Gozetotide (prostate cancer)

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

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Gozetotid (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.

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No advisor on medical and scientific questions was available for the present dossier assessment

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Udo Ehrmann.

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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
AESI	Adverse Event of special Interest
BPI-SF	Brief Pain Inventory-Short Form
BRCA	Breast Cancer Associated Gene
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
FACT-P	Functional Assessment of Cancer Therapy-Prostate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
Gozetotide	gallium-(^{68}GA-)gozetotide
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
Lutetium-177	(^{177}Lu)lutetium vipivotide tetraxetan
mCRPC	metastatic castration-resistant prostate cancer
OECD	Organisation für wirtschaftliche Zusammenarbeit und Entwicklung
PET	positron emission tomography
PSMA	prostate-specific membrane antigen
RCT	randomized controlled trial
rPFS	radiographic progression-free survival
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visuelle Analogskala

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug gallium-(^{68}GA-)gozetotide (gozetotide). 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 15 July 2024.

Research question

The aim of this report is to assess the added value of the diagnostic agent gozetotide for the detection of prostate-specific membrane antigen (PSMA)-positive lesions by positron emission tomography (PET). The assessment was conducted in comparison with the appropriate comparator therapy (ACT) in adult patients with progressive metastatic castration-resistant prostate cancer (mCRPC). The aim of the diagnostics is to identify patients with PSMA-positive mCRPC for whom PSMA-targeted therapy is indicated. Ongoing conventional androgen deprivation therapy (ADT) is assumed to be continued in the patients.

For the detection of PSMA-positive lesions by PET, gozetotide is radiolabelled with gallium-68 prior to use.

For better readability, the (first or only previously approved) PSMA-targeted drug (^{177}LU)lutetium vipivotide tetraxetan is referred to as lutetium-177 in the following. The treatment of adult patients with PSMA-positive, progressive mCRPC previously treated with androgen receptor pathway inhibition and taxane-based chemotherapy, with lutetium-177 in combination with ADT with or without androgen receptor pathway inhibition was already the subject of dossier assessment A23-01 and the associated addendum A23-46.

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

Table 2: Research question for the benefit assessment of gozetotide

Therapeutic indication	**ACT**[a, b]
Adults with progressive mCRPC: identification[c] of patients with PSMA-positive mCRPC for whom PSMA-targeted therapy is indicated[d]	Individualized treatment[e, f] choosing from ▪ abiraterone in combination with prednisone or prednisolone, ▪ enzalutamide, ▪ cabazitaxel, ▪ olaparib, ▪ best supportive care (BSC)[g], under consideration of the prior therapies of the comorbidities, the general condition and the BRCA1/2 mutation status

a. According to the G-BA, various study designs can be considered to answer the research question, whereby a distinction must be made in particular between strategy design, interaction design and enrichment design.
b. Presentation of the ACT specified by the G-BA. Gozetotide is the first approved drug that can be used to identify patients with PSMA-positive, progressive mCRPC for whom PSMA-targeted therapy is indicated. Comparison with another diagnostic test cannot be considered.
c. For the detection of PSMA-positive lesions by PET, gozetotide is radiolabelled with gallium-68 prior to use.
d. (^{177}Lu)lutetium vipivotide tetraxetan in combination with ADT 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 before.
e. 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 GnRH agonists or antagonists.
f. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy 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).
g. 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; gozetotide: gallium (^{68}Ga) gozetotide; mCRPC: metastatic castration-resistant prostate cancer; PET: positron emission tomography; PSMA: prostate-specific membrane antigen

In the company's view, gozetotide is not a reimbursable drug subject to benefit assessment according to §35a SGB V, for which no ACT can be determined either. Irrespective of this, the company presented a dossier and depicted the G-BA's ACT in this dossier.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) on the

diagnostic-therapeutic chain are used to derive the added benefit. This concurs with the company's inclusion criteria.

In principle, various RCT study designs can be considered for the benefit assessment in the present research question, whereby a distinction must be made in particular between strategy design, interaction design and enrichment design. Gozetotide is the only approved diagnostic agent for the detection of PSMA-positive lesions in patients with mCRPC. The present research question is therefore not a situation in which a new diagnostic agent or a new diagnostic test is to replace an established diagnostic agent; consequently, neither a comparison with another diagnostic agent or diagnostic test can be considered, nor is the additional consideration of a concordance question possible.

Study pool and 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 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 (see section on the subpopulation below).

The VISION study followed the enrichment design. In the screening phase prior to study inclusion and randomization, patients were examined with gozetotide for the presence of PSMA-positive lesions using PET (in accordance with the relevant guidelines of the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging). A total of 1003 patients were included in the screening. Of these patients, 172 (17.1%) were not randomized because the majority of them were PSMA-negative and therefore did not meet the inclusion criteria regarding the PSMA status. 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.

Diagnostics with gozetotide was largely in compliance with the Summary of Product Characteristics (SPC). According to the SPC, gozetotide should be administered at a minimum

dose of 111 MBq up to a maximum dose of 259 MBq (1.8 to 2.2 MBq/body weight). In the VISION study, the dosage of gozetotide was planned to range between 111 MBq and 185 MBq. The actually administered maximum dose was 237 MBq in the intervention arm and 288 MBq in the comparator arm. It is assumed that these deviations did not influence the diagnostics with gozetotide and the study results in a relevant way. Lutetium-177 was administered for up to 6 cycles in accordance with the 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.

Suitability of the VISION study for the assessment of the diagnostic agent gozetotide

The VISION study corresponds to an enrichment design. In this design, only some of the patients (in this case the patients with PSMA-positive lesions) are randomized to the intervention or the comparator arm on the basis of the diagnostic agent or diagnostic test to be investigated. The design of the VISION study is considered suitable for the assessment of the diagnostic agent gozetotide. This is explained below:

At first, in the present assessment situation (an added benefit was already determined for PSMA-targeting therapy with lutetium-177 in the early benefit assessment; gozetotide is the only approved diagnostic agent for the detection of PSMA-positive lesions by PET), it is assumed that patients with PSMA-negative lesions do not benefit from PSMA-targeting therapy with lutetium-177. Against this background, it seems appropriate to consider only patients with PSMA-positive lesions.

In addition, in the present assessment situation, it is assumed that gozetotide does not have direct (side) effects to a relevant extent. In the VISION study, side effects under the use of gozetotide were recorded separately. Although these data are not suitable for an assessment of the side effects of gozetotide, partly due to the lack of a comparator group, they do allow the quantitative assessment that no adverse events (AEs) to a relevant extent occur with gozetotide, which fundamentally argues against using the results of the VISION study to compare lutetium-177 with individualized treatment for the benefit assessment of the diagnostic agent gozetotide.

Overall, the requirements for using the VISION study for the assessment of the diagnostic agent gozetotide in the present research question are thus fulfilled.

Subpopulation

After the start of the study, an increased frequency of withdrawn consents was observed in the comparator arm of the VISION study. 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 on the total population are not suitable for the present benefit assessment. In contrast to the other outcomes, overall survival was recorded until the end of the study, namely independent of the receipt of study medication and independent of the duration of treatment.

The study protocol was adapted (Version 3.0, 1 April 2019; for all patients randomized from 5 March 2019) to address the increased frequency of withdrawn consent forms. Prior to version 3.0 of the study protocol (1 April 2019), patients with 1 prior taxane-based chemotherapy could participate in the study if they declined treatment with another taxane-based chemotherapy. 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. Patients eligible for treatment who refused further taxane-based chemotherapy were not to be included in the study from this point onwards, as had still been possible before.

The amendment of the study protocol results in 2 analysis populations for the VISION study. On the one hand, the analysis of all randomized patients (total population of the study), on the other hand analyses on patients who had been randomized from 5 March 2019 onwards under Version 3.0 of the study protocol (relevant subpopulation [approx. 70% of the total population]). For these latter patients, 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. Analyses for this subpopulation are suitable for the benefit assessment and will be used for it.

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,

- best supportive care (BSC),

under consideration of the prior therapies of the comorbidities, the general condition and the breast cancer associated gene (BRCA)1/2 mutation status.

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. Consequently, the VISION study only allows conclusions on the added benefit of gozetotide 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 gozetotide for patients for whom cabazitaxel or olaparib is the most suitable individualized therapy.

Implementation of the ACT

Cabazitaxel

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).

As described in the section on the subpopulation, the total population of the VISION study could include cabazitaxel-eligible patients who refused further taxane-based chemotherapy. As of protocol version 3 (1 April 2019), however, only patients for whom further taxane-based chemotherapy was not an option according to the investigator's assessment (relevant subpopulation) were included in the study. Due to this adjustment of the inclusion criteria, it is assumed for the relevant subpopulation that cabazitaxel is not the most suitable individualized therapy for these patients. Thus, the uncertainty described for the total population in A23-01 regarding the proportion of patients in the VISION study for whom cabazitaxel is the most suitable individualized treatment is considered to be largely resolved for the relevant subpopulation. In this regard, uncertainty remains only for the outcome of overall survival, which is not based on the results of this subpopulation of the VISION study. The handling of this uncertainty for the outcome of overall survival is described in the section on the risk of bias.

