IQWiG Reports – Commission No. A22-89

Olaparib (breast cancer, adjuvant) –

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

Extract

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Olaparib (Mammakarzinom, adjuvant) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 November 2022). Please note: This document was translated by an external translator and 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 (breast cancer, adjuvant) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
25 August 2022

Internal Commission No.
A22-89

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

Patient and family involvement

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

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Keywords: Olaparib, Breast Neoplasms, Benefit Assessment, NCT02032823

Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	adverse event of special interest
AML	acute myeloid leukaemia
BICR	blinded independent independent central review
BRCA	breast cancer gene
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group-Performance Status
EORTC QLQ-30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
FACIT	Functional Assessment of Chronic Illness Therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
iDFS	invasive disease-free survival
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MDS	myelodysplastic syndrome
MMRM	mixed effect model repeated measurement
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SMQ	standardized MedDRA query
SOC	System Organ Class
SPC	Summary of Product Characteristics
TNBC	triple-negative breast cancer

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug olaparib (monotherapy or in combination with endocrine therapy). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 25 August 2022.

Research question

The present report aims to assess the added benefit of olaparib either in the form of monotherapy or in combination with endocrine therapy versus watchful waiting as the appropriate comparator therapy (ACT) for the adjuvant treatment of adult patients with germline breast cancer gene (BRCA) 1 or 2 mutant, human epidermal growth factor receptor 2 (HER2) negative, high recurrence-risk, early breast cancer following prior neoadjuvant or adjuvant chemotherapy.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of olaparib

Therapeutic indication	**ACT[a]**
Adult patients with germline BRCA-mutant, HER2-negative, high recurrence-risk, early breast cancer; after neoadjuvant or adjuvant chemotherapy[b]; adjuvant treatment	Watchful waiting[c]
a. Presented is the respective ACT specified by the G-BA. b. According to the G-BA, (neo)adjuvant chemotherapy and surgery are assumed to have been completed. c. Adjuvant radiotherapy may be performed sequentially or in parallel with endocrine therapy. According to the G-BA, adjuvant radiotherapy is not part of the ACT. ACT: appropriate comparator therapy; BRCA: breast cancer gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The company followed the G-BA's ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) ware used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The OlympiA study was used for the benefit assessment. This study is an ongoing, double-blind RCT comparing olaparib versus placebo. While the study was not designed for a comparison with watchful waiting, it is nonetheless suitable for such a comparison (see below).

The study enrolled adult patients with germline BRCA1-mutant or BRCA2-mutant, HER2-negative, high recurrence-risk, early breast cancer. Initially, only patients with triple-negative

breast cancer (TNBC) were eligible for participation in the OlympiA study. The inclusion of patients with positive hormone receptor status was allowed starting from protocol version 3.0 (21 October 2015). The completion of adequate breast and axilla surgery was an inclusion criterion. In patients with breast-conserving surgery, adjuvant radiotherapy was required. In patients with mastectomy, adjuvant radiotherapy was an option in accordance with local and/or international guidelines. Based on the specifications for adequate breast and axilla surgery, patients presumably underwent a curative treatment approach. Furthermore, patients had to have received prior treatment with at least 6 cycles of neoadjuvant or adjuvant chemotherapy with anthracyclines, taxanes, or a combination of both. Prior treatment with a platinum substance in the context of neoadjuvant or adjuvant chemotherapy was allowed. At enrolment, patients had to be in good general condition corresponding to an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1. According to the inclusion criteria, the existence of a high risk of recurrence depends on the hormone receptor status and the timing of the previous chemotherapy (neoadjuvant versus adjuvant). Patients who meet the OlympiA study's inclusion criteria are presumably at high risk of recurrence.

The OlympiA study included a total of 1836 patients who were randomly allocated in a 1:1 ratio to treatment with olaparib (N = 921) or placebo (N = 915). In compliance with the Summary of Product Characteristics (SPC), olaparib treatment in the intervention arm was conducted for a maximum of 12 months. The study did not provide for any switching between study arms. In both treatment arms, hormone receptor-positive patients were to receive adjuvant endocrine therapy in accordance with local and/or international guidelines. The information in the study report indicates that about 90% of OlympiA participants with hormone receptor-positive breast cancer received endocrine therapy.

The primary outcome of the study was invasive disease-free survival (iDFS). Patient-relevant secondary outcomes were surveyed in the categories of mortality, morbidity, health-related quality of life, and adverse events (AEs).

Presented patient population (prior treatment with platinum substances)

Concurring with the company, the total population of the OlympiA study was deemed relevant and used for the benefit assessment. The patient population does, however, come with one uncertainty, which is described below.

According to the inclusion criteria, treatment with platinum substances was allowed in the context of (neo)adjuvant chemotherapy and was performed in 26.4% of patients. Platinum substances are not approved for the (neo)adjuvant treatment of breast cancer. A discrepancy exists between the marketing authorization and individual guideline recommendations regarding neoadjuvant treatment with a platinum-containing chemotherapy regimen in patients with TNBC. This discrepancy remains without consequence for this benefit assessment because (a) patients were treated with platinum substances before randomization, (b) additional stratification by this criterion ensured balanced distribution between treatment arms, and (c) treatment with platinum substances is covered by some guidelines.

Available data cut-offs

To date, 2 data cut-offs have been implemented for the OlympiA study:

- 1st data cut-off (27 March 2020): planned interim analysis after 165 iDFS events in the first 900 included patients
- 2nd data cut-off (12 July 2021): planned final iDFS analysis after 330 iDFS events

The present benefit assessment uses the results from the 2nd data cut-off (12 July 2021).

Implementation of the ACT of watchful waiting

In the OlympiA study, targeted physical examinations were performed on all patients in the context of follow-up visits, and clinical signs and symptoms were regularly recorded. However, the examinations performed in the OlympiA study do not cover all guideline recommendations. While regular radiological examinations were required, mammography was not. Magnetic resonance tomography of the breast, which the study used as an alternative, fails to reflect the guideline recommendations. Furthermore, rather than being required, breast sonography was performed only at the investigator's discretion, even in female patients with bilateral mastectomy and in men. The study's follow-up intervals are largely in line with the guideline recommendations. Only in the 3rd year after randomization were patients checked semiannually instead of quarterly, in departure from recommendations. Despite the described deviations from guideline recommendations, OlympiA participants were overall monitored closely using specific examinations to detect any recurrences. Therefore, the examination regimen is overall deemed to be a sufficient approximation to the ACT of watchful waiting.

Risk of bias

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

For the results on the outcomes of overall survival and recurrences, the risk of bias was likewise rated as low. The risk of bias was rated as high for the outcomes of symptoms (recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [EORTC QLQ-C30] and Functional Assessment of Chronic Illness Therapy [FACIT] Fatigue) and health-related quality of life (EORTC QLQ-C30) because a relevant percentage of patients (> 10%) was excluded from the analysis. The risk of bias of results for all outcomes in the side effects category is rated as low.

Results

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of olaparib versus placebo. This results in an indication of added benefit of olaparib in comparison with watchful waiting.

Morbidity

Recurrence

Regarding the outcome of recurrence, there was a statistically significant difference in favour of olaparib in comparison with placebo for both recurrence rate and disease-free survival. This results in an indication of an added benefit of olaparib in comparison with watchful waiting.

Symptoms, recorded with the EORTC QLQ-C30

A statistically significant difference to the disadvantage of olaparib compared with placebo was shown for the outcome of nausea and vomiting (symptoms). The 95% confidence interval (CI) for the standardized mean difference (SMD) was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. This results in a hint of lesser benefit of olaparib in comparison with watchful waiting.

A statistically significant difference to the disadvantage of olaparib versus placebo was shown for the symptoms of fatigue, appetite loss, and constipation. However, the respective 95% CIs for SMD are not fully outside the irrelevance range [-0.2; 0.2]. It was therefore impossible to infer the effect to be relevant. This results in no hint of an added benefit of olaparib versus watchful waiting for any of them.

No statistically significant difference between treatment groups was shown for any of the symptoms of pain, dyspnoea, insomnia, or diarrhoea. This results in no hint of an added benefit of olaparib in comparison with watchful waiting for any of them; added benefit is therefore not proven.

Symptoms, recorded using the FACIT-Fatigue

For the outcome of FACIT-Fatigue, a statistically significant difference was found to the disadvantage of olaparib versus placebo. However, the 95% CI of the SMD was not fully outside the irrelevance range [-0.2; 0.2]. The effect can therefore not be inferred to be relevant. This results in no hint of an added benefit of olaparib versus watchful waiting.

Health-related quality of life, recorded with the EORTC QLQ-C30

For the outcome of health-related quality of life, the scale of global health status shows a statistically significant difference to the disadvantage of olaparib versus placebo. However, the 95% CI of the SMD was not fully outside the irrelevance range [-0.2; 0.2]. The effect can therefore not be inferred to be relevant. This results in no hint of an added benefit of olaparib in comparison with watchful waiting.

