Olaparib (prostate cancer)

Addendum to Project A23-03 (dossier assessment)[1]

ADDENDUM

Project: A23-47 Version: 1.0 Status: 16 June 2023

[1] Translation of addendum A23-47 *Olaparib (Prostatakarzinom) – Addendum zum Projekt A23-03 (Dossierbewertung)*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Olaparib (prostate cancer) – Addendum to Project A23-03

Commissioning agency

Federal Joint Committee

Commission awarded on

23 May 2023

Internal Project No.

A23-47

Address of publisher

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Keywords

Olaparib, Abiraterone Acetate, Prednisone, Prednisolone, Prostatic Neoplasms − Castration-Resistant, Benefit Assessment, NCT03732820, NCT01972217

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
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
eCRF	electronic case report form
EMA	European Medicines Agency
FACT-P	Functional Assessment of Cancer Therapy-Prostate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GnRH	gonadotropin-releasing hormone
HRR	homologous recombination repair
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mCRPC	metastatic castration-resistant prostate cancer
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
PSA	prostate-specific antigen
PT	Preferred Term
RCT	randomized controlled trial
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

1 Background

On 23 May 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-03 (Olaparib – Benefit assessment according to § 35a Social Code Book V) [1].

The commission dated 23 May 2023 comprises the assessment of the following analyses presented by the pharmaceutical company (hereinafter referred to as "the company") in the commenting procedure [2], taking into account the information provided in the dossier [3]:

- complete analyses of the third data cut-off of the PROpel study dated 12 October 2022
- data on the censoring of patients for the outcome of symptomatic skeletal-related events
- relevance of Study 8 for the benefit assessment

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

In benefit assessment A23-03 [1], the double-blind randomized controlled trial (RCT) PROpel was used for research question 1, which comprises patients with treatment-naive metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated. The study compared olaparib in combination with abiraterone and prednisone or prednisolone (hereinafter "olaparib + abiraterone + P") with placebo + abiraterone + P. A detailed description of the PROpel study can be found in dossier assessment A23-03. With the comments [2,4], the company presented results of a third data cut-off (12 October 2022) for the PROpel study, which had not been available at the time of the benefit assessment and are assessed below. Furthermore, the company subsequently submitted supplementary information on the censoring of patients for the outcome of symptomatic skeletal-related events (see Section 2.1.2.1).

The company's dossier was incomplete for research question 2 of the benefit assessment (patients with pretreated mCRPC in whom chemotherapy is not clinically indicated). With its comments, the company presented the study documents for the potentially relevant Study 8, whose relevance for the benefit assessment is assessed below.

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

2.1.1 Study characteristics

A detailed description of the PROpel study can be found in dossier assessment A23-03 [1]. The following text describes only those characteristics for which changes resulted from the third data cut-off.

Characteristics of the study population

With the comments, the company presented additional data on the characteristics of the study population (see Table 1). These are aggregate data on homologous recombination repair (HRR) and breast cancer associated gene (BRCA) mutation status. Mutation status was determined using a ctDNA-based test, a tumour tissue test, or a germline mutation test. To be considered mutated, a positive result in one of the tests was sufficient.

Table 1: Characteristics of the study population – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P

Study Characteristic Category	Olaparib + abiraterone + P N[a] = 399	Placebo + abiraterone + P N[a] = 397
PROpel		
HRR mutation status[b]		
HRR mutation	111 (27.8)	115 (29.0)
HRR wild type	279 (69.9)	273 (68.8)
Missing	9 (2.3)	9 (2.3)
BRCA mutation status		
BRCA mutation	47 (11.8)	38 (9.6)
BRCA wild type	343 (86.0)	350 (88.2)
Missing	9 (2.3)	9 (2.3)

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. The following genes were investigated for mutations: ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L.

BRCA: breast cancer associated gene; HRR: homologous recombination repair; n: number of patients in the category; N: number of randomized patients; P: prednisone or prednisolone: RCT: randomized controlled trial

About 1 third of the patients in the PROpel study had an HRR mutation, and about 10 % of the patients had a BRCA1 and/or BRCA2 mutation.

Third data cut-off on 12 October 2022

Benefit assessment A23-03 was based on the second data cut-off of the PROpel study dated 14 March 2022. According to the study protocol, this data cut-off was planned after 453 events in the outcome of radiological progression-free survival (rPFS) (second interim analysis for overall survival and final analysis for rPFS).

In the commenting procedure, the company submitted analyses of a third data cut-off dated 12 October 2022. This is the planned final analysis on overall survival.

Treatment duration and observation period

Table 2 shows the mean and median treatment duration of the patients and the median observation period for individual outcomes.

Table 2: 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, 12 October 2022 data cut-off		
Treatment duration [months]		
For olaparib/placebo		
Median [min; max]	18.5 [0.4; 47.0][b]	15.7 [0.4; 44.6][b]
Mean (SD)	ND	ND
For abiraterone		
Median [min; max]	20.1 [1.0; 47.0][b]	15.7 [0.4; 44.6][b]
Mean (SD)	ND	ND
Observation period [months]		
Overall survival[c]		
Median [Q1; Q3]	33.6 [19.9; 37.8]	32.1 [20.3; 36.9]
[min; max]	[2.0; 47.0]	[0.4; 45.3]
Mean (SD)	ND	ND
Morbidity		
Pain (BPI-SF)		
Median [min; max]	14.7 [0; 46.8]	11.8 [0; 44.0]
Mean (SD)	ND	ND
Symptomatic skeletal-related events		
Median [min; max]	18.4 [0; 46.0]	15.1 [0; 44.3]
Mean (SD)	ND	ND
Health status (EQ-5D VAS)		
Median [min; max]	17.4 [0; 46.9]	13.7 [0; 43.3]
Mean (SD)	ND	ND
Health-related quality of life		
FACT-P		
Median [min; max]	17.4 [0; 46.9]	13.7 [0; 43.3]
Mean (SD)	ND	ND
Side effects		
AEs/SAEs/severe AEs		
Median [min; max]	21.2 [1.9; 47.0]	16.7 [0.4; 44.6]
Mean (SD)	ND	ND
MDS/AML		
Median [min; max]	33.6 [2.0; 47.0]	32.0 [0.4; 45.3]
Mean (SD)	ND	ND

Table 2: 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 control 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 2.5 years, are comparable.

As at the time of the second data cut-off, 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. It is notable that the median observation periods for the patient-reported outcomes on pain, health status and health-related quality of life are 1 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. Besides, as described in the benefit assessment, patient-reported outcomes should also be recorded throughout the entire study period.

Subsequent therapies

Table 3 shows which subsequent therapies patients received after discontinuing the study medication.

Table 3: 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, 12 October 2022 data cut-off		
Drug therapy	179 (45)	216 (54)
Immunotherapy	23 (6)	23 (6)
Hormonal therapy	67 (17)	75 (19)
Abiraterone	28 (7)[b]	24 (6)[b]
Enzalutamide	39 (10)	48 (12)
Cytotoxic chemotherapy	123 (31)	167 (42)
Cabazitaxel	43 (11)	62 (16)
Carboplatin	9 (2)	10 (3)
Docetaxel	95 (24)	141 (36)
Targeted therapy	20 (5)	29 (7)
Radium-223 dichloride	10 (3)	15 (4)
Other	10 (3)[b, c]	24 (6)[b, c]
Radiotherapy	48 (12)	64 (16)

a. Patients can be counted in more than one subsequent therapy.
b. Institute's calculation.
c. 2 patients received olaparib.

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

In the PROpel study, 45% of patients in the intervention arm received subsequent therapy, compared with 54% in the control arm. The most common therapy after study treatment was chemotherapy (31% in the intervention versus 42% in the control arm). Hormonal therapy (including almost exclusively abiraterone or enzalutamide) was given to 17% of patients in the intervention arm and 19% of patients in the control arm. Contrary to guideline recommendations [5], 7% of patients in the intervention arm and 6% in the control arm received subsequent therapy with abiraterone.

The subsequent therapies used are overall comparable to the second data cut-off and there is no indication that the patients' subsequent therapies deviate to a relevant extent from the recommendations of the S3 guideline [5].

2.1.2 Results of the third data cut-off

2.1.2.1 Risk of bias

The risk of bias across outcomes for the PROpel study is rated as low (see A23-03 [1]).

Table 4 describes the risk of bias for the results of the relevant outcomes.

Table 4: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P

Study		Outcomes												
	Study level	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[e, f]	H[f]	H[f]	L[h]	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 or subsequent values.
f. Incomplete observations for potentially informative reasons.
g. No usable data available; proportion of patients not considered in the analysis is > 30%.
h. 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; AML: acute myeloid leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; MDS: myelodysplastic syndrome; P: prednisone or prednisolone; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

For the present third data cut-off, the outcome-specific risk of bias is high for the results of all outcomes except overall survival, the specific adverse events (AEs) of myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), and discontinuation due to AEs, as was already the case for the second data cut-off. This is due to incomplete observations for potentially informative reasons.

For the outcome of symptomatic skeletal-related events, it was unclear in the benefit assessment how many patients had been censored on day 1 and were therefore not included in the analysis. With the comments, the company presented analyses showing that only one

patient treated with olaparib + abiraterone + P and 2 patients treated with placebo + abiraterone + P were censored on day 1. Thus, the proportion of patients affected is to be rated as not relevant for the benefit assessment. However, the risk of bias of the results of the outcome of symptomatic skeletal-related events must still be rated as high due to the incompleteness of the observations for potentially informative reasons.

Regardless of the aspects described regarding the risk of bias, the certainty of conclusions of the study results is reduced due to the uncertainties addressed in A23-03. Firstly, it is unclear whether chemotherapy was not clinically indicated for all patients in the study population. Although it can be assumed that the proportion of asymptomatic/mildly symptomatic patients and/or with docetaxel pretreatment is > 80 %, uncertainty remains as to whether patients for whom chemotherapy would have been indicated were also included in the study. Secondly, it is unclear whether all patients received concomitant androgen deprivation therapy (ADT). Although the company provided further information with the comments on how many patients continued ADT according to information in the electronic case report form (eCRF), the proportions of patients with ADT vary between 74.7 % and 91.1 % depending on how they are presented. The uncertainties as to how many of the patients received concomitant ADT thus remain.

Based on the data subsequently submitted by the company, there is therefore no change in the assessment and, as a result of the described restriction, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

2.1.2.2 Results

Table 5 summarizes the results of the data subsequently submitted on the comparison of olaparib + abiraterone + P versus placebo + abiraterone + P in patients with mCRPC in whom chemotherapy is not clinically indicated, taking into account the third data cut-off of the PROpel study. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Where available, the Kaplan-Meier curves on the presented event time analyses are presented in Appendix A. Results for common AEs, serious AEs (SAEs), severe AEs, and discontinuations due to AEs can be found in Appendix B of this addendum.

Table 5: 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, 12 October 2022 data cut-off					
Mortality					
Overall survival	399	42.1 [38.4; NC] 176 (44.1)	397	34.7 [31.0; 39.3] 205 (51.6)	0.82 [0.67; 1.00][a]; 0.054[b]
Morbidity					
Worst pain (BPI-SF Item 3)[c]	330[d]	NA 97 (29.4[d])	333[d]	NA 89 (26.7[d])	1.00 [0.75; 1.34][a]; 0.945[b]
Pain intensity (BPI-SF Items 3-6)[c] (supplementary information)	*330[d]*	*NA* *69 (20.9[d])*	*333[d]*	*NA* *63 (18.9[d])*	*0.98 [0.70; 1.39][a]; 0.910[b]*
Pain interference (BPI-SF Item 9a-g)[e]	330[d]	NA 76 (23.0[d])	333[d]	NA 82 (24.6[d])	0.84 [0.61; 1.15][a]; 0.299[b]
Symptomatic skeletal-related events	398[f]	NA 46 (11.6[f])	395[f]	NA 51 (12.9[f])	0.82 [0.55; 1.22][a]; 0.321[b]
Radiotherapy to prevent or relieve skeletal symptoms	398[f]	NA 31 (7.8[f])	395[f]	NA 42 (10.6[f])	0.67 [0.42; 1.06][a]; 0.104[b]
New symptomatic pathological bone fracture	398[f]	NA 17 (4.3[f])	395[f]	NA 16 (4.1[f])	0.91 [0.46; 1.83][a]; 0.776[b]
Occurrence of spinal cord compression	398[f]	NA 3 (0.8[f])	395[f]	NA 9 (2.3[f])	0.28 [0.06; 0.94][a]; 0.045[b]
Orthopaedic surgical intervention for bone metastasis	398[f]	NA 2 (0.5[f])	395[f]	NA 6 (1.5[f])	0.27 [0.04; 1.19][a]; 0.099[b]
Health status (EQ-5D VAS)	No usable data				

Table 5: 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**
Health-related quality of life					
FACT-P					
Total score[g]	278[d]	NA 91 (32.7[d])	295[d]	NA 98 (33.2[d])	0.95 [0.71; 1.26][a]; 0.701[b]
Physical wellbeing[h]	278[d]	11.9 [9.1; 19.3] 152 (54.7[d])	295[d]	17.4 [13.7; 24.8] 140 (47.5[d])	1.29 [1.03; 1.63][a]
Social/family wellbeing[h]	278[d]	11.1 [8.2; 21.1] 141 (50.7[d])	295[d]	15.6 [9.1; 37.7] 142 (48.1[d])	1.04 [0.82; 1.32][a]
Emotional wellbeing[i]	278[d]	NA 114 (41.0[d])	295[d]	24.8 [21.1; 34.0] 125 (42.4[d])	0.95 [0.74; 1.23][a]
Functional wellbeing[h]	278[d]	15.6 [11.0; 23.0] 144 (51.8[d])	295[d]	11.1 [9.1; 19.3] 159 (53.9[d])	0.89 [0.71; 1.11][a]
Prostate cancer-specific subscale[j]	278[d]	35.8 [24.8; NC] 100 (36.0[d])	295[d]	35.8 [21.1; NC] 102 (34.6[d])	0.96 [0.73; 1.27][a]

Table 5: 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
Side effects					
AEs (supplementary information)	398	0.5 [0.5; 0.8] 389 (97.7)	396	1.0 [0.8; 1.2] 380 (96.0)	–
SAEs	398	31.7 [25.8; NC] 161 (40.5)	396	39.5 [32.3; NC] 126 (31.8)	1.23 [0.98; 1.56]; 0.079[k]
Severe AEs[l]	398	19.2 [14.1; 24.0] 222 (55.8)	396	27.8 [21.4; 35.4] 171 (43.2)	1.31 [1.08; 1.61]; 0.007[k]
Discontinuation due to AEs[m]	398	NA 71 (17.8)	396	NA 43 (10.9)	1.57 [1.08; 2.30]; 0.019[k]
MDS (PT, AEs)	398	NA 2 (0.5)	396	NA 0 (0)	NC; 0.197[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)	1.62 [0.40; 7.89]; 0.506[k]
Diarrhoea (PT, AEs)	398	NA 82 (20.6)	396	NA 42 (10.6)	1.88 [1.30; 2.75]; < 0.001[k]
Nausea (PT, AEs)	398	NA 122 (30.7)	396	NA 57 (14.4)	2.36 [1.73; 3.25]; < 0.001[k]
Decreased appetite (PT, AEs)	398	NA 66 (16.6)	396	NA 31 (7.8)	2.10 [1.38; 3.25]; < 0.001[k]
Injury, poisoning and procedural complications (SOC, SAEs)	398	NA 20 (5.0)	396	NA 8 (2.0)	2.24 [1.02; 5.42]; 0.048[k]
Pulmonary embolism (PT, severe AEs[l])	398	NA 29 (7.3)	396	NA 9 (2.3)	3.06 [1.51; 6.87]; 0.002[k]
Anaemia (PT, severe AEs[l])	398	NA 64 (16.1)	396	NA 13 (3.3)	4.99 [2.85; 9.48]; < 0.001[k]

Table 5: 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

a. HR and CI: Cox proportional hazards model, adjusted for metastases (bone only vs. visceral vs. other) and docetaxel treatment of mHSPC (yes vs. no).
b. p-value: log-rank test, stratified by metastases (bone only vs. visceral vs. other) and docetaxel treatment of mHSPC (yes vs. no).
c. Time to first deterioration. An increase by ≥ 2 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 10).
d. Institute's calculation; information refers to patients who have a baseline value and at least one subsequent value.
e. Time to first deterioration. An increase by ≥ 1.5 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 10).
f. Institute's calculation; information refers to patients included in the analysis.
g. Time to first deterioration. A decrease by ≥ 23.4 points from baseline is defined as a clinically relevant deterioration (scale range 0–156).
h. Time to first deterioration. A decrease by ≥ 4.2 points from baseline is defined as a clinically relevant deterioration (scale range 0–28).
i. Time to first deterioration. A decrease by ≥ 3.6 points from baseline is defined as a clinically relevant deterioration (scale range 0–24).
j. Time to first deterioration. A decrease by ≥ 7.2 points from baseline is defined as a clinically relevant deterioration (scale range 0–48).
k. HR, 95% 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 2 events of MDS were 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

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

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 BRCA mutation status for this outcome, however (see Section 2.1.2.3). There is a hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P for patients with BRCA mutation. For patients without BRCA mutation (BRCA wild type), 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.

