IQWiG Reports – Commission No. A19-57

Olaparib (breast cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Olaparib (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 October 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BRCA	breast cancer associated gene
BSA	body surface area
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
ER	oestrogen receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
PARP	poly(adenosine diphosphate-ribose) polymerase
PFS	progression-free survival
PR	progesterone receptor
PT	Preferred Term
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug olaparib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 11 July 2019.

Research question

The aim of the present report is the assessment of the added benefit of olaparib as monotherapy in patients with germline breast cancer associated gene (BRCA)1/2-mutations, who have human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer, in comparison with the appropriate comparator therapy (ACT).

For the benefit assessment, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of olaparib

Therapeutic indication	**ACT**[a]
Monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer[b, c]	**Capecitabine** or **vinorelbine** or **eribulin** or, if applicable, anthracycline- or taxane-containing therapy
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. c: Patients with hormone receptor-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy. ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The G-BA specified capecitabine or vinorelbine or eribulin or, if applicable, anthracycline- or taxane-containing therapy as ACT. The company deviated from the G-BA's specification insofar as it did not cite anthracycline- or taxane-containing therapy as part of the ACT. This had no consequence for the present assessment as the check of the company's study pool produced no additional relevant study with olaparib versus anthracycline- or taxane-containing therapy. The present benefit assessment of olaparib was conducted in comparison with the G-BA's ACT.

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

Results

Study pool and study characteristics

The OlympiAD study was included for the assessment of the added benefit. This was an open-label, multicentre, randomized, active-controlled trial on the comparison of olaparib with physician's choice chemotherapy using capecitabine or vinorelbine or eribulin.

Adult patients with (germline) mutation in BRCA1 and/or BRCA2 with HER2-negative, metastatic breast cancer were included in the study. All patients had to be pretreated with an anthracycline and a taxane (in the neoadjuvant, adjuvant or metastatic setting) unless patients had contraindications to these treatments. Hormone receptor-positive (oestrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive) breast cancer patients had to have received and progressed on at least one endocrine therapy, or have disease that the treating physician believed to be inappropriate for endocrine therapy. No more than 2 prior lines of chemotherapy for metastatic disease were allowed.

The study included a total of 302 patients, who were allocated in a 2:1 ratio either to treatment with olaparib (N = 205) or to physician's choice chemotherapy (N = 97). In both study arms, individual treatment for all patients was chosen before randomization. Physicians could choose between the treatment alternatives of capecitabine, vinorelbine and eribulin. Subsequently, the patients in the control arm received the chosen treatment and the patients in the intervention arm received olaparib. In the control arm, 41 patients received capecitabine, 16 vinorelbine, and 34 eribulin. Treatment with olaparib and with the chemotherapeutic regimens used in the control arm was largely in compliance with the Summaries of Product Characteristics (SPCs) of the drugs.

Primary outcome of the study was progression-free survival (PFS); patient-relevant secondary outcomes were overall survival, symptoms, health-related quality of life and adverse events (AEs).

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

- first data cut-off from 9 December 2016: primary analysis, planned after occurrence of about 230 PFS events
- second data cut-off from 25 September 2017: final analysis of the study, planned after about 190 deaths

The company presented results on all patient-relevant outcomes for the second data cut-off. This preplanned, final analysis of the OlympiAD study was the basis for the present benefit assessment.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes was rated as low for the OlympiAD study; the outcome-specific risk of bias for the results of all outcomes except overall survival was rated as high. On the one hand, this was due to the lack of blinding, on the other, to the incomplete observations for potentially informative reasons.

There are no usable data for the outcomes on symptoms and health-related quality of life, measured with the symptom scales and the functional scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) instrument, so that the risk of bias for the results on these outcomes is not assessed.

Results

- Overall survival

There was no statistically significant difference between the treatment groups for the outcome "overall survival".