No statistically significant difference between treatment arms was shown for any of the functioning scales: physical functioning, role functioning, cognitive functioning, emotional functioning, or social functioning. This results in no hint of an added benefit of olaparib in comparison with watchful waiting for any of them; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

No suitable data were available for the outcome of SAEs. This results in no hint of greater or lesser harm from olaparib in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

For the outcome of severe AEs, a statistically significant difference was found to the disadvantage of olaparib versus placebo. This results in an indication of greater harm from olaparib in comparison with watchful waiting.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, a statistically significant difference was found to the disadvantage of olaparib versus placebo. This results in an indication of greater harm from olaparib in comparison with watchful waiting.

Specific AEs

Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) (standardized MedDRA query [SMQ] + Preferred Term [PT] list, AEs)

No statistically significant difference between treatment groups was shown for the outcome of MDS and AML (SMQ + PT list, AEs). This results in no hint of greater or lesser harm from olaparib in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Pneumonitis (SMQ, AEs)

For the outcome of pneumonitis (SMQ, AEs), there was no statistically significant difference between treatment groups. This results in no hint of greater or lesser harm from olaparib in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Fatigue (Preferred Term [PT], AE), gastrointestinal disorders (System Organ Class [SOC], AEs), dysgeusia (PT, AEs), decreased appetite (PT, AEs), anaemia (PT, SAEs), investigations (SOC, severe AEs)

A statistically significant difference to the disadvantage of olaparib versus placebo was found for each of the outcomes of fatigue (PT, AEs), gastrointestinal disorders (SOC, AEs), dysgeusia (PT, AEs), decreased appetite (PT, AEs), anaemia (PT, SAEs), and investigations (SOC, severe AEs; includes the PTs of decreased leukocyte count, decreased neutrophil count, and decreased lymphocyte count, each with a statistically significant effect to the disadvantage of olaparib). For each of these outcomes, this results in an indication of greater harm from olaparib in comparison with watchful waiting.

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

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

Overall, there are both favourable and unfavourable effects for olaparib in comparison with watchful waiting.

In terms of favourable effects for olaparib in comparison with watchful waiting, there is an indication of considerable added benefit for each of the outcomes of overall survival and recurrences.

Unfavourable effects for olaparib in comparison with watchful waiting, on the other hand, were found for non-serious/non-severe symptoms as well as side effects. For the outcome of nausea and vomiting in the outcome category of non-serious / non-severe symptoms, there is a hint of lesser benefit with the extent of minor. Regarding serious/severe side effects, olaparib was associated with an indication of greater harm, with an extent of major for the higher-level outcome of severe AEs and the included SOC of investigations, and an extent of considerable for the outcome of anaemia (SAE). For non-serious/non-severe side effects, this results in indications of greater harm from olaparib in comparison with watchful waiting in the outcomes of discontinuation due to AEs and several specific AEs, each of considerable extent. For the outcome of SAEs, no suitable data are available, but given that progression events were disregarded, olaparib is presumably associated with greater harm in this case as well. The observed unfavourable effects regarding symptoms are based only on the shortened observation period of 24 months, while the effects on adverse events refer only to the shortened time period until treatment end plus 30 days (about 13 months).

Although the described unfavourable effects do not completely outweigh the favourable effects in the outcomes of overall survival and recurrences, they result in a downgrading of the extent of added benefit.

In summary, for the adjuvant treatment of adult patients with germline BRCA-1/2-mutated HER2-negative, high recurrence-risk, early breast cancer following prior treatment with neoadjuvant or adjuvant chemotherapy, there is an indication of minor added benefit of olaparib in comparison with the ACT of watchful waiting.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

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

Table 3: Olaparib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with germline BRCA-mutant, HER2-negative, high recurrence-risk early breast cancer; after neoadjuvant or adjuvant chemotherapy[b]; adjuvant treatment	Watchful waiting[c]	Indication of minor added benefit

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, (neo)adjuvant chemotherapy and surgery are assumed to have been completed.
c. Adjuvant radiotherapy may be performed sequentially or in parallel with endocrine therapy. According to the G-BA, adjuvant radiotherapy is not part of the ACT.

ACT: appropriate comparator therapy; BRCA: breast cancer gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2

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

I 2 Research question

The present report aims to assess the added benefit of olaparib either in the form of monotherapy or in combination with endocrine therapy versus watchful waiting as the ACT for the adjuvant treatment of adult patients with germline BRCA 1 or 2 mutant, HER2-negative, high recurrence-risk early breast cancer following prior neoadjuvant or adjuvant chemotherapy.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of olaparib

Therapeutic indication	**ACT[a]**
Adult patients with germline BRCA-mutant, HER2-negative, high recurrence-risk, early breast cancer; after neoadjuvant or adjuvant chemotherapy[b]; adjuvant treatment	Watchful waiting[c]
a. Presented is the respective ACT specified by the G-BA. b. According to the G-BA, (neo)adjuvant chemotherapy and surgery are assumed to have been completed. c. Adjuvant radiotherapy may be performed sequentially or in parallel with endocrine therapy. According to the G-BA, adjuvant radiotherapy is not part of the ACT. ACT: appropriate comparator therapy; BRCA: breast cancer gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The company followed the G-BA's ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of added benefit. This concurs with the company’s inclusion criteria.

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on olaparib (status: 1 June 2022)
- bibliographical literature search on olaparib (last search on 1 June 2022)
- search in trial registries / trial results databases for studies on olaparib (last search on 2 June 2022)
- search on the G-BA website for olaparib (last search on 3 June 2022)

To check the completeness of the study pool:

- search in trial registries for studies on olaparib (last search on 7 September 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: olaparib versus watchful waiting

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
D081CC00006 study, NSABP B-55, BIG 6-13 (OlympiA[c])	Yes	Yes	No	Yes [3-5]	Yes [6-9]	Yes [10]

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

The OlympiA study was used for the benefit assessment. The study used placebo as the comparator therapy. While the study was not designed for a comparison with watchful waiting, it is nonetheless suitable for such a comparison (see Section I 3.2). The study pool concurs with that of the company.

I 3.2 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: olaparib versus placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
OlympiA	RCT, double-blind, parallel	Adult patients (≥ 18 years of age) with early, high recurrence-risk breast cancer ▪ Documented germline BRCA1/2 mutation ▪ HER2-negative ▪ Completed breast and axillary surgery ▪ Completed neoadjuvant or adjuvant chemotherapy ▪ ECOG-PS of 0 or 1	Olaparib (N = 921)[b] Placebo (N = 915)[b]	Screening: 28 days Treatment: 1 year or until evidence of recurrence or occurrence of unacceptable toxicity, whichever was first Observation[c]: outcome-specific, at the longest until death, discontinuation of study participation, or end of study	A total of 554[d] centres in Argentina, Australia, Austria, Belgium, Canada, China, France, Germany, Hungary, Iceland, Israel, Italy, Japan, Korea, Netherlands, Northern Ireland, Poland, Portugal, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States 4/2014 – ongoing 1st data cut-off: 27 March 2020: interim analysis[e] 2nd data cut-off: 12 July 2021: final iDFS analysis[f]	Primary: iDFS 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 include only information on relevant available outcomes for this benefit assessment.
b. No treatment was received by 10 versus 11 patients (olaparib arm versus placebo arm).
c. Outcome-specific information is provided in Table 8.
d. The study was performed in 554 study centres; 546 centres enrolled patients.
e. Interim analysis prespecified to occur after about 165 iDFS events in the first 900 included patients.
f. Final iDFS analysis prespecified to occur after about 330 iDFS events.

AE: adverse event; BRCA: breast cancer gene; ECOG-PS: Eastern Cooperative Oncology Group-Performance Status; HER2: human epidermal growth factor receptor 2; iDFS: invasive disease-free survival; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the interventions – RCT, direct comparison: olaparib versus placebo

Study	Intervention	Comparison
OlympiA	Olaparib 600 mg/day (2 film-coated 150 mg tablets twice daily), orally, at the same times each day, 12 hours apart	Placebo (2 film-coated tablets twice daily), orally, at the same times each day, 12 hours apart
	Dose adjustments Treatment interruptions[a] and dose reductions[b] were allowed	
	Required pretreatment ▪ Completed breast and axilla surgery ▪ At least 6 cycles of neoadjuvant or adjuvant chemotherapy with anthracyclines, taxanes, or a combination of both[c] (completed ≥ 3 weeks prior to randomization) ▪ Adjuvant radiotherapy[d] ≥ 2 weeks before randomization **Non-permitted pretreatment** ▪ Major surgeries < 2 weeks before randomization ▪ PARP inhibitors (including olaparib) ▪ Allogeneic bone marrow transplantation ▪ Blood transfusions (red cell concentrates and/or platelet transfusions) < 28 days prior to randomization ▪ Investigational products < 30 days or 5 half-lives (whichever was longer) before randomization **Permitted concomitant treatment** ▪ Adjuvant endocrine therapy in line with local and/or international guidelines ▪ Bisphosphonates or denosumab **Non-permitted concomitant treatment** ▪ Other cancer treatments or investigational drugs ▪ Potent or moderate CYP3A inhibitors or inducers[e], sensitive CYP3A substrates ▪ Anticoagulants[f]	

a. Treatment discontinuations for a maximum of 4 weeks.
b. Due to toxicity, dose reductions were allowed to 250 mg twice daily or 200 mg twice daily. Later escalation was not permitted. In case of temporary simultaneous administration of a potent or moderate CYP3A inhibitor, adjusting the dose to 100 mg twice daily or 150 mg twice daily was allowed.
c. Additional treatment with a platinum substance in the context of neoadjuvant or adjuvant chemotherapy was allowed.
d. Patients with breast-conserving procedures had to subsequently undergo adjuvant radiotherapy. Following mastectomy, adjuvant radiotherapy in line with local and/or international guidelines was allowed.
e. The simultaneous administration of potent or moderate CYP3A inhibitors or inducers was defined as an exclusion criterion. During the study, patients were allowed to receive strong or moderate CYP3A inhibitors or inducers in certain situations.
f. Warfarin as well as subcutaneous and low-molecular-weight heparin were allowed.

