(^{177}Lu)lutetium vipivotide tetraxetan (prostate cancer)

Benefit assessment according to §35a SGB V[1]

EXTRACT

Project: A23-01 Version: 1.0 Status: 12 April 2023

[1] Translation of Sections I 1 to I 5 of the dossier assessment *(^{177}Lu)Lutetiumvipivotidtetraxetan (Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V*. 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.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

(177Lu)lutetium vipivotide tetraxetan (prostate cancer) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

11 January 2023

Internal Project No.

A23-01

Address of publisher

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Udo Ehrmann und Hans-Josef Beckers.

IQWiG thanks the respondents for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondents were not involved in the actual preparation of the dossier assessment.

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Keywords

177Lu-PSMA-617, Prostatic Neoplasms - Castration-Resistant, Benefit Assessment, NCT03511664

Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
BPI-SF	Brief Pain Inventory-Short Form
BRCA	breast cancer associated gene
BSC	best supportive care
CSR	clinical study report
ECOG PS	Eastern Cooperative Oncology Group-Performance Status
FACT-P	Functional Assessment of Cancer Therapy-Prostate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GBq	gigabecquerel
GnRH	gonadotropin-releasing hormone
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDH	lactate dehydrogenase
Lutetium-177	(^{177}Lu)lutetium vipivotide tetraxetan
mCRPC	metastatic castration resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model repeated measures
OECD	Organisation for Economic Co-operation and Development
PSMA	prostate-specific membrane antigen
PT	Preferred Term
RCT	randomized controlled trial
rPFS	radiographic progression-free survival
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA query
SPC	Summary of Product Characteristics
VAS	visual analogue scale

I 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 (^{177}Lu)lutetium vipivotide tetraxetan (in combination with androgen deprivation therapy [ADT] with or without inhibition of the androgen receptor pathway). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 11 January 2023.

Research question

The aim of the present report is the assessment of the added benefit of (^{177}Lu)lutetium vipivotide tetraxetan in combination with ADT with or without inhibition of the androgen receptor pathway in comparison with individual treatment as appropriate comparator therapy (ACT) in adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration resistant prostate cancer (mCRPC) who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy.

For better readability, the treatment to be assessed will hereinafter be referred to as "lutetium-177 + ADT".

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of lutetium 177 + ADT[a]

Therapeutic indication	**ACT[b]**
In combination with ADT[c] with or without androgen receptor pathway inhibition for the treatment of adult patients with progressive PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy[d]	Individualized treatment[c] under consideration of the prior therapy choosing from ▪ abiraterone in combination with prednisone or prednisolone, ▪ enzalutamide, ▪ cabazitaxel, ▪ olaparib (only for patients with breast cancer associated gene (BRCA)1/2 mutation), ▪ best supportive care (BSC)[f]

a. With or without androgen receptor pathway inhibition.
b. Presented is the ACT specified by the G-BA.
c. Ongoing conventional ADT is assumed to be continued. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with gonadotropin-releasing hormone (GnRH) agonists or antagonists.
d. For the present therapeutic indication, taxane-based chemotherapy means therapy with docetaxel.
e. For the implementation of individualized treatment in a direct comparative study, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criterion (multicomparator study). The decision on individualized treatment with regard to the comparator therapy at baseline should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). The disease of mCRPC is a palliative therapy situation. Maintaining quality of life and symptom control are therefore of particular importance. Adequate concomitant treatment of bone metastases during the study is assumed (e.g. use of bisphosphonates, denosumab, radiation therapy).
f. 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.

ADT: androgen deprivation therapy; BRCA: breast cancer associated gene; BSC: best supportive care; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; lutetium-177: lutetium (^{177}Lu) vipivotide tetraxetan; mCRPC: metastatic castration-resistant prostate cancer; PSMA: prostate-specific membrane antigen

The company followed the specification of the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. Randomized controlled trials (RCTs) are used for the derivation of added benefit.

Study pool and study design

The study pool for the present benefit assessment consists of the VISION study. This study is an open-label RCT comparing lutetium-177 with continuation of ongoing ADT and individualized treatment versus continuation of ongoing ADT and individualized treatment alone.

The study included adult men with progressive mCRPC and a general condition corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 2. Pretreatment required for inclusion had to include at least 1 androgen receptor pathway inhibitor and 1 to 2 taxane-based chemotherapies.

Patients who had received 1 taxane-based chemotherapy in the prior therapy were only included in the study if, according to the investigator's discretion, further taxane-based chemotherapy was not an option for them, e.g. due to geriatric or health-related frailty or intolerance. Prior to version 3.0 of the study protocol (1 April 2019), patients with 1 prior taxane-based chemotherapy could also participate in the study if they declined treatment with another taxane-based chemotherapy.

The study included a total of 831 patients, randomized in a 2:1 ratio to either the intervention arm (N = 551) or the comparator arm (N = 280). Individualized treatment was to be determined before randomization.

Lutetium-177 was administered for up to 6 cycles according to the Summary of Product Characteristics (SPC). Patients had to maintain their ongoing ADT in the study. Individualized treatment was determined for each patient at the investigator’s discretion prior to randomization and could be adjusted in both treatment arms during the study. In the VISION study, cytotoxic chemotherapies (e.g. taxane-based chemotherapies), systemic treatment with other radioisotopes (e.g. radium-223) and other investigational products (e.g. olaparib, which was not approved for the treatment of mCRPC at the start of the VISION study). After discontinuation of the study medication, patients could participate in up to 2 years of long-term follow-up until the end of the study.

Primary outcomes of the study were “radiographic progression-free survival (rPFS)” and “overall survival”. Patient-relevant outcomes on morbidity, health-related quality of life and side effects were also recorded.

Limitations of the VISION study

VISION allows drawing conclusions on added benefit only for a subpopulation

The G-BA specified individualized treatment as ACT selecting from

- abiraterone in combination with prednisone or prednisolone
- enzalutamide,
- cabazitaxel,
- olaparib (only for patients with BRCA-1/2 mutation) and
- BSC

under consideration of the prior therapy.

Cabazitaxel and olaparib were not allowed in the VISION study. In addition, treatment with other radioisotopes, such as radium-223, was not allowed (within the framework of the BSC). Thus, the comparator therapies used in the study did not cover all treatment options available for individualized treatment in the therapeutic indication. However, due to the lack of comparison with the treatment options, the VISION study only allows conclusions on the added benefit of lutetium-177 + ADT in those patients for whom abiraterone in combination with prednisone or prednisolone, enzalutamide or BSC is the most suitable therapy for the individual patient. In contrast, on the basis of the VISION study, no conclusions can be drawn on the added benefit of lutetium-177 + ADT for patients for whom cabazitaxel or olaparib is the most suitable therapy for the individual patient.

Uncertainties regarding the implementation of the ACT

It is assumed that for the majority of patients in the VISION study, cabazitaxel and olaparib were not considered the most suitable therapy for the individual patient. However, there is uncertainty that these treatment options represent the most suitable individualized treatment for a relevant proportion of patients. Moreover, there is uncertainty regarding the implementation of BSC as radioisotopes were not allowed in the VISION study. This is explained below.

Cabazitaxel

According to the inclusion criteria, patients with 1 or 2 taxane-based chemotherapies in the prior therapy could be included in the VISION study. Patients who had received 1 taxane-based chemotherapy in the prior therapy were only included in the study if, according to the investigator's discretion, further taxane-based chemotherapy was not an option for them, e.g. due to geriatric or health-related frailty or intolerance. Prior to version 3.0 of the study protocol (1 April 2019), patients with 1 prior taxane-based chemotherapy could also participate in the study if they declined treatment with another taxane-based chemotherapy. Overall, 58% of the included patients had 1 taxane-based chemotherapy in the prior treatment. Approx. 30% of all patients were enrolled in the study before 5 March 2019. It is unclear how many of these patients had received only 1 taxane-based chemotherapy as prior treatment and were included in the study because they declined further taxane-based chemotherapy. It is therefore unclear whether treatment with cabazitaxel would not have been the most suitable individualized treatment for a relevant proportion of patients.

Based on the proportion of patients who were enrolled in the study after 5 March 2019, it can be assumed that the majority of patients with 1 prior taxane-based chemotherapy were enrolled in the study based on the investigator's assessment that further taxane-based chemotherapy was not appropriate for them.

According to the S3 guideline "Prostate Cancer", cabazitaxel is a therapy option for patients with 1 taxane-based chemotherapy in the prior therapy (usually docetaxel). However, the treatment suitability for further taxane-based chemotherapy is not clearly defined and appropriate threshold values are lacking. Detailed information on why further taxane-based chemotherapy (especially cabazitaxel) was not suitable for the patients with 1 previous taxane-based chemotherapy is not available. It is therefore unclear whether treatment with cabazitaxel would not have been the most suitable individualized treatment for a relevant proportion of patients with only 1 prior taxane-based treatment.