However, there was an effect modification by the characteristic "prior chemotherapy for metastatic breast cancer". For patients with prior chemotherapy for metastatic breast cancer, there was no hint of an added benefit of olaparib in comparison with the ACT; an added benefit is therefore not proven. For patients without prior chemotherapy for metastatic breast cancer, there is an indication of an added benefit of olaparib in comparison with the ACT.

- Morbidity (EORTC QLQ-C30 symptom scales)

There are no usable data for symptoms, measured with the symptom scales of the cancer-specific instrument EORTC QLQ-C30. This resulted in no hint of an added benefit of olaparib in comparison with the ACT; an added benefit is therefore not proven.

- Health-related quality of life (EORTC QLQ-C30 functional scales)

There are no usable data for health-related quality of life, measured with the functional scales of the cancer-specific instrument EORTC QLQ-C30. This resulted in no hint of an added benefit of olaparib in comparison with the ACT; an added benefit is therefore not proven.

- Side effects

There was no statistically significant difference between the treatment groups for the outcome "serious AEs (SAEs)". This resulted in no hint of greater or lesser harm from olaparib in comparison with the ACT for this outcome; greater or lesser harm is therefore not proven.

There was a statistically significant difference in favour of olaparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin) for the outcomes "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)" and "discontinuation due to AEs". As a result, there was a hint of lesser harm from olaparib in comparison with the ACT.

Specific adverse events

In both arms, no events had occurred in the specific AEs of myelodysplastic syndrome, acute myeloid leukaemia and pneumonitis at the time point of the second data cut-off. This resulted in no hint of greater or lesser harm from olaparib in comparison with the ACT for these outcomes; greater or lesser harm is therefore not proven.

For the outcome "hand-foot syndrome" (Preferred Term [PT], AE), there was a statistically significant difference in favour of olaparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). Due to the size of the effect, there was a high certainty of conclusions of the results for this outcome despite the high risk of bias. As a result, there was an indication of lesser harm from olaparib in comparison with the ACT.

For the outcomes "neutropenia" (PT, severe AEs [CTCAE grade ≥ 3]), "vascular disorders" (System Organ Class [SOC], severe AEs CTCAE grade ≥ 3), "alopecia" (PT, AE) and "general disorders and administration site conditions" (SOC, AE), there was a statistically significant difference in favour of olaparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). As a result, there was a hint of lesser harm from olaparib in comparison with the ACT.

There was a statistically significant difference to the disadvantage of olaparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin) for the outcomes "anaemia" (PT, severe AEs CTCAE grade ≥ 3)" and "nausea" (PT, AE). As a result, there was a hint of greater harm from olaparib in comparison with the ACT.

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

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

Overall, there are both positive and negative effects of olaparib. In the outcome "overall survival", there is additionally an effect modification by the characteristic "prior chemotherapy for metastatic breast cancer". For this reason, there are separate assessments of the positive and negative effects for patients with and for patients without prior chemotherapy for metastatic breast cancer:

[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].

For patients without prior chemotherapy for metastatic breast cancer, there is an indication of considerable added benefit of olaparib in comparison with physician's choice chemotherapy (capecitabine or vinorelbine or eribulin) for overall survival. For these patients, there are additional positive effects, some of which of major extent, in the category of side effects, which were shown both in the superordinate AE outcomes and in the specific AEs. This is accompanied by 2 hints of negative effects in the outcome category of non-serious/non-severe side effects, each with minor extent. The positive effects are not weakened to an important degree by the negative effects. Overall, there is therefore an indication of considerable added benefit for patients without prior chemotherapy for metastatic breast cancer.

For patients with prior chemotherapy for metastatic breast cancer, the positive effect for the outcome "overall survival" is not present in an otherwise identical situation to the one described for patients without prior chemotherapy for metastatic breast cancer. Overall, mostly positive effects were shown under treatment with olaparib in comparison with physician's choice chemotherapy (capecitabine or vinorelbine or eribulin); these only concern the outcome category of side effects, however. The consideration of the results in other outcome categories is therefore of particular importance for the overall conclusion on the added benefit. For this patient group, there was no statistically significant difference between the treatment groups for overall survival; the point estimation for this outcome was numerically on the side of a disadvantage of olaparib. In addition, there were no usable data for the outcome categories of morbidity and health-related quality of life. Hence, the certainty of conclusions was downgraded for patients with prior chemotherapy and a hint of considerable added benefit was derived overall.