CYP3A: cytochrome P450 3A4; PARP: polyadenosine 5'diphosphoribose [poly (adenosine diphosphate ribose)] polymerase; RCT: randomized controlled trial

The OlympiA study is an ongoing, double-blind RCT comparing olaparib versus placebo. The study enrolled adult patients with germline BRCA1- or BRCA2-mutated, high recurrence-risk, HER2-negative, early breast cancer. Initially, only patients with TNBC were eligible for participation in the OlympiA study. The inclusion of patients with positive hormone receptor status was allowed starting from protocol version 3.0 (21 October 2015). An inclusion criterion was the completion of adequate breast and axilla surgery (see I Appendix D of the full dossier

assessment on the criteria). In patients with breast-conserving surgery, adjuvant radiotherapy was required. In patients with mastectomy, adjuvant radiotherapy was an option in accordance with local and/or international guidelines. Based on the specifications for adequate breast and axilla surgery, patients presumably underwent a curative treatment approach. Furthermore, patients had to have received at least 6 cycles of neoadjuvant or adjuvant chemotherapy with anthracyclines, taxanes, or a combination of both. Prior treatment with a platinum substance in the context of neoadjuvant or adjuvant chemotherapy was allowed (see below). BRCA mutation status was determined prior to randomization either via local testing and/or centrally with the aid of the Myriad BRCAnalysis test. For patients whose inclusion was based on a locally determined mutation status, a centralized test for BRCA mutations was to be subsequently conducted. At enrolment, patients had to be in good general condition according to an ECOG-PS of 0 or 1.

The inclusion criteria defined high recurrence risk based on hormone receptor status and the timing of prior chemotherapy (neoadjuvant versus adjuvant). Patients with TNBC and prior neoadjuvant chemotherapy had to exhibit invasive residual disease in the breast and/or the resected lymph nodes. In case of adjuvant chemotherapy, patients with TNBC had to exhibit either positive axillary lymph nodes (≥ pN1, any tumour size) or negative axillary lymph nodes with an invasive primary tumour > 2 cm (≥ pT2) in accordance with the pathological tumour lymph node metastasis (TNM) classification system. Patients with positive hormone receptor status and neoadjuvant chemotherapy had to exhibit both (a) invasive residual disease in the breast and/or the resected lymph node and (b) a score ≥ 3 in the Pretreatment Clinical Stage and Posttreatment Pathologic Stage & Estrogen Receptor Status and Tumor Grade (CPS & EG). If chemotherapy was received in an adjuvant setting, at least 4 pathologically confirmed positive lymph nodes had to be present. In this therapeutic indication, there are no uniform criteria for defining high risk of recurrence. However, patients who meet the described inclusion criteria are presumably at high risk of recurrence.

The OlympiA study included a total of 1836 patients who were randomly allocated in a 1:1 ratio to treatment with olaparib (N = 921) or placebo (N = 915). Randomization was stratified by hormone receptor status (oestrogen receptor-positive and/or progesterone receptor-positive and HER2-negative versus TNBC), by the timing of the previous chemotherapy (adjuvant versus neoadjuvant), and by prior platinum-based chemotherapy (yes versus no). Randomization was to take place ideally within 8 weeks, but no later than within 12 weeks, after completion of the last treatment modality (surgery, chemotherapy, or radiotherapy).

In compliance with the SPC, olaparib treatment in the intervention arm was conducted for a maximum of 12 months [11]. The study did not provide for any switching to the treatment of the other study arm. In both treatment arms, hormone receptor-positive patients were to receive adjuvant endocrine therapy in accordance with local and/or international guidelines. The information in the study report indicates that about 90% of OlympiA participants with hormone receptor-positive breast cancer received endocrine therapy.

The study's primary outcome was invasive disease-free survival (iDFS), which comprises the events of ipsilateral invasive recurrence, locoregional recurrence, contralateral invasive recurrence, distant recurrence, secondary primary tumour (no breast cancer) , and death from any cause. Patient-relevant secondary outcomes were surveyed in the categories of mortality, morbidity, health-related quality of life, and AEs.

Presented patient population (prior treatment with platinum substances)

Concurring with the company, the total population of the OlympiA study was deemed relevant and used for the benefit assessment. However, the patient population is subject to 1 uncertainty, as described below.

According to the inclusion criteria, treatment with platinum substances was allowed in the context of (neo)adjuvant chemotherapy and was performed in a total of 26.4% of patients (23.7% TNBC + 2.8% hormone-receptor-positive breast cancer) (also see Table 9). The majority of patients (18.4%) received platinum substances in a neoadjuvant setting, while 8.1% of patients received them as adjuvant therapy. Platinum substances are not approved for the (neo)adjuvant treatment of breast cancer. Citing German guidelines and recommendations by the Working Group for Gynaecologic Oncology (AGO) Breast Committee, the company argues that neoadjuvant treatment with a platinum-containing chemotherapy regimen represents standard treatment in TNBC, and hence, the majority of patients was treated in accordance with guidelines. However, guidelines differ regarding the use of platinum substances in the (neo)adjuvant therapy of TNBC [12-15]. Overall, there is a discrepancy between the marketing authorization and individual guideline recommendations. However, this remains without consequence for the benefit assessment because (a) treatment with platinum substances occurred before randomization, (b) the stratification by this criterion ensured a balanced distribution between treatment arms, and (c) treatment with platinum substances is recommended by some guidelines.

Available data cut-offs

To date, 2 data cut-offs have been implemented for the OlympiA study:

- 1st data cut-off (27 March 2020): planned interim analysis after 165 iDFS events in the first 900 included patients
- 2nd data cut-off (12 July 2021): planned final iDFS analysis after 330 iDFS events

Furthermore, an interim analysis is prespecified for distant metastasis-free survival and overall survival after about 10 years, and a final analysis is to be conducted for overall survival about 15 years after randomization of the 1st patient. Concurring with the company's approach, the present benefit assessment uses the results from the 2nd data cut-off (12 July 2021).

Implementation of the appropriate comparator therapy

The G-BA specified watchful waiting as the ACT. The OlympiA study used placebo as comparator therapy. The study was not designed for a comparison with watchful waiting, but it is nonetheless suitable for such a comparison. This is explained below.

In the OlympiA study, targeted physical examinations were performed on all patients in the context of follow-up visits, and clinical signs and symptoms were recorded. These visits were to take place at 3-month intervals for the first 2 years after the patient's randomization, every 6 months in Years 3 to 5 after randomization, and then annually until the end of the 10th year. Furthermore, an annual radiological examination of the ipsilateral and/or contralateral breast is required. If any intact breast tissue remains, either mammography and/or magnetic resonance tomography (preferable in patients aged < 50 years) is to be performed. A radiological examination is not required for patients who underwent bilateral mastectomy and no longer possess any intact breast tissue. For this patient group as well as for male study participants, the investigator had the option of adding sonography to the physical examination. During the olaparib and placebo phase in the first 12 months, regular checks of vital parameters and laboratory tests (haematology and clinical chemistry) were additionally performed.

According to the S3 guideline, follow-up care is intended to achieve, among other things, the early detection of recurrences, contralateral recurrences, or distant recurrences which are amenable to curative treatment as well as to monitor long-term therapies. Follow-up visits should take place quarterly for the first 3 years after primary therapy, semiannually for the 4th and 5th year, and annually from the 6th year until at least the 10th year. At these intervals, patients are to be physically examined and to receive (at least) once yearly mammography as well as supplementary sonography of the affected breast and, if necessary, the contralateral breast. Further examinations are to be performed only in case of clinically suspected recurrence and/or metastases [14].

The examinations performed in the OlympiA study did not fully reflect the guideline recommendations. While regular radiological examinations were required, mammography was not. Magnetic resonance tomography of the breast, which the study used as an alternative, fails to reflect the guideline recommendations. In addition, breast sonography was not required. The company does not state which examination methods were employed on OlympiA participants. The study's follow-up intervals are largely in line with guideline recommendations. Only in the 3rd year after randomization were patients checked semiannually instead of quarterly, in departure from the S3 guideline.

Despite the described deviations from guideline recommendations, OlympiA participants were overall monitored closely via specific examinations to survey recurrences, and therefore, the examination regimen is overall deemed to be a sufficient approximation of the ACT of watchful waiting.

