Talazoparib (prostate cancer)

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

EXTRACT

Project: A24-22 Version: 1.0 Status: 13 May 2024 DOI: 10.60584/A24-22_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Talazoparib (Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Talazoparib (prostate cancer) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

7 February 2024

Internal Project No.

A24-22

DOI-URL

https://doi.org/10.60584/A24-22_en

Address of publisher

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

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Keywords

Talazoparib, Enzalutamide, Prostatic Neoplasms – Castration-Resistant, Benefit Assessment, NCT03395197

Part I: Benefit assessment

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

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
AML	acute myeloid leukaemia
BPI-SF	Brief Pain Inventory-Short Form
BRCA	breast cancer susceptibility gene
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GnRH	gonadotropin-releasing hormone
HRR	homologous recombination repair
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mCRPC	metastatic castration-resistant prostate cancer
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mHSPC	metastatic hormone-sensitive prostate cancer
nmCRPC	non-metastatic castration-resistant prostate cancer
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-PR25	Quality of Life Questionnaire-Prostate 25
RCT	randomized controlled trial
rPFS	radiographic progression-free survival
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SAP	Summary of Product Characteristics
SMQ	standardized MedDRA query

Abbreviation	Meaning
SOC	System Organ Class
VAS	visual analogue scale
WHO	World Health Organization

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug talazoparib in combination with enzalutamide. 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 7 February 2024.

Research question

The aim of this report is to assess the added benefit of talazoparib in combination with enzalutamide (hereinafter referred to as "talazoparib + enzalutamide") compared with the appropriate comparator therapy (ACT) in adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated.

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of talazoparib + enzalutamide (multipage table)

Research question	Therapeutic indication	ACT[a]
1	Adults with treatment-naive mCRPC in whom chemotherapy is not clinically indicated[b, c, d]	▪ Abiraterone acetate in combination with prednisone or prednisolone (only for patients whose disease is progressive during or after docetaxel-containing chemotherapy; only for patients with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated) or ▪ **enzalutamide** (only for patients whose disease has progressed during or after docetaxel chemotherapy; only for patients with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated) or ▪ olaparib as monotherapy (only for patients with BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included an NHA) or ▪ olaparib in combination with abiraterone acetate and prednisone or prednisolone (only for patients with BRCA mutations and for patients without BRCA mutations with symptomatic disease)

Table 2: Research questions of the benefit assessment of talazoparib + enzalutamide (multipage table)

Research question	Therapeutic indication	ACT[a]
2	Adults with pretreated mCRPC in whom chemotherapy is not clinically indicated[b, e]	Individualized treatment[f] selected from ▪ abiraterone acetate in combination with prednisone or prednisolone (only for patients who have progressed on or after docetaxel-containing chemotherapy), ▪ enzalutamide (only for patients who have progressed on or after docetaxel chemotherapy), ▪ olaparib in combination with abiraterone acetate and prednisone or prednisolone, and ▪ olaparib as monotherapy (only for patients with BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included an NHA) taking into account pretreatment(s) and BRCA1/2 mutation status.

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**.
b. For the present therapeutic indication, it is assumed according to the G-BA that an existing conventional ADT is continued. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or antagonists. In addition, adequate concomitant treatment of bone metastases during the study is assumed (e.g. use of bisphosphonates, denosumab, radiotherapy).
c. The ACT specified here comprises several alternative treatment options according to the G-BA. However, the treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. The sole comparison with a therapy option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the overall population.
d. When determining the ACT, it is assumed that the patients may have already received prior therapy with docetaxel or NHA in earlier stages of the disease.
e. When determining the ACT, it is assumed that the patients, in addition to prior therapy of the mCRPC, may have already received prior therapy with docetaxel or NHA in earlier stages of the disease.
f. For the implementation of individualized therapy in a study of direct comparison, according to the G-BA, investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multi-comparator study). A rationale must be provided for the choice and any limitation of treatment options. If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.

ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; BRCA: breast cancer susceptibility gene; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mCRPC: metastatic castration-resistant prostate cancer; NHA: novel hormonal agent

In research question 1, the ACT presented by the company in Module 3 A deviates from the ACT specified by the G-BA in some of the alternative treatment options mentioned. However,

since the company selected the option enzalutamide specified by the G-BA as the ACT for research question 1 and presented evidence in comparison with this option, this has no consequences for the benefit assessment. For research question 2, the company deviated from the G-BA's ACT in the specification of individual components of the individualized therapy. Since the company presented no data on research question 2, this also has no consequences for the benefit assessment. The present benefit assessment is conducted in comparison with the ACT specified by the G-BA.

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) are used to derive added benefit.

Research question 1: adults with treatment-naive mCRPC in whom chemotherapy is not clinically indicated

Study pool and study design

The TALAPRO-2 study is used for the benefit assessment in research question 1.

The TALAPRO-2 study consists of 2 parts. The non-randomized Part 1 of the study served to determine the dose of talazoparib in combination with enzalutamide and is not relevant for the present benefit assessment. Part 2 of the TALAPRO-2 study is an ongoing double-blind RCT comparing talazoparib + enzalutamide versus placebo + enzalutamide.

The study included adult patients with mCRPC who had not yet received any prior therapy in the current disease state (mCRPC) or in the non-metastatic castration-resistant prostate cancer (nmCRPC) state. According to the inclusion criteria, patients had progressive disease while they were on androgen deprivation therapy (ADT) by medical or surgical castration. Furthermore, patients had to be in good general condition at study entry, corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, and be asymptomatic or mildly symptomatic (recorded using the Brief Pain Inventory-Short Form [BPI-SF] Item 3 [worst pain] < 4).

A total of 1106 patients were included in 3 cohorts in Part 2 of the TALAPRO-2 study. Randomization was carried out in a 1:1 ratio, stratified according to the factors of presence of a homologous recombination repair (HRR) mutation (yes/no or unclear) and previous treatment with a novel hormonal agent or taxane-based chemotherapy for hormone-sensitive prostate cancer (yes/no).

Treatment with talazoparib and enzalutamide was conducted without relevant deviations from the respective Summaries of Product Characteristics (SPCs). In addition to the study medication, patients who had not undergone bilateral orchiectomy had to continue ADT with a gonadotropin-releasing hormone (GnRH) agonist/antagonist initiated at least 4 weeks

before randomization throughout the entire study. Treatment with the study medication was continued until radiographic progression, unacceptable toxicity, patient or investigator decision to discontinue treatment, or death.

The primary outcome of the study was radiographic progression-free survival (rPFS). Patient-relevant secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Relevance of the cohorts of the TALAPRO-2 study and approach of the company

Part 2 of the TALAPRO-2 study comprises 3 cohorts. The composition of the cohorts is described below:

- Cohort 1: Inclusion was independent of the presence of an HRR mutation. Cohort 1 included 805 patients, 402 patients in the talazoparib + enzalutamide arm and 403 patients in the placebo + enzalutamide arm. According to the clinical study report (CSR), 169 (21%) patients in Cohort 1 had an HRR mutation, 426 (53%) had no HRR mutation, and 210 (26%) patients had an unknown HRR mutation status.
- Cohort 2: Only patients with at least one HRR mutation were included. Cohort 2 included a total of 399 patients with HRR mutation, 200 patients in the talazoparib + enzalutamide arm, and 199 patients in the placebo + enzalutamide arm. Cohort 2 comprised 169 patients with HRR mutation who had already been randomized in Cohort 1 and thus were also additionally analysed in Cohort 1. An additional 230 patients with HRR mutation were recruited exclusively for Cohort 2. This results in an overlap of 169 patients who were included in both Cohort 1 and Cohort 2.
- China extension cohort: Patients were included only in China, irrespective of the presence of an HRR mutation, in order to fulfil requirements for the Chinese regulatory authorities. It included a total of 125 patients, 63 patients in the talazoparib + enzalutamide arm and 62 patients in the placebo + enzalutamide arm. The China extension cohort comprised 54 Chinese patients who had already been randomized as part of Cohort 1. An additional 71 patients were recruited in China exclusively for the China extension cohort. This results in an overlap of 54 patients who were included in both Cohort 1 and the China extension cohort.

The cohorts of the TALAPRO-2 study were conducted under an identical statistical analysis plan (SAP) and study protocol. Thus, all 3 cohorts together should be considered as one study, and the results for the entire study population (N = 1106 patients) should generally be used for the benefit assessment. The 71 patients in the China extension cohort of the TALAPRO-2 study who are not already included in Cohort 1 only account for about 6.4% (71/1106) of the total study population, however. It is therefore assumed that not taking into account the 71 additional Chinese patients does not have a relevant impact on the results. A pooled

analysis of all patients from Cohorts 1 and 2 (without overlap) with a total of 1035 patients can therefore be regarded as a sufficient approximation of the total population of the study.

Although the company presented data on Cohort 1 and Cohort 2, it did not conduct a pooled analysis of Cohort 1 and Cohort 2 without the overlap of the 169 patients included in both cohorts.

The approach of the company is not appropriate. The approval of talazoparib covers both patients without and patients with HRR mutation, and also the G-BA did not differentiate between patients with and without HRR mutation when determining the ACT. Accordingly, the total population of the study (without overlap) represents the relevant population for research question 1 of the present benefit assessment. The company did not present analyses for the total population of the study (without overlap). However, based on the subgroup results of patients without HRR mutation or unknown HRR mutation status from Cohort 1 (summarized below as Cohort 1 without HRR mutation) and the results of all patients from Cohort 2 (with HRR mutation), it is possible to conduct a meta-analysis of the total population of 1035 patients without overlap. The influence of the characteristic of HRR mutation status on the results is analysed in the meta-analysis using a heterogeneity test. However, further subgroup analyses (e.g. for specific HRR mutations or age) are not possible.

To assess the added benefit, the benefit assessment uses the results of the total population (Cohort 1 without mutation and Cohort 2 with mutation, without overlap) pooled in a meta-analysis. For information such as patient characteristics, course of the study, etc., for which only separate information on Cohort 1 and Cohort 2 is available, due to the size of Cohort 1 (78% of the total of 1035 patients from Cohort 1 without mutation and Cohort 2 with mutation), this information is presented as an approximation of the total population relevant for the assessment.

Limitations of the TALAPRO-2 study

Therapeutic indication for chemotherapy in the TALAPRO-2 study

Talazoparib + enzalutamide is approved for adult patients with mCRPC in whom chemotherapy is not clinically indicated. In the TALAPRO-2 study, this was not an explicit inclusion criterion. It was only specified that only patients with a BPI-SF Item 3 (worst pain) < 4 (corresponding to no or mild symptoms) would be included.

It is not clear from the inclusion criteria of the TALAPRO-2 study whether all patients in the study population met the approval restriction “chemotherapy not clinically indicated”. Overall, uncertainty remains as to whether the study also included patients in whom chemotherapy would have been clinically indicated. Against the background that there are no clear criteria as to when chemotherapy is clinically indicated, and taking into account the available information on symptoms and pretreatment of the included patients, it is assumed

in the present situation, however, that this proportion is within a range that allows the meta-analytically summarized analysis of all patients from Cohort 1 and Cohort 2 (without overlap) to be used for the present research question. In the overall view, this uncertainty is taken into account in the certainty of conclusions.

Adequate treatment of bone metastases

According to the G-BA's notes in the document specifying the ACT, adequate concomitant treatment of bone metastases during the study is assumed (e.g. use of bisphosphonates, denosumab, radiotherapy). However, according to the study protocol of the TALAPRO-2 study, palliative radiotherapy or surgery was only permitted after radiographic progression and consultation with the sponsor. It remains unclear whether and in how many patients this restriction of the use of palliative radiotherapy or surgery may have led to inadequate treatment of bone metastases. Other concomitant treatments for bone metastases (e.g. bisphosphonates and denosumab) were not restricted. This existing uncertainty is taken into account in the certainty of conclusions. The described restriction in the use of palliative radiotherapy or surgery also affects the interpretability of other outcomes (e.g. BPI-SF), as the patients only had limited (pain) therapy available for the treatment of bone metastases until progression.

Implementation of the appropriate comparator therapy in the TALAPRO-2 study

The ACT specified by the G-BA for research question 1 comprises several alternative treatment options depending on various patient and disease characteristics. From the options, the company chose enzalutamide, which the G-BA had specified as ACT only for patients whose disease has progressed during or after docetaxel chemotherapy, and only for patients with asymptomatic or mildly symptomatic disease after failure of ADT in whom chemotherapy is not yet clinically indicated.

As described in the section *Therapeutic indication for chemotherapy in the TALAPRO-2 study*, uncertainty remains as to whether patients were included in the study for whom chemotherapy would have been clinically indicated and for whom enzalutamide was therefore not a suitable ACT. As described above, this is taken into account in the certainty of conclusions. However, it is assumed that this proportion is within a range that allows the total population of the TALAPRO-2 study to be used.

Pretreatment in the TALAPRO-2 study

Pretreatment with enzalutamide, darolutamide and apalutamide was not allowed in the study. In addition, prior therapy in the nmCRPC disease state was generally excluded. Abiraterone and docetaxel, on the other hand, were permitted in earlier hormone-sensitive settings of prostate cancer. Overall, it remains unclear how this restriction of prior therapy in

the TALAPRO-2 study can be transferred to the current situation in everyday health care. This remains of no consequence for the benefit assessment.

Data cut-offs

The data provided on the Food and Drug Administration (FDA) data cut-off on 28 March 2023 is used.

Risk of bias and certainty of conclusions

The risk of bias across outcomes for the TALAPRO-2 study is rated as low.

The risk of bias of the results for the outcome of overall survival is rated as low. Due to incomplete observations for potentially informative reasons in the presence of different lengths of follow-up observation periods, the risk of bias of the results is to be rated as high for the following outcomes: symptomatic bone fracture, spinal cord compression, pain (BPI-SF Item 3 and BPI-SF Item 9a-g), symptoms (recorded with the European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Core 30 [QLQ-C30] and the EORTC Quality of Life Questionnaire-Prostate 25 [QLQ-PR25]), health status (EQ-5D visual analogue scale [VAS]), health-related quality of life (recorded with the EORTC QLQ-C30 and the EORTC QLQ-PR25), serious adverse events (SAEs), severe adverse events (AEs), and further specific AEs. In addition, a marked decrease in questionnaire return rates in the course of the study, which differed between treatment arms, contributed to the high risk of bias of the results for the outcomes of pain (BPI-SF Item 3 and BPI-SF Item 9a-g), symptoms (recorded with the EORTC QLQ-C30 and the EORTC QLQ-PR25), health status (EQ-5D VAS), and health-related quality of life (recorded with the EORTC QLQ-C30 and the EORTC QLQ-PR25). The risk of bias for the results of the outcome of discontinuation due to AEs is rated as low. Nevertheless, the certainty of results for the outcome is limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs. Consequently, after treatment discontinuation for other reasons, AEs which would have led to discontinuation may have occurred, but the criterion of discontinuation can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue. Since no suitable analyses are available for the outcomes of myelodysplastic syndrome (MDS) (AEs) and acute myeloid leukaemia (AML) (AEs), the risk of bias for these outcomes is not assessed.

Regardless of the aspects described under the risk of bias, the certainty of conclusions of the study results is reduced due to the uncertainties as to whether chemotherapy was not clinically indicated for all patients in the study population and whether all patients received adequate concomitant treatment of bone metastases. Due to this limitation, overall, at most hints, e.g. of an added benefit, can be determined for all outcomes on the basis of the available information.

Results

Mortality

Overall survival

For the outcome of overall survival, the meta-analysis did not show any statistically significant differences between treatment groups. The results showed a statistically significant advantage for patients with HRR mutation, but there is no statistically significant interaction test. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Morbidity

Symptomatic bone fracture and spinal cord compression

The meta-analysis did not show any statistically significant differences between treatment groups for the outcomes of symptomatic bone fracture or spinal cord compression. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Worst pain (BPI-SF Item 3)

The meta-analysis did not show a statistically significant difference between treatment groups for the outcome of worst pain (BPI-SF Item 3). There is an effect modification for the subgroup characteristic of HRR mutation status for this outcome, however. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide for patients without HRR mutation; an added benefit for this patient group is therefore not proven. For patients with HRR mutation, there is a hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide.

Pain interference (BPI-SF Item 9a-g)

The meta-analysis did not show a statistically significant difference between treatment groups for the outcome of pain interference (BPI-SF Item 9a-g). There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Symptoms

EORTC QLQ-C30

Fatigue, dyspnoea, and appetite loss

For the outcomes of fatigue, dyspnoea, and appetite loss, the meta-analysis showed a statistically significant difference to the disadvantage of talazoparib. However, the difference is no more than marginal for these outcomes in the category of non-serious/non-severe symptoms/late complications. In each case, there is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Nausea and vomiting

For the outcome of nausea and vomiting, the meta-analysis showed a statistically significant difference to the disadvantage of talazoparib. There is a hint of lesser benefit of talazoparib + enzalutamide in comparison with enzalutamide.

Pain

For the outcome of pain, the meta-analysis did not show any statistically significant differences between treatment groups. There is an effect modification for the subgroup characteristic of HRR mutation status for this outcome, however. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide for patients without HRR mutation; an added benefit for this patient group is therefore not proven. For patients with HRR mutation, there is a hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide.