In contrast to dossier assessment A23-03, the company did not use the hazard ratio for the analysis of overall survival, but the relative risk. It justified the change in the type of analysis with the proportional hazards assumption not being fulfilled. The approach of the company was not prespecified. The statistical analysis plan specified the use of the hazard ratio also in case of violation of the proportional hazards assumption. In the present case, there was a mathematical violation of the proportional hazards assumption for the outcome of overall survival, but the hazard ratio can still be interpreted in terms of content because the Kaplan-Meier curves overlap more than they cross (see Figure 1 in Appendix A.1). Thus, the hazard ratio continues to be used.

Morbidity

Worst pain (BPI-SF Item 3)

No statistically significant difference between treatment groups was shown for the outcome of worst pain (Brief Pain Inventory-Short Form [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 an effect modification for the subgroup characteristic of BRCA mutation status for this outcome, however (see Section 2.1.2.3). There is a hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P for patients with BRCA mutation. For patients without BRCA mutation (BRCA wild type), 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.

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 subgroup characteristic of BRCA mutation status in this outcome, however (see Section 2.1.2.3). There

is a hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P for patients with BRCA mutation. For patients without BRCA mutation (BRCA wild type), 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 using the EQ-5D visual analogue scale (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 Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score. No statistically significant difference between treatment groups was shown for the outcome of FACT-P total score. There is an effect modification by BRCA mutation status for this outcome (see Section 2.1.2.3). A statistically significant difference in favour of olaparib + abiraterone + P was shown for patients with BRCA mutation. There is a hint of an added benefit of olaparib + abiraterone + P in comparison with abiraterone + P for this patient group. No statistically significant difference between treatment groups was shown in patients without BRCA mutation (BRCA wild type). 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.

Side effects

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

For the outcome of SAEs, no statistically significant difference between treatment groups was found. There is an effect modification for the characteristic of BRCA mutation status, however (see Section 2.1.2.3). For patients with BRCA mutation, 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. For patients without BRCA mutation (BRCA wild type), 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 shown for the outcomes of severe AEs and discontinuation due to AEs. In each case, there is a hint of greater harm from olaparib + abiraterone + P in comparison with abiraterone + P.

Specific AEs

MDS, AML and pneumonitis

For the outcomes of MDS and AML (each Preferred Term [PT], AEs), 2 and no events 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 all 3 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 nausea and decreased appetite (each PT, AEs). A statistically significant difference to the disadvantage of olaparib + abiraterone + P was also shown for the outcome of diarrhoea (PT, AEs). There is an effect modification for the subgroup characteristic of HRR mutation status, however (see Section 2.1.2.3). For patients with HRR mutation, 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. For patients without HRR mutation (HRR wild type), 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 (System Organ Class [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 each of 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.

2.1.2.3 Subgroups and effect modifiers

The following subgroup characteristics are considered in the present addendum:

- age (< 65 years/≥ 65 years)
- metastases at baseline (bone only/visceral/other)
- BRCA mutation status (BRCA-mutated/BRCA wild type)
- HRR mutation status (HRR-mutated/HRR wild type)

The subgroup analyses on BRCA mutation status and HRR mutation status for the third data cut-off were submitted by the company for the first time. These subgroup analyses were not prespecified, but were requested by the European Medicines Agency [EMA] for the third data cut-off [6] and are considered for the benefit assessment.

Analogous to dossier assessment A23-03, for the subgroup characteristic of metastases at baseline, the subgroups of visceral metastases and other metastases – in distinction from patients with bone metastases only – are meta-analytically combined in one subgroup (see Appendix C).

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 6. The Kaplan-Meier curves on the subgroup results can be found in Appendix A.

Table 6: 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]	Olaparib + abiraterone + P vs. placebo + abiraterone + P p-value[b]
PROpel, 12 October 2022 data cut-off						
Overall survival						
BRCA mutation status						
BRCA-mutated	47	NA 13 (27.7)	38	23.0 [17.8; 34.2] 25 (65.8)	0.29 [0.14; 0.56]	< 0.001
BRCA wild type	343	39.6 [35.9; NC] 158 (46.1)	350	37.9 [32.2; 43.7] 176 (50.3)	0.91 [0.73; 1.13]	0.386
Total					Interaction[c]:	0.001
Symptomatic skeletal-related events						
BRCA mutation status						
BRCA-mutated	47	NA 8 (17.0)	38	19.7 [12.7; NC] 11 (28.9)	0.31 [0.12; 0.78]	0.013
BRCA wild type	343	NA 37 (10.8)	350	NA 40 (11.4)	0.89 [0.57; 1.40]	0.623
Total					Interaction[c]:	0.042
Pain interference (BPI-SF Item 9 a–g)d						
BRCA mutation status						
BRCA-mutated	47[e]	NA 6 (12.8)	38[e]	NA 8 (21.1)	0.29 [0.10; 0.84]	0.023
BRCA wild type	343[e]	NA 69 (20.1)	350[e]	NA 74 (21.1)	0.95 [0.68; 1.32]	0.764
Total					Interaction[c]:	0.037

Table 6: 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]	Olaparib + abiraterone + P vs. placebo + abiraterone + P p-value[b]
FACT-B, total score[f]						
BRCA mutation status						
BRCA-mutated	47[e]	NA 9 (19.1)	38[e]	17.4 [6.4; NC] 12 (36.1)	0.36 [0.15; 0.85]	0.020
BRCA wild type	343[e]	NA 79 (23.0)	350[e]	NA 84 (24.0)	1.04 [0.77; 1.42]	0.790
Total					Interaction[c]:	0.022
Metastases						
Bone only	213[e]	NA 62 (29.1)	53[e]	NA 53 (23.5)	1.45 [1.003; 2.09]	0.048
Visceral and other[g]	186[e, h]	ND 29 (15.6)[h]	171[e, h]	ND 45 (26.3)[h]	0.48 [0.30; 0.76][i]	0.002[i]
Visceral	*67*[e]	*NA* *14 (20.9)*	*73*[e]	*17.4 [7.3; NC]* *20 (27.4)*	*0.47 [0.23; 0.93]*	*0.031*
Other	*199*[e]	*NA* *15 (12.6)*	*98*[e]	*30.3 [13.7; NC]* *25 (25.5)*	*0.48 [0.25; 0.91]*	*0.024*
Total					Interaction[j]:	< 0.001
SAEs						
BRCA mutation status						
BRCA-mutated	47	NA 14 (29.8)	38	20.2 [13.6; NC] 12 (31.6)	0.58 [0.27; 1.29]	0.178
BRCA wild type	342	27.7 [25.2; 33.9] 144 (42.1)	350	39.5 [32.3; NC] 112 (32.0)	1.34 [1.04; 1.71]	0.021
Total					Interaction[c]:	0.0497

Table 6: 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]
Diarrhoea (PT, AEs)						
HRR mutation status						
HRR-mutated	111	NA 17 (15.3)	115	NA 15 (13.0)	0.96 [0.48; 1.94]	0.903
HRR wild type	278	NA 62 (22.3)	273	NA 26 (9.5)	2.40 [1.54; 3.86]	< 0.001
Total					Interaction[c]:	0.031

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. Time to first deterioration. A score increase by ≥ 1.5 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 10).
e. Unclear proportion of patients without baseline or subsequent value in the subgroups who are not included in the analysis (see FN d in Table 5).
f. Time to first deterioration. A decrease by ≥ 23.4 points from baseline is defined as a clinically relevant deterioration.
g. Summary of the subgroups of visceral metastases and other metastases.
h. Institute's calculation.
i. Institute's calculation: meta-analytical summary of the subgroup results for visceral and other metastases (fixed-effect model).
j. Institute's calculation: p-value from Q test for heterogeneity, based on the 2 subgroups of bone only vs. visceral and other.

AE: adverse event; BRCA: breast cancer associated gene; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; 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; P: prednisone or prednisolone; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event

Mortality

Overall survival

There is an effect modification by the characteristic of BRCA mutation status for the outcome of overall survival. In contrast to the second data cut-off, there is no effect modification for the characteristic of age.

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

No statistically significant difference between treatment groups was shown in patients without BRCA mutation (BRCA wild type). 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

Pain interference (BPI-SF Item 9a–g)

There is an effect modification for the characteristic of BRCA mutation status for the outcome of pain interference (BPI-SF Item 9a–g).

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

No statistically significant difference between treatment groups was shown in patients without BRCA mutation (BRCA wild type). 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.

Symptomatic skeletal-related events

There is an effect modification by the characteristic of BRCA mutation status for the outcome of symptomatic skeletal-related events.

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

No statistically significant difference between treatment groups was shown in patients without BRCA mutation (BRCA wild type). 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.

Health-related quality of life

FACT-P

There is an effect modification by the characteristics of metastases at baseline and BRCA mutation status for the outcome of FACT-P. Since an effect modification by the characteristic of BRCA mutation status was also shown for several other outcomes, this subgroup

characteristic is considered to be leading in the present data situation, and only this subgroup characteristic is considered further for the outcome of FACT-P.

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

No statistically significant difference between treatment groups was shown in patients without BRCA mutation (BRCA wild type). 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.

Side effects

SAEs

There is an effect modification by the characteristic of BRCA mutation status for the outcome of SAEs.

No statistically significant difference between treatment groups was shown for patients with BRCA mutation. There is no hint of greater or lesser harm from 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 without BRCA mutation (BRCA wild type). There is a hint of greater harm from olaparib + abiraterone + P in comparison with abiraterone + P for this patient group.

Specific AEs

Diarrhoea (PT, AEs)

There is an effect modification by the characteristic of HRR mutation status for the outcome of diarrhoea (PT, AEs).

No statistically significant difference between treatment groups was shown in patients with HRR mutation. There is no hint of greater or lesser harm from 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 without HRR mutation (HRR wild type). There is a hint of greater harm from olaparib + abiraterone + P in comparison with abiraterone + P for this patient group.

2.1.3 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 [7].

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

2.1.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.1.2.2 and Section 2.1.2.3 (see Table 7).

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.

Pain interference (BPI-SF Item 9a–g)

For the outcome of pain interference, recorded using the BPI-SF Item 9a–g, insufficient severity data are available which would allow classifying them as serious/severe. Therefore, this outcome is assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 7: 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 BRCA mutation status BRCA-mutated	NA vs. NA HR: 0.29 [0.14; 0.56]; p < 0.001 Probability: "hint"	Outcome category: mortality CI_u < 0.85 Added benefit, extent: "major"
BRCA wild type	39.6 vs. 37.9 HR: 0.91 [0.73; 1.13]; p = 0.386	Lesser/added benefit not proven
Side effects		
MDS (AEs)	NA vs. NA HR: NC; p = 0.197	Greater/lesser harm not proven
AML (AEs)	NA vs. NA HR: –[c]	Greater/lesser harm not proven
Outcomes with shortened observation period		
Morbidity		
Worst pain (BPI-SF Item 3)	NA vs. NA HR: 1.00 [0.75; 1.34]; p = 0.945	Lesser/added benefit not proven
Pain interference (BPI-SF Item 9a–g) BRCA mutation status BRCA-mutated	NA vs. NA HR: 0.29 [0.10; 0.84]; p = 0.023 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications 0.80 ≤ CI_u < 0.90 added benefit, extent: "minor"
BRCA wild type	NA vs. NA HR: 0.95 [0.68; 1.32]; p = 0.764	Lesser/added benefit not proven

Table 7: 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		
BRCA mutation status		
BRCA-mutated	NA vs. 19.7 months HR: 0.31 [0.12; 0.78]; p = 0.013 Probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"
BRCA wild type	NA vs. NA HR: 0.89 [0.57; 1.40]; p = 0.623	Lesser/added benefit not proven
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		
BRCA mutation status		
BRCA-mutated	NA vs. 17.4 HR: 0.36 [0.15; 0.85]; p = 0.020 Probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"
BRCA wild type	NA vs. NA HR: 1.04 [0.77; 1.42]; p = 0.790	Lesser/added benefit not proven

Table 7: 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]
Side effects		
SAEs		
BRCA mutation status		
BRCA-mutated	NA vs. 20.2 months HR: 0.58 [0.27; 1.29]; p = 0.178	Greater/lesser harm not proven
BRCA wild type	27.7 vs. 39.5 months HR: 1.34 [1.04; 1.71]; HR: 0.75 [0.58; 0.96][d]; p = 0.021 Probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: “minor”
Severe AEs	19.2 vs. 27.8 months HR: 1.31 [1.08; 1.61]; HR: 0.76 [0.62; 0.93][d]; p = 0.007	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: “minor”
Discontinuation due to AEs	NA vs. NA HR: 1.57 [1.08; 2.30]; HR: 0.64 [0.43; 0.93][d]; p = 0.019 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: 1.62 [0.40; 7.89]; p = 0.506	Greater/lesser harm not proven
Diarrhoea (AEs)		
HRR mutation status		
HRR-mutated	NA vs. NA HR: 0.96 [0.48; 1.94]; p = 0.903	Greater/lesser harm not proven
HRR wild type	NA vs. NA HR: 2.40 [1.54; 3.86]; HR: 0.42 [0.26; 0.65][d]; p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ Greater harm, extent: “considerable”

Table 7: 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]
Nausea (AEs)	NA vs. NA HR: 2.36 [1.73; 3.25]; HR: 0.42 [0.31; 0.58][d]; 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: 2.10 [1.38; 3.25]; HR: 0.48 [0.31; 0.72][d]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.8 Greater harm, extent: "considerable"
Injury, poisoning and procedural complications (SAEs)	NA vs. NA HR: 2.24 [1.02; 5.42]; HR: 0.45 [0.18; 0.98][d]; p = 0.048 Probability: "hint"	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 Greater harm, extent: "minor"
Pulmonary embolism (severe AEs)	NA vs. NA HR: 3.06 [1.51; 6.87]; HR: 0.33 [0.15; 0.66][d]; p = 0.002 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: 4.99 [2.85; 9.48]; HR: 0.20 [0.11; 0.35][d]; 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. No event occurred.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.

