Niraparib/abiraterone acetate (prostate cancer)

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

EXTRACT

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

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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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Part I: Benefit assessment

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I List of tables[2]

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
AML	acute myeloid leukaemia
AR	androgen receptor
BPI-SF	Brief Pain Inventory-Short Form
BRCA	breast cancer susceptibility gene
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FACT-P	Functional Assessment of Cancer Therapy-Prostate
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
PT	Preferred Term
RCT	randomized controlled trial
rPFS	radiographic progression-free survival
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination niraparib/abiraterone acetate (in combination with prednisone or prednisolone). 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 14 November 2023.

Research question

The aim of this report is to assess the added benefit of niraparib/abiraterone acetate in combination with prednisone or prednisolone (hereinafter referred to as "niraparib/abiraterone acetate + P") compared with the appropriate comparator therapy (ACT) in adult patients with metastatic castration-resistant prostate cancer (mCRPC) and breast cancer susceptibility gene (BRCA) 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated.

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

Table 2: Research questions of the benefit assessment of niraparib/abiraterone acetate + P (multipage table)

Research question	Therapeutic indication	ACT[a]
1	Adults with treatment-naive mCRPC and BRCA 1/2 mutations (germline and/or somatic) 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 whose disease has progressed after previous treatment that included an NHA) or ▪ olaparib in combination with abiraterone acetate and prednisone or prednisolone
2	Adults with pretreated mCRPC and BRCA 1/2 mutations (germline and/or somatic) 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 whose disease has progressed on or after docetaxel-containing chemotherapy), ▪ enzalutamide (only for patients whose disease has progressed on or after docetaxel chemotherapy) ▪ olaparib as monotherapy (only for patients whose disease has progressed after previous treatment that included an NHA), taking into accounts any pretreatment(s)

Table 2: Research questions of the benefit assessment of niraparib/abiraterone acetate + P (multipage table)

Research question	Therapeutic indication	ACT[a]
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 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 required (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 (multicomparator study). 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: new hormonal agent; P: prednisone or prednisolone		

In research question 1, the ACT presented by the company in Module 4 A deviates from the ACT specified by the G-BA in some of the alternative treatment options mentioned. However, the company's choice of abiraterone acetate in combination with prednisone or prednisolone (hereafter referred to as "abiraterone acetate + P") has no consequences for the benefit assessment. For research question 2, the company followed the G-BA's ACT.

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 for the derivation of added benefit.

Research question 1: adults with treatment-naive mCRPC and BRCA 1/2 mutations in whom chemotherapy is not clinically indicated

Study pool and study design

The MAGNITUDE study was used for the benefit assessment in research question 1.

The MAGNITUDE study is a double-blind RCT comparing niraparib + abiraterone acetate + P versus placebo + abiraterone acetate + P.

The study included adult patients with mCRPC who had not received any prior therapy at this stage of the disease. According to the inclusion criteria, patients had progressive disease at study entry 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] ≤ 3).

The MAGNITUDE study was divided into 3 cohorts, into which patients were divided depending on the presence or absence of homologous recombination repair (HRR) mutations. Of the 3 cohorts, only Cohort 1 is relevant for the benefit assessment, as Cohort 2 exclusively included patients without HRR mutation, and Cohort 3 is a single-arm cohort for the evaluation of the fixed combination of niraparib/abiraterone acetate.

Within Cohort 1, 423 patients were included and randomly assigned in a 1:1 ratio to treatment with niraparib + abiraterone acetate + P (N = 212) or placebo + abiraterone acetate + P (N = 211). Randomization was stratified by previous taxane-containing chemotherapy (yes/no), previous androgen receptor (AR)-targeted therapy (yes/no), bridging therapy with abiraterone acetate + P in the mCRPC stage (yes/no) and the presence of a gene alteration (BRCA1 or BRCA2/all other HRR alterations).

The dosing of niraparib + abiraterone acetate + P and abiraterone acetate + P was carried out without any relevant deviations from the respective Summaries of Product Characteristics (SPCs). However, the individual drugs rather than the approved fixed-dose combination were administered in Cohort 1. This remains of no consequence for the present benefit assessment.

Patients without history of bilateral orchiectomy were to continue any ongoing ADT in addition to the study medication. This ADT was either by medical castration with gonadotropin-releasing hormone (GnRH) analogue or by subsequent surgical castration with bilateral orchiectomy.

Treatment with the study medication was continued until disease progression, defined by a PSA rise with radiographic confirmation or by clinical progression, until unacceptable toxicity, withdrawal of informed consent by the patient, lost to follow-up, or termination of the study by the sponsor.

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.

Limitations of the study population

Therapeutic indication for chemotherapy in the MAGNITUDE study

Niraparib/abiraterone + P is approved for patients with mCRPC and BRCA1/2 mutations in whom chemotherapy is not clinically indicated. In the MAGNITUDE study, this was not an explicit inclusion criterion. It was only specified that only patients with a BPI-SF Item 3 (worst pain) ≤ 3 (corresponding to no or mild symptoms) were included (even if 5% of the patients in the comparator arm of the relevant subpopulation had a baseline value > 3).

The company presented analyses on a subpopulation of patients with BRCA1/2 mutation from Cohort 1 of the MAGNITUDE study for whom, in its opinion, chemotherapy is not clinically indicated. Following the criticism of the European Medicines Agency (EMA), it defined the following 2 criteria for the definition of this subpopulation:

- patients without prior taxane-containing chemotherapy who are mildly symptomatic or asymptomatic (measured using BPI-SF Item 3) and have no visceral metastases (low disease burden)
- patients with prior taxane-containing chemotherapy (irrespective of symptoms or disease burden)

According to the information on the patients' prior therapies, all patients had docetaxel as previous taxane-containing chemotherapy.

The corresponding subpopulation comprised 92 patients in the intervention arm and 88 patients in the comparator arm.

The company's approach is appropriate. However, it remains unclear whether retreatment with chemotherapy (possibly with cabazitaxel) would have been clinically indicated for the patients with previous taxane-containing chemotherapy. 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. In the overall view, this uncertainty is taken into account in the certainty of conclusions.

Bridging therapy with abiraterone acetate + P

Research question 1 of the present benefit assessment investigates treatment-naive patients. The MAGNITUDE study included adult patients with mCRPC who had not yet received any active treatment for the mCRPC stage. The only exception was treatment with abiraterone acetate + P for up to 4 months prior to randomization. The company justified this by stating that the HRR mutations were tested for during this period, but that some of the patients required rapid initiation of a new therapy to control the disease due to its more aggressive course. In the relevant subpopulation, 25% of patients in the intervention arm and 20% of

patients in the comparator arm received this type of bridging therapy with abiraterone acetate + P. The company provided no information on how long the patients actually received this bridging therapy or how long the patients actually had to wait for the results of the HRR mutation testing.

The company's justification is only partly comprehensible. In individual cases, such bridging therapy may be necessary for patients. However, the period of up to 4 months until the results of the HRR mutation testing were available seems disproportionately long. In the current health care context, it is assumed that the test results should be available within a few weeks.

It is unclear how the administration of the bridging therapy or the potentially relatively long waiting time for the test result before randomization affected the results of the study.

Overall, the possibility of bridging therapy with abiraterone acetate + P, which was used in about 1 quarter of the patients in the subpopulation, does not call into question the relevance of the subpopulation for the benefit assessment. All patients are included in the approved therapeutic indication and can be assigned to research question 1 despite the bridging therapy, as treatment with abiraterone acetate + P is not to be considered a separate line of therapy (patients were not allowed to be progressive during the bridging therapy). The uncertainties described above regarding the transferability to the German health care context due to the long duration of the testing are taken into account in the certainty of conclusions.

Implementation of the appropriate comparator therapy in the MAGNITUDE study

Adequate treatment of bone metastases

In accordance with the ACT specified by the G-BA, adequate concomitant treatment of bone metastases during the study is assumed (e.g. use of bisphosphonates, denosumab, radiation). However, according to the study protocol of the MAGNITUDE study, radiotherapy was not permitted until protocol version 2 (dated 30 September 2019). Then, palliative radiotherapy was allowed, but only in selected cases after discussion with sponsor. It remains unclear whether and in how many patients this restriction may have led to inadequate treatment of bone metastases. However, other concomitant treatments for bone metastases (e.g. bisphosphonates and denosumab) were not restricted. This remaining uncertainty is taken into account in the certainty of conclusions.

Data cut-offs

The analyses of the final data cut-off on 15 May 2023 are used.

Risk of bias and certainty of conclusions

The risk of bias across outcomes for the MAGNITUDE 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, the risk of bias of the results for the following outcomes must be rated as high: pain (BPI-SF Item 3 and BPI-SF Item 9a-g), health status (EQ-5D visual analogue scale [VAS]), health-related quality of life (represented by the Functional Assessment of Cancer Therapy-Prostate [FACT-P]), serious adverse events (SAEs), severe adverse events (AEs), myelodysplastic syndrome (MDS) (Standardized Medical Dictionary for Regulatory Activities Query [SMQ], AEs), and anaemia (Preferred Term [PT], severe AEs). No suitable analyses are available for the outcome of symptomatic progression and acute myeloid leukaemia (AML) (PT, AEs). The risk of bias for the results of the outcome of discontinuation due to AEs is rated as low. Nevertheless, the certainty of conclusions 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.

Irrespective 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 clinically not indicated for all patients in the study population, whether the potentially relatively long duration of HRR mutation testing with permitted bridging therapy is transferable to the current health care context and whether adequate concomitant treatment of bone metastases was possible for all patients. Due to this limitation, overall, at most hints, e.g. of an added benefit, can be determined for all outcomes.