Insomnia, constipation, and diarrhoea

The meta-analysis did not show any statistically significant differences between treatment groups for any of the outcomes of insomnia, constipation, and diarrhoea. In each case, there is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

EORTC QLQ-PR25

Urinary symptoms

The meta-analysis did not show a statistically significant difference between treatment groups for the outcome of urinary symptoms. There is an effect modification for the subgroup characteristic of HRR mutation status for this outcome, however. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide for patients without HRR mutation; an added benefit for this patient group is therefore not proven. For patients with HRR mutation, there is a hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide.

Bowel symptoms and hormonal treatment-related symptoms

For the outcomes of bowel symptoms and hormonal treatment-related symptoms, the meta-analysis did not show a statistically significant difference between treatment groups. In each case, there is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Incontinence aid

No suitable data for the outcome of incontinence aid are available because the company's approach did not ensure that the burden of patients who only developed incontinence in the course of the treatment was also recorded. There is no hint of an added benefit of

talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

For the outcome of health status, the meta-analysis did not show a statistically significant difference between treatment groups. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Global health status

For the outcome of global health status, the meta-analysis showed a statistically significant difference to the disadvantage of talazoparib. There is an effect modification for the subgroup characteristic of HRR mutation status for this outcome, however. There is a hint of lesser benefit of talazoparib + enzalutamide in comparison with enzalutamide for patients without HRR mutation. For patients with HRR mutation, there is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit for this patient group is therefore not proven.

Physical functioning

The meta-analysis showed no statistically significant difference between treatment groups for the outcome of physical functioning. There is an effect modification for the subgroup characteristic of HRR mutation status for this outcome, however. There is a hint of lesser benefit of talazoparib + enzalutamide in comparison with enzalutamide for patients without HRR mutation. For patients with HRR mutation, there is a hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide.

Role functioning

For the outcome of role functioning, the meta-analysis did not show a statistically significant difference between treatment groups. There is an effect modification for the subgroup characteristic of HRR mutation status for this outcome, however. There is a hint of lesser benefit of talazoparib + enzalutamide in comparison with enzalutamide for patients without HRR mutation. For patients with HRR mutation, there is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit for this patient group is therefore not proven.

Emotional functioning, cognitive functioning, and social functioning

The meta-analysis did not show any statistically significant differences between treatment groups for any of the outcomes of emotional functioning, cognitive functioning, and social

functioning. In each case, there is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

EORTC QLQ-PR25

Sexual activity

For the outcome of sexual activity, the meta-analysis did not show a statistically significant difference between treatment groups. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Sexual functioning

No suitable data for the outcome of sexual functioning are available because the company's approach did not ensure that the burden of patients who only became sexually active in the course of the treatment was also recorded. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs, and discontinuation due to AEs

The meta-analysis showed a statistically significant difference to the disadvantage of talazoparib + enzalutamide for each of the outcomes of SAEs, severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), and discontinuation due to AEs. In each case, there is a hint of greater harm from talazoparib + enzalutamide in comparison with enzalutamide.

MDS and AML (each AEs)

No suitable data are available for the outcomes of MDS and AML (each AEs). In each case, there is no hint of greater or lesser harm from talazoparib + enzalutamide in comparison with enzalutamide; greater or lesser harm is therefore not proven.

Dizziness (AEs)

For the outcome of dizziness (AEs), the meta-analysis showed a statistically significant difference to the disadvantage of talazoparib. There is an effect modification for the subgroup characteristic of HRR mutation status for this outcome, however. There is a hint of greater harm of talazoparib + enzalutamide in comparison with enzalutamide for patients without HRR mutation. For patients with HRR mutation, there is no hint of greater or lesser harm of talazoparib + enzalutamide in comparison with enzalutamide; greater or lesser harm for this patient group is therefore not proven.

Infections and infestations (SAEs), anaemia (severe AEs), and investigations (severe AEs)

The meta-analysis showed a statistically significant difference to the disadvantage of talazoparib + enzalutamide for each of the outcomes of infections and infestations (SAEs), anaemia (severe AEs), and investigations (severe AEs). In each case, there is a hint of greater harm from talazoparib + enzalutamide in comparison with enzalutamide.

Probability and extent of added benefit, patient groups with therapeutically important added benefit (research question 1)[3]

Based on the results presented, probability and extent of the added benefit of the drug talazoparib + enzalutamide in comparison with the ACT are assessed as follows:

Overall, both positive and negative effects of talazoparib + enzalutamide were shown in comparison with the ACT, but only for the shortened observation period.

The characteristic of HRR mutation status is an effect modifier for various outcomes. Due to these effect modifications, the results on the added benefit of talazoparib + enzalutamide compared with the ACT are derived separately by HRR mutation status.

Patients without HRR mutation

For patients without HRR mutation, there were only negative effects in the categories of morbidity, health-related quality of life, and side effects (here in different severity categories), ranging from minor to major extent. Overall, there is a hint of lesser benefit for patients without HRR mutation.

Patients with HRR mutation

For patients with HRR mutation, there is a hint of minor added benefit for the morbidity outcomes on pain (worst pain [BPI-SF Item 3] and pain [EORTC QLQ-C30]), as well as for urinary symptoms (EORTC QLQ-PR25). In the health-related quality of life category, there is also a hint of minor added benefit for the outcome of physical functioning (EORTC QLQ-C30). It should be noted that the results showed a statistically significant advantage for the outcome of overall survival for patients with HRR mutation, but there is no statistically significant interaction test. On the other hand, there are several negative effects in the categories of morbidity and side effects (here in different severity categories), ranging from minor to major

[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].

extent. These negative effects completely call into question the positive effects for patients with HRR mutation. Overall, an added benefit is therefore not proven for patients with HRR mutation.

Summary

In summary, there is a hint of lesser benefit of talazoparib + enzalutamide compared with enzalutamide for patients without HRR mutation with treatment-naive mCRPC in whom chemotherapy is not clinically indicated. For patients with HRR mutation, there is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit for this patient group is therefore not proven.

Research question 2: adults with pretreated mCRPC in whom chemotherapy is not clinically indicated

Results

Results on added benefit

Since no relevant study is available for the present research question 2, there is no hint of an added benefit of talazoparib + enzalutamide in comparison with the ACT; an added benefit is therefore not proven for this research question.

Probability and extent of added benefit, patient groups with therapeutically important added benefit (research question 2)

In its dossier, the company presented no data for the assessment of the added benefit of talazoparib + enzalutamide compared with the ACT for patients with pretreated mCRPC in whom chemotherapy is not clinically indicated. An added benefit of talazoparib + enzalutamide versus the ACT is therefore not proven for research question 2.

Probability and extent of added benefit – summary

Table 3 shows a summary of probability and extent of the added benefit of talazoparib + enzalutamide.

Table 3: Talazoparib + enzalutamide – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with treatment-naive mCRPC in whom chemotherapy is not clinically indicated[b, c, d]	▪ Abiraterone acetate in combination with prednisone or prednisolone (only for patients whose disease is progressive during or after docetaxel-containing chemotherapy; only for patients with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated) or ▪ **enzalutamide** (only for patients whose disease has progressed during or after docetaxel chemotherapy; only for patients with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated) or ▪ olaparib as monotherapy (only for patients with BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included an NHA) or ▪ olaparib in combination with abiraterone acetate and prednisone or prednisolone (only for patients with BRCA mutations and for patients without BRCA mutations with symptomatic disease)	▪ Patients without HRR mutation: hint of lesser benefit[e] ▪ Patients with HRR mutation: added benefit not proven
2	Adults with pretreated mCRPC in whom chemotherapy is not clinically indicated[b, f]	Individualized treatment[g] selected from ▪ abiraterone acetate in combination with prednisone or prednisolone (only for patients who have progressed on or after docetaxel-containing chemotherapy), ▪ enzalutamide (only for patients who have progressed on or after docetaxel chemotherapy), ▪ olaparib in combination with abiraterone acetate and prednisone or prednisolone, and ▪ olaparib as monotherapy (only for patients with BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included an NHA) taking into account pretreatment(s) and BRCA1/2 mutation status.	Added benefit not proven

Table 3: Talazoparib + enzalutamide – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**. b. For the present therapeutic indication, it is assumed according to the G-BA that an existing conventional ADT is continued. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or antagonists. In addition, adequate concomitant treatment of bone metastases during the study is assumed (e.g. use of bisphosphonates, denosumab, radiotherapy). c. The ACT specified here comprises several alternative treatment options according to the G-BA. However, the treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. The sole comparison with a therapy option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the overall population. d. When determining the ACT, it is assumed that the patients may have already received prior therapy with docetaxel or NHA in earlier stages of the disease. e. Only patients with ECOG PS of 0 or 1 and a BPI-SF Item 3 < 4 (mildly symptomatic or asymptomatic) were included in the TALAPRO-2 study. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or to patients who were symptomatic at baseline (BPI-SF Item 3 ≥ 4) (see also FN c on the G-BA's notes on the ACT). f. When determining the ACT, it is assumed that the patients, in addition to prior therapy of the mCRPC, may have already received prior therapy with docetaxel or NHA in earlier stages of the disease. g. For the implementation of individualized therapy in a study of direct comparison, according to the G-BA, investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multi-comparator study). A rationale must be provided for the choice and any limitation of treatment options. If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; BRCA: breast cancer susceptibility gene; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mCRPC: metastatic castration-resistant prostate cancer; NHA: novel hormonal agent			

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 benefit of talazoparib in combination with enzalutamide (hereinafter referred to as "talazoparib + enzalutamide") compared with the ACT in adult patients with mCRPC in whom chemotherapy is not clinically indicated.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of talazoparib + enzalutamide (multipage table)

Research question	Therapeutic indication	ACT[a]
1	Adults with treatment-naive mCRPC in whom chemotherapy is not clinically indicated[b, c, d]	▪ Abiraterone acetate in combination with prednisone or prednisolone (only for patients whose disease is progressive during or after docetaxel-containing chemotherapy; only for patients with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated) or ▪ **enzalutamide** (only for patients whose disease has progressed during or after docetaxel chemotherapy; only for patients with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated) or ▪ olaparib as monotherapy (only for patients with BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included an NHA) or ▪ olaparib in combination with abiraterone acetate and prednisone or prednisolone (only for patients with BRCA mutations and for patients without BRCA mutations with symptomatic disease)

Table 4: Research questions of the benefit assessment of talazoparib + enzalutamide (multipage table)

Research question	Therapeutic indication	ACT[a]
2	Adults with pretreated mCRPC in whom chemotherapy is not clinically indicated[b, e]	Individualized treatment[f] selected from ▪ abiraterone acetate in combination with prednisone or prednisolone (only for patients who have progressed on or after docetaxel-containing chemotherapy), ▪ enzalutamide (only for patients who have progressed on or after docetaxel chemotherapy), ▪ olaparib in combination with abiraterone acetate and prednisone or prednisolone, and ▪ olaparib as monotherapy (only for patients with BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included an NHA) taking into account pretreatment(s) and BRCA1/2 mutation status.

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**.
b. For the present therapeutic indication, it is assumed according to the G-BA that an existing conventional ADT is continued. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or antagonists. In addition, adequate concomitant treatment of bone metastases during the study is assumed (e.g. use of bisphosphonates, denosumab, radiotherapy).
c. The ACT specified here comprises several alternative treatment options according to the G-BA. However, the treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. The sole comparison with a therapy option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the overall population.
d. When determining the ACT, it is assumed that the patients may have already received prior therapy with docetaxel or NHA in earlier stages of the disease.
e. When determining the ACT, it is assumed that the patients, in addition to prior therapy of the mCRPC, may have already received prior therapy with docetaxel or NHA in earlier stages of the disease.
f. For the implementation of individualized therapy in a study of direct comparison, according to the G-BA, investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multi-comparator study). A rationale must be provided for the choice and any limitation of treatment options. If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.

ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; BRCA: breast cancer susceptibility gene; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mCRPC: metastatic castration-resistant prostate cancer; NHA: novel hormonal agent

In research question 1, the ACT presented by the company in Module 3 A deviates from the ACT specified by the G-BA in some of the alternative treatment options mentioned. However, since the company selected the option enzalutamide specified by the G-BA as the ACT for research question 1 and presented evidence in comparison with this option, this has no consequences for the benefit assessment. For research question 2, the company deviated from the G-BA's ACT in the specification of individual components of the individualized therapy. Since the company presented no data on research question 2, this also has no consequences for the benefit assessment. The present benefit assessment is conducted in comparison with the ACT specified by the G-BA.

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

I 3 Research question 1: adults with treatment-naive mCRPC in whom chemotherapy is not clinically indicated

I 3.1 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 talazoparib (status: 15 January 2024)
- bibliographical literature search on talazoparib (last search on 15 January 2024)
- search in trial registries/trial results databases for studies on talazoparib (last search on 15 January 2024)
- search on the G-BA website for talazoparib (last search on 15 January 2024)

To check the completeness of the study pool:

- search in trial registries for studies on talazoparib (last search on 20 February 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: talazoparib + enzalutamide vs. enzalutamide

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
C3441021 (TALAPRO-2[c])	Yes	Yes	No	Yes [3-10]	Yes [11,12]	Yes [13-15]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.
CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The TALAPRO-2 study is used for the benefit assessment in research question 1. The study pool is consistent with that selected by the company.

I 3.1.2 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: talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
TALAPRO-2	RCT, double-blind, parallel (Part 2)[b]	Adult patients with mCRPC[c] with ▪ ECOG PS ≤ 1 and ▪ BPI-SF Item 3 score < 4	Cohort 1[d]: ▪ talazoparib + enzalutamide (N = 402) ▪ placebo + enzalutamide (N = 403) Cohort 2[e]: ▪ talazoparib + enzalutamide (N = 200) ▪ placebo + enzalutamide (N = 199) China expansion cohort[f]: ▪ talazoparib + enzalutamide (N = 63) ▪ placebo + enzalutamide (N = 62)	Screening: ≤ 28 days Treatment: until radiographic progression[g], unacceptable toxicity, patient or investigator decision to discontinue treatment, or death Observation[h]: outcome-specific, at most until death, withdrawal of consent, or termination of study by sponsor	287 centres in Argentina, Australia, Belgium, Brazil, Canada, Chile, China, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, Japan, New Zealand, Norway, Peru, Poland, Portugal, South Africa, South Korea, Spain, Sweden, United Kingdom, United States 8/2017–ongoing Data cut-offs: ▪ 16 August 2022 (first data cut-off Cohort 1) ▪ 3 October 2022 (first data cut-off Cohort 2) ▪ 28 March 2023 (FDA data cut-off)	Primary: rPFS Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Part 1 of the TALAPRO-2 study is an open-label, non-randomized part of the study to determine the dose of talazoparib in combination with enzalutamide for Part 2 of the study. Only Part 2 of the study is relevant for the benefit assessment.
c. Histologically or cytologically confirmed mCRPC with a testosterone level of ≤ 50 ng/dL at screening under therapy with a GnRH agonist/antagonist or after bilateral orchiectomy. Progressive disease at baseline had to be demonstrated by PSA progression or radiographic progression. Metastatic disease had to be documented by skeletal scintigraphy (bone), or CT/MRI scan (soft tissue).
d. Adult patients with mCRPC regardless of HRR mutation status.
e. Only patients with HRR mutation were enrolled in Cohort 2. In addition to 169 patients with HRR mutation included in Cohort 1, Cohort 2 includes 230 additional patients with HRR mutation who enrolled after recruitment for Cohort 1 was completed.
f. In addition to 54 Chinese patients included in Cohort 1, the China extension cohort includes 71 additional patients who were included in China after recruitment for Cohort 1 was completed, in order to meet Chinese regulatory requirements. The benefit assessment is based on results of Cohort 1 and Cohort 2 (see section *Relevance of the cohorts of the TALAPRO-2 study*); the China extension cohort is no longer shown in the following tables.
g. Radiographic progression had to be determined by blinded independent central review; in patients included in France due to PSA progression, study treatment had to be discontinued if PSA continued to rise above maximum eligibility level without an initial confirmed biological response (PSA response) without any clinical or radiographic progression. Continued treatment at the investigator's discretion was allowed for as long as the patient was still deriving benefit from the treatment.
h. Outcome-specific information is provided in Table 8.

