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Radium 223 dichloride (prostate cancer) –

Benefit assessment according to §35a Social Code Book V[1] (new scientific findings)

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment Radium-223-dichlorid *(Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 July 2019). 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSC	best supportive care
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LH-RH	luteinizing hormone-releasing hormone
mCRPC	metastatic castration-resistant prostate cancer
RA-223	radium 223 dichloride
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

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 (Ra-223). The assessment of Ra-223 was based on a dossier compiled by the company. The dossier was sent to IQWiG on 3 April 2019.

On 13 December 2014, the pharmaceutical company (hereinafter referred to as "the company") presented a dossier for Ra-223 for the treatment of patients with castration-resistant prostate cancer and symptomatic bone metastases without known visceral metastases. On 1 November 2018, the G-BA requested a new benefit assessment because of new scientific findings, because the European Commission's decision of 28 September 2018 led to a restriction in the approval.

Research question

Ra-223 as monotherapy or in combination with a luteinizing hormone-releasing hormone (LH-RH) analogue in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in adult patients with metastatic castration-resistant prostate cancer (mCRPC) and symptomatic bone metastases without known visceral metastases whose disease has progressed after they had received at least 2 prior systemic lines of treatment for the therapy of the mCRPC (except for luteinizing hormone-releasing hormone [LH-RH] analogues), or for whom no other available systemic mCRPC therapy is indicated.

Table 2 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of Ra-223

Research question	Therapeutic indication	ACT[a]
1	Monotherapy or in combination with an LH-RH analogue for the treatment of adult patients with mCRPC and symptomatic bone metastases without known visceral metastases whose disease has progressed after they had received at least 2 prior systemic lines of treatment for the therapy of the mCRPC (except for LH-RH analogues), or for whom no other available systemic mCRPC therapy is indicated	BSC[b]

a: Presentation of the 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 (particularly adequate pain therapy, treatment with bisphosphonates, denosumab and/or radionuclides).

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; LH-RH: luteinizing hormone-releasing hormone; mCRPC: metastatic castration resistant prostate cancer; Ra-223: radium 223 dichloride

The company subdivided the therapeutic indication into the following patient groups:

- Patients whose disease has progressed after they had received at least 2 prior systemic lines of treatment for the therapy of the mCRPC (except for LH-RH analogues), and
- patients for whom no other available systemic mCRPC therapy is indicated

For the first patient group, the company considered abiraterone, cabazitaxel, docetaxel and enzalutamide as comparator therapy and thus deviated from the ACT specified by the G-BA. For the second patient group, the company considered BSC as comparator therapy and thus followed the G-BA's specification of the ACT.

In the present benefit assessment, the ACT, i.e. BSC, is considered for all patients in the therapeutic indication.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

The company identified no randomized controlled trials (RCTs) on direct comparisons or on adjusted indirect comparisons using a common comparator of Ra-223 versus the ACT or of Ra-223 versus the additionally considered comparators (abiraterone, cabazitaxel, docetaxel and enzalutamide). Therefore, the company used a retrospective data analysis from the Flatiron Health database as well as data from the single-arm studies PARABO and REASSURE conducted with Ra-223. Moreover, the company considered the RCT ALSYMPCA, which had justified the approval of Ra-223 for mCRPC in the original therapeutic indication in 2013.

The data presented by the company were unsuitable for the derivation of an added benefit of Ra-223 versus the BSC in the therapeutic indication.

The data from the Flatiron Health database presented by the company and the single-arm studies PARABO and REASSURE contained no data on BSC. Moreover, the company conducted no systematic information retrieval for the single-arm studies.