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: olaparib versus placebo

Study Outcome category Outcome	Planned follow-up observation
OlympiA	
Mortality	
Overall survival	Until death or end of study[a]
Morbidity	
Recurrences[b] / disease-free survival	Until distant recurrence of breast cancer, death, or study end[a]
Symptoms (EORTC QLQ-C30; FACIT-Fatigue)	Until 24 years after randomization
Health-related quality of life (EORTC QLQ-C30)	Until 24 years after randomization
Side effects	
AEs /SAEs / severe AEs[c]	Until 30 days after the last dose of the study medication
AESI[d]	Until death or end of study[a,e]

a. 10 years after randomization of the last patient.
b. Presented via disease-free survival, which comprises the following events: ipsilateral invasive recurrence, regional invasive recurrence, distant recurrence, contralateral invasive breast cancer, secondary primary carcinoma (no breast cancer), ductal carcinoma in situ, and death from any cause.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. MDS and AML, new primary malignancy (except MDS and AML), and pneumonitis.
e. However, the analyses presented by the company cover only the treatment duration + 30 days (analogously to AEs, SAEs, and severe AEs).

AE: adverse event; AESI: adverse events of special interest; AML: acute myeloid leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; DFS: disease-free survival; EORTC: European Organisation for Research and Treatment of Cancer; FACIT: Functional Assessment of Chronic Illness Therapy; MDS: myelodysplastic syndrome; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event

The observation periods for the outcomes on symptoms, health-related quality of life, and AEs, SAEs, and severe AEs are systematically shortened. The outcomes of symptoms and health-related quality of life were followed up for 24 months; side effects were recorded only for the period of treatment plus 30 days. However, to permit drawing a reliable conclusion regarding the total study period or time to patient death, it would be necessary to likewise record these outcomes for the total period, as was done for survival. According to the study protocol, adverse events of special interest (AESIs) were to be observed until death or study end, but the company submitted analyses only for the treatment duration plus 30 days (also see Section I 4.1).

Characteristics of the study population

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: olaparib versus placebo (multipage table)

Study **Characteristic** **Category**	**Olaparib** **N[a] = 921**	**Placebo** **N[a] = 915**
OlympiA		
Age [years], mean (SD)	43 (10)	44 (10)
Sex [f/m], %	> 99 / < 1	> 99 / < 1
ECOG-PS, n (%)		
0	824 (89)	804 (88)
1	97 (11)	111 (12)
Region, n (%)		
North America	122 (13)	132 (14)
South America	16 (2)	12 (1)
Europe	481 (52)	452 (49)
Asia-Pacific and South Africa	302 (33)	319 (35)
Menopause status[b], n (%)		
Premenopausal	572 (62)	553 (60)
Postmenopausal	347 (38)	358 (39)
Male	2 (< 1)	4 (< 1)
Hormone receptor status[c], n (%)		
TNBC	753 (82)	758 (83)
ER- and/or PgR-positive, HER2-negative	168 (18)	157 (17)
Mutation status acc. to Myriad BRCAnalysis test, n (%)		
BRCA1	579 (63)	588 (64)
BRCA2	235 (26)	216 (24)
BRCA1 and BRCA2	2 (< 1)	3 (< 1)
Clinical tumour stage (AJCC)[d]		
IA	103 (11)	85 (9)
IB	0 (0)	0 (0)
IIA	329 (36)	333 (36)
IIB	190 (21)	195 (21)
IIIA	128 (14)	111 (12)
IIIB	28 (3)	30 (3)
IIIC	42 (5)	56 (6)
IV	0 (0)	0 (0)
Missing	101 (11)	104 (11)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: olaparib versus placebo (multipage table)

Study **Characteristic** **Category**	**Olaparib** **N[a] = 921**	**Placebo** **N[a] = 915**
Pathological tumour stage (AJCC)		
0	3 (< 1)	6 (< 1)
IA	196 (21)	192 (21)
IB	28 (3)	21 (2)
IIA	400 (43)	398 (43)
IIB	109 (12)	116 (13)
IIIA	127 (14)	114 (12)
IIIB	4 (< 1)	6 (< 1)
IIIC	46 (5)	56 (6)
IV	0 (0)	0 (0)
Missing	8 (< 1)	6 (< 1)
Prior chemotherapy[c], n (%)		
Adjuvant	461 (50)	455 (50)
Neoadjuvant	460 (50)	460 (50)
Prior neoadjuvant/adjuvant chemotherapy of breast cancer, n (%)		
Anthracycline and taxane regimen	871 (95)	849 (93)
Anthracycline regimen (without taxanes)	7 (< 1)	13 (1)
Taxane regimen (without anthracyclines)	43 (5)	52 (6)
Missing	0 (0)	1 (< 1)
Platinum pretreatment[c], n (%)	247 (27)	238 (26)
Breast surgery prior to randomization, n (%)		
Breast conserving	223 (24)	240 (26)
Unilateral mastectomy	366 (40)	356 (39)
Bilateral mastectomy	332 (36)	317 (35)
Missing	0 (0)	2 (< 1)
Bilateral oophorectomy (or salpingo-oophorectomy)	184 (20)	164 (18)
Treatment discontinuation, n (%)[e]	237 (26[f])	189 (21[f])
Study discontinuation, n (%)[g]	166 (18[f])	184 (20[f])

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: olaparib versus placebo (multipage table)

Study Characteristic Category	Olaparib N[a] = 921	Placebo N[a] = 915
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. Menopause status was recorded at screening. Women were deemed postmenopausal if they met any of the following definitions: (1) aged ≥ 60 years, (2) aged < 60 years and amenorrhoea for a year or longer without chemotherapy and/or hormonal treatment, (3) aged < 60 years and follicle-stimulating hormone and oestradiol plasma level in postmenopausal range, (4) radiation-induced oophorectomy with last menstruation over 1 year ago, or (5) bilateral oophorectomy. c. According to information provided in the eCRF. d. According to information provided in the eCRF, clinical stage was determined prior to chemotherapy in patients with neoadjuvant chemotherapy and prior to surgery in patients with adjuvant chemotherapy. e. Common reasons for treatment discontinuation in the olaparib arm vs. placebo arm were: AEs (11% vs. 5%), disease recurrence (4% vs. 9%), patient decision (6% vs. 3%). f. Institute's calculation. g. Common reasons for study discontinuation in the olaparib arm vs. placebo arm were: death (8% vs. 12%), patient decision (8% vs. 6%), lost to follow-up (2% vs. 2%). AJCC: American Joint Committee on Cancer; BRCA: breast cancer associated gene; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; eCRF: electronic case report form; ER: oestrogen receptor; f: female; HER2: human epidermal growth factor receptor 2; m: male; n: number of patients in the category; N: number of randomized patients; PgR: progesterone receptor; RCT: randomized controlled trial; SD: standard deviation; TNBC: triple-negative breast cancer		

The study arms were balanced in terms of patients' demographic and clinical characteristics. The mean age of intervention arm patients was between 43 and 44 years. The study population comprised almost exclusively women (men < 1%), and more than 80% of patients had TNBC. A centrally performed Myriad BRCAnalysis test is available for around 90% of patients. Before randomization, half of patients had received neoadjuvant chemotherapy, while the other half received adjuvant chemotherapy. Most patients (> 90%) were treated in line with guidelines using a combined anthracycline and taxane regimen; 26.4% additionally received treatment with a platinum substance.

Information on the course of the study

Table 10 shows the mean/median patient treatment duration and the mean/median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: olaparib versus placebo

Study **Duration of the study phase** **Outcome category**	**Olaparib**	**Placebo**
OlympiA		
Treatment duration [months][a]	N = 911	N = 904
Median [min; max]	12.0 [0.0; 16.2][b]	12.0 [0.1; 13.6][b]
Mean (SD)	ND	ND
Observation period [months]	N = 921	N = 915
Overall survival[c]		
Median [min; max]	41.4 [0.1; 81.4]	40.3 [0.0; 80.1]
Mean (SD)	ND	ND
Morbidity		
Recurrences / disease-free survival		
Median [min; max]	39.2 [0.1; 80.4]	37.5 [0.0; 79.4]
Mean (SD)	ND	ND
Symptoms (EORTC QLQ-C30; FACIT-Fatigue)		
Median [min; max]	23.7 [0.0; 25.3]	23.5 [0.0; 25.3]
Mean (SD)	ND	ND
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	23.7 [0.0; 25.3]	23.5 [0.0; 25.3]
Mean (SD)	ND	ND
Side effects		
AEs, SAEs, severe AEs (CTCAE grade ≥ 3)		
Median [min; max]	13.0 [1.0; 17.1]	13.0 [1.1; 14.6]
Mean (SD)	ND	ND
AESI[d]	ND[e]	

a. For treatment duration, only patients who received treatment are analysed.
b. Institute's calculation.
c. No information is available as to how the observation duration was calculated (e.g. by means of the inverse Kaplan-Meier method).
d. MDS and AML, new primary malignancy (except MDS and AML), and pneumonitis.
e. AESIs were to be observed until death or study end (see Table 8). However, the analyses presented by the company cover only treatment duration + 30 days (analogously to AEs, SAEs, and severe AEs).