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, 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, 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. 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 relevant subpopulation of the VISION study had a BRCA1/2 mutation. The study documents show that only 1 patient in the relevant subpopulation per treatment arm received olaparib as part of the study medication. Based on the information on patient numbers from dossier assessment A20-106, a proportion value for BRCA1/2 mutation of approx. 10% of patients is assumed. It is not assumed that the associated uncertainty alone has a significant impact on the interpretability of the results.

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.

In the relevant subpopulation, < 5% of patients received radioisotopes as subsequent therapy. However, based on these and other available data, it is not possible to estimate for how many patients in the relevant subpopulation radioisotopes were basically an option and represented the most suitable therapy in the context of the BSC. However, this is not assumed to influence the interpretability of the results.

Risk of bias

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

The risk of bias of the results for the outcome of overall survival is rated as low. In contrast to the other outcomes, this assessment is based on the results of the total population of the

VISION study. In the total population, 15 (2.7%) vs. 33 (11.8%) of the patients withdrew their consent to participate in the study during the course of the study and were censored for the outcome of overall survival for this reason. However, the proportion of patients who were censored on Day 1 was 0 vs 2 (0.7%) patients. Thus, the proportion of patients included in the analysis is sufficiently similar despite high differential proportions of withdrawn consents to study participation. As described above, there is uncertainty for the total population regarding the proportion of patients in the VISION study for whom cabazitaxel is the most appropriate individualized treatment. As the results of the outcome of overall survival are consistent for the total population and the subpopulation and the risk of bias is rated as low for the outcome, at most indications, e.g. of an added benefit, can be derived for the outcome in the present benefit assessment.

The analyses of the composite outcome “symptomatic skeletal-related events” are not suitable for the present benefit assessment; in the present data situation, the individual components of the composite outcome are considered as separate outcomes). Therefore, the assessment of the risk of bias applies to the individual components of the composite outcome used in this benefit assessment. Therefore, the outcomes of new symptomatic pathologic bone fracture, spinal cord compression, tumour-related orthopaedic intervention as well as need for radiotherapy for alleviation of bone pain (individual components of the composite outcome “symptomatic skeletal-related events”) have a high risk of bias due to incomplete observation for potentially informative reasons with different follow-up observation periods.

No suitable data are available for patient-reported outcomes (Brief Pain Inventory-Short Form [BPI-SF], Functional Assessment of Cancer Therapy-Prostate [FACT-P], EQ-5D). The risk of bias is therefore not assessed for these outcomes.

Due to incomplete observation for potentially informative reasons with different follow-up observation periods and great differences (> 5%) of patients not included in the analysis between the treatment groups, the outcomes of the category “side effects” have a high risk of bias. For the outcomes of discontinuation due to AEs, dry mouth as well as gastrointestinal disorders and urinary tract infection, the lack of blinding in subjective recording of outcomes is also taken into account in the assessment of the risk of bias. For the outcome of discontinuation due to AEs, symptomatic skeletal-related events were also recorded.

Results

Mortality

overall survival

A statistically significant difference in favour of lutetium-177 + ADT + individualized treatment after PSMA diagnostics with gozetotide was shown for the outcome of overall survival. There

is an indication of added benefit of lutetium-177 + ADT + individualized treatment over ADT + individualized treatment, each after PSMA diagnostics with gozetotide.

Morbidity

Symptomatic skeletal-related events

For each of the outcomes “spinal cord compression” and “need for radiotherapy for alleviation of bone pain”, there is a statistically significant difference in favour of lutetium-177 + ADT + individualized treatment after PSMA diagnostics with gozetotide. There is a hint of added benefit of lutetium-177 + ADT + individualized treatment over ADT + individualized treatment, each after PSMA diagnostics with gozetotide.

No statistically significant difference between treatment groups was shown for the outcomes “new symptomatic bone fracture” and “tumour-related orthopaedic intervention”. There is no hint of an added benefit of lutetium-177 + ADT + individualized treatment in comparison with ADT + individualized treatment, each after PSMA diagnostics with gozetotide; an added benefit is therefore not proven.

Worst pain (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 the outcomes “worst pain” (BPI-SF Item 3), “pain interference“ (BPI-SF Item 9a-g) and “health status” (EQ-5D VAS). There is no hint of an added benefit of lutetium-177 + ADT + individualized treatment in comparison with ADT + individualized treatment, each after PSMA diagnostics with gozetotide; 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, each after PSMA diagnostics with gozetotide; an added benefit is therefore not proven.

Side effects

Serious adverse events (AEs)

A statistically significant difference in favour of lutetium-177 + ADT + individualized treatment after PSMA diagnostics with gozetotide was shown for the outcome of SAEs. There is a hint of lesser harm from lutetium-177 + ADT + individualized treatment compared with ADT + individualized treatment, each after PSMA diagnostics with gozetotide.

Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), discontinuation due to AEs

No statistically significant difference between the treatment groups was shown for the outcomes "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". There is no hint of greater or lesser harm from lutetium-177 + ADT + individualized treatment in comparison with ADT + individualized treatment, each after PSMA diagnostics with gozetotide; greater or lesser harm is therefore not proven.

Specific AEs

Acute renal failure (standardized MedDRA query [SMQ], SAEs)

A statistically significant difference in favour of lutetium-177 + ADT + individualized treatment after PSMA diagnostics with gozetotide was shown for the outcome of acute renal failure (SMQ, SAEs). There is a hint of lesser harm from lutetium-177 + ADT + individualized treatment compared with ADT + individualized treatment, each after PSMA diagnostics with gozetotide.

Myelosuppression (SMQ, severe AEs), dry mouth (PT, AEs), gastrointestinal disorders (System Organ Class [SOC], AEs), urinary tract infection (PT, AEs)

There is a statistically significant difference to the disadvantage of lutetium-177 + ADT + individualized treatment after PSMA diagnostics with gozetotide for each of the outcomes “myelosuppression” (SMQ, severe AEs), “dry mouth” (PT, AEs), “gastrointestinal disorders” (SOC, AEs) as well as “urinary tract infection” (PT, AEs). In each case, there is a hint of greater harm from lutetium-177 + ADT + individualized treatment compared with ADT + individualized treatment, each after PSMA diagnostics with gozetotide.

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 gozetotide in comparison with the ACT is assessed as follows:

Overall, the VISION study showed both positive and negative effects for lutetium-177 + ADT + individualized treatment compared to ADT + individualized treatment, in each case after PSMA diagnostics with gozetotide. Only for overall survival are the observed effects based on the entire observation period. For the outcomes in the categories of morbidity and side

[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].

effects, however, they refer exclusively to a shortened period (up to 30 days after discontinuation of the study medication, but before the start of a subsequent tumour therapy not permitted in the study).

On the positive side, there was an indication of major added benefit for the outcome of overall survival. Moreover, there is a hint of major added benefit for the outcomes of spinal cord compression and need for radiotherapy for alleviation of bone pain. For the outcomes of SAEs and acute renal failure (SAEs), there is a hint of lesser harm with the extent "minor" (SAEs) or "considerable" (acute renal failure). On the negative side, there is a hint of greater harm for the outcomes of myelosuppression (severe AEs), dry mouth (AEs), gastrointestinal disorders (AEs) and urinary tract infection (AEs) with the extent "minor" (myelosuppression) and "considerable" (dry mouth, gastrointestinal disorders and urinary tract infection). Overall, the unfavourable effects do not call into question the added benefit in the outcome of overall survival. Overall, the data situation for the VISION study is therefore unchanged compared to the assessment in Addendum A23-46.

For the drug gozetotide, there are no side effects to a relevant extent that, in view of the added benefit of lutetium-177 + ADT over individualized treatment, fundamentally speak against the use of the VISION study for the benefit assessment of gozetotide in comparison with the ACT. The results of the VISION study (enrichment design) will therefore be used for the benefit assessment of gozetotide (for the identification of patients with PSMA-positive mCRPC for whom PSMA-targeted therapy is indicated) compared to the ACT.

In summary, for patients with progressive mCRPC and for whom abiraterone (in combination with prednisone or prednisolone), enzalutamide or BSC is the most appropriate individualized treatment, there is an indication of major added benefit of gozetotide versus the ACT. The added benefit is not proven for patients with progressive mCRPC for whom cabazitaxel or olaparib is the best suitable individualized treatment.

Table 3 shows a summary of probability and extent of the added benefit of gozetotide.

Table 3: Gozetotide – probability and extent of added benefit

Therapeutic indication	**ACT[a, b]**	**Probability and extent of added benefit**
Adults with progressive mCRPC: identification[c] of patients with PSMA-positive mCRPC for whom PSMA-targeted therapy is indicated[d]	Individualized treatment[e, f] choosing from ▪ abiraterone in combination with prednisone or prednisolone, ▪ enzalutamide, ▪ cabazitaxel, ▪ olaparib, ▪ best supportive care (BSC)[g], under consideration of the prior therapies of the comorbidities, the general condition and the BRCA1/2 mutation status	▪ Patients for whom abiraterone in combination with prednisone or prednisolone, enzalutamide or BSC is the individually optimized treatment: indication of major added benefit ▪ patients for whom cabazitaxel or olaparib is the individually optimized treatment: added benefit not proven

a. According to the G-BA, various study designs can be considered to answer the research question, whereby a distinction must be made in particular between strategy design, interaction design and enrichment design.
b. Presentation of the ACT specified by the G-BA. Gozetotide is the first approved drug that can be used to identify patients with PSMA-positive, progressive mCRPC for whom PSMA-targeted therapy is indicated. Comparison with another diagnostic test cannot be considered.
c. For the detection of PSMA-positive lesions by PET, gozetotide is radiolabelled with gallium-68 prior to use.
d. (^{177}Lu)lutetium vipivotide tetraxetan in combination with ADT 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 before.
e. 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 GnRH agonists or antagonists.
f. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy 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).
g. 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.
h. 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 ≥ 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; gozetotide: gallium-(^{68}GA) gozetotide: mCRPC: metastatic castration resistant prostate cancer; PET: positron emission tomography; PSMA: prostate-specific membrane antigen

The approach for the derivation of 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 this report is to assess the added value of the diagnostic agent gozetotide for the detection of PSMA-positive lesions by PET. The assessment was conducted in comparison with the ACT in adult patients with progressive mCRPC. The aim of the diagnostics is to identify patients with PSMA-positive mCRPC for whom PSMA-targeted therapy is indicated. Ongoing conventional ADT is assumed to be continued in the patients.