Results

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of niraparib + abiraterone acetate + P. There is an effect modification for the subgroup characteristic of prior taxane-containing chemotherapy for this outcome, however. There is a hint of an added benefit of niraparib + abiraterone acetate + P for patients without prior taxane-containing chemotherapy in comparison with abiraterone acetate + P. For patients with prior taxane-containing chemotherapy, there is no hint of an added benefit of niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P; an added benefit is therefore not proven for this patient group.

Morbidity

Symptomatic progression

No suitable data are available for the outcome of symptomatic progression. There is no hint of an added benefit of niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P; an added benefit is therefore not proven.

Worst pain (BPI-SF Item 3)

No statistically significant difference between treatment groups was shown for the outcome of worst pain (BPI-SF Item 3). There is no hint of an added benefit of niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P; an added benefit is therefore not proven.

Pain interference (BPI-SF Item 9a–g)

No statistically significant difference between treatment groups was shown for the outcome of pain interference (BPI-SF Item 9a–g). There is no hint of an added benefit of niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was found for the outcome of health status recorded with the EQ-5D visual analogue scale (VAS). There is no hint of an added benefit of niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P; an added benefit is therefore not proven.

Health-related quality of life

FACT-P

No statistically significant difference between treatment groups was shown for the outcome of FACT-P total score. There is no hint of an added benefit of niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P; an added benefit is therefore not proven.

Side effects

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

No statistically significant difference between the treatment groups was shown for the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3), or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P for these outcomes; greater or lesser harm is therefore not proven.

MDS and AML (each AEs)

For the outcomes of MDS (SMQ, AEs) and AML (PT, AEs), no data were available on the relevant subpopulation. However, in the population of all patients with BRCA mutation in Cohort 1, there was no event for the MDS outcome and only one event for the AML outcome in the comparator arm. In each case, there is no hint of greater or lesser harm from niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P for these outcomes; greater or lesser harm is therefore not proven.

Anaemia (severe AEs)

For the outcome of anaemia (PT, severe AEs), a statistically significant difference was found to the disadvantage of niraparib + abiraterone acetate + P. There is a hint of greater harm from niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P.

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

On the basis of the results presented, the probability and extent of added benefit of the drug combination of niraparib/abiraterone acetate (in combination with prednisone or prednisolone) in comparison with the ACT are assessed as follows:

Overall, both positive and negative effects of niraparib/abiraterone acetate + P were found in comparison with the ACT. Only for overall survival are the observed effects based on the entire observation period. For the side effects, however, they are based exclusively on the shortened period up to 30 days after discontinuation of the study medication. The characteristic of prior taxane-containing chemotherapy is an effect modifier for the outcome of overall survival. Due to this effect modification, the results on the added benefit of niraparib/abiraterone acetate + P compared with the ACT after prior taxane-containing chemotherapy are derived separately below:

Patients without prior taxane-containing chemotherapy

For patients without prior taxane-containing chemotherapy, there is a hint of major added benefit for the outcome of overall survival. On the other hand, there is a hint of greater harm with major extent for the outcome of anaemia in the outcome category of serious/severe side effects. In the weighing of benefit versus harm, this resulted in a downgrading of the extent

[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].

of the added benefit. Overall, there is therefore a hint of considerable added benefit for patients without prior taxane-containing chemotherapy.

Patients with prior taxane-containing chemotherapy

For patients with prior taxane-containing chemotherapy, there is no hint of added benefit for the outcome of overall survival. However, there is a hint of greater harm with major extent for the outcome of anaemia in the outcome category of serious/severe side effects. No effects were shown in the overall rates of SAEs and severe AEs. In the overall view of the available results, for example the barely statistically insignificant effect in favour of the intervention in health-related quality of life, the negative effect in the outcome of anaemia is not sufficient in this data situation to derive lesser benefit of niraparib, however. Overall, the added benefit is therefore not proven for patients with prior taxane-containing chemotherapy.

Summary

In summary, there is a hint of considerable added benefit of niraparib/abiraterone acetate + P versus abiraterone acetate + P for patients without prior taxane-containing chemotherapy with treatment-naive mCRPC and BRCA1/2 mutations for whom chemotherapy is not clinically indicated. For patients with prior taxane-containing chemotherapy, there is no hint of an added benefit in comparison with abiraterone acetate + P; an added benefit is therefore not proven for this patient group.

Research question 2: adults with pretreated mCRPC and BRCA 1/2 mutations 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 added benefit of niraparib/abiraterone acetate + P in comparison with the ACT; an added benefit is therefore not proven.

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 niraparib/abiraterone acetate + P compared with the ACT for patients with pretreated mCRPC and BRCA1/2 mutations in whom chemotherapy is not clinically indicated. An added benefit of niraparib/abiraterone acetate + P 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 niraparib/abiraterone acetate + P.

Table 3: Niraparib/abiraterone acetate + P – 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 and BRCA 1/2 mutations (germline and/or somatic) 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 whose disease has progressed after previous treatment that included an NHA) or ▪ olaparib in combination with abiraterone acetate and prednisone or prednisolone	▪ Patients without prior taxane-containing chemotherapy: hint of considerable added benefit[e] ▪ Patients with prior taxane-containing chemotherapy: added benefit not proven
2	Adults with pretreated mCRPC and BRCA 1/2 mutations (germline and/or somatic) 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 whose disease has progressed on or after docetaxel-containing chemotherapy), ▪ enzalutamide (only for patients whose disease has progressed on or after docetaxel chemotherapy) ▪ olaparib as monotherapy (only for patients whose disease has progressed after previous treatment that included an NHA), taking into accounts any pretreatment(s)	Added benefit not proven

Table 3: Niraparib/abiraterone acetate + P – 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 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.
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 ≤ 3 (mildly symptomatic or asymptomatic) were included in the MAGNITUDE 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 > 3) (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 (multicomparator study).

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

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 niraparib/abiraterone acetate in combination with prednisone or prednisolone (hereinafter referred to as "niraparib/abiraterone acetate + P") compared with the ACT in adult patients with mCRPC and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated.

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

Table 4: Research questions of the benefit assessment of niraparib/abiraterone acetate + P (multipage table)

Research question	Therapeutic indication	ACT[a]
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Table 4: Research questions of the benefit assessment of niraparib/abiraterone acetate + P (multipage table)

Research question	Therapeutic indication	ACT[a]
2	Adults with pretreated mCRPC and BRCA 1/2 mutations (germline and/or somatic) 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 whose disease has progressed on or after docetaxel-containing chemotherapy), ▪ enzalutamide (only for patients whose disease has progressed on or after docetaxel chemotherapy) ▪ olaparib as monotherapy (only for patients whose disease has progressed after previous treatment that included an NHA), taking into accounts any pretreatment(s)

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 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 required (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 (multicomparator study).

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: new hormonal agent; P: prednisone or prednisolone

In research question 1, the ACT presented by the company in Module 4 A deviates from the ACT specified by the G-BA in some of the alternative treatment options mentioned. However, the company's choice of abiraterone acetate in combination with prednisone or prednisolone (hereafter referred to as "abiraterone acetate + P") has no consequences for the benefit assessment. For research question 2, the company followed the G-BA's ACT.

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 for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Research question 1: adults with treatment-naive mCRPC and BRCA 1/2 mutations 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 niraparib + abiraterone acetate (status: 25 October 2023)
- bibliographical literature search on niraparib + abiraterone acetate (last search on 19 September 2023)
- search in trial registries/trial results databases for studies on niraparib + abiraterone acetate (last search on 21 September 2023)
- search on the G-BA website for niraparib + abiraterone acetate (last search on 21 September 2023)

To check the completeness of the study pool:

- search in trial registries for studies on niraparib + abiraterone acetate (last search on 24 November 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P

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])
64091742PCR3001 (MAGNITUDE[c])	Yes	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the 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; P: prednisone or prednisolone; RCT: randomized controlled trial