ALSYMPCA is a double-blind RCT on the comparison of Ra-223 + BSC with placebo + BSC in patients with CRPC and symptomatic bone metastases without known visceral metastases. In the original therapeutic indication, the ALSYMPCA study demonstrated considerable added benefit of Ra-223 in comparison with BSC. With the new therapeutic indication, the indication was restricted to patients whose disease has progressed after they had received at least 2 prior systemic lines of treatment for the therapy of the mCRPC (except for LH-RH analogues), or for whom no other available systemic therapy is indicated. The patients included in the ALSYMPCA study had either been pretreated with docetaxel or they were treatment-naive, in which case treatment with docetaxel had not been indicated or available or had been rejected by the patient. After completion of the recruitment in the ALSYMPCA study, further drugs like

abiraterone, cabazitaxel and enzalutamide were approved in addition to docetaxel. Approval of these drugs resulted in a radical change of the treatment situation in the therapeutic indication. Study results yielded under the conditions of this former treatment situation can thus not be transferred to the present treatment situation. The data of the ALSYMPCA study are thus unsuitable for the derivation of an added benefit of Ra-223 versus BSC.

Due to the reasons described above, there are no suitable data for the assessment of Ra-223 in the therapeutic indication. Hence, there was no hint of an added benefit of Ra-223 in comparison with the ACT BSC. An added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of the added benefit of Ra-223.

Table 3: Ra-223 – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Monotherapy or in combination with an LH-RH analogue for the treatment of adult patients with mCRPC and symptomatic bone metastases without known visceral metastases whose disease has progressed after they had received at least 2 prior systemic lines of treatment for the therapy of the mCRPC (except for LH-RH analogues), or for whom no other available systemic mCRPC therapy is indicated	BSC[b]	Added benefit not proven
a: Presentation of the 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 (particularly adequate pain therapy, treatment with bisphosphonates, denosumab and/or radionuclides). ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; LH-RH: luteinizing hormone-releasing hormone; mCRPC: metastatic castration resistant prostate cancer; Ra-223: radium 223 dichloride		

The G-BA decides on the added benefit.

2.2 Research question

Radium-223-dichloride (Ra-223) as monotherapy or in combination with a luteinizing hormone-releasing hormone (LH-RH) analogue in comparison with BSC as ACT in adult

[3] 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). 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, added benefit not proven, or less benefit). For further details see [1,2].

patients with mCRPC and symptomatic bone metastases without known visceral metastases whose disease has progressed after they had received at least 2 prior systemic lines of treatment for the therapy of the mCRPC (except for LH-RH analogues), or for whom no other available systemic mCRPC therapy is indicated.

Table 4 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of Ra-223

Research question	**Therapeutic indication**	**ACT[a]**
1	Monotherapy or in combination with an LH-RH analogue for the treatment of adult patients with mCRPC and symptomatic bone metastases without known visceral metastases whose disease has progressed after they had received at least 2 prior systemic lines of treatment for the therapy of the mCRPC (except for LH-RH analogues), or for whom no other available systemic mCRPC therapy is indicated	BSC[b]

a: Presentation of the 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 (particularly adequate pain therapy, treatment with bisphosphonates, denosumab and/or radionuclides).
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; LH-RH: luteinizing hormone-releasing hormone; mCRPC: metastatic castration resistant prostate cancer; Ra-223: radium 223 dichloride

The company subdivided the therapeutic indication into the following patient groups:

- Patients whose disease has progressed after they had received at least 2 prior systemic lines of mCRPC treatment (except for LH-RH analogues); according to the company, these are patients who are candidates for systemic treatment aimed at prolonging the patient's life, and
- patients for whom no other available systemic mCRPC therapy is indicated

For the first patient group, the company considered abiraterone, cabazitaxel, docetaxel and enzalutamide as comparator therapy and thus deviated from the ACT specified by the G-BA. For the second patient group, the company considered BSC as comparator therapy and thus followed the G-BA's specification of the ACT.

In the present benefit assessment, the ACT, i.e. BSC, is considered for all patients in the therapeutic indication.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

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 lists on Ra-223 (status: 4 March 2019)
- bibliographical literature search on Ra-223 (last search on 9 January 2019)
- search in trial registries for studies on Ra-223 (last search on 8 January 2019)

To check the completeness of the study pool:

- search in trial registries for studies on Ra-223 (last search on 24 April 2019)

The check of the completeness of the study pool identified no RCTs on the direct comparison or on the adjusted indirect comparison using a common comparator of Ra-223 versus the ACT.