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

Table 3: Olaparib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Olaparib as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer[b, c]	**Capecitabine** or **vinorelbine** or **eribulin** or, if applicable, anthracycline- or taxane-containing therapy	▪ Patients without prior chemotherapy for metastatic breast cancer: indication of considerable added benefit[d] ▪ Patients with prior chemotherapy for metastatic breast cancer: hint of considerable added[d]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments.
c: Patients with hormone receptor-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.
d: The OlympiAD study included only patients with an ECOG PS of 0 or 1 and patients in the metastatic stage. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or to patients in the locally advanced stage.
ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of olaparib as monotherapy in adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer, in comparison with the ACT. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.

For the benefit assessment, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of olaparib

Therapeutic indication	**ACT**[a]
Monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer[b, c]	**Capecitabine** or **vinorelbine** or **eribulin** or, if applicable, anthracycline- or taxane-containing therapy
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. c: Patients with hormone receptor-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy. ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The G-BA specified capecitabine or vinorelbine or eribulin or, if applicable, anthracycline- or taxane-containing therapy as ACT. The company deviated from the G-BA's specification insofar as it did not cite anthracycline- or taxane-containing therapy as part of the ACT. This had no consequence for the present assessment as the check of the company's study pool produced no additional relevant study with olaparib versus anthracycline- or taxane-containing therapy. The present benefit assessment of olaparib was conducted in comparison with the G-BA's ACT.

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on olaparib (status: 2 May 2019)
- bibliographical literature search on olaparib (last search on 10 May 2019)
- search in trial registries for studies on olaparib (last search on 8 May 2019)

To check the completeness of the study pool:

- search in trial registries for studies on olaparib (last search on 25 July 2019)

The check identified no additional relevant study.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Study D0819C00003 (OlympiAD[b])	Yes	Yes	No
a: Study sponsored by the company. b: In the following tables, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
OlympiAD	RCT, open-label, parallel	▪ Adult patients (≥ 18 years) with metastatic breast cancer ▪ documented germline BRCA1/2-mutations ▪ pretreatment with an anthracycline and a taxane[b] unless patients had contraindications to these treatments ▪ in hormone receptor-positive breast cancer: progression on endocrine therapy or unsuitability for endocrine therapy ▪ no more than 2 prior lines of chemotherapy for metastatic disease ▪ HER2-negative ▪ ECOG PS of 0 or 1	▪ Olaparib (N = 205) ▪ Physician's choice chemotherapy[c] (N = 97)[d], thereof: ▫ capecitabine (N = 41) ▫ vinorelbine (N = 16) ▫ eribulin (N = 34)	▪ Screening: ▫ within 28 days before start of treatment[e] ▪ Treatment: ▫ until confirmed progression (RECIST criteria, version 1.1) or until another criterion for discontinuation is met[f] ▫ treatment could also be continued despite radiological progression if, in the physician's opinion, the patient continued to benefit from the treatment ▪ Observation[g]: ▫ outcome-specific, at most until death, discontinuation of participation in the study or end of study	125 study centres in Bulgaria, China, Czech Republic, France, Hungary, Italy, Japan, Mexico, Peru, Poland, Romania, Russia, South Korea, Spain, Switzerland, Taiwan, Turkey, United Kingdom, USA 3/2014–ongoing Prespecified: ▪ first data cut-off: 9 Dec 2016[h] ▪ second data cut-off: 25 Sep 2017[i] Post hoc[j]: ▪ third data cut-off: 16 Sep 2018 ▪ fourth data cut-off: 3 March 2019	Primary: PFS Secondary: overall survival, symptoms, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the study included – RCT, direct comparison: olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (continued)