The MAGNITUDE study was 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: niraparib + abiraterone acetate + P vs. placebo + abiraterone + P (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MAGNITUDE	RCT, double-blind, parallel	Adult patients with mCRPC[b] with/without HRR mutations with: ▪ ECOG PS ≤ 1 and ▪ BPI-SF Item 3 ≤ 3[c]	Cohort 1: ▪ Niraparib + abiraterone acetate + P (N = 212) ▪ Placebo + abiraterone acetate + P (N = 211) Relevant subpopulation thereof (Cohort 1): ▪ Niraparib + abiraterone acetate + P (n = 92) ▪ Placebo + abiraterone acetate + P (n = 88) Cohort 2[d]: ▪ Niraparib + abiraterone acetate + P (N = 123) ▪ Placebo + abiraterone acetate + P (N = 124) Cohort 3[d]: ▪ Niraparib/abiraterone acetate + P (fixed combination) (N = 95)	Screening: ≤ 28 days[e] Treatment: until disease progression[f], unacceptable toxicity, withdrawal of consent, lost to follow-up, or termination of the study by the sponsor. Observation[g]: outcome-specific, at most up to 5 years after end of treatment, or until death, lost to follow-up, withdrawal of consent, or end of study	205 centres in Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, France, Germany, Hungary, Italy, Malaysia, Mexico, Netherlands, Poland, Portugal, Russia, South Korea, Spain, Sweden, Taiwan, Turkey, Ukraine, United Kingdom, USA 2/2019–ongoing[h] Data cut-offs: ▪ 13 August 2020 (futility analysis)[i] ▪ 8 October 2021 (first data cut-off)[j, k] ▪ 17 June 2022 (second data cut-off)[j] ▪ 15 May 2023 (final analysis)[j]	Primary: rPFS Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone + P (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. mCRPC with a testosterone level of ≤ 50 ng/dL on treatment with a GnRH analogue or after bilateral orchiectomy, as evidenced by PSA progression or radiographic progression. Metastases documented by bone scan or CT or MRI. c. Worst pain within the last 24 hours at the time of screening. d. Cohort 2 (adult patients with mCRPC without HRR mutations) and Cohort 3 (non-randomized, open-label cohort for the evaluation of the fixed combination of niraparib/abiraterone acetate; adult patients with mCRPC with HRR mutations) are not relevant for the assessment and are not shown in the tables below. e. As part of a prescreening phase, the patients' biomarker status was first determined using plasma/tissue samples. Patients were to enter the screening phase within 6 weeks of receiving the final result of the HRR gene alteration status. f. Progression with a PSA rise had to be confirmed radiographically or defined by clinical progression (deterioration in ECOG status ≥ 3, initiation of alternative anticancer therapy, radiotherapy or surgical intervention for complications due to tumour progression). Radiographic disease progression had to have been confirmed by central radiology review; further treatment was permitted at the investigator's discretion after discussion with sponsor if the patient showed no unequivocal clinical progression and no alternative treatment was indicated. g. Outcome-specific information is provided in Table 8. h. Patients could enter an extension phase after final analysis. i. Prespecified futility analysis for Cohort 2 after inclusion of 247 patients. The futility criteria were met and Cohort 2 was declared futile. The patients in Cohort 2 were unblinded (except for 14 patients with a CDK12 mutation). Under protocol amendment 4, these 14 patients were included in Cohort 1. j. For Cohorts 1 and 3. Two interim analyses and one final analysis were planned for the secondary outcomes at the time point of approximately 100, 170 and 246 OS events in Cohort 1. k. Final analysis for the primary outcome of rPFS. AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CDK12: cyclin-dependent kinase 12; 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: relevant subpopulation; N: number of randomized patients; OS: overall survival; P: prednisone or prednisolone; PSA: prostate-specific antigen; RCT: randomized controlled trial; rPFS: radiographic progression-free survival						

Table 7: Characteristics of the intervention – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P (multipage table)

Study	Intervention	Comparison
MAGNITUDE	Niraparib 200 mg (once daily 2 × 100 mg), orally + abiraterone acetate 1000 mg (1 × daily 4 × 250 mg), orally + prednisone 10 mg (2 × daily 5 mg), orally	Placebo, orally + abiraterone acetate 1000 mg (1 × daily 4 × 250 mg), orally + prednisone 10 mg (2 × daily 5 mg), orally
	Dose adjustment[a]: ▪ Niraparib or placebo[b]: treatment interruption and dose reduction to 100 mg (once daily) permitted in case of toxicity ▪ Abiraterone acetate: treatment interruption and 2 dose reductions of 250 mg each permitted in case of toxicity (grade ≥ 3) ▪ Prednisone[c]: The prednisone dose could remain unchanged with dose modifications of niraparib or abiraterone acetate.	
	Pretreatment Required ▪ Continuation of conventional ADT (GnRH analogues) in patients who have not undergone surgical castration by bilateral orchiectomy[d] Allowed ▪ Up to 4 months abiraterone acetate plus prednisone before randomization[e] Not allowed ▪ Treatment with a PARP inhibitor ▪ Systematic therapy in mCRPC (e.g. new second generation treatment targeting androgen receptors, such as enzalutamide, apalutamide or darolutamide, taxane-containing chemotherapy) ▪ Opioid analgesics at the time of screening ▪ Within 28 days prior to randomization: a transfusion (platelets or red blood cells), haematopoietic growth factors, major surgery, investigational drug for prostate cancer, radiotherapy	
	Concomitant treatment **Not allowed** ▪ Investigational drugs or other anticancer therapies, chemotherapy or immunotherapy, radiotherapy for tumour progression[f] ▪ Other drugs that target the androgen axis (e.g. antiandrogens such as enzalutamide and apalutamide, CYP17 inhibitors such as ketoconazole) ▪ Radiopharmaceuticals ▪ Strong CYP3A inhibitors	

Table 7: Characteristics of the intervention – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P (multipage table)

Study	Intervention	Comparison
a. If one study medication was discontinued due to toxicity (niraparib or placebo or abiraterone acetate), the other study medication could be continued. Niraparib/placebo was restarted ≥ 7 days after restarting abiraterone acetate. b. If non-haematological toxicity (grade ≥ 3) lasted for > 28 days, treatment was discontinued. c. If abiraterone acetate was discontinued, prednisone was also discontinued. d. Patients were allowed to undergo bilateral orchiectomy instead of conventional ADT during the study. e. Patients were allowed to receive abiraterone acetate + prednisone in mCRPC for a short period (up to 4 months before randomization) (see also text section on bridging therapy with abiraterone acetate + P). Progression under abiraterone acetate was excluded for the respective patients by PSA testing (according to PCWG 3 criteria) or by the investigator during the prescreening and screening phase. Treatment with abiraterone acetate + prednisone or prednisolone outside of mCRPC was not permitted. f. Palliative radiotherapy was permitted after discussion with sponsor (from protocol amendment 2 dated 30 September 2019) (see also text section on adequate treatment of bone metastases). ADT: androgen deprivation therapy; CYP17: 17α hydroxylase; CYP3A: cytochrome P450 3A; GnRH: gonadotropin-releasing hormone; mCRPC: metastatic castration-resistant prostate cancer; P: prednisone or prednisolone; PARP: poly(adenosine diphosphate-ribose) polymerase; PCWG 3: Prostate Cancer Working Group 3; PSA: prostate-specific antigen; RCT: randomized controlled trial		

Study design

The MAGNITUDE study is a double-blind RCT comparing niraparib + abiraterone acetate + P versus placebo + abiraterone acetate + P.

The study included adult patients with mCRPC who had not received any prior therapy at this stage of the disease. According to the inclusion criteria, patients had progressive disease at study entry 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] ≤ 3).

The MAGNITUDE study was divided into 3 cohorts, into which patients were divided depending on the presence or absence of HRR mutations. Of the 3 cohorts, only Cohort 1 is relevant for the benefit assessment, as Cohort 2 exclusively included patients without HRR mutation, and Cohort 3 is a single-arm cohort for the evaluation of the fixed combination of niraparib/abiraterone acetate.

Within Cohort 1, 423 patients were included and randomly assigned in a 1:1 ratio to treatment with niraparib + abiraterone acetate + P (N = 212) or placebo + abiraterone acetate + P (N = 211). Randomization was stratified by previous taxane-containing chemotherapy (yes/no), previous androgen receptor (AR)-targeted therapy (yes/no), bridging therapy with abiraterone acetate + P in the mCRPC stage (yes/no) and the presence of a gene alteration (BRCA1 or BRCA2/all other HRR alterations).

The dosing of niraparib + abiraterone acetate + P and abiraterone acetate + P was carried out without any relevant deviations from the respective SPCs [8,9]. However, the individual drugs rather than the approved fixed-dose combination were administered in Cohort 1. Data on the fixed combination were only recorded in Cohort 3 of the MAGNITUDE study, which is not relevant for the present benefit assessment due to the single-arm design. The EMA describes in the European Public Assessment Report (EPAR) that bioequivalence of the regular-strength fixed-dose combination has been adequately demonstrated. According to the EPAR, a level of uncertainty remains regarding the potential higher exposure of abiraterone acetate with the low-strength fixed-dose combination [10]. In the relevant subpopulation of the MAGNITUDE study, 21.7% of patients in the intervention arm were affected by a dose reduction according to the information in Module 4 A. For these patients, it is therefore unclear whether they would have higher exposure of abiraterone acetate when taking the fixed-dose combination. This remains of no consequence for the present benefit assessment.

Patients without history of bilateral orchiectomy were to continue any ongoing ADT in addition to the study medication. This ADT was either by medical castration with GnRH analogue or by subsequent surgical castration with bilateral orchiectomy.

Treatment with the study medication was continued until disease progression, defined by a PSA rise with radiographic confirmation or by clinical progression, until unacceptable toxicity, withdrawal of informed consent by the patient, lost to follow-up, or termination of the study by the sponsor. For patients who were still receiving treatment at the time of the final analysis, continued treatment with niraparib + abiraterone acetate + P was possible as part of an extension phase.

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.

Limitations of the study population

Therapeutic indication for chemotherapy in the MAGNITUDE study

Niraparib/abiraterone + P is approved for patients with mCRPC and BRCA1/2 mutations in whom chemotherapy is not clinically indicated. In the MAGNITUDE study, this was not an explicit inclusion criterion. It was only specified that only patients with a BPI-SF Item 3 (worst pain) ≤ 3 (corresponding to no or mild symptoms) were included (even if 5% of the patients in the comparator arm of the relevant subpopulation had a baseline value > 3; see Table 9). According to the S3 guideline, treatment eligibility for chemotherapy is not a clearly defined variable [11]. 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 [11].

It is not clear from the inclusion criteria of the study whether all patients in the MAGNITUDE study population met the eligibility restriction “chemotherapy not clinically indicated”. The EMA discussed in the EPAR [10] whether, in particular for the group of patients with symptomatic disease and/or visceral metastases and without prior chemotherapy in the mHSPC, chemotherapy might be the better treatment option on the comparator side than abiraterone.

