IQWiG Reports – Commission No. A20-106

Olaparib (prostate cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Olaparib (Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 March 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Olaparib (Prostate Cancer) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
2 December 2020

Internal Commission No.
A20-106

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Keywords: Olaparib, Prostatic Neoplasms − Castration-Resistant, Benefit Assessment, NCT02987543

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
AML	acute myeloid leukaemia
ATM	*Ataxia Telangiectasia Mutated*
BPI-SF	Brief Pain Inventory-Short Form
BRCA	breast cancer associated gene
CI	confidence interval
CRPC	castration-resistant prostate cancer
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D	European Quality of Life-5 Dimensions
FACT-P	Functional Assessment of Cancer Therapy-Prostate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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
mPC	metastatic prostate cancer
NHA	new hormonal agent
P	prednisone/prednisolone
PCWG3	Prostate Cancer Working Group 3
PRO	patient-reported outcome
PT	Preferred Term
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
rPFS	radiographic progression-free survival
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug olaparib. 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 2 December 2020.

Research question

The aim of the present report is the assessment of the added benefit of olaparib in comparison with the appropriate comparator therapy (ACT) in adult patients with metastatic castration-resistant prostate cancer (mCRPC) and breast cancer associated gene (BRCA)1/2-mutations (germline and/or somatic) whose disease is progressive after previous treatment that included a new hormonal agent (NHA).

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

Table 2: Research question of the benefit assessment of olaparib

Therapeutic indication	**ACT[a]**
Adult patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) whose disease is progressive after previous treatment that included an NHA[b,c]	Individual therapy choosing from abiraterone, enzalutamide, cabazitaxel and docetaxel; taking into account the previous therapies as well as the approval of the respective medicinal products
a. Presentation of the respective ACT specified by the G-BA. b. For the present therapeutic indication, it is assumed that ongoing conventional ADT (surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists) is continued. c. The G-BA specified the present ACT only for those patients whose disease is progressive after previous treatment with abiraterone and/or enzalutamide. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mCRPC: metastatic castration resistant prostate cancer; NHA: new hormonal agent	

At first, the company followed the G-BA's specification. In the following, it limited the options specified by the G-BA and specified an individual therapy choosing from abiraterone or enzalutamide as comparator therapy. However, when selecting relevant studies, it considered all individual treatment options specified by the G-BA. The present benefit assessment of olaparib was conducted in comparison with the G-BA's ACT.

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

Results

Study pool and study characteristics

The PROfound study is relevant for the benefit assessment. PROfound is a randomized, open-label study that compares olaparib under continuation of the ongoing androgen deprivation therapy (ADT) (hereinafter referred to as olaparib + ADT) with physician's choice therapy choosing from abiraterone or enzalutamide. Both treatment with abiraterone or enzalutamide was also carried out under continuation of the ongoing ADT, and abiraterone was additionally combined with prednisone or, if necessary, prednisolone (P), as required (hereinafter referred to as abiraterone + P + ADT or enzalutamide + ADT).

The study included adult men with mCRPC and mutation in a gene involved in homologous recombination repair (HRR), provided that their disease was progressive under previous therapy with an NHA and they had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, 1 or 2. Prior NHA therapy should have been performed for the treatment of metastatic prostate cancer (mPC) or castration-resistant prostate cancer (CRPC). At the time of study inclusion, patients should have radiological progression under ongoing ADT (medical or surgical castration).

Depending on the mutation, a total of 387 patients were included in the study and assigned to cohort A *(BRCA1, BRCA2, Ataxia Telangiectasia Mutated [ATM]*) or cohort B (other genes involved in HRR). The patients were randomly assigned either to treatment with olaparib or to the corresponding physician's choice therapy (abiraterone or enzalutamide) in a 2:1 ratio.

Treatment of the patients was in compliance with the specifications of the respective Summary of Product Characteristics (SPC).

Primary outcome of the study was "radiographic progression-free survival (rPFS)"; patient-relevant secondary outcomes included "overall survival" and outcomes on morbidity, health-related quality of life and adverse events (AEs).

Subpopulation relevant for the benefit assessment

The PROfound study included patients with mutations in several genes involved in HRR. The company presented analyses of the subpopulation of patients with BRCA1/2-mutations. These are relevant for the benefit assessment and include a total of 160 patients, 102 patients in the intervention arm and 58 patients in the comparator arm.

Implementation of the ACT

PROfound is a multi-comparator study that only included patients who were eligible for treatment with abiraterone or enzalutamide. Thus, not all treatment options specified by the G-BA within the framework of individual therapy are comprised. It is assumed that abiraterone or enzalutamide was best suited for the individual patients in the relevant subpopulation, and therefore the ACT was adequately implemented.

Based on the PROfound study, conclusions for the benefit assessment can only be drawn for patients for whom abiraterone or enzalutamide was best suited on an individual basis within the framework of the ACT due to the limitations in the therapy options. No data are available on patients for whom docetaxel or cabazitaxel was best suited on an individual basis within the framework of the ACT.

Risk of bias

The risk of bias across outcomes was rated as low. The risk of bias for the results on all outcomes was rated as high.

Mortality

Overall survival

A statistically significant difference in favour of olaparib + ADT versus abiraterone + P + ADT or enzalutamide + ADT was shown between the treatment groups for the outcome "overall survival". This resulted in a hint of an added benefit of olaparib versus individual therapy (abiraterone or enzalutamide).

Morbidity

Worst pain (Brief Pain Inventory-Short Form [BPI-SF] Item 3)

A statistically significant difference in favour of olaparib + ADT versus abiraterone + P + ADT or enzalutamide + ADT was shown between treatment groups for the outcome "worst pain (BPI-SF Item 3)". This resulted in a hint of an added benefit of olaparib versus individual therapy (abiraterone or enzalutamide).

Pain interference (BPI-SF Items 9a–g)

A statistically significant difference in favour of olaparib + ADT versus abiraterone + P + ADT or enzalutamide + ADT was shown between the treatment groups for the outcome "pain interference (BPI-SF Items 9a–g)". The standardized mean difference (SMD) in the form of Hedges' g was considered to check the relevance of the result. The 95% confidence interval (CI) of the SMD was fully outside the irrelevance range of −0.2 to 0.2. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of olaparib versus individual therapy (abiraterone or enzalutamide).

Symptomatic skeletal-related events

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

- New symptomatic pathologic bone fractures
- Radiotherapy to prevent or alleviate skeletal symptoms
- Spinal cord compression
- Orthopaedic-surgical intervention due to bone metastases

No statistically significant difference between the treatment groups was shown for the composite outcome "symptomatic skeletal-related events". This resulted in no hint of an added benefit of olaparib versus individual therapy (abiraterone or enzalutamide); an added benefit is therefore not proven.

New symptomatic pathologic bone fractures, radiotherapy to prevent or alleviate skeletal symptoms, orthopaedic surgery due to bone metastases

No statistically significant difference between the treatment arms was shown for the outcomes "new symptomatic pathologic bone fractures", "radiotherapy to prevent or alleviate skeletal symptoms" and "orthopaedic surgery due to bone metastases". This resulted in no hint of an added benefit of olaparib versus individual therapy (abiraterone or enzalutamide) in each case; an added benefit is therefore not proven.

Spinal cord compression

A statistically significant difference in favour of olaparib + ADT versus abiraterone + P + ADT or enzalutamide + ADT was shown between the treatment groups for the outcome "spinal cord compression". This resulted in a hint of an added benefit of olaparib in comparison with individual therapy (abiraterone or enzalutamide).

Health status (EQ-5D VAS)

No usable analyses were available for the outcome "health status", recorded using the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D). This resulted in no hint of an added benefit of olaparib in comparison with individual therapy (abiraterone or enzalutamide); an added benefit is therefore not proven.

Health-related quality of life

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

No usable analyses were available for the outcome "health-related quality of life", recorded with the FACT-P. This resulted in no hint of an added benefit of olaparib in comparison with individual therapy (abiraterone or enzalutamide); an added benefit is therefore not proven.

Side effects

Serious adverse events (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 "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from olaparib in comparison with individual therapy (abiraterone or enzalutamide); greater or lesser harm is therefore not proven.

Patient-reported outcome (PRO)-CTCAE

No data are available on the outcome "PRO-CTCAE". This resulted in no hint of greater or lesser harm from olaparib in comparison with individual therapy (abiraterone or enzalutamide); greater or lesser harm is therefore not proven.

Specific AEs

Myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML) and pneumonitis (each Preferred Term (PT), AEs)

No data are available on the specific AEs "MDS" and "AML" (PT, AEs each), and there are no usable analyses on the specific AE "pneumonitis (PT, AEs)". This resulted in no hint of greater or lesser harm from olaparib in comparison with individual therapy (abiraterone or enzalutamide); greater or lesser harm is therefore not proven.