AE: adverse event; AESI: adverse event of special interest; AML: acute myeloid leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; DFS: disease-free survival; EORTC: European Organisation for Research and Treatment of Cancer; FACIT: Functional Assessment of Chronic Illness Therapy; max: maximum; min: minimum; MDS: myelodysplastic syndrome; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation

The OlympiA study's analysis presented by the company shows that the median treatment duration was approximately equal in its 2 study arms. The median observation periods for the

outcomes of the mortality, morbidity, health-related quality of life, and side effects categories were also comparable in both treatment arms.

While the outcomes of overall survival and recurrences were to be observed until death or study end, the observation duration for the outcomes on symptoms and health-related quality of life were limited to a maximum of 24 months, and those of the side effects category were linked to treatment end (see Table 8). This results in a median observation duration of about 24 months for the symptoms and quality of life outcomes (equalling about 60% of the observation duration for overall survival) and 13 months for the outcomes of the side effects category (equalling about 30% of observation duration for overall survival). Hence, the observation durations for these outcomes were shortened in comparison with median overall survival. Data for the entire observation period are missing for these outcomes.

Information on subsequent therapies

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

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: olaparib versus placebo (multipage table)

Study	**Patients with subsequent therapy n (%)[a]**	
Drug class **Drug**	**Olaparib** **N = 921**	**Placebo** **N = 915**
OlympiA		
Patients with event[b]	143 (15.5)	218 (23.8)
Radiotherapy	39 (4.2)	70 (7.7)
Surgical interventions	53 (5.8)	79 (8.6)
Systemic therapy	100 (10.9)	158 (17.3)
Detoxifying agents for treatment with cytostatics	0 (0)	1 (0.1)
Alkylsulfonates	0 (0)	1 (0.1)
Anthracyclines and related substances	7 (0.8)	13 (1.4)
CDK inhibitors	6 (0.7)	12 (1.3)
Folic acid analogues	2 (0.2)	6 (0.7)
MEK inhibitors	2 (0.2)	0 (0)
Monoclonal antibodies	25 (2.7)	29 (3.2)
Atezolizumab	9 (1.0)	6 (0.7)
Avelumab	0 (0)	1 (0.1)
Bevacizumab	13 (1.4)	10 (1.1)
Durvalumab	0 (0)	4 (0.4)
Lag 525	1 (0.1)	0 (0)
Nivolumab	1 (0.1)	1 (0.1)
Pembrolizumab	1 (0.1)	5 (0.5)
Sacituzumab govitecan	1 (0.1)	0 (0)
Trastuzumab	0 (0)	1 (0.1)

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: olaparib versus placebo (multipage table)

Study Drug class Drug	Patients with subsequent therapy n (%)[a] Olaparib N = 921	 Placebo N = 915
Alkylating agents	6 (0.7)	14 (1.5)
Other alkylating agents	1 (0.1)	0 (0)
Other antineoplastic agents	8 (0.9)	14 (1.5)
Other cytotoxic antibiotics	0 (0)	2 (0.2)
Other protein kinase inhibitors	1 (0.1)	0 (0)
Platinum-containing compounds	43 (4.7)	77 (8.4)
Podophyllotoxin derivatives	0 (0)	2 (0.2)
PARP inhibitors	17 (1.8)	49 (5.4)
Purine analogues	0 (0)	1 (0.1)
Pyrimidine analogues	38 (4.1)	60 (6.6)
Taxanes	42 (4.6)	44 (4.8)
VEGFR tyrosine kinase inhibitors	1 (0.1)	0 (0)
Vinca alkaloids and analogues	9 (1.0)	7 (0.8)
Corticosteroids	1 (0.1)	0 (0)
Endocrine therapy	13 (1.4)	19 (2.1)
Antioestrogens	5 (0.5)	13 (1.4)
Aromatase inhibitors	8 (0.9)	9 (1.0)
Gonadotropin releasing hormone antagonists	1 (0.1)	2 (0.2)
Immunostimulants	0 (0)	1 (0.1)
Immunosuppressants	2 (0.2)	1 (0.1)

a. Each therapy is counted a maximum of once per patient.
b. Comprises the events of the primary outcome of iDFS as well as further malignancies which are excluded from the primary outcome of the study.

CDK: cyclin-dependent kinase; iDFS: invasive disease-free survival; MEK: mitogen-activated protein kinase; n: number of patients with subsequent therapy; N: number of analysed patients; PARP: poly (adenosine diphosphate ribose) polymerase; RCT: randomized controlled trial; VEGFR: vascular endothelial growth factor receptor

With regard to subsequent therapies, the study protocol specified no limitations. The information on subsequent therapies is found only in the study report (no information provided in Module 4 A), with its analysis not being fully informative. The analyses in the study report do not identify the therapy line in which the respective treatment was administered. However, the presented analyses on subsequent therapies do not show any evidence of the treatment administered in the OlympiA study after recurrence substantially departing from guideline recommendations [14,16-18].

Risk of bias across outcomes (study level)

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

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: olaparib versus placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of additional aspects	Risk of bias at study level
			Patients	Treatment providers			
OlympiA	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

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

Transferability of the study results to the German health care context

In the company's view, the results of the OlympiA study are transferable to the German health care context. According to the company, general patient characteristics, such as sex, age, ethnicity, disease-specific criteria, and treatment-related aspects, did not substantially differ between study participants versus patients with early breast cancer in the German healthcare system.

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - recurrence
  - symptoms surveyed using the EORTC QLQ-C30 and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue)
- Health-related quality of life
  - recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - MDS and AML (SMQ + PT list, AEs)
  - pneumonitis (SMQ, AEs)
  - further specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: olaparib versus placebo

Study	Outcomes										
	Overall survival	Recurrences[a] / disease-free survival	Symptoms (EORTC QLQ-C30)	Symptoms (FACIT-Fatigue)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	MDS and AML (SMQ + PT list, AEs)[c]	Pneumonitis (SMQ, AEs)[c]	Further specific AEs[d]
OlympiA	Yes	Yes	Yes	Yes	Yes	No[e]	Yes	Yes	Yes	Yes	Yes

a. Presented via recurrence rate and disease-free survival; includes the events of ipsilateral invasive recurrence, regional invasive recurrence, distant recurrence, contralateral invasive breast cancer, secondary primary carcinoma (no breast cancer), ductal carcinoma in situ, and death from any cause.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Predefined in the study as AESIs.
d. The following events were assessed (MedDRA coding): fatigue (PT, AEs), gastrointestinal disorders (SOC, AEs), dysgeusia (PT, AEs), decreased appetite (PT, AEs), anaemia (PT, SAEs), and investigations (SOC, severe AEs).
e. No suitable data available; for justification, see body of text below.

AE: adverse event; AESI: adverse events of special interest; AML: acute myeloid leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FACIT: Functional Assessment of Chronic Illness Therapy; MDS: myelodysplastic syndrome; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class

Analyses of the outcome of recurrences

For the outcome of recurrences, the benefit assessment uses the analysis presented by the company on the combined outcome consisting of the components of ipsilateral recurrence, locoregional invasive recurrence, distant recurrence, contralateral invasive breast cancer, secondary primary tumour (no breast cancer), ductal carcinoma in situ, and death of any cause. The results of the operationalizations were presented as the percentage of patients with recurrence (recurrence rate) and as disease-free survival (time from randomization until the first occurrence of one of the above events).

According to the study protocol, a recurrence or a 2nd primary tumour requires histological and/or radiological confirmation. The diagnosis of a recurrence or 2nd primary tumour was based on the investigator's assessment – the protocol did not provide for blinded independent central review (BICR). An assessment by means of BICR is explicitly recommended by the European Medicines Agency (EMA), particularly in oncological studies whose treatment arms

exhibit different toxicity profiles [19]. However, the missing analysis by BICR remains of no consequence for the present benefit assessment.

Furthermore, it must be noted that the median observation duration of 39 months in the olaparib arm and 38 months in the placebo arm is insufficient for conclusively evaluating the sustainability of the effect of olaparib on the outcome of recurrences.

Analyses of patient-reported outcomes on symptoms and health-related quality of life

For the outcomes of symptoms (EORTC QLQ-C30; FACIT-Fatigue), and health-related quality of life (EORTC QLQ-C30), the company presents only the prespecified analyses by means of mixed effect model repeated measurement (MMRM). These analyses were used for the benefit assessment. The presented MMRM analyses are based on all patients for whom 1 measurement is available at baseline and at least 1 additional measurement at a later point in time. However, a relevant percentage of included patients (> 10%) did not meet this criterion. These patients were therefore not included in the analyses. The resulting uncertainty was taken into account in the assessment of risk of bias (see Section I 4.2).

Analyses of the outcomes in the side effects category

Analyses of SAEs are unsuitable for the benefit assessment

The analysis presented by the company on SAEs includes a relevant percentage of progression events from the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps) (see Table 21 of the full dossier assessment). The benefit assessment already represents these events via the outcome of recurrences, which shows a statistically significant advantage of olaparib versus placebo. Additionally including progression events in the outcome of SAEs substantially biases the results in favour of olaparib (by concealing any disadvantages of olaparib through the increased occurrence of progression events in the placebo arm). The company's dossier does not present any analyses disregarding progression events. Hence, no suitable data were available for the outcome of SAEs.