According to the S3 guideline "Prostate Cancer", there are no explicit recommendations for further taxane-based chemotherapy for patients who have received 2 taxane-based chemotherapies with docetaxel and cabazitaxel in the prior therapy. However, further taxane-based chemotherapies are conceivable in patients with good general health and the desire for treatment beyond supportive therapies. In the VISION study, 6% of all patients had received 2 taxane-based chemotherapies without cabazitaxel in the prior therapy. For these patients, it is unclear whether cabazitaxel was an option for the most appropriate individualized treatment, especially if both enzalutamide and abiraterone had already been exhausted as treatment options.

Olaparib

According to the G-BA's specification, olaparib is only an option for the most appropriate individualized treatment in patients with a BRCA1/2 mutation. This is in line with the recommendation in the S3 guideline "Prostate Cancer" that olaparib should be offered if a BRCA1/2 mutation is evidenced.

Since November 2020, olaparib has been approved for the treatment of patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) whose disease is progressive after previous treatment that included a new hormonal agent (e.g. abiraterone or enzalutamide). Thus, approval was only granted after the start of the VISION study. Investigational preparations were not allowed in the VISION study, so olaparib could be administered as part of the individualized treatment at the earliest from the time of approval. As the last patient was randomized in October 2019 and the median treatment duration in the comparator arm was 2.1 months, it is assumed that olaparib was not available as a study medication for the majority of patients in the comparator arm.

According to the S3 guideline "Prostate Cancer", patients with disease progression after prior therapy with an androgen receptor pathway inhibitor should be offered testing for BRCA1/2 mutations. According to the study documents, testing of patients for BRCA1/2 mutations was not planned in the VISION study. Accordingly, no information is available on how many of the patients in the VISION study had a BRCA1/2 mutation.

Radioisotopes

According to the G-BA, 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. Treatment with other radioisotopes such as radium-223 in the framework of the BSC was not allowed in the VISION study.

Based on the available data, it is not possible to estimate for how many patients in the VISION study radioisotopes were basically eligible and represented the most suitable therapy in the context of the BSC. This uncertainty has been taken into account in the assessment of the certainty of conclusions.

Summary

In summary, the VISION study only allows conclusions on the added benefit of lutetium-177 + ADT in those patients for whom abiraterone in combination with prednisone or prednisolone, enzalutamide or BSC is the most suitable individualized treatment. In contrast, on the basis of the VISION study, no conclusions can be drawn on the added benefit of lutetium-177 + ADT for patients for whom cabazitaxel or olaparib is the most suitable therapy for the individual patient.

Overall, it is assumed that for the majority of patients in the VISION study, cabazitaxel and olaparib were not considered the most suitable therapy for the individual patient. Existing uncertainties regarding the proportion of patients in the VISION study for whom cabazitaxel or olaparib was the most suitable individualized treatment are taken into account in the reliability of the results. Moreover, there is uncertainty regarding the implementation of BSC as radioisotopes were not allowed in the VISION study. This issue has also been taken into account in the assessment of the certainty of conclusions.

Increased frequency of withdrawn consents

After the start of the study, an increased frequency of withdrawn consents was observed in the comparator arm of the VISION study. 47 (56.0%) of the first 84 patients included in the comparator arm did not receive study medication, predominantly due to withdrawn consents (24 [28.6%] patients) and required unapproved treatment (12 [14.3%] patients). However, patients who withdrew their consent for therapy only could participate in the long-term follow-up. According to the company's information, after randomization to the comparator arm, many patients expressed the wish for a taxane-based chemotherapy that was not permitted in the study. Due to the withdrawn consents, no complete data could be collected for the outcome of rPFS. To counteract this, various measures, such as training of the investigators, came into force on 5 March 2019 and the study protocol was adapted (Version 3.0, 1 April 2019).

Analysis populations

In Module 4 A, the company presents analyses based on all randomized patients (551 patients in the intervention arm vs. 280 patients in the comparator arm). The analyses for the outcomes on side effects are based on those patients who received at least 1 dose of the study medication (529 patients in the intervention arm vs. 205 patients in the comparator arm). A total of 79 (28.2%) patients in the comparator arm received no study medication. In the intervention arm, in contrast, significantly fewer patients did not receive study medication (18 [3.3%] patients). The differential proportion of patients who did not receive study medication is > 15 percentage points between treatment arms. Therefore, with the exception of the analysis on overall survival, the analyses are not suitable for the present benefit assessment. In contrast to the other outcomes, overall survival was recorded until study end.

Due to the frequent withdrawal of consents in the comparator arm to take the study medication, analyses were conducted for relevant outcomes, with the exception of side effects, which included only patients randomized as of 5 March 2019 (385 patients in the intervention arm vs. 196 patients in the comparator arm). These are provided in the clinical study report (CSR). Thereby, the differential proportion of patients who did not receive study medication between the treatment arms is 12.1 percentage points (16 [4.2%] vs. 32 [16.3%] patients), which is lower than in the overall population. Therefore, analyses for this population would in principle be suitable for the present benefit assessment.

The resulting effects on the suitability of the analysis populations described are taken into account when assessing the suitability of the analyses on the individual relevant outcomes.

Risk of bias

The risk of bias across outcomes is rated as low for the VISION study.

The results on the outcome of overall survival have a high risk of bias. It can be inferred from the information in Module 4 A that 15 (2.7%) vs. 33 (11.8%) patients withdrew their informed consent for participation in the study. It is unclear whether these patients were censored at day 1 or to what extent they were censored at day 1. If patients were censored at day 1, de facto no times entered the analysis through them and they were thus not taken into account. It remains unclear whether there is a clear difference between the treatment arms regarding the proportion of patients who were not considered in the analysis.

For the outcomes of the categories of morbidity, health-related quality of life and side effects, no suitable data are available. Therefore the risk of bias for is not assessed for these outcomes.

Regardless of this, the uncertainty described in the Section "Limitations of the VISION study" regarding the proportion of included patients for whom cabazitaxel or olaparib was the most suitable individualized treatment or for whom radioisotopes were an option as part of the BSC

and for whom thus the ACT was not implemented, means that at most hints, e.g. of added benefit, can be derived for all outcomes. For the present benefit assessment, this only applies to the outcome of overall survival, as no suitable data are available for the other relevant outcomes.

Results

Mortality

Overall survival

A statistically significant difference in favour of lutetium-177 + ADT + individualized treatment was shown for the outcome "overall survival". There is a hint of added benefit of lutetium-177 + ADT + individualized treatment over ADT + individualized treatment.

Morbidity

Symptomatic skeletal-related events (composite outcome and individual components), worst pain (Brief Pain Inventory-Short Form [BPI-SF] Item 3), pain interference (BPI-SF Item 9a-g) and health status (EQ-5D visual analogue scale [VAS])

No suitable data are available for outcomes in the morbidity category. There is no hint of an added benefit of lutetium-177 + ADT + individualized treatment in comparison with ADT + individualized treatment in each case; an added benefit is therefore not proven.

Health-related quality of life

Functional Assessment of Cancer Therapy-Prostate (FACT-P)

No suitable data were available for the outcome "health-related quality of life", recorded with the FACT-P. There is no hint of an added benefit of lutetium-177 + ADT + individualized treatment in comparison with ADT + individualized treatment; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), severe adverse events (AEs; CTCAE Grade ≥ 3) and specific AEs (myelosuppression [standardized MedDRA Query (SMQ), severe AEs] and dry mouth [Preferred Term (PT), AEs])

No suitable data are available for outcomes in the side effects category. There is no hint of an added benefit of lutetium-177 + ADT + individualized treatment in comparison with ADT + individualized treatment in each case; an added benefit is therefore not proven.

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

On the basis of the results presented, the probability and extent of added benefit of the drug lutetium-177 + ADT compared with the ACT are assessed as follows:

The overall picture shows a hint of an added benefit with the extent "considerable" for overall survival. The results on the outcomes of the categories of morbidity, health-related quality of life and side effects are unsuitable for the present benefit assessment. However, under qualitative consideration of the results on side effects used by the company, no disadvantages are suspected to an extent that could call into question the positive effect on overall survival.

In summary, for adult patients with progressive PSMA-positive mCRPC who have been previously treated with androgen receptor pathway inhibition and taxane-based chemotherapy, and for whom abiraterone in combination with prednisone or prednisolone, enzalutamide or BSC is the most appropriate individualized treatment, there is a hint of non-quantifiable added benefit of lutetium-177 compared with the ACT. The added benefit is not proven for patients for whom cabazitaxel or olaparib is the individually optimized treatment.

Table 3 shows a summary of probability and extent of the added benefit of lutetium-177 + ADT.

[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].