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CT: computed tomography; ECOG PS: Eastern Cooperative Oncology Group Performance Status; GnRH: gonadotropin-releasing hormone; HRR: homologous recombination repair; mCRPC: metastatic castration-resistant prostate cancer; MRI: magnetic resonance imaging; N: number of randomized patients; PSA: prostate-specific antigen; RCT: randomized controlled trial; rPFS: radiographic progression-free survival

Table 7: Characteristics of the intervention – RCT, direct comparison: talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Study	Intervention	Comparison
TALAPRO-2	Talazoparib[a] 0.5 mg (once daily), orally + enzalutamide 160 mg (once daily), orally	Placebo, orally + enzalutamide 160 mg (once daily), orally
	Dose adjustment[b]: ▪ Talazoparib/placebo: interruption of therapy and sequential dose reduction to 0.35 mg, 0.25 mg and 0.1 mg (once daily) in case of toxicity ▪ Enzalutamide: Dose reductions in accordance with the SPC in case of toxicity	
	Required prior and concomitant treatment ▪ bilateral orchiectomy or ADT with GnRH agonists/antagonists[c] **Prior treatment** **Allowed** ▪ abiraterone, hormonal therapy (e.g. bicalutamide, nilutamide, flutamide, oestrogens) in HSPC ▪ up to ≥ 2 weeks before randomization: major surgery ▪ up to ≥ 3 weeks before randomization: palliative localized radiation therapy ▪ up to ≥ 28 days before randomization: cytotoxic chemotherapy (such as docetaxel), biologic therapy including sipuleucel-T, or radionuclide therapy in hormone-sensitive prostate cancer; opioids for pain related to either primary prostate cancer or metastasis; investigational agents ▪ up to ≥ 6 months before randomization: platinum-based chemotherapy **Disallowed** ▪ any systemic cancer treatment initiated in the nmCRPC or mCRPC disease state[d] ▪ second-generation androgen receptor inhibitors (enzalutamide, apalutamide, and darolutamide), PARP inhibitors, cyclophosphamide, or mitoxantrone for prostate cancer ▪ prednisone > 10 mg/day (or equivalent) ▪ platinum-based chemotherapy if disease progression occurred within 6 months thereafter	
	Concomitant treatment **Allowed** ▪ **treatment with bisphosphonates or denosumab** ▪ haematopoietic growth factors (e.g. granulocyte colony-stimulating factor[e], granulocyte macrophage colony-stimulating factor) ▪ red blood cell transfusions, erythropoietin and erythropoiesis-stimulating agents[f] ▪ thrombopoietin analogues and/or platelet transfusions[f] ▪ analgesics for prostate cancer pain (including opioids) **Disallowed** ▪ prednisone > 10 mg/day (or equivalent)[g] ▪ chemotherapy (e.g. platinum-based chemotherapy, cyclophosphamide, taxanes, or mitoxantrone) for metastatic prostate cancer ▪ hormonal therapy (e.g. bicalutamide, nilutamide, flutamide, oestrogens, 5-alpha reductase inhibitors), NHA[h] (e.g. abiraterone, apalutamide, darolutamide), biologic therapy, or radionuclide therapy for prostate cancer or any other investigational agent ▪ other PARP inhibitors ▪ radiation therapy or surgery[i]	

Table 7: Characteristics of the intervention – RCT, direct comparison: talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Study	Intervention	Comparison
a. The starting dose of talazoparib for patients with moderate renal impairment was 0.35 mg once daily. b. If one study drug was discontinued due to toxicity (talazoparib/placebo or enzalutamide), the other study drug could be continued. 6 weeks after discontinuation of enzalutamide, the dose of talazoparib/placebo could be increased after consultation with the investigator (depending on the talazoparib/placebo dose at the time of discontinuation of enzalutamide). c. Any ADT had to be initiated at least 4 weeks before randomization and had to be continued during the study. d. With the exception of ADT and first-generation antiandrogens. e. Only permitted for the treatment of neutropenia, or as secondary prophylaxis at the discretion of the investigator, but not as primary prophylaxis. f. At the discretion of the investigator for the supportive treatment of anaemia or thrombocytopenia. g. Short-term use (≤ 4 weeks) was permitted if no alternative therapy was available. h. With the exception of enzalutamide. i. Palliative radiotherapy or surgery was only permitted after radiographic progression and consultation with the sponsor; see section *Adequate treatment of bone metastases*. ADT: androgen deprivation therapy; GnRH: gonadotropin-releasing hormone; HSPC: hormone-sensitive prostate cancer; mCRPC: metastatic castration-resistant prostate cancer; NHA: novel hormonal agent; nmCRPC: non-metastatic castration-resistant prostate cancer; PARP: poly(adenosine diphosphate-ribose) polymerase; RCT: randomized controlled trial; SPC: Summary of Product Characteristics		

Study design

The TALAPRO-2 study consists of 2 parts. The non-randomized Part 1 of the study served to determine the dose of talazoparib in combination with enzalutamide and is not relevant for the present benefit assessment. Part 2 of the TALAPRO-2 study is an ongoing double-blind RCT comparing talazoparib + enzalutamide versus placebo + enzalutamide.

The study included adult patients with mCRPC who had not yet received any prior therapy in the current disease state (mCRPC) or in the nmCRPC state. According to the inclusion criteria, patients had progressive disease while they were on ADT by medical or surgical castration. Furthermore, patients had to be in good general condition at study entry, corresponding to an ECOG PS of 0 or 1, and be asymptomatic or mildly symptomatic (recorded using the BPI-SF Item 3 [worst pain] < 4).

A total of 1106 patients were included in 3 cohorts in Part 2 of the TALAPRO-2 study (for a detailed description of the cohorts and their relevance to research question 1 of this benefit assessment, see the following section). Randomization was carried out in a 1:1 ratio, stratified according to the factors of presence of an HRR mutation (yes/no or unclear) and previous treatment with a novel hormonal agent or taxane-based chemotherapy for hormone-sensitive prostate cancer (yes/no).

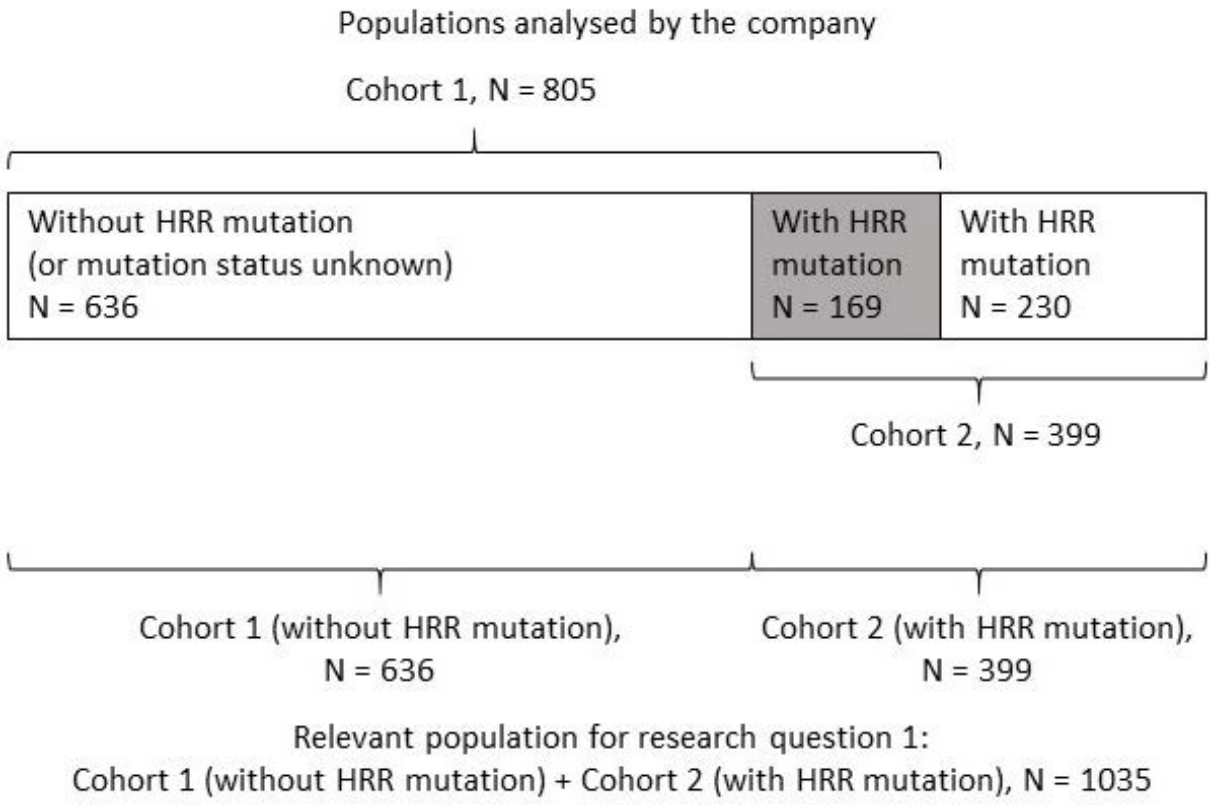
Treatment with talazoparib and enzalutamide was conducted without relevant deviations from the respective SPCs [16,17]. In addition to the study medication, patients who had not undergone bilateral orchiectomy had to continue ADT with a GnRH agonist/antagonist initiated at least 4 weeks before randomization throughout the entire study. Treatment with the study medication was continued until radiographic progression, unacceptable toxicity, patient or investigator decision to discontinue treatment, or death.

The primary outcome of the study was rPFS. Patient-relevant secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Relevance of the cohorts of the TALAPRO-2 study and approach of the company

Part 2 of the TALAPRO-2 study comprises 3 cohorts. The composition of the cohorts is described below:

- Cohort 1: Inclusion was independent of the presence of an HRR mutation. Cohort 1 included 805 patients, 402 patients in the talazoparib + enzalutamide arm and 403 patients in the placebo + enzalutamide arm. According to the CSR, 169 (21%) patients in Cohort 1 had an HRR mutation, 426 (53%) had no HRR mutation, and 210 (26%) patients had an unknown HRR mutation status.
- Cohort 2 included only patients with at least one HRR mutation, detected by prospective analysis of blood (liquid biopsy) or tissue (de novo or archival tissue) or historical analysis of most recent tumour tissue per FoundationOne test. Cohort 2 included a total of 399 patients with HRR mutation, 200 patients in the talazoparib + enzalutamide arm, and 199 patients in the placebo + enzalutamide arm. Cohort 2 comprised 169 patients with HRR mutation who had already been randomized in Cohort 1 and thus were also additionally analysed in Cohort 1. An additional 230 patients with HRR mutation were recruited exclusively for Cohort 2. This results in an overlap of 169 patients who were included in both Cohort 1 and Cohort 2 (see Figure 1).
- China extension cohort: Patients were included only in China, irrespective of the presence of an HRR mutation, in order to fulfil requirements for the Chinese regulatory authorities. It included a total of 125 patients, 63 patients in the talazoparib + enzalutamide arm and 62 patients in the placebo + enzalutamide arm. The China extension cohort comprised 54 Chinese patients who had already been randomized as part of Cohort 1. An additional 71 patients were recruited in China exclusively for the China extension cohort. This results in an overlap of 54 patients who were included in both Cohort 1 and the China extension cohort.



The composition of Cohort 1 and Cohort 2 of the TALAPRO-2 study described above is shown. A meta-analysis of all patients from Cohort 1 and Cohort 2 without overlap is possible via subgroup results on patients without HRR mutation or unclear mutation status (hereinafter summarized as "patients without HRR mutation") from Cohort 1 and results of all patients from Cohort 2 (with HRR mutation).

HRR: homologous recombination repair; N: number of randomized patients

Figure 1: Overview of the composition of Cohort 1 and Cohort 2 of the TALAPRO-2 study

The company exclusively used separate data of Cohort 1 and Cohort 2 of the TALAPRO-2 study for its benefit assessment. It did not consider the results of the China extension cohort without giving reasons for this. The company did not present the data of the China extension cohort separately in Module 4 A, but submitted CSRs on an interim data cut-off dated 16 August 2022 and on the final data cut-off dated 25 November 2023 for this cohort.

The cohorts of the TALAPRO-2 study were conducted under an identical SAP and study protocol. Thus, all 3 cohorts together should be considered as one study, and the results for the entire study population (N = 1106 patients) should generally be used for the benefit assessment. The 71 patients in the China extension cohort of the TALAPRO-2 study who are not already included in Cohort 1 only account for about 6.4% (71/1106) of the total study population, however. It is therefore assumed that not taking into account the 71 additional Chinese patients does not have a relevant impact on the results. A pooled analysis of all patients from Cohorts 1 and 2 (without overlap) with a total of 1035 patients can therefore be regarded as a sufficient approximation of the total population of the study.

Although the company presented data on Cohort 1 and Cohort 2, it did not conduct a pooled analysis of Cohort 1 and Cohort 2 without the overlap of the 169 patients included in both cohorts. The company justified this with what it considered as the obvious heterogeneity of the patient populations, as Cohort 1 included patients with and without HRR mutation, while Cohort 2 only included patients with HRR mutation. It also argued that patients with HRR mutations would be overrepresented in a pooled analysis of Cohort 1 and Cohort 2.

The approach of the company is not appropriate. The approval of talazoparib covers both patients without and patients with HRR mutation, and also the G-BA did not differentiate between patients with and without HRR mutation when determining the ACT. Accordingly, the total population of the study (without overlap) represents the relevant population for research question 1 of the present benefit assessment. The company did not present analyses for the total population of the study (without overlap). However, based on the subgroup results of patients without HRR mutation or unknown HRR mutation status from Cohort 1 (summarized below as Cohort 1 without HRR mutation) and the results of all patients from Cohort 2 (with HRR mutation), it is possible to conduct a meta-analysis of the total population of 1035 patients without overlap (see Figure 1). The influence of the characteristic of HRR mutation status on the results is analysed in the meta-analysis using a heterogeneity test. Further subgroup analyses (e.g. for specific HRR mutations or age) are not possible.

To assess the added benefit, the benefit assessment uses the results of the total population (Cohort 1 without HRR mutation and Cohort 2 with HRR mutation, without overlap; see Figure 1) pooled in a meta-analysis. For information such as patient characteristics and course of the study, for which only separate information on Cohort 1 and Cohort 2 is available, due to the size of Cohort 1 (78% of the total of 1035 patients from Cohort 1 without HRR mutation and Cohort 2 with HRR mutation), this information is presented as an approximation of the total population relevant for the assessment.

Limitations of the TALAPRO-2 study

Therapeutic indication for chemotherapy in the TALAPRO-2 study

Talazoparib + enzalutamide is approved for adult patients with mCRPC in whom chemotherapy is not clinically indicated. In the TALAPRO-2 study, this was not an explicit inclusion criterion. It was only specified that only patients with a BPI-SF Item 3 (worst pain) < 4 (corresponding to no or mild symptoms) would be included. According to the S3 guideline, treatment eligibility for chemotherapy is not a clearly defined variable [18]. Criteria that can be used for this assessment are the patient's health status, prior therapies and response to these therapies, symptoms, and the patient's wishes. Whether the prerequisites for chemotherapy are fulfilled must be decided on a patient-specific basis [18].

It is not clear from the inclusion criteria of the TALAPRO-2 study whether all patients in the study population met the approval restriction “chemotherapy not clinically indicated”.

The company did not address this issue. The study also included patients with visceral metastases (high disease burden) (see Table 9), for whom chemotherapy may be a more suitable treatment option, especially if no chemotherapy was given at an earlier stage of the disease [18]. Data on the number of patients with visceral metastases who had not received prior chemotherapy are not available. The European Medicines Agency (EMA) describes in the European Public Assessment Report (EPAR) [19] that the patients with visceral disease who have not yet received prior chemotherapy with docetaxel for metastatic hormone-sensitive prostate cancer (mHSPC) are, according to international guidelines, not eligible for enzalutamide treatment, which questions the external validity of the obtained results in this subset.

According to the information in the CSR on the patients’ prior therapies, the previous taxane-containing chemotherapy was almost exclusively a therapy with docetaxel. No information is available on the line of therapy in which the patients received this treatment. It remains unclear whether retreatment with chemotherapy (possibly with cabazitaxel) would have been clinically indicated for the patients with previous taxane-containing chemotherapy. According to the S3 guideline, cabazitaxel is a therapy option for patients with taxane-based chemotherapy in the prior therapy (usually docetaxel). However, the treatment suitability for further taxane-based chemotherapy is not clearly defined and appropriate criteria are lacking. Detailed information on why further taxane-based chemotherapy (especially cabazitaxel) was not suitable for the patients with one previous taxane-based chemotherapy is not available.

Overall, uncertainty remains as to whether the study also included patients in whom chemotherapy would have been clinically indicated. Against the background that there are no clear criteria as to when chemotherapy is clinically indicated, and taking into account the available information on symptoms and pretreatment of the included patients, it is assumed in the present situation, however, that this proportion is within a range that allows the meta-analytically summarized analysis of all patients from Cohort 1 and Cohort 2 (without overlap) to be used for the present research question. In the overall view, this uncertainty is taken into account in the certainty of conclusions (see Section I 3.2.2).

Adequate treatment of bone metastases

According to the G-BA’s notes in the document specifying the ACT, adequate concomitant treatment of bone metastases during the study is assumed (e.g. use of bisphosphonates, denosumab, radiotherapy; see Table 4). However, according to the study protocol of the TALAPRO-2 study, palliative radiotherapy or surgery was only permitted after radiographic progression and consultation with the sponsor. This does not correspond to the

recommendation of the S3 guideline, which describes that patients with bone metastases should be offered the following treatment options: drug-based pain therapy, localized radiotherapy, surgical intervention [18]. The transferability to the German health care context is therefore limited. It remains unclear whether and in how many patients this restriction of the use of palliative radiotherapy or surgery may have led to inadequate treatment of bone metastases. Other concomitant treatments for bone metastases (e.g. bisphosphonates and denosumab) were not restricted. The existing uncertainty is taken into account in the certainty of conclusions (see Section I 3.2.2). The described restriction in the use of palliative radiotherapy or surgery also affects the interpretability of other outcomes (e.g. BPI-SF), as the patients only had limited (pain) therapy available for the treatment of bone metastases until progression (see Section I 3.2.1).

Implementation of the appropriate comparator therapy in the TALAPRO-2 study

The ACT specified by the G-BA for research question 1 comprises several alternative treatment options depending on various patient and disease characteristics. From the options, the company chose enzalutamide, which the G-BA had specified as ACT only for patients whose disease has progressed during or after docetaxel chemotherapy, and only for patients with asymptomatic or mildly symptomatic disease after failure of ADT in whom chemotherapy is not yet clinically indicated.