Anaemia (PT, severe AEs), nausea (PT, AEs)

A statistically significant difference to the disadvantage of olaparib + ADT versus abiraterone + P + ADT or enzalutamide + ADT was shown between the treatment groups for the specific AEs "anaemia (PT, severe AEs)" and "nausea (PTs, AEs)". This resulted in a hint of greater harm from olaparib in comparison with individual therapy (abiraterone or enzalutamide) in each case.

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

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

Patients for whom abiraterone or enzalutamide was best suited on an individual basis within the framework of the ACT

In the overall consideration, there were mostly positive and only few negative effects of olaparib in comparison with individual therapy (abiraterone or enzalutamide).

For overall survival, there was a hint of a minor added benefit. In the categories "serious/severe symptoms/ secondary complications" and "non-serious/non-severe symptoms/secondary complications", there are several hints of positive effects with the extents "minor" to

[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].

"considerable". In contrast, there are hints of negative effects with extents of up to "major". These did not raise doubts about the positive effects, however.

In summary, there is a hint of minor added benefit of olaparib versus individual therapy (abiraterone or enzalutamide) for adult patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) whose disease is progressive after previous treatment that included an NHA and for whom abiraterone or enzalutamide is best suited on an individual basis within the framework of the ACT.

Patients for whom docetaxel or cabazitaxel was best suited on an individual basis within the framework of the ACT

For adult patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) whose disease is progressive after previous treatment that included an NHA and for whom docetaxel or cabazitaxel is best suited on an individual basis within the framework of the ACT, the company presented no data for the assessment of the added benefit of olaparib in comparison with individual therapy (docetaxel or cabazitaxel); an added benefit is therefore not proven.

Table 3 summarizes the result of the assessment of the added benefit of olaparib in comparison with the ACT.

Table 3: Olaparib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) whose disease is progressive after previous treatment that included an NHA[b,c]	Individual therapy choosing from abiraterone, enzalutamide, cabazitaxel and docetaxel; taking into account the previous therapies as well as the approval of the respective medicinal products	Patients for whom abiraterone or enzalutamide is the best individual choice: hint of minor added benefit
		Patients for whom docetaxel or cabazitaxel is the best individual choice: added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. b. For the present therapeutic indication, it is assumed that ongoing conventional ADT (surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists) is continued. c. The G-BA specified the present ACT only for those patients whose disease is progressive after previous treatment with abiraterone and/or enzalutamide. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mCRPC: metastatic castration resistant prostate cancer; NHA: new hormonal agent		

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of olaparib in comparison with the ACT in adult patients with mCRPC and BRCA1/2-mutations (germline and/or somatic) whose disease is progressive after previous treatment that included an NHA.

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

Table 4: Research question of the benefit assessment of olaparib

Therapeutic indication	**ACT[a]**
Adult patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) whose disease is progressive after previous treatment that included an NHA[b,c]	Individual therapy choosing from abiraterone, enzalutamide, cabazitaxel and docetaxel; taking into account the previous therapies as well as the approval of the respective medicinal products
a. Presentation of the respective ACT specified by the G-BA. b. For the present therapeutic indication, it is assumed that ongoing conventional ADT (surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists) is continued. c. The G-BA specified the present ACT only for those patients whose disease is progressive after previous treatment with abiraterone and/or enzalutamide. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mCRPC: metastatic castration resistant prostate cancer; NHA: new hormonal agent	

At first, the company followed the G-BA's specification. In the following, it limited the options specified by the G-BA and specified an individual therapy choosing from abiraterone or enzalutamide as comparator therapy. However, when selecting relevant studies, it considered all individual treatment options specified by the G-BA. The present benefit assessment of olaparib was conducted in comparison with the G-BA's ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on olaparib (status: 21 September 2020)
- bibliographical literature search on olaparib (last search on 21 September 2020)
- search in trial registries/trial results databases for studies on olaparib (last search on 21 September 2020)
- search on the G-BA website for olaparib (last search on 21 September 2020)

To check the completeness of the study pool:

- search in trial registries for studies on olaparib (last search on 4 December 2020)

The check did not identify any additional relevant studies.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: olaparib + ADT vs. abiraterone + P +ADT or enzalutamide + ADT

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 and other sources[c] yes/no [citation])
D081DC00007 (PROfound[d])	Yes	Yes	No	No[e]	Yes [3-5]	Yes [6-8]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: EPAR.
d. In the following tables, the study is referred to with this abbreviated form.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

ADT: androgen deprivation therapy; CSR: clinical study report; EPAR: European Public Assessment Report; P: prednisone/prednisolone; RCT: randomized controlled trial

The study pool concurs with that of the company.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: olaparib + ADT vs. abiraterone + P +ADT or enzalutamide + ADT (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PROfound	RCT, open-label, parallel	Adult patients with mCRPC[b] and mutation of genes involved in HRR[c], whose disease progressed under prior therapy with an NHA, with ECOG PS ≤ 2	Cohort A[c]: ▪ olaparib + ADT (N = 162) ▪ abiraterone + P + ADT or enzalutamide + ADT[d] (N = 83) cohort B[c]: ▪ olaparib + ADT (N = 94) ▪ abiraterone + P + ADT or enzalutamide + ADT[d] (N = 48) relevant subpopulation thereof[e]: ▪ olaparib + ADT (n = 102) ▪ abiraterone + P + ADT or enzalutamide + ADT[d] (n = 58)	Screening: up to 28 days before randomization treatment: until radiologically confirmed disease progression[f] or fulfilment of another criterion for discontinuation[g] observation[h]: outcome-specific, at most until death or end of study	206 study centres in Argentina, Australia, Austria, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Japan, Netherlands, Norway, South Korea, Spain, Sweden, Taiwan, Turkey, United Kingdom, USA 02/2017–ongoing data cut-offs[i]: ▪ first data cut-off: 4 September 2019 ▪ second data cut-off: 20 March 2020	Primary: rPFS secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: olaparib + ADT vs. abiraterone + P +ADT or enzalutamide + ADT (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 consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Evidence of radiological progression under ongoing ADT or after surgical castration and serum testosterone level ≤ 50 ng/dL (≤ 1.75 nmol/L) ≤ 28 days before randomization; patients with local recurrence, regional metastasis (pelvic lymph nodes), brain metastases or spinal compression (unless conclusively treated and stable ≥ 28 days) were not included.
c. Examination of the tumour sample using the Lynparza HRR assay developed for the study for mutations in genes involved in HRR, based on the FoundationOne CDx test [9]; depending on the affected gene, patients were assigned to cohort A *(BRCA1, BRCA2, ATM*) or cohort B (other genes involved in HRR).
d. Patients in the comparator arm of the study received the therapy determined for them by the treating physician prior to randomization (abiraterone or enzalutamide).
e. Subpopulation of patients with *BRCA1/2 mutation*
f. Until the first data cut-off, patients were to be treated with the study medication until radiological progression was confirmed by a blinded independent review committee according to RECIST criteria version 1.1 (soft tissue) or PCWG3 criteria (bones). After this time point, the investigator's assessment was sufficient (progression in bones requires confirmatory scan ≥ 6 weeks).
g. Other criteria for discontinuation: unacceptable toxicity, MDS/AML, patient's decision, clear clinical progression (start of continuous opioid medication for the treatment of cancer-related pain, direct need for chemotherapy, radiotherapy or surgery to treat progression-related complications, deterioration in ECOG PS to ≥ 3), start of non-permitted cancer therapy (see Table 7).
h. Outcome-specific information is provided in Table 8.
i. First data cut-off: planned primary analysis after approx. 143 rPFS events in cohort A; second data cut-off: planned final analysis after approx. 146 deaths.

