Olaparib
(prostate cancer)

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

EXTRACT

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

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

Patient and family involvement

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

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
AML	acute myeloid leukaemia
BPI-SF	Brief Pain Inventory-Short Form
BRCA	breast cancer associated gene
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FACT-P	Functional Assessment of Cancer Therapy-Prostate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GnRH	gonadotropin-releasing hormone
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mCRPC	metastatic castration-resistant prostate cancer
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mHSPC	metastatic hormone-sensitive prostate cancer
PCWG-3	Prostate Cancer Working Group 3
PT	Preferred Term
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
rPFS	radiological progression-free survival
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug olaparib (in combination with abiraterone and prednisone or prednisolone). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 16 January 2023.

Research question

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

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

Table 2: Research questions of the benefit assessment of olaparib + abiraterone + P

Research question	Therapeutic indication	ACT[a]
1	Adults with treatment-naive mCRPC in whom chemotherapy is not clinically indicated[b]	Treatment of physician's choice[c, d]
2	Adults with pretreated mCRPC in whom chemotherapy is not clinically indicated[b]	Individualized therapy[d e] taking into account prior therapy and BRCA1/2 mutation status

a. Presented is the respective ACT specified by the G-BA.
b. For the present therapeutic indication, it is assumed according to the G-BA that an existing conventional ADT is continued. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or antagonists.
c. As part of a clinical study, the following treatments are deemed suitable comparators for treatment of physician's choice: abiraterone in combination with prednisone or prednisolone, enzalutamide. The added benefit can be proven in comparison with one of the cited treatment options; this can typically be achieved in the context of a single-comparator study.
d. The drugs abiraterone and enzalutamide are indicated for use in patients with asymptomatic or mildly symptomatic course of disease. However, the approved therapeutic indication of olaparib in combination with abiraterone and prednisone or prednisolone also includes patients with symptomatic course of disease. There is a discrepancy between the drugs approved in the therapeutic indication versus those used in practice and/or recommended by the guidelines.
e. As part of a clinical study, the following treatments are deemed suitable comparators for individualized therapy: abiraterone in combination with prednisone or prednisolone, enzalutamide, olaparib. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criterion (multicomparator study).

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; P: prednisone or prednisolone

The G-BA consulted the company on the ACT on the basis of the originally planned therapeutic indication of olaparib + abiraterone + P. However, the determination of the ACT by the G-BA is based on the approved therapeutic indication. In deviation from the G-BA, the company cited treatment of physician's choice with the comparators abiraterone + P or enzalutamide as ACT for the entire approved therapeutic indication, irrespective of the pretreatment of the patients. The company thus followed the G-BA's specification for research question 1, but deviated from the G-BA's ACT for research question 2.

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

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

Study pool and study design

For research question 1, the PROpel study is used for the benefit assessment.

The PROpel study is a double-blind RCT comparing olaparib + abiraterone + P with placebo + abiraterone + P.

The study included adult patients with mCRPC who had not received any prior therapy at this stage of the disease. According to the inclusion criteria, patients were candidates for abiraterone therapy with progressive disease at study entry while they were on androgen deprivation therapy (ADT) by medical or surgical castration. Furthermore, patients had to be in good general condition according to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 at study entry.

The PROpel study included a total of 796 patients who were randomly allocated in a 1:1 ratio to treatment with olaparib + abiraterone + P (N = 399) or placebo + abiraterone + P (N = 397). Randomization was stratified by presence of metastases (bone only/visceral/other) and docetaxel pretreatment at metastatic hormone-sensitive prostate cancer (mHSPC) stage (yes/no).

Treatment with olaparib + abiraterone + P and abiraterone + P was in compliance with the respective Summary of Product Characteristics (SPC). According to the inclusion criteria, patients receiving ADT at study entry should continue to do so in addition to the study medication. ADT was either by medical castration with gonadotropin-releasing hormone (GnRH) analogue or by surgical castration with bilateral orchiectomy.

Treatment with the study medication was continued until radiologically confirmed disease progression, unacceptable toxicity, or treatment discontinuation following the patient's decision.

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

Limitations of the study population

Lack of therapeutic indication for chemotherapy in the PROpel study

Olaparib + abiraterone + P is approved for patients with mCRPC in whom chemotherapy is not clinically indicated. In the PROpel study, this was not an explicit inclusion criterion. It was only specified that patients had to be candidates for treatment with abiraterone + P. No further information is available on what criteria were used to make this decision.

Overall, uncertainty remains as to whether the study also included patients in whom chemotherapy would have been clinically indicated. Against the background that there are no clear criteria as to when chemotherapy is clinically indicated, and taking into account the available information on symptoms and pretreatment of the included patients, it is assumed in the present situation, however, that this proportion is within a range that allows the total population of the PROpel study to be used for the present research question. In the overall view, this uncertainty is taken into account in the certainty of conclusions.

Concomitant treatment with ADT

According to the SPC both of olaparib and of abiraterone, therapy with a GnRH analogue should be continued during treatment in the present therapeutic indication, or patients should have had previous bilateral orchiectomy. For the present assessment, an enquiry was made to the Federal Institute for Drugs and Medical Devices on 2 March 2023, which informed on 14 March 2023 that using olaparib + abiraterone + P or abiraterone + P without concomitant ADT was not in compliance with the approval.

According to the inclusion criteria of the PROpel study, all patients had to have continuous therapy with a GnRH analogue or bilateral orchiectomy, with serum testosterone ≤ 50 ng/dL (≤ 2.0 nmol/L) within 28 days before randomization. Patients receiving ADT at study entry had to continue to do so throughout the study. The study protocol also described under concomitant medication that continuous ADT with GnRH agonists/antagonists had to be continued.

This information does not match the information on documented concomitant treatments available in the study documents. These documents only show that 53.9% (54.6% versus 53.1%) of all patients received concomitant therapy with GnRH analogues, 5.0% of patients

received therapy with degarelix/degarelix acetate, 0.1% of patients received therapy with relugolix (both GnRH antagonists) and 5.7% had previous bilateral orchiectomy. Based on this documentation, a maximum of 64.7% of the patients in the PROpel study received concomitant ADT.

Overall, on the basis of the available data, uncertainty remains as to whether all patients continued the existing continuous ADT in accordance with the inclusion criteria. This uncertainty is taken into account in the certainty of conclusions.

Data cut-offs

The results from the second interim analysis of the data cut-off on 14 March 2022 are used.

Risk of bias and certainty of conclusions

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

The risk of bias of the results for the outcomes of overall survival, myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) is rated as low. The risk of bias is rated as high for the results of the outcomes on pain (Brief Pain Inventory-Short Form [BPI-SF] Item 3 and BPI-SF Item 9a–g), on health-related quality of life (represented by the Functional Assessment of Cancer Therapy-Prostate [FACT-P]), on symptomatic skeletal-related events, as well as on the side effects outcomes of serious adverse events (SAEs), severe adverse events (AEs), pneumonitis, and further specific AEs. The certainty of results for the outcome of discontinuation due to AEs is limited despite a low risk of bias. No usable analyses are available for the outcome of health status (EQ-5D visual analogue scale [VAS]) because the proportion of patients who were censored on day 1 and thus not included in the analysis is > 30%.

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

Results

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. There is an effect modification for the subgroup characteristic of age for this outcome, however. There is a hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P for patients aged < 65 years. For patients aged ≥ 65 years,

there is no hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P; an added benefit is therefore not proven for this patient group.

Morbidity

Worst pain (BPI-SF Item 3)

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

Pain interference (BPI-SF Item 9a–g)

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

Symptomatic skeletal-related events

No statistically significant difference between treatment groups was shown for the outcome of symptomatic skeletal-related events. However, there is an effect modification for the characteristic of age. There is a hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P for patients aged ≥ 65 years. For patients aged < 65 years, there is no hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P; an added benefit is therefore not proven for this patient group.

Health status (EQ-5D VAS)

No usable data are available for the outcome of health status, recorded with the EQ-5D VAS. There is no hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P; an added benefit is therefore not proven.

Health-related quality of life

FACT-P

No statistically significant difference between treatment groups was shown for the outcome of FACT-P total score. However, there is an effect modification for the characteristic of metastases at baseline. There is a hint of greater harm from olaparib + abiraterone + P in comparison with abiraterone + P for patients with bone metastases only. For patients with visceral and other metastases, there is a hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P.

Side effects

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

Statistically significant differences to the disadvantage of olaparib + abiraterone + P were shown for each of the outcomes of SAEs and discontinuation due to AEs. In each case, there is a hint of greater harm from olaparib + abiraterone + P in comparison with abiraterone + P.

A statistically significant difference to the disadvantage of olaparib + abiraterone + P was also shown for the outcome of severe AEs (CTCAE grade ≥ 3). However, there is an effect modification for the characteristic of metastases at baseline. There is a hint of greater harm from olaparib + abiraterone + P in comparison with abiraterone + P for patients with visceral and other metastases. For patients with bone metastases only, there is no hint of greater or lesser harm from olaparib + abiraterone + P in comparison with abiraterone + P; greater or lesser harm for this patient group is therefore not proven.

MDS, AML and pneumonitis

For the outcomes of MDS and AML (each PT, AEs), one and no event occurred, respectively. No statistically significant differences between treatment groups were shown for the outcomes of MDS (PT, AEs) and pneumonitis (AE). In each case, there is no hint of greater or lesser harm from olaparib + abiraterone + P in comparison with abiraterone + P for these outcomes; greater or lesser harm is therefore not proven.

Diarrhoea, nausea, decreased appetite (each Preferred Term [PT], AEs)

Statistically significant differences to the disadvantage of olaparib + abiraterone + P were shown for the outcomes of diarrhoea, nausea, and decreased appetite (each PT, AEs). In each case, there is a hint of greater harm from olaparib + abiraterone + P in comparison with abiraterone + P.

Injury, poisoning and procedural complications (System Organ Class [SOC], SAEs)

A statistically significant difference to the disadvantage of olaparib + abiraterone + P was shown for the outcome of injury, poisoning and procedural complications (SOC, SAEs). There is a hint of greater harm from olaparib + abiraterone + P in comparison with abiraterone + P.