For the detection of PSMA-positive lesions by PET, gozetotide is radiolabelled with gallium-68 prior to use.

For better readability, the (first or only previously approved) PSMA-targeted drug $^{(177}$LU)lutetium vipivotide tetraxetan is referred to as lutetium-177 in the following. The treatment of adult patients with PSMA-positive, progressive mCRPC previously treated with androgen receptor pathway inhibition and taxane-based chemotherapy, with lutetium-177 in combination with ADT with or without androgen receptor pathway inhibition was already the subject of dossier assessment A23-01 and the associated addendum A23-46 [3,4].

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

Table 4: Research question for the benefit assessment of gozetotide

Therapeutic indication	**ACT**[a, b]
Adults with progressive mCRPC: identification[c] of patients with PSMA-positive mCRPC for whom PSMA-targeted therapy is indicated[d]	Individualized treatment[e, f] choosing from ▪ abiraterone in combination with prednisone or prednisolone, ▪ enzalutamide, ▪ cabazitaxel, ▪ olaparib, ▪ best supportive care (BSC)[g], under consideration of the prior therapies of the comorbidities, the general condition and the BRCA1/2 mutation status

a. According to the G-BA, various study designs can be considered to answer the research question, whereby a distinction must be made in particular between strategy design, interaction design and enrichment design.
b. Presentation of the ACT specified by the G-BA. Gozetotide is the first approved drug that can be used to identify patients with PSMA-positive, progressive mCRPC for whom PSMA-targeted therapy is indicated. Comparison with another diagnostic test cannot be considered.
c. For the detection of PSMA-positive lesions by PET, gozetotide is radiolabelled with gallium-68 prior to use.
d. (^{177}Lu)lutetium vipivotide tetraxetan in combination with ADT 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 before.
e. 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 GnRH agonists or antagonists.
f. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy 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).
g. 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; gozetotide: gallium (^{68}Ga) gozetotide; mCRPC: metastatic castration-resistant prostate cancer; PET: positron emission tomography; PSMA: prostate-specific membrane antigen

In the company's view, gozetotide is not a reimbursable drug subject to benefit assessment according to §35a SGB V, for which no ACT can be determined either. Irrespective of this, the company presented a dossier and depicted the G-BA's ACT in this dossier.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs on the diagnostic-therapeutic chain are used to derive the added benefit. This concurs with the company's inclusion criteria.

In principle, various RCT study designs can be considered for the benefit assessment in the present research question, whereby a distinction must be made in particular between strategy design, interaction design and enrichment design. Gozetotide is the only approved diagnostic agent for the detection of PSMA-positive lesions in patients with mCRPC. The present research question is therefore not a situation in which a new diagnostic agent or a new diagnostic test is to replace an established diagnostic agent (see A24-37 [5]); consequently, neither a comparison with another diagnostic agent or diagnostic test can be considered, nor is the additional consideration of a concordance question possible.

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 gozetotide (status: 11 June 2024)
- bibliographical literature search on gozetotide (last search on 23 April 2024)
- search in trial registries/trial results databases for studies on gozetotide (last search on 23 April 2024)
- search on the G-BA website for gozetotide (last search on 01 July 2024)

To check the completeness of the study pool:

- search in trial registries for studies on gozetotide (last search on 26 July 2024); 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 VISION study presented in the following table was included in the benefit assessment. This is an enrichment design study. In this design, randomization (and thus inclusion) of only some of the patients (in the present case patients with PSMA-positive, progressive mCRPC), who then received 1 of 2 forms of treatment, takes place on the basis of the diagnostic agent or diagnostic test to be assessed. The forms of treatment in the VISION study are PSMA-targeted therapy with lutetium-177 (with continuation of the ongoing ADT and individualized treatment) in the intervention arm and a sole continuation of the ongoing ADT and individualized treatment in the comparator arm (see also Section I 3.2.1 for the justification of the suitability of the VISION study [in the enrichment design] for the assessment of the diagnostic agent gozetotide).

Table 5: Study pool – RCT, direct comparison: lutetium-177 + ADT + individualized treatmenta 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 and other sources[d] (yes/no [citation])
VISION	Yes	Yes	No	Yes [6]	Yes [7,8]	Yes [9,10]

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates, external radiotherapy and blood transfusions.
b. Study for which the company was sponsor.
c. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
d. Other sources: documents from the search on the G-BA website and other publicly available sources.

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

The study pool is consistent with the study pool 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 chemotherapiesd	Diagnostics with gozetotide (N* = 1003)[e] total population: lutetium-177 + ADT + individualized treatment[a] (N = 551) ADT + individualized treatment[a] (N = 280) relevant subpopulation[f]: lutetium 177 + ADT + individualized treatment[a] (N = 385) ADT + individualized treatment[a] (N = 196)	screening: ≤ 4 weeks before randomization treatment[g]: once every 6 weeks for up to 6 cycles[h] observation[i]: outcome-specific, at most until death, disease progression, discontinuation of participation in the study or end of study[j]	86 study centres: Belgium, Canada, Denmark, France, Germany, Netherlands, Puerto Rico, Sweden, United Kingdom and United States 05/2018–12/2023 data cut-offs: ▪ 27 January 2021 (primary analysis) ▪ 28 June 2021[k]	Primary: ▪ rPFS ▪ overall survival secondary: morbidity, health-related quality of life, AEs

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]
a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates, external radiotherapy and blood transfusions. 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. Detection of PSMA-positive lesions to assess the suitability of PSMA-targeted therapy; 172 patients with PSMA-negative lesions (17.1%) were not randomized. f. Patients randomized as of 5 March 2019 (version 3.0 of the study protocol) (see Section I 3.2.1). g. 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. h. After the 4th cycle, it was investigated whether the respective patient could receive 2 further cycles of lutetium-177. i. Outcome-specific information is provided in Table 8. j. 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. k. According to information provided by the company, this data cut-off was a safety update after 90 days for the regulatory authorities. AE: adverse event; ADT: androgen deprivation therapy; CT: computed tomography; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; GBq: gigabecquerel; gozetotide: gallium-(^{68}GA) gozetotide; IV: intravenous; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; mCRPC: metastatic castration-resistant prostate cancer; MRI: magnetic resonance imaging; N: number of randomized patients; N*: number of patients with assessment of eligibility for PSMA-targeted therapy; n: number of patients in the relevant subpopulation; PSMA: prostate-specific membrane antigen; RCT: randomized controlled trial; rPFS: radiological 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	PSMA diagnostics: Gozetotide IV; 111 MBq to 185 MBq once; subsequent PET/CT[b]	
	lutetium-177 IV; 7.4 GBq (± 10%)[b] every 6 weeks for up to 6 cycles[d] + ADT + individualized treatment[a]	ADT + individualized treatment[a]
	from cycle 7 onwards, patients received ADT + individualized treatment[a] with a cycle duration of 12 weeks until the end of study[e]	
	pretreatment ▪ ≥ 1 androgen receptor pathway inhibitor (e.g. enzalutamide or abiraterone) ▪ 1-2 taxane-based chemotherapies ▪ ADT (medical castration or prior orchiectomy) not allowed: ▪ 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) ▪ individualized treatment[a] not allowed: ▪ other investigational drugs ▪ 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, external radiotherapy and blood transfusions.
b. According to EANM and SNMMI guidelines [11].
c. 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.
d. After the 4th cycle, it was investigated whether the respective patient could receive 2 further cycles of lutetium-177.
e. After discontinuation of the study medication, patients could participate in up to 2 years of long-term follow-up.

ADT: androgen deprivation therapy; Bq: becquerel; CT: computed tomography; EANM: European Association of Nuclear Medicine; gozetotide: gallium-(^{68}GA) gozetotide; IV: intravenous; Lutetium-177:(^{177}Lu)lutetium vipivotide tetraxetan; PET: positron emission tomography; PSMA: prostate-specific membrane antigen; RCT: randomized controlled trial; SNMMI: Society of Nuclear Medicine and Molecular Imaging

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 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 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 (see section on the subpopulation below).

The VISION study was conducted according to the enrichment design (see Section I 4.1). In the screening phase prior to study inclusion and randomization, patients were examined with gozetotide for the presence of PSMA-positive lesions using PET (in accordance with the relevant guidelines of the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging [11]). A total of 1003 patients were included in the screening. Of these patients, 172 (17.1%) were not randomized because the majority of them were PSMA-negative and therefore did not meet the inclusion criteria regarding the PSMA status. 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).