As described in the section *Therapeutic indication for chemotherapy in the TALAPRO-2 study*, uncertainty remains as to whether patients were included in the study for whom chemotherapy would have been clinically indicated and for whom enzalutamide was therefore not a suitable ACT. As described above, this is taken into account in the certainty of conclusions. However, it is assumed that this proportion is within a range that allows the total population of the TALAPRO-2 study to be used.

Pretreatment in the TALAPRO-2 study

Pretreatment with enzalutamide, darolutamide and apalutamide was not allowed in the study (see Table 7). In addition, prior therapy in the nmCRPC disease state was generally excluded. Abiraterone and docetaxel, on the other hand, were permitted in earlier hormone-sensitive settings of prostate cancer. Approximately 7% of patients in Cohort 1 of the TALAPRO-2 study were pretreated with a novel hormonal agent, and approximately 23% of patients were pretreated with docetaxel (see Table 9). According to the recommendations of the S3 guideline, apalutamide and enzalutamide are possible treatment options alongside abiraterone and docetaxel in mHSPC. Apalutamide, enzalutamide and darolutamide are recommended as possible treatment options for nmCRPC. According to the S3 guideline, the group of patients with mCRPC without prior therapy with a novel hormonal agent (abiraterone, apalutamide, darolutamide or enzalutamide) will also become smaller in the coming years [18]. Thus, it remains unclear how this restriction of prior therapy in the

TALAPRO-2 study can be transferred to the current situation in everyday health care. This remains of no consequence for the benefit assessment.

Data cut-offs

Three data cut-offs are available for the TALAPRO-2 study:

- Data cut-off Cohort 1 on 16 August 2022: first interim analysis for overall survival and final analysis for the primary outcome of rPFS (planned after about 333 rPFS events [radiographic progression or death] in Cohort 1)
- Data cut-off Cohort 2 on 3 October 2022: first interim analysis for overall survival and final analysis for the primary outcome of rPFS (planned after about 157 rPFS events [radiographic progression or death] in Cohort 2)
- FDA data cut-off on 28 March 2023: second interim analysis for overall survival (according to the company, this was requested by the FDA)

In the dossier, the company used the FDA data cut-off dated 28 March 2023 to derive the added benefit and presented results for all patient-relevant outcomes for this data cut-off. It additionally presented the study results for the other 2 data cut-offs as supplementary information in Module 4 A, Appendix 4-G1 and Appendix 4-G2. Concurring with the company's approach, the present benefit assessment uses the data from the FDA data cut-off.

Planned after approximately 438 deaths in Cohort 1, the final analysis for overall survival in Cohort 1 of the TALAPRO-2 study is still pending. The final analysis for overall survival in Cohort 2 is also planned for the same point in time.

It can be inferred from the study documents that the study was unblinded by the sponsor after the final analysis of the primary outcome of rPFS (Cohort 1: 16 August 2022, and Cohort 2: 3 October 2022). However, this does not have any consequences for the present benefit assessment (for justification see Section I 3.2.2).

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: talazoparib + enzalutamide vs. placebo + enzalutamide

Study **Outcome category** **Outcome**	**Planned follow-up observation**
TALAPRO-2	
Mortality	
Overall survival	Until death or end of study
Morbidity	
Symptomatic bone fracture, spinal cord compression, pain (BPI-SF), symptoms (EORTC QLQ-C30, EORTC QLQ-PR25), health status (EQ-5D VAS)	Until death, withdrawal of consent, or end of study
Health-related quality of life	
EORTC QLQ-C30, EORTC QLQ-PR25	Until death, withdrawal of consent, or end of study
Side effects	
AEs/SAEs/severe AEs[a]	Up to 28 days after discontinuation of treatment, start of a new antineoplastic or investigational therapy, whichever comes first
AML/MDS	Until death, withdrawal of consent, or end of study

a. Severe AEs are operationalized as CTCAE grade ≥ 3.

AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MDS: myelodysplastic syndrome; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for the outcomes in the side effects category (with the exception of AML and MDS) are systematically shortened because they were recorded only during treatment with the study medication (plus 28 days). Although the outcomes on morbidity and health-related quality of life were to be assessed over the entire study period, their observation periods are also shortened (see also information on the course of the study in Table 10). 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.

Characteristics of the study population

In Module 4 A of the dossier assessment, the company did not present any joint analyses on patient characteristics for the total population relevant for the assessment (all patients in Cohort 1 and Cohort 2, without overlap). Due to the size of Cohort 1, the information on patient characteristics for Cohort 1 is presented as an approximation, see Table 9.

Table 9: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Study Characteristic Category	Talazoparib + enzalutamide N = 402	Placebo + enzalutamide N = 403
TALAPRO-2 Cohort 1		
Age [years], mean (SD)	71 (8)	70 (8)
Family origin, n (%)		
White	243 (60)	255 (63)
Asian	127 (32)	120 (30)
Other	32 (8)	28 (7)
Geographical region, n (%)		
North America	59 (15)	63 (16)
EU/Great Britain	150 (37)	155 (38)
Asia	124 (31)	117 (29)
Rest of the world	69 (17)	68 (17)
Gleason score at initial diagnosis, n (%)		
< 8	117 (29)	113 (28)
≥ 8	281 (70)	283 (70)
Not reported	4 (1)	7 (2)
Baseline pain score by BPI-SF, n (%)		
0–1	273 (68)	251 (62)
2–3	127 (32)	149 (37)
> 3	1 (< 1)	2 (< 1)
Not reported	1 (< 1)	1 (< 1)
ECOG PS at baseline, n (%)		
0	259 (64)	271 (67)
1	143 (36)	132 (33)
Distribution of disease at screening, n (%)		
Bone (incl. bone with connective tissue)	349 (87)	342 (85)
Lymph nodes	148 (37)	168 (42)
Visceral disease (lung or liver)	54 (13)	71 (18)
Visceral diseases (lung)	45 (11)	60 (15)
Visceral diseases (liver)	12 (3)	16 (4)
Other connective tissue[a]	37 (9)	33 (8)

Table 9: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Study Characteristic Category	Talazoparib + enzalutamide N = 402	Placebo + enzalutamide N = 403
HRR mutation (IWRS), n (%)	85 (21)	84 (21)
Prior systemic anti-cancer treatment, n (%)		
Taxanes	87 (22)[b]	93 (23)
Anti-androgens (first generation)	239 (59)	237 (59)
Novel hormonal agent	23 (6)	27 (7)
ADT at baseline, n (%)		
Chemical castration	378 (94)	376 (93)
Bilateral orchiectomy	24 (6)	27 (7)
Treatment discontinuation (talazoparib/placebo), n (%)[c]	274 (69)	302 (75)
Treatment discontinuation (enzalutamide), n (%)[d]	259 (65)	300 (75)
Study discontinuation, n (%)	ND	ND

a. Other connective tissue includes: adrenal gland, abdomen, urinary bladder, large and small intestine, kidneys, pancreas, penis, pericardium, peritoneum, rectum, renal pelvis, spleen, thyroid gland, and ureter.
b. According to the information in the CSR (data cut-off from 16 August 2022), and in contrast to the information in Module 4 A, 86 (21%) patients in Cohort 1 had received prior therapy with taxanes.
c. Common reasons for treatment discontinuation of talazoparib/placebo in the intervention arm vs. the control arm were disease progression (21% vs. 33%), AEs (19% vs. 11%), general deterioration of health status (14% vs. 12%), and patient decision (7% vs. 9%). 4 patients in the intervention arm and 2 patients in the control arm received no treatment; one additional patient in the intervention arm and one in the control arm received only enzalutamide.
d. Common reasons for treatment discontinuation of enzalutamide in the intervention arm vs. the control arm were disease progression (23% vs. 33%), AEs (11% vs. 9%), general deterioration of health status (15% vs. 13%), and patient decision (8% vs. 9%). 4 patients in the intervention arm and 2 patients in the control arm received no treatment; one additional patient in the intervention arm and one in the control arm received only enzalutamide.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CSR: clinical study report; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HRR: homologous recombination repair; IWRS: interactive web response system; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics of the patients in Cohort 1 were generally well balanced between the 2 treatment arms. The mean patient age was between 70 and 71 years, and most patients were from Europe. The majority of patients had a baseline BPI-SF Item 3 (worst pain in the last 24 hours) of 0 to 1. Although the inclusion criteria required all patients to have a BPI-SF Item 3 (worst pain) < 4, individual patients (< 1%) in both treatment arms had a baseline BPI-SF pain score > 3 or had no reported score.

The majority of patients (70%) had a Gleason score of ≥ 8 at diagnosis and an ECOG PS score of 0 (64% versus 67%) at baseline. 87% versus 85% of patients had bone metastases at screening. There were minor differences between the treatment arms in the distribution of disease at screening for lymph node metastasis (37% versus 42%) and visceral metastases in the lung or liver (13% versus 18%).

According to the exclusion criterion, all mCRPC patients were treatment-naive. However, the majority of patients had already received systemic therapy in a previous stage of the disease. Pretreatments were comparable between the 2 study arms. These included first generation anti-androgens (59%), taxanes (22% versus 23%) and novel hormonal agents (6% to 7%). According to the S3 guideline [18], the group of patients with mCRPC without prior therapy with a novel hormonal agent will become smaller in the coming years. It therefore remains unclear how the low proportion of patients who had previously received treatment with a novel hormonal agent can be transferred to the current situation in everyday health care (see text section on pretreatment under limitations of the TALAPRO-2 study in this chapter).

At the time of the data cut-off, 65-69% versus 75% of patients had discontinued treatment with talazoparib/placebo or enzalutamide. The most common reasons for treatment discontinuation of talazoparib/placebo were disease progression (21% versus 33%) and AEs (19% versus 11%). The most common reasons for treatment discontinuation of enzalutamide were disease progression (23% versus 33%) and general deterioration of health status (15% versus 13%). Information on treatment discontinuations of both study drugs and on study discontinuations is not available for the data cut-off under consideration.

Treatment duration and observation period

In Module 4 A of the dossier assessment, the company did not present any joint analyses on observation period and treatment duration for the total population relevant for the assessment (all patients in Cohort 1 and Cohort 2, without overlap). Due to the size of Cohort 1, the information for Cohort 1 is used as an approximation. Table 10 shows the patients' mean and median treatment duration and the mean and median observation period for individual outcomes in Cohort 1.

Table 10: Information on the course of the study – RCT, direct comparison: talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Study **Duration of the study phase** **Outcome category**	**Talazoparib + enzalutamide**	**Placebo + enzalutamide**
TALAPRO-2 Cohort 1	N = 402	N = 403
Treatment duration[a] [months]		
Median [Q1; Q3]	22.36 [9.92; 33.38]	16.56 [6.70; 31.08]
Mean (SD)	22.32 (13.09)	18.64 (13.04)
For talazoparib/placebo		
Median [Q1; Q3]	19.78 [8.80; 32.66]	16.07 [6.49; 31.03]
Mean (SD)	20.82 (13.40)	18.46 (12.93)
For enzalutamide		
Median [Q1; Q3]	22.36 [9.92; 33.35]	16.56 [6.70; 31.08]
Mean (SD)	22.30 (13.08)	18.65 (13.04)
Observation period [months]		
Overall survival[b]		
Median [Q1; Q3]	30.77 [17.45; 35.98]	30.36 [16.10; 35.68]
Mean (SD)	27.29 (11.33)	25.97 (11.58)
Morbidity		
Symptomatic bone fracture[c]		
Median [Q1; Q3]	27.66 [13.31; 34.07]	24.90 [11.30; 33.12]
Mean (SD)	24.16 (12.07)	22.86 (12.30)
Spinal cord compression[c]		
Median [Q1; Q3]	28.70 [13.60; 35.81]	25.10 [11.96; 33.12]
Mean (SD)	24.72 (12.18)	23.02 (12.33)
Worst pain (BPI-SF Item 3)[d]		
Median [Q1; Q3]	26.09 [11.27; 34.04]	19.29 [8.31; 30.65]
Mean (SD)	23.20 (12.65)	19.97 (12.51)
Pain interference (BPI-SF Item 9 a-g)[d]		
Median [Q1; Q3]	23.05 [10.68; 32.30]	17.51 [7.39; 30.39]
Mean (SD)	22.13 (12.82)	18.99 (12.44)
Symptoms (EORTC QLQ-C30)[d]		
Median [Q1; Q3]	23.05 [10.68; 32.30]	17.48 [7.39; 30.39]
Mean (SD)	22.09 (12.82)	18.83 (12.53)
Symptoms (EORTC QLQ-PR25)[d]		
Median [Q1; Q3]	23.05 [10.50; 32.30]	17.48 [7.39; 30.39]
Mean (SD)	22.06 (12.83)	18.82 (12.55)

Table 10: Information on the course of the study – RCT, direct comparison: talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Study **Duration of the study phase** **Outcome category**	**Talazoparib + enzalutamide**	**Placebo + enzalutamide**
Symptoms (EORTC QLQ-PR25 – incontinence aid)[d, e]		
Median [Q1; Q3]	19.12 [7.59; 30.42]	14.05 [5.52; 27.63]
Mean (SD)	19.17 (12.78)	16.66 (12.27)
Health status (EQ-5D VAS)[d]		
Median [Q1; Q3]	23.06 [10.78; 32.30]	17.48 [7.39; 30.39]
Mean (SD)	22.19 (12.77)	18.86 (12.55)
Health-related quality of life		
EORTC QLQ-C30[d]		
Median [Q1; Q3]	23.05 [10.68; 32.30]	17.48 [7.39; 30.39]
Mean (SD)	22.09 (12.82)	18.83 (12.53)
EORTC QLQ-PR25 (sexual activity)[d]		
Median [Q1; Q3]	23.05 [10.50; 32.30]	17.48 [7.39; 30.39]
Mean (SD)	22.06 (12.83)	18.82 (12.54)
EORTC QLQ-PR25 (sexual functioning)[d, f]		
Median [Q1; Q3]	13.86 [4.63; 24.77]	8.31 [2.79; 19.22]
Mean (SD)	15.08 (11.14)	11.36 (10.55)
Side effects[g]		
AEs/SAEs/severe AEs[h]		
Median [Q1; Q3]	23.24 [10.68; 33.25]	16.69 [7.43; 30.46]
Mean (SD)	22.63 (12.68)	18.93 (12.68)
MDS/AML		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND

a. According to the company, the treatment duration is defined as the time from the date of the first dose to the date of the last dose.
b. According to the company, the observation period is defined as the time from the date of randomization to the date of death or last contact.
c. According to the company, the observation period is defined as the time from the date of randomization to the date of the event or the last recording.
d. According to the company, the observation period is defined as the time from the date of the first dose to the date of the last recording.
e. Data based on 347 patients vs. 346 patients.
f. Data based on 103 patients vs. 97 patients.
g. According to the company, the observation period for patients with discontinuation is defined as the time from the date of the first dose to the date of the last dose + 28 days, date of initiation of new antineoplastic cancer therapy, date of death from any cause or date of data cut-off, whichever occurred earlier. For patients without discontinuation, the observation period is defined as the time from the date of the first dose to the last contact.
h. Operationalized as CTCAE grade ≥ 3.

Table 10: Information on the course of the study – RCT, direct comparison: talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Study	**Talazoparib + enzalutamide**	**Placebo + enzalutamide**
Duration of the study phase		
Outcome category		
AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MDS: myelodysplastic syndrome; N: number of randomized patients; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale		

In Cohort 1 of the TALAPRO-2 study, the median treatment duration was longer in the intervention arm than in the comparator arm (19.8 months for talazoparib and 22.4 months for enzalutamide versus 16.1 months for placebo and 16.6 months for enzalutamide).

The median observation period for overall survival was about 30 months in both treatment arms. The median observation periods cited by the company for the outcomes of symptomatic bone fracture and spinal cord compression were about 28 months in the intervention arm and about 25 months in the comparator arm, and thus about 2 and 5 months shorter, respectively, despite the follow-up observation period planned analogously to the outcome of overall survival. It remains unclear how this discrepancy is to be explained.

The median observation periods for all other outcomes on morbidity, health-related quality of life and side effects differ notably between the treatment arms and are about 5 to 7 months longer in the intervention arm than in the comparator arm. It is notable that the median observation periods for the outcomes on morbidity (excluding the outcomes of symptomatic bone fracture and spinal cord compression) and health-related quality of life are between 4 and 22 months shorter than the median observation period for overall survival, although follow-up observation of these outcomes was to be analogous, according to the study protocol.

Subsequent therapies

The choice of subsequent therapies was not restricted in the TALAPRO-2 study. With the dossier, the company presented no information on the subsequent therapies used, neither for the total population relevant for the assessment (patients in Cohort 1 and Cohort 2, without overlap) nor for the individual cohorts, for the data cut-off of 28 March 2023 used for the assessment. Information on subsequent therapies is generally required for the benefit assessment, especially for the assessment of results on outcomes that are observed beyond the end of treatment.

The CSR contains information on the earlier data cut-off date of 16 August 2022 for Cohort 1. This information on the use of subsequent therapies (including docetaxel, cabazitaxel and abiraterone and olaparib, for example, see I Appendix E of the full dossier assessment) appears generally comprehensible for the present therapeutic indication and provides no indication that the subsequent therapy of patients deviates to a relevant extent from guideline recommendations.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: talazoparib + enzalutamide vs. placebo + enzalutamide

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			
TALAPRO-2	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the TALAPRO-2 study is rated as low.