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b: Administration of anthracycline/taxane could be in the neoadjuvant, adjuvant or metastatic setting.
c: The patients in the comparator arm of the study received chemotherapy chosen by the physicians for all patients before randomization. Physicians could choose between capecitabine, vinorelbine and eribulin.
d: A total of 6 patients decided after randomization to the chemotherapy arm that they did not want to start treatment and therefore did not receive any study medication.
e: Blood samples were taken in advance from patients with unknown BRCA receptor status to determine their BRCA receptor status (using the Myriad CDx test).
f: Other criteria for discontinuation: patient's decision, AEs, severe protocol violations, and death.
g: Outcome-specific information is provided in Table 8.
h: Corresponds to the primary analysis, which was planned after occurrence of about 230 PFS events.
i: Corresponds to the final analysis, which was planned after about 190 deaths.
j: Study protocol version 6.0 (2 March 2018): prolongation of follow-up by at least 2 years (recording of overall survival, subsequent therapies, SAEs and AESIs) for all patients who still consented to participation (see Section 2.7.4.3.3 of the full dossier assessment).

AE: adverse event; AESI: adverse event of specific interest; BRCA: breast cancer associated gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HER2: human epidermal growth factor receptor 2; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; SAE: serious adverse event; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study	Intervention	Comparison
OlympiAD	▪ Twice daily 300 mg olaparib (each dose consisting of 2x150 mg film-coated tablets), orally, at 12 hour intervals; total daily dose: 600 mg ▪ Recommended treatment interruptions and dose reductions due to side effects comply with the specifications of the SPC. Re-escalation after dose reduction was not allowed.	▪ One of the following chemotherapeutic regimens chosen by the physician for the individual patient before randomization: ▫ capecitabine 2500 mg/m² BSA: daily oral administration (divided into 2 doses) for 14 days, repeated every 21 days ▫ vinorelbine 30 mg/m² BSA: IV on day 1 and day 8, repeated every 21 days ▫ eribulin mesylate 1.4 mg/m² BSA or eribulin (active substance) 1.23 mg/m² BSA: IV on day 1 and day 8, repeated every 21 days ▪ dose adjustments in case of toxicities in compliance with local SPCs
	Pretreatment ▪ Patients who had received platinum-based chemotherapy (cisplatin or carboplatin as mono- or combination therapy) for advanced breast cancer were able to participate in the study if there was no proof of disease progression during platinum-based chemotherapy. ▪ pretreatment with an anthracycline and a taxane[a] unless patients had contraindications to these treatments ▪ Hormone receptor-positive breast cancer patients had to have received and progressed on at least one endocrine therapy, or have disease that the treating physician believed to be inappropriate for endocrine therapy. ▪ no more than 2 lines of cytotoxic chemotherapy for metastatic disease[b] **Non-permitted pretreatment** ▪ cytotoxic chemotherapy or non-hormonal targeted therapy within 21 days before start of treatment ▪ endocrine therapy had to be discontinued ≥ 7 days before start of treatment ▪ palliative radiotherapy had to be discontinued ≥ 14 days before start of treatment ▪ prior treatment with PARP inhibitors (including olaparib) ▪ prior allogeneic bone marrow transplantation **Concomitant treatment** ▪ any medication considered necessary for the patient's wellbeing and not interacting with the study medication could be administered at the physician's discretion (e.g. antiemetics) ▪ bisphosphonates or denosumab were allowed as long as their intake started at least 5 days prior to randomization **Non-permitted concomitant treatment** ▪ further cancer treatments (including investigational drugs) ▪ CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir ▪ Live vaccines were not to be administered during study treatment and the 30-day follow-up phase.	

a: Administration of anthracycline/taxane could be in the neoadjuvant, adjuvant or metastatic setting.
b: Previous treatments with hormonal therapy and non-hormonal targeted therapy were allowed and were not counted as a previous line of cytotoxic chemotherapy. The combination of an aromatase inhibitor and everolimus was not considered cytotoxic chemotherapy.