In Module 4 A, the company presented analyses on a subpopulation of patients with BRCA1/2 mutation from Cohort 1 of the MAGNITUDE study for whom, in its opinion, chemotherapy is not clinically indicated. Following the criticism of the EMA, it defined the following 2 criteria for the definition of this subpopulation:

- patients without prior taxane-containing chemotherapy who are mildly symptomatic or asymptomatic (measured using BPI-SF Item 3) and have no visceral metastases (low disease burden)
- patients with prior taxane-containing chemotherapy (irrespective of symptoms or disease burden)

According to the information on the patients’ prior therapies, all patients had docetaxel as previous taxane-containing chemotherapy. No information is available on the line of therapy in which the patients received this treatment.

The corresponding subpopulation comprised 92 patients in the intervention arm and 88 patients in the comparator arm.

The company’s approach is appropriate. However, 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 “Prostate Cancer”, 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. In the overall view, this uncertainty is taken into account in the certainty of conclusions (see Section I 3.2.2).

Bridging therapy with abiraterone acetate + P

Research question 1 of the present benefit assessment investigates treatment-naive patients. The MAGNITUDE study included adult patients with mCRPC who had not yet received any active treatment for the mCRPC stage. The only exception was treatment with abiraterone acetate + P for up to 4 months prior to randomization. The company justified this by stating

that the HRR mutations were tested for during this period, but that some of the patients required rapid initiation of a new therapy to control the disease due to its more aggressive course. In the relevant subpopulation, 25% of patients in the intervention arm and 20% of patients in the comparator arm received this type of bridging therapy with abiraterone acetate + P. The company provided no information on how long the patients actually received this bridging therapy or how long the patients actually had to wait for the results of the HRR mutation testing.

The company's justification is only partly comprehensible. In individual cases, such bridging therapy may be necessary for patients. However, the period of up to 4 months until the results of the HRR mutation testing were available seems disproportionately long. In the current health care context, it is assumed that the test results should be available within a few weeks.

It is unclear how the administration of the bridging therapy or the potentially relatively long waiting time for the test result before randomization affected the results of the study. The company did not present subgroup analyses for this characteristic (these are presented as supplementary information for the outcome of overall survival in I Appendix D of the full dossier assessment). However, it is unclear whether the significant effect modification observed for the outcome of overall survival is due to the characteristic "bridging therapy", as similar effects were also observed for the subgroup characteristic "previous taxane-based chemotherapy" (see Table 16). In the overall view of the data, it is assumed that the need for bridging therapy with abiraterone acetate + P is an indication of a potentially more rapidly progressing and therefore more severe disease. In the consideration of the subgroup analyses, this characteristic is reflected by the characteristic "previous taxane-based chemotherapy" (see also Section I 3.2.4). The characteristic "bridging therapy" is therefore not considered further.

Overall, the possibility of bridging therapy with abiraterone acetate + P, which was used in about 1 quarter of the patients in the subpopulation, does not call into question the relevance of the subpopulation for the benefit assessment. All patients are included in the approved therapeutic indication and can be assigned to research question 1 despite the bridging therapy, as treatment with abiraterone acetate + P is not to be considered a separate line of therapy (patients were not allowed to be progressive during the bridging therapy). The uncertainties described above regarding the transferability to the German health care context due to the long duration of the testing are taken into account in the certainty of conclusions (see Section I 3.2.2).

Implementation of the appropriate comparator therapy in the MAGNITUDE study

Abiraterone acetate + P

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 abiraterone acetate + P, which the G-BA specified as ACT only for patients whose disease is progressive during or after docetaxel-containing chemotherapy, or only for patients with asymptomatic or mildly symptomatic disease after failure of ADT in whom chemotherapy is not yet clinically indicated.

Due to the definition of the relevant subpopulation by the company (see details above on the therapeutic indication for chemotherapy in the MAGNITUDE study), the characteristics mentioned by the G-BA are adequately considered. In the relevant subpopulation of the MAGNITUDE study, prior treatment with a taxane-containing chemotherapy is exclusively pretreatment with docetaxel.

Adequate treatment of bone metastases

In accordance with the ACT specified by the G-BA, adequate concomitant treatment of bone metastases during the study is assumed (e.g. use of bisphosphonates, denosumab, radiation). However, according to the study protocol of the MAGNITUDE study, radiotherapy was not permitted until protocol version 2 (dated 30 September 2019). Then, palliative radiotherapy was allowed, but only in selected cases after discussion with sponsor. It remains unclear whether and in how many patients this restriction may have led to inadequate treatment of bone metastases. However, other concomitant treatments for bone metastases (e.g. bisphosphonates and denosumab) were not restricted. The remaining uncertainty is taken into account in the certainty of conclusions (see Section I 3.2.2).

Data cut-offs

Three preplanned data cut-offs are available for Cohort 1 of the MAGNITUDE study:

- First data cut-off dated 8 October 2021: first interim analysis for the secondary outcomes and final analysis for the primary outcome of rPFS (planned after about 100 deaths)
- Second data cut-off dated 17 June 2022: interim analysis for the secondary outcomes (planned after about 170 deaths)
- Final data cut-off dated 15 May 2023: final analysis for the secondary outcomes (planned after about 246 deaths)

Concurring with the company’s approach, the present benefit assessment uses the analyses of the final data cut-off.

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: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P

Study Outcome category Outcome	Planned follow-up observation
MAGNITUDE	
Mortality	
Overall survival	Up to 5 years after end of treatment or until death, lost to follow-up, withdrawal of consent, or end of study
Morbidity	
Symptomatic progression	Up to 5 years after end of treatment or until death, lost to follow-up, withdrawal of consent, or end of study
Worst pain (BPI-SF Item 3), pain interference (BPI-SF Item 9a-g) and health status (EQ-5D VAS)	Up to 2 years after end of treatment or until death, lost to follow-up, withdrawal of consent, or end of study
Health-related quality of life (FACT-P)	Up to 2 years after end of treatment or until death, lost to follow-up, withdrawal of consent, or end of study
Side effects	
All outcomes in the side effects category	Up to 30 days after the last administration of study medication or until the start of a new prostate cancer treatment, until death, lost to follow-up or withdrawal of consent

BPI-SF: Brief Pain Inventory-Short Form; FACT-P: Functional Assessment of Cancer Therapy-Prostate; P: prednisone or prednisolone; RCT: randomized controlled trial; VAS: visual analogue scale

The observation periods for the outcomes of the category of side effects are systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days). Although the outcomes on morbidity (with the exception of symptomatic progression) and health-related quality of life were to be assessed up to 2 years after the end of treatment, 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 overall survival.

Characteristics of the study population

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

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P (multipage table)

Study Characteristic Category	Niraparib + abiraterone acetate + P N[a] = 92	Placebo + abiraterone acetate + P N[a] = 88
MAGNITUDE		
Age [years], mean (SD)	68 (9)	68 (8)
Region, n (%)		
Asia-Pacific	19 (21)	19 (22)
Europe	52 (57)	48 (55)
America	21 (23)	21 (24)
Family origin, n (%)		
Caucasian	63 (69)	69 (78)
Asian	12 (13)	13 (15)
Other	17 (18)	6 (7)
ECOG PS, n (%)		
0	57 (62)	61 (69)
1	35 (38)	27 (31)
Gleason score, n (%)		
< 7	7 (8)	8 (9)
7	13 (14)	19 (22)
≥ 8	67 (73)	58 (66)
Unknown	5 (5)	3 (3)
BPI-SF Item 3 (worst pain in the last 24 hours) at baseline, n (%)		
0	52 (57)	49 (56)
1−3	40 (44)	35 (40)
> 3	0 (0)	4 (5)
Extent of disease at baseline, n (%)		
Bone metastases	80 (87)	73 (83)
Bone metastases only	37 (40)	39 (44)
Visceral metastases	8 (9)	8 (9)
Other metastases	3 (3)	5 (6)
Soft tissue metastases	3 (3)	5 (6)
Lymph node metastasis	52 (57)	41 (47)
Prostate (local recurrence/progression)	0 (0)	2 (2)
Time from mCRPC diagnosis to first treatment dose [months], mean (SD)[b]	4.2 (3.8)	5.3 (5.8)

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P (multipage table)

Study Characteristic Category	Niraparib + abiraterone acetate + P N[a] = 92	Placebo + abiraterone acetate + P N[a] = 88
Prior therapies at a stage prior to mCRPC, n (%)		
Taxane-containing chemotherapy	26 (28)	29 (33)
AR-targeted therapy[c]	6 (7)	5 (6)
Radiotherapy	44 (48)	36 (41)
Surgery	53 (58)	61 (69)
Radiotherapy or surgery	71 (77)	73 (83)
Hormonal therapy[c]	88 (96)	83 (94)
Bridging therapy in mCRPC, n (%)		
Abiraterone acetate + P[d]	23 (25)	18 (20)
Treatment discontinuation, n (%)[e]	ND	ND
Study discontinuation, n (%)[f]	ND	ND

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. It is unclear whether the information includes the duration of a potential bridging therapy. Additionally discrepancy between the dossier's Module 4 A and 5. Institute's calculation based on data from additional analyses in Module 5.
c. The company provided no information on which drugs are in the respective category.
d. Bridging therapy with abiraterone acetate + P was permitted for a period of up to 4 months.
e. No data available for the respective treatment arms. A total of 143 (79%) patients in the subpopulation discontinued the study medication. The most common reasons for treatment discontinuation in the intervention vs. comparator arm were the following (data per treatment arm available): disease progression (51% vs. 80%), side effects (16% vs. 8%).
f. No data available for the relevant subpopulation. According to Module 5, 55% vs. 66% of all patients with BRCA mutation from Cohort 1 discontinued the study. The most common reason for study discontinuation in the intervention vs. the comparator arm was death (53% vs. 62%).