ADT: androgen deprivation therapy; AE: adverse event; AML: acute myeloid leukaemia; ATM: Ataxia Telangiectasia Mutated; BRCA: breast cancer associated gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HRR: homologous recombination repair; mCRPC: metastatic castration-resistant prostate cancer; MDS: myelodysplastic syndrome; n: relevant subpopulation; N: number of randomized patients; NHA: new hormonal agent; P: prednisone/prednisolone; PCWG3: Prostate Cancer Working Group 3; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours; rPFS: radiographic progression-free survival

Table 7: Characteristics of the intervention – RCT, direct comparison: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT (multipage table)

Study	Intervention	Comparison
PROfound	▪ Olaparib: 600 mg/day (2 film-coated tablets of 150 mg twice daily), orally + ADT[a]	▪ Abiraterone: 1000 mg/day (4 film-coated tablets of 250 mg or 2 film-coated tablets of 500 mg once daily), orally + prednisone[b]: 10 mg/day (5 mg twice daily), orally + ADT[a] or ▪ enzalutamide: 160 mg/day (4 capsules/tablets of 40 mg each, once daily), orally + ADT[a]
	▪ Dose adjustments in case of side effects largely correspond to the specifications of the SPC. Re-escalation after dose reduction was not allowed.	▪ Dose adjustments in case of side effects must adhere to the SPC and local guidelines
	Pretreatment required: ▪ NHA (e.g. abiraterone and/or enzalutamide)[c] ▪ ADT with a GnRH analogue (agonist or antagonist) or surgical castration allowed: ▪ radiotherapy ▪ surgery > 2 weeks before start of study medication and after recovery from the surgical intervention **not allowed:** ▪ PARP inhibitors (including olaparib) ▪ DNA-damaging chemotherapies[d] for the treatment of prostate carcinoma (e.g. mitoxantrone, platinum-based chemotherapy) ▪ systemic anticancer therapies (except radiotherapy) ≤ 3 weeks before start of study medication **concomitant treatment** allowed: ▪ palliative radiotherapy for the treatment of bone metastases[e] if already available at baseline ▪ bisphosphonates or denosumab at a stable dose ≥ 4 weeks before the start of the study medication ▪ any other medication deemed necessary for the patient's well-being at the discretion of the physician **not allowed:** ▪ other anticancer therapies (except GnRH analogues), biologics, investigational products or other new therapies (including corticosteroids if used for anticancer therapy) ▪ strong/moderate CYP3A inhibitors and inducers[f] as well as strong CYP2C8 inhibitors[g] should be avoided	

Table 7: Characteristics of the intervention – RCT, direct comparison: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT (multipage table)

Study	Intervention	Comparison
a. Drug treatment by means of GnRH analogue or condition after surgical castration. b. Or if necessary prednisolone. c. For the treatment of mPC and/or CRPC. d. These therapies were allowed for the treatment of other diseases if the last dose was administered > 5 years prior to randomization. Previous treatment with estramustine was principally allowed. e. Therefore, treatment with olaparib had to be discontinued ≥ 3 days before; re-initiation of treatment with olaparib was to take place ≤ 4 weeks after radiotherapy, provided that the bone marrow had recovered from the radiation. f. Reduction of the olaparib dose in accordance with the SPC in case of simultaneous intake of strong/moderate CYP3A inhibitors; thereafter, re-escalation was possible. Use of strong/moderate CYP3A inducers requires monitoring of interactions with olaparib. g. In case of simultaneous intake: reduction of the enzalutamide dose to 80 mg/day. ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; CYP2C8: cytochrome P450 2C8; CYP3A: cytochrome P450 3A; DNA: deoxyribonucleic acid; GnRH: gonadotropin-releasing hormone; mPC: metastatic prostate cancer; NHA: new hormonal agent; P: prednisone/prednisolone; PARP: poly(adenosine diphosphate-ribose) polymerase; RCT: randomized controlled trial		

Study design

PROfound is a randomized, open-label study that compares olaparib under continuation of the ongoing ADT, (hereinafter referred to as olaparib + ADT) with physician's choice therapy choosing from abiraterone or enzalutamide. Both treatment with abiraterone or enzalutamide was also carried out under continuation of the ongoing ADT, and abiraterone was additionally combined with prednisone or prednisolone, as required (hereinafter referred to as abiraterone + P + ADT or enzalutamide + ADT).

The study included adult men with mCRPC and mutation in a gene involved in HRR, provided that their disease was progressive under previous therapy with an NHA and they had an ECOG PS of 0, 1 or 2. Prior NHA therapy should have been performed for the treatment of mPC or CRPC. At the time of study inclusion, patients should have radiological progression under ongoing ADT (medical or surgical castration, and serum testosterone level ≤ 50 ng/dL or ≤ 1.75 nmol/L).

To confirm the mutation, a tumour sample was screened for mutations in 15 genes involved in HRR using the Lynparza HRR assay developed for the study, based on the FoundationOne CDx test [9]. Depending on the affected gene, patients were assigned to cohort A *(BRCA1, BRCA2, ATM*) or cohort B (other genes involved in HRR).

A total of 387 patients were included in the study, for whom treatment with abiraterone or enzalutamide had to be suitable according to the inclusion criteria. Prior to randomization, the physician determined which of the cited treatment options each patient should receive if assigned to the comparator arm. In the individual cohorts, the patients were randomly assigned either to treatment with olaparib or to the corresponding physician's choice therapy (abiraterone

or enzalutamide) in a 2:1 ratio. Randomization was stratified by previous receipt of taxane-containing chemotherapy (yes/no) and measurable disease at baseline (yes/no).

Treatment with olaparib, abiraterone or enzalutamide was performed according to the respective SPC [10-12]. Abiraterone was administered in combination with prednisone (prednisolone, if appropriate), as required by the SPC [11]. In addition to the study medication, patients had to maintain their ongoing ADT in the study. This was either medical castration using a GnRH analogue, or previous surgical castration.

Patients were treated until radiologically confirmed disease progression (Response Evaluation Criteria In Solid Tumours [RECIST] criteria version 1.1 [soft tissue] or Prostate Cancer Working Group 3 [PCWG3] criteria [bones]), unless one of the other criteria for treatment discontinuation already applied. After disease progression, the choice of subsequent therapy was at the physician's discretion; patients from the comparator arm could receive olaparib.

Primary outcome of the study was "rPFS", patient-relevant secondary outcomes included "overall survival" and outcomes on morbidity, health-related quality of life and AEs.

Subpopulation relevant for the benefit assessment

The PROfound study included patients with mutations in 15 different genes involved in HRR, which were assigned to cohort A *(BRCA1, BRCA2, ATM*) or cohort B (other genes involved in HRR) depending on the affected gene. Approval by the EMA was only granted for patients with mutations in the *BRCA1* or *BRCA2* genes [8]. The company presented analyses of the subpopulation of patients with BRCA1/2-mutations. These are relevant for the benefit assessment and include a total of 160 patients, 102 patients in the intervention arm and 58 patients in the comparator arm. According to the company, 2 patients with a BRCA2 mutation who had been assigned to cohort B by mistake were included in the relevant subpopulation.

Implementation of the ACT

The G-BA specified individual therapy as ACT choosing from abiraterone, enzalutamide, cabazitaxel and docetaxel, taking into account the prior therapies as well as the approval of the respective drugs.

The PROfound study is a multi-comparator study choosing from abiraterone and enzalutamide. According to the inclusion criteria, only patients for whom treatment with abiraterone or enzalutamide was an option could be included in the study. The study protocol did not specify the criteria on which this decision should be based. Prior to randomization, the physician determined the treatment option for each individual patient (abiraterone or enzalutamide) in case he was randomly assigned to the comparator arm.

A look at the previous therapies shows that approx. 18% of the patients had already been pretreated with both abiraterone and enzalutamide (see Table 9). Although the German S3 Guideline on Early Detection, Diagnostics and Therapy of the different stages of prostate cancer

does not specify any lines of treatment beyond second-line therapy, it states that a sequential therapy using one of the other effective drugs can be offered after androgen receptor-targeted treatment [13]. For patients pretreated with abiraterone and enzalutamide, it is therefore questionable whether retreatment with abiraterone or enzalutamide was the most suitable individual therapy, or whether treatment with docetaxel or cabazitaxel would have been more suitable for these patients, whereby cabazitaxel is only approved after pretreatment with a docetaxel-based therapy regimen [14,15]. However, as this concerned less than 20% of the patients, this has no consequence for the benefit assessment. In the relevant subpopulation, the ACT was considered adequately implemented.

Based on the PROfound study, conclusions for the benefit assessment can only be drawn for patients for whom abiraterone or enzalutamide was best suited on an individual basis within the framework of the ACT. No data are available on patients for whom docetaxel or cabazitaxel was best suited on an individual basis within the framework of the ACT.

Data cut-offs

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

- First data cut-off of 4 September 2019: planned primary analysis after approximately 143 rPFS events in cohort A
- Second data cut-off of 20 March 2020: planned final analysis after approx. 146 deaths

The company presented results on all patient-relevant outcomes for the second data cut-off for the relevant subpopulation. This preplanned, final analysis of the PROfound study served as a basis for the benefit assessment.