Pulmonary embolism, anaemia (each PT, severe AEs)

Statistically significant differences to the disadvantage of olaparib + abiraterone + P were shown for the outcomes of pulmonary embolism and anaemia (each PT, severe AEs). In each case, there is a hint of greater harm from olaparib + abiraterone + P in comparison with abiraterone + P.

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

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

Overall, both positive and negative effects of olaparib + abiraterone + P were found in comparison with the ACT. The characteristics of age and metastases are effect modifiers for several outcomes. Due to the effect modification in overall survival by the characteristic of age, the results on the added benefit of olaparib + abiraterone + P compared with the ACT are derived separately according to age below:

Patients < 65 years

For patients < 65 years, there is a hint of considerable added benefit for the outcome of overall survival. No conclusion on health-related quality of life, measured with the FACT-P, can be derived for patients < 65 years, as there are positive or negative effects for this outcome depending on the site of metastasis at baseline, but there is no information on how these advantages or disadvantages are shown within the subgroup of patients < 65 years.

On the other hand, there is a series of negative effects in the side effects category of varying severity categories and with varying, partly major extent. Overall, these negative effects are not assumed to completely call into question the considerable survival advantage for patients < 65 years. Overall, a hint of minor added benefit is therefore derived for patients < 65 years.

Patients ≥ 65 years

For patients ≥ 65 years, there is no hint of an added benefit for the outcome of overall survival. There is a hint of minor added benefit for the composite outcome of symptomatic skeletal-related events for this patient group. No conclusion on health-related quality of life, measured with the FACT-P, can be derived for patients ≥ 65 years, as there are positive or negative effects for this outcome depending on the site of metastasis at baseline, but there is no information on how these advantages or disadvantages are shown within the subgroup of patients ≥ 65 years.

[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].

On the other hand, there is a series of negative effects in the side effects category of varying severity categories and with varying, partly major extent. Overall, the negative effects predominate for patients ≥ 65 years. The only positive effect of minor extent for the outcome of symptomatic skeletal-related events, which is mainly determined by the component of radiotherapy to prevent or relieve skeletal symptoms, is contrasted by negative effects in serious/severe side effects: In addition to negative effects of minor extent in the overall rates of SAEs and discontinuations due to AEs, negative effects of major extent were shown in severe pulmonary embolisms and severe anaemia. Overall, a hint of lesser benefit is derived for patients ≥ 65 years.

Summary

In summary, there is a hint of minor added benefit of olaparib + abiraterone + P compared with the ACT for patients < 65 years with treatment-naive mCRPC in whom chemotherapy is not clinically indicated. For patients ≥ 65 years of age, there is a hint of lesser benefit in comparison with the ACT.

Data are available only for patients for whom abiraterone + P is a suitable treatment option in accordance with treatment of physician's choice. No data are available for patients for whom enzalutamide is a suitable treatment option in accordance with treatment of physician's choice.

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

Study pool

The company presented no data for research question 2.

Incompleteness of the dossier for research question 2

The potentially relevant Study 8 was identified from the check of the completeness. Study 8, sponsored by the company, investigated olaparib + abiraterone + P compared with placebo + abiraterone + P in patients with pretreated mCRPC. The study was used as a supportive measure in the context of the approval by the European Medicines Agency (EMA).

The company neither included the study in the study list for olaparib + abiraterone + P nor did it submit the study protocol or clinical study report (CSR) or other documents on Study 8. There is no explanation as to why the company did not take this study into account.

The approach of the company is not appropriate. Since this is a study by the company in the approved therapeutic indication, it would be necessary for the company to both include this study in the study list for olaparib + abiraterone + P in Module 4 A and to submit the corresponding documents (study protocol, CSR, etc.). For the present research question, the dossier is therefore incomplete. Irrespective of this, it cannot be conclusively clarified due to

the incomplete documents whether Study 8 is relevant or unsuitable for the benefit assessment due to a lack of implementation of the comparator therapy.

Relevance of Study 8 for the benefit assessment

Study 8 is a double-blind RCT comparing olaparib + abiraterone + P with placebo + abiraterone + P in patients with pretreated mCRPC. These are patients within the approved therapeutic indication of olaparib + abiraterone + P and the present research question. The ACT specified by the G-BA for research question 2 is individualized therapy taking into account prior therapy and breast cancer associated gene (BRCA)1/2 mutation status. Abiraterone + P, enzalutamide or olaparib were specified as suitable comparators. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criterion (multicomparator study). Study 8, on the other hand, is not a multicomparator study, but a comparison versus treatment with abiraterone + P. However, it is not possible to assess from the available information whether the ACT was implemented in Study 8 or was possibly only implemented for a subpopulation. Overall, the relevance of Study 8 for research question 2 thus remains unclear.

Results

In its dossier, the company did not present any data to assess the added benefit of olaparib + abiraterone + P compared with the ACT for patients with pretreated mCRPC. There is no hint of an added benefit of olaparib + abiraterone + P in comparison with the ACT; an added benefit is therefore not proven for this research question.

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

In its dossier, the company did not present any data to assess the added benefit of olaparib + abiraterone + P compared with the ACT for patients with pretreated mCRPC. An added benefit of olaparib + abiraterone + P versus the ACT is therefore not proven for research question 2.

Probability and extent of added benefit – summary

Table 3 shows a summary of probability and extent of the added benefit of olaparib + abiraterone + P.

Table 3: Olaparib + abiraterone + P – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with treatment-naive mCRPC in whom chemotherapy is not clinically indicated[b]	Treatment of physician's choice[c]	▪ Patients < 65 years: hint of minor added benefit[d, e] ▪ Patients ≥ 65 years: hint of lesser benefit[d, e]
2	Adults with pretreated mCRPC in whom chemotherapy is not clinically indicated[b]	Individualized therapy[f] taking into account prior therapy and BRCA1/2 mutation status	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. For the present therapeutic indication, it is assumed according to the G-BA that an existing conventional ADT is continued. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or antagonists.
c. As part of a clinical study, the following treatments are deemed suitable comparators for treatment of physician's choice: abiraterone in combination with prednisone or prednisolone, enzalutamide.
d. In the PROpel study, abiraterone in combination with prednisone or prednisolone was used as a comparator. No data are available for patients for whom enzalutamide is a suitable treatment option in accordance with treatment of physician's choice.
e. Only patients with an ECOG PS of 0 or 1 were included in the PROpel study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
f. As part of a clinical study, the following treatments are deemed suitable comparators for individualized therapy: abiraterone in combination with prednisone or prednisolone, enzalutamide, olaparib.

ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; BRCA: breast cancer associated gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mCRPC: metastatic castration-resistant prostate cancer; P: prednisone or prednisolone

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

I 2 Research question

The aim of this report is to assess the added benefit of olaparib in combination with abiraterone and prednisone or prednisolone (hereinafter referred to as "olaparib + abiraterone + P") compared with the ACT in adult patients with mCRPC in whom chemotherapy is not clinically indicated.

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

Table 4: Research questions of the benefit assessment of olaparib + abiraterone + P

Research question	Therapeutic indication	ACT[a]
1	Adults with treatment-naive mCRPC in whom chemotherapy is not clinically indicated[b]	Treatment of physician's choice[c, d]
2	Adults with pretreated mCRPC in whom chemotherapy is not clinically indicated[b]	Individualized therapy[d e] taking into account prior therapy and BRCA1/2 mutation status

a. Presented is the respective ACT specified by the G-BA.
b. For the present therapeutic indication, it is assumed according to the G-BA that an existing conventional ADT is continued. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or antagonists.
c. As part of a clinical study, the following treatments are deemed suitable comparators for treatment of physician's choice: abiraterone in combination with prednisone or prednisolone, enzalutamide. The added benefit can be proven in comparison with one of the cited treatment options; this can typically be achieved in the context of a single-comparator study.
d. The drugs abiraterone and enzalutamide are indicated for use in patients with asymptomatic or mildly symptomatic course of disease. However, the approved therapeutic indication of olaparib in combination with abiraterone and prednisone or prednisolone also includes patients with symptomatic course of disease. There is a discrepancy between the drugs approved in the therapeutic indication versus those used in practice and/or recommended by the guidelines.
e. As part of a clinical study, the following treatments are deemed suitable comparators for individualized therapy: abiraterone in combination with prednisone or prednisolone, enzalutamide, olaparib. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criterion (multicomparator study).

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; P: prednisone or prednisolone

The G-BA consulted the company on the ACT on the basis of the originally planned therapeutic indication of olaparib + abiraterone + P. However, the determination of the ACT by the G-BA is based on the approved therapeutic indication. In deviation from the G-BA, the company cited treatment of physician's choice with the comparators abiraterone + P or enzalutamide as ACT for the entire approved therapeutic indication, irrespective of the pretreatment of the patients. The company thus followed the G-BA's specification for research question 1, but deviated from the G-BA's ACT for research question 2.

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

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

I 3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on olaparib + abiraterone + P (status: 15 November 2022)
- bibliographical literature search on olaparib + abiraterone + P (last search on 15 November 2022)
- search in trial registries/trial results databases for studies on olaparib + abiraterone + P (last search on 17 November 2022)
- search on the G-BA website for olaparib + abiraterone + P (last search on 15 November 2022)

To check the completeness of the study pool:

- search in trial registries for studies on olaparib + abiraterone + P (last search on 30 January 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1.1 Study included

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

Table 5: Study pool – RCT, direct comparison: olaparib + abiraterone + P versus placebo + abiraterone + P

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
D081SC00001 (PROpel[d])	Yes	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7,8]

a. Study for which the company was sponsor.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; P: prednisone or prednisolone; RCT: randomized controlled trial

For research question 1, the PROpel study is used for the benefit assessment. The study pool concurs with that of the company, which used this study pool to assess the entire approved therapeutic indication for olaparib + abiraterone + P, however.