Analyses on severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs

Like in the analyses of SAEs, the analyses of severe AEs and discontinuation due to AEs include progression events from the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps). For these outcomes, however, the analyses of severe AEs and discontinuation due to AEs already show such a pronounced disadvantage of olaparib in comparison with placebo that no relevant changes in results are expected from disregarding progression events in the analyses. The outcomes of severe AEs and discontinuation due to AEs are therefore included in the benefit assessment.

Analyses of AESIs

The company defines AESIs in the study protocol (MDS and AML, new primary malignancy [except MDS and AML], and pneumonitis). Out of this list, the benefit assessment included the combined outcome of MDS and AML as well as the outcome of pneumonitis (SMQ). The

combined outcome of MDS and AML is operationalized as MDS (SMQ) plus AML (list of MedDRA PTs which are typically allocated to AML; PT list). This operationalization is deemed a sufficient approximation for the illustration of MDS and AML events.

According to the study protocol, AESIs were to be observed until study end or death. However, the company's dossier presents an analysis only for treatment duration plus 30 days for these outcomes, like for the other outcomes of the side effects category. This approach is not appropriate. In principle, the benefit assessment requires analyses for the entire observation period. Given the available evidence, the submitted analyses were nevertheless used for the benefit assessment because the study report shows that events did not occur to a relevant extent in the period after treatment end.

In addition, the company's Module 4A reports results on other AESIs (PT lists on nausea, vomiting, anaemia, neutropenia, thrombocytopenia, fatigue & asthenia), which the study protocol refers to as AEs for summarizing long-term tolerability. The study documents fail to clarify whether these outcomes were likewise to be observed for more than 30 days after treatment end. Module 4A as well as the study documents contain analyses only for up to 30 days after the end of treatment.

I 4.2 Risk of bias

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

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: olaparib versus placebo

Study	Study level	Outcomes										
		Overall survival	Recurrences[a] / disease-free survival	Symptoms (EORTC QLQ-C30)	Symptoms (FACIT-Fatigue)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	MDS and AML (SMQ + PT list, AEs)[c]	Pneumonitis (SMQ, AEs)	Further specific AEs[d]
OlympiA	L	L	L	H[e]	H[e]	H[e]	–[f]	L	N	N	L	L

a. Presented via recurrence rate and disease-free survival; includes the events of ipsilateral invasive recurrence, regional invasive recurrence, distant recurrence, contralateral invasive breast cancer, secondary primary carcinoma (no breast cancer), ductal carcinoma in situ, and death from any cause.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Predefined in the study as AESIs.
d. The following events were assessed (MedDRA coding): fatigue (PT, AEs), gastrointestinal disorders (SOC, AEs), dysgeusia (PT, AEs), decreased appetite (PT, AEs), anaemia (PT, SAEs), and investigations (SOC, severe AEs).
e. Large proportion of patients (> 10%) not considered in the analysis.
f. No suitable data available; see Section I 4.1 of the present dossier assessment for reasons.

AE: adverse event; AESI: adverse events of special interest; AML: acute myeloid leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FACIT: Functional Assessment of Chronic Illness Therapy; H: high; L: low; MDS: myelodysplastic syndrome; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class

For the results on the outcomes of overall survival and recurrences, the risk of bias was rated as low. For the outcomes of symptoms (EORTC QLQ-C30), FACIT-Fatigue, and health-related quality of life (EORTC QLQ-C30), the risk of bias is rated as high because a relevant percentage of patients (> 10%) was excluded from the analysis (see Section I 4.1).

The risk of bias of results for all outcomes in the side effects category is rated as low.

I 4.3 Results

Table 15 and Table 16 summarize the results on the comparison of olaparib with placebo in adult patients with germline BRCA-1/2 mutated, HER2-negative, high recurrence-risk, early breast cancer following prior treatment with neoadjuvant or adjuvant chemotherapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

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

Table 15: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: olaparib versus placebo (multipage table)

Study Outcome category Outcome	Olaparib N	Olaparib Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Olaparib vs. placebo RR [95% CI]; p-value[a]
OlympiA					
Mortality					
Overall survival	921	75 (8.1) Median time to event: NR [NC]	915	109 (11.9) Median time to event: NR [NC]	HR[b]: 0.68 [0.50; 0.91]; 009
Morbidity					
Recurrence					
Recurrence rate[c]	921	138 (15.0)	915	210 (23.0)	0.65 [0.54; 0.79]; < 0.001
Ipsilateral invasive recurrence	921	9 (1.0)	915	12 (1.3)	–
Locoregional invasive recurrence	921	9 (1.0)	915	18 (2.0)	–
Distant recurrence	921	88 (9.6)	915	135 (14.8)	–
Contralateral invasive recurrence	921	15 (1.6)	915	18 (2.0)	–
Secondary primary tumour (no breast cancer)	921	11 (1.2)	915	23 (2.5)	–
Ductal carcinoma in situ	921	4 (0.4)	915	4 (0.4)	–
Death from any cause	921	2 (0.2)	915	0 (0)	–
Disease-free survival	921	138 (15.0) Median time to event: NR [NC]	915	210 (23.0) Median time to event: NR [NC]	HR[b]: 0.64 [0.51; 0.79]; < 0.001

Table 15: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: olaparib versus placebo (multipage table)

Study Outcome category Outcome	Olaparib N	Olaparib Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Olaparib vs. placebo RR [95% CI]; p-value[a]
Side effects					
AEs (supplementary information)	911	836 (91.8)	904	758 (83.8)	–
SAEs				No suitable data[d]	
Severe AEs[e]	911	170 (18.7)	904	82 (9.1)	2.06 [1.61; 2.63]; < 0.001
Discontinuation due to AEs	911	98 (10.8)	904	42 (4.6)	2.32 [1.63; 3.28]; < 0.001
MDS and AML (SMQ + PT list, AEs)[f]	911	1 (0.1)	904	1 (0.1)	0.99 [0.06; 15.84]; > 0.999
Pneumonitis (SMQ, AEs)[f]	911	9 (1.0)	904	11 (1.2)	0.81 [0.34; 1.95]; 0.683
Fatigue (PT, AEs)	911	366 (40.2)	904	246 (27.2)	1.48 [1.29; 1.69]; < 0.001
Gastrointestinal disorders (SOC, AEs)	911	654 (71.8)	904	430 (47.6)	1.51 [1.39; 1.63]; < 0.001
Dysgeusia (PT, AEs)	911	107 (11.7)	904	38 (4.2)	2.79 [1.95; 4.00]; < 0.001
Decreased appetite (PT, AEs)	911	119 (13.1)	904	53 (5.9)	2.23 [1.63; 3.04]; < 0.001
Anaemia (PT, SAEs)	911	15 (1.6)	904	1 (0.1)	14.88 [1.97; 112.45]; < 0.001
Investigations (SOC, severe AEs[e,g])	911	50 (5.5)	904	10 (1.1)	4.96 [2.53; 9.72]; < 0.001

a. Institute's calculation of RR, 95% CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [20].
b. Cox proportional hazards model (HR, 95% CI), and log-rank test (p-value), stratified by hormone receptor status, type of prior chemotherapy, and prior platinum-based chemotherapy in breast cancer.
c. The individual components of the combined outcome are presented in the rows below.
d. See Section I 4.1 of the present dossier assessment for the reasoning.
e. Operationalized as CTCAE grade ≥ 3.
f. Predefined in the study as AESIs.
g. The SOC investigations includes the following PTs with statistically significant effect: leukocyte count decreased, neutrophil count decreased, and lymphocyte count decreased.

AE: adverse event; AESI: adverse events of special interest; AML: acute myeloid leukaemia; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; MDS: myelodysplastic syndrome; N: number of analysed patients; n: number of patients with (at least 1) event; NR: not reached; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standard MedDRA Query; SOC: System Organ Class

Table 16: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: olaparib versus placebo (multipage table)

Study Outcome category Outcome	Olaparib			Placebo			Olaparib vs. placebo
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)	MD [95% CI]; p-value[b]
OlympiA							
Morbidity							
Symptoms (EORTC QLQ-C30)[c]							
Fatigue	772	29.30 (22.63)	0.10 (0.57)	774	29.10 (21.35)	-1.88 (0.57)	1.98 [0.41; 3.55]; 0.014 SMD [95% CI]: 0.13 [0.03; 0.23]
Nausea and vomiting	772	2.94 (8.49)	3.76 (0.30)	774	3.36 (10.08)	0.86 (0.30)	2.90 [2.07; 3.74]; < 0.001 SMD [95% CI]: 0.35 [0.25; 0.45]
Pain	772	20.60 (23.94)	-1.76 (0.58)	775	20.75 (23.51)	-2.01 (0.58)	0.26 [-1.34; 1.86]; 0.752
Dyspnoea	769	13.48 (21.56)	0.66 (0.52)	770	12.25 (20.29)	-0.74 (0.52)	1.41 [-0.03; 2.84]; 0.055
Insomnia	771	27.15 (28.18)	0.03 (0.74)	773	28.76 (29.62)	-0.40 (0.74)	0.44 [-1.61; 2.48]; 0.677
Appetite loss	771	8.21 (18.03)	1.96 (0.46)	772	8.03 (17.93)	-0.63 (0.46)	2.60 [1.33; 3.86]; < 0.001 SMD [95% CI]: 0.20 [0.11; 0.31]
Constipation	769	9.67 (19.48)	2.52 (0.53)	772	9.67 (19.91)	0.39 (0.52)	2.13 [0.67; 3.59]; 0.004 SMD [95% CI]: 0.15 [0.05; 0.25]
Diarrhoea	769	5.77 (15.02)	0.88 (0.42)	772	6.00 (15.18)	0.74 (0.41)	0.14 [-1.01; 1.30]; 0.806
FACIT-Fatigue[d]							
Fatigue scale	766	40.27 (9.67)	-0.02 (0.23)	773	40.43 (8.88)	0.79 (0.23)	-0.80 [-1.45; -0.16]; 0.015 SMD [95% CI]: -0.12 [-0.23; -0.03]