AE: adverse event; AML: acute myeloid leukaemia; BPI-SF: Brief Pain Inventory-Short Form; BRCA: breast cancer associated gene; CI: confidence interval; CI_u: upper limit of confidence interval; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; HRR: homologous recombination repair; MDS: myelodysplastic syndrome; NA: not achieved; NC: not calculable; ND: no data; SAE: serious adverse event; VAS: visual analogue scale

2.1.3.2 Overall conclusion on added benefit

Table 8 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 8: 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 ▫ BRCA-mutated: hint of an added benefit – extent: “major”	–
Outcomes with shortened observation period	
Morbidity Serious/severe symptoms/late complications ▪ Symptomatic skeletal-related events ▫ BRCA-mutated: hint of an added benefit – extent: “considerable” Non-serious/non-severe symptoms/late complications ▪ Pain interference (BPI-SF Item 9a–g) ▫ BRCA-mutated: hint of an added benefit – extent: “minor”	–
Health-related quality of life ▪ FACT-P ▫ BRCA-mutated: hint of an added benefit – extent: “considerable”	–
–	Serious/severe side effects ▪ SAEs: ▫ BRCA wild type: hint of greater harm – extent: “minor” ▪ Severe AEs: hint of greater harm – extent: “minor” ▪ discontinuation 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): ▫ HRR wild type: 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; BPI-SF: Brief Pain Inventory-Short Form; BRCA: breast cancer associated gene; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HRR: homologous recombination repair; SAE: serious adverse event	

Overall, both positive and negative effects of olaparib + abiraterone + P were found in comparison with the appropriate comparator therapy (ACT) for the third data cut-off (in each case hints). The characteristics of BRCA and HRR mutation status are effect modifiers for several outcomes. Due to the effect modification in overall survival by the characteristic of BRCA mutation status, the results on the added benefit of olaparib + abiraterone + P compared with the ACT are derived separately according to BRCA mutation status below:

Patients with BRCA mutation

For patients with BRCA mutation, there is a hint of major added benefit for the outcome of overall survival. In the outcome category of morbidity, there is a hint of considerable added benefit for the outcome of symptomatic skeletal-related events and a hint of minor added benefit for the outcome of pain interference (BPI-SF Item 9a-g). For health-related quality of life, measured by FACT-P, there is a hint of considerable added benefit for patients with BRCA mutation.

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 call into question the major survival advantage for patients with BRCA mutation. Overall, a hint of major added benefit is therefore derived for patients with the BRCA mutation.

Patients without BRCA mutation (BRCA wild type)

For patients without BRCA mutation (BRCA wild type), there are exclusively negative effects in the category of side effects of different severity categories and with varying, in part major, extent. In addition to negative effects of minor extent in discontinuations due to AEs, negative effects of major extent were shown in severe pulmonary embolisms and severe anaemia. Also for the overall rate of SAEs, there is a hint of greater harm of minor extent for patients without BRCA mutation. Overall, a hint of lesser benefit is derived for patients without BRCA mutation.

Summary

In summary, there is a hint of major added benefit of olaparib + abiraterone + P compared with the ACT for patients with BRCA mutation with treatment-naive mCRPC in whom chemotherapy is not clinically indicated. For patients without BRCA mutation, 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.

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

2.2.1 Study pool

The company did not identify any relevant study for research question 2 of the benefit assessment (see A23-03). In the dossier, the company did not address its sponsored and potentially relevant Study 8 comparing olaparib + abiraterone + P versus placebo + abiraterone + P and did not provide any study documents. The company subsequently submitted the complete study documents (study protocol, statistical analysis plan, clinical study report [CSR], etc.) with the comments, but without any preparation of the data in accordance with the module templates.

From the perspective of the company, Study 8 is not relevant for the benefit assessment because it is not a multi-comparator study and therefore does not represent the ACT specified by the G-BA. Based on the information on Study 8 subsequently submitted by the company, the relevance for the benefit assessment is assessed below.

Study characteristics

Table 9 and Table 10 describe Study 8.

Table 9: Characteristics of Study 8 – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study 8	RCT, double-blind, parallel	Adult patients with mCRPC[b], after chemotherapy with docetaxel at mCRPC stage, with ECOG PS ≤ 2	Olaparib + abiraterone + P (N = 71) Placebo + abiraterone + P (N = 71)	Screening: 28 days Treatment: until disease progression[c], side effects, decision of patient or physician, lost to follow-up Observation: outcome-specific, at most until death or final OS analysis	41 centres in Belgium, Canada, Czech Republic, France, Italy, Netherlands, Poland, Russia, Spain, United Kingdom, and USA 4/2014 – ongoing Data cut-off: 22 September 2017[d]	Primary: rPFS Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes comprise exclusively data on relevant available outcomes based on the information provided by the company in the comments.
b. Histologically or cytologically proven castration resistance was defined as increased PSA levels or other signs of disease progression despite ADT and serum testosterone levels ≤ 50 ng/dL. Metastatic status was 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. Assessment based on RECIST 1.1 criteria and PCWG-3 criteria; however, further treatment was allowed if, in the investigator's assessment, the patient would benefit from the further treatment.
d. The primary rPFS analysis was planned after 100 events, the final analysis was planned after 60% deaths. Before the database lock for the primary analysis, it was anticipated that ≥ 60% of patients in the study had already died at this point, and the analysis at this data cut-off was therefore considered final.

ADT: androgen deprivation therapy; AE: adverse event; CT: computed tomography; ECOG PS: Eastern Cooperative Oncology Group Performance Status; 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 10: Characteristics of the intervention in Study 8 – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P

Study	Intervention	Comparison
Study 8	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/placebo: in case of toxicity, 2 dose reductions in 50 mg steps allowed (250 mg twice daily and then 200 mg twice daily) ▪ Abiraterone, prednisone and prednisolone: in case of toxicity, dose reductions are allowed in accordance with the SPC ▪ Olaparib/placebo and abiraterone could be discontinued independently. When abiraterone alone was discontinued, investigations were conducted as planned. When olaparib/placebo was discontinued, only the follow-up investigations were carried out.	
	Pretreatment **Required** ▪ ADT with serum testosterone < 50 ng/dL ▪ ≥ 2 cycles of docetaxel treatment at mCRPC stage **Allowed** **Disallowed** ▪ any treatment with PARP inhibitors (including olaparib) ▪ any exposure to a CYP17 inhibitor ▪ second-generation anti-androgen agents (including abiraterone and enzalutamide) ▪ ≥ 2 courses of chemotherapy for mCRPC ▪ immunotherapy or radium-223 for mCRPC ▪ investigational treatment ≤ 30 days of the first dose of study treatment ▪ substrates of CYP2D6 with a narrow therapeutic index (e.g. thioridazine) ▪ potent inhibitors or inducers of CYP3A4 ≤ 2 weeks before the first dose of study treatment (3 weeks for St. John's Wort) ▪ major surgery < 2 weeks of starting study treatment	
	Concomitant treatment **Allowed** ▪ palliative radiotherapy for the treatment of bone metastases ▪ bisphosphonates or denosumab for the prevention of skeletal-related events in bone metastases ▪ corticosteroids, provided the dose was stable for ≥ 4 weeks before the first dose of study medication and during the study **Disallowed** ▪ other anti-cancer therapies: chemotherapy, immunotherapy, biologics, other therapies (except GnRH analogues) ▪ strong or moderate CYP3A inhibitors and inducers had to be avoided	

ADT: androgen deprivation therapy; CYP3A4: cytochrome P450 3A4; 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; SPC: Summary of Product Characteristics

Study 8 [8] is a double-blind RCT comparing olaparib + abiraterone + P with placebo + abiraterone + P in adult patients with pretreated mCRPC. A prerequisite for study participation was chemotherapy with docetaxel at the mCRPC stage. Patients who had discontinued docetaxel treatment due to toxicity were allowed to participate in the study provided they had received at least 2 cycles of docetaxel.

According to the inclusion criteria, patients had to be candidates for abiraterone therapy and have disease progression with ongoing ADT at baseline. Patients who had previously received second-generation anti-androgen agents or had already received more than 2 courses of chemotherapy for metastatic prostate cancer were not allowed to participate in the study. In addition, patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≥ 2.

Study 8 included a total of 142 patients who were randomly allocated in a 1:1 ratio to treatment with olaparib + abiraterone + P (N = 71) or placebo + abiraterone + P (N = 71). Randomization was not based on stratification factors.

Treatment with olaparib + abiraterone + P and abiraterone + P was in compliance with the respective Summary of Product Characteristics (SPC) [9,10].

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

Relevance of Study 8 for the benefit assessment

Implementation of the ACT in Study 8

For research question 2, the G-BA designated individualized therapy taking into account prior therapy and BRCA1/2 mutation status as ACT, designating abiraterone + P, enzalutamide or olaparib 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). If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment. The relevance the comparators olaparib, abiraterone and enzalutamide, which are comprised by individualized therapy, has for the Study 8 population is described below. According to the SPC, monotherapy with olaparib is indicated for the treatment of patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) who have progressed

following prior therapy that included a new hormonal agent [9]. Based on the information in the CSR of Study 8, none of the patients had a BRCA1 mutation, and 6 patients (4.2%) had a BRCA2 mutation. In 3 patients each (2.1 %), a variant of unknown relevance was present for BRCA1 and BRCA2. The proportion of patients with no mutation was 25.4 % for BRCA1 and 24.6 % for BRCA2. For the majority (> 65 %) of patients, the mutation status was documented as unknown, absent or with failed documentation. Thus, based on the documented BRCA mutation status alone, monotherapy with olaparib would have been an option only for a very small proportion of patients in Study 8. In addition, prior treatment with a second-generation anti-androgen agent (including abiraterone and enzalutamide) was an exclusion criterion in Study 8, which would be a prerequisite for treatment with olaparib monotherapy in compliance with the approval. Overall, there was no therapeutic indication for olaparib monotherapy for the patient population investigated in Study 8.

The remaining options for patient-relevant therapy were therefore the comparators abiraterone + P and enzalutamide specified by the G-BA. According to the inclusion criterion of Study 8, patients had to be candidates for treatment with abiraterone + P, but no further information is available on the basis of which criteria this decision was made. The approved therapeutic indications of abiraterone + P and enzalutamide are identical, and the guidelines do not specify any patient-specific criteria for the treatment decision. Based on Study 8, conclusions can thus be drawn on the added benefit of olaparib + abiraterone + P for those patients for whom abiraterone + P is a suitable individualized therapy.

Concomitant treatment with ADT

As already described in A23-03, in the present therapeutic indication, the use of olaparib + abiraterone + P or abiraterone + P without concomitant therapy with a gonadotropin-releasing hormone (GnRH) analogue is not in compliance with the approval. In Study 8, castration resistance was defined as increased prostate-specific antigen (PSA) levels or other signs of disease progression despite ADT and serum testosterone levels ≤ 50 ng/dL. It cannot be inferred from the study protocol that the continuation of an existing treatment with GnRH analogues was mandatory. According to the information in the CSR, a total of 39.4 % of the patients (40.8 % intervention arm versus 38.0 % control arm) received treatment with a GnRH analogue during Study 8. In addition, 7% had previous bilateral orchiectomy (5.6% intervention arm versus 8.5% control arm). Based on available data, a maximum of 46.4% had received ADT. It can be inferred from the discussion in the comments and the oral hearing on olaparib [11] that the continuation of ADT in the present therapeutic indication is a treatment standard. It remains open whether comprehensive documentation of the concomitant ADT took place in Study 8. Accordingly, there is uncertainty as to whether all patients continued their ongoing ADT in compliance with the approval during the study.

Lack of therapeutic indication for chemotherapy in Study 8

Olaparib + abiraterone + P is approved for patients with mCRPC in whom chemotherapy is not clinically indicated. In Study 8, this was not an explicit inclusion criterion. The inclusion criteria 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. Against the background that there are no clear criteria as to when chemotherapy is clinically indicated, and the fact that all patients had already received chemotherapy with docetaxel in their previous line of treatment, it is assumed in the present situation that this proportion is within a range that allows the total population of Study 8 to be used for the present research question.

Summary

Study 8 was conducted within the approved therapeutic indication of olaparib + abiraterone + P and the present research question. Although the company submitted the study documents of Study 8, it did not provide any data preparation in accordance with the module templates. The dossier of the company is therefore incomplete for research question 2.

Analogous to the PROpel study, which was used for research question 1, there are uncertainties regarding the lack of therapeutic indication for chemotherapy and concomitant treatment with ADT. From Study 8, conclusions can be derived on the subpopulation of patients for whom abiraterone + P represents a suitable individualized therapy.

3 Probability and extent of added benefit – summary

The data subsequently submitted by the company in the commenting procedure change the conclusion on added benefit of olaparib + abiraterone + P drawn in dossier assessment A23-03 for research question 1: Based on the results of the third data cut-off, there is a hint of major added benefit of olaparib + abiraterone + P in comparison with the ACT for patients with BRCA mutation. For research question 2, there is no change from dossier assessment A23-03.

The following Table 11 shows the result of the benefit assessment of olaparib + abiraterone + P under consideration of dossier assessment A23-03 and the present addendum.

Table 11: 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 with BRCA mutation: hint of major added benefit[d, e] ▪ Patients without BRCA mutation (BRCA wild type): 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 G-BA decides on the added benefit.

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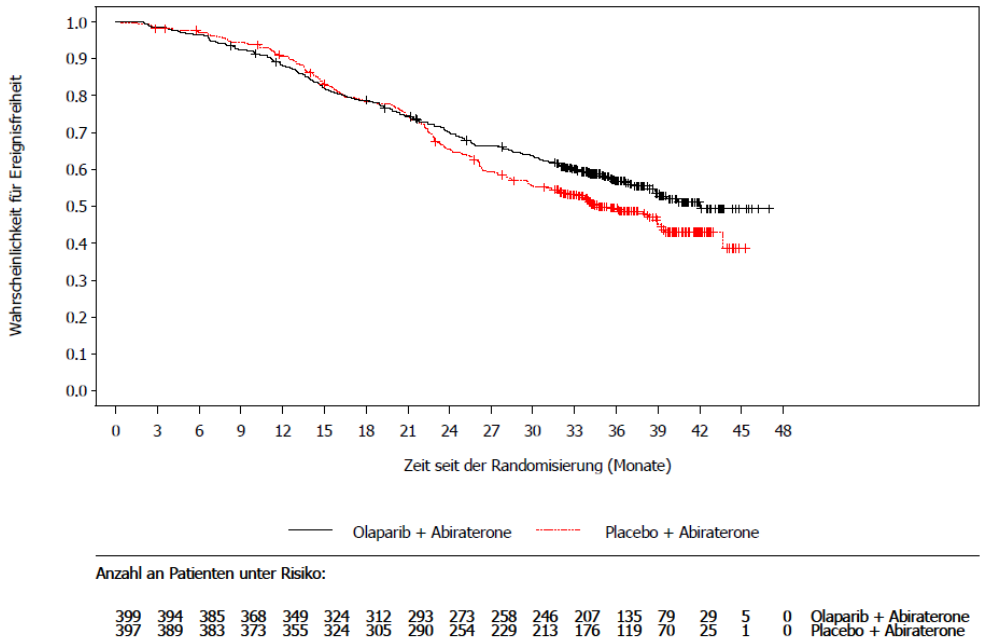
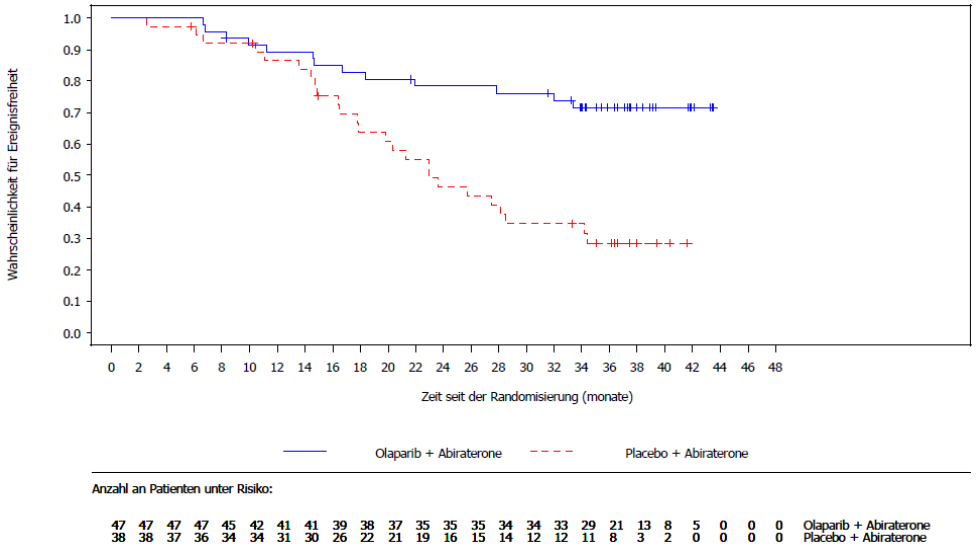
Appendix A Graphic display of the event time analyses presented in the benefit assessment (Kaplan-Meier curves)