Diagnostics with gozetotide was largely in compliance with the SPC [12]. According to the SPC, gozetotide should be administered at a minimum dose of 111 MBq up to a maximum dose of 259 MBq (1.8 to 2.2 MBq/body weight). In the VISION study, the dosage of gozetotide was planned to range between 111 MBq and 185 MBq. The actually administered maximum dose was 237 MBq in the intervention arm and 288 MBq in the comparator arm. It is assumed that these deviations did not influence the diagnostics with gozetotide and the study results in a relevant way. Lutetium-177 was administered for up to 6 cycles according to the SPC [13]. 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 3.2.6.

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.

Data cut-off

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

- 1st data cut-off of 27 January 2021: preplanned primary analysis on the outcome of rPFS 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

As described in A23-01 [3] and A23-46 [4], the first data cut-off of the VISION study from 27 January 2021 as an a priori planned primary analysis on the outcome of rPFS and as final analysis on overall survival is used as relevant data cut-off for the present benefit assessment.

Suitability of the VISION study for the assessment of the diagnostic agent gozetotide

The VISION study corresponds to an enrichment design. In this design, only some of the patients (in this case the patients with PSMA-positive lesions) are randomized to the intervention or the comparator arm on the basis of the diagnostic agent or diagnostic test to be investigated. The design of the VISION study is considered suitable for the assessment of the diagnostic agent gozetotide. This is explained below:

At first, in the present assessment situation (an added benefit had already been determined for PSMA-targeted therapy with lutetium-177 in the early benefit assessment [4,10]; gozetotide is the only approved diagnostic agent for the detection of PSMA-positive lesions by PET), it is assumed that patients with PSMA-negative lesions do not benefit from PSMA-targeting therapy with lutetium-177. Against this background, it seems appropriate to consider only patients with PSMA-positive lesions.

In addition, in the present assessment situation, it is assumed that gozetotide does not have direct (side) effects to a relevant extent. In the VISION study, side effects under the use of gozetotide were recorded separately. Although these data are not suitable for an assessment

of the side effects of gozetotide (for reasons, see Section I 4.1), they do allow the qualitative assessment that no AEs to a relevant extent occur under gozetotide, which fundamentally argues against using the results of the VISION study to compare lutetium-177 with individualized treatment for the benefit assessment of the diagnostic agent gozetotide.

Overall, the requirements for using the VISION study for the assessment of the diagnostic agent gozetotide in the present research question are thus fulfilled.

Subpopulation

After the start of the study, an increased frequency of withdrawn consents was observed in the comparator arm of the VISION study. 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 on the total population are not suitable for the present benefit assessment. In contrast to the other outcomes, overall survival was recorded until the end of the study, namely independent of the receipt of study medication and independent of the duration of treatment (see Section I 3.2.5).

The study protocol was adapted (Version 3.0, 1 April 2019; for all patients randomized from 5 March 2019) to address the increased frequency of withdrawn consent forms. Prior to version 3.0 of the study protocol (1 April 2019), patients with 1 prior taxane-based chemotherapy could participate in the study if they declined treatment with another taxane-based chemotherapy. 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. Patients eligible for treatment who refused further taxane-based chemotherapy were not to be included in the study from this point onwards, as had still been possible before. In addition, investigators were trained with regard to the conduct of the study, permitted treatment options in the comparator arm and patient education.

The amendment of the study protocol results in 2 analysis populations for the VISION study. On the one hand, the analysis of all randomized patients (total population of the study), on the other hand analyses on patients who had been randomized from 5 March 2019 onwards under Version 3.0 of the study protocol (relevant subpopulation [approx. 70% of the total population]). For these latter patients, 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. Analyses for this subpopulation are suitable for the benefit assessment and will be used for it.

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,
- BSC,

under consideration of the prior therapies of the comorbidities, the general condition and the BRCA1/2 mutation status.

Cabazitaxel and olaparib were not allowed in the VISION study (see Section I 3.1). 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. Consequently, the VISION study only allows conclusions on the added benefit of gozetotide 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 gozetotide for patients for whom cabazitaxel or olaparib is the most suitable individualized therapy.

Implementation of the ACT

Cabazitaxel

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) [14].

As described in Section I 3.2.1 (subpopulation), the total population of the VISION study could include cabazitaxel-eligible patients who refused further taxane-based chemotherapy. As of protocol version 3 (1 April 2019), however, only patients for whom further taxane-based chemotherapy was not an option according to the investigator's assessment (relevant subpopulation) were included in the study. Due to this adjustment of the inclusion criteria, it is assumed for the relevant subpopulation that cabazitaxel is not the most suitable individualized therapy for these patients. Thus, the uncertainty described for the total population in A23-01 [3] regarding the proportion of patients in the VISION study for whom cabazitaxel is the most suitable individualized treatment is considered to be largely resolved for the relevant subpopulation. In this regard, a relevant uncertainty remains only for the outcome of overall survival, which is not based on the results of this subpopulation of the

VISION study. The handling of this uncertainty for the outcome of overall survival is described in Section I 4.2.

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 [14].

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) [15,16]. 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 [14]. 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 relevant subpopulation of the VISION study had a BRCA1/2 mutation. The study documents show that only 1 patient in the relevant subpopulation per treatment arm received olaparib as part of the study medication. Based on the information on patient numbers from dossier assessment A20-106 [17], a proportion value for BRCA1/2 mutation of approx. 10% of patients is assumed. It is not assumed that the associated uncertainty alone has a significant impact on the interpretability of the results.

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.

In the relevant subpopulation, < 5% of patients received radioisotopes as subsequent therapy. However, based on these and other available data, it is not possible to estimate for how many

patients in the relevant subpopulation radioisotopes were basically an option and represented the most suitable therapy in the context of the BSC. However, this is not assumed to influence the interpretability of the results.

I 3.2.3 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]

Table 8:

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 side effects category	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, external radiotherapy and blood transfusions.
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 and side effects 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 beyond 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 these outcomes for the total period, as was done for survival.

I 3.2.4 Patient characteristics

Table 9 shows the characteristics of the patients in the relevant subpopulation of the included VISION study.

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 = 385	ADT + individualized treatment[a] N = 196
VISION (relevant subpopulation: patients randomized from 5 March 2019 onwards)		
Age [years], mean (SD)	70 (7)	71 (7)
Family origin, n (%)		
White	336 (87)	166 (85)
Black/African American	29 (8)	14 (7)
Asian	6 (2)	9 (5)
Other[b]	2 (< 1)	0 (0)
No data	12 (3)	7 (4)
ECOG PS, n (%)		
0–1	352 (91)	179 (91)
2	33 (9)	17 (9)
Disease duration: time since first diagnosis [years], median [min; max]	7.3 (0.9; 28.9)	7.0 (0.7; 26.2)
Original Gleason score, n (%)		
2–3	1 (< 1)	0 (0)
4–7	130 (34)	59 (30)
8–10	226 (59)	118 (60)
Unknown	28 (7)	19 (10)
Location of target and non-target lesions, n (%)		
Lung	35 (9)	20 (10)
Liver	47 (12)	26 (13)
Lymph nodes	193 (50)	99 (51)
Bones	351 (91)	179 (91)
PSA concentration [ng/mL] at baseline, median (min; max)	93.2 (0; 6988)	90.7 (0; 6600)
Prior radiotherapy, n (%)	286 (74)	152 (78)
Prior treatment with radium-223 dichloride, n (%)	63 (16)	36 (18)
Prior androgen receptor pathway inhibitors		
Number, n (%)		
1	213 (55)	98 (50)
2	150 (39)	86 (44)
> 2	22 (6)	12 (6)
Drug		
Enzalutamide	280 (73)	145 (74)
Abiraterone	157 (41)	85 (44)
Abiraterone acetate	110 (29)	62 (32)
Apalutamide	8 (2)	5 (3)

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 = 385	ADT + individualized treatment[a] N = 196
Prior taxane-containing chemotherapy		
Number, n (%)		
1	207 (54)	102 (52)
2	173 (45)	92 (47)
> 2	5 (1)	2 (1)
Drugs, n (%)		
Cabazitaxel	161 (42)	84 (43)
Docetaxel	377 (98)	191 (97)
Paclitaxel	2 (< 1)	1 (< 1)
Paclitaxel albumin	1 (< 1)	0 (0)
Treatment discontinuation, n (%)[c]	332 (86)	160 (82)
Common reasons for the discontinuation of lutetium-177		
Progression	91 (24)	-
Adverse event	35 (9)	-
No more clinical benefit	27 (7)	-
Common reasons for the discontinuation of ADT/individualized treatment[a]		
Progression	162 (42)	67 (34)
No more clinical benefit	49 (13)	40 (20)
Physician's decision	32 (8)	5 (3)
Study discontinuation, n (%)	247 (64)	153 (78)
Common reasons for study discontinuation		
Death	232 (60)	117 (60)
Withdrawal of consent	14 (4)	33 (17)

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates, external radiotherapy and blood transfusions.
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.

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 of the relevant subpopulation were largely balanced between the 2 treatment arms.