I 3.1.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PROpel	RCT, double-blind, parallel	Adult patients with mCRPC[b], without prior therapy at mCRPC stage and ECOG PS ≤ 1	Global cohort[c]: olaparib + abiraterone + P (N = 399)[d] placebo + abiraterone + P (N = 397)[d]	Screening: 28 days Treatment: until radiologically confirmed disease progression[e], unacceptable toxicity, or treatment discontinuation following the patient's decision Observation[f]: outcome-specific, at most until death or end of study	126 centres in Australia, Belgium, Brazil, Canada, Chile, Czech Republic, France, Germany, Italy, Japan, Netherlands, Slovakia, South Korea, Spain, Turkey, United Kingdom, United States 10/2018–ongoing Data cut-offs: ▪ first data cut-off: 30 July 2021[g] ▪ second data cut-off: 14 March 2022[h]	Primary: rPFS (according to investigator) Secondary: overall survival, morbidity, health-related quality of life, AEs

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment. b. Histologically or cytologically confirmed, evidence of radiological progression with existing ADT or after surgical castration, and serum testosterone ≤ 50 ng/dL (≤ 2.0 nmol/L) ≤ 28 days before randomization Metastatic status defined as ≥ 1 documented metastatic lesion on either a bone scan or a CT/MRI scan; patients with brain metastases were not allowed to enter the study. c. According to the amendment to the study protocol dated 5 January 2021, a Chinese cohort was added to include about 108 patients. No analyses of this cohort are available at the time point of the present benefit assessment. d. One patient in the intervention arm and one patient in the comparator arm received no treatment. e. Assessed by the investigator (for soft tissue per RECIST 1.1, for metastatic bone lesions per PCWG-3 criteria); however, further treatment was allowed if the investigator and the principal investigator agreed that the patient would benefit from the further treatment. f. Outcome-specific information is provided in Table 8. g. Interim analysis for rPFS and overall survival (planned after 379 events [progression or death]). h. Second interim analysis for overall survival and final analysis for rPFS (planned after 453 events [progression or death]). ADT: androgen deprivation therapy; AE: adverse event; CT: computed tomography; ECOG PS: Eastern Cooperative Oncology Group Performance Status; GnRH: gonadotropin-releasing hormone; mCRPC: metastatic castration-resistant prostate cancer; MRI: magnetic resonance imaging; N: number of randomized patients; P: prednisone or prednisolone; PCWG 3: Prostate Cancer Working Group 3; RCT: randomized controlled trial; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; rPFS: radiological progression-free survival					

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

Study	Intervention	Comparison
PROpel	Olaparib 600 mg/day (300 mg twice), orally + abiraterone 1000 mg/day, orally + prednisone or prednisolone 10 mg/day (5 mg twice), orally	Placebo, orally + abiraterone 1000 mg/day, orally + prednisone or prednisolone 10 mg/day (5 mg twice), orally
	Dose adjustments Olaparib: ▪ in case of toxicity, 2 dose reductions in 50 mg steps allowed (250 mg twice daily and then 200 mg twice daily) ▪ in moderate renal function disorder, dose reduction to 200 mg twice daily ▪ if strong CYP3A inhibitors are taken at the same time, dose reduction to 100 mg twice daily; if moderate CYP3A inhibitors are taken, dose reduction to 150 mg twice daily Abiraterone, prednisone and prednisolone: in case of toxicity, dose reductions are allowed in accordance with the SPC	
	Pretreatment **Required** ▪ ADT with GnRH analogue[a] or bilateral orchiectomy, with serum testosterone ≤ 50 ng/dL (≤ 2.0 nmol/L) ≤ 28 days before randomization. **Allowed** ▪ first-generation anti-androgen agents until ≥ 4 weeks before randomization ▪ prior to mCRPC stage, second-generation anti-androgen agents (except abiraterone) ≥ 12 months before randomization[b] ▪ docetaxel during localized or mHSPC stage[b] **Not allowed** ▪ pretreatment at mCRPC stage ▪ any treatment with PARP inhibitors (including olaparib) ▪ systemic chemotherapy or radiotherapy[c] ≤ 3 weeks prior to study treatment ▪ any exposure to a CYP17 inhibitor (e.g. abiraterone).	
	Concomitant treatment **Allowed** ▪ palliative radiotherapy for the treatment of bone metastases[d] ▪ bisphosphonates or denosumab for the prevention of skeletal-related events in bone metastases **Not allowed** ▪ other anti-cancer therapies: chemotherapy, immunotherapy, biologics, other novel therapies (except GnRH analogues) ▪ strong or moderate CYP3A inhibitors and inducers	

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

Study	Intervention	Comparison
a. Patients receiving ADT at study entry should continue to do so throughout the study.		
b. Provided no progression occurred during or immediately after such treatment.		
c. Except palliative radiotherapy, if this was completed 1 week before randomization.		
d. For this purpose, treatment with olaparib had to be discontinued for ≥ 3 days previously; re-initiation of treatment with olaparib was to take place ≤ 4 weeks after radiotherapy, as long as the bone marrow had recovered from the radiation.		
ADT: androgen deprivation therapy; CYP3A: cytochrome P450 3A; CYP17: 17alpha-hydroxylase; GnRH: gonadotropin-releasing hormone; mCRPC: metastatic castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; P: prednisone or prednisolone; PARP: poly(adenosine diphosphate-ribose) polymerase; RCT: randomized controlled trial		

Study design

The PROpel study is a double-blind RCT comparing olaparib + abiraterone + P with placebo + abiraterone + P.

The study included adult patients with mCRPC who had not received any prior therapy at this stage of the disease. According to the inclusion criteria, patients were candidates for abiraterone therapy with progressive disease at study entry while they were on ADT by medical or surgical castration. Furthermore, patients had to be in good general condition according to an ECOG PS of 0 or 1 at study entry.

The PROpel study included a total of 796 patients who were randomly allocated in a 1:1 ratio to treatment with olaparib + abiraterone + P (N = 399) or placebo + abiraterone + P (N = 397). Randomization was stratified by presence of metastases (bone only/visceral/other) and docetaxel pretreatment at mHSPC stage (yes/no). With the first protocol amendment (5 January 2021) of the PROpel study, a Chinese cohort was added to include 108 patients. As no results for this cohort were available at the time of the benefit assessment, this cohort was not considered in the benefit assessment.

Treatment with olaparib + abiraterone + P and abiraterone + P was in compliance with the respective SPC [9,10]. According to the inclusion criteria, patients receiving ADT at study entry should continue to do so in addition to the study medication. ADT was either by medical castration with a GnRH analogue or by surgical castration with bilateral orchiectomy.

Treatment with the study medication was until radiologically confirmed disease progression assessed by the investigator based on the Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 for soft tissue, or on the Prostate Cancer Working Group 3 (PCWG-3) criteria for metastatic bone lesions, unacceptable toxicity or discontinuation following the patient's decision. Further treatment with olaparib + abiraterone + P was allowed if the

investigator and the principal investigator agreed that the patient would benefit from the further treatment.

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

Limitations of the study population

Lack of therapeutic indication for chemotherapy in the PROpel study

Olaparib + abiraterone + P is approved for patients with mCRPC in whom chemotherapy is not clinically indicated. In the PROpel study, this was not an explicit inclusion criterion. It was only specified that patients had to be candidates for treatment with abiraterone + P. No further information is available on what criteria were used to make this decision. According to the S3 guideline, treatment eligibility for chemotherapy is not a clearly defined variable [11]. Criteria that can be used for this assessment are the patient's health status, prior therapies and response to these therapies, symptoms and the patient's wishes. Whether the prerequisites for chemotherapy are fulfilled must be decided on a patient-specific basis [11].

It is not clear from the inclusion criteria of the study whether all patients in the PROpel study population met the eligibility restriction "chemotherapy not clinically indicated". The EMA discussed in the European Public Assessment Report (EPAR) whether, in particular for the group of patients with symptomatic disease and/or visceral metastases and without prior docetaxel therapy at mHSPC stage (23% of the PROpel study population), chemotherapy might be the better treatment option on the comparator side than abiraterone. In this context, the EMA restricted the approval for olaparib + abiraterone + P to patients with mCRPC in whom chemotherapy is not clinically indicated, without providing any more details. Rather, the EMA described that this applied regardless of symptomatic disease status or previous treatment with docetaxel.

This issue was not addressed by the company. The company justified the supplementary analyses it presented in Module 4 A on a subpopulation of asymptomatic/mildly symptomatic patients (defined as BPI-SF Item 3, worst pain < 4, and no use of opiates) with the importance of symptoms in guideline recommendations, clinical practice, and the specific approval of abiraterone. However, the subpopulation presented by the company is not an adequate representation of the approved therapeutic indication because the approval for olaparib + abiraterone + P is explicitly not limited to asymptomatic/mildly symptomatic patients, but also includes symptomatic patients in whom chemotherapy is not suitable [8]. Accordingly, when specifying the ACT, the G-BA also described that the approved therapeutic indication of olaparib + abiraterone + P includes symptomatic patients as well.

Overall, uncertainty remains as to whether the study also included patients in whom chemotherapy would have been clinically indicated. Against the background that there are no clear criteria as to when chemotherapy is clinically indicated, and taking into account the available information on symptoms and pretreatment of the included patients, it is assumed in the present situation, however, that this proportion is within a range that allows the total population of the PROpel study to be used for the present research question. In the overall view, this uncertainty is taken into account in the certainty of conclusions (see Section I 3.2.2).

Concomitant treatment with ADT

According to the SPC both of olaparib and of abiraterone [9,10], therapy with a GnRH analogue should be continued during treatment in the present therapeutic indication, or patients should have had previous bilateral orchiectomy. For the present assessment, an enquiry was made to the Federal Institute for Drugs and Medical Devices on 2 March 2023, which informed on 14 March 2023 that using olaparib + abiraterone + P or abiraterone + P without concomitant ADT was not in compliance with the approval.

According to the inclusion criteria of the PROpel study, all patients had to have continuous therapy with a GnRH analogue or bilateral orchiectomy, with serum testosterone ≤ 50 ng/dL (≤ 2.0 nmol/L) within 28 days before randomization. Patients receiving ADT at study entry had to continue to do so throughout the study. The study protocol also described under concomitant medication that continuous ADT with GnRH agonists/antagonists had to be continued. The company also stated in Module 4 A that conventional ADT was administered in both study arms as background therapy or concomitantly, but did not provide any specific information on the ADT used during the study.

This information does not match the information on documented concomitant treatments available in the study documents. These documents only show that 53.9% (54.6% versus 53.1%) of all patients received concomitant therapy with GnRH analogues, 5.0% of patients received therapy with degarelix/degarelix acetate, 0.1% of patients received therapy with relugolix (both GnRH antagonists) and 5.7% had previous bilateral orchiectomy [3]. Based on this documentation, a maximum of 64.7% of the patients in the PROpel study received concomitant ADT.

