Concomitant bisphosphonate treatment		
Yes	Median: 19.6 vs. 10.2 months HR: 0.49 [0.33; 0.74] p < 0.001 probability: "indication"	Outcome category: serious/severe symptoms/late complications $CI_u < 0.75$ added benefit, extent: "major"
No	Median: 11.8 vs. 8.4 months HR: 0.77 [0.58; 1.02] p = 0.068 probability: "hint"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable" (not more than "considerable")
Health-related quality of life		
Improvement (FACT-P)	The results of sensitivity analyses were not robust	Added benefit not proven
EQ-5D	No evaluable results available	

(continued)

Table 16: Extent of added benefit at outcome level: radium-223 + BSC vs. BSC (continued)

Outcome category **outcome** effect modifier subgroup	**Radium-223 + BSC vs. BSC** **quantile of time to event or proportion of events/** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Adverse events[e]		
Serious adverse events	45.2% vs. 53.8% RR: 0.84 [0.73; 0.96] p = 0.014	
Opiate treatment at baseline		
Yes	49.9% vs. 55.2% RR: 0.90 [0.76; 1.08] p = 0.299 probability: "hint"	Outcome category: serious/severe adverse events lesser harm, extent: "minor"
No	39.2% vs. 52.2% RR: 0.75 [0.60; 0.93] p = 0.013 probability: "indication"	Outcome category: serious/severe adverse events $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Discontinuation due to adverse events	16.0% vs. 19.3% RR: 0.83 [0.62; 1.12] p = 0.238	Greater/lesser harm not proven
Severe adverse events (CTCAE grade 3 or 4)	54.0% vs. 59.1% RR: 0.91 [0.81; 1.03] p = 0.146	
Opiate treatment at baseline		
Yes	57.9% vs. 58.3% RR: 0.99 [0.85; 1.16] p = 0.949	Greater/lesser harm not proven
No	49.0% vs. 60.1% RR: 0.82 [0.68; 0.98] p = 0.035 probability: "hint"	Outcome category: serious/severe adverse events $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Docetaxel pretreatment		
Yes	55.3% vs. 65.5% RR: 0.84 [0.73; 0.98] p = 0.028 probability: "hint"	Outcome category: serious/severe adverse events $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
No	52.2% vs. 50.8% RR: 1.03 [0.84; 1.26] p = 0.846	Greater/lesser harm not proven

(continued)

Table 16: Extent of added benefit at outcome level: radium-223 + BSC vs. BSC (continued)

Outcome category **outcome** effect modifier subgroup	**Radium-223 + BSC vs. BSC** **quantile of time to event or proportion of events/** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Adverse events		
Diarrhoea	25.2% vs. 15.0% RR: 1.68 [1.24; 2.28] RR[c] 0.60 [0.44; 0.81] p < 0.001	
Docetaxel pretreatment		
Yes	24.5% vs. 17.5% RR: 1.40 [0.96; 2.03] p = 0.075	Greater/lesser harm not proven
No	25.7% vs. 11.5% RR: 2.23 [1.32; 3.75] RR[c] 0.45 [0.27; 0.76] p = 0.001 probability: "hint"	Outcome category: non-serious/non-severe adverse events[f] CI_u < 0.80 greater harm, extent: "considerable"

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Pooled estimate from meta-analysis, Institute's calculation.
d: Reversed direction of effect to enable direct use of limits to derive added benefit.
e: Analysis under exclusion of events associated with skeletal-related events and reported at the same time.
f: Classification into the outcome category "non-serious/non-severe adverse events" because almost exclusively non-severe diarrhoea occurred in the BC-06 study (of the 195 patients with ≥ 1 diarrhoea, 138 [70.8%] had CTCAE grade 1, and 44 [22.6%] had CTCAE grade 2 as highest severity grade).

BSC: best supportive care; CI: confidence interval; CI_u: upper limit of the CI; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

2.5.2.2 Overall conclusion on added benefit

Table 17 summarizes the results that were considered in the overall conclusion on added benefit.

Table 17: Positive and negative effects from the assessment of radium-223 + BSC compared with BSC

Positive effects	Negative effects
Mortality: ▪ overall survival ▫ age (< 65 years) indication of added benefit; extent: “major” ▫ age (≥ 65 years) indication of added benefit; extent: “minor”	
Serious/severe late complications ▪ time to first symptomatic skeletal-related event ▫ concomitant bisphosphonate treatment – yes indication of added benefit; extent: “major” ▫ concomitant bisphosphonate treatment – no hint of added benefit; extent: “non-quantifiable” (not more than “considerable”)	
Serious/severe adverse events: ▪ SAEs ▫ opiate treatment at baseline – yes hint of lesser harm, extent: “minor” ▫ opiate treatment at baseline – no indication of lesser harm, extent: “minor” ▪ severe AEs (CTCAE grade 3 or 4) ▫ opiate treatment at baseline – no hint of lesser harm, extent: “minor” ▫ docetaxel pretreatment – yes hint of lesser harm, extent: “minor”	Non-serious/non-severe AEs ▪ diarrhoea ▫ docetaxel pretreatment – no hint of greater harm, extent: “considerable”
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event	

Overall, positive effects and one negative effect remain. Positive effects were shown in the outcome categories “mortality”, “serious/severe late complications” and “serious/severe AEs”, each of which depends on different subgroup characteristics. The negative effect was shown in the outcome category “non-serious/non-severe AEs” and only in the subgroup of patients without docetaxel pretreatment.