Table 3: Lutetium-177 + ADT[a] – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
In combination with ADT[c] with or without androgen receptor pathway inhibition for the treatment of adult patients with progressive PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy[d]	Individualized treatment[c] under consideration of the prior therapy choosing from ▪ abiraterone in combination with prednisone or prednisolone, ▪ enzalutamide, ▪ cabazitaxel, ▪ olaparib (only for patients with BRCA1/2 mutation), ▪ (BSC[f]	▪ Patients for whom abiraterone in combination with prednisone or prednisolone, enzalutamide or BSC is the individually optimized treatment: hint of a non-quantifiable added benefit[g] ▪ patients for whom cabazitaxel or olaparib is the individually optimized treatment: added benefit not proven

a. With or without androgen receptor pathway inhibition.
b. Presented is the ACT specified by the G-BA.
c. Ongoing conventional ADT is assumed to be continued. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with gonadotropin-releasing hormone (GnRH) agonists or antagonists.
d. For the present therapeutic indication, taxane-based chemotherapy means therapy with docetaxel.
e. For the implementation of individualized therapy in a direct comparative study, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criterion (multicomparator study). The decision on individualized treatment with regard to the comparator therapy at baseline should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). The disease of mCRPC is a palliative therapy situation. Maintaining quality of life and symptom control are therefore of particular importance. Adequate concomitant treatment of bone metastases during the study is assumed (e.g. use of bisphosphonates, denosumab, radiation therapy).
f. 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.
g. Only patients with an ECOG PS of 0 to 2 were included in the VISION study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of > 2.

ADT: androgen deprivation therapy; BRCA: breast cancer associated gene; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; lutetium-177: (^{177}Lu) lutetium vipivotide tetraxetan; mCRPC: metastatic castration-resistant prostate cancer; PSMA: prostate-specific membrane antigen

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

I 2 Research question

The aim of the present report is the assessment of the added benefit of (^{177}Lu)lutetium vipivotide tetraxetan in combination with ADT with or without inhibition of the androgen receptor pathway in comparison with individual treatment as appropriate comparator therapy (ACT) in adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration resistant prostate cancer (mCRPC) who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy.

For better readability, the treatment to be assessed will hereinafter be referred to as "lutetium-177 + ADT".

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of lutetium 177 + ADT[a]

Therapeutic indication	**ACT[b]**
In combination with ADT[c] with or without androgen receptor pathway inhibition for the treatment of adult patients with progressive PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy[d]	Individualized treatment[c] under consideration of the prior therapy choosing from: ▪ abiraterone in combination with prednisone or prednisolone, ▪ enzalutamide, ▪ cabazitaxel, ▪ olaparib (only for patients with breast cancer associated gene (BRCA)1/2 mutation), ▪ BSC[f]

a. With or without androgen receptor pathway inhibition.
b. Presented is the ACT specified by the G-BA.
c. Ongoing conventional ADT is assumed to be continued. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with gonadotropin-releasing hormone (GnRH) agonists or antagonists.
d. For the present therapeutic indication, taxane-based chemotherapy means therapy with docetaxel.
e. For the implementation of individualized treatment in a direct comparative study, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criterion (multicomparator study). The decision on individualized treatment with regard to the comparator therapy at baseline should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). The disease of mCRPC is a palliative therapy situation. Maintaining quality of life and symptom control are therefore of particular importance. Adequate concomitant treatment of bone metastases during the study is assumed (e.g. use of bisphosphonates, denosumab, radiation therapy).
f. 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.

ADT: androgen deprivation therapy; BRCA: breast cancer associated gene; BSC: best supportive care; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; lutetium-177: lutetium (^{177}Lu) vipivotide tetraxetan; mCRPC: metastatic castration-resistant prostate cancer; PSMA: prostate-specific membrane antigen

The company followed the specification of the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 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 lutetium-177 + ADT (status: 17 October 2022)

- bibliographical literature search on lutetium-177 + ADT (last search on 26 September 2022)
- search in trial registries/trial results databases for studies on lutetium-177 + ADT (last search on 26 September 2022)
- search on the G-BA website for lutetium-177 + ADT (last search on 3 November 2022)

To check the completeness of the study pool:

- search in trial registries for studies on lutetium-177 + ADT (last search on 25 January 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool - RCT, direct comparison: lutetium-177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a]

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication (yes/no [citation])
VISION	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6]

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates and external radiotherapy.
b. Study for which the company was sponsor.
c. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.

ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; lutetium-177: (177Lu)lutetium vipivotide tetraxetan; RCT: randomized controlled trial

The study pool concurs with that of the company.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included - RCT, direct comparison: lutetium-177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
VISION	RCT, open-label, parallel	Adult patients with progressive PSMA-positive mCRPC[c] (ECOG PS ≤ 2), previously treated with ▪ ≥ 1 androgen receptor pathway inhibitor (e.g. enzalutamide, abiraterone) ▪ 1-2 taxane-based chemotherapies[d]	Lutetium-177 + ADT + individualized treatment[a] (N = 551) ADT + individualized treatment[a] (N = 280)	Screening: ≤ 4 weeks before randomization treatment[e]: once every 6 weeks for up to 6 cycles[f] observation[g]: outcome-specific, at most until death, disease progression, discontinuation of participation in the study or end of study[h]	86 study centres: Belgium, Canada, Denmark, France, Germany, Netherlands, Puerto Rico, Sweden, United Kingdom and United States 05/2018–ongoing data cut-offs: ▪ 27 January 2021 (primary analysis) ▪ 28 June 2021[i]	Primary: ▪ rPFS ▪ overall survival secondary: morbidity, health-related quality of life, AEs

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates and external radiotherapy.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
c. Documented disease progression with a serum or plasma testosterone level of < 50 ng/dL or < 1.7 nmol/L.; patients had to have ≥ 1 metastasis (CT, MRI or bone scan) within 28 days prior to study drug administration.
d. Patients with 1 prior taxane-based chemotherapy were only included if the physician considered a second taxane-based chemotherapy as unsuitable for the patients (e.g. due to geriatric or health-related frailty, intolerance). Until version 3.0 of the study protocol (1 April 2019), patients with 1 taxane-based chemotherapy could also be included in the study if they refused a second taxane-based chemotherapy.
e. From cycle 7 onwards, patients only received ADT + individualized treatment with a cycle duration of 12 weeks until the end of the study; after discontinuation of the study medication, patients could participate in up to 2 years of long-term follow-up.
f. After the 4th cycle, it was investigated whether the respective patient could receive 2 further cycles of lutetium-177.
g. Outcome-specific information is described in Table 8.
h. The end of the study was planned after up to 2 years of long-term follow-up (after discontinuation of the study medication) or after the occurrence of 508 deaths, whichever occurred first.
i. According to information provided by the company, this data cut-off was a safety update after 90 days for the regulatory authorities.

Table 6: Characteristics of the study included - RCT, direct comparison: lutetium-177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
ADT: androgen deprivation therapy; AE: adverse event; CT: computed tomography; ECOG PS: Eastern Cooperative Oncology Group Performance Status; GBq: gigabecquerel; IV: intravenous; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; n: relevant subpopulation; mCRPC: metastatic castration-resistant prostate cancer; MRI: magnetic resonance imaging; N: number of randomized patients; PSMA: prostate-specific membrane antigen; RCT: randomized controlled trial; rPFS: radiographic progression-free survival						

Table 7: Characteristics of the intervention - RCT, direct comparison: lutetium-177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a]

Study	Intervention	Comparison
VISION	Lutetium-177 IV; 7.4 GBq (± 10 %)[b] every 6 weeks for up to 6 cycles[c] + ADT + individualized treatment[a]	 ADT + individualized treatment[a]
	From cycle 7, patients received ADT + individualized treatment[a] with a cycle duration of 12 weeks until the end of study[d]	
	Prior treatment ▪ ≥ 1 androgen receptor pathway inhibitor (e.g. enzalutamide or abiraterone) ▪ 1-2 taxane-based chemotherapies ▪ ADT (medical castration or prior orchiectomy) <u>not allowed:</u> ▪ radiation with strontium-89, samarium-153, rhenium-186, rhenium-188, radium-223 or half-body radiation within 6 months before randomization ▪ PSMA-targeted radioligand therapy ▪ any systemic tumour therapy within 28 days before randomization **concomitant treatment** ▪ mandatory continuation of the ongoing ADT (medical castration or prior orchiectomy)v ▪ individualized treatment[a] <u>not allowed:</u> ▪ other investigational preparations ▪ cytotoxic chemotherapy ▪ immunotherapy ▪ systematic treatment with other radioisotopes (e.g. radium-223) ▪ half-body radiation	

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates and external radiotherapy.
b. 1-time dose adjustment of 20% possible at investigator's discretion; no increase was allowed after reduction, and if further toxicities occurred requiring further reduction, treatment was discontinued; just as in the case of treatment delay ≥ 4 weeks.
c. After the 4th cycle, it was investigated whether the respective patient could receive 2 further cycles of lutetium-177.
d. After discontinuation of the study medication, patients could participate in up to 2 years of long-term follow-up.

ADT: androgen deprivation therapy; GBq: gigabecquerel; IV: intravenous; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; PSMA: prostate-specific membrane antigen; RCT: randomized controlled trial

I 3.2.1 Study design

The VISION study is an open-label RCT comparing lutetium-177 with continuation of ongoing ADT and individualized treatment versus continuation of ongoing ADT and individualized treatment alone.

The study included adult men with progressive mCRPC and a general condition corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 2. Pretreatment required for inclusion had to include at least 1 androgen receptor pathway inhibitor and 1 to 2 taxane-based chemotherapies.