A.1 Mortality



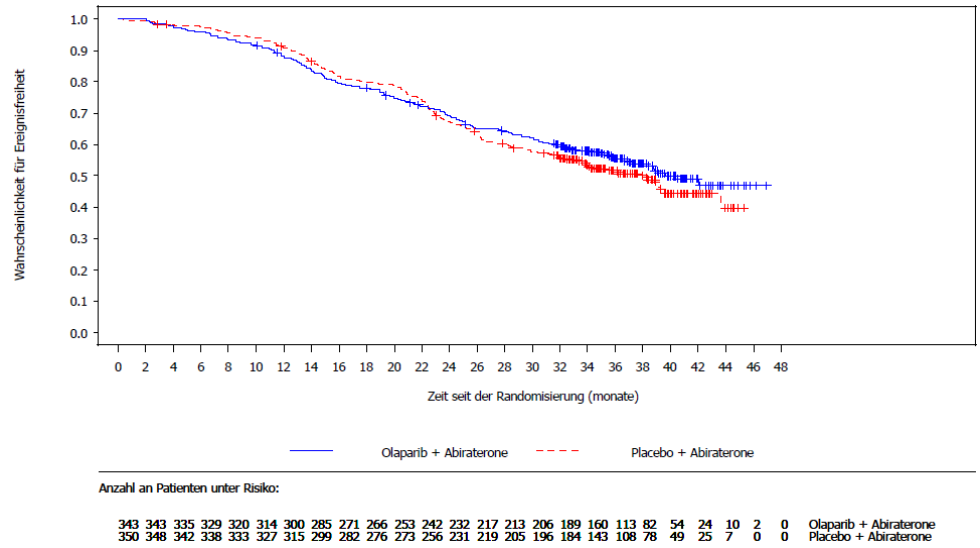
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 1: Kaplan-Meier curves for the outcome of overall survival – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

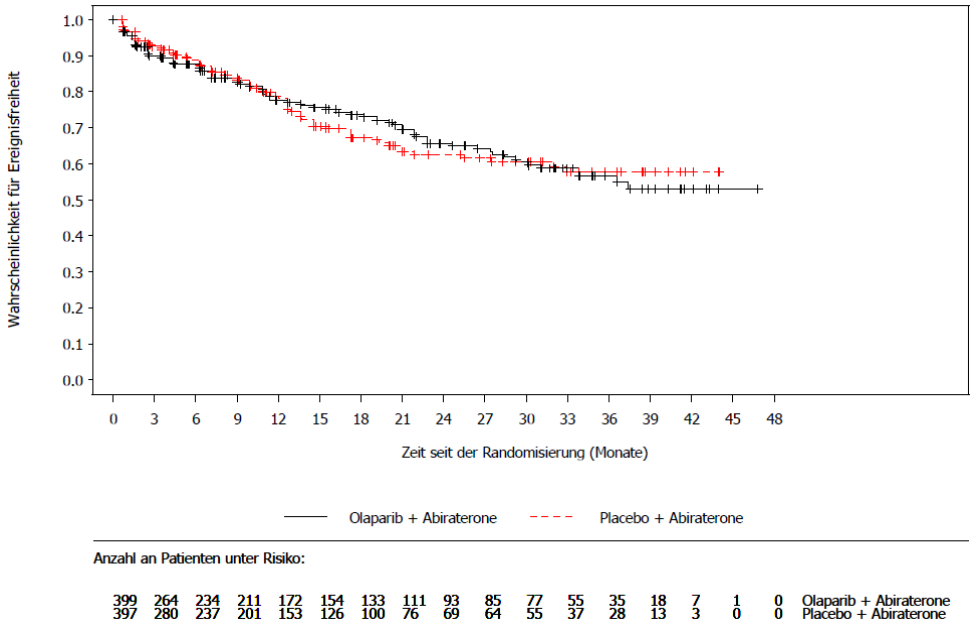
Figure 2: Kaplan-Meier curves for the outcome of overall survival in patients with BRCA mutation – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

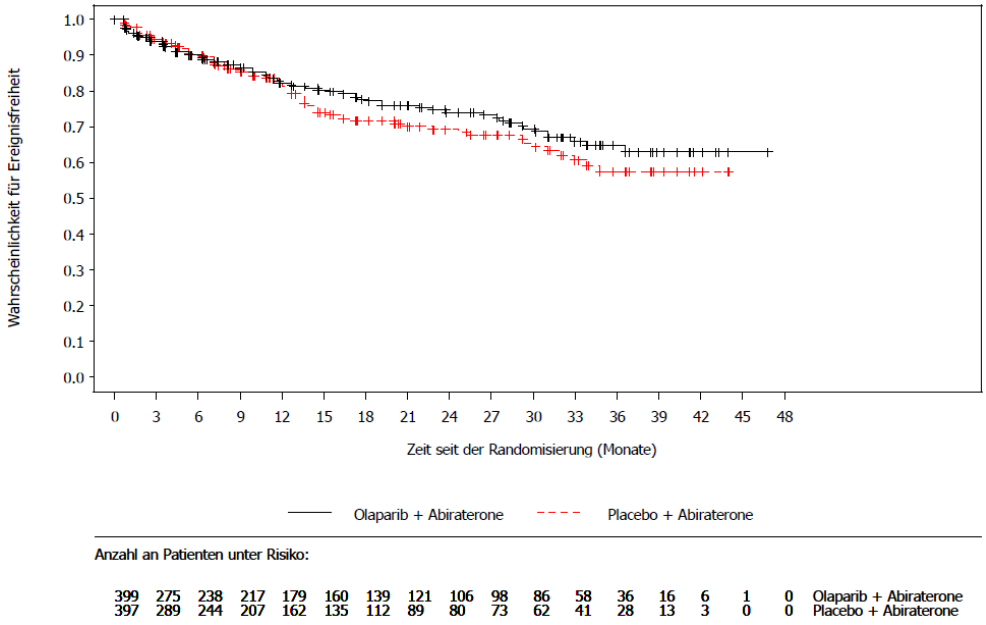
Figure 3: Kaplan-Meier curves for the outcome of overall survival in patients without BRCA mutation (BRCA wild type) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)

A.2 Morbidity



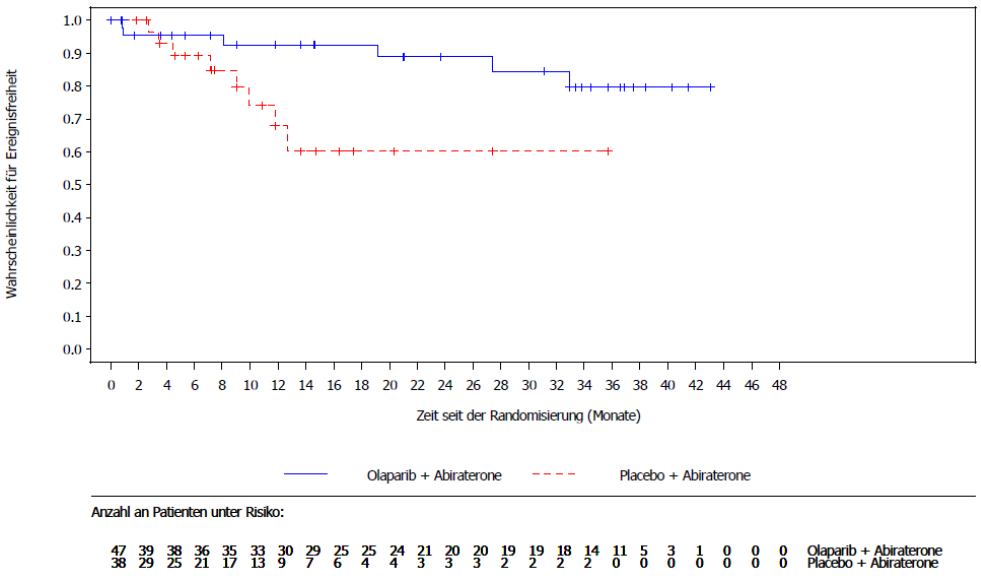
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 4: Kaplan-Meier curves for the outcome of worst pain (BPI-SF Item 3) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



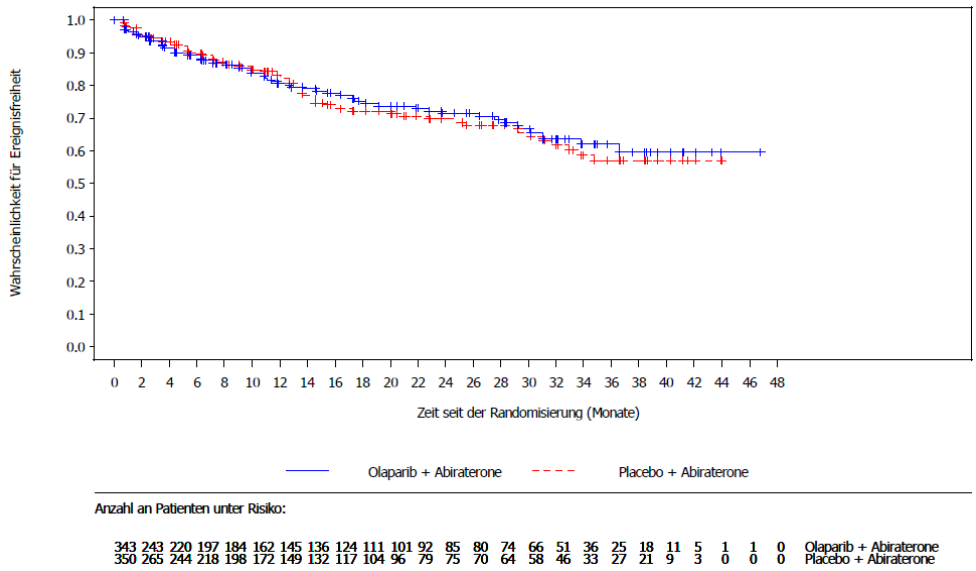
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 5: Kaplan-Meier curves for the outcome of pain interference (BPI-SF Item 9a–g) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



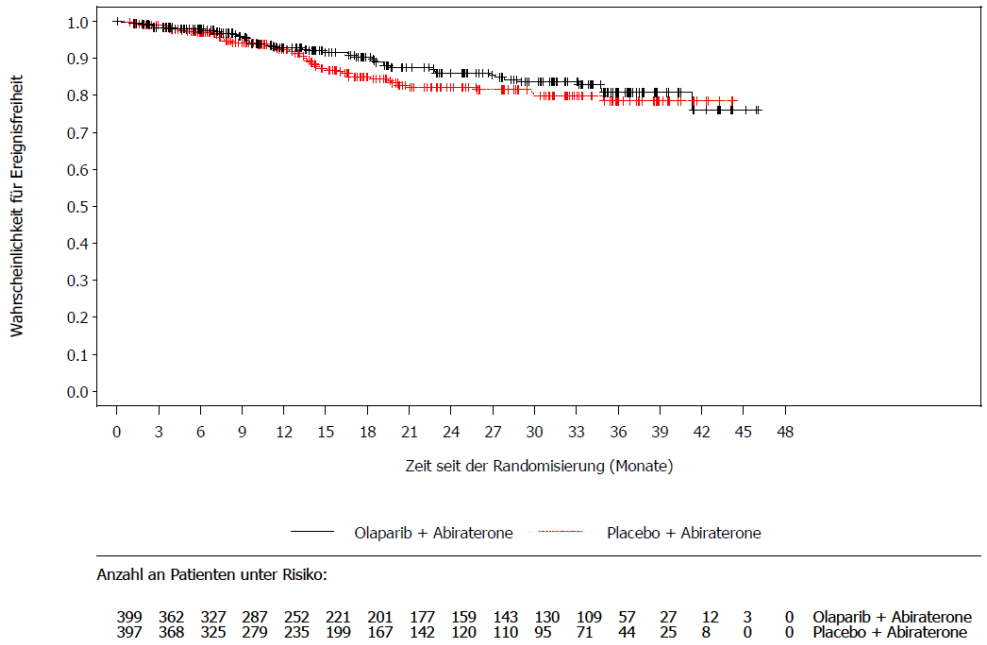
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 6: Kaplan-Meier curves for the outcome of pain interference (BPI-SF Item 9a–g) in patients with BRCA mutation – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



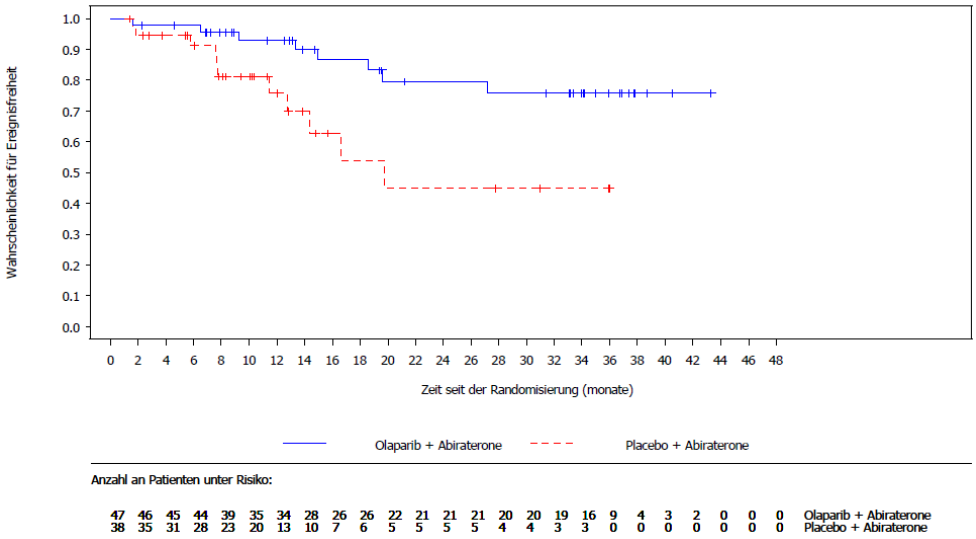
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 7: Kaplan-Meier curves for the outcome of pain interference (BPI-SF Item 9a–g) in patients without BRCA mutation (BRCA wild type) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