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 the follow-up observation – RCT, direct comparison: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT

Study **outcome category** **outcome**	**Planned follow-up observation**
PROfound	
Mortality	
Overall survival	Until death or end of study
Morbidity	
Symptomatic skeletal-related events	Until discontinuation of the study medication
Pain (BPI-SF)	Until 6 months after radiological disease progression[a]
Health status (EQ-5D VAS)	Until 6 months after radiological disease progression[a]
Health-related quality of life (FACT-P)	Until 6 months after radiological disease progression[a]
Side effects	
AEs/SAEs/severe AEs[b]	Until 30 days after discontinuation of the study medication
PRO-CTCAE	Until 6 months after radiological disease progression[a]
Secondary malignancies (including MDS/AML, among others)	Until death or end of study

a. Discrepant information in Module 4 A and in the study protocol. In Module 4 A, the company states that the patient-reported outcomes were observed until progression. However, according to the study protocol, these outcomes should also be observed beyond progression.
b. Operationalized as CTCAE grade ≥ 3.

ADT: androgen deprivation therapy; AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; MDS: myelodysplastic syndrome; P: prednisone/prednisolone; PRO: patient-reported outcome; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for the outcomes of the categories “morbidity” and “health-related quality of life” as well as the side effect outcomes “AEs”, “SAEs” and “severe AEs” (CTCAE grade ≥ 3) and PRO-CTCAE were systematically shortened. For instance, symptomatic skeletal-related events were to be recorded only for the period of treatment with the study medication. The other outcomes of the category “morbidity” and “health-related quality of life” were to be observed beyond progression, but at most until 6 month following progression. For the outcomes on side effects, AEs, SAEs and severe AEs should be recorded until 30 days after discontinuation of the study medication and PRO-CTCAE until 6 months after progression. However, secondary malignancies, such as MDS and AML, should be monitored until death or until the end of the study.

To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record all outcomes over the total period of time, as was the case for survival.

Patient characteristics

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

Table 9: Characteristics of the study population – RCT, direct comparison: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT (multipage table)

Study characteristic category	Olaparib + ADT N[a] = 102	Abiraterone + P + ADT or enzalutamide + ADT N[a] = 58
PROfound		
Age [years], mean (SD)	67 (8)	67 (8)
Family origin, n (%)		
Caucasian	67 (66)	41 (71)
Black or African American	2 (2)	0 (0)
Asian	27 (27)	10 (17)
Other	0 (0)	1 (2)
Missing	6 (6)	6 (10)
Region, n (%)		
Asia	35 (34[b])	19 (33[b])
Europe	44 (43[b])	26 (45[b])
North/South America	23 (23[b])	13 (22[b])
BRCA mutation, n (%)		
BRCA1	10 (10)[b]	5 (9)[b]
BRCA2	92 (90)[b]	53 (91)[b]
Disease duration: time between first diagnosis of CRPC and randomization [months], median [min; max]	23.3 [−6[c]; 119]	22.1 [1; 87]
Gleason score at diagnosis, n (%)		
≤ 6	7 (7)[b]	3 (5)[b]
7	25 (25)	17 (29)
≥ 8	66 (65)[b]	37 (64)[b]
Missing	4 (4)	1 (2)
Metastases at baseline (eCRF), n (%)		
Bones[d]	91 (89)	50 (86)
Bones only	34 (33)	15 (26)
Visceral	30 (29)	22 (38)
Other	33 (32)	18 (31)
Unknown/missing	5 (5)	3 (5)
ECOG PS, n (%)		
0	51 (50)	22 (38)
1	43 (42)	33 (57)
2	8 (8)	3 (5)
Worst pain at baseline (BPI-SF Item 3)[e], n (%)		
≤ 1	53 (52)	26 (45)
2–3	10 (10)	4 (7)
> 3	35 (34)	26 (45)

Table 9: Characteristics of the study population – RCT, direct comparison: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT (multipage table)

Study characteristic category	**Olaparib + ADT N[a] = 102**	**Abiraterone + P + ADT or enzalutamide + ADT N[a] = 58**
Missing	4 (4)	2 (3)
Pretreatment for prostate cancer, n (%)		
Immunotherapy	7 (7)	7 (12)
NHA[f]	100 (98[g])	58 (100)
Enzalutamide	42 (41)	29 (50)
Abiraterone	38 (37)	21 (36)
Enzalutamide and abiraterone	20 (20)	8 (14)
Local therapy with curative intent for prostate cancer	45 (44)	23 (40)
Chemotherapy with taxanes	72 (71)	35 (60)
for the treatment of mCRPC	61 (60)	29 (50)
Docetaxel	41 (40)	18 (31)
Cabazitaxel	2 (2)	1 (2)
Docetaxel and cabazitaxel	18 (18)	10 (17)
Radiotherapy	65 (64)	38 (66)
Other treatments	24 (24)	15 (26)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. In Module 4 A, the company explained that diagnosis of CRPC was made for a patient prior to randomization, and that the information on time is based on an incorrect input.
d. According to the opinion of the investigator.
e. Assessment of the worst pain within the last 24 hours on an 11-point scale from 0 (no pain) to 10 (worst pain imaginable).
f. According to the inclusion criteria, all patients should have disease progression during therapy with an NHA for the treatment of mPC and/or CRPC. Until Amendment 3 of the study protocol of 4 June 2018, pretreatment with an NHA was still limited to the treatment of mCRPC. Accordingly, the EPAR information on the total study population indicates that almost all patients (approx. 98%) had received therapy with an NHA for the treatment of the mCRPC.
g. In Module 4 A, the company states that all patients received prior therapy with an NHA, but that the data on this pretreatment from the eCRF were missing for 2 of the patients at the date of the database closure.

ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory-Short Form; BRCA: breast cancer associated gene; CRPC: castration-resistant prostate cancer; DNA: deoxyribonucleic acid; ECOG PS: Eastern Cooperative Oncology Group Performance Status; eCRF: electronic case report form; mCRPC: metastatic castration-resistant prostate cancer; n: number of patients in the category; N: number of randomized patients; ND: no data; NHA: new hormonal agent; P: prednisone/prednisolone; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics of the patients in both treatment arms were largely comparable. The mean age of the patients was 67 years, and the majority of them (approx. 65%)

had a Gleason score ≥ 8 at diagnosis. There were minor differences in the proportion of patients with visceral metastases and ECOG PS of 0 or 1. 29% of the patients in the olaparib arm and 38% in the comparator arm had visceral metastases at baseline. The proportion of patients with ECOG PS of 0 was 50% in the olaparib arm and thus higher than in the comparator arm (38%). Correspondingly, the proportion of patients with ECOG PS of 1 was slightly lower in the olaparib arm (42%) than in the comparator arm (57%).

According to the inclusion criteria, all patients had already received treatment with an NHA. According to the inclusion criteria, all patients should have had disease progression during therapy with an NHA for the treatment of mPC and/or CRPC. Until Amendment 3 of the study protocol of 4 June 2018, pretreatment with an NHA was still limited to the treatment of mCRPC. Accordingly, the EPAR information on the total study population of the PROfound study indicates that almost all patients (approx. 98%) had received therapy with an NHA for the treatment of the mCRPC. No separate data were available for the relevant subpopulation.

Moreover, the majority of patients - 72 patients (71%) in the olaparib arm and 35 patients (60%) in the comparator arm - had already received taxane-containing chemotherapy, mostly for the treatment of mCPRC. About 18% of the patients had already received therapy with docetaxel and cabazitaxel. There was no information on patients who discontinued the therapy or the study.

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: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT

Study **duration of the study phase** **outcome category**	**Olaparib + ADT** **N = 102**	**Abiraterone + P + ADT or enzalutamide + ADT** **N = 58**
PROfound		
Treatment duration [months]		
Median [min; max]	9.6 [0.0; 28.9]	3.8 [0.7; 14.7]
Mean (SD)	ND	ND
Observation period [months]		
Overall survival		
Median [min; max]	17.4 [0.3; 33.4]	14.4 [1.1; 32.8]
Mean (SD)	ND	ND
Pain (BPI-SF)		
Median [min; max]	7.3 [0.0; 28.3]	2.2 [0.0; 14.6]
Mean (SD)	ND	ND
Symptomatic skeletal-related events		
Median [min; max]	14.5 [0.3; 27.6]	9.2 [1.1; 25.8]
Mean (SD)	ND	ND
Health status (EQ-5D VAS)		
Median [min; max]	9.1 [0.0; 27.5]	1.9 [0.0; 14.8]
Mean (SD)	ND	ND
Health-related quality of life (FACT-P)		
Median [min; max]	9.1 [0.0; 27.5]	1.9 [0.0; 14.8]
Mean (SD)	ND	ND
AEs, SAEs, severe AEs[a]		
Median [min; max]	10.3 [0.3; 28.9]	3.9 [0.9; 15.2]
Mean (SD)	ND	ND
PRO-CTCAE	ND	ND
Secondary malignancies (including MDS/AML, among others)	ND	ND

a. Operationalized as CTCAE grade ≥ 3.