Patients who had received 1 taxane-based chemotherapy in the prior therapy were only included in the study if, according to the investigator's discretion, further taxane-based chemotherapy was not an option for them, e.g. due to geriatric or health-related frailty or intolerance. Prior to version 3.0 of the study protocol (1 April 2019), patients with 1 prior taxane-based chemotherapy could also participate in the study if they declined treatment with another taxane-based chemotherapy.

The study included a total of 831 patients, randomized in a 2:1 ratio to either the intervention arm (N = 551) or the comparator arm (N = 280). Individualized treatment was to be determined before randomization. Randomization in the VISION study was stratified by lactate dehydrogenase (LDH) concentration (≤ 260 IU/L vs. > 260 IU/l), liver metastases at baseline (yes vs. no), ECOG PS (0-1 vs. 2) and androgen receptor pathway inhibitor as part of individualized treatment (yes vs. no).

Lutetium-177 was administered for up to 6 cycles according to the SPC [7]. Patients had to maintain their ongoing ADT in the study. This was either medical castration or prior orchiectomy. Individualized treatment was determined for each patient at the investigator’s discretion prior to randomization and could be adjusted in both treatment arms during the study. Individualized treatment was continued as long as the patients derived clinical benefit in the investigator’s opinion or until a non-permitted treatment was required in the study. In the VISION study, cytotoxic chemotherapies (e.g. taxane-based chemotherapies), systemic treatment with other radioisotopes (e.g. radium-223) and other investigational products (e.g. olaparib, which was not approved for the treatment of mCRPC at the start of the VISION study). After discontinuation of the study medication, patients could participate in up to 2 years of long-term follow-up until the end of the study. There were no restrictions on the choice of subsequent therapy. Information on subsequent antineoplastic therapies performed in the VISION study are found in Section I 3.2.7.

Primary outcomes of the study were “rPFS” and “overall survival”. Patient-relevant outcomes on morbidity, health-related quality of life and side effects were also recorded.

I 3.2.2 Limitations of the VISION study

VISION allows drawing conclusions on added benefit only for a subpopulation

The G-BA specified individualized treatment as ACT selecting from

- abiraterone in combination with prednisone or prednisolone
- enzalutamide,
- cabazitaxel,
- olaparib (only for patients with BRCA-1/2 mutation) and
- BSC

under consideration of the prior therapy.

Cabazitaxel and olaparib were not allowed in the VISION study. In addition, treatment with other radioisotopes, such as radium-223, was not allowed (within the framework of the BSC). Thus, the comparator therapies used in the study did not cover all treatment options available for individualized treatment in the therapeutic indication. Due to the lack of comparison with the treatment options, the VISION study only allows conclusions on the added benefit of lutetium-177 + ADT in those patients for whom abiraterone in combination with prednisone or prednisolone, enzalutamide or BSC is the most suitable therapy for the individual patient. In contrast, on the basis of the VISION study, no conclusions can be drawn on the added benefit of lutetium-177 + ADT for patients for whom cabazitaxel or olaparib is the most suitable therapy for the individual patient.

Uncertainties regarding the implementation of the ACT

It is assumed that for the majority of patients in the VISION study, cabazitaxel and olaparib were not considered the most suitable therapy for the individual patient. However, there is uncertainty that these treatment options represent the most suitable individualized treatment for a relevant proportion of patients. Moreover, there is uncertainty regarding the implementation of BSC as radioisotopes were not allowed in the VISION study. This is explained below.

Cabazitaxel

According to the inclusion criteria, patients with 1 or 2 taxane-based chemotherapies in the prior therapy could be included in the VISION study. Patients who had received 1 taxane-based chemotherapy in the prior therapy were only included in the study if, according to the investigator's discretion, further taxane-based chemotherapy was not an option for them, e.g. due to geriatric or health-related frailty or intolerance. Prior to version 3.0 of the study protocol (1 April 2019), patients with 1 prior taxane-based chemotherapy could also participate in the study if they declined treatment with another taxane-based chemotherapy.

Overall, 58% of the included patients had only 1 taxane-based chemotherapy in the prior treatment. Approx. 30% of all patients were enrolled in the study before 5 March 2019. It is unclear how many of these patients had received only 1 taxane-based chemotherapy as prior treatment and were included in the study because they declined further taxane-based chemotherapy. It is therefore unclear whether treatment with cabazitaxel would not have been the most suitable individualized treatment for a relevant proportion of patients.

Based on the proportion of patients who were enrolled in the study after 5 March 2019, it can be assumed that the majority of patients with 1 prior taxane-based chemotherapy were enrolled in the study based on the investigator's assessment that further taxane-based chemotherapy was not appropriate for them. According to the S3 guideline "Prostate Cancer", cabazitaxel is a therapy option for patients with 1 taxane-based chemotherapy in the prior therapy (usually docetaxel) [8]. However, the treatment suitability for further taxane-based chemotherapy is not clearly defined and appropriate threshold values are lacking. For example, patients with reduced general condition can also be offered chemotherapy in addition to supportive treatment, if the general condition is mainly due to the mCRPC [8]. Detailed information on why further taxane-based chemotherapy (especially cabazitaxel) was not suitable for the patients with 1 previous taxane-based chemotherapy is not available. The treatment suitability cannot be assessed on the basis of the patient characteristics. However, for example, the ECOG PS was 0 or 1 in more than 90% of the patients in the VISION study, so the patients' general condition was assumed to be good. It is therefore unclear whether treatment with cabazitaxel would not have been the most suitable individualized treatment for a relevant proportion of patients with only 1 prior taxane-based treatment.

According to the S3 guideline "Prostate Cancer", there are no explicit recommendations for further taxane-based chemotherapy for patients who have received 2 taxane-based chemotherapies with docetaxel and cabazitaxel in the prior therapy [8]. However, further taxane-based chemotherapies are particularly conceivable in patients with good general health and the desire for treatment beyond supportive therapies. In the VISION study, 44% of patients in the comparator arm had received 2 taxane-based chemotherapies in the prior therapy, with cabazitaxel used in 38% of patients. Accordingly, 6% of all patients had received 2 taxane-based chemotherapies without cabazitaxel in the prior therapy. For these patients, it is unclear whether cabazitaxel was an option for the most appropriate individualized treatment, especially if both enzalutamide and abiraterone had already been exhausted as treatment options.

Olaparib

According to the G-BA's specification, olaparib is only an option for the most appropriate individualized treatment in patients with a BRCA1/2 mutation. This is in line with the

recommendation in the S3 guideline "Prostate Cancer" that olaparib should be offered if a BRCA1/2 mutation is evidenced [8].

Since November 2020, olaparib has been approved for the treatment of patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) whose disease is progressive after previous treatment that included a new hormonal agent (e.g. abiraterone or enzalutamide) [9,10]. Thus, approval was only granted after the start of the VISION study. Investigational preparations were not allowed in the VISION study, so olaparib could be administered as part of the individualized treatment at the earliest from the time of approval. As the last patient was randomized in October 2019, none of the patients had olaparib available from the start of treatment with the study medication. Based on the median treatment duration of 2.1 months in the comparator arm (see Table 10), it is also assumed that the majority of patients in the comparator arm had already completed treatment with the study medication at the time of approval of olaparib. Thus, olaparib was not available as a study medication for the majority of patients in the comparator arm.

According to the S3 guideline "Prostate Cancer", patients with disease progression after prior therapy with an androgen receptor pathway inhibitor should be offered testing for BRCA1/2 mutations [8]. According to the study documents, testing of patients for BRCA1/2 mutations was not planned in the VISION study. Accordingly, no information is available on how many of the patients in the VISION study had a BRCA1/2 mutation. The study documents show that only 1 patient per treatment arm received olaparib as part of the study medication. Based on the information on patient numbers from dossier assessment A20-106 [11], a proportion value for BRCA1/2 mutation of approx. 10% of patients is assumed.

Radioisotopes

According to the G-BA, 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. Treatment with other radioisotopes such as radium-223 in the framework of the BSC was not allowed in the VISION study.

Based on the available data, it is not possible to estimate for how many patients in the VISION study radioisotopes were basically eligible and represented the most suitable therapy in the context of the BSC. This uncertainty is taken into account in the assessment of the certainty of conclusions (see Section I 4.2).

Summary

In summary, the comparator therapies used in the VISION study represent relevant treatment options in the present therapeutic indication. However, the comparator therapies used did not cover all treatment options available for individualized treatment in the therapeutic indication. Consequently, the VISION study only allows conclusions on the added benefit of

lutetium-177 + ADT in those patients for whom abiraterone in combination with prednisone or prednisolone, enzalutamide or BSC is the most suitable individualized treatment. In contrast, on the basis of the VISION study, no conclusions can be drawn on the added benefit of lutetium-177 + ADT for patients for whom cabazitaxel or olaparib is the most suitable therapy for the individual patient.

Overall, it is assumed that for the majority of patients in the VISION study, cabazitaxel and olaparib were not considered the most suitable therapy for the individual patient. Existing uncertainties regarding the proportion of patients in the VISION study for whom cabazitaxel or olaparib was the most suitable individualized treatment are taken into account in the assessment of the reliability of the results (see Section I 4.2). In addition, there is uncertainty regarding the implementation of BSC, as radioisotopes were not allowed in the VISION study, which were also taken into account when assessing the reliability of the results.