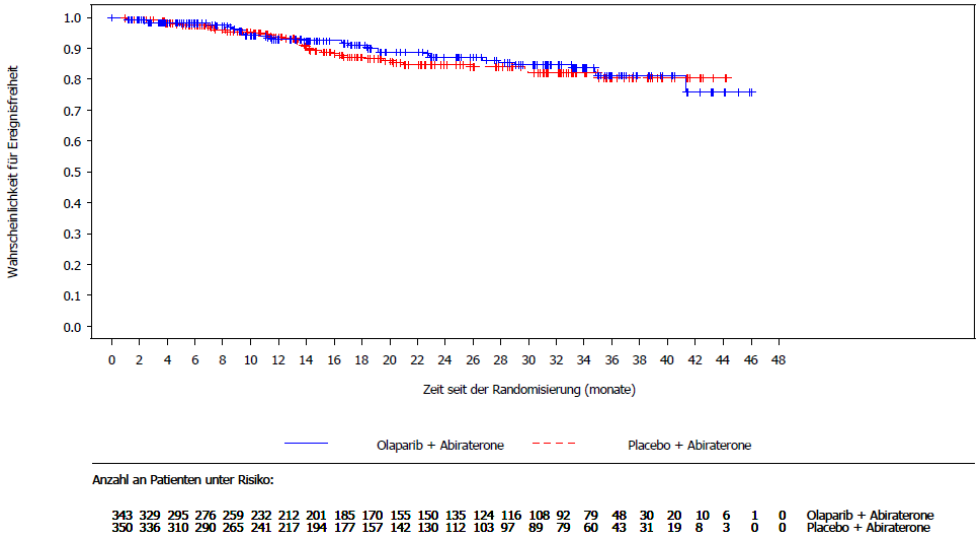
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 8: Kaplan-Meier curves for the outcome of symptomatic skeletal-related events – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

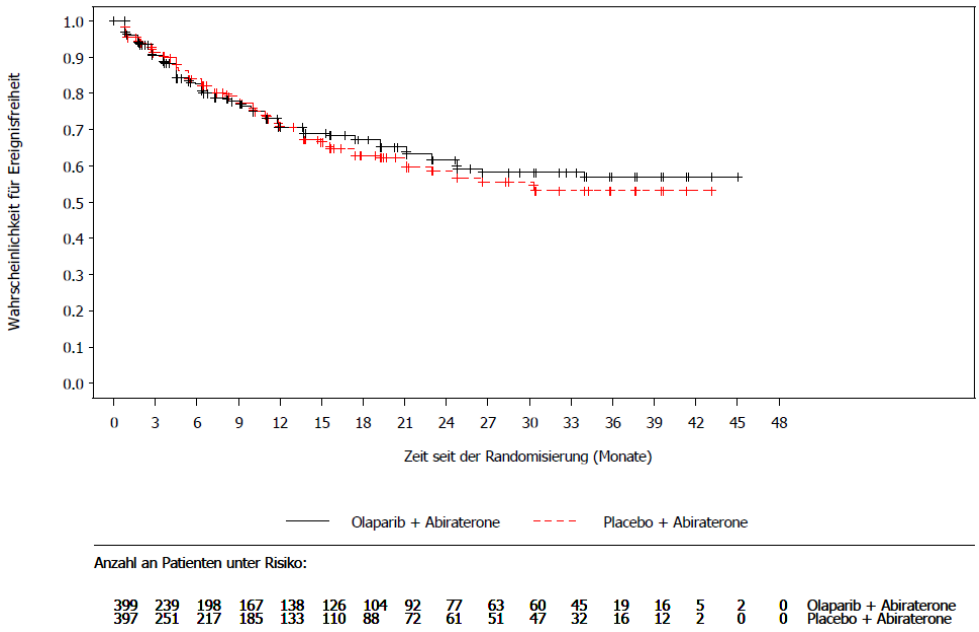
Figure 9: Kaplan-Meier curves for the outcome of symptomatic skeletal-related events in patients with BRCA mutation – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

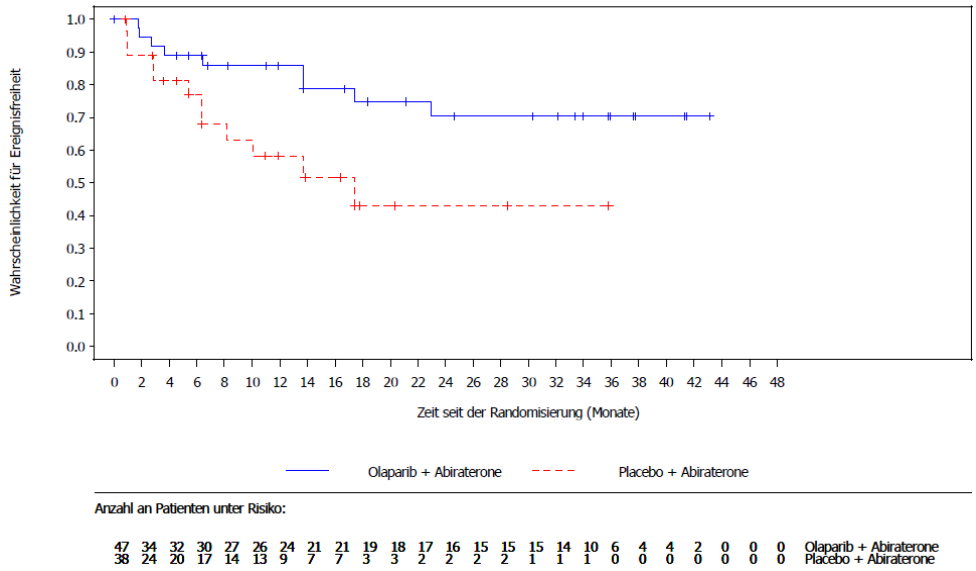
Figure 10: Kaplan-Meier curves for the outcome of symptomatic skeletal-related events in patients without BRCA mutation (BRCA wild type) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)

A.3 Health-related quality of life



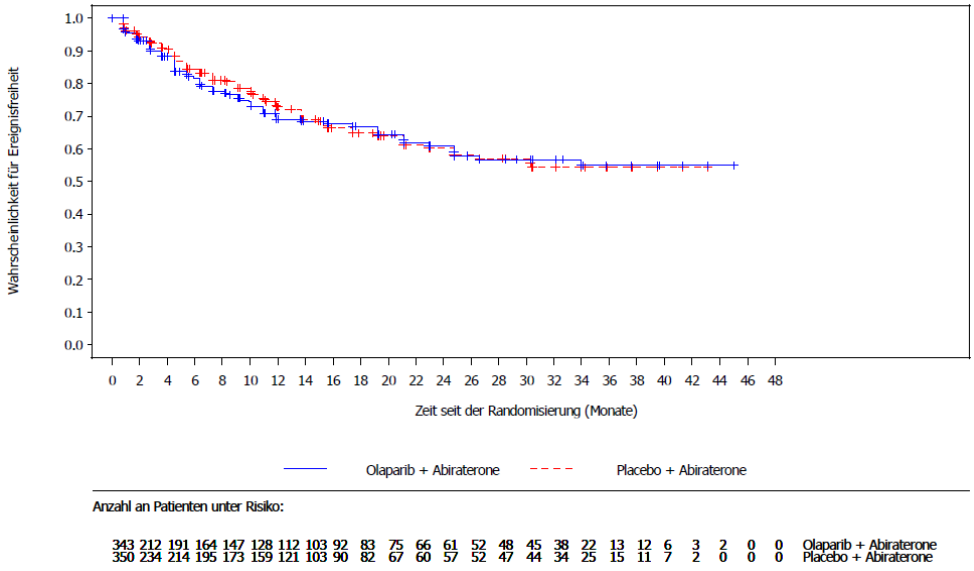
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 11: Kaplan-Meier curves for the outcome of FACT-P total score – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



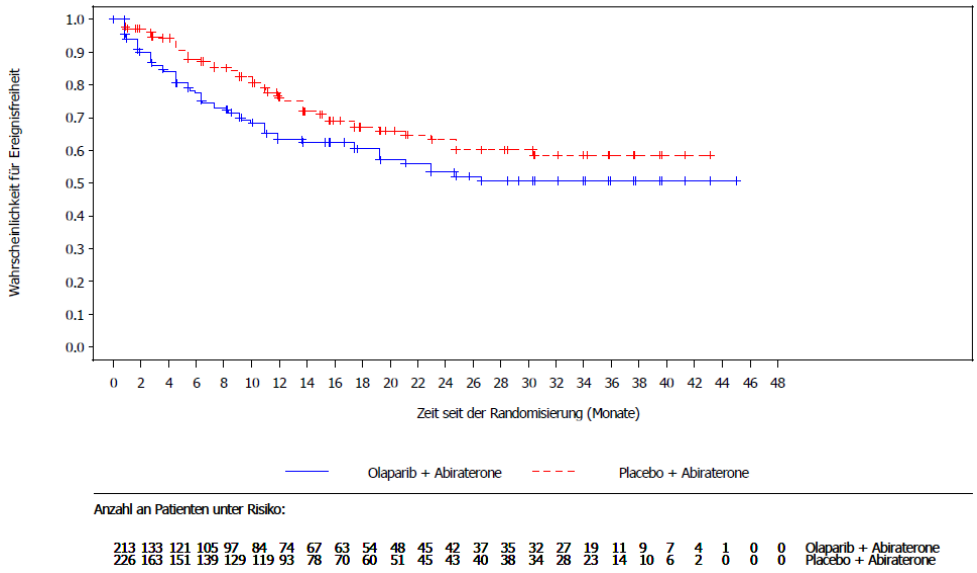
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 12: Kaplan-Meier curves for the outcome of FACT-P total score in patients with BRCA mutation – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



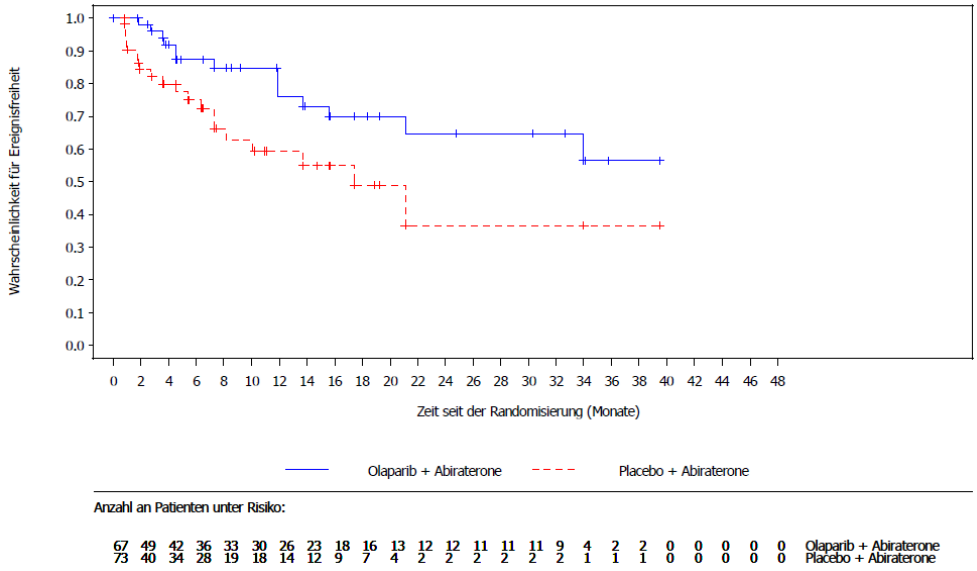
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 13: Kaplan-Meier curves for the outcome of FACT-P total score in patients without BRCA mutation (BRCA wild type) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



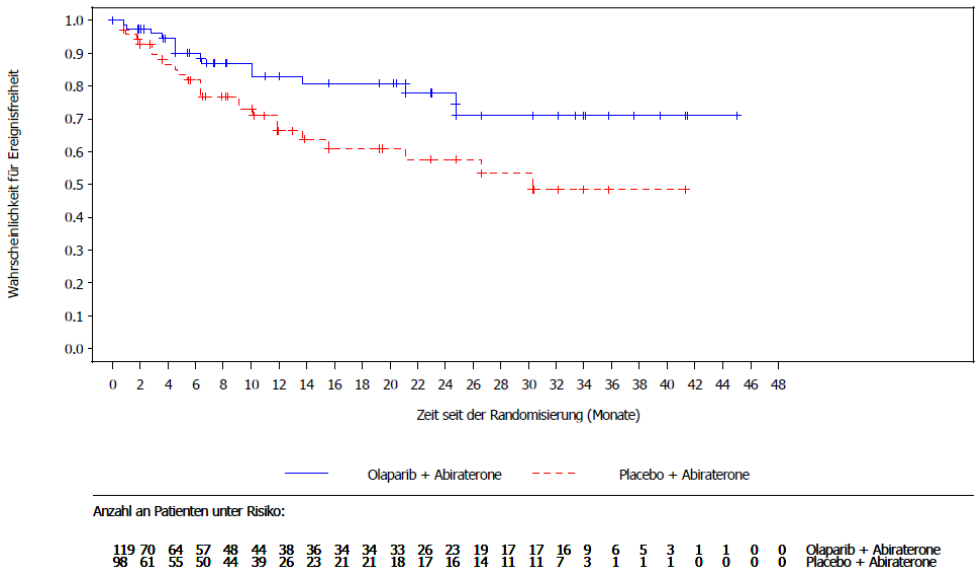
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 14: Kaplan-Meier curves for the outcome of FACT-P total score in patients with bone metastases (bone only) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

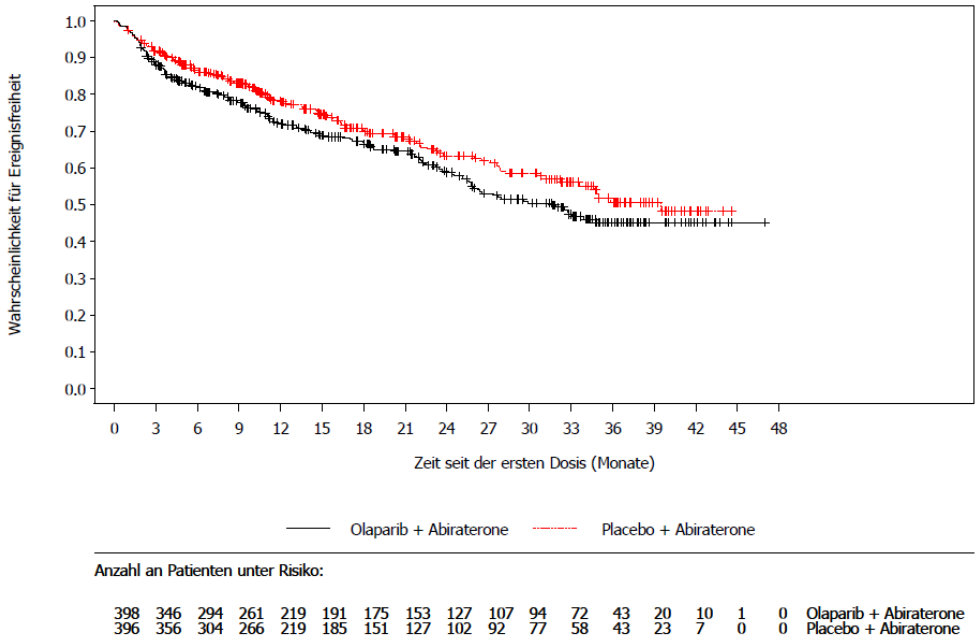
Figure 15: Kaplan-Meier curves for the outcome of FACT-P total score in patients with visceral metastases – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der Randomisierung (Monate) – Time since randomization (months); Anzahl an Patienten unter Risiko – Number of patients at risk