The company also identified no RCTs on direct comparisons or on adjusted indirect comparisons using a common comparator of Ra-223 versus the ACT or of Ra-223 versus the additionally considered comparators (abiraterone, cabazitaxel, docetaxel and enzalutamide). Therefore, the company used a retrospective data analysis from the Flatiron Health database [3] as well as data from the single-arm studies PARABO [4] and REASSURE [5]. Moreover, the company considered the RCT ALSYMPCA [6], which had justified the approval of Ra-223 for mCRPC in the original therapeutic indication in 2013.

The data presented by the company were unsuitable for the derivation of an added benefit of Ra-223 versus the BSC in the therapeutic indication. This is justified below. For this purpose, the data considered by the company and the company's approach are described at first. Then it is explained why the data presented permit no derivation of conclusions on the added benefit of Ra-223 in comparison with the ACT.

Data presented by the company

Flatiron Health

The Flatiron Health database [3] is a longitudinal database containing data from electronic patient records of more than 2 million cancer patients in more than 265 oncological clinics (approx. 800 locations) in the USA. From this database, the company extracted data of patients with mCRPC who had received Ra-223 or another drug from the comparators additionally considered by the company (abiraterone, cabazitaxel, docetaxel, enzalutamide) or a combination therapy of at least 2 of the drugs abiraterone, cabazitaxel, docetaxel, enzalutamide, Ra-223 and sipuleucel-T from the third line of treatment. The company did not state whether all patients considered in the analyses had symptomatic bone metastases.

PARABO and REASSURE

The studies PARABO [4] and REASSURE [5] are single-arm non-interventional studies on Ra-223. The PARABO study included 346 adult patients with mCRPC with symptomatic bone metastases without known visceral metastases, 42 of whom the company considered relevant. The REASSURE study included 1476 adult patients with mCRPC with bone metastases, 348 of whom the company considered relevant. In the dossier, the company presented data of those patients who complied with the conditions according to the therapeutic indication.

ALSYMPCA

The ALSYMPCA study [6] is the approval study for the original therapeutic indication of Ra-223 and is described in detail in the first assessment (A14-02 [7]). It is a double-blind RCT on the comparison of Ra-223 + BSC with placebo + BSC. It included a total of 921 adult patients with mCRPC with symptomatic bone metastases without known visceral metastases. According to the inclusion criteria, patients with and without docetaxel pretreatment had been recruited. For patients without docetaxel pretreatment, treatment with docetaxel had to be either not indicated or not available or had to be rejected by the patient.

The proportion of patients who had received docetaxel pretreatment was 58%; information on whether and how many patients had received further systemic pretreatment was not provided in the sources [6-8].

Approach of the company

The company used the retrospective comparative data analysis for patients with mCRPC and at least 2 prior systemic treatments from the Flatiron Health database for the retrieval of data on overall survival under Ra-223 in comparison with the comparators additionally considered by it (abiraterone, cabazitaxel, docetaxel and enzalutamide as well as a combination therapy of at least 2 of the drugs abiraterone, cabazitaxel, docetaxel, enzalutamide, Ra-223 and Sipuleucel-T).

The company used the two single-arm studies PARABO and REASSURE, which it considered the best available evidence for patients who had received Ra-223 from the third line of treatment, for the retrieval of data on Ra-223 for further outcomes such as “pain”, “fractures”, “health-related quality of life” and “side effects” for patients of the total target population.

In the summarized presentation of the results (Module 4 A, Section 4.3.2.4), the company compared the data from the sources mentioned above with the results of the approval study ALSYMPCA. On the one hand, the company wants to compare the results of an Ra-223 therapy from every-day health care (retrospective analysis on the basis of the Flatiron Health database) with those achieved under the conditions of an RCT. On the other hand, the study would provide information on patient-relevant outcomes under Ra-223 therapy for patients for whom no other available systemic mCRPC therapy is indicated.

The company pointed out that the ALSYMPCA study was conducted for the primary analysis from June 2008 to July 2011 and thus at a time when the systemic therapies cabazitaxel, abiraterone and enzalutamide had not been approved yet. The study would thus include a population of patients for whom no other systemic mCRPC therapy was indicated. Retrospectively, it would be impossible to differentiate patients for whom systemic treatment with the currently available drugs had been an option. Transferability of the data of the total population of the ALSYMPCA study to patients for whom no other available systemic mCRPC therapy was indicated, would thus be possible to a limited extent.