The balancing of the positive and negative effects is conducted below separately for the 2 age groups considered.

Patients < 65 years

There is an indication of a major added benefit for the outcome “overall survival” for patients < 65 years. This effect is decisive at first for the overall conclusion on added benefit. In the outcome categories “serious/severe late complications” and “serious/severe AEs”, there are also at most indications of an added benefit with the extent also being at most major. These effects do not change the overall conclusion. This is offset by a hint of considerably greater harm from radium-223 + BSC. Against the background that this effect was only shown in a

subgroup and that the diarrhoea occurred was almost exclusively non-severe, this does not raise doubts about the overall conclusion.

Patients ≥ 65 years

There is an indication of a minor added benefit for patients ≥ 65 years for the outcome "overall survival". Furthermore, there is an additional positive effect for the outcome "time to first symptomatic skeletal-related event". This effect depends on the presence of baseline concomitant bisphosphonate treatment. There is an indication of a major added benefit for this outcome for patients receiving concomitant bisphosphonate treatment. Hence for these patients, this effect is decisive at first for the overall conclusion on added benefit. For patients who do not receive concomitant bisphosphonate treatment, there is a hint of a non-quantifiable (at most considerable) added benefit for the outcome "time to first symptomatic skeletal-related event". Overall, an indication of a minor added benefit remains at first for these patients due to the greater certainty of results for the outcome "overall survival". In the outcome category "serious/severe AEs", there are also at most indications of an added benefit with the extent being at most minor. This does not change the respective overall conclusion. This is offset by a hint of considerably greater harm from radium-223 + BSC in each case. Against the background that this effect was only shown in a subgroup and that the diarrhoea occurred was almost exclusively non-severe, this does not raise doubts about the overall conclusion.

In summary, there is an indication of a major added benefit for patients < 65 years and for patients ≥ 65 years with concomitant bisphosphonate treatment. There is an indication of a minor added benefit for patients ≥ 65 years without concomitant bisphosphonate treatment.

2.5.3 Extent and probability of added benefit – summary

The added benefit for patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases, which results from the assessment of radium-223 versus the ACT, is displayed in Table 18.

Table 18: Patient groups, ACTs and extent and probability of added benefit of radium-223 in patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases

Patient group	**ACT**[a]	**Subgroup**	**Extent and probability of added benefit**
Patients with the treatment goal of prolongation of life (docetaxel population)	Docetaxel in combination with prednisone or prednisolone	-	Added benefit not proven
Patients with the treatment goal of symptom control and prevention of late complications and patients for whom treatment with docetaxel is not an option (BSC population)	BSC[b]	Age < 65 years	Indication of a major added benefit
		Age ≥ 65 years, concomitant bisphosphonate treatment	Indication of a major added benefit
		Age ≥ 65 years, no concomitant bisphosphonate treatment	Indication of a minor added benefit

a: Presentation of the respective ACT specified by the G-BA.
b: BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care

The overall assessment deviates considerably from that of the company. The company claimed proof of a major added benefit for the group of patients who are not eligible for docetaxel treatment. For the group of patients who are eligible for docetaxel treatment, the company claimed a hint of a non-quantifiable added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

BC1-06 (ALSYMPCA)

M4A_BC1-06_Posthoc-Analysen_JUL2011.pdf [unpublished]. 2011.

M4A_BC1-06_Posthoc-Analysen_OKT2010.pdf [unpublished]. 2010.

M4A_BC1-06_Posthoc-Analysen_QoL.pdf [unpublished].

Algeta ASA. A double-blind, randomized, multiple dose, phase III, multicenter study of Alpharadin in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases: study BC1-06; clinical study report no A58799 [unpublished]. 2012.

Algeta ASA. A double-blind, randomized, multiple dose, phase III, multicenter study of Alpharadin in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases: study BC1-06; clinical study report no A58800 [unpublished]. 2012.

Bayer. A double-blind, randomised, multiple dose, phase III multicentre study of alpharadin in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases: full text view [online]. In: Clinicaltrials.gov. 15 April 2013 [accessed: 10 March 2014]. URL: http://clinicaltrials.gov/show/NCT00699751.

European Medicines Agency. Xofigo: radium-223 chloride; rapporteurs' day 128 joint response assessment report [unpublished]. 2013.

Oxford Outcomes. Quality of life analysis of castrate resistant prostate cancer patients in the placebo-controlled ALSYMPCA trial evaluating radium-223 [unpublished]. 2012.

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