AR: androgen receptor; BPI-SF: Brief Pain Inventory-Short Form; ECOG PS: Eastern Cooperative Oncology Group Performance Status; mCRPC: metastatic castration-resistant prostate cancer; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; P: prednisone or prednisolone; RCT: randomized controlled trial; SD: standard deviation

Patient characteristics are largely balanced between the 2 treatment arms. The mean patient age was 68 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. Although the inclusion criteria required all patients to have a BPI-SF Item 3 (worst pain) ≤ 3, 5% of patients in the comparator arm had a baseline BPI-SF pain score > 3. All patients had metastases at baseline, the most common being bone metastases, which occurred in 87% versus 83% of patients. Minor differences at baseline were seen in the ECOG PS score of 0 (62% versus 69%), in the Gleason score ≥ 8 (73%

versus 66%), and in the time from the diagnosis of mCRPC stage to the first treatment dose, which patients in the comparator arm received on average about 1 month later.

According to the inclusion criteria, all patients were treatment-naive for the mCRPC stage, but up to 4 months of bridging therapy with abiraterone acetate + P was permitted prior to randomization, which was administered to 25% of patients in the intervention arm and 20% of patients in the comparator arm. A large proportion of patients had already received one or more treatments at a previous stage. These mainly included hormonal therapy (96% to 94%), taxane-containing chemotherapy (28% to 33%) and radiotherapy or surgery (77% to 83%). Overall, the pretreatments were sufficiently comparable in both study arms.

At the time of the data cut-off, 143 (79%) of the patients had discontinued their treatment. The most common reasons were disease progression (51% versus 80%) or discontinuation due to side effects (16% versus 8%). No data about study discontinuations are available for the relevant subpopulation. According to Module 5, 55% versus 66% of patients with BRCA mutation in Cohort 1 discontinued the study. The most common reason for study discontinuation was death (53% versus 62%).

Treatment duration and observation period

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

Table 10: Information on the course of the study – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P

Study **Duration of the study phase** **Outcome category**	**Niraparib + abiraterone acetate + P** **N = 92**	**Placebo + abiraterone acetate + P** **N = 88**
MAGNITUDE		
Treatment duration[a] [months]		
Median [Q1; Q3]	22.0 [ND]	14.1 [ND]
Mean (SD)	ND	ND
Observation period[b] [months]		
Overall survival[c]		
Median [Q1; Q3]	35.9 [ND]	36.0 [ND]
Mean (SD)	ND	ND
Morbidity		
Symptomatic progression[c]		
Median [Q1; Q3]	31.3 [ND]	29.8 [ND]
Mean (SD)	ND	ND
Pain according to BPI-SF		
Median [Q1; Q3]	25.2 [ND]	18.5 [ND]
Mean (SD)	ND	ND
EQ-5D VAS		
Median [Q1; Q3]	22.1 [ND]	18.2 [ND]
Mean (SD)	ND	ND
Health-related quality of life		
FACT-P		
Median [Q1; Q3]	22.1 [ND]	15.2 [ND]
Mean (SD)	ND	ND
Side effects		
Median [Q1; Q3]	22.9 [ND]	15.0 [ND]
Mean (SD)	ND	ND

a. According to the company, the treatment duration is the time from the date of randomization until discontinuation of the study medication.
b. Unless otherwise stated, the observation period according to the company is the time from the date of randomization until the date of the investigated event. For patient-reported outcomes, the end of the observation period is the date of the last recorded questionnaire.
c. The calculation of the observation period for the outcome is based on the reverse Kaplan-Meier method.

BPI-SF: Brief Pain Inventory – Short Form; FACT-P: Functional Assessment of Cancer Therapy-Prostate; N: number of patients analysed; ND: no data; P: prednisone or prednisolone; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation, VAS: visual analogue scale

For the relevant subpopulation, the median treatment duration was longer in the intervention arm than in the comparator arm (22.0 months for niraparib + abiraterone acetate + P versus 14.1 months for placebo + abiraterone acetate + P).

The median observation period for overall survival was about 36 months in both treatment arms. The median observation period cited by the company for the outcome of symptomatic progression was 31.3 months in the intervention arm and 29.8 months in the comparator arm, and thus 4.6 and 6.2 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 4 to 8 months longer in the intervention arm than in the comparator arm. It is notable that the median observation periods for these outcomes are only a maximum of 4 months longer than the median treatment duration, although these outcomes were to be monitored for up to 2 years after the end of treatment, according to the study protocol. This can probably be explained by the decline in response rates early in the course of the study. However, as described above, patient-reported outcomes should also be recorded throughout the entire study period.

Subsequent therapies

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

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P

Study **Drug class** **Drug**	**Patients with subsequent therapy[a] n (%)**	
	Niraparib + abiraterone acetate + P **N = 92**	**Placebo + abiraterone acetate + P** **N = 88**
MAGNITUDE		
Total	43 (46.7)	61 (69.3)
Chemotherapy		
Docetaxel	19 (20.7)	34 (38.6)
Cabazitaxel	11 (12.0)	14 (15.9)
Other	11 (12.0)	11 (12.0)
AR-targeted therapy		
Enzalutamide	8 (8.7)	10 (11.4)
Apalutamide	0 (0)	1 (1.1)
Darolutamide	1 (1.1)	0 (0)
Hormonal therapy		
Abiraterone	4 (4.3)	6 (6.8)
Bicalutamide	0 (0)	2 (2.3)
PARP inhibitors		
Olaparib	3 (3.3)	23 (26.1)
Niraparib	0 (0)	2 (2.3)
Rucaparib	0 (0)	1 (1.1)
Talazoparib	0 (0)	1 (1.1)
Further therapies		
Prednisone/prednisolone	8 (8.7)	11 (12.5)
Lutetium-177	2 (2.2)	3 (3.4)
Radium-223 dichloride	1 (1.1)	1 (1.1)
Other	4 (4.3)	10 (11.4)

a. Patients can be counted in more than one subsequent therapy.

AR: androgen receptor; n: number of patients with subsequent therapy; N: number of analysed patients; P: prednisone or prednisolone; PARP: poly(adenosine diphosphate ribose) polymerase; RCT: randomized controlled trial

The choice of subsequent medication was not restricted in the MAGNITUDE study. 46.7% of patients received subsequent therapy in the intervention arm, and 69.3% in the comparator arm. The most common therapy after study treatment was chemotherapy with docetaxel (20.7% in the intervention versus 38.6% in the comparator arm). Since a large proportion of patients had not received taxane-containing chemotherapy at an earlier stage of the disease (about 70% in both study arms, see Table 9), the frequent use of this treatment option in

confirmed progressive disease is comprehensible [11]. Another frequently used subsequent therapy, particularly in the comparator arm, was olaparib at 3.3% in the intervention arm and 26.1% in the comparator arm. This corresponds to the guideline recommendation for progression after treatment with a new hormonal substance (such as abiraterone) and the presence of a BRCA1/2 mutation, according to which olaparib (as monotherapy) should be offered [11]. It remains unclear whether, in current everyday health care, a higher proportion of patients in the comparator arm could be expected to receive olaparib as subsequent therapy.

In addition, some of the patients received androgen receptor (AR)-targeted or hormonal therapy as subsequent therapy, which mainly consisted of treatment with enzalutamide (8.7% of patients in the intervention arm and 11.4% of patients in the comparator arm) and abiraterone (4.3% in the intervention arm and 6.8% in the comparator arm). According to the S3 guideline, sequential therapy using one of the other effective drugs can be offered after AR-targeted therapy, although currently it cannot be conclusively assessed whether a second AR-targeted treatment after progression under first-line treatment with the respective other drug may be less effective than second-line chemotherapy [11]. Subsequent therapy with abiraterone, however, is not in line with guideline recommendations.

It remains unclear how many of the patients did not receive subsequent therapy despite being eligible for it. For example, 79% of patients discontinued treatment (see Table 9); on average, about 20% fewer patients received subsequent treatment.

Overall, the available information on subsequent therapies provided by the company does not provide any evidence that the subsequent treatment of the patients deviates to a relevant extent from the guideline recommendations.

Risk of bias across outcomes (study level)

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

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P

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			
MAGNITUDE	Yes	Yes	Yes	Yes	Yes	Yes	Low
P: prednisone or prednisolone: RCT: randomized controlled trial							

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

Transferability of the study results to the German health care context

The company described that the MAGNITUDE study was conducted in 205 study centres in 26 countries, including 3 study centres in Germany. Based on this and the patient characteristics, the company drew conclusions about the German health care context. The company stated that the median age at primary diagnosis of patients with mCRPC in first-line therapy was 70 years [12], which was comparable to the median age of the study participants in both arms (niraparib + abiraterone acetate + P: 67.5 years and abiraterone acetate + P: 68.0 years), that the vast majority of patients came from Europe (55.6%) and that approx. 73.3% of the study participants were of white skin colour. With regard to the patients' possible previous and subsequent therapies, all treatments in accordance with the German health care context and the guideline recommendations were permitted and represented in the study, according to the company.

According to the company, there was no evidence of biodynamic or kinetic differences between the individual population groups or regarding health services received in Germany to an extent which would significantly impact study results. Therefore, the company assumed that, when taking into account the uncertainty associated with the transferability of clinical data, the results are in principle transferable to the German health care context.

The company also explained that the treatment regimen used in the comparator arm of the MAGNITUDE study (abiraterone + prednisone/prednisolone) is approved and used in clinical practice in Germany.