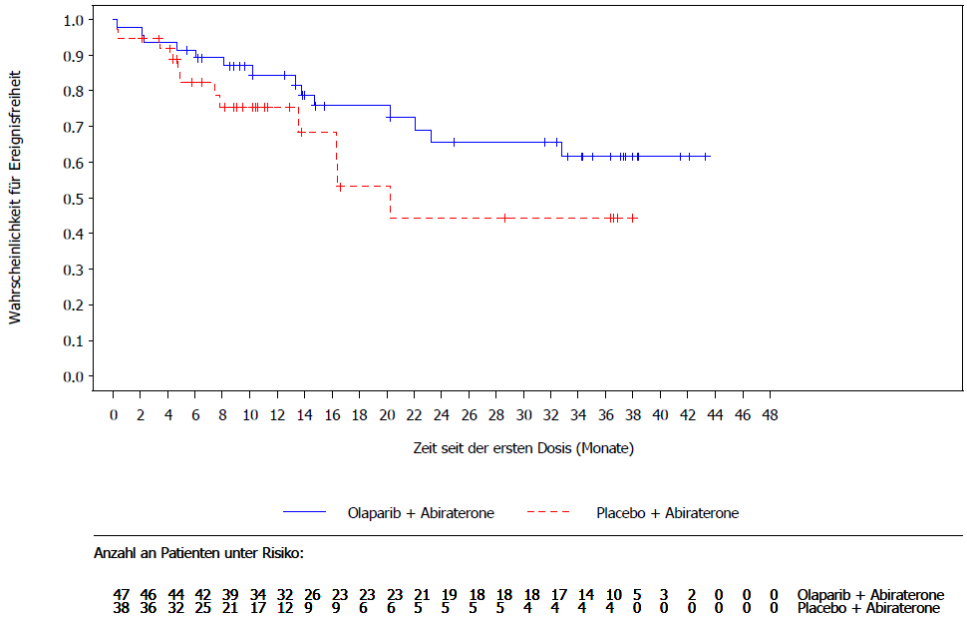
Figure 16: Kaplan-Meier curves for the outcome of FACT-P total score in patients with other metastases – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)

A.4 Side effects



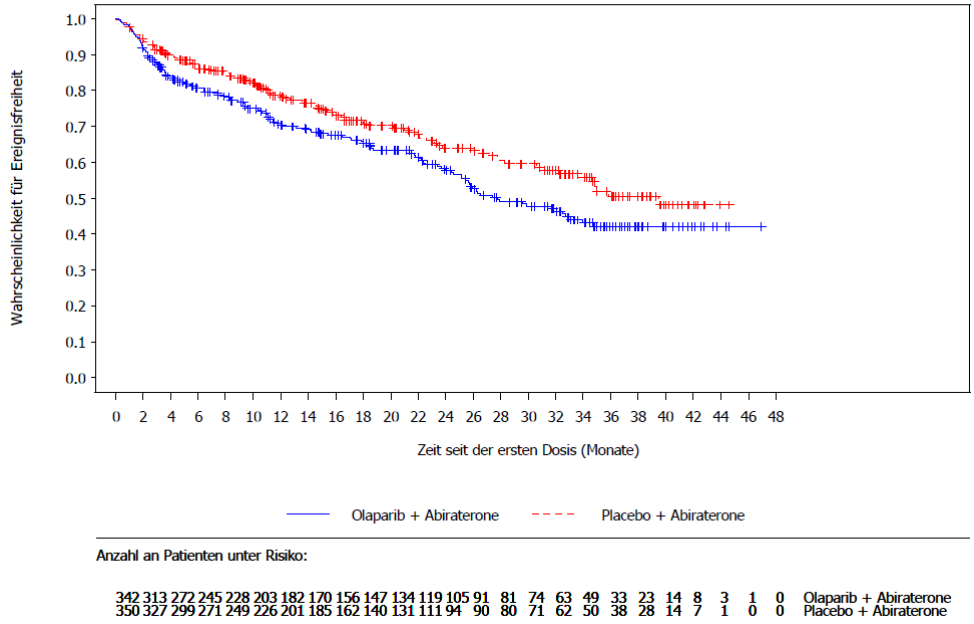
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der ersten Dosis (Monate) – Time since first dose (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 17: Kaplan-Meier curves for the outcome of SAEs – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



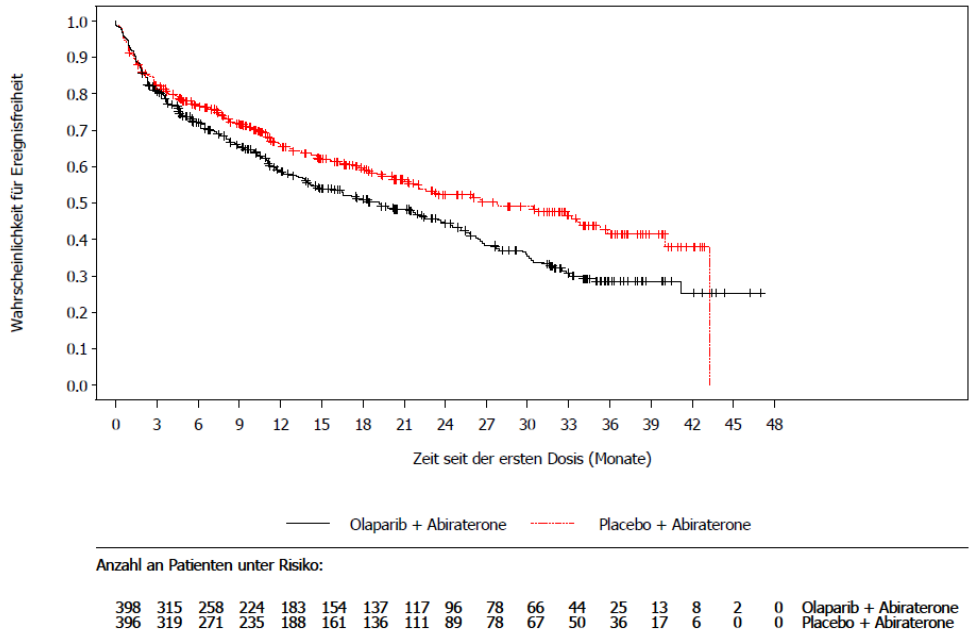
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der ersten Dosis (Monate) – Time since first dose (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 18: Kaplan-Meier curves for the outcome of SAEs in patients with BRCA mutation – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



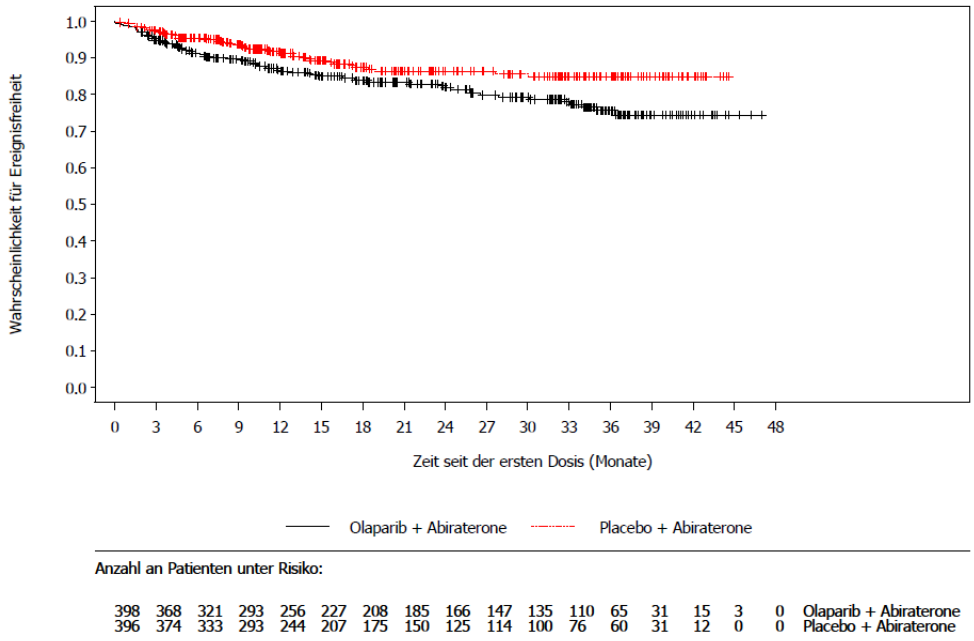
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der ersten Dosis (Monate) – Time since first dose (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 19: Kaplan-Meier curves for the outcome of SAEs in patients without BRCA mutation (BRCA wild type) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



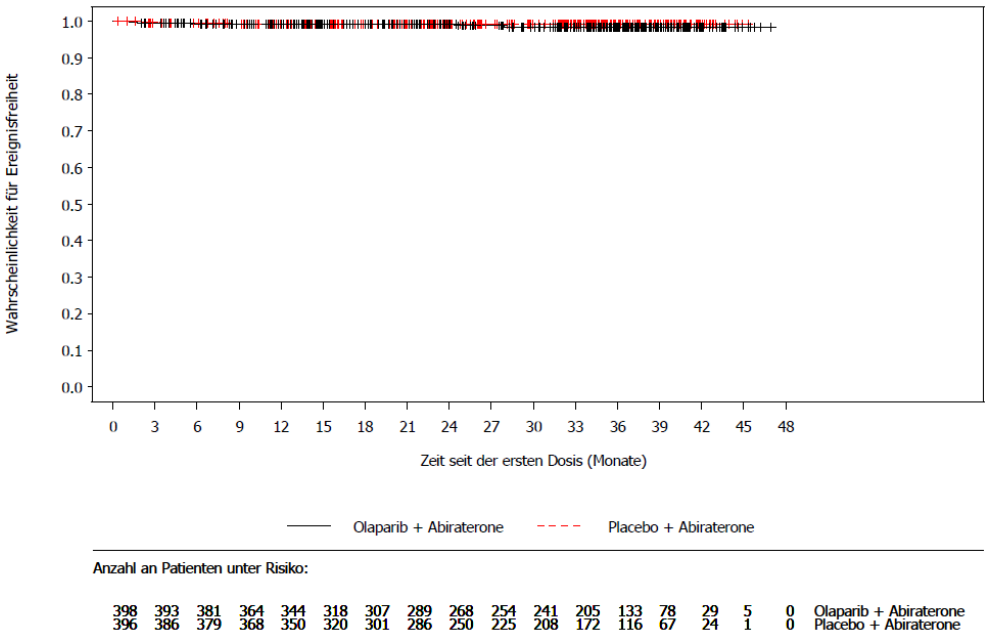
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der ersten Dosis (Monate) – Time since first dose (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 20: Kaplan-Meier curves for the outcome of severe AEs – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



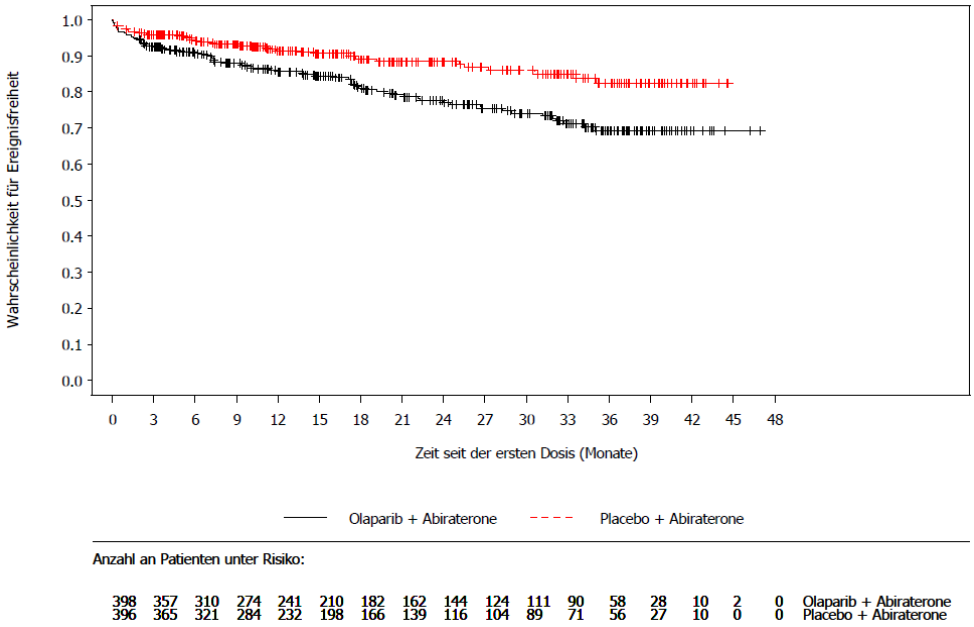
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der ersten Dosis (Monate) – Time since first dose (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 21: Kaplan-Meier curves for the outcome of discontinuation due to AEs – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



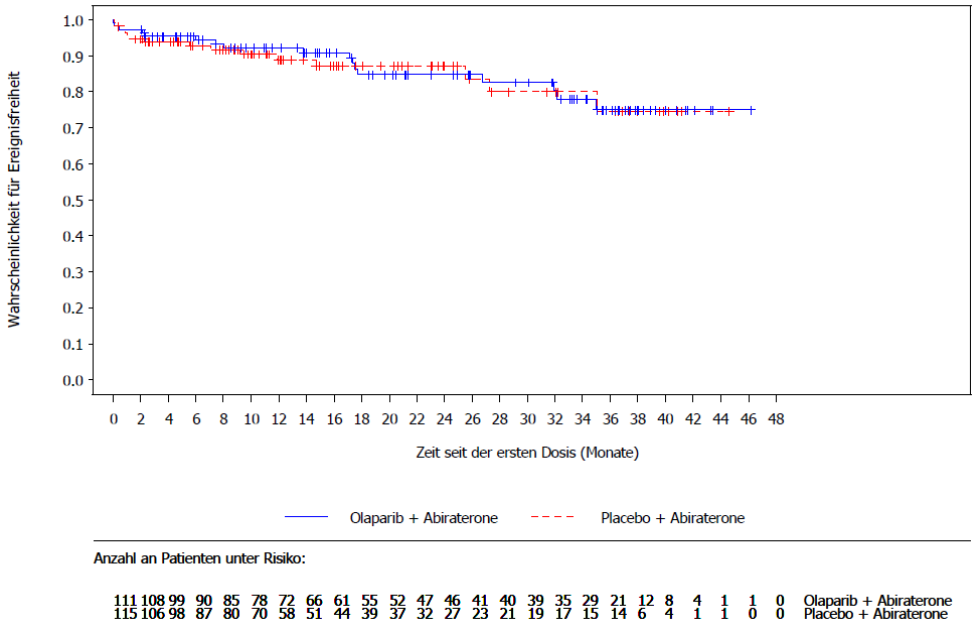
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der ersten Dosis (Monate) – Time since first dose (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 22: Kaplan-Meier curves for the outcome of pneumonitis (AEs) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



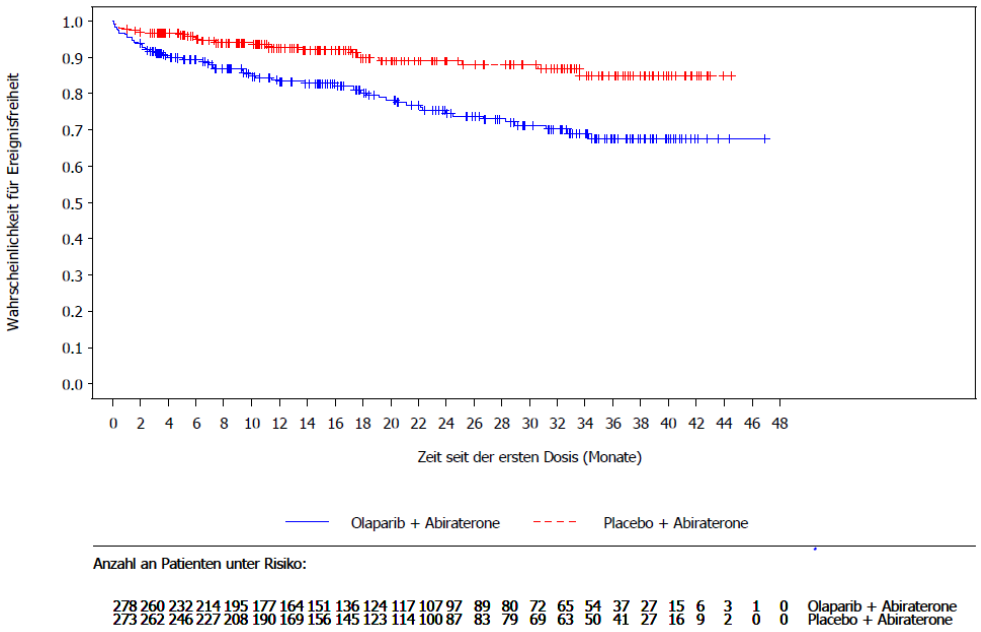
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der ersten Dosis (Monate) – Time since first dose (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 23: Kaplan-Meier curves for the outcome of diarrhoea (AEs) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