The mean patient age was about 70 years, and most patients 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 about 7 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 1 taxane-based chemotherapy. With 55%, the proportion of patients with 1 prior androgen receptor pathway inhibitor was slightly higher in the intervention arm than in the comparator arm (50%). 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 (44%). 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 45% 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 slightly higher in the intervention arm (86%) than in the comparator arm (82%). However, the proportion of patients who did not receive study medication was clearly higher in the comparator arm (16.3%) than in the intervention arm (4.2%).

64% of the patients in the intervention arm and 78% of those in the comparator arm discontinued the study. The difference is mainly based on the high proportion of withdrawn consents (17%) in the comparator arm compared to 4% in the intervention arm.

I 3.2.5 Treatment duration and observation period

Table 10 shows the median and mean treatment duration of the patients in the relevant subpopulation 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] (multipage table)

Study **duration of the study phase** **outcome category**	**lutetium-177 + ADT + individualized treatment[a]** **N = 385**	**ADT + individualized treatment[a]** **N = 196**
VISION (relevant subpopulation: patients randomized from 5 March 2019 onwards)		
Treatment duration [months][b]		
Median [min; max]	7.9 [0.6; 19.8]	2.1 [0.1; 21.0]
Mean (SD)	7.9 (4.2)	3.4 (3.6)
Observation period [months]		
Overall survival[c]		
Median [min; max]	18.8 [3.3; 22.8]	18.3 [0; 22.8]
Mean (SD)	ND	
Morbidity		
Symptomatic skeletal-related event[d]		
Median [min; max]	8.4 [0; 22.6]	2.3 [0; 19.8]
Mean (SD)	ND	
Worst pain (BPI-SF Item 3)	No usable data available[e]	
Pain interference (BPI-SF item 9a–g)	No usable data available[e]	
Health status (EQ-5D VAS)	No usable data available[e]	
Health-related quality of life		
FACT-P	No usable data available[e]	
Side effects[b]		
AEs		
Median [min; max]	11.1 [4.2; 13.0]	3.0 [0.2; 5.3]
Mean (SD)	ND	
Severe AEs[f]		
Median [min; max]	11.5 [1.6; 22.6]	3.7 [0.2; 19.8]
Mean (SD)	ND	
Serious adverse events (SAEs)		
Median [min; max]	10.2 [1.6; 22.6]	3.0 [0.2; 19.8]
Mean (SD)	ND	
Discontinuation due to AEs		
Median [min; max]	9.3 [1.1; 22.6]	2.7 [0.2; 19.8]
Mean (SD)	ND	
Myelosuppression (SMQ[g], severe AEs[h])	ND	
Dry mouth (PT, AEs)	ND	
Acute renal failure (SMQ, SAEs)	ND	
Gastrointestinal disorders (SOC, AEs)	ND	
Urinary tract infection (PT, AEs)	ND	

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

Study **duration of the study phase** **outcome category**	**lutetium-177 + ADT + individualized treatment[a]** **N = 385**	**ADT + individualized treatment[a]** **N = 196**

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, bisphosphonates, external radiotherapy and blood transfusions.
b. Data refer to the full analysis set (FAS), which includes all patients who received (at least) one dose of the study medication (366 vs. 167 patients).
c. The observation period was calculated based on the observed time to event/censoring/end of study of all patients (deceased and non-deceased).
d. Comprises: new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic intervention, need for radiotherapy for alleviation of bone pain.
e. High differential proportion (> 15 percentage points) of patients not included in the analysis between the study arms, (for detailed reasoning, see Section I 4.1.
f. Severe AEs are operationalized as CTCAE grade ≥ 3.
g. SMQ "haematopoietic cytopenias".

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; FAS: full analysis set; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; max: maximum; MedDRA: Medical Dictionary for Regulatory Activities; min: minimum; N: number of randomized patients; n: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; SMQ: Standardized MedDRA query; SOC: System Organ Class; VAS: visual analogue scale

The information on treatment and observation periods is based on different patient numbers. While data on the treatment duration and the observation period of side effects are based on those patients in the relevant subpopulation who received at least 1 dose of the study medication (366 patients in the intervention arm vs. 167 patients in the comparator arm), the data on the observation period of overall survival and symptomatic skeletal-related events are based on all randomized patients (385 patients in the intervention arm vs. 196 patients in the comparator arm).

The median treatment duration in the intervention arm was 7.9 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 18 months in both treatment arms.

According to the company's information, the median observation periods for the side effect outcomes of AEs, severe AEs (CTCAE grade ≥ 3), serious AEs (SAEs) and discontinuation due to AEs differ from each other. The reason for this is unclear, as according to the study protocol, all outcomes in the side effects category were followed up until 30 days after discontinuation of the study medication, but before the start of a subsequent tumour therapy not permitted in the study. However, taking into account the median treatment duration, the observation

periods submitted by the company for the outcomes of AEs, severe AEs (CTCAE grade ≥ 3), SAEs and discontinuation due to AEs appear basically plausible.

I 3.2.6 Subsequent therapies

Table 11 shows the subsequent therapies patients of the relevant subpopulation received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies[a] – (≥ 1% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: lutetium-177 + ADT + individualized treatment[b] vs. ADT + individualized treatment[b] (multipage table)

Study **drug class** **drug**	**Patients with subsequent therapy[c] n (%)**	
	lutetium-177 + ADT + individualized treatment[b] (N = 385)	**ADT + individualized treatment[b] N = 196**
VISION (relevant subpopulation: patients randomized from 5 March 2019 onwards)		
Total	97 (25.2)	63 (32.1)
Anti-androgens		
Enzalutamide	6 (1.6)	4 (2.0)
Apalutamide	3 (0.8)	2 (1.0)
Darolutamide	2 (0.5)	3 (1.5)
Monoclonal antibodies		
Nivolumab	3 (0.8)	2 (1.0)
Pembrolizumab	2 (0.5)	7 (3.6)
Atezolizumab	1 (0.3)	3 (1.5)
Bevacizumab	0 (0)	3 (1.5)
Chemotherapy		
Carboplatin	22 (5.7)	16 (8.2)
Etoposide	6 (1.6)	1 (0.5)
Cabozantinib	1 (0.3)	2 (1.0)
Cabazitaxel	51 (13.2)	38 (19.4)
Docetaxel	17 (4.4)	8 (4.1)
Paclitaxel	2 (0.5)	2 (1.0)
Cyclophosphamide	3 (0.8)	3 (1.5)
Therapeutic radiopharmaceuticals		
Radium Ra 223 dichloride	7 (1.8)	6 (3.1)
Various therapeutic radiopharmaceuticals	0 (0)	2 (1.0)

Table 11: Information on subsequent antineoplastic therapies[a] – (≥ 1% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: lutetium-177 + ADT + individualized treatment[b] vs. ADT + individualized treatment[b] (multipage table)

Study drug class drug	Patients with subsequent therapy[c] n (%)	
	lutetium-177 + ADT + individualized treatment[b] (N = 385)	ADT + individualized treatment[b] N = 196
Further therapies		
Investigational drug	7 (1.8)	12 (6.1)
Olaparib	5 (1.3)	6 (3.1)
Abiraterone[d]	11 (2.9)	2 (1.0)
Sipuleucel-T	1 (0.3)	2 (1.0)

a. Excluding radiotherapy; in the total population, 49 (8.9%) of the patients in the intervention arm and 31 (11.1%) of the patients in the comparator arm received ≥ 1 radiotherapy as subsequent therapy (no data available for the subpopulation).
b. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, denosumab, bisphosphonates, external radiotherapy and blood transfusions.
c. Patients may be counted in more than one subsequent therapy.
d. Abiraterone (9 patients in the intervention arm [2.3%] vs. 1 patient in the comparator arm [0.5%]) and abiraterone acetate (2 patients in the intervention arm [0.5%] vs. 1 patient in the comparator arm [0.5%]).

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. The S3 guideline "Prostate Cancer" provides no recommendations for the further treatment of the patients [14].

25.2% of patients in the intervention arm and 32.1% of patients in the comparator arm in the relevant subpopulation in the VISION study 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 13.2% of patients in the intervention arm and 19.4% of patients in the comparator arm. The proportion of patients in the relevant subpopulation with subsequent therapy with cabazitaxel is thus in the same order of magnitude as in the total population (see A23-01[3]). Patients for whom cabazitaxel was an option should not be included in the relevant subpopulation (see Section I 3.2.1). It therefore remains unclear why so many patients received subsequent therapy with cabazitaxel, even though a few months earlier the investigator had determined that they were not eligible for further taxane-based chemotherapy. There are no reasons why the patients' eligibility for treatment with cabazitaxel was assessed differently for the subsequent therapy and which subsequent therapy line was involved.

I 3.2.7 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, external radiotherapy and blood transfusions.
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.

Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

I 3.2.8 Transferability of the study results to the German health care context

The company states that the VISION study is a multinational trial, with over 99% of all patients being randomized in Organisation for Economic Co-operation and Development (OECD) countries [6]. According to the explanations of the company, OECD countries have a comparatively high per capita income and an efficient health care system. According to the company, the OECD has, moreover, been pursuing a joint reporting on selected quality indicators of health care since 2003 [18]. Since more than 99% of the patients included in the VISION study come from an OECD country, the company assumes that the relevant study results are transferable to the German health care context.