Thus, the inclusion criterion of the study cannot be fully ascertained based on the documentation of the concomitant treatment. At the same time, however, no protocol violations regarding this inclusion criterion are recorded in the study documents. Overall, on the basis of the available data, uncertainty remains as to whether all patients continued the existing continuous ADT in accordance with the inclusion criteria. This uncertainty is taken into account in the certainty of conclusions (see Section I 3.2.2).

Implementation of the appropriate comparator therapy in the PROpel study

The G-BA designated treatment of physician's choice with the selection of abiraterone + P or enzalutamide as ACT for research question 1. The G-BA pointed out that the added benefit in comparison with one of the designated comparators can be proven within the framework of a single-comparator study.

Abiraterone + P was used as a comparator in the PROpel study presented by the company. No comparison with enzalutamide is available. Consequently, the study lends itself only to drawing conclusions on the added benefit of olaparib + abiraterone + P for patients for whom abiraterone + P is a suitable treatment of physician's choice.

Data cut-offs

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

- First data cut-off on 30 July 2021: interim analysis for rPFS and overall survival (planned after about 379 rPFS events [progression or death])
- Second data cut-off on 14 March 2022: second interim analysis for overall survival and final analysis for rPFS (planned after about 453 rPFS events [progression or death])

A third data cut-off with the final analysis on overall survival is planned after about 48 months after randomization of the first patient. At the time of the benefit assessment, no data were available for this data cut-off, however. According to the information in the EPAR, the company should provide the final analyses from the third data cut-off in April 2023. Concurring with the company's approach, the present benefit assessment uses the analyses of the second data cut-off (14 March 2022).

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P

Study **Outcome category** **Outcome**	**Planned follow-up observation**
PROpel	
Mortality	
Overall survival	Until death or end of study
Morbidity	
Symptomatic skeletal-related events	Until progression of the disease
Pain (BPI-SF)	Up to 12 weeks after confirmed disease progression
Health status (EQ-5D VAS)	Up to 12 weeks after confirmed disease progression
Health-related quality of life (FACT-P)	Up to 12 weeks after confirmed disease progression
Side effects	
AEs/SAEs/severe AEs[a]	Up to 30 days after discontinuation of the study medication
Secondary malignancies (including MDS/AML)	Until death or end of study

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

AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; FACT-P: Functional Assessment of Cancer Therapy-Prostate; MDS: myelodysplastic syndrome; P: prednisone or prednisolone; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for the outcomes of the categories of morbidity, health-related quality of life, and the side effects outcomes of AEs, SAEs, and severe AEs are systematically shortened. Symptomatic skeletal-related events were to be observed only until disease progression. The remaining outcomes in the morbidity category as well as health-related quality of life were to be observed up to 12 weeks after confirmed disease progression. Regarding the side effects outcomes, AEs, SAEs and severe AEs were to be recorded only for the period of treatment with the study medication (plus 30 days). Secondary malignancies (including AML and MDS, for example), however, were to be observed until death or the end of the study.

However, to be able to draw a reliable conclusion on the total study period or the time to patient death, it would be necessary to record all outcomes for the total period, as was the case for survival and secondary malignancies.

Characteristics of the study population

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

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

Study Characteristic Category	**Olaparib + abiraterone + P N[a] = 399**	**Placebo + abiraterone + P N[a] = 397**
PROpel		
Age [years], mean (SD)	69 (9)	70 (8)
Family origin, n (%)		
Asian	66 (17)	72 (18)
Black or African American	14 (4)	11 (3)
White	282 (71)	275 (69)
Other	15 (4)[b]	9 (2)
Missing	22 (6)	30 (8)
Region, n (%)		
Asia	91 (23)	104 (26)
Europe	178 (45)	172 (43)
North and South America	130 (33)	121 (30)
Gleason score, n (%)		
≤ 6	16 (4)[b]	25 (6)[b]
7	105 (26)	109 (27)
≥ 8	265 (66)[b]	258 (65)[b]
Missing	13 (3)	5 (1)
Metastases at baseline (eCRF), n (%)		
Bones	349 (88)	339 (85)
Bone only	213 (53[b])	226 (57[b])
Visceral	67 (17[b])	73 (18[b])
Other	119 (30[b])	98 (25[b])
Time between mCRPC diagnosis and randomization [months], median [min; max]	2.1 [0; 101]	2.3 [0; 108]
ECOG PS, n (%)		
0	286 (72)	272 (69)
1	112 (28)	124 (31)
Missing	1 (< 1)	1 (< 1)
Symptoms at baseline, n (%)		
Asymptomatic/mildly symptomatic[c]	266 (67)	294 (74)
Symptomatic[d]	103 (26)	80 (20)
Missing	30 (8)	23 (6)

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

Study Characteristic Category	Olaparib + abiraterone + P N[a] = 399	Placebo + abiraterone + P N[a] = 397
Pretreatment[e, f], n (%)	365 (91)	381 (96)
Immunotherapy	4 (1)	3 (< 1)
Hormonal therapy	303 (76)	325 (82)
Cytotoxic chemotherapy	98 (25)	101 (25)
Targeted therapy	0 (0)	1 (< 1)
Radiotherapy	206 (52)	195 (49)
Other	6 (2)	4 (1)
Prior orchiectomy, n (%)		
Bilateral orchiectomy	26 (7)	19 (5)
Orchiectomy	12 (3)	5 (1)
Prior docetaxel treatment at mHSPC stage, n (%)		
Yes	90 (23)	90 (23)
No	309 (77)	307 (77)
Treatment discontinuation, n (%)[g]	260 (65)	292 (74)
Study discontinuation, n (%)[h]	160 (40)	181 (46)

a. Number of randomized patients. Values that are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. Patients who had a baseline score of < 4 in the BPI-SF Item 3 (worst pain) and were not using opiates.
d. Patients who had a baseline score of ≥ 4 in the BPI-SF Item 3 or were already using opiates.
e. Patients can be counted in more than one treatment modality.
f. At a stage prior to mCRPC.
g. At the second data cut-off. Common reasons for treatment discontinuation in the intervention vs. control arm (based on number of randomized patients): disease progression (28% vs. 43% for discontinuation of olaparib/placebo and 30% vs. 42% for discontinuation of abiraterone) and discontinuations due to AEs (13% vs. 7% for discontinuation of olaparib/placebo and 9% vs. 7% for discontinuation of abiraterone). Patients could be counted in ≥ 1 category.
h. At the second data cut-off. The most common reason for study discontinuation in the intervention vs. control arm (based on number of randomized patients) was death (36% vs. 43%).

BPI-SF: Brief Pain Inventory-Short Form; ECOG PS: Eastern Cooperative Oncology Group Performance Status; eCRF: electronic case report form; max: maximum; mCRPC: metastatic castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; min: minimum; n: number of patients in the category; N: number of randomized patients; P: prednisone or prednisolone; RCT: randomized controlled trial; SD: standard deviation

The patients' demographic and clinical characteristics were largely balanced between the 2 treatment arms. The mean age of the patients was 69 to 70 years, and the majority of them (about 65%) had a Gleason score of ≥ 8 at diagnosis. All patients had metastases at baseline, the most common being bone metastases, which occurred in 88% versus 85% of patients. The

majority of patients (about 70%) had an ECOG PS of 0. There were marginal differences in the symptoms of the patients at baseline. The proportion of patients with asymptomatic/mildly symptomatic course of disease was lower in the intervention arm than in the comparator arm (67% versus 74%), and correspondingly, the proportion of patients with symptomatic course of disease was higher in the intervention arm than in the comparator arm (26% versus 20%).

According to the inclusion criterion, all patients were treatment-naive at mCRPC stage, but a large proportion of patients (> 90%) had already received one or more treatments at a previous stage. These mainly included hormonal therapy (about 76% to 82%), cytotoxic chemotherapy (about 25%) and radiotherapy (about 49% to 52%). The majority of patients (about 77%) had not received prior chemotherapy with docetaxel at mHSPC stage. Pretreatments were comparable between the 2 study arms.

Treatment discontinuation occurred in about 65% of patients in the intervention arm and was slightly higher in the control arm at about 74%. The most common reasons were disease progression or discontinuations due to AEs. The proportion of patients who discontinued the study was almost balanced in both study arms (40% versus 46%). The most common reason for study discontinuation was death (36% versus 43%).

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 + abiraterone + P vs. placebo + abiraterone + P (multipage table)

Study **Duration of the study phase** **Outcome category** **Outcome**	**Olaparib + abiraterone + P** **N = 399[a]**	**Placebo + abiraterone + P** **N = 397[a]**
PROpel		
Treatment duration [months]		
For olaparib/placebo		
Median [min; max]	18.5 [0.4; 40.0][b]	15.7 [0.4; 37.9][b]
Mean (SD)	ND	ND
For abiraterone		
Median [min; max]	20.1 [1.0; 40.0][b]	15.7 [0.4; 37.9][b]
Mean (SD)	ND	ND
Observation period [months]		
Overall survival[c]		
Median [min; max]	27.6 [0; 40.0]	26.3 [0.4; 38.3]
Mean (SD)	ND	ND
Morbidity		
Pain (BPI-SF)		
Median [min; max]	15.4 [0; 39.4]	11.8 [0; 37.5]
Mean (SD)	ND	ND
Symptomatic skeletal-related events		
Median [min; max]	18.4 [0; 39.7]	15.1 [0; 37.7]
Mean (SD)	ND	ND
Health status (EQ-5D VAS)		
Median [min; max]	17.4 [0.0; 39.5]	12.0 [0.0; 37.7]
Mean (SD)	ND	ND
Health-related quality of life		
FACT-P		
Median [min; max]	17.4 [0; 39.5]	13.7 [0; 37.7]
Mean (SD)	ND	ND
Side effects		
AEs/SAEs/severe AEs		
Median [min; max]	21.2 [1.9; 40.0]	16.7 [0.4; 37.9]
Mean (SD)	ND	ND
MDS/AML		
Median [min; max]	27.6 [2.0; 40.0]	26.3 [0.4; 38.3]
Mean (SD)	ND	ND

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

Study **Duration of the study phase** **Outcome category** **Outcome**	**Olaparib + abiraterone + P** **N = 399[a]**	**Placebo + abiraterone + P** **N = 397[a]**
a. One patient without values for treatment duration and observation period of side effects (AEs/SAEs/severe AEs and MDS/AML). b. Institute's calculation from data in days. c. Information on how the observation period was calculated is not available. AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; FACT-P: Functional Assessment of Cancer Therapy-Prostate; max: maximum; MDS: myelodysplastic syndrome; min: minimum; N: number of analysed patients; ND: no data; P: prednisone or prednisolone; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale		

The median treatment duration in the PROpel study was slightly longer in the intervention arm than in the comparator arm (18.5 months for olaparib and 20.1 months for abiraterone versus 15.7 months for placebo and abiraterone).