BSA: body surface area; CYP3A4: cytochrome P450 3A4; IV: intravenous; PARP: polyadenosine 5'diphosphoribose (poly [ADP ribose)] polymerase; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

The OlympiAD study was an open-label, multicentre, randomized, active-controlled trial on the comparison of olaparib with physician's choice chemotherapy using capecitabine or vinorelbine or eribulin. Adult patients with (germline) mutation in BRCA1 or BRCA2 with HER2-negative, metastatic breast cancer were included in the study. All patients had to be pretreated with an anthracycline and a taxane (in the neoadjuvant, adjuvant or metastatic setting) unless patients had contraindications to these treatments. Hormone receptor-positive (ER-positive and/or PR-positive) breast cancer patients had to have received and progressed on at least one endocrine therapy, or have disease that the treating physician believed to be inappropriate for endocrine therapy. No more than 2 prior lines of chemotherapy for metastatic disease were allowed. The included study population was heterogeneous with respect to pretreatment and included patients in whom the study treatment was the first-, second- or third-line therapy for metastatic breast cancer. Patients who had received platinum-based chemotherapy (cisplatin or carboplatin as mono- or combination therapy) for the advanced breast cancer were able to participate in the study if there was no proof of disease progression during platinum-based chemotherapy. The patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS of 0 or 1) and normal bone marrow and organ function.

The study included a total of 302 patients, who were allocated in a 2:1 ratio either to treatment with olaparib (N = 205) or to physician's choice chemotherapy (N = 97). In both study arms, individual treatment for all patients was chosen before randomization. Physicians could choose between the treatment alternatives of capecitabine, vinorelbine and eribulin. Subsequently, the patients in the control arm received the chosen treatment and the patients in the intervention arm received olaparib. In the control arm, 41 patients received capecitabine, 16 vinorelbine, and 34 eribulin. After randomization, a total of 6 patients in the chemotherapy arm decided against their allocated treatment and therefore did not receive any study medication. Randomization was stratified by prior chemotherapy in the metastatic stage (yes/no), oestrogen and/or progesterone receptor status (ER- and/or PR-positive/ER- and PR-negative), and prior platinum-based chemotherapy for breast cancer (yes/no).

Treatment with olaparib was conducted in compliance with the German approval status [3]. Likewise, the treatments with capecitabine and eribulin in the comparator arm were administered in compliance with the respective SPCs [4,5].

In the OlympiAD study, vinorelbine was administered at a dosage of 30 mg/m^2 body surface area (BSA) intravenously. Administration was to be administered on day 1 and day 8 of a 21-day cycle. This dosing regimen is also in line with guideline recommendations [6,7]. According to the recommendations of the SPC, vinorelbine should normally be administered at a dosage of 25 to 30 mg/m² once a week [8]. After clarification with the responsible regulatory authority (Federal Institute for Drugs and Medical Devices [BfArM]), the dosing regimen used in the OlympiAD study is compatible with the approved dosing recommendation [9]. Consequently, the vinorelbine dosing regimen used in the OlympiAD study is considered adequate.

Patients were treated until confirmed progression (Response Evaluation Criteria in Solid Tumours [RECIST] criteria, version 1.1) or fulfilment of another criterion for discontinuation (patient's decision, AEs, severe protocol violations, or death). Treatment could also be continued despite radiological progression if, in the physician's opinion, the patient continued to benefit from the treatment. Subsequent therapies after termination of the study medication were not specified in the study protocol, so that any medical intervention was freely determined at the discretion of the treating physician together with the patient. The subsequent therapies in the OlympiAD study were largely evenly distributed between the study arms (see Appendix C, Table 26, of the full dossier assessment). The study did not provide for a planned switching of patients from the control arm to treatment with olaparib. Nevertheless, some of the patients included in the chemotherapy arm received subsequent therapy with a poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor. As only 2 patients were receiving olaparib at the time of the final analysis (25 September 2017), this was overall not considered to be relevant for the benefit assessment.