ADT: androgen deprivation therapy; AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; max: maximum; MDS: myelodysplastic syndrome; min: minimum; ND: no data; N: number of analysed patients; P: prednisone/prednisolone; PRO: patient-reported outcome; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale

In the PROfound study, median treatment duration in the olaparib arm was 9.6 months, slightly more than twice as long as in the comparator arm (3.8 months).

Most of the observation periods for the individual outcomes were clearly longer (up to almost 5-fold) in the olaparib arm than in the comparator arm. Data on the observation periods for PRO-CTCAE or secondary malignancies, such as MDS or AML, are not available.

It becomes clear that the observation periods for the PROs almost correspond to the median time to rPFS (median: 9.8 months in the olaparib arm vs. 3.0 months in the comparator arm). In Module 4 A, the company states that the PROs were only recorded until disease progression. However, according to the study protocol, PROs ("pain", "health status" and "health-related quality of life") were to be recorded until 6 months after disease progression (see Table 8), and it can be assumed that these data were recorded in line with the requirements of the study protocol. The company did not present these data in Module 4 A of the dossier. This approach is not appropriate. The benefit assessment requires analyses that take into account all data recorded in the relevant period.

It is unclear why the observation periods for symptomatic skeletal-related events, which should only be recorded until discontinuation of the study medication, are significantly longer than the respective median treatment duration.

Subsequent therapies

In the PROfound study, subsequent therapies were chosen at the physician's discretion. Patients in the comparator arm had the option to receive olaparib after disease progression. 40 patients (69%) in the comparator arm had received olaparib at the relevant data cut-off. At the time the study was conducted, olaparib as subsequent therapy was not an approved treatment option. Switching from the control to the experimental intervention can have a potentially biasing effect on the results of the benefit assessment. This aspect was therefore taken into account in the assessment of the outcome-specific risk of bias for outcomes where the switch of treatment may have affected the results (see Section 2.4.2). Further information on subsequent therapies received by the relevant subpopulation is missing.

Risk of bias across outcomes (study level)

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

Table 11: Risk of bias across outcomes (study level) - RCT, direct comparison: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT

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			
PROfound	Yes	Yes	No	No	Yes	Yes	Low
ADT: androgen deprivation therapy; P: prednisone/prednisolone: RCT: randomized controlled trial							

The risk of bias across outcomes for the PROfound study was rated as low. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.4 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company stated that there was no established treatment algorithm in Europe for the present therapy situation. With regard to the ACT specified by the G-BA, it explained that only those patients were included in the PROfound study for whom, according to the physician's assessment, treatment with abiraterone or enzalutamide represented the most suitable individual therapy at that time. Patients for whom taxane-based chemotherapy was the most suitable individual therapy at the time were not included in the PROfound study. Moreover, the company stated that patients could also be included in the study after receipt of a taxane-containing therapy. In addition, concomitant ADT had been performed in accordance with the recommendations of the German S3 guideline [13]. Based on this information, the company concluded that each patient in the study had received the individual therapy best suited for her/him in this line of treatment.

The company stated that in the PROfound study the dosage of olaparib was in compliance with the approval [10]. From the company's point of view, the target population corresponds to the German health care context, since the median age of the target population at disease onset is similar to the data from the Robert Koch Institute [16] and the majority of the patients are of Caucasian origin.

With regard to the mutation screening performed in the study, the company states that the observed frequency and distribution of BRCA1/2 mutations are similar to other studies [17-20]. Despite the fact that molecular testing was currently not recommended by the German S3 guideline [13], it could not be assumed that there was a deviation from the German health care context. Moreover, the study had been conducted in accordance with the principles of good clinical practice.

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - Overall survival

- Morbidity
  - Worst pain (measured using the BPI-SF Item 3).
  - Pain interference (measured using BPI-SF Items 9a–g).
  - Symptomatic skeletal-related events, including:
    - New symptomatic pathologic bone fractures
    - Radiotherapy to prevent or alleviate skeletal symptoms
    - Spinal cord compression
    - Orthopaedic-surgical intervention due to bone metastases
  - Health status (EQ-5D VAS)
- Health-related quality of life
  - Measured using the FACT-P total score
- Side effects
  - SAEs
  - Severe AEs (operationalized as CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - PRO-CTCAE
  - MDS (PT, AEs)
  - AML (PT, AEs)
  - Pneumonitis (PT, AEs)
  - Further specific AEs, if any

The selection of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A), but did not list PRO-CTCAE among the outcomes.

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of the outcomes – RCT, direct comparison: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT

Study	Outcomes																	
	Overall survival	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF Items 9a–g)	Symptomatic skeletal-related events[a]	New symptomatic pathologic bone fractures	Radiotherapy to prevent or alleviate skeletal symptoms	Spinal cord compression	Orthopaedic-surgical intervention due to bone metastases	Health status (EQ-5D VAS)	Health-related quality of life (FACT-P)	SAEs	Severe AEs[b]	Discontinuation due to AEs	PRO-CTCAE	MDS (PT, AEs)	AML (PT, AEs)	Pneumonitis (PT, AE)	Further specific AEs[c]
PROfound	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[d]	No[d]	Yes	Yes	Yes	No[e]	No[d]	No[d]	No[d]	Yes

a. Included: New symptomatic pathologic bone fractures, radiotherapy to prevent or alleviate skeletal symptoms, occurrence of spinal cord compression, orthopaedic surgery due to bone metastases.
b. Operationalized as CTCAE grade ≥ 3.
c. The following events (MedDRA coding) are considered: "anaemia (PT, severe AEs[b])", "nausea (PT, AEs)".
d. No usable analyses available; for reasons, see the text passage following the table.
e. No data available.

ADT: androgen deprivation therapy; AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; MDS: myelodysplastic syndrome; MedDRA: Medical Dictionary for Regulatory Activities; P: prednisone/prednisolone; PRO: patient-reported outcome; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Notes on the analyses presented in Module 4 A

- The company presented continuous analyses for the EQ-5D VAS and the FACT-P. The information in Module 4 A shows that the proportion of patients not considered in the analysis was > 30% in each case. Therefore, these analyses were not usable for the present benefit assessment.
- For the EQ-5D VAS, the company presented responder analyses on the first deterioration by at least 10 and 7 points. For the FACT-P, the company presented responder analyses for the total score for the first deterioration by at least 10 points. The responder analyses on the EQ-5D VAS and the FACT-P submitted by the company were not used for the dossier assessment. As explained in the General Methods of the Institute [21,22], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument on a predefined basis (in post-hoc analyses exactly 15% of the scale range). In the responder analyses, the proportion of patients not considered in the analysis is also assumed to be > 30%. Although more patients were formally included in these analyses than in the continuous analyses, these patients were counted as censored on day 1 and thus have no impact on the results.
- According to the study protocol, side effects were also recorded with PRO-CTCAE in the PROfound study. For a general assessment of the PRO-CTCAE system, see the corresponding explanations in benefit assessment A20-87 [1]. According to the study protocol, 8 symptomatic AEs were to be recorded from the PRO-CTCAE system: fatigue/tiredness or lack of energy, decreased appetite, soft or watery stools (diarrhoea), nausea, vomiting, dizziness, concentration problems and memory disorders. In the study protocol, the choice of the mentioned AEs is justified by the fact that they are considered relevant for the treatment in the study arms. The PRO-CTCAE instrument was to be recorded only in countries where a translation of the questionnaire into the national language was available. Module 4 A provides no results for the PRO-CTCAE.
- In Module 4 A, the company announces to present analyses for the specific AEs “MDS”, “AML” and “pneumonitis” based on the prespecified AEs of special interest for a period of 30 days after discontinuation of the study medication. However, it only presented results on pneumonitis, but not on MDS and AML. The analyses for pneumonitis are not usable, as it is unclear which PTs were included in these analyses. Moreover, it should be noted that, according to the study protocol, secondary malignancies, such as MDS and AML, should be recorded until the death of the patient or the end of the study (see Section 2.3.2 for planned duration of follow-up observation). Accordingly, analyses of MDS and AML should consider the entire survey period.