Increased frequency of withdrawn consents

After the start of the study, an increased frequency of withdrawn consents was observed in the comparator arm of the VISION study. 47 (56.0%) of the first 84 patients included in the comparator arm did not receive study medication, predominantly due to withdrawn consents (24 [28.6%] patients) and required unapproved treatment (12 [14.3%] patients). However, patients who withdrew their consent for therapy only could participate in the long-term follow-up. As a reason for the increased frequency of withdrawn consents, the company states misunderstandings among the investigators regarding the permitted and non-permitted options for individualized treatment, the open-label study design and published information on the potential efficacy of lutetium-177. According to the company's information, after randomization to the comparator arm, many patients expressed the wish for a taxane-based chemotherapy that was not permitted in the study. Due to the withdrawn consents, no complete data could be collected for the outcome of rPFS. To counteract this, various measures, such as training of the investigators, came into force on 5 March 2019 and the study protocol was adapted (Version 3.0, 1 April 2019). According to the protocol amendment, patients who had received 1 taxane-based chemotherapy in the prior treatment could only be included in the study if the investigator determined a lack of treatment suitability for further taxane-based chemotherapy. Suitable patients who refused further taxane-based chemotherapy should no longer be included in the study.

Analysis populations

In Module 4 A, the company presents analyses based on all randomized patients (551 patients in the intervention arm vs. 280 patients in the comparator arm). The analyses for the outcomes on side effects are based on those patients who received at least 1 dose of the study medication (529 patients in the intervention arm vs. 205 patients in the comparator arm). A total of 79 (28.2%) patients in the comparator arm received no study medication. In the

intervention arm, in contrast, significantly fewer patients did not receive study medication (18 [3.3%] patients). The differential proportion of patients who did not receive study medication is > 15 percentage points between treatment arms. Therefore, with the exception of the analysis on overall survival, the analyses are not suitable for the present benefit assessment (see Section I 4.1).

Due to the frequent withdrawal of consents in the comparator arm to take the study medication, analyses were conducted for relevant outcomes, with the exception of side effects, which included only patients randomized as of 5 March 2019 (385 patients in the intervention arm vs. 196 patients in the comparator arm). These are provided in the clinical study report (CSR). Thereby, the differential proportion of patients who did not receive study medication between the treatment arms is 12.1 percentage points (16 [4.2%] vs. 32 [16.3%] patients), which is lower than in the overall population. Therefore, analyses for this population would in principle be suitable for the present benefit assessment.

The resulting effects on the suitability of the analysis populations described are taken into account when assessing the suitability of the analyses on the individual relevant outcomes (see Section I 4.1).

I 3.2.3 Data cut-offs

2 data cut-offs are available for the VISION study:

- 1st data cut-off of 27 January 2021: preplanned primary analysis on the outcome of PFS and final analysis on overall survival, planned after the occurrence of 508 deaths
- 2nd data cut-off of 28 June 2021: safety update after 90 days for the regulatory authorities

For the 2nd data cut-off, there are only results on the side effects. According to the dossier templates [12] complete analyses of all surveyed patient-relevant outcomes must be conducted and submitted for all data cut-offs relevant to the benefit assessment, even in cases where a data cut-off was originally planned for the analysis of only some of the outcomes. The presentation of the results of a data cut-off can be omitted only if no substantial gain in information is to be expected compared to another data cut-off. In the present benefit assessment, only the analysis on overall survival is suitable (see Section I 4). Due to the marked effects in overall survival at the 1st data cut-off, it is not assumed in the present situation that an analysis at the 2nd data cut-off could call the effect into question. For this reason, the 1st data cut-off of the VISION study serves as the basis for the present benefit assessment.

I 3.2.4 Planned duration of follow-up observation

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: lutetium-177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a]

Study **outcome category** **outcome**	**Planned follow-up observation**
VISION	
Mortality	
Overall survival	Until death or end of study[b]
Morbidity	
Symptomatic skeletal-related events, pain (BPI-SF) and health status (EQ-5D VAS)	Until 30 days after discontinuation of the study medication, but before initiation of a non-permitted subsequent tumour therapy
Health-related quality of life (FACT-P)	Until 30 days after discontinuation of the study medication, but before initiation of a non-permitted subsequent tumour therapy
Side effects	
All outcomes in the category of side effects	Until 30 days after discontinuation of the study medication[c], but before initiation of a non-permitted subsequent tumour therapy

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates and external radiotherapy.
b. The end of the study was planned after up to 2 years of long-term follow-up (after discontinuation of the study medication) or after the occurrence of 508 deaths, whichever occurred first.
c. Thereafter, patients could participate in a long-term follow-up until the end of study.

ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory-Short Form; FACT-P: Functional Assessment of Cancer Therapy-Prostate; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; RCT: randomized controlled trial; VAS: visual analogue scale

In the VISION study, only overall survival was recorded until study end. The monitoring periods for the outcomes of the categories of morbidity and health-related quality of life were systematically shortened, because they were only recorded for the time of treatment with the study medication (plus 30 days, but before the initiation of a subsequent tumour therapy not permitted in the study). Side effects were also recorded over the period of treatment with the study medication (plus 30 days, but before initiation of a subsequent tumour therapy not permitted in the study) (long-term follow-up). However, analyses are only available for the individual study phases (treatment phase and long-term follow-up).

However, to permit drawing a reliable conclusion regarding the total study period or time to patient death, it would be necessary to likewise record or analyse these outcomes for the total period, as was done for survival.

I 3.2.5 Patient characteristics

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population as well as study/treatment discontinuation - RCT, direct comparison: lutetium-177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a] (multipage table)

Study characteristic category	Lutetium-177 + ADT + individualized treatment[a] N = 551	ADT + individualized treatment[a] N = 280
VISION		
Age [years], mean (SD)	70 (7)	71 (8)
Family origin, n (%)		
White	486 (88)	235 (84)
Black/African American	34 (6)	21 (8)
Asian	9 (2)	11 (4)
Other[b]	2 (< 1)	0 (0)
No data	20 (4)	13 (5)
ECOG PS, n (%)		
0-1	510 (93)	258 (92)
2	41 (7)	22 (8)
Disease duration: time since first diagnosis [years], median [min; max]	7.4 [0.9; 28.9]	7.4 [0.7; 26.2]
Original Gleason score, n (%)		
2-3	4 (1)	0 (0)
4-7	181 (33)	86 (31)
8-10	324 (59)	170 (61)
Unknown	42 (8)	24 (9)
Location of target and non-target lesions, n (%)		
Lung	49 (9)	28 (10)
Liver	63 (11)	38 (14)
Lymph nodes	274 (50)	141 (50)
Bones	504 (92)	256 (91)
PSA concentration [ng/mL] at baseline, median (min; max)	77.5 [0; 6,988]	74.6 [0; 8,995]
Prior radiotherapy, n (%)	415 (75)	217 (78)
Prior treatment with radium-223 dichloride, n (%)	97 (18)	48 (17)
Prior androgen receptor pathway inhibitors		
Number, n (%)		
1	298 (54)	128 (46)
2	213 (39)	128 (46)
> 2	40 (7)	24 (9)

Table 9: Characteristics of the study population as well as study/treatment discontinuation - RCT, direct comparison: lutetium-177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a] (multipage table)

Study characteristic category	Lutetium-177 + ADT + individualized treatment[a] N = 551	ADT + individualized treatment[a] N = 280
Drugs, n (%)		
Enzalutamide	395 (72)	206 (74)
Abiraterone	187 (34)	106 (38)
Abiraterone acetate	210 (38)	114 (41)
Apalutamide	13 (2)	5 (2)
Prior taxane-based chemotherapy		
Number, n (%)		
1	325 (59)	156 (56)
2	220 (40)	122 (44)
> 2	6 (1)	2 (1)
Drugs, n (%)		
Cabazitaxel	209 (38)	107 (38)
Docetaxel	534 (97)	273 (98)
Paclitaxel	2 (< 1)	1 (< 1)
Paclitaxel albumin	1 (< 1)	0 (0)
Treatment discontinuation, n (%)[c]	484 (88)	196 (70)
Common reasons for the discontinuation of lutetium-177, n (%)		
Progression	127 (23.0)	–
Adverse event	54 (9.8)	–
No more clinical benefit	36 (6.5)	–
Common reasons for the discontinuation of ADT/individualized treatment[a], n (%)		
Progression	224 (40.7)	73 (26.1)
No more clinical benefit	72 (13.1)	50 (17.9)
Withdrawal of consent	51 (9.3)	36 (12.9)
Study discontinuation, n (%)	362 (66)	225 (80)
Common reasons for study discontinuation, n (%)		
Death	329 (59.7)	167 (59.6)
Withdrawal of consent	29 (5.3)	53 (18.9)

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates and external radiotherapy.
b. Native Hawaiians or other Pacific Islanders, native Americans or Alaskans and more than only one reported family origin.
c. Data based on treatment discontinuation of all components.