The company did not provide any further information on the transferability of the 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 (recorded using the BPI-SF item 3).
  - pain interference, recorded using the BPI-SF Item 9a-g
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the Functional Assessment of Cancer Therapy – Prostate (FACT-P) total score
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - myelosuppression (SMQ “haematopoietic cytopenias“, severe AEs)
  - dry mouth (PT, AEs)
  - other specific AEs, if any

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

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

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 event[b]	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF item 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[e]
VISION[f]	Yes	Yes	No[g]	No[g]	No[g]	No[g]	Yes	Yes	Yes	Yes	Yes	Yes

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, bisphosphonates, external radiotherapy and blood transfusions.
b. Composite outcome, comprises: new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic intervention, need for radiotherapy for alleviation of bone pain. In the present data situation, the analyses on the composite outcome are not suitable for the benefit assessment; the individual components are used as separate outcomes (see Section I 4.3).
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. SMQ "haematopoietic cytopenias".
e. Further specific AEs selected were: acute renal failure (SMQ, SAEs), gastrointestinal disorders (SOC, AEs), urinary tract infection (PT, AEs)
f. Patients randomized from 5 March 2019 onwards.
g. No suitable data available; see Section I 4.1 for reasons.

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; SOC: System Organ Class; VAS: visual analogue scale

Notes on the included outcomes and analyses

Overall survival

For the outcome of overall survival, analyses based on all randomized patients are used. This is due to the fact that overall survival in the VISION study was recorded until the end of the study, in contrast to all other outcomes (for information on planned follow-up for all outcomes, see Section I 3.2.3). Patients who withdrew their consent to treatment but agreed to participate in the long-term follow-up of the study were also included in the analysis.

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. In addition, results on the outcome of overall survival are presented based on patients randomized from 5 March 2019 onwards (relevant subpopulation).

Symptomatic skeletal-related events

The composite outcome "symptomatic skeletal-related events" is composed of the following individual components:

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

The analyses of the individual components without consideration of deaths are relevant for the present benefit assessment (for reasons, see Section I 4.3).

The company stated that 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. However, the company did not provide any information on whether patients who did not receive any study medication were also followed up for 30 days for the outcome of symptomatic skeletal-related events. The company provides information on patients who were censored on Day 1 (2 [1%] vs. 6 [3%] patients in the relevant subpopulation). However, it still remains unclear whether or how long patients who did not receive any study medication were actually followed up. Nevertheless, the results of the individual components of the outcome "symptomatic skeletal-related events" based on patients in the relevant subpopulation can be used. In contrast to the total population, the differential proportions of patients not included in the assessment are < 15 percentage points for these patients, even in the case that all patients with withdrawn consent were not followed up. Moreover, only those analyses of the company that do not take deaths into account are used.

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

The company submitted analyses on the patient-reported outcomes of worst pain (BPI-SF Item 3), pain interference (BPI-SF Items 9a–g), health status (EQ-5D VAS) and health-related quality of life (FACT-P) based on the results of patients in the relevant subpopulation. However, for this patient population as well as for analyses based on the total population of the VISION study, the differential proportion of patients not included in the analysis between the treatment arms was > 15 percentage points (for all scales approx. 20 percentage points). In addition, the proportion of patients with a survey during the course of the study,

particularly in the control arm, declined sharply. For example, from Cycle 5 (corresponds to Week 30), the difference in response rates between the treatment arms was > 40 percentage points, with the proportion of patients with a survey in the control arm already falling to below 12%. This means that structural equality between the treatment arms can no longer be assumed. For the reasons mentioned above, the analyses on patient-reported outcomes are not suitable for the present benefit assessment. Furthermore, it should be noted that the follow-up for these outcomes was only planned for up to 30 days after treatment discontinuation, and thus, there were censoring for potentially informative reasons, since, for example, the patient-reported outcomes were not further recorded after progression.

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 total population of 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. Corresponding information is not available for the relevant subpopulation. 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

Gozetotide

In the VISION study, AEs under the use of gozetotide were recorded separately. However, there was no comparator group without PSMA diagnostics with gozetotide. Furthermore, the recording of adverse events for gozetotide is potentially incomplete. In the VISION study, the side effect outcomes of AEs, severe AEs, SAEs and AEs of special interest (AESI) were recorded from the administration of the drug gozetotide up to 6 days afterwards. Since PSMA diagnostics with gozetotide could be performed up to 6 weeks before the 1st day of the 1st cycle of the study medication, there is a possible gap in the follow-up of side effects for gozetotide of up to 5 weeks between the administration of gozetotide and the administration of the study medication. In addition, the patients received individualized treatment, including ADT, at the time of PSMA diagnosis with gozetotide and in the period up to administration of the study medication. Side effects can therefore not be clearly assigned to the diagnostic agent gozetotide. For the reasons mentioned, the data on all side effect outcomes of

gozetotide cannot be used for the benefit assessment and are presented in the Appendix as supplementary information (see I Appendix B.1).

However, after a qualitative consideration of the side effects of gozetotide presented, it is not assumed that there are any relevant direct side effects of gozetotide that would call into question the results of the VISION study on the comparison of lutetium-177 and patient-specific therapy (see also Section I 3.2).

Lutetium-177 + ADT + individualized treatment vs. ADT + individualized treatment

The analyses based on the results of patients who had been randomized from 5 March 2019 onwards (relevant subpopulation) are relevant for the side effect outcomes of severe AEs, SAEs, discontinuation due to AEs, myelosuppression (SMQ, severe AEs), dry mouth (PT, AEs), acute renal failure (SMQ, SAEs), gastrointestinal disorders (SOC, AEs) and urinary tract infection (PT, AEs). This is due to the fact that the differential proportion of patients not included in the analysis is > 15 percentage points for this population.

In the present assessment, analyses on side effects are considered that do not include symptomatic skeletal-related events. In contrast to the other outcomes on side effects, the company only presented analyses including symptomatic skeletal-related events for the outcome of discontinuation due to AEs: 0 vs. 3 (1.8%) patients discontinued treatment due to spinal cord compression (see Table 27). For the comparator arm, this represents 21% of discontinuations due to AEs. This issue has been taken into account in the assessment of the risk of bias of this outcome (see Section I 4.2).

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	Study level	Outcomes												
		Overall survival	Symptomatic skeletal-related event[b]	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF item 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[e]
VISION[f]	L	L	H[g, h]	–[i]	–[i]	–[i]	–[i]	H[h, j]	H[h, j]	H[j, k, l]	H[h, j]	H[h, j, k]	H[h, j, m]

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, bisphosphonates, external radiotherapy and blood transfusions.
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. Further specific AEs selected were: acute renal failure (SMQ, SAEs), gastrointestinal disorders (SOC, AEs), urinary tract infection (PT, AEs)
f. Patients who were randomized from 5 March 2019; the total population is also shown for overall survival.
g. Effects of the individual components not consistent (for details see Section I 4.1); assessment of the risk of bias applies to the individual components of the composite outcome.
h. Incomplete observations for potentially informative reasons with different follow-up observation periods.
i. No usable data available; see Section I 4.1 for the reasoning.
j. Important difference in the patients not included in the analysis between the treatment groups (> 5 percentage points).
k. Lack of blinding in subjective recording of outcomes.
l. Includes skeletal-related events (for details, see Section I 4.1)
m. For gastrointestinal disorders, urinary tract infection: lack of blinding in subjective recording of outcomes.

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; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the results for the outcome of overall survival is rated as low. In contrast to the other outcomes, this assessment is based on the results of the total population of the

VISION study (see Section I 4.1). In the total population, 15 (2.7%) vs. 33 (11.8%) of the patients withdrew their consent to participate in the study during the course of the study and were censored for the outcome of overall survival for this reason. However, the proportion of patients who were censored on Day 1 was 0 vs 2 (0.7%) patients. Thus, the proportion of patients included in the analysis is sufficiently similar despite high differential proportions of withdrawn consents to study participation. As described in Section I 3.2.2, there is uncertainty for the total population regarding the proportion of patients in the VISION study for whom cabazitaxel is the most appropriate individualized treatment. As the results of the outcome of overall survival are consistent for the total population and the subpopulation and the risk of bias is rated as low for the outcome, at most indications, e.g. of an added benefit, can be derived for this outcome in the present benefit assessment (see Section I 4.3).

The analyses of the composite outcome “symptomatic skeletal-related events” are not suitable for the present benefit assessment; in the present data situation, the individual components of the composite outcome are considered as separate outcomes (see Section I 4.3). Therefore, the assessment of the risk of bias presented in Table 14 applies to the individual components of the composite outcome used in this benefit assessment. Therefore, the outcomes of new symptomatic pathologic bone fracture, spinal cord compression, tumour-related orthopaedic intervention as well as need for radiotherapy for alleviation of bone pain (individual components of the composite outcome “symptomatic skeletal-related events”) have a high risk of bias due to incomplete observation for potentially informative reasons with different follow-up observation periods.

No suitable data are available for patient-reported outcomes (BPI-SF, FACT-P, EQ-5D) (see Section I 4.1). The risk of bias is therefore not assessed for these outcomes.

Due to incomplete observation for potentially informative reasons with different follow-up observation periods and great differences (> 5 percentage points) of patients not included in the analysis between the treatment groups, the outcomes of the category “side effects” have a high risk of bias. For the outcomes of discontinuation due to AEs, dry mouth as well as gastrointestinal disorders and urinary tract infection, the lack of blinding in subjective recording of outcomes is also taken into account in the assessment of the risk of bias. For the outcome of discontinuation due to AEs, symptomatic skeletal-related events were also recorded (see Section I 4.1).