The median observation periods for the outcomes with a planned observation period until the end of the study (overall survival and MDS/AML), at just over 2 years, are comparable.

The median observation periods for all other outcomes on morbidity, health-related quality of life and side effects differ and are about 3 to 5 months longer in the intervention arm than in the control arm. For the outcomes of symptomatic skeletal-related events and side effects outcomes, this approximately corresponds to the planned follow-up observation (see Table 8). It is notable that the median observation periods for the patient-reported outcomes on pain, health status and health-related quality of life are 2 to 4 months shorter than the median treatment duration. This can probably be explained by the decline in response rates early in the course of the study. Thus, despite the follow-up observation of up to 12 weeks after disease progression planned for these outcomes according to the study protocol, it is questionable whether conclusions can be drawn about the 12 weeks after progression on the basis of the available data (see Table 8). Rather, as described in Section I 3.1.2, patient-reported outcomes should also be recorded throughout the entire study period.

Subsequent therapies

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

Table 11: Information on subsequent therapies (≥ 2% of patients in ≥ 1 treatment arm) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P

Study Treatment Drug	Patients with subsequent therapy[a] n (%) Olaparib + abiraterone + P N = 399	 Placebo + abiraterone + P N = 397
PROpel		
Total	157 (39)	198 (50)
Immunotherapy	16 (4)	17 (4)
Hormonal therapy	58 (15)	69 (17)
Abiraterone	22 (6)[b]	20 (5)[b]
Enzalutamide	34 (9)	44 (11)
Cytotoxic chemotherapy	105 (26)	150 (38)
Cabazitaxel	35 (9)	54 (14)
Carboplatin	8 (2)	8 (2)
Docetaxel	79 (20)	127 (32)
Targeted therapy	14 (4)	22 (6)
Radium-223 dichloride	8 (2)	12 (3)
Other	6 (2)[b]	18 (5)[b, c]
Radiotherapy	40 (10)	61 (15)

a. Patients can be counted in more than one subsequent therapy.
b. Institute's calculation.
c. One patient received olaparib.

n: number of patients with subsequent therapy; N: number of analysed patients; P: prednisone or prednisolone; RCT: randomized controlled trial

The choice of subsequent medication was not restricted in the PROpel study. 39% of patients received subsequent therapy in the intervention arm, and 50% in the comparator arm. The most common therapy after study treatment was chemotherapy (26% in the intervention versus 38% in the control arm). Since a large proportion of patients had not received prior chemotherapy (about 75% in both study arms, see Table 9), the frequent use of this treatment option in confirmed progressive disease is comprehensible [11].

Hormonal therapy (including almost exclusively abiraterone or enzalutamide) was given to 15% of patients in the intervention arm and 17% of patients in the comparator arm. According to the S3 guideline [11], sequential therapy using one of the other agents can be offered after androgen receptor-targeted therapy, although it cannot currently be conclusively assessed whether a second androgen receptor-targeted treatment after progression under first-line treatment with the respective other agent may be less effective than second-line chemotherapy. The fact that 6% of patients in the intervention arm and 5% of patients in the control arm received subsequent therapy with abiraterone does not correspond to the guideline recommendation, however.

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

Risk of bias across outcomes (study level)

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

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

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
PROpel	Yes	Yes	Yes	Yes	Yes	Yes	Low
P: prednisone or prednisolone: RCT: randomized controlled trial							

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

Transferability of the study results to the German health care context

From the perspective of the company, the target population corresponds to the German health care context, as the median age of disease onset in Germany (71 years, according to the Robert Koch Institute for 2018) [12] is comparable to the median age of the population in the PROpel study (69 years), and the majority of patients (70%) were of Caucasian family origin.

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

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - worst pain (measured with BPI-SF Item 3)
  - pain interference (measured with BPI-SF Item 9a–g)
  - symptomatic skeletal-related events, composed of:
    - radiotherapy to prevent or relieve skeletal symptoms
    - new symptomatic pathological bone fracture
    - occurrence of spinal cord compression
    - orthopaedic surgical intervention for bone metastasis
  - health status, recorded with the EQ-5D VAS
- Health-related quality of life
  - measured with the FACT-P total score
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - MDS (PT, AEs)
  - AML (PT, AEs)
  - pneumonitis (AEs)
  - further specific AEs, if any

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

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

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

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

a. Including: radiotherapy to prevent or relieve skeletal symptoms, occurrence of new symptomatic pathological bone fracture, occurrence of spinal cord compression, orthopaedic surgical intervention for bone metastasis.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. AESI defined by the company.
d. The following events are considered (coded according to MedDRA): diarrhoea (PT, AEs), nausea (PT, AEs), decreased appetite (PT, AEs), injury, poisoning and procedural complications (SOC, SAEs), pulmonary embolism (PT, severe AEs), anaemia (PT, severe AEs).
e. No usable data available; proportion of patients not considered in the analysis is > 30%.

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

- The outcome of health status was recorded with the EQ-5D VAS. The company provided responder analyses for the first deterioration by ≥ 15 points. The information in Module 4 A shows that > 30% of the patients do not have a baseline or follow-up value and were thus censored on day 1. Even though, according to the company, these patients were included in the survival time analyses, no times of these patients were actually included in the analysis, and they were therefore not taken into account. Therefore, the analyses are not usable for the present benefit assessment. Patients were also censored on day 1 for the other patient-reported outcomes, but their proportion was lower so that the analyses are usable. The resulting high risk of bias is explained in the corresponding section.
- In the study protocol, the company defined, among others, the AEs of special interest (AESIs) of MDS/AML and pneumonitis, without providing any information on the respective operationalizations. However, the study report contains extensive PT lists for the AESIs, but it remains unclear whether these were prespecified. No event occurred for the AESI of AML, one event occurred for the AESI of MDS for the PT MDS. Since in both cases the AESI corresponds to the respective PT MDS or AML, these are included in the benefit assessment operationalized as PT. For the AESI of pneumonitis, the PT list, checked against the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query interstitial lung disease, can be considered a sufficient operationalization. The AESI of pneumonitis is therefore included in the benefit assessment.

I 3.2.2 Risk of bias

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

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

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

a. Including: radiotherapy to prevent or relieve skeletal symptoms, occurrence of new symptomatic pathological bone fracture, occurrence of spinal cord compression, orthopaedic surgical intervention for bone metastasis.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. AESI defined by the company.
d. The following events are considered (coded according to MedDRA): diarrhoea (PT, AEs), nausea (PT, AEs), decreased appetite (PT, AEs), injury, poisoning and procedural complications (SOC, SAEs), pulmonary embolism (PT, severe AEs), anaemia (PT, severe AEs).
e. High proportion of patients censored on day 1. The reason for this was the lack of baseline values or follow-up values.
f. Incomplete observations for potentially informative reasons.
g. Unclear proportion of patients censored on day 1.
h. No usable data available; proportion of patients not considered in the analysis is > 30%.
i. Despite the low risk of bias, the certainty of results is presumably limited for the outcome of discontinuation due to AE.

AE: adverse event; AESI: adverse event of special interest; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; P: prednisone or prednisolone; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

The risk of bias of the results for the outcomes of overall survival, MDS and AML is rated as low.

The risk of bias of the results for the outcomes on pain (BPI-SF Item 3 and BPI-SF Item 9a–g) and on health-related quality of life (represented by the FACT-P) is to be rated as high. This is partly because baseline values and follow-up values were missing for a relevant proportion of patients (> 15%), so that these patients were censored on day 1 and were not included in the analysis, and partly because of incomplete observations for potentially informative reasons.

The risk of bias of the results on the outcomes of symptomatic skeletal-related events, SAEs, severe AEs, pneumonitis and other specific AEs is also rated as high due to incomplete observations for potentially informative reasons. Furthermore, it is unclear for the outcome of symptomatic skeletal-related events how many patients were censored on day 1 and were thus not included in the analysis, which contributed to the high risk of bias for this outcome.

No usable analyses are available for the outcome of health status (EQ-5D VAS) because the proportion of patients who were censored on day 1 and were thus not included in the analysis is > 30%.