Table 9: Characteristics of the study population as well as study/treatment discontinuation - RCT, direct comparison: lutetium-177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a] (multipage table)

Study characteristic category	Lutetium-177 + ADT + individualized treatment[a] N = 551	ADT + individualized treatment[a] N = 280
ADT: androgen deprivation therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized (or included) patients; PSA: prostate-specific antigen; RCT: randomized controlled trial; SD: standard deviation		

The demographic and clinical characteristics are largely balanced between the 2 treatment arms.

The mean age of the patients was about 70 years, and most were of white family origin. The proportion of patients with an ECOG PS of 0-1 was over 90% and the median initial diagnosis was 7.4 years before the start of the study.

According to the inclusion criteria of the VISION study, prior treatment of the patients had to comprise at least 1 androgen receptor pathway inhibitor and 12 taxane-based chemotherapies. With 54%, the proportion of patients with 1 prior androgen receptor pathway inhibitor was higher in the intervention arm than in the comparator arm (46%). Correspondingly, the proportion of patients with 2 prior androgen receptor pathway inhibitors was slightly lower in the intervention arm (39%) than in the comparator arm (46%). The proportions of androgen receptor pathway inhibitors used (mainly enzalutamide and abiraterone, which are approved in the therapeutic indication) were balanced in both treatment arms. More than half of the patients had received 1 prior taxane-based chemotherapy, and about 40% of the patients had 2 prior taxane-based chemotherapies. Docetaxel was used in the majority of patients with 1 prior taxane-based chemotherapy and docetaxel and cabazitaxel were used in patients with 2 prior taxane-based chemotherapies.

The proportion of patients with treatment discontinuation was higher in the intervention arm (88%) than in the comparator arm (70%). However, the proportion of patients who did not receive study medication was clearly higher in the comparator arm (28.2%) than in the intervention arm (3.3%).

66% of the patients in the intervention arm and 80% of those in the comparator arm discontinued the study. The difference is mainly based on the high proportion of withdrawn consents of 18.9% in the comparator arm compared to 5.3% in the intervention arm (see Section I 3.2.2).

I 3.2.6 Treatment duration and observation period

Table 10 shows the median and mean treatment duration of the patients and the median observation period for individual outcomes.

Table 10: Information on the course of the study - RCT, direct comparison: lutetium-177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a]

Study **duration of the study phase** **outcome category**	**Lutetium-177 + ADT + individualized treatment[a]** **N = 551**	**ADT + individualized treatment[a]** **N = 280**
VISION		
Treatment duration [months]		
N	529	205
Median [min; max]	7.8 [0.3–24.9]	2.1 (0.0–26.0)
Mean (SD)	7.9 (4.3)	3.5 (3.9)
Observation period [months]		
Overall survival [b]		
N	551	280
Median [min; max]	20.3 [0.0–31.5]	19.8 [0.0–27.1]
Mean (SD)	ND	ND
Symptomatic skeletal-related events[c]	ND[d]	
Worst pain (BPI-SF Item 3)	ND[e]	
Pain interference (BPI-SF Items 9a–g)	ND[e]	
Health status (EQ-5D VAS)	ND[e]	
Health-related quality of life (FACT-P)	ND[e]	
Side effects	ND[f]	

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates and external radiotherapy.
b. The observation period was calculated based on the observed time to event/censoring/end of study of all patients (deceased and non-deceased).
c. Comprises: new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic intervention, need for radiotherapy for alleviation of bone pain.
d. Data of the company (median observation period 14.5 vs. 6.7 months) not plausible, as the outcome is followed up for a maximum of 30 days after discontinuation of the study medication.
e. Data of the company (min = 0.0 in the comparator arm) not plausible, as the analysed population only includes patients for whom 1 survey at the start of the study and at least 1 further survey is available.
f. Data of the company based on time to event or censoring for the respective overall rate; this does not represent the time patients were actually under observation for the recording of AEs, SAEs and severe AEs (operationalized as CTCAE grade ≥ 3).

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy-Prostate; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; max: maximum; min: minimum; ND: no data; N: number of randomized patients; n: number of analysed patients; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale

The information on treatment and observation periods is based on different patient numbers. While data on treatment duration are based on those patients who received at least 1 dose of the study medication (529 patients in the intervention arm vs. 205 patients in the comparator arm), the data on the observation period of overall survival are based on all randomized patients (551 patients in the intervention arm vs. 280 patients in the comparator arm).

The median treatment duration in the intervention arm was 7.8 months, more than 3.5 times as long as in the comparator arm (2.1 months). The median observation period for overall survival was about 20 months in both treatment arms.

In Module 4 A, the company provides information on the observation period for other outcomes relevant to the present benefit assessment. However, these data are not plausible for various reasons and do not represent the time patients were under observation to record the outcomes (for reasons for the individual outcomes see Table 10).

I 3.2.7 Subsequent therapies

Table 11 shows which subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies[a] - RCT, direct comparison: lutetium-177 + ADT + individualized treatment[b] vs. ADT + individualized treatment[b]

Study drug	Patients with subsequent therapy n (%)	
	lutetium-177 + ADT + individualized treatment[b] N = 551	ADT + individualized treatment[b] N = 280
VISION		
Total	155 (28.1)	97 (34.6)
Cabazitaxel	82 (14.9)	53 (18.9)
Carboplatin	35 (6.4)	25 (8.9)
Radium Ra 223 Dichloride	14 (2.5)	15 (5.4)
Investigational drug	9 (1.6)	15 (5.4)
Docetaxel	27 (4.9)	10 (3.6)
Pembrolizumab	5 (0.9)	10 (3.6)
Enzalutamide	12 (2.2)	7 (2.5)
Olaparib	10 (1.8)	7 (2.5)
Bevacizumab	4 (0.7)	7 (2.5)
Abiraterone	10 (1.8)	1 (0.4)
Various therapeutic radiopharmaceuticals	0 (0)	5 (1.8)
Etoposide	8 (1.5)	2 (0.7)
Cisplatin	7 (1.3)	4 (1.4)
Nivolumab	6 (1.1)	4 (1.4)
Darolutamide	5 (0.9)	3 (1.1)
Cyclophosphamide	3 (0.5)	3 (1.1)
Atezolizumab	2 (0.4)	3 (1.1)
Lutetium (^{177}Lu) PSMA-617	2 (0.4)	3 (1.1)
Sipuleucel-T	2 (0.4)	3 (1.1)

a. Excluding radiotherapy; 49 (8.9%) of patients in the intervention arm and 31 (11.1%) of patients in the comparator arm received ≥ 1 radiotherapy as subsequent therapy; shown are subsequent therapies received by ≥ 1% of patients in at least 1 study arm.
b. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates and external radiotherapy.

ADT: androgen deprivation therapy; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

According to the study protocol, the choice of the subsequent therapy was not restricted. 28.1% of patients in the intervention arm and 34.6% of patients in the comparator arm received subsequent therapy. The proportion of the drugs used were largely balanced between the treatment arms. The drug most frequently used as a subsequent therapy was cabazitaxel, accounting for 14.9% of patients in the intervention arm and 18.9% of patients in

the comparator arm. Cytotoxic chemotherapies, which include treatment with cabazitaxel, were not allowed in the VISION study. The S3 guideline "Prostate Cancer" provides no recommendations for the further treatment of the patients [8].

I 3.2.8 Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: lutetium 177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a]

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
VISION	Yes	Yes	No	No	Yes	Yes[b]	Low

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates and external radiotherapy.
b. Subsequent amendment of the study protocol to improve patient information and thus counteract the increased frequency of withdrawn consents in the comparator arm. Effects are assessed on an outcome-specific basis.

ADT: androgen deprivation therapy; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; RCT: randomized controlled trial

The risk of bias across outcomes is rated as low for the VISION study.

I 3.2.9 Transferability of the study results to the German health care context

The company states that more than 99% of all patients in the multinational VISION study come from countries belonging to the Organisation for Economic Co-operation and Development (OECD). According to the company, these countries have a comparatively high per capita income and an efficient health care system and a joint reporting on selected quality indicators of health care has been strived within the OECD for since 2003. Therefore, the company assumed transferability of the study results to the German health care context.

The company did not provide any further information on the transferability of study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptomatic skeletal-related events
  - worst pain (measured using the BPI-SF Item 3).
  - pain interference (measured using BPI-SF Items 9a–g).
  - health status (recorded using the EQ-5D VAS)
- Health-related quality of life
  - measured using the FACT-P total score
- Side effects
  - SAEs
  - severe AEs (operationalized as CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - myelosuppression (SMQ “haematopoietic cytopenias“, severe AEs)
  - dry mouth (PT, AEs)
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that taken by the company, which used further outcomes in the dossier (Module 4A).

Table 13 shows the outcomes for which data were available in the included study.