Transferability of the study results to the German health care context

The company describes that the TALAPRO-2 study is an international multicentre Phase 3 study with 287 study centres in a total of 26 countries, including 8 study centres in Germany. According to the company, half of the study participants came from Europe or North America and about 65% of the patients included were of Caucasian family origin.

It described that the age distribution in Cohort 1 and Cohort 2 was in line with the corresponding distribution among patients with mCRPC in everyday health care in Germany (≤ 65 years: 27.6%, 66-75 years: 40.1%, ≥ 75 years: 32.4) [20]. It added that the patient population in Cohort 1 and Cohort 2 largely matched the patients with mCRPC in everyday health care in Germany with regard to the characteristics of distant metastases at initial diagnosis, ECOG PS of 0 or 1 at baseline, Gleason score. With regard to the characteristic of bone metastases, the company stated that the proportion of patients in Cohort 1 at 83.9% and in Cohort 2 at 81.7% was only slightly above the proportion of 74.6% of mCRPC patients with bone metastases in everyday health care in Germany [20]. The company added that 22.4% of patients in Cohort 1 and 29.3% of patients in Cohort 2 had received prior

chemotherapy and that in everyday health care in Germany, 36.1% of patients with mCRPC were pretreated with chemotherapy [20].

According to the company, there was overall a high degree of agreement in the patient characteristics between the study population and patients with mCRPC in everyday health care in Germany for most parameters. The company therefore presumed the study results to be 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. For the transferability of the study results, see also the sections *Adequate treatment of bone metastases* and *Pretreatment in the TALAPRO-2 study* under *Limitations of the TALAPRO-2 study* in Section I 3.1.2.

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptomatic bone fracture
  - spinal cord compression
  - worst pain (recorded using the BPI-SF Item 3)
  - pain interference (recorded using the BPI-SF Item 9a-g)
  - symptoms, recorded using the EORTC QLQ-C30 and the EORTC QLQ-PR25
  - Health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the EORTC QLQ-C30 and the EORTC QLQ-PR25
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - MDS (Preferred Term [PT], AEs)
  - AML (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 12 shows the outcomes for which data were available in the included study.

Table 12: Matrix of outcomes – RCT, direct comparison: talazoparib + enzalutamide vs. placebo + enzalutamide

Study	Outcomes													
	Overall survival	Symptomatic bone fracture	Spinal cord compression	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF Item 9a-g)	Symptoms (EORTC QLQ-C30 and EORTC QLQ-PR25)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-PR25)	SAEs	Severe AEs[a]	Discontinuation due to AEs	MDS (PT, AEs)	AML (PT, AEs)	Further specific AEs[a, b]
TALAPRO-2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	No[c]	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (coded according to MedDRA): dizziness (PT, AEs), infections and infestations (SOC, SAEs), anaemia (PT, severe AEs), and investigations (SOC, severe AEs).
c. No suitable data; for reasons, see the section following the table.

AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MDS: myelodysplastic syndrome; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes of the morbidity, health-related quality of life, and side effects categories

Outcome of symptomatic skeletal-related events

The outcome of symptomatic skeletal-related events is a composite outcome. It was predefined as the time from randomization to the first documentation of one of the following events:

- symptomatic bone fracture
- surgery to the bone
- radiotherapy to the bone

- spinal cord compression

However, the composite outcome cannot be used for the benefit assessment in the present operationalization. This is justified below.

Firstly, it is unclear whether all individual components are patient-relevant, as it is not described for the individual components “surgery to the bone” and “radiotherapy to the bone” that these were associated with symptoms. Secondly, radiotherapy and surgery were only permitted in the TALAPRO-2 study after radiographic progression and consultation with the sponsor (see also Section I 3.1.2). This means that differences in these components are potentially due to earlier progression in the control arm, which only makes it possible for radiotherapy and surgery to take place, and thus for events in the outcomes of surgery and radiotherapy to the bone to occur. The results on these outcomes are therefore not interpretable. In addition, patients had only limited (pain) therapy available for the treatment of bone metastases until progression due to the described limitation. This does not correspond to the recommendation of the S3 guideline, which describes that patients with bone metastases should be offered the following treatment options: drug-based pain therapy, localized radiotherapy, surgical intervention [18]. Transferability to the German health care context is therefore limited (see also the section on *Adequate treatment of bone metastases* in Section I 3.1.2). The individual components “symptomatic bone fracture” and “spinal cord compression” of the composite outcome are not affected by the restriction and are used as separate outcomes for the assessment.

Outcomes on pain (BPI-SF)

In the TALAPRO-2 study, the BPI-SF questionnaire is used to record pain. In Module 4 A, the company presented analyses of worst pain (BPI-SF Item 3) and pain interference (BPI-SF Item 9a-g), providing the following operationalizations:

- time to deterioration referred to as definitive by the company (from ≥ 2 points and from ≥ 15% of the scale range [scale range 0-10])
- time to first deterioration (from ≥ 2 points and from ≥ 15% of the scale range [scale range 0-10])
- mean differences at the respective time point of observation

The benefit assessment uses the responder analyses over the time to first deterioration (of ≥ 2 points for worst pain [BPI-SF Item 3] or of ≥ 15% for pain interference [BPI-SF Item 9a-g]), as the time to definitive deterioration is not suitable for the benefit assessment in the present data situation. This is justified below.

The onset of pain progression was predefined in the study documents as a ≥ 2-points increase from baseline in BFI-SF Item 3 confirmed at to 2 consecutive visits without a decrease in World Health Organization (WHO) analgesic usage score. The response threshold of ≥ 2 points was thus predefined only for Item 3 of the BPI-SF and, in accordance with the IQWiG *General Methods* [1], is therefore used for worst pain. Since no response threshold was predefined for pain interference (BPI-SF Item 9a-g), in accordance with the IQWiG *General Methods* [1], the response threshold of ≥ 15% is used for the assessment.

The definition of pain progression described in the study documents, which was also cited by the company in Module 4 A, corresponds to a single confirmed deterioration. It is unclear how the deterioration described as definitive by the company in M4 A was operationalized. It is also unclear how missing values (e.g. due to discontinuation or death) after the first occurrence of a deterioration were dealt with for the deterioration confirmed once and the deterioration referred to by the company as definitive, and how many patients this may have affected. Furthermore, there is a marked difference in the observation periods between the treatment arms for Cohort 1 (see Table 10 and the following Section I 3.2.2). The operationalization of the deterioration referred to by the company as definitive is therefore not used for the benefit assessment. The company did not present analyses of the BPI-SF Items 4, 5 and 6. These can therefore not be presented as supplementary information. However, this is of no consequence for the benefit assessment, as BPI-SF Item 3 (worst pain) and Item 9a-g (pain interference) are used to derive the added benefit.

The described problem of limited treatment options until progression for palliative radiotherapy and surgery also affects the interpretability of the BPI-SF, as palliative radiotherapy and surgery for the treatment of bone metastases and of the resulting pain were only available to patients after radiographic progression. The pain outcomes recorded via the BPI-SF are nevertheless used for the assessment, as these do not only reflect pain due to bone metastases.

Health status (EQ-5D VAS)

In its dossier, the company presented responder analyses for health status for the proportion of patients with a deterioration of 15% of the scale range (scale range 0 to 100) as well as analyses of mean differences at the respective time point of observation. Also for this outcome did the company present the operationalizations of time to first deterioration and time to deterioration referred to by the company as definitive for the responder analyses. Neither the study documents nor Module 4 A describe how the deterioration referred to by the company as definitive was defined. In addition, it is also unclear for this outcome, as is the case for the deterioration referred to as definitive by the company, how missing values (e.g. due to discontinuation or death) after the first occurrence of a deterioration were dealt with for the deterioration confirmed once and the deterioration referred to by the company as

definitive, and how many patients this may have affected. Furthermore, there is a marked difference in the observation periods for this outcome between the treatment arms in Cohort 1 (see Table 10 and the following Section I 3.2.2). Analogous to the procedure for the BPI-SF, the time to first deterioration is therefore used for the benefit assessment.

Symptoms and health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-PR25)

The TALAPRO-2 study assessed symptoms and health-related quality of life using the EORTC QLQ-C30 and the EORTC QLQ-PR25. In its dossier, the company presented analyses of mean differences at the respective time points of observation and responder analyses for the proportion of patients with a deterioration of ≥ 10 points for the EORTC QLQ-C30 and the EORTC QLQ-PR25 or, for the EORTC QLQ-PR25 only, an additional deterioration of ≥ 15% of the scale range (respective scale range 0 to 100). For the benefit assessment procedure, only analyses for the response criterion of 10 points are to be presented in the dossier for EORTC questionnaires [21]. These are used for the benefit assessment.

Also for these outcomes did the company present the operationalizations of time to first deterioration and time to deterioration referred to by the company as definitive for the responder analyses. Module 4 A provides the following definition for the deterioration referred to by the company as definitive for these outcomes: a deterioration of ≥ 10 points from baseline and no subsequent assessment below this threshold. As already described for the previous outcomes, it is also unclear here how missing values (e.g. due to discontinuation or death) after the first occurrence of a deterioration were dealt with for the deterioration confirmed once and the deterioration referred to by the company as definitive, and how many patients were affected. In addition, there is a marked difference in the observation periods for the EORTC QLQ-C30 and the EORTC QLQ-PR25 between the treatment arms for Cohort 1 (see Table 10 and the following Section I 3.2.2). Therefore, the benefit assessment uses the time to first deterioration also for these outcomes.

The described problem of limited treatment options until progression for palliative radiotherapy and surgery also affects symptoms and health-related quality of life, as palliative radiotherapy and surgery for the treatment of bone metastases and of the resulting pain were not available before progression. These outcomes can nevertheless be used for the assessment, as they do not only reflect pain due to bone metastases.

MDS (AEs) and AML (AEs)

The company considered the standardized Medical Dictionary for Regulatory Activities (MedDRA) query (broad SMQ) MDS for the AE of special interest (AESI) MDS. For the present benefit assessment, this does not represent a sufficiently specific operationalization to depict the events of MDS that are actually of interest. According to the information in Module 4 A, one event for the AESI MDS occurred in the intervention arm in Cohort 1. The comparison

with the CSR, which is only available for the first data cut-off (16 August 2022) however, shows that this event corresponds to the PT MDS.

For the AESI AML, the company considered a Customized Query AML as operationalization. This is not suitable for the present benefit assessment, as it is unclear which PTs were included in this analysis. According to the information in Module 4 A, no event for the AESI AML occurred either in Cohort 1 or in Cohort 2. However, the CSR for Cohort 1 shows for the first data cut-off (16 August 2022) that one event for the AESI AML occurred in the intervention arm during the follow-up observation.

The data for the AESI MDS and the AESI AML in Module 4 A and in the AE tables in the CSR for the first data cut-off only refer to the follow-up period of a maximum of 28 days after treatment discontinuation. However, according to the study protocol, the outcomes of MDS and AML had to be observed until patient death or the end of study. Therefore, analyses of MDS and AML should take into account the entire recording period. Overall, no suitable data are therefore available for both outcomes for the FDA data cut-off used. Based on the available data, however, it is not assumed that there are any relevant differences between the treatment arms in these outcomes.

Other specific AEs

In the dossier, the company presented time-to-event analyses for AEs, SAEs and severe AEs at System Organ Class (SOC) and PT level separately for Cohorts 1 and 2. In contrast, no analyses are available for the total study population (all patients from Cohorts 1 and 2, without overlap) on outcomes in the side effects category at SOC and PT level. Cohort 1 is used as an approximation for the selection of further specific AEs. This is justified in the present data situation, as it can be excluded with sufficient certainty that adding the results from Cohort 2 would yield substantially different or further specific AEs relevant for the conclusion in favour or to the disadvantage of talazoparib + enzalutamide compared with placebo + enzalutamide.

I 3.2.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: talazoparib + enzalutamide vs. placebo + enzalutamide

Study		Outcomes													
	Study level	Overall survival	Symptomatic bone fracture	Spinal cord compression	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF Item 9a-g)	Symptoms (EORTC QLQ-C30 and EORTC QLQ-PR25)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-PR25)	SAEs	Severe AEs[a]	Discontinuation due to AEs	MDS (PT, AEs)	AML (PT, AEs)	Further specific AEs[a, b]
TALAPRO-2	L	L	H[c]	H[c]	H[c, d]	H[c, d]	H[c, d]	H[c, d]	H[c, d]	H[c]	H[c]	L[e]	–[f]	–[f]	H[c]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (coded according to MedDRA): dizziness (PT, AEs), infections and infestations (SOC, SAEs), anaemia (PT, severe AEs), and investigations (SOC, severe AEs).
c. Incomplete observations for potentially informative reasons with different lengths of follow-up observation.
d. Marked decrease in questionnaire return rates in the course of the study, which differed between treatment arms.
e. Despite the low risk of bias, the certainty of results is presumably limited for the outcome of discontinuation due to AEs.
f. No suitable data available; see Section I 3.2.1 for the reasoning.

AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; MDS: myelodysplastic syndrome; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; RCT: randomized controlled trial; SAE: serious adverse event; 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.

Due to incomplete observations for potentially informative reasons in the presence of different lengths of follow-up observation periods, the risk of bias of the results is to be rated as high for the following outcomes: symptomatic bone fracture, spinal cord compression, pain (BPI-SF Item 3 and BPI-SF Item 9a-g), symptoms (recorded with the EORTC QLQ-C30 and the EORTC QLQ-PR25), health status (EQ-5D VAS), health-related quality of life (recorded with the EORTC QLQ-C30 and the EORTC QLQ-PR25), SAEs, severe AEs, and further specific AEs. In addition, a marked decrease in questionnaire return rates in the course of the study, which differed between treatment arms, contributed to the high risk of bias of the results for the outcomes of pain (BPI-SF Item 3 and BPI-SF Item 9a-g), symptoms (recorded with the EORTC QLQ-C30 and the EORTC QLQ-PR25), health status (EQ-5D VAS), and health-related quality of life (recorded with the EORTC QLQ-C30 and the EORTC QLQ-PR25).

The risk of bias for the results of the outcome of discontinuation due to AEs is rated as low. Nevertheless, the certainty of results for the outcome is limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs. Consequently, after treatment discontinuation for other reasons, AEs which would have led to discontinuation may have occurred, but the criterion of discontinuation can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

Since no suitable analyses are available for the outcomes of MDS (AEs) and AML (AEs) (see Section I 3.2.1), the risk of bias for these outcomes is not assessed.

It should also be noted that the study was unblinded by the sponsor after the final analysis of the primary outcome of rPFS (Cohort 1: 16 August 2022 and Cohort 2: 3 October 2022) (see Section I 3.1.2). Due to the small differences in the number of events between the previous data cut-offs and the used FDA data cut-off, the premature unblinding is not assumed to have an important effect on the risk of bias of the results.

Summary assessment of the certainty of conclusions

Regardless of the aspects described under the risk of bias, the certainty of conclusions of the study results is reduced due to the uncertainties described in Section I 3.1.2 as to whether chemotherapy was not clinically indicated for all patients in the study population and whether all patients received adequate concomitant treatment of bone metastases.

Due to this limitation, overall, at most hints, e.g. of an added benefit, can be determined for all outcomes on the basis of the available information.

I 3.2.3 Results

Table 14 summarizes the results of the comparison of talazoparib + enzalutamide with placebo + enzalutamide in patients with mCRPC in whom chemotherapy is not clinically indicated. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier. The meta-analytically summarized results of the total population calculated by the Institute (all patients of Cohorts 1 and 2, without overlap) are used.