2.4.2 Risk of bias

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

Table 13: Risk of bias across outcomes and outcome-specific risk of bias - RCT, direct comparison: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT (multipage table)

Study		Outcomes																	
	Study level	Overall survival	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF Items 9a–g)	Symptomatic skeletal-related events[a]	New symptomatic pathologic bone fractures	Radiotherapy to prevent or alleviate skeletal symptoms	Spinal cord compression	Orthopaedic-surgical intervention due to bone metastases	Health status (EQ-5D VAS)	Health-related quality of life (FACT-P)	SAEs	Severe AEs[b]	Discontinuation due to AEs	PRO-CTCAE	MDS (PT, AEs)	AML (PT, AEs)	Pneumonitis (PT, AEs)	Further specific AEs[c]
PROfound	L	H[d]	H[e, f]	H[e, g]	H[h]	H[h]	H[h]	H[h]	H[h]	–[i]	–[i]	H[h]	H[h]	H[e]	–[i]	–[i]	–[i]	–[i]	H[e, h]

a. Included: New symptomatic pathologic bone fractures, radiotherapy to prevent or alleviate skeletal symptoms, occurrence of spinal cord compression, orthopaedic surgery due to bone metastases.
b. Operationalized as CTCAE grade ≥ 3.
c. The following events (MedDRA coding) are considered: "anaemia (PT, severe AEs[b])", "nausea (PT, AEs)".
d. Switch of treatment from control to experimental intervention in 40 patients (69%) in the comparator arm who received olaparib as subsequent therapy.
e. Lack of blinding in subjective recording of outcomes (except for specific AEs with CTCAE grade ≥ 3) or subjective request for treatment discontinuation (discontinuation due to AEs).
f. Unclear proportion of patients with missing values at baseline and at least 1 subsequent time point who were counted as censored on day 1. Moreover, incomplete observations for potentially informative reasons due to lack of consideration of observation after progression (median time to progression: 9.8 months [intervention] vs. 3.0 months [control]). In addition, increasingly high and differential proportions of missing observations in the course of the study.
g. High proportion of patients not included in the analysis (intervention: 27.5% vs. control: 22.4%). As the data in Module 4 A were contradictory compared to the the SAP, it is also unclear whether observations were only considered in the analysis if values for the change at baseline were available for ≥ 25% of patients in both treatment arms at the time of the visit. Observations at the end of treatment and 30 days afterwards were not included; it is unclear how many patients are affected by this. Moreover, incomplete observations for potentially informative reasons due to lack of consideration of observation after progression (median time to progression: 9.8 months [intervention] vs. 3.0 months [control]). In addition, increasingly high and differential proportions of missing observations in the course of the study.
h. Incomplete observations for potentially informative reasons due to lack of follow-up observation after end of treatment (symptomatic skeletal-related events) or from 30 days onwards (AEs).
i. No usable analyses were available for these outcomes, for reasons, see Section 2.4.1.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias - RCT, direct comparison: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT (multipage table)

Study	Study level	Outcomes																	
		Overall survival	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF Items 9a–g)	Symptomatic skeletal-related events[a]	New symptomatic pathologic bone fractures	Radiotherapy to prevent or alleviate skeletal symptoms	Spinal cord compression	Orthopaedic-surgical intervention due to bone metastases	Health status (EQ-5D VAS)	Health-related quality of life (FACT-P)	SAEs	Severe AEs[b]	Discontinuation due to AEs	PRO-CTCAE	MDS (PT, AEs)	AML (PT, AEs)	Pneumonitis (PT, AEs)	Further specific AEs[c]

ADT: androgen deprivation therapy; AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; H: high; L: low; MDS: myelodysplastic syndrome; MedDRA: Medical Dictionary for Regulatory Activities; P: prednisone/prednisolone; PRO: patient-reported outcome; RCT: randomized controlled trial; SAE: serious adverse event; SAP: statistical analysis plan; VAS: visual analogue scale

The risk for bias of the result of "overall survival" was rated as high, because 40 patients (69%) in the comparator arm received olaparib as subsequent therapy. At the time the study was conducted, this was not an approved treatment option (see Section 2.3.2 on subsequent therapies).

The lack of blinding in subjective recording of outcomes resulted in a high risk of bias of the results on the outcomes "worst pain (BPI-SF Item 3)", "pain interference (BPI-SF Items 9a–g)", "discontinuation due to AEs" as well as the specific AE "nausea".

Moreover, the high risk of bias for the results of the outcome "worst pain (BPI-SF Item 3)" is additionally due to the unclear proportion of patients with missing values at baseline and at least 1 subsequent time point who had been censored on day 1 and must therefore be considered as patients not included in the analysis. Moreover, the lack of consideration of recordings after disease progression as well as increasingly high and differential proportions of missing observations over the course of the study lead to a high risk of bias in the results for this outcome.

For the results on the outcome '"pain interference (BPI-SF Items 9a-g)", the high risk for bias is additionally due to the fact that a high proportion of patients were not included in the analysis and it is also unclear whether observations were only considered in the analysis if values for the change at baseline were available for ≥ 25% of patients in both treatment arms at the time of the visit. Moreover, observations at the end of treatment and 30 days afterwards, as well as observations after disease progression, were not included in the analysis. In addition, the increasingly high and differential proportions of missing observations in the course of the study add to the assessment of a high risk of bias.

Due to incomplete observations for potentially informative reasons, the assessment is subject to a high risk of bias in the results on the outcomes "symptomatic skeletal-related events", including "new symptomatic pathologic bone fractures", "radiotherapy to prevent or alleviate skeletal symptoms", "occurrence of spinal cord compression" and "orthopaedic surgery due to bone metastases", as well as SAEs, severe AEs and the specific AEs "anaemia" and "nausea" (in this case plus the lack of blinding, see above).

No usable analyses were available for the outcomes on health status (EQ-5D VAS), health-related quality of life (FACT-P) and the specific AE "pneumonitis" and there were no data on PRO-CTCAE and the specific AEs "MDS" and "AML"; therefore, the risk of bias was not assessed for these outcomes.

Deviating from this, the company rated the risk of bias for the result on "overall survival" as low. Due to the lack of blinding, the company rated the risk of bias for the results of the outcomes on pain (BPI-SF), health status (EQ-5D VAS), health-related quality of life and all AEs as high. The company considered the risk of bias for the result of the outcome "symptomatic skeletal-related events" to be low.

2.4.3 Results

Table 14 and Table 15 summarize the results of the comparison of olaparib + ADT with abiraterone + P + ADT or enzalutamide + ADT in patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) whose disease is progressive after previous treatment that included an NHA. Where necessary, data from the company's dossier are supplemented by Institute's calculations.

Results on common AEs, SAEs and severe AEs (operationalized as CTCAE grade- ≥ 3) are presented in Appendix A of the full dossier assessment. Kaplan-Meier curves on the outcomes included are presented in Appendix B of the full dossier assessment.

Table 14: Results (mortality, morbidity, side effects, time to event) – RCT, direct comparison: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT (multipage table)

Study Outcome category Outcome	Olaparib + ADT		Abiraterone + P + ADT or enzalutamide + ADT		Olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT
	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]
PROfound					
Mortality					
Overall survival	102	20.1 [17.4; 26.8] 53 (52.0[b])	58	14.4 [10.7; 18.9] 41 (70.7[b])	0.63 [0.42; 0.95]; ND[c]
Morbidity					
Worst pain (BPI-SF Item 3)[d]	102[e]	22.8 [14.5; NC] 25 (24.5)	58[e]	5.5 [2.6; NC] 19 (32.8)	0.35 [0.18; 0.67]; < 0.001
Pain intensity (BPI-SF Items 3–6)[d] (supplementary information)	*102[e]*	*NA* *19 (18.6)*	*58[e]*	*5.5 [3.6; NC]* *15 (25.9)*	*0.33 [0.15; 0.69]; 0.002*
Symptomatic skeletal-related events[f]	102	NA 18 (17.6)	58	NA 12 (20.7)	0.64 [0.31; 1.39]; 0.255
New symptomatic, pathological bone fractures	102	NA 5 (4.9)	58	NA 4 (6.9)	0.56 [0.15; 2.31]; 0.310
Radiotherapy to prevent or alleviate skeletal symptoms	102	NA 15 (14.7)	58	NA 8 (13.8)	0.88 [0.38; 2.20]; 0.862
Occurrence of spinal cord compression	102	NA 4 (3.9)	58	NA 7 (12.1)	0.28 [0.07; 0.92]; 0.026
Orthopaedic surgery due to bone metastases	102	NA 1 (1.0)	58	NA 2 (3.4)	0.22 [0.01; 2.29]; 0.207
Side effects					
AEs (supplementary information)	102	0.5 [0.4; 0.9] 99 (97.1)	58	0.9 [0.7; 1.0] 52 (89.7)	–
SAEs	102	NA 38 (37.3)	58	11.1 [6.7; NC] 14 (24.1)	0.99 [0.53; 1.93]; 0.999
Severe AEs[g]	102	8.3 [5.7; NC] 56 (54.9)	58	12.7 [3.4; NC] 23 (39.7)	0.97 [0.60; 1.63]; 0.887