Table 13: Matrix of outcomes - RCT, direct comparison: lutetium-177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a]

Study	Outcomes											
	Overall survival	Symptomatic skeletal-related events[b]	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF Items 9a–g)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-P)	SAEs	Severe AEs[c]	Discontinuation due to AEs	Myelosuppression (SMQ[d], severe AEs[c])	Dry mouth (PT, AEs)	Further specific AEs
VISION	Yes	No[e]	No[e]	No[e]	No[e]	No[e]	No[e]	No[e]	No[e]	No[e]	No[e]	No[f]

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates and external radiotherapy.
b. Comprises: new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic intervention, need for radiotherapy for alleviation of bone pain.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. SMQ "haematopoietic cytopenias".
e. No suitable data available; for the reasoning, see the following sections of the present dossier assessment.
f. Suitable analyses on AEs are not available, therefore, a choice of specific AEs was therefore impossible.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy-Prostate; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; VAS: visual analogue scale

Notes on analyses

Overall survival

For overall survival, analyses based on all randomized patients are available. In addition, analyses are available based on those patients randomized from 5 March 2019 (see Section I 3.2.2).

In contrast to the other outcomes, overall survival was recorded or analysed until study end. Patients who withdrew their consent to treatment but agreed to participate in the long-term follow-up were also included in the analyses. Therefore, the increased frequency of withdrawn consents to treatment does not mean that the results on overall survival are not

suitable for the present benefit assessment. Thus, the results on overall survival were used for the present benefit assessment.

Due to clear differences in the proportions of the individual reasons for censoring between the treatment arms, several sensitivity analyses were conducted post hoc by the company, which are also presented in Module 4 A. Multiple imputation of the event time was performed for patients with the censoring reasons "lost to follow-up" and "withdrawal of consent" under different assumptions. Overall, the company does not sufficiently justify the basis on which the respective scenarios, with corresponding cut-offs, are selected. For example, it is unclear why in the multiple imputation of the censored observations in the comparator arm these are imputed according to the drop-out risk of 20% of the patients with the longest survival time.

For the present benefit assessment, the analysis based on all randomized patients is used. The sensitivity analyses are not taken into account due to the ambiguities in the assessment of the results.

There are no relevant differences regarding the reasons for censoring and the proportions in the treatment groups between the two analysis populations (see above). Thus, the analysis of overall survival of patients randomized from 5 March 2019 onwards does not represent an information gain for the present benefit assessment and will not be considered.

Symptomatic skeletal-related events

The outcome “symptomatic skeletal-related events” is a composite outcome that includes the following events:

- New symptomatic pathological bone fracture
- Spinal cord compression
- Tumour-related orthopaedic intervention
- Need for radiotherapy for alleviation of bone pain

According to the company, Module 4 A presents analyses on symptomatic skeletal-related events with or without consideration of deaths, as well as analyses on the individual components of symptomatic skeletal-related events for all randomized patients. The analyses of the individual components and those without consideration of deaths are relevant for the present benefit assessment. For these operationalizations, only the analyses in Module 4 A are available.

According to information provided by the company, symptomatic skeletal-related events were recorded up to 30 days after discontinuation of the study medication, but before the start of a subsequent tumour therapy not permitted in the study. In the VISION study, 3.3% of the

randomized patients in the intervention arm and 28.2% of the patients in the comparator arm received no study medication. The company did not state whether the follow-up up to 30 days also applied to these patients. There is a possibility that patients who did not receive study medication were censored at baseline. De facto, these patients would not be included in the analysis. Thus, it cannot be excluded that the differential proportion of patients included in the analysis is > 15 percentage points between the treatment arms. Therefore, these analyses are not suitable for the present benefit assessment.

For patients randomized on or after 5 March 2019, no analyses are available for symptomatic skeletal-related events excluding deaths.

Patient-reported outcomes (BPI-SF, EQ-5D VAS, FACT-P)

For the BPI-SF, the EQ-5D VAS as well as for the FACT-P, the company presents post hoc specified analyses for the time to first deterioration with a response criterion of 15% of the scale range based on all randomized patients for whom 1 survey at baseline and at least 1 further survey are available. Due to the shortened follow-up of the outcomes in combination with the increased frequency of withdrawn consents in the comparator arm even before receiving the study medication, the differential proportion of patients included in the analysis between the treatment arms is > 15 percentage points. Therefore, each of these analyses is unsuitable for the present benefit assessment.

For each of the patient-reported outcomes, the company states that analyses using a mixed model with repeated measures (MMRM) are presented in Appendix 4-G.2 of Module 4A as supplementary information. However, the same results table is shown for each outcome. This is not plausible and therefore these analyses are not considered for the present benefit assessment. Irrespective of this fact, the differential proportion of patients included in the analysis is > 15 percentage points between the treatment arms in each case. Therefore, these analyses are also not suitable for the present benefit assessment.

For patients randomized on or after 5 March 2019, there are no analyses with a prespecified response criterion of ≥ 15% of the scale range. In the study report, results on the change since the beginning of the study are available in each case. At the second time point of documentation, data were available for > 85% of the patients in the intervention arm and only for 52% of the patients in the comparator arm. Due to this high differential proportion of early drop-outs between the treatment arms (> 25 percentage points), the continuous analyses are not suitable for the present benefit assessment. For this analysis population, it can therefore be assumed, even for responder analyses with a post hoc defined response criterion of 15% of the scale range, that the differential proportion of patients included in the analysis between the treatment arms is > 15 percentage points and the analyses would therefore not be suitable for the present benefit assessment.

First intake of an opioid

In Module 4 A, the company presents, among other things, 2 analyses on the time to first intake of an opioid, one analysis including the events “clinical progression” or “death” and one analysis excluding “progression” or “death” for the outcome of pain.

In principle, “pain” or “pain progression” is a patient-relevant outcome, but it can only be measured indirectly via the first intake of an opioid. Moreover, first intake of an opioid allows no statement on pain progression in patients who already received opioids before the study medication. In the VISION study, > 20% of those patients who received at least 1 dose of the study medication had previously received opioids. For these patients, the first intake of an opioid during the study probably represents a continuation of the existing pain therapy. There is no information on performed dose escalations of the opioids taken. The analyses on the first intake of an opioid are therefore not used for the present benefit assessment.

Side effects

The analyses on the outcomes of the side effects category are based on those patients who received at least 1 dose of the study medication. In relation to the total population, 96.0% of the randomized patients in the intervention arm and 73.2% of the patients in the comparator arm received at least 1 dose of the study medication. The differential proportion of patients not included in the analysis is thus > 15 percentage points. Therefore, the analyses are not suitable for the present benefit assessment.

Results on the overall rates of AEs, SAEs and severe AEs are available with and - specified post hoc - without consideration of symptomatic skeletal-related events. It is not plausible that the event rate of severe AEs without consideration of symptomatic skeletal-related events is higher than the event rate with consideration of symptomatic skeletal-related events.

I Appendix B shows the results on the overall rates of AEs, SAEs and severe AEs used by the company, each including symptomatic skeletal-related events, as supplementary information.

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: lutetium 177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a]

Study		Outcomes												
	Study level	Overall survival	Symptomatic skeletal-related events[b]	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF Items 9a–g)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-P)	SAEs	Severe AEs[c]	Discontinuation due to AEs	Myelosuppression (SMQ[d], severe AEs[c])	Dry mouth (PT, AEs)	Further specific AEs
VISION	L	H[e]	–[f]	–[f]	–[f]	–[f]	–[f]	–[f]	–[f]	–[f]	–[f]	–[f]	–[g]

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates and external radiotherapy.
b. Comprises: new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic intervention, need for radiotherapy for alleviation of bone pain.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. SMQ "haematopoietic cytopenias".
e. Clear differences in the proportions of patients who withdrew consent (15 [2.7%] vs. 33 [11.8%]) between treatment arms; it is unclear whether the patients were included in the analysis.
f. No suitable data available; for the reasoning, see Section I 4.1 of the present dossier assessment.
g. Suitable analyses on AEs are not available, a choice of specific AEs was therefore impossible.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy-Prostate; H: high; L: low; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; VAS: visual analogue scale

The results on the outcome of overall survival have a high risk of bias. It can be inferred from the information in Module 4 A that 15 (2.7%) vs. 33 (11.8%) patients withdrew their informed consent for participation in the study. It is unclear whether these patients were censored at day 1 or to what extent they were censored at day 1. The Kaplan-Meier curves show that censoring was done on day 1 (see Figure 1). If patients were censored at day 1, de facto no times entered the analysis through them and they were thus not taken into account. It remains unclear whether there is a clear difference between the treatment arms regarding the proportion of patients who were not considered in the analysis.

No suitable data are available for the outcomes of the categories “morbidity, health-related quality of life” and “side effects” (see Section I 4.1). The risk of bias is therefore not assessed for these outcomes.

Regardless of this, the uncertainty described in Section I 3.2.2 regarding the proportion of included patients for whom cabazitaxel or olaparib was the most suitable individualized treatment or for whom radioisotopes were an option as part of the BSC and for whom thus the ACT was not implemented, means that at most hints, e.g. of added benefit, can be derived for all outcomes. For the present benefit assessment, this only applies to the outcome of overall survival, as no suitable data are available for the other relevant outcomes.

I 4.3 Results

Table 15 summarizes the results for the comparison of lutetium 177 + ADT + individualized treatment with ADT + individualized treatment in adult patients with progressive PSMA-positive mCRPC who have previously been treated with androgen receptor pathway inhibition and taxane-based chemotherapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier.