Kaplan-Meier curves for the total population are not available. The Kaplan-Meier curves for the time-to-event analyses of the outcomes for the subgroup from Cohort 1 (without HRR mutation) and Cohort 2 (with HRR mutation) are shown in I Appendix B of the full dossier assessment. Forest plots for the calculations conducted by the Institute are shown in I Appendix C of the full dossier assessment. The tables on common AEs, SAEs, severe AEs and discontinuations due to AEs from Cohort 1 are presented in I Appendix D of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Outcome category Outcome Study	Talazoparib + enzalutamide		Placebo + enzalutamide		Talazoparib + enzalutamide vs. placebo + enzalutamide
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
TALAPRO-2					
Mortality					
Overall survival					
Cohort 1 (without HRR mutation)	317	NA [37.0; NC] 125 (39.4)	319	38.7 [35.0; NC] 133 (41.7)	0.93 [0.73; 1.18]; 0.538
Cohort 2 (with HRR mutation)	200	41.9 [34.5; NC] 60 (30.0)	199	30.8 [26.8; 38.8] 76 (38.2)	0.67 [0.47; 0.94]; 0.018
Total[b]					0.84 [0.69; 1.02]; 0.076
Morbidity					
Symptomatic bone fracture					
Cohort 1 (without HRR mutation)	317	NA 30 (9.5)	319	NA 21 (6.6)	1.43 [0.82; 2.49]; 0.209
Cohort 2 (with HRR mutation)	200	NA 19 (9.5)	199	NA 14 (7.0)	1.17 [0.59; 2.34]; 0.651
Total[b]					1.32 [0.86; 2.04]; 0.207
Spinal cord compression					
Cohort 1 (without HRR mutation)	317	NA 17 (5.4)	319	NA 19 (6.0)	0.88 [0.46; 1.69]; 0.701
Cohort 2 (with HRR mutation)	200	NA 12 (6.0)	199	NA 12 (6.0)	0.88 [0.39; 1.96]; 0.755
Total[b]					0.88 [0.53; 1.46]; 0.621
Worst pain (BPI-SF Question 3 – time to first deterioration[c])					
Cohort 1 (without HRR mutation)	311	NA 99 (31.8)	314	NA 83 (26.4)	1.18 [0.88; 1.59]; 0.255
Cohort 2 (with HRR mutation)	197	NA 43 (21.8)	197	NA [19.4; NC] 61 (31.0)	0.57 [0.38; 0.84]; 0.004
Total[b]					0.91 [0.72; 1.15]; 0.435
Pain interference (BPI-SF Question 9a-g – time to first deterioration[d])					
Cohort 1 (without HRR mutation)	311	21.2 [12.1; 26.7] 157 (50.5)	314	26.7 [19.3; NC] 130 (41.4)	1.14 [0.90; 1.43]; 0.277
Cohort 2 (with HRR mutation)	197	NA [17.8; NC] 74 (37.6)	197	15.7 [10.1; 19.4] 94 (47.7)	0.66 [0.49; 0.90]; 0.008
Total[b]					0.93 [0.78; 1.12]; 0.459

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Outcome category Outcome Study	Talazoparib + enzalutamide		Placebo + enzalutamide		Talazoparib + enzalutamide vs. placebo + enzalutamide
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Symptoms (EORTC QLQ-C30 – time to first deterioration[e])					
Fatigue					
Cohort 1 (without HRR mutation)	311	1.9 [1.9; 2.8] 239 (76.8)	314	3.7 [2.8; 4.6] 226 (72.0)	1.26 [1.05; 1.52]; 0.012
Cohort 2 (with HRR mutation)	197	2.8 [1.9; 3.7] 138 (70.1)	197	3.7 [2.3; 4.6] 127 (64.5)	1.10 [0.86; 1.41]; 0.401
Total[b]					1.20 [1.03; 1.39]; 0.016
Nausea and vomiting					
Cohort 1 (without HRR mutation)	311	9.2 [5.6; 16.3] 159 (51.1)	314	34.0 [17.5; NC] 122 (8.9)	1.54 [1.22; 1.95]; < 0.001
Cohort 2 (with HRR mutation)	197	10.6 [7.4; 19.4] 91 (46.2)	197	13.8 [8.3; 27.7] 79 (40.1)	1.11 [0.82; 1.51]; 0.500
Total[b]					1.36 [1.13; 1.64]; 0.001
Pain					
Cohort 1 (without HRR mutation)	311	7.4 [4.7; 9.2] 186 (59.8)	314	9.3 [7.4; 11.7] 179 (57.0)	1.09 [0.89; 1.34]; 0.397
Cohort 2 (with HRR mutation)	197	9.3 [6.5; 15.6] 108 (54.8)	197	5.6 [3.7; 6.6] 121 (61.4)	0.64 [0.49; 0.83]; < 0.001
Total[b]					0.89 [0.76; 1.05]; 0.166
Dyspnoea					
Cohort 1 (without HRR mutation)	311	6.4 [4.9; 9.3] 183 (58.8)	314	16.4 [10.3; 23.0] 151 (48.1)	1.43 [1.16; 1.78]; 0.001
Cohort 2 (with HRR mutation)	197	8.3 [5.6; 13.8] 99 (50.3)	197	9.2 [5.6; 13.9] 91 (46.2)	1.02 [0.77; 1.36]; 0.883
Total[b]					1.27 [1.07; 1.50]; 0.007
Insomnia					
Cohort 1 (without HRR mutation)	311	11.1 [8.4; 15.7] 157 (50.5)	314	9.1 [5.6; 15.7] 163 (51.9)	0.91 [0.73; 1.14]; 0.414
Cohort 2 (with HRR mutation)	197	16.6 [10.2; 24.9] 86 (43.7)	197	10.2 [5.6; 17.4] 91 (46.2)	0.82 [0.61; 1.10]; 0.168
Total[b]					0.88 [0.73; 1.05]; 0.145

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Outcome category Outcome Study	Talazoparib + enzalutamide N	Talazoparib + enzalutamide Median time to event in months [95% CI] Patients with event n (%)	Placebo + enzalutamide N	Placebo + enzalutamide Median time to event in months [95% CI] Patients with event n (%)	Talazoparib + enzalutamide vs. placebo + enzalutamide HR [95% CI]; p-value[a]
Appetite loss					
Cohort 1 (without HRR mutation)	311	5.6 [4.0; 9.2] 187 (60.1)	314	15.7 [11.1; 21.2] 155 (49.4)	1.44 [1.17; 1.78]; < 0.001
Cohort 2 (with HRR mutation)	197	7.4 [4.7; 11.9] 104 (52.8)	197	11.1 [7.5; 13.8] 96 (48.7)	1.09 [0.82; 1.44]; 0.573
Total[b]					1.30 [1.10; 1.54]; 0.002
Constipation					
Cohort 1 (without HRR mutation)	311	11.0 [7.3; 15.7] 156 (50.2)	314	18.5 [11.1; 25.0] 139 (44.3)	1.17 [0.93; 1.47]; 0.176
Cohort 2 (with HRR mutation)	197	15.7 [7.5; 24.0] 89 (45.2)	197	11.1 [7.4; 19.4] 87 (44.2)	0.91 [0.67; 1.22]; 0.512
Total[b]					1.07 [0.89; 1.28]; 0.488
Diarrhoea					
Cohort 1 (without HRR mutation)	311	34.1 [21.2; NC] 116 (37.3)	314	26.1 [21.2; NC] 116 (36.9)	0.92 [0.71; 1.19]; 0.520
Cohort 2 (with HRR mutation)	197	19.3 [14.1; 27.6] 77 (39.1)	197	26.1 [19.4; NC] 58 (29.4)	1.23 [0.88; 1.74]; 0.229
Total[b]					1.02 [0.83; 1.26]; 0.830
Symptoms (EORTC QLQ-PR25 – time to first deterioration[e])					
Urinary symptoms					
Cohort 1 (without HRR mutation)	311	24.9 [13.9; 32.3] 136 (43.7)	314	32.2 [19.3; NC] 119 (37.9)	1.10 [0.86; 1.40]; 0.455
Cohort 2 (with HRR mutation)	197	32.3 [23.0; NC] 62 (31.5)	197	15.6 [9.5; 21.7] 76 (38.6)	0.58 [0.41; 0.82]; 0.002
Total[b]					0.89 [0.73; 1.09]; 0.252
Bowel symptoms					
Cohort 1 (without HRR mutation)	311	NA [30.8; NC] 98 (31.5)	314	NA [34.4; NC] 83 (26.4)	1.16 [0.87; 1.55]; 0.320
Cohort 2 (with HRR mutation)	197	NA [28.6; NC] 49 (24.9)	197	NA [27.9; NC] 51 (25.9)	0.75 [0.51; 1.12]; 0.154
Total[b]					1.00 [0.79; 1.26]; 0.971

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Outcome category Outcome Study	Talazoparib + enzalutamide		Placebo + enzalutamide		Talazoparib + enzalutamide vs. placebo + enzalutamide
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Hormonal treatment-related symptoms					
Cohort 1 (without HRR mutation)	311	9.3 [7.4; 12.6] 162 (52.1)	314	12.5 [8.3; 21.9] 148 (47.1)	1.12 [0.90; 1.40]; 0.326
Cohort 2 (with HRR mutation)	197	9.3 [5.6; 15.6] 96 (48.7)	197	7.4 [4.7; 11.0] 92 (46.7)	0.86 [0.64; 1.15]; 0.306
Total[b]					1.02 [0.85; 1.21]; 0.845
Incontinence aid					
Cohort 1 (without HRR mutation)				No suitable data[f]	
Cohort 2 (with HRR mutation)				No suitable data[f]	
Health status (EQ-5D VAS – time to first deterioration[g])					
Cohort 1 (without HRR mutation)	311	12.0 [6.5; 21.3] 157 (50.5)	314	15.7 [8.4; 21.4] 151 (48.1)	1.05 [0.84; 1.31]; 0.685
Cohort 2 (with HRR mutation)	197	16.1 [7.5; 30.4] 88 (44.7)	197	9.2 [7.3; 12.0] 96 (48.7)	0.76 [0.57; 1.01]; 0.062
Total[b]					0.93 [0.78; 1.11]; 0.416
Health-related quality of life					
EORTC QLQ-C30 – time to first deterioration[h]					
Global health status					
Cohort 1 (without HRR mutation)	311	3.7 [2.9; 4.7] 213 (68.5)	314	7.6 [6.4; 9.4] 189 (60.2)	1.32 [1.09; 1.61]; 0.005
Cohort 2 (with HRR mutation)	197	6.4 [4.6; 8.4] 116 (58.9)	197	6.5 [3.7; 8.3] 111 (56.3)	0.94 [0.72; 1.22]; 0.649
Total[b]					1.17 [1.001; 1.37]; 0.049
Physical functioning					
Cohort 1 (without HRR mutation)	311	5.6 [3.7; 7.4] 211 (67.8)	314	8.3 [6.5; 13.7] 184 (58.6)	1.30 [1.07; 1.59]; 0.009
Cohort 2 (with HRR mutation)	197	8.3 [5.6; 10.3] 108 (54.8)	197	5.6 [4.5; 7.5] 117 (59.4)	0.76 [0.59; 0.99]; 0.043
Total[b]					1.07 [0.91; 1.25]; 0.424

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Outcome category Outcome Study	Talazoparib + enzalutamide		Placebo + enzalutamide		Talazoparib + enzalutamide vs. placebo + enzalutamide
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Role functioning					
Cohort 1 (without HRR mutation)	311	5.5 [3.7; 6.5] 218 (70.1)	314	7.4 [5.6; 9.2] 181 (57.6)	1.32 [1.08; 1.60]; 0.006
Cohort 2 (with HRR mutation)	197	7.4 [4.8; 10.2] 114 (57.9)	197	6.5 [4.5; 9.2] 111 (56.3)	0.88 [0.68; 1.15]; 0.351
Total[b]					1.14 [0.98; 1.34]; 0.100
Emotional functioning					
Cohort 1 (without HRR mutation)	311	17.5 [9.2; 28.6] 143 (46.0)	314	23.1 [17.5; 31.5] 132 (42.0)	1.12 [0.88; 1.42]; 0.360
Cohort 2 (with HRR mutation)	197	13.6 [8.2; 21.1] 86 (43.7)	197	9.3 [8.2; 15.6] 90 (45.7)	0.82 [0.61; 1.10]; 0.187
Total[b]					0.99 [0.82; 1.19]; 0.912
Cognitive functioning					
Cohort 1 (without HRR mutation)	311	4.6 [2.8; 6.5] 208 (66.9)	314	4.6 [3.7; 6.4] 195 (62.1)	1.06 [0.87; 1.29]; 0.551
Cohort 2 (with HRR mutation)	197	5.7 [3.7; 9.2] 113 (57.4)	197	4.6 [2.8; 6.5] 113 (57.4)	0.85 [0.66; 1.11]; 0.232
Total[b]					0.98 [0.84; 1.14]; 0.781
Social functioning					
Cohort 1 (without HRR mutation)	311	4.6 [3.7; 6.5] 199 (64.0)	314	8.9 [6.4; 11.7] 180 (57.3)	1.18 [0.96; 1.44]; 0.107
Cohort 2 (with HRR mutation)	197	6.5 [4.7; 10.6] 110 (55.8)	197	7.4 [5.5; 12.0] 100 (50.8)	1.01 [0.77; 1.33]; 0.912
Total[b]					1.12 [0.95; 1.31]; 0.184
EORTC QLQ-PR25 – time to first deterioration[h]					
Sexual activity					
Cohort 1 (without HRR mutation)	311	NA [26.7; NC] 103 (33.1)	314	NA 89 (28.3)	1.19 [0.89; 1.58]; 0.237
Cohort 2 (with HRR mutation)	197	NA 52 (26.4)	197	NA 43 (21.8)	1.07 [0.71; 1.60]; 0.751
Total[b]					1.15 [0.91; 1.45]; 0.247

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Outcome category Outcome Study	Talazoparib + enzalutamide		Placebo + enzalutamide		Talazoparib + enzalutamide vs. placebo + enzalutamide
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Sexual functioning					
Cohort 1 (without HRR mutation)				No suitable data[f]	
Cohort 2 (with HRR mutation)				No suitable data[f]	
Side effects					
AEs (supplementary information)[i]					
Cohort 1 (without HRR mutation)	314	0.6 [0.5; 0.9] 310 (98.7)	317	1.0 [0.8; 1.2] 301 (95.0)	–
Cohort 2 (with HRR mutation)	198	0.5 [0.5; 0.7] 196 (99.0)	199	0.6 [0.5; 0.8] 194 (97.5)	–
SAEs[i]					
Cohort 1 (without HRR mutation)	314	35.3 [25.0; NC] 133 (42.4)	317	40.5 [40.5; 46.5] 90 (28.4)	1.51 [1.15; 1.97]; 0.002
Cohort 2 (with HRR mutation)	198	44.4 [33.9; 44.4] 67 (33.8)	199	NA [32.7; NC] 42 (21.1)	1.39 [0.94; 2.04]; 0.098
Total[b]					1.47 [1.18; 1.83]; < 0.001
Severe AEs[i, j]					
Cohort 1 (without HRR mutation)	314	3.7 [3.3; 4.6] 249 (79.3)	317	21.4 [17.6; 29.0] 145 (45.7)	2.40 [1.95; 2.94]; < 0.001
Cohort 2 (with HRR mutation)	198	4.7 [4.1; 6.6] 137 (69.2)	199	23.7 [17.6; NC] 81 (40.7)	2.00 [1.52; 2.64]; < 0.001
Total[b]					2.25 [1.91; 2.65]; < 0.001
Discontinuation due to AEs[i, k]					
Cohort 1 (without HRR mutation)	314	NA 70 (22.3)	317	NA 38 (12.0)	1.78 [1.20; 2.64]; 0.004
Cohort 2 (with HRR mutation)	198	44.4 [NC] 23 (11.6)	199	NA 16 (8.0)	1.12 [0.58; 2.13]; 0.740
Total[b]					1.57 [1.12; 2.20]; 0.009

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Outcome category Outcome Study	Talazoparib + enzalutamide		Placebo + enzalutamide		Talazoparib + enzalutamide vs. placebo + enzalutamide
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
MDS (PT, AEs)					
Cohort 1 (without HRR mutation)				No suitable data[l]	
Cohort 2 (with HRR mutation)				No suitable data[l]	
AML (PT, AEs)					
Cohort 1 (without HRR mutation)				No suitable data[l]	
Cohort 2 (with HRR mutation)				No suitable data[l]	
Dizziness (PT, AEs)					
Cohort 1 (without HRR mutation)	314	NA 44 (14.0)	317	NA 15 (4.7)	2.85 [1.59; 5.13]; < 0.001
Cohort 2 (with HRR mutation)	198	NA 20 (10.1)	199	NA 16 (8.0)	1.16 [0.60; 2.24]; 0.657
Total[b]					1.92 [1.24; 2.97]; 0.004
Infections and infestations (SOC, SAEs)					
Cohort 1 (without HRR mutation)	314	NA 25 (8.0)	317	NA 10 (3.2)	2.26 [1.09; 4.71]; 0.025
Cohort 2 (with HRR mutation)	198	NA 13 (6.6)	199	NA 8 (4.0)	1.30 [0.54; 3.14]; 0.565
Total[b]					1.80 [1.03; 3.16]; 0.040
Anaemia (PT, severe AEs[j])					
Cohort 1 (without HRR mutation)	314	19.3 [9.2; 38.2] 157 (50.0)	317	NA 12 (3.8)	16.76 (9.31; 30.15); < 0.001
Cohort 2 (with HRR mutation)	198	36.0 [20.3; NC] 83 (41.9)	199	NA 9 (4.5)	10.27 (5.16; 20.44); < 0.001
Total[b]					13.63 [8.72; 21.31]; < 0.001

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Outcome category Outcome Study	Talazoparib + enzalutamide		Placebo + enzalutamide		Talazoparib + enzalutamide vs. placebo + enzalutamide
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Investigations (SOC, severe AEs[j])					
Cohort 1 (without HRR mutation)	314	NA 97 (30.9)	317	NA 22 (6.9)	4.79 (3.01; 7.60); < 0.001
Cohort 2 (with HRR mutation)	198	NA [35.9; NC] 55 (27.8)	199	NA 17 (8.5)	3.22 [1.87; 5.56]; < 0.001
Total[b]					4.05 [2.85; 5.77]; < 0.001

a. Cox proportional hazards model; for Cohort 1 (without HRR mutation) unadjusted, for Cohort 2 (with HRR mutation) adjusted by stratification factor of previous treatment with taxanes or treatment with novel hormonal agents (yes vs. no).
b. Institute's calculation by means of a meta-analysis using a fixed effect.
c. A score increase by ≥ 2 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 10).
d. A score increase by ≥ 15% of the scale range from baseline is deemed a clinically relevant deterioration (scale range of 0 to 10).
e. A score increase by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).
f. For about 50% and 91% of patients, respectively, no recording regarding incontinence aid or sexual functioning was available at baseline. This proportion of patients at least was not included in the analysis. The approach of the company does not ensure that the burden of patients who develop incontinence or impairment of their sexual functioning in the course of the treatment is recorded.
g. A decrease by ≥ 15% of the scale range from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).
h. A score decrease by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100).
i. Without disease-related events (the PTs disease progression, prostatic specific antigen increased, prostate cancer, and tumour pain were disregarded; overall, only very few events occurred in the disregarded PTs [up to a maximum of 1%]).
j. Operationalized as CTCAE grade ≥ 3.
k. Discontinuation of at least one therapy component (talazoparib/placebo and/or enzalutamide).
l. See Section I 3.2.1 of the present dossier assessment for the reasoning.

AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; HRR: homologous recombination repair; MDS: myelodysplastic syndrome; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

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

Mortality

Overall survival

For the outcome of overall survival, the meta-analysis did not show any statistically significant differences between treatment groups. The results showed a statistically significant advantage for patients with HRR mutation, but there is no statistically significant interaction test. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Morbidity

Symptomatic bone fracture and spinal cord compression

The meta-analysis did not show any statistically significant differences between treatment groups for the outcomes of symptomatic bone fracture or spinal cord compression. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Worst pain (BPI-SF Item 3)

The meta-analysis did not show a statistically significant difference between treatment groups for the outcome of worst pain (BPI-SF Item 3). There is an effect modification for the subgroup characteristic of HRR mutation status for this outcome, however (see Section I 3.2.4). There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide for patients without HRR mutation; an added benefit for this patient group is therefore not proven. For patients with HRR mutation, there is a hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide.

Pain interference (BPI-SF Item 9a-g)

The meta-analysis did not show a statistically significant difference between treatment groups for the outcome of pain interference (BPI-SF Item 9a-g). There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Symptoms

EORTC QLQ-C30

Fatigue, dyspnoea, and appetite loss

For the outcomes of fatigue, dyspnoea, and appetite loss, the meta-analysis showed a statistically significant difference to the disadvantage of talazoparib. However, the difference is no more than marginal for these outcomes of the non-serious/non-severe symptoms/late

complications category (see Section I 3.3.2). In each case, there is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Nausea and vomiting

For the outcome of nausea and vomiting, the meta-analysis showed a statistically significant difference to the disadvantage of talazoparib. There is a hint of lesser benefit of talazoparib + enzalutamide in comparison with enzalutamide.

Pain

For the outcome of pain, the meta-analysis did not show any statistically significant differences between treatment groups. There is an effect modification for the subgroup characteristic of HRR mutation status for this outcome, however (see Section I 3.2.4). There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide for patients without HRR mutation; an added benefit for this patient group is therefore not proven. For patients with HRR mutation, there is a hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide.

Insomnia, constipation, and diarrhoea

The meta-analysis did not show any statistically significant differences between treatment groups for any of the outcomes of insomnia, constipation, and diarrhoea. In each case, there is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

EORTC QLQ-PR25

Urinary symptoms

The meta-analysis did not show a statistically significant difference between treatment groups for the outcome of urinary symptoms. There is an effect modification for the subgroup characteristic of HRR mutation status for this outcome, however (see Section I 3.2.4). There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide for patients without HRR mutation; an added benefit for this patient group is therefore not proven. For patients with HRR mutation, there is a hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide.

Bowel symptoms and hormonal treatment-related symptoms

For the outcomes of bowel symptoms and hormonal treatment-related symptoms, the meta-analysis did not show a statistically significant difference between treatment groups. In each case, there is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Incontinence aid

No suitable data for the outcome of incontinence aid are available because the company's approach did not ensure that the burden of patients who only developed incontinence in the course of the treatment was also recorded. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

For the outcome of health status, the meta-analysis did not show a statistically significant difference between treatment groups. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Global health status

For the outcome of global health status, the meta-analysis showed a statistically significant difference to the disadvantage of talazoparib. There is an effect modification for the subgroup characteristic of HRR mutation status for this outcome, however (see Section I 3.2.4). There is a hint of lesser benefit of talazoparib + enzalutamide in comparison with enzalutamide for patients without HRR mutation. For patients with HRR mutation, there is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit for this patient group is therefore not proven.

Physical functioning

The meta-analysis showed no statistically significant difference between treatment groups for the outcome of physical functioning. There is an effect modification for the subgroup characteristic of HRR mutation status for this outcome, however (see Section I 3.2.4). There is a hint of lesser benefit of talazoparib + enzalutamide in comparison with enzalutamide for patients without HRR mutation. For patients with HRR mutation, there is a hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide.

Role functioning

For the outcome of role functioning, the meta-analysis did not show a statistically significant difference between treatment groups. There is an effect modification for the subgroup characteristic of HRR mutation status for this outcome, however (see Section I 3.2.4). There is a hint of lesser benefit of talazoparib + enzalutamide in comparison with enzalutamide for patients without HRR mutation. For patients with HRR mutation, there is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit for this patient group is therefore not proven.

Emotional functioning, cognitive functioning, and social functioning

The meta-analysis did not show any statistically significant differences between treatment groups for any of the outcomes of emotional functioning, cognitive functioning, and social functioning. In each case, there is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

EORTC QLQ-PR25

Sexual activity

For the outcome of sexual activity, the meta-analysis did not show a statistically significant difference between treatment groups. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Sexual functioning

No suitable data for the outcome of sexual functioning are available because the company's approach did not ensure that the burden of patients who only became sexually active in the course of the treatment was also recorded. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs, and discontinuation due to AEs

The meta-analysis showed a statistically significant difference to the disadvantage of talazoparib + enzalutamide for each of the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs. In each case, there is a hint of greater harm from talazoparib + enzalutamide in comparison with enzalutamide.

Specific AEs

MDS and AML (each AEs)

No suitable data are available for the outcomes of MDS and AML (each AEs) (see Section I 3.2.1 for reasoning). In each case, there is no hint of greater or lesser harm from talazoparib + enzalutamide in comparison with enzalutamide; greater or lesser harm is therefore not proven.

Dizziness (AEs)

For the outcome of dizziness (AEs), the meta-analysis showed a statistically significant difference to the disadvantage of talazoparib. There is an effect modification for the subgroup characteristic of HRR mutation status for this outcome, however (see Section I 3.2.4). There is a hint of greater harm of talazoparib + enzalutamide in comparison with enzalutamide for patients without HRR mutation. For patients with HRR mutation, there is no hint of greater or

lesser harm of talazoparib + enzalutamide in comparison with enzalutamide; greater or lesser harm for this patient group is therefore not proven.

Infections and infestations (SAEs), anaemia (severe AEs), and investigations (severe AEs)

The meta-analysis showed a statistically significant difference to the disadvantage of talazoparib + enzalutamide for each of the outcomes of infections and infestations (SAEs), anaemia (severe AEs), and investigations (severe AEs). In each case, there is a hint of greater harm from talazoparib + enzalutamide in comparison with enzalutamide.

I 3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are taken into account in the present benefit assessment:

- HRR mutation status (without HRR mutation/with HRR mutation)

According to the EPAR, mutations in an HRR gene or a breast cancer susceptibility gene (BRCA) are known to be strong effect modifiers for overall survival when using PARP inhibitors [19]. Subgroup analyses according to HRR mutation status are carried out via the meta-analysis conducted by the Institute for the total population relevant to the assessment; differentiated subgroup analyses for specific HRR mutations (e.g. BRCA1/2) are not possible, however. Subgroup analyses for the characteristics of age and disease severity are also not possible on the basis of the available data for the total population of the TALAPRO-2 study relevant for the assessment.

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

The results are presented in Table 15. The Kaplan-Meier curves on the subgroup results are presented in I Appendix B of the full dossier assessment. Forest plots of the calculations conducted by the Institute can be found in I Appendix C of the full dossier assessment.

Table 15: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Study Outcome Characteristic Subgroup	Talazoparib + enzalutamide N	Talazoparib + enzalutamide Median time to event in months [95% CI] Patients with event n (%)	Placebo + enzalutamide N	Placebo + enzalutamide Median time to event in months [95% CI] Patients with event n (%)	Talazoparib + enzalutamide vs. placebo + enzalutamide HR [95% CI][a]	 p-value[a]
TALAPRO-2						
Morbidity						
Worst pain (BPI-SF Question 3 – time to first deterioration[b])						
HRR mutation status						
Without HRR mutation (Cohort 1)	311	NA 99 (31.8)	314	NA 83 (26.4)	1.18 [0.88; 1.59]	0.255
With HRR mutation (Cohort 2)	197	NA 43 (21.8)	197	NA [19.4; NC] 61 (31.0)	0.57 [0.38; 0.84]	0.004
Total					Interaction[c]:	0.004
Symptoms (EORTC QLQ-C30 – time to first deterioration[d])						
Pain						
HRR mutation status						
Without HRR mutation (Cohort 1)	311	7.4 [4.7; 9.2] 186 (59.8)	314	9.3 [7.4; 11.7] 179 (57.0)	1.09 [0.89; 1.34]	0.397
With HRR mutation (Cohort 2)	197	9.3 [6.5; 15.6] 108 (54.8)	197	5.6 [3.7; 6.6] 121 (61.4)	0.64 [0.49; 0.83]	< 0.001
Total					Interaction[c]:	0.002
Symptoms (EORTC QLQ-PR25 – time to first deterioration[d])						
Urinary symptoms						
HRR mutation status						
Without HRR mutation (Cohort 1)	311	24.9 [13.9; 32.3] 136 (43.7)	314	32.2 [19.3; NC] 119 (37.9)	1.10 [0.86; 1.40]	0.455
With HRR mutation (Cohort 2)	197	32.3 [23.0; NC] 62 (31.5)	197	15.6 [9.5; 21.7] 76 (38.6)	0.58 [0.41; 0.82]	0.002
Total					Interaction[c]:	0.003

Table 15: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Study Outcome Characteristic Subgroup	Talazoparib + enzalutamide N	Median time to event in months [95% CI] Patients with event n (%)	Placebo + enzalutamide N	Median time to event in months [95% CI] Patients with event n (%)	Talazoparib + enzalutamide vs. placebo + enzalutamide HR [95% CI][a]	p-value[a]
Health-related quality of life (EORTC QLQ-C30 – time to first deterioration[e])						
Global health status						
HRR mutation status						
Without HRR mutation (Cohort 1)	311	3.7 [2.9; 4.7] 213 (68.5)	314	7.6 [6.4; 9.4] 189 (60.2)	1.32 [1.09; 1.61]	0.005
With HRR mutation (Cohort 2)	197	6.4 [4.6; 8.4] 116 (58.9)	197	6.5 [3.7; 8.3] 111 (56.3)	0.94 [0.72; 1.22]	0.649
Total					Interaction[c]:	0.042
Physical functioning						
HRR mutation status						
Without HRR mutation (Cohort 1)	311	5.6 [3.7; 7.4] 211 (67.8)	314	8.3 [6.5; 13.7] 184 (58.6)	1.30 [1.07; 1.59]	0.009
With HRR mutation (Cohort 2)	197	8.3 [5.6; 10.3] 108 (54.8)	197	5.6 [4.5; 7.5] 117 (59.4)	0.76 [0.59; 0.99]	0.043
Total					Interaction[c]:	0.001
Role functioning						
HRR mutation status						
Without HRR mutation (Cohort 1)	311	5.5 [3.7; 6.5] 218 (70.1)	314	7.4 [5.6; 9.2] 181 (57.6)	1.32 [1.08; 1.60]	0.006
With HRR mutation (Cohort 2)	197	7.4 [4.8; 10.2] 114 (57.9)	197	6.5 [4.5; 9.2] 111 (56.3)	0.88 [0.68; 1.15]	0.351
Total					Interaction[c]:	0.015
Side effects						
Dizziness (PT, AEs)						
HRR mutation status						
Without HRR mutation (Cohort 1)	314	NA 44 (14.0)	317	NA 15 (4.7)	2.85 [1.59; 5.13]	< 0.001
With HRR mutation (Cohort 2)	198	NA 20 (10.1)	199	NA 16 (8.0)	1.16 [0.60; 2.24]	0.657
Total					Interaction[c]:	0.046

Table 15: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: talazoparib + enzalutamide vs. placebo + enzalutamide (multipage table)

Study Outcome Characteristic Subgroup	Talazoparib + enzalutamide N	Talazoparib + enzalutamide Median time to event in months [95% CI] Patients with event n (%)	Placebo + enzalutamide N	Placebo + enzalutamide Median time to event in months [95% CI] Patients with event n (%)	Talazoparib + enzalutamide vs. placebo + enzalutamide HR [95% CI][a]	 p-value[a]
a. Cox proportional hazards model; for Cohort 1 (without HRR mutation) unadjusted, for Cohort 2 (with HRR mutation) adjusted by stratification factor of previous treatment with taxanes or treatment with novel hormonal agents (yes vs. no). b. A score increase by ≥ 2 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 10). c. Institute's calculation by means of the Q test from a meta-analysis using a fixed effect. d. A score increase by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100). e. A score decrease by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100). AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; HRR: homologous recombination repair; MDS: myelodysplastic syndrome; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; RCT: randomized controlled trial						

Morbidity

Worst pain (BPI-SF Item 3)

There is an effect modification for the characteristic of HRR mutation status for the outcome of worst pain (BPI-SF Item 3).

No statistically significant difference between treatment groups was shown for patients without HRR mutation. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide for this patient group; an added benefit is therefore not proven.

A statistically significant difference in favour of talazoparib + enzalutamide was shown for patients with HRR mutation. There is a hint of added benefit of talazoparib + enzalutamide in comparison with enzalutamide for this patient group.

Symptoms

Pain (EORTC QLQ-C30) and urinary symptoms (EORTC QLQ-PR25)

For each of the outcomes of pain (EORTC QLQ-C30) and urinary symptoms (EORTC QLQ-PR25), there is an effect modification for the characteristic of HRR mutation status.

In each case, no statistically significant difference between treatment groups was shown for patients without HRR mutation. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide for this patient group; an added benefit is therefore not proven.

In each case, a statistically significant difference in favour of talazoparib + enzalutamide was shown for patients with HRR mutation. There is a hint of added benefit of talazoparib + enzalutamide in comparison with enzalutamide for this patient group.

Health-related quality of life

EORTC QLQ-C30

Global health status and role functioning

For each of the outcomes of global health status and role functioning, there is an effect modification for the characteristic of HRR mutation status.

In each case, a statistically significant difference to the disadvantage of talazoparib + enzalutamide was shown for patients without HRR mutation. There is a hint of lesser benefit of talazoparib + enzalutamide in comparison with enzalutamide for this patient group.

In each case, no statistically significant difference between treatment groups was shown for patients with HRR mutation. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide for this patient group; an added benefit is therefore not proven.

Physical functioning

There is an effect modification for the characteristic of HRR mutation status for the outcome of physical functioning.

A statistically significant difference to the disadvantage of talazoparib + enzalutamide was shown for patients without HRR mutation. There is a hint of lesser benefit of talazoparib + enzalutamide in comparison with enzalutamide for this patient group.

A statistically significant difference in favour of talazoparib + enzalutamide was shown for patients with HRR mutation. There is a hint of added benefit of talazoparib + enzalutamide in comparison with enzalutamide for this patient group.

Side effects

Dizziness (AEs)

There is an effect modification for the characteristic of HRR mutation status for the outcome of dizziness (AEs).

A statistically significant difference to the disadvantage of talazoparib + enzalutamide was shown for patients without HRR mutation. There is a hint of greater harm of talazoparib + enzalutamide in comparison with enzalutamide for this patient group.

No statistically significant difference between treatment groups was shown for patients with HRR mutation. There is no hint of greater or lesser harm from talazoparib + enzalutamide in comparison with enzalutamide for this patient group; greater or lesser harm is therefore not proven.

I 3.3 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 3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 3.2 (see Table 16).

Determination of the outcome category for outcomes on morbidity and side effects

The dossier does not provide any details as to whether the outcomes regarding morbidity and side effects were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Worst pain (BPI-SF Item 3)

At baseline (according to the inclusion criteria), the score for worst pain (BPI-SF Item 3) was 0 to 1 in about 65%, and 2 to 3 in about 34% of patients in Cohort 1 (see Table 9), which corresponds to no pain or mild pain. The company did not present any information on patients' scores after pain progression. However, the mean values of the patients in Cohort 1 were ≤ 3 also during the course of the study. Therefore, the outcome of worst pain (BPI-SF Item 3) was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Symptoms

Fatigue (EORTC QLQ-C30), nausea and vomiting (EORTC QLQ-C30), pain (EORTC QLQ-C30), dyspnoea (EORTC QLQ-C30), appetite loss (EORTC QLQ-C30), and urinary symptoms (EORTC QLQ-PR25)

For the outcomes of fatigue (EORTC QLQ-C30), nausea and vomiting (EORTC QLQ-C30), pain (EORTC QLQ-C30), dyspnoea (EORTC QLQ-C30), appetite loss (EORTC QLQ-C30), and urinary symptoms (EORTC QLQ-PR25), the available severity data are insufficient for a classification as serious/severe. These outcomes are therefore each assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Discontinuations due to AEs

For the outcome of discontinuation due to AEs, the available severity data are insufficient for a classification as serious/severe. This outcome is therefore assigned to the outcome category of non-serious/non-severe side effects.