Primary outcome of the study was PFS; patient-relevant secondary outcomes were overall survival, symptoms, health-related quality of life and AEs.

Data cut-offs

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

- first data cut-off from 9 December 2016: primary analysis, planned after occurrence of about 230 PFS events
- second data cut-off from 25 September 2017: final analysis of the study, planned after about 190 deaths

The company presented results on all patient-relevant outcomes for the second data cut-off. This preplanned, final analysis of the OlympiAD study was the basis for the present benefit assessment.

In addition, on 2 March 2018, following a protocol change, the follow-up of the study was extended by at least 2 years for all patients who continued to actively consent to further study participation. Based on the data of this extension phase, the company presented supplementary results on 2 further data cut-offs:

- third data cut-off from 16 September 2018: data cut-off of the extension phase planned post hoc
- fourth data cut-off from 3 March 2019: data cut-off of the extension phase planned post hoc

These 2 data cut-offs planned post hoc were not included in the benefit assessment, as not all patients or their relatives subsequently agreed to the extended recording of survival, and therefore the analysis was not based on the intention-to-treat (ITT) population. In addition, the

number of patients who agreed to continued participation in the study varied between the arms. Further explanations can be found in Section 2.7.4.3.3 of the full dossier assessment.

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study **Outcome category** **Outcome**	**Planned follow-up observation**
OlympiAD (second data cut-off: 25 September 2017)	
Mortality	
Overall survival	▪ Every 8 weeks ± 7 days after objective radiological progression until death, withdrawal of consent, lost to follow-up or final survival time analysis
Morbidity	
EORTC QLQ-C30 (symptom scales)	▪ Every 6 weeks until progression
Health-related quality of life	
EORTC QLQ-C30 (functional scales)	▪ Every 6 weeks until progression
Side effects	▪
All outcomes in the category "side effects"	▪ Until 30 days after the last dose of the study medication
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; vs.: versus	

Except for the outcome "overall survival", the observation periods for the outcomes were systematically shortened because they were recorded only until progression (morbidity, health-related quality of life) or for the period of treatment with the study medication plus 30 days (side effects). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for "survival".

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

Table 9: Characteristics of the study population – olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study Characteristics Category	**Olaparib**	**Physician's choice chemotherapy[a]**
OlympiAD	N[b] = 205	N[b] = 97
Age [years], mean (SD)	45 (11)	46 (10)
Age groups, n (%)		
< 50 years	138 (67.3)	63 (64.9)
≥ 50 years to < 65 years	56 (27.3)	30 (30.9)
≥ 65 years	11 (5.4)	4 (4.1)
Sex (female/male), n (%)	200 (97.6)/5 (2.4)	95 (97.9)/2 (2.1)
Region, n (%)		
Europe	97 (47.3[c])	45 (46.4[c])
Asia	59 (28.8[c])	28 (28.9[c])
North and South America	49 (23.9[c])	24 (24.7[c])
Family origin, n (%)		
Caucasian family origin	134 (65.4)	63 (64.9)
Asian family origin	66 (32.2)	28 (28.9)
Other[d]	6 (2.9)[c]	7 (7.2)[c]
ECOG PS, n (%)		
0	148 (72.2)	62 (63.9)
1	57 (27.8)	35 (36.1)
BRCA mutation (confirmed with Myriad CDx test)		
BRCA1	114 (55.6)	50 (51.5)
BRCA2	84 (41.0)	45 (46.4)
Both	4 (2.0)	0 (0.0)
Not reported	3 (1.5)	2 (2.1)
(Hormone) receptor status, n (%)		
ER- and/or PR-positive, HER2-negative	103 (50.2)	49 (50.5)
ER- and PR-negative, HER2-negative (TNBC)	102 (49.8)	48 (49.5)
Disease duration: time between first diagnosis and randomization [years], mean (SD)	4.8 (4.2)	4.7 (3.5)
Disease duration: time between last disease progression and randomization [days], median [min; max]	36 [1; 2610]	41 [3; 704]
Disease classification, n (%)		
Metastatic	205 (100)	97 (100)
Locally advanced	0 (0)	0 (0)