Kaplan-Meier curves for the results on overall survival are presented in I Appendix C of the full dossier assessment. I Appendix B provides results on side effects as supplementary information.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: lutetium 177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a] (multipage table)

Study outcome category outcome	Lutetium-177 + ADT + individualized treatment[a]		ADT + individualized treatment[a]		Lutetium-177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a]
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value
Study VISION					
Mortality					
Overall survival	551	15.3 [14.2; 16.9] 343 (62.3)	280	11.3 [9.8; 13.5] 187 (66.8)	0.62 [0.52; 0.74]; < 0.001[b]
Morbidity					
Symptomatic skeletal-related events[c]	No suitable data available[d]				
New symptomatic pathological bone fracture	No suitable data available[d]				
Spinal cord compression	No suitable data available[d]				
Tumour-related orthopaedic intervention	No suitable data available[d]				
Need for radiotherapy for alleviation of bone pain	No suitable data available[d]				
Worst pain (BPI-SF Item 3)[e]	No suitable data available[d]				
Pain interference (BPI-SF Items 9a–g)[e]	No suitable data available[d]				
Health status (EQ-5D VAS)[f]	No suitable data available[d]				
Health-related quality of life					
Health-related quality of life (FACT-P)[g]	No suitable data available[d]				
Side effects					
AEs (supplementary information)	No suitable data available[d]				
SAEs	No suitable data available[d]				
Severe AEs[d]	No suitable data available[d]				
Discontinuation due to AEs	No suitable data available[d]				
Myelosuppression (SMQ[i], severe AEs[h])	No suitable data available[d]				
Dry mouth (PT, AEs)	No suitable data available[d]				
Further specific AEs[j]	No suitable data available[d]				

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: lutetium 177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a] (multipage table)

Study outcome category outcome	Lutetium-177 + ADT + individualized treatment[a]		ADT + individualized treatment[a]		Lutetium-177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a]
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates and external radiotherapy.
b. Effect and CI: Cox proportional hazards model; p-value: log-rank test. Each stratified by LDH level at baseline (≤ 260 IU/L vs. > 260 IU/L), presence of liver metastases at baseline (yes vs. no), ECOG PS at baseline (0 or 1 vs. 2) and androgen receptor pathway inhibitor as part of the study medication at baseline (yes vs. no).
c. Comprises: new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic intervention, need for radiotherapy for alleviation of bone pain.
d. See Section I 4.1 of the present dossier assessment for the reasoning.
e. Time to first deterioration. A score increase by ≥ 1.5 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 10).
f. Time to first deterioration. A decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
g. Time to first deterioration. A score increase by ≥ 23.4 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 156).
h. Severe AEs are operationalized as CTCAE grade ≥ 3.
i. SMQ "haematopoietic cytopenias".
j. Suitable analyses on AEs are not available, a choice of specific AEs was therefore impossible.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; LDH: lactate dehydrogenase; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; n: number of patients with (at least 1) event; N: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: standardized MedDRA Query; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be derived for all outcomes (see Sections I 3.2.2 und I 4.2 for the reasoning).

Mortality

Overall survival

A statistically significant difference in favour of lutetium-177 + ADT + individualized treatment was shown for the outcome "overall survival". There is a hint of added benefit of lutetium-177 + ADT + individualized treatment over ADT + individualized treatment.

Morbidity

Symptomatic skeletal-related events (composite outcome and individual components), worst pain (BPI-SF Item 3), pain interference (BPI-SF Item 9a-g) and health status (EQ-5D VAS)

No suitable data are available for outcomes in the morbidity category. There is no hint of an added benefit of lutetium-177 + ADT + individualized treatment in comparison with ADT + individualized treatment in each case; an added benefit is therefore not proven.

Health-related quality of life

FACT-P

No suitable data were available for the outcome "health-related quality of life", recorded with the FACT-P. There is no hint of an added benefit of lutetium-177 + ADT + individualized treatment in comparison with ADT + individualized treatment; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3) and specific AEs (myelosuppression [SMQ, severe AEs] and dry mouth (PT, AEs)

No suitable data are available for outcomes in the side effects category. There is no hint of an added benefit of lutetium-177 + ADT + individualized treatment in comparison with ADT + individualized treatment in each case; an added benefit is therefore not proven.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics are considered in the present benefit assessment:

- Age (< 65 years versus ≥ 65 years)
- Liver metastases at baseline (yes versus no)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup

results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

For the outcome of overall survival, the only relevant outcome for which a suitable analysis is available, no relevant effect modification by the subgroup characteristics “age” or “liver metastases at baseline” was identified according to the methods described.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, 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 the 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.

I 5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4 (see Table 16).

Table 16: Extent of the added benefit at outcome level: lutetium-177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a]

Observation period **outcome category** **outcome**	**Lutetium-177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a]** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	15.3 vs. 11.3 months HR: 0.62 [0.52; 0.74]; p < 0.001 probability: "hint"	Outcome category: mortality CI_u < 0.85 added benefit; extent: major
Outcomes with shortened observation period		
Morbidity		
Symptomatic skeletal-related events	No suitable data available	Lesser/added benefit not proven
Worst pain (BPI-SF Item 3)	No suitable data available	Lesser/added benefit not proven
Pain interference (BPI-SF Items 9a–g)	No suitable data available	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No suitable data available	Lesser/added benefit not proven
Health-related quality of life		
FACT-P	No suitable data available	Lesser/added benefit not proven
Side effects		
SAEs	No suitable data available	Greater/lesser harm not proven
Severe AEs	No suitable data available	Greater/lesser harm not proven
Discontinuation due to AEs	No suitable data available	Greater/lesser harm not proven
Myelosuppression (severe AEs)	No suitable data available	Greater/lesser harm not proven
Dry mouth (AEs)	No suitable data available	Greater/lesser harm not proven

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates and external radiotherapy.
b. Probability provided if a statistically significant and relevant effect is present.
c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u).

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of confidence interval; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of lutetium-177 + ADT[a] compared with individualized treatment

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival: hint of added benefit – extent: major	–
Suitable data on all outcomes of the categories “morbidity”, “health-related quality of life” and “side effects” are lacking.	
a. With or without androgen receptor pathway inhibition. ADT: androgen deprivation therapy; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan	

The overall picture shows a hint of an added benefit with the extent “considerable” for overall survival. The results on the outcomes of the categories of morbidity, health-related quality of life and side effects are unsuitable for the present benefit assessment. However, under qualitative consideration of the results on side effects used by the company, no disadvantages are suspected to an extent that could call into question the positive effect on overall survival.

In summary, for adult patients with progressive PSMA-positive mCRPC who have been previously treated with androgen receptor pathway inhibition and taxane-based chemotherapy, and for whom abiraterone in combination with prednisone or prednisolone, enzalutamide or BSC is the most appropriate individualized treatment, there is a hint of non-quantifiable added benefit of lutetium-177 compared with the ACT. The added benefit is not proven for patients for whom cabazitaxel or olaparib is the individually optimized treatment.

Table 18 summarizes the result of the assessment of the added benefit of lutetium-177 + ADT in comparison with the ACT.

Table 18: Lutetium-177 + ADT[a] – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
In combination with ADT[c] with or without androgen receptor pathway inhibition for the treatment of adult patients with progressive PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy[d]	Individualized treatment[c] under consideration of the prior therapy choosing from ▪ abiraterone in combination with prednisone or prednisolone, ▪ enzalutamide, ▪ cabazitaxel, ▪ olaparib (only for patients with breast cancer associated gene (BRCA)1/2 mutation), ▪ best supportive care (BSC)[f]	▪ Patients for whom abiraterone in combination with prednisone or prednisolone, enzalutamide or BSC is the individually optimized treatment: hint of a non-quantifiable added benefit[g] ▪ patients for whom cabazitaxel or olaparib is the individually optimized treatment: added benefit not proven

a. With or without androgen receptor pathway inhibition.
b. Presented is the ACT specified by the G-BA.
c. Ongoing conventional ADT is assumed to be continued. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with gonadotropin-releasing hormone (GnRH) agonists or antagonists.
d. For the present therapeutic indication, taxane-based chemotherapy means therapy with docetaxel.
e. For the implementation of individualized treatment in a direct comparative study, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criterion (multicomparator study). The decision on individualized treatment with regard to the comparator therapy at baseline should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). The disease of mCRPC is a palliative therapy situation. Maintaining quality of life and symptom control are therefore of particular importance. Adequate concomitant treatment of bone metastases during the study is assumed (e.g. use of bisphosphonates, denosumab, radiation therapy).
f. 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.
g. Only patients with an ECOG PS of 0 to 2 were included in the VISION study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of > 2.

ADT: androgen deprivation therapy; BRCA: breast cancer associated gene; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; lutetium-177: (^{177}Lu) lutetium vipivotide tetraxetan; mCRPC: metastatic castration-resistant prostate cancer; PSMA: prostate-specific membrane antigen

The assessment described above deviates from that of the company, which derived an indication of major added benefit for all patients in the therapeutic indication.

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

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Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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