Table 16: Extent of added benefit at outcome level: talazoparib + enzalutamide vs. enzalutamide (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Talazoparib + enzalutamide vs. placebo + enzalutamide** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA–41.9 vs. 30.8–38.7[c] HR: 0.84 [0.69; 1.02]; p = 0.076	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptomatic bone fracture	NA vs. NA HR: 1.32 [0.86; 2.04]; p = 0.207	Lesser/added benefit not proven
Spinal cord compression	NA vs. NA HR: 0.88 [0.53; 1.46]; p = 0.621	Lesser/added benefit not proven
Worst pain (BPI-SF Item 3, time to first deterioration) HRR mutation status Without HRR mutation	NA vs. NA HR: 1.18 [0.88; 1.59]; p = 0.255	Lesser/added benefit not proven
With HRR mutation	NA vs. NA HR: 0.57 [0.38; 0.84]; p = 0.004 Probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: “minor”
Pain interference (BPI-SF Item 9a-g, time to first deterioration)	NA–21.2 vs. 15.7–26.7[c] HR: 0.93 [0.78; 1.12]; p = 0.459	Lesser/added benefit not proven
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue	1.9–2.8 vs. 3.7[c] HR: 1.20 [1.03; 1.39]; HR: 0.83 [0.72; 0.97][d]; p = 0.016	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1$ Lesser/added benefit not proven[e]
Nausea and vomiting	9.2–10.6 vs. 13.8–34.0[c] HR: 1.36 [1.13; 1.64]; HR: 0.74 [0.61; 0.88][d]; p = 0.001 Probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Lesser benefit, extent: “minor”

Table 16: Extent of added benefit at outcome level: talazoparib + enzalutamide vs. enzalutamide (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Talazoparib + enzalutamide vs. placebo + enzalutamide** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Pain HRR mutation status Without HRR mutation	7.4 vs. 9.3 HR: 1.09 [0.89; 1.34]; p = 0.397	Lesser/added benefit not proven
With HRR mutation	9.3 vs. 5.6 HR: 0.64 [0.49; 0.83]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: "minor"
Dyspnoea	6.4–8.3 vs. 9.2–16.4[c] HR: 1.27 [1.07; 1.50] HR: 0.79 [0.67; 0.93][d]; p = 0.007	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1$ Lesser/added benefit not proven[e]
Insomnia	11.1–16.6 vs. 9.1–10.2[c] HR: 0.88 [0.73; 1.05]; p = 0.145	Lesser/added benefit not proven
Appetite loss	5.6–7.4 vs. 11.1–15.7[c] HR: 1.30 [1.10; 1.54]; HR: 0.77 [0.65; 0.91][d]; p = 0.002	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1$ Lesser/added benefit not proven[e]
Constipation	11.0–15.7 vs. 11.1–18.5[c] HR: 1.07 [0.89; 1.28]; p = 0.488	Lesser/added benefit not proven
Diarrhoea	19.3–34.1 vs. 26.1[c] HR: 1.02 [0.83; 1.26]; p = 0.830	Lesser/added benefit not proven

Table 16: Extent of added benefit at outcome level: talazoparib + enzalutamide vs. enzalutamide (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Talazoparib + enzalutamide vs. placebo + enzalutamide** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Symptoms (EORTC QLQ-PR25 – time to first deterioration)		
Urinary symptoms HRR mutation status Without HRR mutation	24.9 vs. 32.2 HR: 1.10 [0.86; 1.40]; p = 0.455	Lesser/added benefit not proven
With HRR mutation	32.3 vs. 15.6 HR: 0.58 [0.41; 0.82]; p = 0.002 Probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: “minor”
Bowel symptoms	NA vs. NA HR: 1.00 [0.79; 1.26]; p = 0.971	Lesser/added benefit not proven
Hormonal treatment-related symptoms	9.3 vs. 7.4–12.5[c] HR: 1.02 [0.85; 1.21]; p = 0.845	Lesser/added benefit not proven
Incontinence aid	No suitable data	Lesser/added benefit not proven
Health status (EQ-5D VAS – time to first deterioration)	12.0–16.1 vs. 9.2–15.7[c] HR: 0.93 [0.78; 1.11]; p = 0.416	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – time to first deterioration		
Global health status HRR mutation status Without HRR mutation	3.7 vs. 7.6 HR: 1.32 [1.09; 1.61] HR: 0.76 [0.62; 0.92][d]; p = 0.005 Probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Lesser benefit, extent: “minor”
With HRR mutation	6.4 vs. 6.5 HR: 0.94 [0.72; 1.22]; p = 0.649	Lesser/added benefit not proven

Table 16: Extent of added benefit at outcome level: talazoparib + enzalutamide vs. enzalutamide (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Talazoparib + enzalutamide vs. placebo + enzalutamide** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Physical functioning HRR mutation status Without HRR mutation	5.6 vs. 8.3 HR: 1.30 [1.07; 1.59] HR: 0.77 [0.63; 0.93][d]; p = 0.009 Probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Lesser benefit, extent: "minor"
With HRR mutation	8.3 vs. 5.6 HR: 0.76 [0.59; 0.99]; p = 0.043 Probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"
Role functioning HRR mutation status Without HRR mutation	5.5 vs. 7.4 HR: 1.32 [1.08; 1.60] HR: 0.76 [0.63; 0.93][d]; p = 0.006 Probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Lesser benefit, extent: "minor"
With HRR mutation	7.4 vs. 6.5 HR: 0.88 [0.68; 1.15]; p = 0.351	Lesser/added benefit not proven
Emotional functioning	13.6–17.5 vs. 9.3–23.1[c] HR: 0.99 [0.82; 1.19]; p = 0.912	Lesser/added benefit not proven
Cognitive functioning	4.6–5.7 vs. 4.6[c] HR: 0.98 [0.84; 1.14]; p = 0.781	Lesser/added benefit not proven
Social functioning	4.6–6.5 vs. 7.4–8.9[c] HR: 1.12 [0.95; 1.31]; p = 0.184	Lesser/added benefit not proven
EORTC QLQ-PR25 – time to first deterioration		
Sexual activity	NA vs. NA HR: 1.15 [0.91; 1.45]; p = 0.247	Lesser/added benefit not proven
Sexual functioning	No suitable data	Lesser/added benefit not proven

Table 16: Extent of added benefit at outcome level: talazoparib + enzalutamide vs. enzalutamide (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Talazoparib + enzalutamide vs. placebo + enzalutamide** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	35.3–44.4 vs. NA –40.5[c] HR: 1.47 [1.18; 1.83] HR: 0.68 [0.55; 0.85][d]; p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: "considerable"
Severe AEs	3.7–4.7 vs. 21.4–23.7[c] HR: 2.25 [1.91; 2.65] HR: 0.44 [0.38; 0.52][d]; p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
Discontinuation due to AEs	NA–44.4 vs. NA[c] HR: 1.57 [1.12; 2.20] HR: 0.64 [0.45; 0.89][d]; p = 0.009 Probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ Greater harm, extent: "minor"
MDS (AEs)	No suitable data	Greater/lesser harm not proven
AML (AEs)	No suitable data	Greater/lesser harm not proven
Dizziness (AEs) HRR mutation status Without HRR mutation	NA vs. NA HR: 2.85 [1.59; 5.13]; HR: 0.35 [0.19; 0.63][d]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
With HRR mutation	NA vs. NA HR: 1.16 [0.60; 2.24]; p = 0.657	Greater/lesser harm not proven
Infections and infestations (SAEs)	NA vs. NA HR: 1.80 [1.03; 3.16]; HR: 0.56 [0.32; 0.97][d]; p = 0.040 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: "minor"

Table 16: Extent of added benefit at outcome level: talazoparib + enzalutamide vs. enzalutamide (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Talazoparib + enzalutamide vs. placebo + enzalutamide** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Anaemia (severe AEs)	19.3–36.0 vs. NA[c] HR: 13.63 [8.72; 21.31]; HR: 0.07 [0.05; 0.11][d]; p < 0.001 Probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Greater harm, extent: “major”
Investigations (severe AEs)	NA vs. NA HR: 4.05 [2.85; 5.77]; HR: 0.25 [0.17; 0.35][d]; p < 0.001 Probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Greater harm, extent: “major”

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Minimum and maximum median time to event per treatment arm in the included cohorts.
d. Institute’s calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; HRR: homologous recombination repair; MDS: myelodysplastic syndrome; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; SAE: serious adverse event; VAS: visual analogue scale

I 3.3.2 Overall conclusion on added benefit

Overall, both positive and negative effects of talazoparib + enzalutamide were shown in comparison with the ACT, but only for the shortened observation period.

The characteristic of HRR mutation status is an effect modifier for various outcomes. Due to these effect modifications, the results on the added benefit of talazoparib + enzalutamide compared with the ACT are derived separately by HRR mutation status.

Patients without HRR mutation

Table 17 summarizes the results taken into account to derive an overall conclusion on the extent of added benefit for patients without HRR mutation.

Table 17: Positive and negative effects from the assessment of talazoparib + enzalutamide in comparison with enzalutamide for patients without HRR mutation

Positive effects	Negative effects
Outcomes with shortened observation period	
–	Morbidity Non-serious/non-severe symptoms/late complications ▪ Symptoms (EORTC QLQ-C30) – nausea and vomiting: hint of lesser benefit – extent: “minor”
–	Health-related quality of life ▪ EORTC QLQ-C30 – global health status: hint of lesser benefit – extent: “minor” ▪ EORTC QLQ-C30 – physical functioning: hint of lesser benefit – extent: “minor” ▪ EORTC QLQ-C30 – role functioning: hint of lesser benefit – extent: “minor”
–	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: “considerable” ▪ Severe AEs: hint of greater harm – extent: “major” ▪ Infections and infestations (SAEs): hint of greater harm – extent: “minor” ▪ Anaemia (severe AEs): hint of greater harm – extent “major” ▪ Investigations (severe AEs): hint of greater harm – extent: “major”
–	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: hint of greater harm – extent: “minor” ▪ Dizziness (AEs): hint of greater harm – extent: “considerable”
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; HRR: homologous recombination repair; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event	

For patients without HRR mutation, there were only negative effects in the categories of morbidity, health-related quality of life, and side effects (here in different severity categories), ranging from minor to major extent. Overall, there is a hint of lesser benefit for patients without HRR mutation.

Patients with HRR mutation

Table 18 summarizes the results taken into account to derive an overall conclusion on the extent of added benefit for patients with HRR mutation.

Table 18: Positive and negative effects from the assessment of talazoparib + enzalutamide in comparison with enzalutamide for patients with HRR mutation

Positive effects	**Negative effects**
Outcomes with shortened observation period	
Morbidity Non-serious/non-severe symptoms/late complications ▪ Worst pain (BPI-SF Item 3): hint of an added benefit – extent: “minor” ▪ Symptoms (EORTC QLQ-C30) – pain: hint of an added benefit – extent: “minor” ▪ Symptoms (EORTC QLQ-PR25) – urinary symptoms: hint of an added benefit – extent: “minor”	Morbidity Non-serious/non-severe symptoms/late complications ▪ Symptoms (EORTC QLQ-C30) – nausea and vomiting: hint of lesser benefit – extent: “minor”
Health-related quality of life ▪ EORTC QLQ-C30 – physical functioning: hint of an added benefit – extent: “minor”	–
–	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: “considerable” ▪ Severe AEs: hint of greater harm – extent: “major” ▪ Infections and infestations (SAEs): hint of greater harm – extent: “minor” ▪ Anaemia (severe AEs): hint of greater harm – extent “major” ▪ Investigations (severe AEs): hint of greater harm – extent: “major”
–	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: hint of greater harm – extent: “minor”
AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; EORTC: European Organisation for Research and Treatment of Cancer; HRR: homologous recombination repair; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; SAE: serious adverse event	

For patients with HRR mutation, there is a hint of minor added benefit for the morbidity outcomes on pain (worst pain [BPI-SF Item 3] and pain [EORTC QLQ-C30]), as well as for urinary symptoms (EORTC QLQ-PR25). In the health-related quality of life category, there is also a hint of minor added benefit for the outcome of physical functioning (EORTC QLQ-C30). It should be noted that the results showed a statistically significant advantage for the outcome of overall survival for patients with HRR mutation, but there is no statistically significant interaction test.

On the other hand, there are several negative effects in the categories of morbidity and side effects (here in different severity categories), ranging from minor to major extent. These

negative effects completely call into question the positive effects for patients with HRR mutation. Overall, an added benefit is therefore not proven for patients with HRR mutation.

Summary

In summary, there is a hint of lesser benefit of talazoparib + enzalutamide compared with enzalutamide for patients without HRR mutation with treatment-naive mCRPC in whom chemotherapy is not clinically indicated. For patients with HRR mutation, there is no hint of an added benefit of talazoparib + enzalutamide in comparison with enzalutamide; an added benefit for this patient group is therefore not proven.

The assessment described above differs from that of the company, which, based on the TALAPRO-2 study, derived an indication of a minor added benefit of talazoparib + enzalutamide compared with enzalutamide for research question 1 for patients with and without HRR mutation (entire Cohort 1) as well as for patients without HRR mutation from Cohort 1, and an indication of considerable added benefit for patients with HRR mutation (Cohort 2).

I 4 Research question 2: adults with pretreated mCRPC in whom chemotherapy is not clinically indicated

I 4.1 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 talazoparib (status: 15 January 2024)
- bibliographical literature search on talazoparib (last search on 15 January 2024)
- search in trial registries/trial results databases for studies on talazoparib (last search on 15 January 2024)
- search on the G-BA website for talazoparib (last search on 15 January 2024)

To check the completeness of the study pool:

- search in trial registries for studies on talazoparib (last search on 20 February 2024); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check identified no RCT for the direct comparison of talazoparib + enzalutamide versus the ACT.

I 4.2 Results on added benefit

In its dossier, the company presented no data for the assessment of the added benefit of talazoparib + enzalutamide compared with the ACT for patients with pretreated mCRPC in whom chemotherapy is not clinically indicated. There is no hint of an added benefit of talazoparib + enzalutamide in comparison with the ACT; an added benefit is therefore not proven for this research question.

I 4.3 Probability and extent of added benefit

In its dossier, the company presented no data for the assessment of the added benefit of talazoparib + enzalutamide compared with the ACT for patients with pretreated mCRPC in whom chemotherapy is not clinically indicated. An added benefit of talazoparib + enzalutamide versus the ACT is therefore not proven for research question 2.

This assessment is in accordance with that of the company, which derived no added benefit for research question 2.

I 5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of talazoparib + enzalutamide in comparison with the ACT is summarized in Table 19.

Table 19: Talazoparib + enzalutamide – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with treatment-naive mCRPC in whom chemotherapy is not clinically indicated[b, c, d]	▪ Abiraterone acetate in combination with prednisone or prednisolone (only for patients whose disease is progressive during or after docetaxel-containing chemotherapy; only for patients with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated) or ▪ **enzalutamide** (only for patients whose disease has progressed during or after docetaxel chemotherapy; only for patients with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated) or ▪ olaparib as monotherapy (only for patients with BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included an NHA) or ▪ olaparib in combination with abiraterone acetate and prednisone or prednisolone (only for patients with BRCA mutations and for patients without BRCA mutations with symptomatic disease)	▪ Patients without HRR mutation: hint of lesser benefit[e] ▪ Patients with HRR mutation: added benefit not proven
2	Adults with pretreated mCRPC in whom chemotherapy is not clinically indicated[b, f]	Individualized treatment[g] selected from ▪ abiraterone acetate in combination with prednisone or prednisolone (only for patients who have progressed on or after docetaxel-containing chemotherapy), ▪ enzalutamide (only for patients who have progressed on or after docetaxel chemotherapy), ▪ olaparib in combination with abiraterone acetate and prednisone or prednisolone, and ▪ olaparib as monotherapy (only for patients with BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included an NHA) taking into account pretreatment(s) and BRCA1/2 mutation status.	Added benefit not proven

Table 19: Talazoparib + enzalutamide – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**. b. For the present therapeutic indication, it is assumed according to the G-BA that an existing conventional ADT is continued. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or antagonists. In addition, adequate concomitant treatment of bone metastases during the study is assumed (e.g. use of bisphosphonates, denosumab, radiotherapy). c. The ACT specified here comprises several alternative treatment options according to the G-BA. However, the treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. The sole comparison with a therapy option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the overall population. d. When determining the ACT, it is assumed that the patients may have already received prior therapy with docetaxel or NHA in earlier stages of the disease. e. Only patients with ECOG PS of 0 or 1 and a BPI-SF Item 3 < 4 (mildly symptomatic or asymptomatic) were included in the TALAPRO-2 study. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or to patients who were symptomatic at baseline (BPI-SF Item 3 ≥ 4) (see also FN c on the G-BA's notes on the ACT). f. When determining the ACT, it is assumed that the patients, in addition to prior therapy of the mCRPC, may have already received prior therapy with docetaxel or NHA in earlier stages of the disease. g. For the implementation of individualized therapy in a study of direct comparison, according to the G-BA, investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multi-comparator study). A rationale must be provided for the choice and any limitation of treatment options. If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; BRCA: breast cancer susceptibility gene; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mCRPC: metastatic castration-resistant prostate cancer; NHA: novel hormonal agent			

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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