Table 14: Results (mortality, morbidity, side effects, time to event) – RCT, direct comparison: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT (multipage table)

Study Outcome category Outcome	Olaparib + ADT		Abiraterone + P + ADT or enzalutamide + ADT		Olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT
	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]
Discontinuation due to AEs	102	NA 19 (18.6)	58	NA 6 (10.3)	1.15 [0.47; 3.23]; 0.689
PRO-CTCAE				No data available[h]	
MDS[i] (PT, AEs)	102	ND	58	ND	ND
AML[i] (PT, AEs)	102	ND	58	ND	ND
Pneumonitis[i] (PT, AEs)	102	ND	58	ND	ND
Anaemia (PT, severe AEs[g])	102	NA 24 (23.5)	58	NA 1 (1.7)	11.60 [2.42; 208.02]; 0.003
Nausea (PT, AEs)	102	14.8 [3.6; NC] 47 (46.1)	58	NA 10 (17.2)	2.79 [1.46; 5.90]; 0.003

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; each stratified according to previous taxane treatment (yes/no) and measurable disease at baseline (yes/no).
b. Institute's calculation.
c. Discrepancy between information in Module 4 A and the EPAR. The presented data are from the EPAR. According to the information in Module 4 A, the HR at the data cut-off of 20 March 2020 is 0.60 and the corresponding 95% CI is [0,40; 0,91].
d. Time to first deterioration by ≥ 2 points.
e. The proportion of patients with missing values at baseline and at least 1 subsequent time point who were counted as censored on day 1 is unclear. These must not be considered as patients included in the analysis.
f. Included: new symptomatic pathologic bone fractures, radiotherapy to prevent or alleviate skeletal symptoms, spinal cord compression, orthopaedic surgery due to bone metastases.
g. Operationalized as CTCAE grade ≥ 3.
h. The company presented no data for this outcome in Module 4 A (see Section 2.4.1).
i. In Module 4 A, the company declares to provide analyses based on the AEs of particular interest for MDS/AML and pneumonitis, although it does not comment on the respective operationalization. These analyses on pneumonitis show that 2 patients in the intervention arm and no patient in the comparator arm had an event. The company presented no results for MDS/AML. Deviating from other AEs, occurrence of MDS/AML should not only be recorded until 30 days after discontinuation of the study medication, but until death of the patient or end of the study.

ADT: androgen deprivation therapy; AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; BRCA: breast cancer associated gene; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EPAR: European Public Assessment Report; 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; ND: no data; P: prednisone/prednisolone; PRO: patient-reported outcome; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event

Table 15: Results (morbidity, health-related quality of life, continuous) - RCT, direct comparison: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT

Study outcome category outcome	Olaparib + ADT			Abiraterone + P + ADT or enzalutamide + ADT			Olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT
	N[a]	Values at baseline mean (SD)	Change at the date of analysis mean (SE)	N[a]	Values at baseline mean (SD)	Change at the date of analysis mean (SE)	MD [95% CI]; p-value[b]
PROfound							
Morbidity							
Pain interference (BPI-SF Items 9a-g)[c]	74	1.73 (2.19)	-0.3 (0.18)	45	1.79 (2.15)	0.78 (0.25)	-1.08 [-1.69; -0.48]; < 0.001 Hedges' g: -0.66 [-1.04; -0.28]
Health status (EQ-5D VAS)	No usable analyses[d]						
Health-related quality of life							
FACT-P	No usable analyses[d]						

a. Number of patients considered in the analysis for the calculation of the effect estimation.
b. Effect, CI and p-value: mixed-effects model repeated measures (MMRM).
c. Lower (decreasing) values indicate better symptoms; negative effects (intervention–control) indicate an advantage for the intervention.
d. Data are not presented since the proportion of patients not considered in the analysis was > 30%. For information on the documentation period not considered in the company's analysis, see Section 2.3.2 and Section 2.4.1.

ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; ITT: intention to treat; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; P: prednisone/prednisolone; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale

Based on the available data, at most hints, e.g. of an added benefit, can be determined for all outcomes because of the high risk of bias.

Mortality

Overall survival

For the outcome "overall survival", there are discrepant results in Module 4 A and in the EPAR. The reason for this discrepancy is not clear from the information in Module 4 A. The results on "overall survival" from the EPAR were used for the present benefit assessment.

A statistically significant difference in favour of olaparib + ADT versus abiraterone + P + ADT or enzalutamide + ADT was shown between the treatment groups for the outcome "overall survival". This resulted in a hint of an added benefit of olaparib versus individual therapy (abiraterone or enzalutamide).

This deviates from the assessment of the company, which derived an indication of an added benefit for this outcome.

Morbidity

Worst pain (BPI-SF Item 3)

A statistically significant difference in favour of olaparib + ADT versus abiraterone + P + ADT or enzalutamide + ADT was shown between the treatment groups for the outcome "worst pain (BPI-SF Item 3)". This resulted in a hint of an added benefit of olaparib versus individual therapy (abiraterone or enzalutamide).

This deviates from the assessment of the company, which derived an indication of an added benefit for this outcome.

Pain interference (BPI-SF Items 9a–g)

A statistically significant difference in favour of olaparib + ADT versus abiraterone + P + ADT or enzalutamide + ADT was shown between the treatment groups for the outcome "pain interference (BPI-SF Items 9a–g)". The SMD in the form of Hedges' g was considered to check the relevance of the result. The 95% CI of the SMD was fully outside the irrelevance range of −0.2 to 0.2. This was interpreted to a relevant effect. This resulted in a hint of an added benefit of olaparib versus individual therapy (abiraterone or enzalutamide).

This deviates from the assessment of the company, which presented the results on this outcome, but did not use them for the derivation of the added benefit.

Symptomatic skeletal-related events

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

- New symptomatic pathologic bone fracture
- Radiotherapy to prevent or alleviate skeletal symptoms
- Spinal cord compression
- Orthopaedic-surgical intervention due to bone metastases

No statistically significant difference between the treatment groups was shown for the composite outcome "symptomatic skeletal-related events". This resulted in no hint of an added benefit of olaparib versus individual therapy (abiraterone or enzalutamide); an added benefit is therefore not proven.

New symptomatic pathologic bone fractures, radiotherapy to prevent or alleviate skeletal symptoms, orthopaedic surgery due to bone metastases

No statistically significant difference between the treatment arms was shown for the outcomes "new symptomatic pathologic bone fractures", "radiotherapy to prevent or alleviate skeletal

symptoms" and "orthopaedic surgery due to bone metastases". This resulted in no hint of an added benefit of olaparib versus individual therapy (abiraterone or enzalutamide) in each case; an added benefit is therefore not proven.

Spinal cord compression

A statistically significant difference in favour of olaparib + ADT versus abiraterone + P + ADT or enzalutamide + ADT was shown between the treatment groups for the outcome "spinal cord compression". This resulted in a hint of an added benefit of olaparib in comparison with individual therapy (abiraterone or enzalutamide).

This deviates from the approach of the company insofar as the company derived an indication of an added benefit based on the result on spinal cord compression for the composite outcome.

Health status (EQ-5D VAS)

No usable analyses were available for the outcome "health status" recorded with the EQ-5D VAS. This resulted in no hint of an added benefit of olaparib in comparison with individual therapy (abiraterone or enzalutamide); an added benefit is therefore not proven.

This deviates from the approach of the company, which derived an indication of an added benefit based on the responder analyses on the time to deterioration by at least 10 points.

Health-related quality of life

FACT-P

No usable analyses were available for the outcome "health-related quality of life", recorded with the FACT-P. This resulted in no hint of an added benefit of olaparib in comparison with individual therapy (abiraterone or enzalutamide); an added benefit is therefore not proven.

This corresponds to the assessment of the company insofar as the company also considered an added benefit as not proven, but used the analyses on the FACT-P considered by it for this purpose.

Side effects

According to the study protocol, AEs that are clearly due to a progression of the underlying disease should not be reported as AEs.

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

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from olaparib in comparison with individual therapy (abiraterone or enzalutamide); greater or lesser harm is therefore not proven.

In each case, this concurs with the company's assessment.

PRO-CTCAE

No data are available on the outcome "PRO-CTCAE". This resulted no hint of greater or lesser harm from olaparib in comparison with individual therapy (abiraterone or enzalutamide); greater or lesser harm is therefore not proven.

The company did not consider this outcome in Module 4 A.

Specific AEs

MDS, AML and pneumonitis (each PT, AEs)

No data are available on the specific AEs "MDS" and "AML" (PT, AEs each), and there are no usable analyses on the specific AE "pneumonitis (PT, AEs)". This resulted in no hint of greater or lesser harm from olaparib in comparison with individual therapy (abiraterone or enzalutamide); greater or lesser harm is therefore not proven.