Based on the above data, the company stated that an added benefit of Ra-223 in comparison with the ACT considered by it cannot be proven for patients who are candidates for further systemic treatment. The company derived a non-quantifiable benefit in comparison with BSC for patients for whom no other available systemic treatment is indicated.

Data presented by the company are unsuitable for the derivation of the added benefit

Data on Ra-223, but not on the ACT BSC, can be found in the retrospective data analysis from the Flatiron Health database and the two single-arm studies PARABO and REASSURE. The data presented by the company were unsuitable for the derivation of an added benefit of Ra-223 versus the ACT. Moreover, the company conducted no systematic information retrieval for the single-arm studies.

The ALSYMPCA study compares Ra-223 + BSC with Placebo + BSC. The patients included had either been pretreated with docetaxel or they were treatment-naive, in which case treatment with docetaxel had not been indicated or available or had been rejected by the patient. In the first assessment, the ALSYMPCA study demonstrated considerable added benefit of Ra-223 in comparison with BSC in the original therapeutic indication [9].

With the new therapeutic indication, the indication was restricted to patients whose disease has progressed after they had received at least 2 prior systemic lines of treatment for the therapy of the mCRPC (except for LH-RH analogues), or for whom no other available systemic therapy is indicated. After completion of the recruitment in the ALSYMPCA study, further drugs like abiraterone [10], cabazitaxel [11] and enzalutamide [12] were approved in addition to docetaxel. Approval of these drugs resulted in a radical change of the treatment situation in the therapeutic indication. For this reason, the 3 drugs mentioned above are now available treatment options for patients from the ALSYMPCA study for whom treatment with docetaxel had not been indicated or was rejected by them at the time. Moreover, it is unknown whether administration of the new drugs as prior therapy has an impact on the effect from the third line of treatment and how this impact affects the comparison of Ra-223 versus BSC. Study results yielded under the conditions of this former treatment situation can thus not be transferred to the present treatment situation. Finally, it remains unclear how many patients in the ALSYMPCA study had received at least 2 prior systemic therapies. For these reasons, the data from the ALSYMPCA study are not suitable for the derivation of an added benefit of Ra-223 versus BSC.

2.4 Results on added benefit

There are no suitable data for the assessment of Ra-223 as monotherapy or in combination with an LH-RH analogue for the treatment of adult patients with mCRPC and symptomatic bone metastases without known visceral metastases whose disease has progressed after they had received at least 2 prior systemic lines of treatment for the therapy of the mCRPC (except for LH-RH analogues), or for whom no other available systemic mCRPC therapy is indicated. Hence, there was no hint of an added benefit of Ra-223 in comparison with the ACT BSC. An added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of Ra-223 in comparison with the ACT is summarized in Table 5.

Table 5: Ra-223 – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Monotherapy or in combination with an LH-RH analogue for the treatment of adult patients with mCRPC and symptomatic bone metastases without known visceral metastases whose disease has progressed after they had received at least 2 prior systemic lines of treatment for the therapy of the mCRPC (except for LH-RH analogues), or for whom no other available systemic mCRPC therapy is indicated	BSC[b]	Added benefit not proven
a: Presentation of the 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 (particularly adequate pain therapy, treatment with bisphosphonates, denosumab and/or radionuclides). ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; LH-RH: luteinizing hormone-releasing hormone; mCRPC: metastatic castration resistant prostate cancer; Ra-223: radium 223 dichloride		

The assessment described above deviates from that of the company, which subdivided the target population and stated that an added benefit in comparison with the drugs additionally considered by it as comparators (abiraterone, cabazitaxel, docetaxel and enzalutamide) could not be proven for patients whose disease has progressed after they had received at least 2 prior systemic lines of treatment (except for LH-RH analogues). The company derived a non-quantifiable added benefit in comparison with BSC for patients for whom no other available systemic mCRPC therapy is indicated. The company did not assess the probability of the added benefit.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

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Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-32-radium-223-dichloride-mcrpc-benefit-assessment-according-to-35a-social-code-book-v-new-scientific-findings.12204.html