Table 16: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: olaparib versus placebo (multipage table)

Study Outcome category Outcome	Olaparib			Placebo			Olaparib vs. placebo
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)	MD [95% CI]; p-value[b]
Health-related quality of life							
EORTC QLQ-C30[e]							
Global health status	768	70.64 (19.31)	1.62 (0.51)	773	70.20 (19.07)	3.45 (0.50)	-1.83 [-3.23; -0.43]; 0.011 SMD [95% CI]: -0.13 [-0.23; -0.03]
Physical functioning	772	86.32 (14.55)	0.82 (0.35)	774	86.40 (14.43)	1.68 (0.35)	-0.86 [-1.83; 0.11]; 0.084
Role functioning	772	80.12 (24.22)	2.45 (0.58)	774	81.31 (23.89)	3.21 (0.58)	-0.76 [-2.38; 0.85]; 0.355
Cognitive functioning	769	81.64 (20.99)	-1.82 (0.54)	772	82.82 (20.22)	-1.73 (0.54)	-0.09 [-1.60; 1.42]; 0.908
Emotional functioning	769	76.99 (22.33)	-0.05 (0.54)	771	77.77 (20.80)	-0.04 (0.54)	-0.02 [-1.51; 1.48]; 0.984
Social functioning	769	78.63 (25.07)	5.34 (0.57)	773	79.28 (24.03)	5.94 (0.57)	-0.60 [-2.19; 0.99]; 0.457

a. Number of patients with 1 value at baseline and at least 1 value at a later visit.
b. MMRM of change at baseline with the covariates of treatment, visit, interaction of treatment and visit, baseline value, and interaction of baseline value and visit.
c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention (scale range of 0 to 100).
d. Higher (increasing) values indicate improved symptoms; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 52).
e. Higher (increasing) values indicate better health-related quality of life; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference

Based on the available information, at most indications, e.g. of an added benefit, can be determined for the outcomes of overall survival, recurrences, and for all outcomes of the category of side effects, while at most hints can be derived for the outcomes of symptoms and health-related quality of life due to the associated high risk of bias.

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of olaparib versus placebo. This results in an indication of added benefit of olaparib in comparison with watchful waiting.

Morbidity

Recurrence

Regarding the outcome of recurrence, there was a statistically significant difference in favour of olaparib in comparison with placebo for both recurrence rate and disease-free survival. This results in an indication of an added benefit of olaparib in comparison with watchful waiting.

Symptoms, recorded with the EORTC QLQ-C30

A statistically significant difference to the disadvantage of olaparib compared with placebo was shown for the outcome of nausea and vomiting (symptoms). The 95% CI for the standardized mean difference (SMD) was fully outside the irrelevance range [-0.2; 0.2]. This was interpreted to be a relevant effect. This results in a hint of lesser benefit of olaparib in comparison with watchful waiting.

A statistically significant difference to the disadvantage of olaparib versus placebo was shown for the symptoms of fatigue, appetite loss, and constipation. However, the respective 95% CIs for SMD are not fully outside the irrelevance range [-0.2; 0.2]. It was therefore impossible to infer the effect to be relevant. This results in no hint of an added benefit of olaparib versus watchful waiting for any of them.

No statistically significant difference between treatment groups was shown for any of the symptoms of pain, dyspnoea, insomnia, or diarrhoea. This results in no hint of an added benefit of olaparib in comparison with watchful waiting for any of them; added benefit is therefore not proven.

Symptoms, recorded using the FACIT-Fatigue

For the outcome of FACIT-Fatigue, a statistically significant difference was found to the disadvantage of olaparib versus placebo. However, the 95% CI of the SMD was not fully outside the irrelevance range [-0.2; 0.2]. The effect can therefore not be inferred to be relevant. This results in no hint of an added benefit of olaparib versus watchful waiting.

Health-related quality of life, recorded with the EORTC QLQ-C30

For the outcome of health-related quality of life, the scale of global health status shows a statistically significant difference to the disadvantage of olaparib versus placebo. However, the 95% CI of the SMD was not fully outside the irrelevance range [-0.2; 0.2]. The effect can therefore not be inferred to be relevant. This results in no hint of an added benefit of olaparib in comparison with watchful waiting.

No statistically significant difference between treatment arms was shown for any of the functioning scales: physical functioning, role functioning, cognitive functioning, emotional functioning, or social functioning. This results in no hint of an added benefit of olaparib in comparison with watchful waiting for any of them; an added benefit is therefore not proven.

Side effects

SAEs

No suitable data are available for the outcome of SAEs (see Section I 4.1 for reasoning). This results in no hint of greater or lesser harm from olaparib in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

For the outcome of severe AEs, a statistically significant difference was found to the disadvantage of olaparib versus placebo. This results in an indication of greater harm from olaparib in comparison with watchful waiting.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, a statistically significant difference was found to the disadvantage of olaparib versus placebo. This results in an indication of greater harm from olaparib in comparison with watchful waiting.

Specific AEs

MDS and AML (SMQ + PT list, AEs)

No statistically significant difference between treatment groups was shown for the outcome of MDS and AML (SMQ + PT list, AEs). This results in no hint of greater or lesser harm from olaparib in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Pneumonitis (SMQ, AE)

For the outcome of pneumonitis (SMQ, AEs), there was no statistically significant difference between treatment groups. This results in no hint of greater or lesser harm from olaparib in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Fatigue (PT, AE), gastrointestinal disorders (SOC, AE), dysgeusia (PT, AE), decreased appetite (PT, AE), anaemia (PT, SAE), investigations (SOC, severe AE)

A statistically significant difference to the disadvantage of olaparib versus placebo was found for each of the outcomes of fatigue (PT, AEs), gastrointestinal disorders (SOC, AEs), dysgeusia (PT, AEs), decreased appetite (PT, AEs), anaemia (PT, SAEs), and investigations (SOC, severe AEs; includes the PTs of decreased leukocyte count, decreased neutrophil count, and decreased lymphocyte count, each with a statistically significant effect to the disadvantage of olaparib). For each of these outcomes, this results in an indication of greater harm from olaparib in comparison with watchful waiting.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristic was taken into account in the present benefit assessment:

- age (< 50 years versus 50 to 64 years versus ≥ 65 years)

The characteristic of sex was disregarded because the OlympiA study population included only 6 men. No suitable characteristic is available for disease severity.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

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

Using the above-described methods, the available subgroup analyses do not reveal any relevant effect modifications.

I 5 Probability and extent of added benefit

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

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

I 5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4 (see Table 17).

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

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

Recurrence

The outcome of recurrence is considered to be serious/severe. On the one hand, recurrence of cancer can be life-threatening, and a recurrence shows that the attempt to cure a potentially life-threatening disease with the curative therapy approach has not been successful. On the other hand, the event of death from any cause is a component of the outcome of recurrence.

Symptoms (EORTC QLQ-C30): nausea and vomiting

The EORTC QLQ-C30 scale ranges from 0 and 100, with higher scores indicating more pronounced symptoms. Throughout the survey period, OlympiA participants exhibited mean scores in the lower range of the scale (< 50 points). Therefore, this outcome was assigned to the outcome category of non-serious/non-severe symptoms / late complications.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, no information is available on the CTCAE-rated severity of the AEs on the basis of which treatment was discontinued. Since insufficient information is therefore available for categorizing the severity as serious/severe, this outcome is allocated to the outcome category of non-serious/non-severe side effects.