I 4.3 Results

Table 15 summarizes the results of the comparison of lutetium-177 + ADT with individualized treatment in patients with PSMA-positive, progressive mCRPC. Where necessary, IQWiG calculations are provided to supplement the data from the company’s dossier.

The Kaplan-Meier curves on the time-to-event analyses are presented in I Appendix C of the full dossier assessment. I Appendix B shows additionally presented results on the side effects of gozetotide and the results on common AEs, SAEs and discontinuations due to AEs for the relevant subpopulation in the VISION study.

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]**
	L	**median time to event in months [95% CI]** **patients with event n (%)**	**L**	**median time to event in months [95% CI]** **patients with event n (%)**	**HR [95 %-CI]; p-value[b]**
VISION (relevant subpopulation: patients randomized from 5 March 2019 onwards)					
Mortality					
Overall survival (total population[c])	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
Overall survival (subpopulation)	385	14.6 [13.2; 16.0] 240 (62.3)	196	10.5 [8.5; 13.6] 129 (65.8)	0.63 [0.5; 0.78]; < 0.001
Morbidity					
Symptomatic skeletal-related event[c] (presented as supplementary information[e])	*385*	*NA* *60 (15.6)*	*196*	*NA* *34 (17.3)*	*0.36 [0.23; 0.56]; < 0.001*
New symptomatic pathological bone fracture	385	NA 16 (4.2)	196	NA 1 (0.5)	4.27 [0.56; 32.72]; 0.129
Spinal cord compression	385	NA 7 (1.8)	196	NA 12 (6.1)	0.14 [0.05; 0.38]; < 0.001
Tumour-related orthopaedic intervention	385	NA 10 (2.6)	196	NA 3 (1.5)	0.64 [0.16; 2.47]; 0.509
Need for radiotherapy for alleviation of bone pain	385	NA 54 (14.0)	196	NA 31 (15.8)	0.39 [0.25; 0.63]; < 0.001
Worst pain (BPI-SF Item 3)[f]			No suitable data available[g]		
Pain interference (BPI-SF Item 9a–g)f			No suitable data available[g]		
Health status (EQ-5D VAS)[h]			No suitable data available[g]		
Health-related quality of life					
Health-related quality of life (FACT-P)i			No suitable data available[g]		

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]
	L	median time to event in months [95% CI] patients with event n (%)	L	median time to event in months [95% CI] patients with event n (%)	HR [95 %-CI]; p-value[b]
Side effects[j]					
AEs (supplementary information)	366	0.69 [0.66; 0.76] 361 (98.6)	167	0.72 [0.53; 0.92] 143 (85.6)	-
SAEs	366	18.20 [NC; NC] 129 (35.2)	167	13.34 [NC; NC] 44 (26.3)	0.64 [0.45; 0.91]; 0.013
Severe AEs[k]	366	8.08 [6.77; 11.5] 187 (51.1)	167	6.05 [NC; NC] 59 (35.3)	0.79 [0.58; 1.07]; 0.121
Discontinuation due to AEs[l]	366	NA 63 (17.2)	167	NA 14 (8.4)	0.98 [0.54; 1.77]; 0.940
Myelosuppression (SMQ[m], severe AEs[k])	366	NA 88 (24.0)	167	NA 10 (6.0)	2.16 [1.11; 4.19]; 0.020
Dry mouth (PT, AEs)	366	NA 140 (38.3)	167	NA 1 (0.6)	51.27 (7.17; 366.89); < 0.001
Acute renal failure (SMQ, SAEs)	366	NA 4 (1.1)	167	NA 5 (3.0)	0.18 [0.05; 0.74]; 0.009
Gastrointestinal disorders (SOC, AEs)	366	1.97 [1.71; 2.56] 277 (75.7)	167	6.47 [NC; NC] 59 (35.3)	2.04 (1.54; 2.70); < 0.001
Urinary tract infection (PT, AEs)	366	NA 45 (12.3)	167	NA 1 (0.6)	11.53 [1.58; 84.10]; 0.002

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]
	L	median time to event in months [95% CI] patients with event n (%)	L	median time to event in months [95% CI] patients with event n (%)	HR [95 %-CI]; p-value[b]

a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, bisphosphonates, external radiotherapy and blood transfusions.
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). Unstratified for outcomes on side effects.
c. From dossier assessment A23-01 [3].
d. Comprises: new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic intervention, need for radiotherapy for alleviation of bone pain.
e. The composite outcome is presented as supplementary information as the effects in the individual components were not in the same direction. See Section I 4.1 of the full dossier assessment for more details.
f. 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).
g. See Section I 4.1 for reasons.
h. Time to first deterioration. A decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
i. 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).
j. According to Version 3.0 of the study protocol, events attributable to progression of the underlying disease should not be reported as AE. However, 10 (2.7%) vs. 2 (1.2%) patients with event for SOC "benign, malignant and non-specific neoplasms (including cysts and polyps)" were documented under AEs.
k. Severe AEs are operationalized as CTCAE grade ≥ 3.
l. The numbers are based on the data provided by the company on discontinuations due to AEs including events that occurred within the framework of a symptomatic skeletal-related event. This includes 3 patients in the comparator arm who discontinued treatment due to spinal cord compression (compared to 0 patients in the intervention arm).
m. SMQ “haematopoietic cytopenias“.

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; IU: international unit; LDH: lactate dehydrogenase; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most a hint, e.g. of an added benefit, can be derived for the outcome of overall survival, and at most hints can be derived for all other outcomes due to the high risk of bias.

Mortality

overall survival

A statistically significant difference in favour of lutetium-177 + ADT + individualized treatment after PSMA diagnostics with gozetotide was shown for the outcome of overall survival. There is an indication of added benefit of lutetium-177 + ADT + individualized treatment over ADT + individualized treatment, each after PSMA diagnostics with gozetotide.

morbidity

Symptomatic skeletal-related events

The effects of the individual components of the composite outcome "symptomatic skeletal-related events" are not consistent. Quantitatively, a disadvantage of lutetium-177 after PSMA diagnostics with gozetotide is shown for the outcome of new symptomatic pathologic bone fracture, while advantages are shown for the remaining individual components. It is unclear to what extent the events of the outcome "new symptomatic pathologic bone fracture" were included in the result of the composite outcome and how this affects the effect of the composite outcome. In the present data situation, the composite outcome is thus presented as supplementary information, but the results are not considered in the derivation of the added benefit (see Section I 4.1). The individual components of the composite outcome are included in the present assessment as relevant outcomes.

For each of the outcomes "spinal cord compression" and "need for radiotherapy for alleviation of bone pain", there is a statistically significant difference in favour of lutetium-177 + ADT + individualized treatment after PSMA diagnostics with gozetotide. There is a hint of added benefit of lutetium-177 + ADT + individualized treatment over ADT + individualized treatment, each after PSMA diagnostics with gozetotide.

No statistically significant difference between treatment groups was shown for the outcomes "new symptomatic bone fracture" and "tumour-related orthopaedic intervention". There is no hint of an added benefit of lutetium-177 + ADT + individualized treatment in comparison with ADT + individualized treatment, each after PSMA diagnostics with gozetotide; an added benefit is therefore not proven.

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 the outcomes "worst pain" (BPI-SF Item 3), "pain interference" (BPI-SF Item 9a-g) and "health status" (EQ-5D VAS). There is no hint of an added

benefit of lutetium-177 + ADT + individualized treatment in comparison with ADT + individualized treatment, each after PSMA diagnostics with gozetotide; 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, each after PSMA diagnostics with gozetotide; an added benefit is therefore not proven.

Side effects

SAEs

A statistically significant difference in favour of lutetium-177 + ADT + individualized treatment after PSMA diagnostics with gozetotide was shown for the outcome of SAEs. There is a hint of lesser harm from lutetium-177 + ADT + individualized treatment compared with ADT + individualized treatment, each after PSMA diagnostics with gozetotide.

Severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs

No statistically significant difference between the treatment groups was shown for the outcomes "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". There is no hint of greater or lesser harm from lutetium-177 + ADT + individualized treatment in comparison with ADT + individualized treatment, each after PSMA diagnostics with gozetotide; greater or lesser harm is therefore not proven.

Specific AEs

Acute renal failure (SMQ, SAEs)

A statistically significant difference in favour of lutetium-177 + ADT + individualized treatment after PSMA diagnostics with gozetotide was shown for the outcome of acute renal failure (SMQ, SAEs). There is a hint of lesser harm from lutetium-177 + ADT + individualized treatment compared with ADT + individualized treatment, each after PSMA diagnostics with gozetotide.

Myelosuppression (SMQ, severe AEs), dry mouth (PT, AEs), gastrointestinal disorders (SOC, AEs), urinary tract infection (PT, AEs)

There is a statistically significant difference to the disadvantage of lutetium-177 + ADT + individualized treatment after PSMA diagnostics with gozetotide for each of the outcomes “myelosuppression” (SMQ, severe AEs), “dry mouth” (PT, AEs), “gastrointestinal disorders” (SOC, AEs) as well as “urinary tract infection” (PT, AEs). In each case, there is a hint of greater harm from lutetium-177 + ADT + individualized treatment compared with ADT + individualized treatment, each after PSMA diagnostics with gozetotide.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics are considered for patients in the relevant subpopulation of the VISION study:

- age (< 65 years versus ≥ 65 years)
- liver metastases at baseline (yes versus no)

Interaction tests are conducted 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 one 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.