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 text section on bridging therapy with abiraterone acetate + P 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 progression
  - worst pain (measured using the BPI-SF Item 3)
  - pain interference (measured using the BPI-SF Item 9a–g)

- health status, recorded using the EQ-5D VAS

- Health-related quality of life
  - measured using the FACT-P total score
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - MDS (SMQ, AEs)
  - AML (PT, AEs)
  - further specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P

Study	Outcomes											
	Overall survival	**Symptomatic progression[a]**	**Worst pain (BPI-SF Item 3)**	**Pain interference (BPI-SF Item 9a–g)**	**Health status (EQ-5D VAS)**	**Health-related quality of life (FACT-P)**	**SAEs**	**Severe AEs[b]**	**Discontinuation due to AEs**	**MDS (SMQ, AEs)[c]**	**AML (PT, AEs)**	**Anaemia (PT, severe AEs[b])**
MAGNITUDE	Yes	No[d]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[e]	Yes

a. For the operationalization, see text section below
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. AESI defined by the company.
d. No suitable data available; for the reasoning, see Section I 3.2.1 of the present dossier assessment.
e. No data on relevant subpopulation available.

AE: adverse event; AESI: adverse event of special interest; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy-Prostate; MDS: myelodysplastic syndrome; MedDRA: Medical Dictionary for Regulatory Activities; P: prednisone or prednisolone; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; VAS: visual analogue scale

Outcome of symptomatic progression

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

- cancer-related morbid events (for example: fractures [symptomatic and/or pathological], spinal cord compression, urinary obstructive events)
- use of external radiotherapy for skeletal events
- need for tumour-related orthopaedic surgical intervention
- initiation of a new systemic anti-cancer therapy because of cancer pain
- use of other cancer-related procedures (e.g. nephrostomy insertion, bladder catheter insertion, external radiotherapy, or surgery for tumour symptoms other than skeletal)

In addition, the company presented a sensitivity analysis for this outcome, in which it added the component of time to chronic opioid use.

Symptomatic progression is generally a patient-relevant outcome. However, based on the information available, it is not possible to assess whether the outcome can be used in the present operationalization. This is justified below.

Although the outcome was predefined by the company, there is no precise and detailed information on how this composite outcome was recorded and analysed. The electronic case report form (eCRF) shows that patients were asked whether they had experienced a symptomatic progression event. However, it remains unclear which events were defined as symptomatic and how the exact operationalization was carried out (e.g. whether only events that could be linked to an AE were included in the analysis). The symptoms relevant to progression should be defined in advance if possible. When recording via AEs, this would be possible, as in other studies, via a predefined list of relevant PTs. However, patient-reported questionnaires that explicitly record the specific symptoms and their relevance for the patient are preferable.

For a composite outcome to be eligible for inclusion in a benefit assessment, the individual components of the outcome must be both patient relevant and of similar severity. For the present operationalization of the outcome of symptomatic progression, it remains unclear whether all events included (in particular for the components “cancer-related morbid events” and “use of other cancer-related procedures”) are necessarily patient relevant (such as haematuria, which was mentioned as an example in the eCRF), and to what extent events of varying severity were included in the analysis. By way of example, the eCRF mentions events such as micturition urgency, cystitis or haematuria, which can be classified as less severe compared with other events such as fractures, spinal cord compression and tumour symptoms

associated with radiotherapy or surgery. The assessment requires both a precise list of events actually included in the composite outcome and the number of patients with a qualifying event per individual component. The component of morbidity events in particular accounts for a relevant proportion of the overall outcome (see supplementary presentation of the results in I Appendix E of the full dossier assessment), so that the outcome cannot be used for the benefit assessment without further information.

The component “initiation of a new systemic anti-cancer therapy because of cancer pain” was only included in eCRF version 5 dated 16 January 2020. It can therefore be assumed that this component was not recorded in the first year after recruitment. The company did not provide any information on how it dealt with this in the analysis of this component. Information on how many patients were already included in the study at this time and, if applicable, were progressive, is required for the assessment of the outcome. In addition, as already described in previous benefit assessments [13,14], linking the initiation of systemic therapy to the symptoms, as was done in the study, is insufficient to record the events of symptomatic progression with sufficient sensitivity.

To address this criticism, the company presented a sensitivity analysis that additionally considers the component of time to chronic opioid use. However, even this component does not ensure a comprehensive recording of the events of pain progression. Thus, the sensitivity analysis only records the start of opioid therapy, but not, for example, other supportive, symptom-relieving therapies. To ensure reliable measurement, the symptomatic event should be recorded directly and not indirectly by recording the initiation of treatment.

In general, it remains unclear for the symptomatic progression outcome whether recording was retrospective or continuous based on the symptoms that occurred. Based on the questions in the eCRF, it can be assumed for symptomatic progression events which are linked to treatment (e.g. radiotherapy, surgery, cancer-related interventions) that the date of treatment was rated as the date of the event. However, the event of interest for the outcome is the time of symptom onset. No information is available on the period between the onset of symptoms and subsequent treatment.

In addition, it remains unclear for the component “use of external radiotherapy for skeletal events” whether palliative radiotherapy was possible without restriction throughout the course of the study. The uncertainty described in the text section *Adequate treatment of bone metastases* in Section I 3.1.2 applies equally to this component of the symptomatic progression outcome.

Overall, the outcome of symptomatic progression is not usable for the present benefit assessment without the further information and clarifications described above.

Recording of pain (BPI-SF)

In the MAGNITUDE study, the BPI-SF questionnaire is used to record pain. In Module 4 A, the company presented the following operationalizations of this outcome:

- worst pain (BPI-SF Item 3)
- pain intensity (BPI-SF Items 3–6), and
- pain interference (BPI-SF Item 9a–g)

each in the following operationalizations:

  - time to first improvement or deterioration (by ≥ 1.5 points)
  - time to first improvement or deterioration designated by the company as definitive (by ≥ 1.5 points)
- time to pain progression (defined as a ≥ 2-point increase in Item 3 of the BPI-SF questionnaire [worst pain within the last 24 hours] confirmed at 2 consecutive visits)

Given the progressive course of disease to be expected in the present therapeutic indication and taking into account the distribution of absolute scale values at baseline, an analysis of deterioration of health status is of primary relevance in the present benefit assessment. Of the available operationalizations, the time to deterioration is therefore used in the present benefit assessment.

Due to the shortened observation periods, which differ between the arms, the operationalization of the first deterioration is used in each case. Although the company stated in Module 4 A that the follow-up observation period was not shortened, this statement is not comprehensible based on the observation periods provided for the BPI-SF (see Table 10 and Section I 3.2.2 below). The operationalization of confirmed deterioration (referred to by the company as pain progression) is also unsuitable for this reason.

The outcome was analysed in several operationalizations. In order to avoid double counting, worst pain (Item 3) and pain interference (BPI-SF Item 9a–g) are primarily considered for the derivation of the added benefit. The results on average pain intensity (BPI-SF Items 3–6) are presented as supplementary information.

Additional patient-reported outcomes

The company presented 4 different operationalizations also for the other patient-reported outcomes (EQ-5D VAS and FACT-P): time to first improvement or deterioration, or to improvement or deterioration described by the company as definitive. As described for the outcome of pain, only the operationalization of the first deterioration is considered in the present benefit assessment.

Side effects

The study protocol describes that progression of the underlying disease should not be documented as an AE. However, signs and symptoms of disease progression that are considered clinically relevant by the investigator should be reported as AEs, for example. The company provided no further information on this. The available information on the documented AEs (at SOC and PT level) does not provide any indications that AEs attributable to progression of the underlying disease are included to a relevant extent. Accordingly, the overall rates of AEs, SAEs and severe AEs (CTCAE grade ≥ 3) can be used for the benefit assessment.

AML (AEs)

For the outcome of AML (PT, AEs), no data were available on the relevant subpopulation.

I 3.2.2 Risk of bias

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

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P

Study		Outcomes											
	Study level	Overall survival	Symptomatic progression[a]	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF Item 9a–g)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-P)	SAEs	Severe AEs[b]	Discontinuation due to AEs	MDS (SMQ, AEs)[c]	AML (PT, AEs)	Anaemia (PT, severe AEs[b])
MAGNITUDE	L	L	–[d]	H[e]	H[e]	H[e]	H[e]	H[e]	H[e]	L[f]	H[e]	–[g]	H[e]

a. For the operationalization, see Section I 3.2.1.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. AESI defined by the company.
d. No suitable data available; see Section I 3.2.1 for the reasoning.
e. Incomplete observations for potentially informative reasons in the presence of differences in follow-up observation periods between the arms.
f. Despite the low risk of bias, the certainty of results is presumably limited for the outcome of discontinuation due to AE.
g. No data on relevant subpopulation available.

AE: adverse event; AESI: adverse event of special interest; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy-Prostate; H: high; L: low; MDS: myelodysplastic syndrome; MedDRA: Medical Dictionary for Regulatory Activities; P: prednisone or prednisolone; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; 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, the risk of bias of the results for the following outcomes must be rated as high: pain (BPI-SF Item 3 and BPI-SF Item 9a-g), health status (EQ-5D VAS), health-related quality of life (represented by the FACT-P), SAEs, severe AEs, MDS (SMQ, AEs), and anaemia (PT, severe AEs).

No suitable analyses are available for the outcome of symptomatic progression and AML (PT, AEs), see Section I 3.2.1.

The risk of bias for the results of the outcome of discontinuation due to AEs is rated as low. Nevertheless, the certainty of conclusions 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.

Summary assessment of the certainty of conclusions

Irrespective 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 clinically not indicated for all patients in the study population, whether the potentially relatively long duration of HRR mutation testing with permitted bridging therapy is transferable to the current health care context and whether adequate concomitant treatment of bone metastases was possible for all patients.