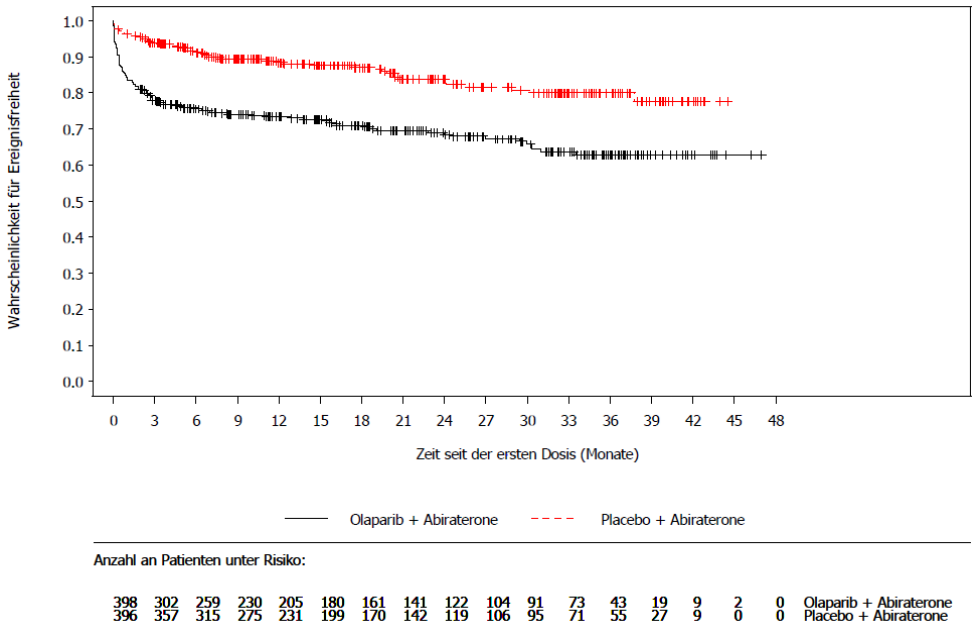
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der ersten Dosis (Monate) – Time since first dose (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 24: Kaplan-Meier curves for the outcome of diarrhoea (AEs) in patients with HRR mutation – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



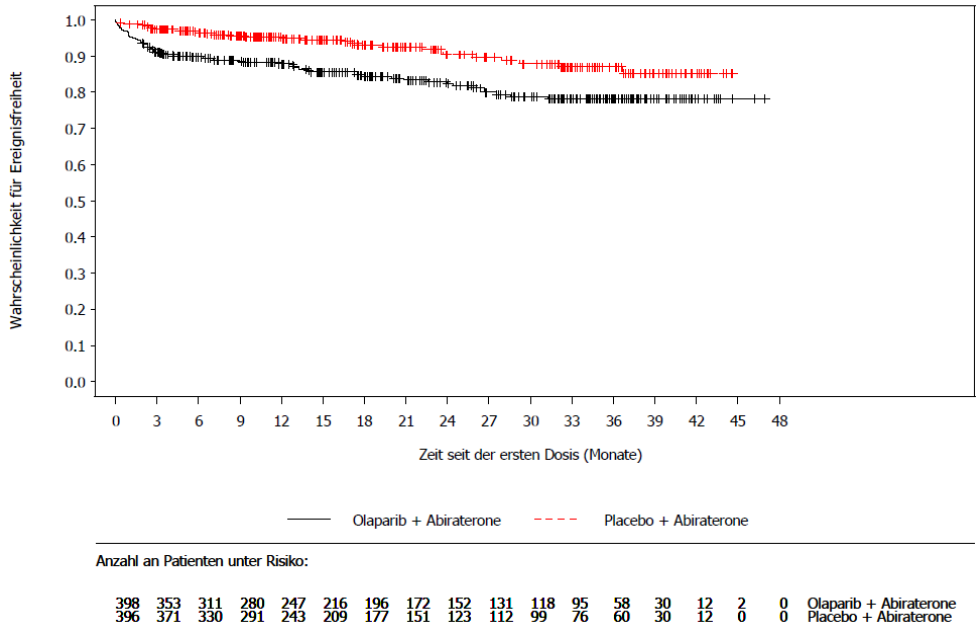
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der ersten Dosis (Monate) – Time since first dose (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 25: Kaplan-Meier curves for the outcome of diarrhoea (AEs) in patients without HRR mutation (HRR wild type) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



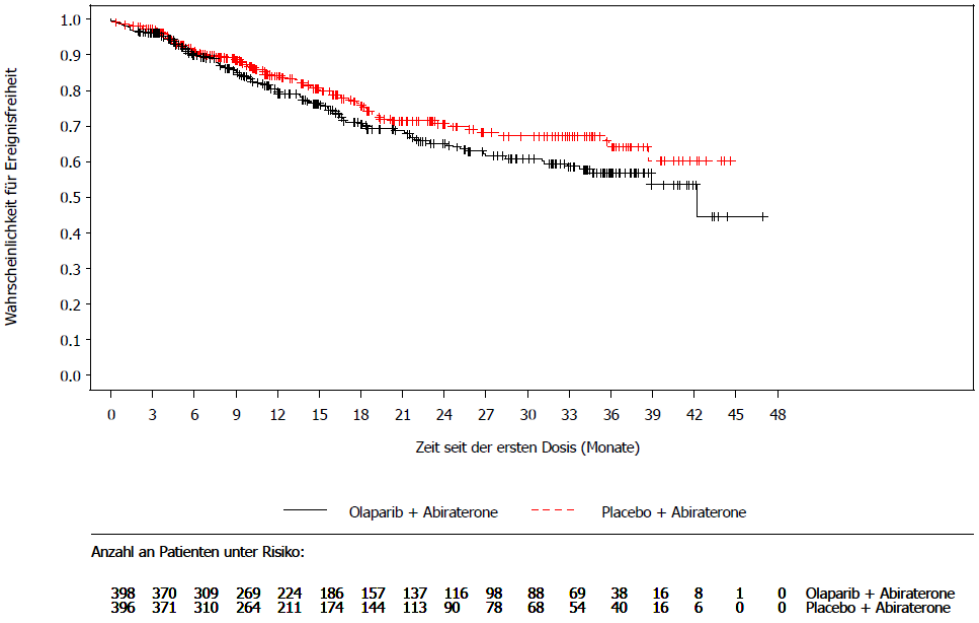
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der ersten Dosis (Monate) – Time since first dose (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 26: Kaplan-Meier curves for the outcome of nausea (PT, AEs) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



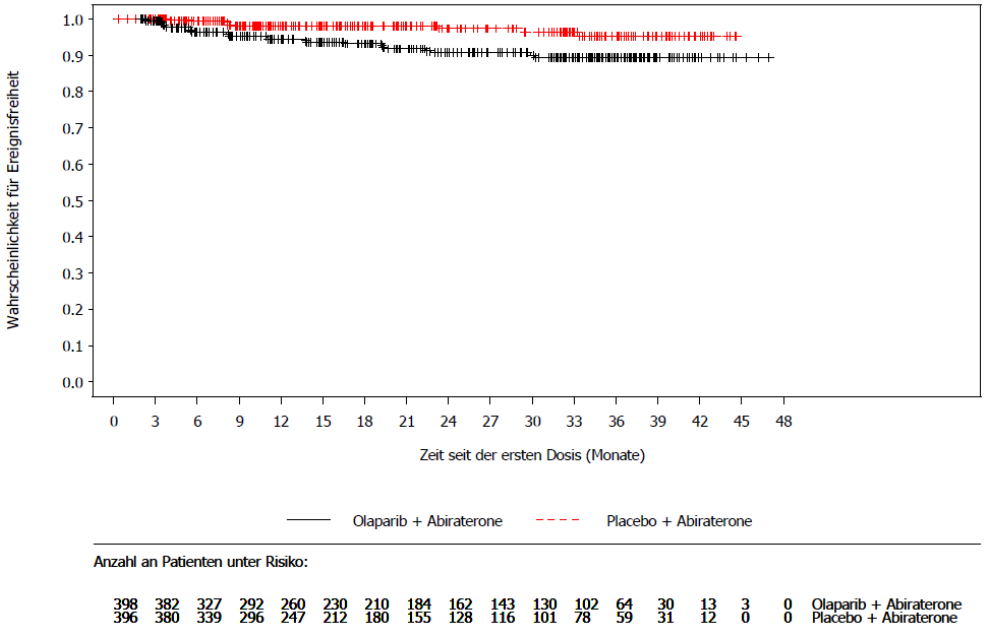
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der ersten Dosis (Monate) – Time since first dose (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 27: Kaplan-Meier curves for the outcome of decreased appetite (PT, AEs) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



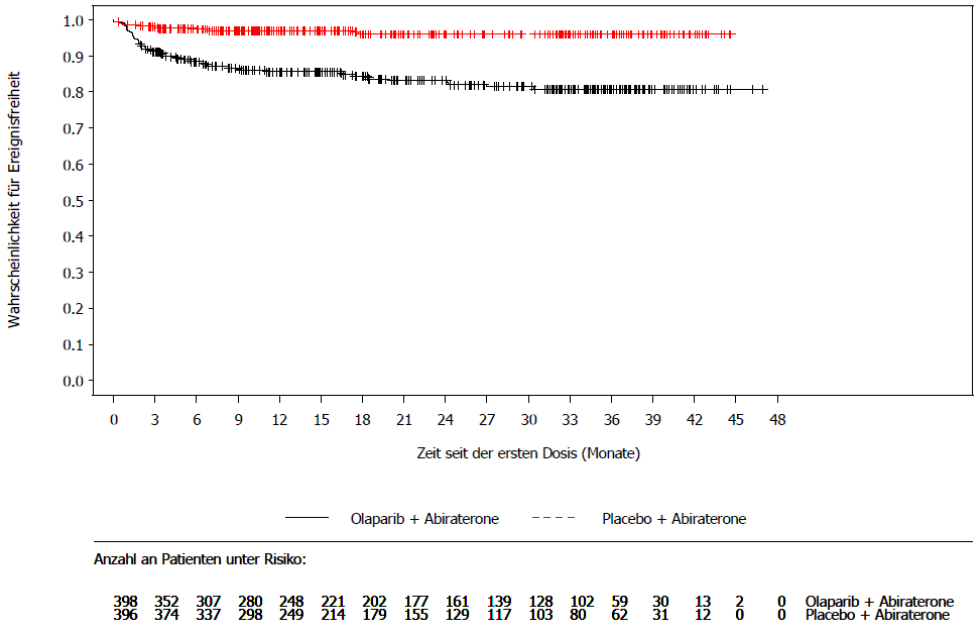
Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der ersten Dosis (Monate) – Time since first dose (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 28: Kaplan-Meier curves for the outcome of injury, poisoning and procedural complications (SOC, SAEs) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der ersten Dosis (Monate) – Time since first dose (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 29: Kaplan-Meier curves for the outcome of pulmonary embolism (PT, severe AEs) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)



Wahrscheinlichkeit für Ereignisfreiheit – Probability of freedom from events; Zeit seit der ersten Dosis (Monate) – Time since first dose (months); Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 30: Kaplan-Meier curves for the outcome of anaemia (PT, severe AEs) – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P, PROpel study, third data cut-off (12 October 2022)

Appendix B Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the following tables present events for SOCs and PTs according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- overall rate of AEs (irrespective of severity): events which occurred in at least 10% of patients in one study arm
- overall rates of severe AEs (CTCAE grade ≥ 3) and SAEs: events which occurred in at least 5 % of patients in one study arm
- additionally, for all events irrespective of severity: events which occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 12: Common AEs[a] – RCT, direct comparison: olaparib + abiraterone + P versus placebo + abiraterone + P (multipage table)

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**Olaparib + abiraterone + P** **N = 398**	**Placebo + abiraterone + P** **N = 396**
PROpel, 12 October 2022 data cut-off		
Overall AE rate	389 (97.7)	380 (96.0)
General disorders and administration site conditions	213 (53.5)	181 (45.7)
Asthenia	48 (12.1)	40 (10.1)
Fatigue	114 (28.6)	81 (20.5)
Pyrexia	29 (7.3)	21 (5.3)
Oedema peripheral	49 (12.3)	50 (12.6)
Malaise	15 (3.8)	10 (2.5)
Eye disorders	32 (8.0)	25 (6.3)
Cataract	10 (2.5)	9 (2.3)
Endocrine disorders	13 (3.3)	7 (1.8)
Respiratory, thoracic and mediastinal disorders	134 (33.7)	90 (22.7)
Dyspnoea	39 (9.8)	27 (6.8)
Cough	47 (11.8)	29 (7.3)
Pulmonary embolism	29 (7.3)	9 (2.3)
Nasal congestion	3 (0.8)	11 (2.8)
Oropharyngeal pain	14 (3.5)	6 (1.5)
Reproductive system and breast disorders	18 (4.5)	21 (5.3)
Skin and subcutaneous tissue disorders	93 (23.4)	87 (22.0)
Rash	13 (3.3)	15 (3.8)
Rash maculo-papular	10 (2.5)	4 (1.0)
Pruritus	9 (2.3)	11 (2.8)
Dry skin	18 (4.5)	10 (2.5)
Renal and urinary disorders	101 (25.4)	80 (20.2)
Acute kidney injury	13 (3.3)	9 (2.3)
Dysuria	22 (5.5)	19 (4.8)
Haematuria	19 (4.8)	14 (3.5)
Urinary incontinence	10 (2.5)	10 (2.5)
Nocturia	15 (3.8)	7 (1.8)
Pollakiuria	16 (4.0)	14 (3.5)

Table 12: Common AEs[a] – RCT, direct comparison: olaparib + abiraterone + P versus placebo + abiraterone + P (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	Olaparib + abiraterone + P N = 398	Placebo + abiraterone + P N = 396
Blood and lymphatic system disorders	216 (54.3)	96 (24.2)
Anaemia	197 (49.5)	69 (17.4)
Leukopenia	12 (3.0)	2 (0.5)
Lymphopenia	24 (6.0)	10 (2.5)
Neutropenia	21 (5.3)	4 (1.0)
Thrombocytopenia	14 (3.5)	12 (3.0)
Gastrointestinal disorders	248 (62.3)	197 (49.7)
Abdominal pain	27 (6.8)	16 (4.0)
Abdominal distension	15 (3.8)	13 (3.3)
Diarrhoea	82 (20.6)	42 (10.6)
Dyspepsia	29 (7.3)	17 (4.3)
Vomiting	62 (15.6)	37 (9.3)
Flatulence	12 (3.0)	6 (1.5)
Gastrooesophageal reflux disease	14 (3.5)	15 (3.8)
Constipation	74 (18.6)	59 (14.9)
Abdominal pain upper	26 (6.5)	16 (4.0)
Stomatitis	10 (2.5)	2 (0.5)
Nausea	122 (30.7)	57 (14.4)
Nervous system disorders	147 (36.9)	109 (27.5)
Dysgeusia	24 (6.0)	7 (1.8)
Memory impairment	10 (2.5)	3 (0.8)
Dysgeusia	10 (2.5)	2 (0.5)
Headache	39 (9.8)	26 (6.6)
Paraesthesia	11 (2.8)	4 (1.0)
Dizziness	49 (12.3)	27 (6.8)
Syncope	8 (2.0)	10 (2.5)
Ear and labyrinth disorders	19 (4.8)	12 (3.0)
Vertigo	11 (2.8)	5 (1.3)
Vascular disorders	130 (32.7)	134 (33.8)
Hot flush	35 (8.8)	51 (12.9)
Hypertension	61 (15.3)	74 (18.7)
Hypotension	19 (4.8)	9 (2.3)
Deep vein thrombosis	10 (2.5)	3 (0.8)