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

Summary assessment of the certainty of conclusions

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

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

I 3.2.3 Results

Table 15 summarizes the results of the comparison of olaparib + abiraterone + P versus placebo + abiraterone + P in patients with mCRPC in whom chemotherapy is not clinically indicated. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

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

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

Study Outcome category Outcome	Olaparib + abiraterone + P		Placebo + abiraterone + P		Olaparib + abiraterone + P vs. placebo + abiraterone + P
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
PROpel					
Mortality					
Overall survival[a]	399	NA 148 (37.1)	397	NA 171 (43.1)	0.83 [0.66; 1.03][b]; 0.113[c]
Morbidity					
Worst pain (BPI-SF Item 3)[d]	330[e]	36.6 [30.2; NC] 92 (27.9[e])	332[e]	NA 88 (26.5[e])	0.97 [0.72; 1.30][b]; 0.866[c]
Pain intensity (BPI-SF Items 3-6)[d](supplementary information)	*330[e]*	*NA* *63 (19.1[e])*	*332[e]*	*NA* *60 (18.1[e])*	*0.96 [0.67; 1.37][b]; 0.812[c]*
Pain interference (BPI-SF Item 9a–g)[f]	330[e]	36.6 [36.6; NC] 73 (22.1[e])	332[e]	NA 78 (23.5[e])	0.85 [0.62; 1.18][b]; 0.413[c]
Symptomatic skeletal-related events[a]	399	NA 41 (10.3)	397	NA 49 (12.3)	0.76 [0.50; 1.16][b]; 0.213[c]
Radiotherapy to prevent or relieve skeletal symptoms	399	NA 28 (7.0)	397	NA 40 (10.1)	0.64 [0.39; 1.03][b]; 0.087[c]
New symptomatic pathological bone fracture	399	NA 15 (3.8)	397	NA 15 (3.8)	0.87 [0.42; 1.80][b]; 0.678[c]
Occurrence of spinal cord compression	399	NA 3 (0.8)	397	NA 8 (2.0)	0.31 [0.07; 1.09][b]; 0.078[c]
Orthopaedic surgical intervention for bone metastasis	399	NA 2 (0.5)	397	NA 6 (1.5)	0.27 [0.04; 1.19][b]; 0.099[c]
Health status (EQ-5D VAS)	No usable data				
Health-related quality of life					
FACT-P					
Total score[g]	277[e]	NA 90 (32.5[e])	294[e]	NA 97 (33[e])	0.95 [0.71; 1.27][b]; 0.760[c]
Physical wellbeing[h]	277[e]	11.9 [9.1; 19.1] 150 (54.2[e])	294[e]	17.4 [13.7; 24.8] 137 (46.6[e])	1.31 [1.04; 1.65][b]
Social/family wellbeing[h]	277[e]	11.1 [8.2; 21.1] 141 (50.9[e])	294[e]	13.8 [9.1; NC] 141 (48[e])	1.05 [0.83; 1.33][b]

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

Study Outcome category Outcome	Olaparib + abiraterone + P		Placebo + abiraterone + P		Olaparib + abiraterone + P vs. placebo + abiraterone + P
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
Emotional wellbeing[i]	277[e]	28.6 [19.3; NC] 113 (40.8[e])	294[e]	24.8 [17.4; NC] 121 (41.2[e])	0.98 [0.76; 1.27][b]
Functional wellbeing[h]	277[e]	15.6 [11.0; 23.0] 143 (51.6[e])	294[e]	11.1 [9.1; 17.4] 156 (53.1[e])	0.89 [0.71; 1.12][b]
Prostate cancer-specific subscale[j]	277[e]	35.8 [24.8; NC] 96 (34.7[e])	294[e]	NA 100 (34[e])	0.94 [0.71; 1.25][b]
Side effects					
AEs (supplementary information)	398	0.5 [0.5; 0.8] 389 (97.7)	396	1.0 [0.9; 1.2] 378 (95.5)	–
SAEs	398	31.9 [26.0; NC] 154 (38.7)	396	NA 117 (29.5)	1.28 [1.004; 1.63]; 0.047[k]
Severe AEs[l]	398	19.8 [14.4; 24.7] 210 (52.8)	396	27.8 [21.4; NC] 160 (40.4)	1.32 [1.08; 1.62]; 0.008[k]
Discontinuation due to AEs[m]	398	NA 65 (16.3)	396	NA 41 (10.4)	1.52 [1.03; 2.27]; 0.034[k]
MDS (PT, AEs)	398	NA 1 (0.3)	396	NA 0 (0)	NC; 0.362[k, n]
AML (PT, AEs)	398	NA 0 (0)	396	NA 0 (0)	–
Pneumonitis (AEs)[o]	398	NA 5 (1.3)	396	NA 3 (0.8)	1.60 [0.39; 7.82]; 0.514[k]
Diarrhoea (PT, AEs)	398	NA 75 (18.8)	396	NA 39 (9.8)	1.88 [1.28; 2.79]; 0.001[k]
Nausea (PT, AEs)	398	NA 118 (29.6)	396	NA 55 (13.9)	2.37 [1.73; 3.28]; < 0.001[k]
Decreased appetite (PT, AEs)	398	NA 64 (16.1)	396	NA 28 (7.1)	2.26 [1.47; 3.58]; < 0.001[k]
Injury, poisoning and procedural complications (SOC, SAEs)	398	NA 19 (4.8)	396	NA 7 (1.8)	2.47 [1.08; 6.32]; 0.035[k]
Pulmonary embolism (PT, severe AEs[m])	398	NA 28 (7.0)	396	NA 7 (1.8)	3.87 [1.79; 9.62]; < 0.001[k]

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

Study Outcome category Outcome	Olaparib + abiraterone + P		Placebo + abiraterone + P		Olaparib + abiraterone + P vs. placebo + abiraterone + P
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
Anaemia (PT, severe AEs[m])	398	NA 63 (15.8)	396	NA 13 (3.3)	4.92 [2.80; 9.35]; < 0.001[k]

a. Due to patients censored at baseline, the number of patients included in the analysis may be reduced by up to 5%.
b. HR and CI: Cox proportional hazards model, adjusted for metastases (bone only vs. visceral vs. other) and docetaxel treatment of mHSPC (yes vs. no).
c. p-value: log-rank test, stratified by metastases (bone only vs. visceral vs. other) and docetaxel treatment of mHSPC (yes vs. no).
d. Time to first deterioration. An increase by ≥ 2 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 10).
e: Institute's calculations; data refer to patients who have a baseline value and at least one follow-up value.
f. Time to first deterioration. An increase by ≥ 1.5 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 10).
g. Time to first deterioration. A decrease by ≥ 23.4 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 156).
h. Time to first deterioration. A decrease by ≥ 4.2 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 28).
i. Time to first deterioration. A decrease by ≥ 3.6 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 24).
j. Time to first deterioration. A decrease by ≥ 7.2 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 48).
k. HR, CI, and p-value: Cox proportional hazards model with corresponding log-rank test.
l. Operationalized as CTCAE grade ≥ 3.
m. If one of the drugs was discontinued prematurely, the entire therapy was considered discontinued.
n. For the p-value, the data from the analysis for the composite outcome of MDS/AML were used, as only one event of MDS was observed in this analysis as well. The censoring and event times are assumed to be identical for both outcomes.
o. AESI defined by the company. The PTs pneumonitis, interstitial lung disease, and radiation pneumonitis occurred.

AE: adverse event; AESI: adverse event of special interest; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; MDS: myelodysplastic syndrome; mHSPC: metastatic hormone-sensitive prostate cancer; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; P: prednisone or prednisolone; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

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

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. There is an effect modification for the subgroup characteristic of age for this outcome, however (see Section I 3.2.4). There is a hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P for patients aged < 65 years. For patients aged ≥ 65 years, there is no hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P; an added benefit is therefore not proven for this patient group.

Morbidity

Worst pain (BPI-SF Item 3)

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

Pain interference (BPI-SF Item 9a–g)

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

Symptomatic skeletal-related events

No statistically significant difference between treatment groups was shown for the outcome of symptomatic skeletal-related events. There is an effect modification for the characteristic of age, however (see Section I 3.2.4). There is a hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P for patients aged ≥ 65 years. For patients aged < 65 years, there is no hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P; an added benefit is therefore not proven for this patient group.

Health status (EQ-5D VAS)

No usable data are available for the outcome of health status, recorded with the EQ-5D VAS. There is no hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P; an added benefit is therefore not proven.

Health-related quality of life

FACT-P

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

No statistically significant difference between treatment groups was shown for the outcome of FACT-P total score. However, there is an effect modification for the characteristic of metastases at baseline (see Section I 3.2.4). There is a hint of greater harm from olaparib + abiraterone + P in comparison with abiraterone + P for patients with bone metastases only. For patients with visceral and other metastases, there is a hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P.

Side effects

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

Statistically significant differences to the disadvantage of olaparib + abiraterone + P were shown for each of the outcomes of SAEs and discontinuation due to AEs. In each case, there is a hint of greater harm from olaparib + abiraterone + P in comparison with abiraterone + P.

A statistically significant difference to the disadvantage of olaparib + abiraterone + P was also shown for the outcome of severe AEs (CTCAE grade ≥ 3). However, there is an effect modification for the characteristic of metastases at baseline (see Section I 3.2.4). There is a hint of greater harm from olaparib + abiraterone + P in comparison with abiraterone + P for patients with visceral and other metastases. For patients with bone metastases only, there is no hint of greater or lesser harm from olaparib + abiraterone + P in comparison with abiraterone + P; greater or lesser harm for this patient group is therefore not proven.

Specific AEs

MDS, AML and pneumonitis

For the outcomes of MDS and AML (each PT, AEs), one and no event occurred, respectively. No statistically significant differences between treatment groups were shown for the outcomes of MDS (PT, AEs) and pneumonitis (AE). In each case, there is no hint of greater or lesser harm from olaparib + abiraterone + P in comparison with abiraterone + P for these outcomes; greater or lesser harm is therefore not proven.

Diarrhoea, nausea, decreased appetite (each PT, AEs)

Statistically significant differences to the disadvantage of olaparib + abiraterone + P were shown for the outcomes of diarrhoea, nausea, and decreased appetite (each PT, AEs). In each case, there is a hint of greater harm from olaparib + abiraterone + P in comparison with abiraterone + P.

Injury, poisoning and procedural complications (SOC, SAEs)

A statistically significant difference to the disadvantage of olaparib + abiraterone + P was shown for the outcome of injury, poisoning and procedural complications (SOC, SAEs). There is a hint of greater harm from olaparib + abiraterone + P in comparison with abiraterone + P.

Pulmonary embolism, anaemia (each PT, severe AEs)

Statistically significant differences to the disadvantage of olaparib + abiraterone + P were shown for the outcomes of pulmonary embolism and anaemia (each PT, severe AEs). In each case, there is a hint of greater harm from olaparib + abiraterone + P in comparison with abiraterone + P.

I 3.2.4 Subgroups and other effect modifiers

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

- age (< 65 years/≥ 65 years)
- metastases at baseline (bone only/visceral/other)

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

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

The results are presented in Table 16. The Kaplan-Meier curves on the subgroup results are presented in I Appendix B of the full dossier assessment.