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

I 3.2.3 Results

Table 15 summarizes the results of the comparison of niraparib/abiraterone acetate + P versus placebo + abiraterone acetate + P in patients with mCRPC and BRCA1/2 mutations in whom chemotherapy is not clinically indicated. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves on the time-to-event analyses are presented in I Appendix B of the full dossier assessment, and the tables on common AEs, SAEs, severe AEs, and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P (multipage table)

Study **Outcome category** **Outcome**	**Niraparib + abiraterone acetate + P**		**Placebo + abiraterone acetate + P**		**Niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P**
	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]**
MAGNITUDE					
Mortality					
Overall survival	92	35.9 [29.2; NC] 44 (47.8)	88	28.3 [20.8; 32.4] 58 (65.9)	0.62 [0.42; 0.91]; 0.015
Morbidity					
Symptomatic progression			No suitable data[b]		
Occurrence of cancer-related morbid events			No suitable data[b]		
External radiotherapy for skeletal events			No suitable data[b]		
Tumour-related orthopaedic surgical intervention			No suitable data[b]		
Initiation of a new systemic anti-cancer therapy because of cancer pain			No suitable data[b]		
Use of other cancer-related procedures			No suitable data[b]		
Worst pain (BPI-SF Item 3)[c]	92	11.3 [8.3; 20.1] 61 (66.3)	88	8.4 [6.4; 13.0] 65 (73.9)	0.75 [0.52; 1.07]; 0.110[d]
Pain intensity (BPI-SF Items 3–6) (supplementary information)[c]	*92*	*16.6 [12.8; 33.2]* *46 (50)*	*88*	*14.9 [9.2; 18.5]* *50 (56.8)*	*0.66 [0.44; 0.99]; 0.044*[d]
Pain interference (BPI-SF Item 9a-g)[c]	92	22.1 [16.6; 35.1] 41 (44.6)	88	22.1 [13.0; 30.4] 44 (50)	0.79 [0.52; 1.21]; 0.283[d]
Health status (EQ-5D VAS)[e]	92	18.4 [8.3; 35.1] 45 (48.9)	88	14.1 [6.0; 16.9] 51 (58.0)	0.85 [0.57; 1.27]; 0.417[d]
Health-related quality of life					
FACT-P					
Total score[f]	92	22.1 [14.8; 33.2] 35 (38.0)	88	16.5 [11.1; 17.5] 41 (46.6)	0.64 [0.41; 1.01]; 0.056[d]

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P (multipage table)

Study **Outcome category** **Outcome**	**Niraparib + abiraterone acetate + P**		**Placebo + abiraterone acetate + P**		**Niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P**
	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]**
Physical wellbeing[g]	92	3.8 [2.8; 7.5] 50 (54.3)	88	12.8 [6.0; 16.6] 47 (53.4)	1.29 [0.87; 1.93]
Social/family wellbeing[g]	92	4.7 [2.8; 14.8] 34 (37.0)	88	4.2 [2.8; 10.9] 34 (38.6)	0.94 [0.58; 1.53]
Emotional wellbeing[h]	92	4.8 [2.8; 7.5] 47 (51.1)	88	5.1 [2.8; 9.3] 45 (51.1)	0.90 [0.60; 1.36]
Functional wellbeing[g]	92	3.8 [2.8; 7.4] 47 (51.1)	88	4.9 [2.8; 7.5] 52 (59.1)	0.82 [0.55; 1.22]
Prostate cancer subscale[i]	92	21.4 [10.6; 26.8] 43 (46.7)	88	16.5 [13.0; 18.5] 44 (50.0)	0.86 [0.56; 1.31]
Side effects					
AEs (supplementary information)	92	0.5 [0.3; 0.5] 92 (100.0)	88	0.6 [0.5; 1.4] 87 (98.9)	–
SAEs	92	30.1 [21.7; NC] 39 (42.4)	88	33.4 [21.5; NC] 26 (29.5)	1.19 [0.72; 1.96]; 0.494[d]
Severe AEs[j]	92	4.5 [2.7; 12.4] 65 (70.7)	88	10.3 [5.9; 16.7] 53 (60.2)	1.22 [0.85; 1.76]; 0.281[d]
Discontinuation due to AEs[k]	92	NA [38.2; NC] 15 (16.3)	88	NA 7 (8.0)	1.69 [0.68; 4.18]; 0.256[d]
MDS (SMQ, AEs)[l]	92	NA 0 (0)	88	NA 0 (0)	–
AML (PT, AEs)[m]	92	ND	88	ND	ND
Anaemia (PT, severe AEs)[j]	92	NA [34.3; NC] 25 (27.2)	88	NA 7 (8.0)	3.77 [1.63; 8.72]; 0.002[d]

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P (multipage table)

Study Outcome category Outcome	Niraparib + abiraterone acetate + P		Placebo + abiraterone acetate + P		Niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P
	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]

a. Unless stated otherwise: HR, 95% CI calculated using unstratified Cox proportional hazards model; p-value using an unstratified log-rank test.
b. See Section I 3.2.1 of the present dossier assessment for the reasoning.
c. Time to first deterioration. A score increase by ≥ 1.5 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 10).
d. HR, 95% CI, and p-value calculated using an unstratified Cox proportional hazards model.
e. Time to first deterioration. A decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0–100).
f. Time to first deterioration. A decrease by ≥ 23.4 points from baseline is defined as a clinically relevant deterioration (scale range 0–156).
g. Time to first deterioration. A decrease by ≥ 4.2 points from baseline is defined as a clinically relevant deterioration (scale range 0–28).
h. Time to first deterioration. A decrease by ≥ 3.6 points from baseline is defined as a clinically relevant deterioration (scale range 0–24).
i. Time to first deterioration. A decrease by ≥ 7.2 points from baseline is defined as a clinically relevant deterioration (scale range 0–48).
j. Operationalized as CTCAE grade ≥ 3.
k. Premature discontinuation of at least one therapy component.
l. AESI defined by the company; according to Module 4 A, there is no information on the relevant subpopulation; however, according to information in Module 5, there are no events for all patients with BRCA mutation in Cohort 1.
m. There is no information on the relevant subpopulation; according to information in Module 5, one event in patients with BRCA mutation in Cohort 1 was observed in the comparator arm.

AE: adverse event; AESI: adverse event of special interest; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; MDS: myelodysplastic syndrome; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; P: prednisone or prednisolone; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; 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, a statistically significant difference was found in favour of niraparib + abiraterone acetate + P. There is an effect modification for the subgroup characteristic of prior taxane-containing chemotherapy for this outcome, however (see Section I 3.2.4). There is a hint of an added benefit of niraparib + abiraterone acetate + P for patients without prior taxane-containing chemotherapy in comparison with abiraterone acetate + P. For patients with prior taxane-containing chemotherapy, there is no hint of an added benefit of niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P; an added benefit is therefore not proven for this patient group.

Morbidity

Symptomatic progression

No suitable data are available for the outcome of symptomatic progression (see Section I 3.2.1 for reasoning). There is no hint of an added benefit of niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P; an added benefit is therefore not proven.

Worst pain (BPI-SF Item 3)

No statistically significant difference between treatment groups was shown for the outcome of worst pain (BPI-SF Item 3). A statistically significant difference between treatment groups was shown for the outcome presented as supplementary information (BPI-SF Items 3–6). However, assuming that the outcome can be assigned to the non-severe/non-serious outcome category (no information is available that would allow categorization as serious/severe), the effect is no more than minor. Overall, there is no hint of an added benefit of niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P; an added benefit is therefore not proven.

Pain interference (BPI-SF Item 9a–g)

No statistically significant difference between treatment groups was shown for the outcome of pain interference (BPI-SF Item 9a–g). There is no hint of an added benefit of niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was found for the outcome of health status recorded with the EQ-5D VAS. There is no hint of an added benefit of niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P; an added benefit is therefore not proven.

Health-related quality of life

FACT-P

The outcome of health-related quality of life was recorded using the FACT-P total score.

No statistically significant difference between treatment groups was shown for the outcome of FACT-P total score. There is no hint of an added benefit of niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs

No statistically significant difference between the treatment groups was shown for the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3), or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P for these outcomes; greater or lesser harm is therefore not proven.

Specific AEs

MDS and AML (each AEs)

For the outcomes of MDS (SMQ, AEs) and AML (PT, AEs), no data were available on the relevant subpopulation. However, in the population of all patients with BRCA mutation in Cohort 1, there was no event for the MDS outcome and only one event for the AML outcome in the comparator arm. In each case, there is no hint of greater or lesser harm from niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P for these outcomes; greater or lesser harm is therefore not proven.

Anaemia (severe AEs)

For the outcome of anaemia (PT, severe AEs), a statistically significant difference was found to the disadvantage of niraparib + abiraterone acetate + P. There is a hint of greater harm from niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P.

I 3.2.4 Subgroups and other effect modifiers

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

- age (< 65 years/≥ 65 years to < 75 years/≥ 75 years)
- prior taxane-containing chemotherapy (yes/no)

In the present benefit assessment, the consideration of the subgroup characteristic of prior taxane-containing chemotherapy is justified as follows. Niraparib/abiraterone acetate + P is

approved for patients in whom chemotherapy is not clinically indicated. Patients in the relevant subpopulation can be divided into 2 groups with regard to the clinical indication for chemotherapy: on the one hand, the group of patients for whom chemotherapy is not yet clinically indicated (especially asymptomatic or mildly symptomatic patients), and on the other, the group of patients for whom chemotherapy is not indicated because, for example, they have already received chemotherapy at another stage of the disease. It can be assumed that the latter already had a higher disease burden at an earlier stage of prostate cancer, resulting in the clinical indication of chemotherapy [11]. Furthermore, since, in accordance with the definition of the relevant subpopulation by the company, only patients with visceral metastases were included in the group with prior taxane-containing chemotherapy, prior taxane-containing chemotherapy (yes/no) was considered as a subgroup characteristic for the present benefit assessment.