Anaemia (PT, severe AEs), nausea (PT, AEs)

A statistically significant difference to the disadvantage of olaparib + ADT versus abiraterone + P + ADT or enzalutamide + ADT was shown between the treatment groups for the specific AEs "anaemia (PT, severe AEs)" and "nausea (PTs, AEs)". This resulted in a hint of greater harm from olaparib in comparison with individual therapy (abiraterone or enzalutamide) in each case.

This deviates from the approach of the company as the company did not consider specific AEs in the assessment of the added benefit.

2.4.4 Subgroups and other effect modifiers

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

- Age (< 65 years, ≥ 65 years)
- Metastases at baseline (bone metastases only, visceral metastases, other)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be 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 only presented if there is a statistically significant and relevant effect in at least one subgroup.

In accordance with the methods described, no relevant effect modification by the subgroup characteristics "age" or "metastases at baseline" was identified for the outcomes for which usable analyses were available.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below. Taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the General Methods of IQWiG [21].

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.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 16).

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

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Pain (BPI-SF Item 3), pain interference (BPI-SF Items 9a–g)

At baseline, the score for "most severe pain (BPI-SF item 3)" was 0 to 1 in about 50% of patients (see Table 9), corresponding to no pain or mild pain. The company did not present any information on the values the patients had after pain progression. On average, the patients showed low values for the outcome "pain interference (BPI-SF Items 9a-g)" at baseline (approx. 1.7; see Table 15), which changed by less than 1 point in the course of the study. Overall, the two outcomes "most severe pain (BPI-SF Item 3)" and "pain interference (BPI-SF Items 9a–g)" were therefore assigned to the outcome category "non-serious/non-severe symptoms/secondary complications".

Nausea (PT, AEs)

Module 4 A shows that the majority of events were non-serious or non-severe (CTCAE grade ≥ 3). The specific AE "nausea" was therefore allocated to the category of non-serious/non-severe side effects.

Table 16: Extent of the added benefit at outcome level: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT (multipage table)

Outcome category **outcome**	**Olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT** **median time to event (months) or mean change** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	20.1 vs. 14.4 months HR 0.63 [0.42; 0.95]; ND probability: "hint"	Outcome category: mortality $0.95 \leq CI_u < 1.00$ added benefit, extent: "minor"
Morbidity		
Worst Pain (BPI-SF Item 3) – time to first deterioration by ≥ 2 points	22.8 vs. 5.5 months HR: 0.35 [0.18; 0.67]; $p < 0.001$ probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Pain interference (BPI-SF Items 9a–g)	Mean change: -0.3 vs. 0.78 MD: -1.08 [-1.69; -0.48]; $p < 0.001$ Hedges' g: -0.66 [-1.04; -0.28][c] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Symptomatic skeletal-related events[d]	NA vs. NA HR: 0.64 [0.31; 1.39]; $p = 0.255$	Lesser benefit/added benefit not proven
New symptomatic pathologic bone fracture	NA vs. NA HR: 0.56 [0.15; 2.31]; $p = 0.310$	Lesser benefit/added benefit not proven
Radiotherapy to prevent or alleviate skeletal symptoms	NA vs. NA HR: 0.88 [0.38; 2.20]; $p = 0.862$	Lesser benefit/added benefit not proven
Spinal cord compression	NA vs. NA HR: 0.28 [0.07; 0.92]; $p = 0.026$ probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Orthopaedic-surgical intervention due to bone metastases	NA vs. NA HR: 0.22 [0.01; 2.29]; $p = 0.207$	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable analyses	Lesser benefit/added benefit not proven
Health-related quality of life		
FACT-P	No usable analyses	Lesser benefit/added benefit not proven
Side effects		

Table 16: Extent of the added benefit at outcome level: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT (multipage table)

Outcome category outcome	**Olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT median time to event (months) or mean change effect estimation [95% CI]; p-value probability[a]**	**Derivation of extent[b]**
SAEs	NA vs. 11.1 months HR: 0.99 [0.53; 1.93]; p = 0.999	Greater/lesser harm not proven
Severe AEs	8.3 vs. 12.7 months HR: 0.97 [0.60; 1.63]; p = 0.887	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. NA HR: 1.15 [0.47; 3.23]; p = 0.689	Greater/lesser harm not proven
PRO-CTCAE	No data available	Greater/lesser harm not proven
MDS (AEs)	No data available	Greater/lesser harm not proven
AML (AEs)	No data available	Greater/lesser harm not proven
Pneumonitis (AEs)	No usable data available	Greater/lesser harm not proven
Anaemia (severe AEs)	NA vs. NA HR: 11.60 [2.42; 208.02] HR: 0.09 [0.005; 0.41][e] p = 0.003 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"
Nausea (AEs)	14.8 months vs. NA HR: 2.79 [1.46; 5.90] HR: 0.36 [0.17; 0.68][e] p = 0.003 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be inferred.
d. Included: New symptomatic pathologic bone fractures, radiotherapy to prevent or alleviate skeletal symptoms, occurrence of spinal cord compression, orthopaedic surgery due to bone metastases.
e. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

ADT: androgen deprivation therapy; AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of the confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EPAR: European Public Assessment Report; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; MD: mean difference; MDS: myelodysplastic syndrome; NA: not achieved; ND: no data; P: prednisone/prednisolone; PRO: patient-reported outcome; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of olaparib + ADT in comparison with abiraterone + P + ADT or enzalutamide + ADT

Positive effects	**Negative effects**
Mortality ▪ overall survival: hint of an added benefit – extent: "minor"	–
Serious/severe symptoms/late complications ▪ spinal cord compression: hint of an added benefit – extent "minor"	–
Non-serious/non-severe symptoms/late complications ▪ pain ▫ worst pain (BPI-SF item 3): hint of an added benefit - extent: "considerable" ▫ pain interference (BPI-SF items 9a-g): hint of an added benefit - extent: "not quantifiable"	–
–	Serious/severe side effects ▪ anaemia (severe AEs): Hint of greater harm - extent "major"
–	Non-serious/non-severe side effects ▪ nausea (AEs): Hint of greater harm - extent: "considerable"
AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form	

Based on the PROfound study, conclusions on the present benefit assessment can only be drawn for patients for whom abiraterone or enzalutamide was the individual therapy best suited within the framework of the ACT. No data are available for patients for whom docetaxel or cabazitaxel was best suited on an individual basis within the framework of the ACT. The added benefit is therefore derived separately for these two patient groups.

Patients for whom abiraterone or enzalutamide was best suited on an individual basis within the framework of the ACT

In the overall consideration, there were mostly positive and only few negative effects of olaparib in comparison with individual therapy (abiraterone or enzalutamide).

For overall survival, there was a hint of a minor added benefit. In the categories "serious/severe symptoms/ secondary complications" and "non-serious/non-severe symptoms/secondary complications", there are several hints of positive effects with the extents "minor" to "considerable". In contrast, there are hints of negative effects with extents of up to "major". These did not raise doubts about the positive effects, however.

In summary, there is a hint of minor added benefit of olaparib versus individual therapy (abiraterone or enzalutamide) for adult patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) whose disease is progressive after previous treatment that included an NHA and for whom abiraterone or enzalutamide is best suited on an individual basis within the framework of the ACT.

Patients for whom docetaxel or cabazitaxel was best suited on an individual basis within the framework of the ACT

For adult patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) whose disease is progressive after previous treatment that included an NHA and for whom docetaxel or cabazitaxel is best suited on an individual basis within the framework of the ACT, the company presented no data for the assessment of the added benefit of olaparib in comparison with individual therapy (docetaxel or cabazitaxel); an added benefit is therefore not proven.

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

Table 18: Olaparib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) whose disease is progressive after previous treatment that included an NHA[b,c]	Individual therapy choosing from abiraterone, enzalutamide, cabazitaxel and docetaxel; taking into account the previous therapies as well as the approval of the respective medicinal products	Patients for whom abiraterone or enzalutamide is the best individual choice: hint of minor added benefit
		Patients for whom docetaxel or cabazitaxel is the best individual choice: added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. For the present therapeutic indication, it is assumed that ongoing conventional ADT (surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists) is continued.
c. The G-BA specified the present ACT only for those patients whose disease is progressive after previous treatment with abiraterone and/or enzalutamide.

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

The assessment described above differs from that of the company, which derived an indication of considerable added benefit for patients for whom abiraterone or enzalutamide is the best individual choice in the context of the ACT.

For patients for whom docetaxel or cabazitaxel is the best individual choice within the framework of the ACT, the assessment is consistent with that of the company insofar as it states that no evidence was available.

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

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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