Table 12: Common AEs[a] – RCT, direct comparison: olaparib + abiraterone + P versus placebo + abiraterone + P (multipage table)

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**Olaparib + abiraterone + P** **N = 398**	**Placebo + abiraterone + P** **N = 396**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	37 (9.3)	23 (5.8)
Cardiac disorders	65 (16.3)	53 (13.4)
Palpitations	13 (3.3)	3 (0.8)
Atrial fibrillation	22 (5.5)	12 (3.0)
Infections and infestations	204 (51.3)	175 (44.2)
Bronchitis	10 (2.5)	4 (1.0)
COVID-19	51 (12.8)	35 (8.8)
Gastroenteritis	11 (2.8)	3 (0.8)
Influenza	13 (3.3)	8 (2.0)
Urinary tract infection	46 (11.6)	35 (8.8)
Upper respiratory tract infection	21 (5.3)	22 (5.6)
Nasopharyngitis	17 (4.3)	11 (2.8)
Pneumonia	25 (6.3)	13 (3.3)
Hepatobiliary disorders	17 (4.3)	23 (5.8)
Psychiatric disorders	59 (14.8)	61 (15.4)
Anxiety	12 (3.0)	12 (3.0)
Depression	11 (2.8)	11 (2.8)
Insomnia	31 (7.8)	28 (7.1)
Musculoskeletal and connective tissue disorders	217 (54.5)	204 (51.5)
Arthralgia	58 (14.6)	77 (19.4)
Musculoskeletal chest pain	33 (8.3)	28 (7.1)
Bone pain	17 (4.3)	7 (1.8)
Muscle spasms	34 (8.5)	19 (4.8)
Muscular weakness	13 (3.3)	7 (1.8)
Myalgia	22 (5.5)	23 (5.8)
Neck pain	16 (4.0)	7 (1.8)
Osteonecrosis of jaw	10 (2.5)	6 (1.5)
Back pain	86 (21.6)	79 (19.9)
Pain in extremity	38 (9.5)	38 (9.6)
Musculoskeletal pain	11 (2.8)	6 (1.5)

Table 12: Common AEs[a] – RCT, direct comparison: olaparib + abiraterone + P versus placebo + abiraterone + P (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	Olaparib + abiraterone + P N = 398	Placebo + abiraterone + P N = 396
Metabolism and nutrition disorders	183 (46.0)	125 (31.6)
Decreased appetite	66 (16.6)	31 (7.8)
Dehydration	12 (3.0)	3 (0.8)
Diabetes mellitus	7 (1.8)	14 (3.5)
Hyperglycaemia	30 (7.5)	28 (7.1)
Hypertriglyceridaemia	24 (6.0)	18 (4.5)
Hypokalaemia	34 (8.5)	18 (4.5)
Hypocalcaemia	18 (4.5)	14 (3.5)
Hypophosphataemia	11 (2.8)	8 (2.0)
Investigations	167 (42.0)	151 (38.1)
Alanine aminotransferase increased	15 (3.8)	28 (7.1)
Blood alkaline phosphatase increased	22 (5.5)	21 (5.3)
Amylase increased	15 (3.8)	19 (4.8)
Aspartate aminotransferase increased	16 (4.0)	23 (5.8)
Blood bilirubin increased	18 (4.5)	9 (2.3)
Electrocardiogram QT prolonged	14 (3.5)	2 (0.5)
Weight increased	5 (1.3)	10 (2.5)
Weight decreased	27 (6.8)	15 (3.8)
Blood creatinine increased	28 (7.0)	19 (4.8)
White blood cell count decreased	26 (6.5)	10 (2.5)
Lymphocyte count decreased	34 (8.5)	17 (4.3)
Neutrophil count decreased	18 (4.5)	7 (1.8)
Platelet count decreased	13 (3.3)	5 (1.3)
Injury, poisoning and procedural complications	116 (29.1)	87 (22.0)
Skin laceration	11 (2.8)	5 (1.3)
Contusion	31 (7.8)	19 (4.8)
Rib fracture	8 (2.0)	12 (3.0)
Fall	29 (7.3)	29 (7.3)

a. Events which occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken from the data subsequently submitted by the company for the third data cut-off.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; P: prednisone or prednisolone; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 13: Common SAEs[a] – RCT, direct comparison: olaparib + abiraterone + P versus placebo + abiraterone + P

Study	Patients with event n (%)	
SOC[b] PT[b]	Olaparib + abiraterone + P N = 398	Placebo + abiraterone + P N = 396
PROpel		
Overall SAE rate	161 (40.5)	126 (31.8)
General disorders and administration site conditions	13 (3.3)	11 (2.8)
Respiratory, thoracic and mediastinal disorders	23 (5.8)	8 (2.0)
Pulmonary embolism	15 (3.8)	3 (0.8)
Renal and urinary disorders	8 (2.0)	10 (2.5)
Blood and lymphatic system disorders	30 (7.5)	6 (1.5)
Anaemia	23 (5.8)	3 (0.8)
Gastrointestinal disorders	14 (3.5)	12 (3.0)
Nervous system disorders	14 (3.5)	16 (4.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	18 (4.5)	10 (2.5)
Cardiac disorders	15 (3.8)	13 (3.3)
Infections and infestations	68 (17.1)	43 (10.9)
COVID-19	15 (3.8)	10 (2.5)
Pneumonia	11 (2.8)	5 (1.3)
Musculoskeletal and connective tissue disorders	13 (3.3)	7 (1.8)
Metabolism and nutrition disorders	10 (2.5)	7 (1.8)
Injury, poisoning and procedural complications	20 (5.0)	8 (2.0)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken from the data subsequently submitted by the company for the third data cut-off.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; P: prednisone or prednisolone; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 14: Common severe AEs (CTCAE grade ≥ 3)[a] – RCT, direct comparison: olaparib + abiraterone + P versus placebo + abiraterone + P

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Olaparib + abiraterone + P** **N = 398**	**Placebo + abiraterone + P** **N = 396**
PROpel		
Overall rate of severe AEs (CTCAE grade ≥ 3)	222 (55.8)	171 (43.2)
General disorders and administration site conditions	17 (4.3)	13 (3.3)
Respiratory, thoracic and mediastinal disorders	37 (9.3)	13 (3.3)
Pulmonary embolism	29 (7.3)	9 (2.3)
Renal and urinary disorders	12 (3.0)	9 (2.3)
Blood and lymphatic system disorders	73 (18.3)	23 (5.8)
Anaemia	64 (16.1)	13 (3.3)
Gastrointestinal disorders	21 (5.3)	12 (3.0)
Nervous system disorders	13 (3.3)	16 (4.0)
Vascular disorders	21 (5.3)	18 (4.5)
Hypertension	15 (3.8)	18 (4.5)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	15 (3.8)	10 (2.5)
Cardiac disorders	17 (4.3)	11 (2.8)
Infections and infestations	59 (14.8)	40 (10.1)
COVID-19	15 (3.8)	8 (2.0)
Urinary tract infection	10 (2.5)	4 (1.0)
Pneumonia	10 (2.5)	4 (1.0)
Musculoskeletal and connective tissue disorders	16 (4.0)	13 (3.3)
Metabolism and nutrition disorders	33 (8.3)	22 (5.6)
Investigations	47 (11.8)	34 (8.6)
Lymphocyte count decreased	15 (3.8)	6 (1.5)
Neutrophil count decreased	11 (2.8)	3 (0.8)
Injury, poisoning and procedural complications	17 (4.3)	8 (2.0)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken from the data subsequently submitted by the company for the third data cut-off.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; P: prednisone or prednisolone; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 15: Discontinuations due to AEs – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Olaparib + abiraterone + P** **N = 398**	**Placebo + abiraterone + P** **N = 396**
PROpel		
Overall rate of discontinuations due to AEs	71 (17.8)	43 (10.9)
General disorders and administration site conditions	7 (1.8)	5 (1.3)
Asthenia	0 (0)	2 (0.5)
Fatigue	5 (1.3)	1 (0.3)
General physical health deterioration	1 (0.3)	1 (0.3)
Performance status decreased	1 (0.3)	0 (0)
Peripheral oedema	0 (0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	4 (1.0)	5 (1.3)
Acute pulmonary oedema	0 (0)	2 (0.5)
Dyspnoea	1 (0.3)	0 (0)
Interstitial lung disease	0 (0)	1 (0.3)
Pulmonary embolism	0 (0)	1 (0.3)
Pneumonitis	3 (0.8)	1 (0.3)
Skin and subcutaneous tissue disorders	0 (0)	1 (0.3)
Cutaneous vasculitis	0 (0)	1 (0.3)
Renal and urinary disorders	2 (0.5)	2 (0.5)
Acute kidney injury	1 (0.3)	1 (0.3)
Chronic kidney disease	0 (0)	1 (0.3)
Renal insufficiency	1 (0.3)	0 (0)
Blood and lymphatic system disorders	19 (4.8)	3 (0.8)
Anaemia	17 (4.3)	3 (0.8)
Leukopenia	1 (0.3)	0 (0)
Lymphopenia	2 (0.5)	0 (0)
Neutropenia	1 (0.3)	0 (0)
Thrombocytopenia	1 (0.3)	0 (0)
Gastrointestinal disorders	3 (0.8)	3 (0.8)
Abdominal distension	0 (0)	1 (0.3)
Colitis ulcerative	0 (0)	1 (0.3)
Gastric ulcer perforation	1 (0.3)	0 (0)
Constipation	0 (0)	1 (0.3)
Nausea	1 (0.3)	0 (0)
Duodenal ulcer	1 (0.3)	0 (0)

Table 15: Discontinuations due to AEs – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Olaparib + abiraterone + P** **N = 398**	**Placebo + abiraterone + P** **N = 396**
Nervous system disorders	4 (1.0)	2 (0.5)
Cerebrovascular accident	1 (0.3)	0 (0)
Dysgeusia	1 (0.3)	0 (0)
Epilepsy	1 (0.3)	0 (0)
Ischaemic stroke	0 (0)	1 (0.3)
Headache	1 (0.3)	0 (0)
Thalamic infarction	0 (0)	1 (0.3)
Vascular disorders	2 (0.5)	0 (0)
Aortic dissection	1 (0.3)	0 (0)
Hypotension	1 (0.3)	0 (0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	7 (1.8)	1 (0.3)
Lung adenocarcinoma	1 (0.3)	0 (0)
Malignant melanoma	1 (0.3)	0 (0)
Colon cancer	1 (0.3)	0 (0)
Myelodysplastic syndrome	1 (0.3)	0 (0)
Neuroendocrine carcinoma of the skin	1 (0.3)	0 (0)
Oropharyngeal cancer	0 (0)	1 (0.3)
Plasma cell myeloma	1 (0.3)	0 (0)
Rectal cancer	1 (0.3)	0 (0)
Cardiac disorders	5 (1.3)	4 (1.0)
Acute myocardial infarction	1 (0.3)	2 (0.5)
Acute coronary syndrome	0 (0)	1 (0.3)
Ventricular extrasystoles	1 (0.3)	0 (0)
Atrial flutter	1 (0.3)	0 (0)
Atrial fibrillation	2 (0.5)	1 (0.3)
Infections and infestations	13 (3.3)	0 (0)
Bacterial sepsis	1 (0.3)	0 (0)
COVID-19	4 (1.0)	0 (0)
Urinary tract infection	1 (0.3)	0 (0)
Pneumocystis jirovecii pneumonia	3 (0.8)	0 (0)
Pneumonia	2 (0.5)	0 (0)
Pneumonia bacterial	1 (0.3)	0 (0)
Sepsis	1 (0.3)	0 (0)

Table 15: Discontinuations due to AEs – RCT, direct comparison: olaparib + abiraterone + P vs. placebo + abiraterone + P (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Olaparib + abiraterone + P** **N = 398**	**Placebo + abiraterone + P** **N = 396**
Hepatobiliary disorders	0 (0)	4 (1.0)
Drug-induced liver injury	0 (0)	1 (0.3)
Bile duct stone	0 (0)	1 (0.3)
Abnormal liver function	0 (0)	1 (0.3)
Hepatotoxicity	0 (0)	1 (0.3)
Psychiatric disorders	1 (0.3)	0 (0)
Insomnia	1 (0.3)	0 (0)
Musculoskeletal and connective tissue disorders	1 (0.3)	6 (1.5)
Arthralgia	0 (0)	4 (1.0)
Musculoskeletal chest pain	0 (0)	2 (0.5)
Myopathy	1 (0.3)	0 (0)
Metabolism and nutrition disorders	4 (1.0)	3 (0.8)
Decreased appetite	2 (0.5)	2 (0.5)
Dehydration	1 (0.3)	0 (0)
Hypertriglyceridaemia	0 (0)	1 (0.3)
Hypophosphataemia	1 (0.3)	0 (0)
Investigations	5 (1.3)	8 (2.0)
Alanine aminotransferase increased	1 (0.3)	4 (1.0)
Blood alkaline phosphatase increased	1 (0.3)	0 (0)
Aspartate aminotransferase increased	1 (0.3)	3 (0.8)
Electrocardiogram QT prolonged	1 (0.3)	0 (0)
Blood creatinine increased	0 (0)	1 (0.3)
Lymphocyte count decreased	2 (0.5)	2 (0.5)
Creatine renal clearance decreased	0 (0)	1 (0.3)
Injury, poisoning and procedural complications	2 (0.5)	0 (0)
Cervical vertebral fracture	1 (0.3)	0 (0)
Craniocerebral injury	1 (0.3)	0 (0)

a. MedDRA version 25.0; SOC and PT notation taken from the data subsequently submitted by the company for the third data cut-off.
b. If one of the drugs was discontinued prematurely, the entire therapy was considered discontinued.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; P: prednisone or prednisolone; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Appendix C Institute's calculation

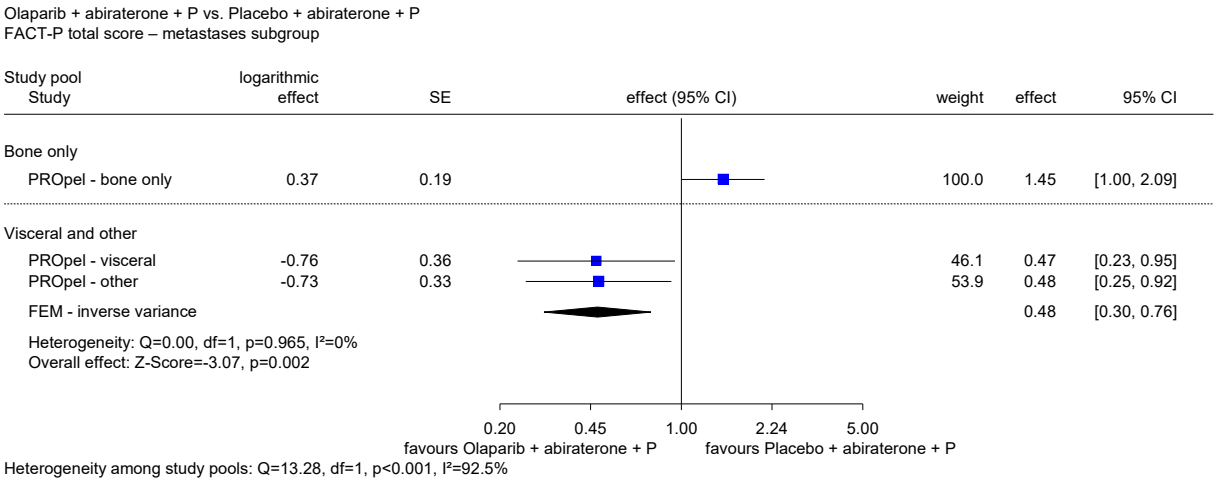


Figure 31: Institute's calculation to pool the subgroups of patients with visceral metastases and other metastases for the outcome of FACT-P total score