Using the characteristics described above, the available subgroup results do not reveal any effect modifications.

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 IQWiG *General Methods* [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 added benefit at outcome level

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

Determination of the outcome category for the outcomes of new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic intervention as well as need for radiotherapy for alleviation of bone pain

The outcomes “new symptomatic pathologic bone fracture”, “spinal cord compression”, “tumour-related orthopaedic intervention” and “need for radiotherapy for alleviation of bone pain” (as individual components of the composite outcome “symptomatic skeletal-related events”) are considered serious/severe. These are events that have a distressing impact on patients and their daily activities.

Table 16: Extent of added benefit at outcome level: Lutetium 177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a], each after PSMA diagnostics with gozetotide (multipage table)

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 (total population)	15.3 vs. 11.3 months HR: 0.62 [0.52; 0.74]; p < 0.001 probability: “indication”	Outcome category: mortality CI_u < 0.85 added benefit, extent: “major”
Overall survival (subpopulation)	14.6 vs. 10.5 months HR: 0.63 [0.5; 0.78]; p < 0.001 probability: “indication”	Outcome category: mortality CI_u < 0.85 added benefit, extent: “major”

Table 16: Extent of added benefit at outcome level: Lutetium 177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a], each after PSMA diagnostics with gozetotide (multipage table)

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 shortened observation period		
Morbidity		
New symptomatic pathological bone fracture	NA vs. NA HR: 4.27 [0.56; 32.72]; p = 0.129	Lesser/added benefit not proven
Spinal cord compression	NA vs. NA HR: 0.14 [0.05; 0.38]; p < 0.001 probability: “hint”	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% added benefit, extent: “major”
Tumour-related orthopaedic intervention	NA vs. NA HR: 0.64 [0.16; 2.47]; p = 0.509	Lesser/added benefit not proven
Need for radiotherapy for alleviation of bone pain	NA vs. NA HR: 0.39 [0.25; 0,63]; p < 0.001 probability: “hint”	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% added benefit, extent: “major”
Worst pain (BPI-SF Item 3)	No suitable data available	Lesser/added benefit not proven
Pain interference (BPI-SF item 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

Table 16: Extent of added benefit at outcome level: Lutetium 177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a], each after PSMA diagnostics with gozetotide (multipage table)

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]**
Side effects		
SAEs	18.20 vs. 13.34 HR: 0.64 [0.45; 0.91]; p = 0.013 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Severe AEs	8.08 vs. 6.05 HR: 0.79 [0.58; 1.07]; p = 0.121	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. NA HR: 0.98 [0.54; 1.77]; p = 0.940	Greater/lesser harm not proven
Myelosuppression (severe AEs)	NA vs. NA HR: 2.16 [1.11; 4.19] HR: 0.46 [0.24; 0.90][d]; p = 0.020 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Dry mouth (AEs)	NA vs. NA HR: 51.27 [7.17; 366.89] HR: 0.02 [0.003; 0.14]d p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm; extent: "considerable"
Acute renal failure (SAEs)	NA vs. NA HR: 0.18 [0.05; 0.74]; p = 0.009 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk < 5% lesser harm, extent: "considerable"
Gastrointestinal disorders (AEs)	1.97 vs. 6.47 HR: 2.04 [1.54; 2.70] HR: 0.49 [0.37; 0.65]d; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm; extent: "considerable"
Urinary tract infection (AEs)	NA vs. NA HR: 11.53 [1.58; 84.10] HR: 0.09 [0.01; 0.63][d]; p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm; extent: "considerable"

Table 16: Extent of added benefit at outcome level: Lutetium 177 + ADT + individualized treatment[a] vs. ADT + individualized treatment[a], each after PSMA diagnostics with gozetotide (multipage table)

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]**
a. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, bisphosphonates, external radiotherapy and blood transfusions. 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). d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit. 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; gozetotide: gallium-(^{68}GA) gozetotide; HR: hazard ratio; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; NA: not achieved; PSMA: prostate-specific membrane antigen; 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[b], each after PSMA diagnostics with gozetotide

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival: indication of added benefit – extent: "major"	–
Outcomes with shortened observation period	
Serious/severe symptoms/late complications ▪ spinal cord compression: hint of added benefit – extent: “major” ▪ need for radiotherapy for alleviation of bone pain: hint of added benefit – extent: “major”	–
Serious/severe side effects ▪ SAEs: hint of lesser harm – extent: "minor" ▪ acute renal failure: hint of lesser harm – extent: considerable	Serious/severe side effects ▪ myelosuppression: hint of greater harm – extent: "considerable"
–	Non-serious/non-severe side effects ▪ dry mouth: hint of greater harm – extent: "considerable" ▪ gastrointestinal disorders: hint of greater harm – extent: "considerable" ▪ urinary tract infection: hint of greater harm – extent: "considerable"
No suitable data on the outcomes “worst pain”, “pain interference” and “health status” as well as on the outcomes of the category “health-related quality of life"	

a. With or without androgen receptor pathway inhibition with e.g. enzalutamide or abiraterone.
b. Includes but is not limited to androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha reductase inhibitors, bisphosphonates, external radiotherapy and blood transfusions.

ADT: androgen deprivation therapy; gozetotide: gallium-(^{68}GA) gozetotide; lutetium-177: (^{177}Lu)lutetium vipivotide tetraxetan; PSMA: prostate-specific membrane antigen; SAE: serious adverse event

Overall, the VISION study showed both positive and negative effects for lutetium-177 + ADT + individualized treatment compared to ADT + individualized treatment, in each case after PSMA diagnostics with gozetotide. Only for overall survival are the observed effects based on the entire observation period. For the outcomes in the categories of morbidity and side effects, however, they refer exclusively to a shortened period (up to 30 days after discontinuation of the study medication, but before the start of a subsequent tumour therapy not permitted in the study).

On the positive side, there was an indication of major added benefit for the outcome of overall survival. Moreover, there is a hint of major added benefit for the outcomes of spinal cord compression and need for radiotherapy for alleviation of bone pain. For the outcomes of SAEs

and acute renal failure (SAEs), there is a hint of lesser harm with the extent “minor” (SAEs) or “considerable” (acute renal failure). On the negative side, there is a hint of greater harm for the outcomes of myelosuppression (severe AEs), dry mouth (AEs), gastrointestinal disorders (AEs) and urinary tract infection (AEs) with the extent “minor” (myelosuppression) and “considerable” (dry mouth, gastrointestinal disorders and urinary tract infection). Overall, the unfavourable effects do not call into question the added benefit in the outcome of overall survival. Overall, the data situation for the VISION study is thus unchanged compared to the assessment in Addendum A23-46 [4].

For the drug gozetotide, there are no side effects to a relevant extent that, in view of the added benefit of lutetium-177 + ADT over individualized treatment, fundamentally speak against the use of the VISION study for the benefit assessment of gozetotide in comparison with the ACT (see Section I 4.1). The results of the VISION study (enrichment design) will therefore be used for the benefit assessment of gozetotide (for the identification of patients with PSMA-positive mCRPC for whom PSMA-targeted therapy is indicated) compared to the ACT.

In summary, for patients with progressive mCRPC and for whom abiraterone (in combination with prednisone or prednisolone), enzalutamide or BSC is the most appropriate individualized treatment, there is an indication of major added benefit of gozetotide versus the ACT. The added benefit is not proven for patients with progressive mCRPC for whom cabazitaxel or olaparib is the best suitable individualized treatment.

Table 18 summarizes the result of the assessment of the added benefit of gozetotide in comparison with the ACT.

Table 18: Gozetotide – probability and extent of added benefit

Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
Adults with progressive mCRPC: identification[c] of patients with PSMA-positive mCRPC for whom PSMA-targeted therapy is indicated[d]	Individualized treatment[e, f] choosing from ▪ abiraterone in combination with prednisone or prednisolone, ▪ enzalutamide, ▪ cabazitaxel, ▪ olaparib, ▪ best supportive care (BSC)[g], under consideration of the prior therapies of the comorbidities, the general condition and the BRCA1/2 mutation status	▪ Patients for whom abiraterone in combination with prednisone or prednisolone, enzalutamide or BSC is the individually optimized treatment: indication of major added benefit ▪ patients for whom cabazitaxel or olaparib is the individually optimized treatment: added benefit not proven

a. According to the G-BA, various study designs can be considered to answer the research question, whereby a distinction must be made in particular between strategy design, interaction design and enrichment design.
b. Presentation of the ACT specified by the G-BA. Gozetotide is the first approved drug that can be used to identify patients with PSMA-positive, progressive mCRPC for whom PSMA-targeted therapy is indicated. Comparison with another diagnostic test cannot be considered.
c. For the detection of PSMA-positive lesions by PET, gozetotide is radiolabelled with gallium-68 prior to use.
d. (^{177}Lu)lutetium vipivotide tetraxetan in combination with ADT 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 before.
e. 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 GnRH agonists or antagonists.
f. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy 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).
g. 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.
h. 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 ≥ 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; gozetotide: gallium-(^{68}GA) gozetotide: mCRPC: metastatic castration resistant prostate cancer; PET: positron emission tomography; 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 the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

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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