Table 16: Subgroups (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P (multipage table)

Study Outcome Characteristic Subgroup	Olaparib + abiraterone + P N	Olaparib + abiraterone + P Median time to event in months [95% CI] Patients with event n (%)	Placebo + abiraterone + P N	Placebo + abiraterone + P Median time to event in months [95% CI] Patients with event n (%)	Olaparib + abiraterone + P vs. placebo + abiraterone + P HR [95% CI][a]	 p-value[b]
PROpel						
Overall survival						
Age						
< 65 years	130	NA 35 (26.9)	97	NA 42 (43.3)	0.57 [0.36; 0.90]	0.015
≥ 65 years	269	NA 113 (42.0)	300	NA 129 (43.0)	0.98 [0.76; 1.26]	0.846
Total					Interaction[c]:	0.044
Symptomatic skeletal-related events[d]						
Age						
< 65 years	130	NA 20 (15.4)	97	NA 9 (9.3)	1.42 [0.67; 3.29]	0.371
≥ 65 years	269	NA 21 (7.8)	300	NA 40 (13.3)	0.56 [0.32; 0.93]	0.025
Total					Interaction[c]:	0.046
FACT-B, total score[e]						
Metastases						
Bone only	213	26.6 [19.3; NC] 62 (29.1)	226	NA 53 (23.5)	1.45 [1.003; 2.09]	0.048
Visceral and other[f]	186[g]	ND 28 (15.1)[g]	171[g]	ND 44 (25.7)[g]	0.48 [0.30; 0.77][h]	0.003[h]
Visceral	*67*	*NA* *13 (19.4)*	*73*	*17.4 [7.3; NC]* *20 (27.4)*	*0.45 [0.22; 0.89]*	*0.023*
Other	*119*	*NA* *15 (12.6)*	*98*	*NA* *24 (24.5)*	*0.51 [0.26; 0.95]*	*0.035*
Total					Interaction[i]:	< 0.001

Table 16: Subgroups (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P (multipage table)

Study Outcome Characteristic Subgroup	Olaparib + abiraterone + P N	Olaparib + abiraterone + P Median time to event in months [95% CI] Patients with event n (%)	Placebo + abiraterone + P N	Placebo + abiraterone + P Median time to event in months [95% CI] Patients with event n (%)	Olaparib + abiraterone + P vs. placebo + abiraterone + P HR [95% CI][a]	 p-value[b]
Severe AEs[j]						
Metastases						
Bone only	213	23.4 [17.1; 26.9] 110 (51.6)	226	22.1 [18.0; NC] 105 (46.5)	1.10 [0.84; 1.44]	0.487
Visceral and other[f]	185[g]	ND 100 (54.5)[g]	170[g]	ND 55 (32.6)[g]	1.70 [1.22; 2.36][h]	0.002[h]
Visceral	*66*	*14.8 [8.8; 21.7]* *36 (54.5)*	*72*	*NA* *17 (23.6)*	*2.42 [1.38; 4.42]*	*0.002*
Other	*119*	*14.1 [10.9; 26.7]* *64 (53.8)*	*98*	*30.5 [12.9; NC]* *38 (38.8)*	*1.43 [0.96; 2.15]*	*0.077*
Total					Interaction[i]:	0.047

a. HR and CI based on Cox proportional hazards model, including the variables of treatment, subgroup, and the interaction term of treatment and subgroup.
b. p-value is based on log-rank test.
c. p-value from interaction test is based on likelihood ratio test.
d. Subgroup results for the composite outcome mainly include events for the single component of radiotherapy to prevent or relieve skeletal symptoms; patients < 65 years HR: 1.35 [0.57; 3.54]; patients ≥ 65 years HR: 0.42 [0.21; 0.77]; interaction p-value: 0.031.
e. Time to first deterioration. A decrease by ≥ 23.4 points from baseline is defined as a clinically relevant deterioration.
f. Summary of the subgroups of visceral metastases and other metastases
g. Institute's calculation.
h. Institute's calculation: meta-analytical summary of the subgroup results for visceral and other metastases (fixed-effect model).
i. Institute's calculation: p-value from Q test for heterogeneity, based on the 2 subgroups of bone only vs. visceral and other.
j. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; 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 or prednisolone; RCT: randomized controlled trial

Mortality

Overall survival

There is an effect modification for the characteristic of age for the outcome of overall survival.

A statistically significant difference in favour of olaparib + abiraterone + P was shown for the age group < 65 years. There is a hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P for this patient group. However, the survival advantage only becomes apparent after about 16 months (see Kaplan-Meier curves, Figure 2 in I Appendix B).

No statistically significant difference between treatment groups was shown in patients ≥ 65 years. There is no hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P for this patient group; an added benefit is therefore not proven.

Morbidity

Symptomatic skeletal-related events

For the outcome of symptomatic skeletal-related events, there is an effect modification for the characteristic of age.

No statistically significant difference between treatment groups was shown in the age group < 65 years. There is no hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P for this patient group; an added benefit is therefore not proven.

A statistically significant difference in favour of olaparib + abiraterone + P was shown for the age group ≥ 65 years. There is a hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P for this patient group.

Health-related quality of life

FACT-P

There is an effect modification for the characteristic of metastases at baseline for the outcome of FACT-P total score. Due to the homogeneity of the subgroups of visceral metastases and other metastases, these were meta-analytically combined in one subgroup (see I Appendix D of the full dossier assessment). Below, the derivation of added benefit for the outcome of FACT-P is based on the results of calculations conducted by the Institute.

A statistically significant difference to the disadvantage of olaparib + abiraterone + P was shown for patients with bone metastases only. There is a hint of greater harm of olaparib + abiraterone + P in comparison with abiraterone + P for this patient group.

A statistically significant difference in favour of olaparib + abiraterone + P was shown for patients with visceral and other metastases. There is a hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P for this patient group.

Side effects

Severe AEs (CTCAE grade ≥ 3)

There is an effect modification for the characteristic of metastases at baseline for the outcome of severe AEs. Due to homogeneity and content considerations, the subgroups of visceral metastases and other metastases – in distinction from patients with bone metastases only – were meta-analytically combined in one subgroup (see I Appendix D of the full dossier assessment). Below, the derivation of added benefit for the outcome of severe AEs is based on the results of calculations conducted by the Institute.

No statistically significant difference between treatment groups was shown for patients with bone metastases only. There is no hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P for this patient group; greater or lesser harm is therefore not proven.

A statistically significant difference to the disadvantage of olaparib + abiraterone + P was shown for patients with visceral and other metastases. There is a hint of greater harm of olaparib + abiraterone + P in comparison with abiraterone + P for this patient group.

I 3.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 3.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 3.2 (see Table 17).

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

It cannot be inferred from the dossier whether the following outcomes are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptomatic skeletal-related events

The outcome of symptomatic skeletal-related events is deemed to be serious/severe. The outcome is a composite outcome consisting of the components of radiotherapy to prevent or relieve skeletal symptoms, new symptomatic pathological bone fracture, occurrence of spinal cord compression, and orthopaedic surgical intervention for bone metastasis. These events

have a distressing impact on patients and their daily activities. Overall, the outcome is to be considered as severe or serious.

Discontinuations due to AEs

For the outcome of discontinuation due to AEs, the CSR contains information on AE severity according to CTCAE, which shows that > 50% of AEs leading to discontinuation were CTCAE grade ≥ 3 events, and are thus to be classified as severe. Therefore, the outcome of discontinuation due to AEs is rated as serious/severe.

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

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Olaparib + abiraterone + P vs. placebo + abiraterone + P** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival Age < 65 years	NA vs. NA HR: 0.57 [0.36; 0.90]; p = 0.015 Probability: "hint"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"[c]
≥ 65 years	NA vs. NA HR: 0.98 [0.76; 1.26]; p = 0.846	Lesser/added benefit not proven
MDS (AEs)	NA vs. NA HR: NC; p = 0.362	Greater/lesser harm not proven
AML (AEs)	NA vs. NA HR: -[d]	Greater/lesser harm not proven
Outcomes with shortened observation period		
Morbidity		
Worst pain (BPI-SF Item 3)	36.6 months vs. NA HR: 0.97 [0.72; 1.30]; p = 0.866	Lesser/added benefit not proven
Pain interference (BPI-SF Item 9a–g)	36.6 months vs. NA HR: 0.85 [0.62; 1.18]; p = 0.413	Lesser/added benefit not proven

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

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Olaparib + abiraterone + P vs. placebo + abiraterone + P** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Symptomatic skeletal-related events[e]		
Age		
< 65 years	NA vs. NA HR: 1.42 [0.67; 3.29]; p = 0.371	Lesser/added benefit not proven
≥ 65 years	NA vs. NA HR: 0.56 [0.32; 0.93]; p = 0.025 Probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Health status (EQ-5D VAS)	No usable analyses	Lesser/added benefit not proven
Health-related quality of life		
FACT-P total score, deterioration by ≥ 23.4 points		
Metastases		
Bone only	26.6 months vs. NA HR: 1.45 [1.003; 2.09] HR: 0.69 [0.48; 0.997][e]; p = 0.048 Probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Lesser benefit, extent: "minor"
Visceral + other	ND HR: 0.48 [0.30; 0.77]; p = 0.003 Probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"
Side effects		
SAEs	31.9 months vs. NA HR: 1.28 [1.004; 1.63] HR: 0.78 [0.61; 0.996][e]; p = 0.047 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: "minor"

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

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Olaparib + abiraterone + P vs. placebo + abiraterone + P** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Severe AEs Metastases Bone only	23.4 vs. 22.1 months HR: 1.10 [0.84; 1.44]; p = 0.487	Greater/lesser harm not proven
Visceral + other	ND HR: 1.70 [1.22; 3.36] HR: 0.59 [0.30; 0.82][e]; p = 0.002 Probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: “considerable”
Discontinuation due to AEs	NA vs. NA HR: 1.52 [1.03; 2.27] HR: 0.66 [0.44; 0.97][e]; p = 0.034 Probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: “minor”
Pneumonitis (AEs)	NA vs. NA HR: 1.60 [0.39; 7.82]; p = 0.514	Greater/lesser harm not proven
Diarrhoea (AEs)	NA vs. NA HR: 1.88 [1.28; 2.79] HR: 0.53 [0.36; 0.78][e]; p = 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ Greater harm, extent: “considerable”
Nausea (AEs)	NA vs. NA HR: 2.37 [1.73; 3.28] HR: 0.42 [0.30; 0.58][e]; p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ Greater harm, extent: “considerable”
Decreased appetite (AEs)	NA vs. NA HR: 2.26 [1.47; 3.58] HR: 0.44 [0.28; 0.68][e]; p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ Greater harm, extent: “considerable”