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

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Table 16 summarizes the subgroup results of the comparison of niraparib/abiraterone acetate + P with placebo + abiraterone acetate + P in patients with mCRPC and BRCA1/2 mutations in whom chemotherapy is not clinically indicated.

Table 16: Subgroups (mortality) – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P

Study Outcome Characteristic Subgroup	Niraparib + abiraterone acetate + P N	Niraparib + abiraterone acetate + P Median time to event in months [95% CI] Patients with event n (%)	Placebo + abiraterone acetate + P N	Placebo + abiraterone acetate + P Median time to event in months [95% CI] Patients with event n (%)	Niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P HR [95% CI][a]	 p-value[b]
MAGNITUDE						
Overall survival						
Prior taxane-containing chemotherapy						
Yes	26	25.4 [14.9; 41.9] 18 (69.2)	27[c]	31.3 [20.2; NC] 15 (55.6)	1.19 [0.59; 2.41]	0.625
No	66	NA [30.4; NC] 26 (39.4)	61	28.3 [19.5; 33.0] 43 (70.5)	0.46 [0.28; 0.75]	0.001
Total					Interaction:	0.029

a. HR and 95% CI calculated using an unstratified Cox proportional hazards model.
b. p-value calculated using an unstratified log-rank test.
c. Discrepancy with the information on patient characteristics in Module 4 A (see also Table 9), according to which 29 patients had received prior taxane-containing chemotherapy.

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; P: prednisone or prednisolone; RCT: randomized controlled trial

Mortality

Overall survival

There is an effect modification for the characteristic of prior taxane-containing chemotherapy for the outcome of overall survival. A statistically significant difference in favour of niraparib + abiraterone acetate + P was shown for patients without prior taxane-containing chemotherapy. There is a hint of added benefit of niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P. No statistically significant difference between treatment groups was shown for patients with prior taxane-containing chemotherapy. There is no hint of an added benefit of niraparib + abiraterone acetate + P in comparison with abiraterone acetate + P for this patient group; an added benefit 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 17).

Table 17: Extent of added benefit at outcome level: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P** **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		
Prior taxane-containing chemotherapy		
Yes	25.4 vs. 31.3 HR: 1.19 [0.59; 2.41]; p = 0.625	Lesser/added benefit not proven
No	NA vs. 28.3 HR: 0.46 [0.28; 0.75]; p = 0.001 Probability: "hint"	Outcome category: mortality $CI_u < 0.85$ Added benefit, extent: "major"
Outcomes with shortened observation period		
Morbidity		
Symptomatic progression	No suitable data	Lesser/added benefit not proven
Worst pain (BPI-SF Item 3, time to first deterioration)	11.3 vs. 8.4 HR: 0.75 [0.52; 1.07]; p = 0.110	Lesser/added benefit not proven
Pain interference (BPI-SF Items 9a–g, time to first deterioration)	22.1 vs. 22.1 HR: 0.79 [0.52; 1.21]; p = 0.283	Lesser/added benefit not proven
Health status (EQ-5D VAS, time to first deterioration)	18.4 vs. 14.1 HR: 0.85 [0.57; 1.27]; p = 0.417	Lesser/added benefit not proven
Health-related quality of life		
FACT-P total score (time to first deterioration)	22.1 vs. 16.5 HR: 0.64 [0.41; 1.01]; p = 0.056	Lesser/added benefit not proven
Side effects		
SAEs	30.1 vs. 33.4 HR: 1.19 [0.72; 1.96]; p = 0.494	Greater/lesser harm not proven
Severe AEs	4.5 vs. 10.3 HR: 1.22 [0.85; 1.76] p = 0.281	Greater/lesser harm not proven

Table 17: Extent of added benefit at outcome level: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs	NA vs. NA HR: 1.69 [0.68; 4.18]; p = 0.256	Greater/lesser harm not proven
MDS (AE)	NA vs. NA HR: –[c]	Greater/lesser harm not proven
AML (AE)	ND[d]	Greater/lesser harm not proven
Anaemia (severe AEs)	NA vs. NA HR: 3.77 [1.63; 8.72]; HR: 0.27 [0.11; 0.61][e]; p = 0.002 Probability: “hint”	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: “major”

a. Probability provided if there is a statistically significant and relevant effect.
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. According to Module 4 A, there is no information on the relevant subpopulation; however, according to information in Module 5, there are no events for all patients with BRCA mutation in Cohort 1.
d. There is no information on the relevant subpopulation; according to information in Module 5, one event in patients with BRCA mutation in Cohort 1 was observed in the comparator arm.
e. Institute’s calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of confidence interval; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; MDS: myelodysplastic syndrome; NA: not achieved; NC: not calculable; SAE: serious adverse event

I 3.3.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of niraparib/abiraterone acetate + P in comparison with abiraterone acetate + P

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival ▫ Prior taxane-containing chemotherapy (no): hint of an added benefit – extent: “major”	
Outcomes with shortened observation period	
	Serious/severe side effects ▪ Anaemia (severe AEs): hint of greater harm – extent “major”
AE: adverse event	

Overall, both positive and negative effects of niraparib/abiraterone acetate + P were found in comparison with the ACT. Only for overall survival are the observed effects based on the entire observation period. For the side effects, however, they are based exclusively on the shortened period up to 30 days after discontinuation of the study medication.

The characteristic of prior taxane-containing chemotherapy is an effect modifier for the outcome of overall survival. Due to this effect modification, the results on the added benefit of niraparib/abiraterone acetate + P compared with the ACT after prior taxane-containing chemotherapy are derived separately below:

Patients without prior taxane-containing chemotherapy

For patients without prior taxane-containing chemotherapy, there is a hint of major added benefit for the outcome of overall survival. On the other hand, there is a hint of greater harm with major extent for the outcome of anaemia in the outcome category of serious/severe side effects. In the weighing of benefit versus harm, this resulted in a downgrading of the extent of the added benefit. Overall, there is therefore a hint of considerable added benefit for patients without prior taxane-containing chemotherapy.

Patients with prior taxane-containing chemotherapy

For patients with prior taxane-containing chemotherapy, there is no hint of added benefit for the outcome of overall survival. However, there is a hint of greater harm with major extent for the outcome of anaemia in the outcome category of serious/severe side effects. No effects were shown in the overall rates of SAEs and severe AEs. In the overall view of the available results, for example the barely statistically insignificant effect in favour of the intervention in health-related quality of life, the negative effect in the outcome of anaemia is not sufficient in

this data situation to derive lesser benefit of niraparib, however. Overall, the added benefit is therefore not proven for patients with prior taxane-containing chemotherapy.

Summary

In summary, there is a hint of considerable added benefit of niraparib/abiraterone acetate + P versus abiraterone acetate + P for patients without prior taxane-containing chemotherapy with treatment-naive mCRPC and BRCA1/2 mutations for whom chemotherapy is not clinically indicated. For patients with prior taxane-containing chemotherapy, there is no hint of an added benefit in comparison with abiraterone acetate + P; an added benefit is therefore not proven for this patient group.

The assessment described above departs from that by the company, which, based on the MAGNITUDE study, derived an indication of a considerable added benefit for niraparib + abiraterone acetate + P compared with abiraterone acetate + P for research question 1.

I 4 Research question 2: adults with pretreated mCRPC and BRCA 1/2 mutations 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 niraparib + abiraterone acetate (status: 25 October 2023)
- bibliographical literature search on niraparib + abiraterone acetate (last search on 19 September 2023)
- search in trial registries/trial results databases for studies on niraparib + abiraterone acetate (last search on 21 September 2023)
- search on the G-BA website for niraparib + abiraterone acetate (last search on 21 September 2023)

To check the completeness of the study pool:

- search in trial registries for studies on niraparib + abiraterone acetate (last search on 24 November 2023); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool identified no RCT for the direct comparison of niraparib + abiraterone acetate versus the ACT.

I 4.2 Results on added benefit

In its dossier, the company did not present any data to assess the added benefit of niraparib/abiraterone acetate+ P compared with the ACT for patients with pretreated mCRPC. There is no hint of an added benefit of niraparib + abiraterone acetate + P 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 niraparib/abiraterone acetate + P compared with the ACT for patients with pretreated mCRPC and BRCA1/2 mutations in whom chemotherapy is not clinically indicated. An added benefit of niraparib/abiraterone acetate + P 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 niraparib/abiraterone acetate + P in comparison with the ACT is summarized in Table 19.

Table 19: Niraparib/abiraterone acetate + P – 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 and BRCA 1/2 mutations (germline and/or somatic) 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 whose disease has progressed after previous treatment that included an NHA) or ▪ olaparib in combination with abiraterone acetate and prednisone or prednisolone	▪ Patients without prior taxane-containing chemotherapy: hint of considerable added benefit[e] ▪ Patients with prior taxane-containing chemotherapy: added benefit not proven
2	Adults with pretreated mCRPC and BRCA 1/2 mutations (germline and/or somatic) 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 whose disease has progressed on or after docetaxel-containing chemotherapy), ▪ enzalutamide (only for patients whose disease has progressed on or after docetaxel chemotherapy) ▪ olaparib as monotherapy (only for patients whose disease has progressed after previous treatment that included an NHA), taking into accounts any pretreatment(s)	Added benefit not proven

Table 19: Niraparib/abiraterone acetate + P – 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 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.
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 ≤ 3 (mildly symptomatic or asymptomatic) were included in the MAGNITUDE 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 > 3) (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 (multicomparator study).

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

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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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-107.html.