Table 17: Extent of added benefit at outcome level: olaparib versus watchful waiting (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Olaparib vs. placebo** **Median time to event (months) or proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Total observation period		
Mortality		
Overall survival	NR vs. NR HR: 0.68 [0.50; 0.91] p = 0.009 Probability: indication	Outcome category: all-cause mortality $0.85 \leq CI_u < 0.95$ Added benefit; extent: considerable
Morbidity		
Recurrence[c]		Outcome category: serious/severe symptoms / late complications $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable
Recurrence rate	15.0% vs. 23.0% RR: 0.65 [0.54; 0.79] p < 0.001 Probability: indication	
Disease-free survival	NR vs. NR HR: 0.64 [0.51; 0.79] p < 0.001 Probability: indication	
Shortened observation period		
Symptoms		
EORTC QLQ-C30		
Fatigue	0.10 vs. -1.88 MD: 1.98 [0.41; 3.55] p = 0.014 SMD: 0.13 [0.03; 0.23][d]	Lesser/added benefit not proven
Nausea and vomiting	3.76 vs. 0.86 MD: 2.90 [2.07; 3.74] p < 0.001 SMD: 0.35 [0.25; 0.45][d] Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.2 < CI_L \leq 0.4$ Lesser benefit; extent: minor
Pain	-1.76 vs. -2.01 MD: 0.26 [-1.34; 1.86] p = 0.752	Lesser/added benefit not proven
Dyspnoea	0.66 vs. -0.74 MD: 1.41 [-0.03; 2.84] p = 0.055	Lesser/added benefit not proven
Insomnia	0.03 vs. -0.40 MD: 0.44 [-1.61; 2.48] p = 0.677	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: olaparib versus watchful waiting (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Olaparib vs. placebo** **Median time to event (months) or proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Appetite loss	1.96 vs. -0.63 MD: 2.60 [1.33; 3.86] p < 0.001 SMD: 0.20 [0.11; 0.31][d]	Lesser/added benefit not proven
Constipation	2.52 vs. 0.39 MD: 2.13 [0.67; 3.59] p = 0.004 SMD: 0.15 [0.05; 0.25][d]	Lesser/added benefit not proven
Diarrhoea	0.88 vs. 0.74 MD: 0.14 [-1.01; 1.30] p = 0.806	Lesser/added benefit not proven
FACIT-Fatigue Fatigue Scale	-0.02 vs. 0.79 MD: -0.80 [-1.45; -0.16] p = 0.015 SMD: -0.12 [-0.23; -0.03] SMD: 0.12 [0.03; 0.23][d,e]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 Global health status	1.62 vs. 3.45 MD: -1.83 [-3.23; -0.43] p = 0.011 SMD: -0.13 [-0.23; -0.03] SMD: 0.13 [0.03; 0.23][d,e]	Lesser/added benefit not proven
Physical functioning	0.82 vs. 1.68 MD: -0.86 [-1.83; 0.11] p = 0.084	Lesser/added benefit not proven
Role functioning	2.45 vs. 3.21 MD: -0.76 [-2.38; 0.85] p = 0.355	Lesser/added benefit not proven
Cognitive functioning	-1.82 vs. -1.73 MD: -0.09 [-1.60; 1.42] p = 0.908	Lesser/added benefit not proven
Emotional functioning	-0.05 vs. -0.04 MD: -0.02 [-1.51; 1.48] p = 0.984	Lesser/added benefit not proven
Social functioning	5.34 vs. 5.94 MD: -0.60 [-2.19; 0.99] p = 0.457	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: olaparib versus watchful waiting (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Olaparib vs. placebo** **Median time to event (months) or proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	No usable data[f]	Greater/lesser harm not proven
Severe AEs	18.7% vs. 9.1% RR: 2.06 [1.61; 2.63] RR: 0.49 [0.38; 0.62][e] p < 0.001 Probability: indication	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Greater harm; extent: major
Discontinuation due to AEs	10.8% vs. 4.6% RR: 2.32 [1.63; 3.28] RR: 0.43 [0.30; 0.61][e] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm; extent: considerable
MDS/AML (AE)	0.1% vs. 0.1% RR: 0.99 [0.06; 15.84] p > 0.999	Greater/lesser harm not proven
Pneumonitis (AE)	1.0% vs. 1.2% RR: 0.81 [0.34; 1.95] p = 0.683	Greater/lesser harm not proven
Fatigue (AE)	40.2% vs. 27.2% RR: 1.48 [1.29; 1.69] RR: 0.68 [0.59; 0.78][e] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm; extent: considerable
Gastrointestinal disorders (AE)	71.8% vs. 47.6% RR: 1.51 [1.39; 1.63] RR: 0.66 [0.61; 0.72][e] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm; extent: considerable
Dysgeusia (AE)	11.7% vs. 4.2% RR: 2.79 [1.95; 4.00] RR: 0.36 [0.25; 0.51][e] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm; extent: considerable
Decreased appetite (AE)	13.1% vs. 5.9% RR: 2.23 [1.63; 3.04] RR: 0.45 [0.33; 0.61][e] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm; extent: considerable

Table 17: Extent of added benefit at outcome level: olaparib versus watchful waiting (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Olaparib vs. placebo** **Median time to event (months) or proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Anaemia (SAE)	1.6% vs. 0.1% RR: 14.88 [1.97; 112.45]; RR: 0.07 [0.01; 0.51][e] $p < 0.001$ Probability: indication	Outcome category: serious/severe side effects $CI_u < 0.75$; risk < 5% Greater harm; extent: considerable
Investigations (severe AEs)	5.5% vs. 1.1% RR: 4.96 [2.53; 9.72]; RR: 0.20 [0.10; 0.40][e] $p < 0.001$ Probability: indication	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% Greater harm; extent: major

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size and the scale of the outcome are made with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. Presented via the recurrence rate and disease-free survival; includes the following events: ipsilateral locoregional, or contralateral invasive recurrence of breast cancer, distant recurrence, secondary primary carcinoma (no breast cancer), DCIS, and death from any cause.
d. If the CI for the SMD is fully outside the irrelevance range [-0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
f. See Section I 4.1 of the present dossier assessment for the reasoning.

AE: adverse event; CI: confidence interval; CI_L: lower limit of the confidence interval; CI_U: upper limit of the confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; FACIT: Functional Assessment of Chronic Illness Therapy; HR: hazard ratio; MD: mean difference; QLQ-C30: Quality of Life Questionnaire – Core 30; RR: relative risk; SAE: serious adverse event; SMD: standardized mean difference

I 5.2 Overall conclusion on added benefit

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

Table 18: Favourable and unfavourable effects from the assessment of olaparib in comparison with watchful waiting

Favourable effects	**Unfavourable effects**
Total observation period	
Mortality ▪ Overall survival: indication of an added benefit – extent: considerable	–
Morbidity Serious/severe symptoms / late complications ▪ Recurrences: indication of an added benefit – extent: considerable	–
Shortened observation period	
▪ –	Morbidity Non-serious/non-severe symptoms / late complications ▪ Nausea and vomiting (symptoms, EORTC QLQ-C30): hint of lesser benefit – extent: minor
–	Serious/severe side effects ▪ Severe AEs: indication of greater harm – extent: major ▫ Investigations (severe AEs): indication of greater harm – extent: major ▪ Anaemia (SAEs): indication of greater harm – extent considerable
–	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: indication of greater harm – extent: considerable ▪ Fatigue (AEs), gastrointestinal disorders (AEs), dysgeusia (AEs), appetite decreased (AEs): each hint of greater harm – extent: considerable
No suitable data were available for the outcome of SAEs.	
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire – Core 30; SAE: serious adverse event	

Overall, there are both favourable and unfavourable effects for olaparib in comparison with watchful waiting.

In terms of favourable effects for olaparib in comparison with watchful waiting, there is an indication of considerable added benefit for each of the outcomes of overall survival and recurrences.

Unfavourable effects for olaparib in comparison with watchful waiting, on the other hand, were found for non-serious/non-severe symptoms as well as side effects. For the outcome of nausea and vomiting in the outcome category of non-serious/non-severe symptoms, there is a hint of lesser benefit with the extent of minor. Regarding serious/severe side effects, olaparib was associated with an indication of greater harm, with an extent of major for the higher-level outcome of severe AEs and the included SOC of investigations, and an extent of considerable for the outcome of anaemia (SAE). For non-serious/non-severe side effects, this results in

indications of greater harm from olaparib in comparison with watchful waiting in the outcomes of discontinuation due to AEs and several specific AEs, each of considerable extent. For the outcome of SAEs, no suitable data are available, but given that progression events were disregarded, olaparib is presumably associated with greater harm in this case as well. The observed unfavourable effects regarding symptoms are based only on the shortened observation period of 24 months, while the effects on adverse events refer only to the shortened time period until treatment end plus 30 days (about 13 months).

Although the described unfavourable effects do not completely outweigh the favourable effects in the outcomes of overall survival and recurrences, they result in a downgrading of the extent of added benefit.

In summary, for the adjuvant treatment of adult patients with germline BRCA-1/2-mutated HER2-negative, high recurrence-risk, early breast cancer following prior treatment with neoadjuvant or adjuvant chemotherapy, there is an indication of minor added benefit of olaparib in comparison with the ACT of watchful waiting.

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

Table 19: Olaparib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with germline BRCA-mutant, HER2-negative, high recurrence-risk early breast cancer; after neoadjuvant or adjuvant chemotherapy[b]; adjuvant treatment	Watchful waiting[c]	Indication of minor added benefit

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, (neo)adjuvant chemotherapy and surgery are assumed to have been completed.
c. Adjuvant radiotherapy may be performed sequentially or in parallel with endocrine therapy. According to the G-BA, adjuvant radiotherapy is not part of the ACT.

ACT: appropriate comparator therapy; BRCA: breast cancer gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2

The assessment described above deviates from that by the company, which derived an indication of considerable added benefit.

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

References for English extract

Please see full dossier assessment for full reference list.

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