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

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Olaparib + abiraterone + P vs. placebo + abiraterone + P** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Injury, poisoning and procedural complications (SAEs)	NA vs. NA HR: 2.47 [1.08; 6.32] HR: 0.40 [0.16; 0.93][e]; p = 0.035 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: "minor"
Pulmonary embolism (severe AEs)	NA vs. NA HR: 3.87 [1.79; 9.62] HR: 0.26 [0.10; 0.56][e]; p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% Greater harm, extent: "major"
Anaemia (severe AEs)	NA vs. NA HR: 4.92 [2.80; 9.35] HR: 0.20 [0.11; 0.36][e]; p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% Greater harm, extent: "major"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. The considerable added benefit only becomes apparent in the later course of disease (after about 16 months).
d. No event occurred.
e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

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

I 3.3.2 Overall conclusion on added benefit

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

Table 18: Positive and negative effects from the assessment of olaparib + abiraterone + P in comparison with abiraterone + P (multipage table)

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival ▫ Age (< 65 years): hint of added benefit – extent: “considerable”	–
Outcomes with shortened observation period	
Morbidity Serious/severe symptoms/late complications ▪ Symptomatic skeletal-related events ▫ Age (≥ 65 years): hint of added benefit – extent: “minor”	–
Health-related quality of life ▪ FACT-P ▫ Metastases (visceral and other): hint of added benefit – extent: “considerable”	Health-related quality of life ▪ FACT-P ▫ Metastases (bone only): hint of greater harm – extent: “minor”
–	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: “minor” ▪ Severe AEs ▫ Metastases (visceral and other): hint of greater harm – extent: “considerable” ▪ Discontinuations due to AEs: hint of greater harm – extent: “minor” ▪ Injury, poisoning and procedural complications (SAEs): hint of greater harm – extent: “minor” ▪ Pulmonary embolism (severe AEs): hint of greater harm – extent “major” ▪ Anaemia (severe AEs): hint of greater harm – extent “major”
–	Non-serious/non-severe side effects ▪ Diarrhoea (AEs): hint of greater harm – extent: “considerable” ▪ Nausea (AEs): Hint of greater harm – extent: “considerable” ▪ Decreased appetite (AEs): hint of greater harm – extent: "considerable"
AE: adverse event; FACT-P: Functional Assessment of Cancer Therapy-Prostate; SAE: serious adverse event	

Overall, both positive and negative effects of olaparib + abiraterone + P were found in comparison with the ACT. The characteristics of age and metastases are effect modifiers for several outcomes. Due to the effect modification in overall survival by the characteristic of age, the results on the added benefit of olaparib + abiraterone + P compared with the ACT are derived separately according to age below:

Patients < 65 years

For patients < 65 years, there is a hint of considerable added benefit for the outcome of overall survival. No conclusion on health-related quality of life, measured with the FACT-P, can be derived for patients < 65 years, as there are positive or negative effects for this outcome depending on the site of metastasis at baseline, but there is no information on how these advantages or disadvantages are shown within the subgroup of patients < 65 years.

On the other hand, there is a series of negative effects in the side effects category of varying severity categories and with varying, partly major extent. Overall, these negative effects are not assumed to completely call into question the considerable survival advantage for patients < 65 years. Overall, a hint of minor added benefit is therefore derived for patients < 65 years.

Patients ≥ 65 years

For patients ≥ 65 years, there is no hint of an added benefit for the outcome of overall survival. There is a hint of minor added benefit for the composite outcome of symptomatic skeletal-related events for this patient group. No conclusion on health-related quality of life, measured with the FACT-P, can be derived for patients ≥ 65 years, as there are positive or negative effects for this outcome depending on the site of metastasis at baseline, but there is no information on how these advantages or disadvantages are shown within the subgroup of patients ≥ 65 years.

On the other hand, there is a series of negative effects in the side effects category of varying severity categories and with varying, partly major extent. Overall, the negative effects predominate for patients ≥ 65 years. The only positive effect of minor extent for the outcome of symptomatic skeletal-related events, which is mainly determined by the component of radiotherapy to prevent or relieve skeletal symptoms, is contrasted by negative effects in serious/severe side effects: In addition to negative effects of minor extent in the overall rates of SAEs and discontinuations due to AEs, negative effects of major extent were shown in severe pulmonary embolisms and severe anaemia. Overall, a hint of lesser benefit is derived for patients ≥ 65 years.

Summary

In summary, there is a hint of minor added benefit of olaparib + abiraterone + P compared with the ACT for patients < 65 years with treatment-naive mCRPC in whom chemotherapy is not clinically indicated. For patients ≥ 65 years of age, there is a hint of lesser benefit in comparison with the ACT. Data are available only for patients for whom abiraterone + P is a suitable treatment option in accordance with treatment of physician’s choice. No data are available for patients for whom enzalutamide is a suitable treatment option in accordance with treatment of physician’s choice.

The assessment described above differs from that of the company, which, based on the PROpel study, derived an indication of considerable added benefit of olaparib + abiraterone + P in comparison with the ACT for the entire approved therapeutic indication, i.e. patients with mCRPC in whom chemotherapy is not clinically indicated.

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

I 4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on olaparib + abiraterone + P (status: 15 November 2022)
- bibliographical literature search on olaparib + abiraterone + P (last search on 15 November 2022)
- search in trial registries/trial results databases for studies on olaparib + abiraterone + P (last search on 17 November 2022)
- search on the G-BA website for olaparib + abiraterone + P (last search on 15 November 2022)

To check the completeness of the study pool:

- search in trial registries for studies on olaparib + abiraterone + P (last search on 30 January 2023); for search strategies, see I Appendix A of the full dossier assessment

The potentially relevant Study 8 [6,13] was identified from the check of the completeness.

The company conducted its information retrieval for the entire therapeutic indication (irrespective of the patients' pretreatment). From this information retrieval, it only selected the PROpel study, which investigated patients with treatment-naive mCRPC and is therefore described under research question 1 (see Table 4) of this report.

Incompleteness of the dossier for research question 2

Study 8, sponsored by the company, investigated olaparib + abiraterone + P compared with placebo + abiraterone + P in patients with pretreated mCRPC. The study was used as a supportive measure in the context of the approval by the EMA [8].

The company neither included the study in the study list for olaparib + abiraterone + P nor did it submit the study protocol or CSR or other documents on Study 8. Only in the search in trial registries and the bibliographic search did the company identify this study and excluded it with the exclusion reason "population". There is no further explanation as to why the company did not take this study into account.

The approach of the company is not appropriate. Since this is a study by the company in the approved therapeutic indication, it would be necessary for the company to both include this

study in the study list for olaparib + abiraterone + P in Module 4 A and to submit the corresponding documents (study protocol, CSR, etc.). For the present research question, the dossier is therefore incomplete. Irrespective of this, it cannot be conclusively clarified due to the incomplete documents whether Study 8 is relevant or unsuitable for the benefit assessment due to a lack of implementation of the comparator therapy.

Relevance of Study 8 for the benefit assessment

Study 8 is a double-blind RCT comparing olaparib + abiraterone + P with placebo + abiraterone + P in patients with pretreated mCRPC. These are patients within the approved therapeutic indication of olaparib + abiraterone + P and the present research question. The ACT specified by the G-BA for research question 2 is individualized therapy taking into account prior therapy and BRCA1/2 mutation status. Abiraterone + P, enzalutamide or olaparib were specified as suitable comparators. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criterion (multicomparator study). Study 8, on the other hand, is not a multicomparator study, but a comparison versus treatment with abiraterone + P. However, it is not possible to assess from the available information whether the ACT was implemented in Study 8 or was possibly only implemented for a subpopulation. Overall, the relevance of Study 8 for research question 2 thus remains unclear.

I 4.2 Results on added benefit

In its dossier, the company did not present any data to assess the added benefit of olaparib + abiraterone + P compared with the ACT for patients with pretreated mCRPC. There is no hint of an added benefit of olaparib + abiraterone + P in comparison with the ACT; an added benefit is therefore not proven for this research question.

I 4.3 Probability and extent of added benefit

In its dossier, the company did not present any data to assess the added benefit of olaparib + abiraterone + P compared with the ACT for patients with pretreated mCRPC. An added benefit of olaparib + abiraterone + P versus the ACT is therefore not proven for research question 2. This differs from the assessment of the company, which derived an indication of considerable added benefit of olaparib + abiraterone + P in comparison with the ACT for the entire approved therapeutic indication, i.e. patients with mCRPC, regardless of pretreatment at this disease stage, in whom chemotherapy is not clinically indicated.

I 5 Probability and extent of added benefit – summary

Table 19 summarizes the result of the assessment of added benefit of olaparib + abiraterone + P in comparison with the ACT.

Table 19: Olaparib + abiraterone + P – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with treatment-naive mCRPC in whom chemotherapy is not clinically indicated[b]	Treatment of physician's choice[c]	▪ Patients < 65 years: hint of minor added benefit[d, e] ▪ Patients ≥ 65 years: hint of lesser benefit[d, e]
2	Adults with pretreated mCRPC in whom chemotherapy is not clinically indicated[b]	Individualized therapy[f] taking into account prior therapy and BRCA1/2 mutation status	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. For the present therapeutic indication, it is assumed according to the G-BA that an existing conventional ADT is continued. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or antagonists.
c. As part of a clinical study, the following treatments are deemed suitable comparators for treatment of physician's choice: abiraterone in combination with prednisone or prednisolone, enzalutamide.
d. In the PROpel study, abiraterone in combination with prednisone or prednisolone was used as a comparator. No data are available for patients for whom enzalutamide is a suitable treatment option in accordance with treatment of physician's choice.
e. Only patients with an ECOG PS of 0 or 1 were included in the PROpel study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
f. As part of a clinical study, the following treatments are deemed suitable comparators for individualized therapy: abiraterone in combination with prednisone or prednisolone, enzalutamide, olaparib.

ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; BRCA: breast cancer associated gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mCRPC: metastatic castration-resistant prostate cancer; P: prednisone or prednisolone

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-03.html.