(continued)

Table 9: Characteristics of the study population – olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (continued)

Study Characteristics Category	Olaparib	Physician's choice chemotherapy[a]
OlympiAD	N[b] = 205	N[b] = 97
Number of metastatic sites at baseline, n (%)		
1	46 (22.4)	25 (25.8)
≥ 2	159 (77.6)	72 (74.2)
Primary location of the metastasis at baseline, n (%)		
Only bone or locomotor system	16 (7.8)	6 (6.2)
Other[e]	189 (92.2)	91 (93.8)
Prior chemotherapy for metastatic breast cancer, n (%)		
Yes	146 (71.2)	69 (71.1)
No	59 (28.8)	28 (28.9)
Prior platinum-based chemotherapy for breast cancer, n (%)		
Yes	60 (29.3)	26 (26.8)
No	145 (70.7)	71 (73.2)
Treatment discontinuation[f], n (%)	179 (87.3)	91 (93.8[c])
Study discontinuation[f, g], n (%)	10 (4.9)[c]	7 (7.2)

a: Capecitabine or vinorelbine or eribulin at the physician's discretion.
b: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c: Institute's calculation.
d: Includes "black or Afro-American", "native Indians or native Alaskans", "other" and "unknown".
e: Includes patients with visceral metastasis (including adrenal glands, bladder, CNS, oesophagus, liver, lungs, peritoneum, pleura, kidneys, small bowel, stomach, pancreas, thyroid, large bowel, ovaries, bile ducts, ascites, pericardial effusion, spleen or pleural effusion) with or without metastasis in the bones/the locomotor system.
f: Second data cut-off: 25 September 2017.
g: Without deaths; reasons for discontinuation were: "patient's decision", "lost to follow-up" and "other".
BRCA: breast cancer associated gene; CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; max: maximum; min: minimum; n: number of patients in the category, N: number of randomized patients; PR: progesterone receptor; RCT: randomized controlled trial; SD: standard deviation; TNBC: triple-negative breast cancer, vs.: versus

The characteristics of the included study population were largely comparable between both treatment arms.

The mean age of the patients was about 45 years. Both women and a small proportion of men (5 patients in the olaparib arm and 2 patients in the comparator group) were included in the study. About half of the patients included came from Europe and about a quarter each from Asia or North and South America. Regarding the ECOG PS, the majority of patients had a good

general condition (72.2% versus 63.9%). About 53% of the patients had a BRCA1 mutation, about 44% had a BRCA2 mutation, and about 2% had mutations in both BRCA genes. Approximately half of the population were hormone-receptor-positive and half of the population were hormone-receptor-negative (and thus triple-negative). The mean duration of disease since first diagnosis was almost 5 years in both study arms. The majority of the patients included had more than 2 metastases at baseline (about 76% in both study arms). All patients in the study were in the metastatic stage at baseline, so that the study as a whole did not provide any results from patients in the locally advanced stage. In terms of prior therapy, approximately 71% of the patients in both arms had received prior chemotherapy for metastatic breast cancer and approximately 28% had received platinum-based chemotherapy for breast cancer.

Since no patients with ECOG PS 2 and higher and no patients with breast cancer in the locally advanced stage were included in the study, it remains unclear whether the study results can be transferred to these patients, who are also comprised by the therapeutic indication to be assessed.

Table 10 shows the mean and median treatment durations of the patients and the median observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study **Duration of the study phase** **Outcome category**	**Olaparib**	**Physician's choice chemotherapy[a]**
OlympiAD (second data cut-off, 25 September 2017)	N = 205	N = 91
Treatment duration [days]		
Median [min; max]	251 [14; 1165]	105 [21; 759]
Mean (SD)	316 (249)	156 (151)
Observation period [months]	N = 205	N = 97
Overall survival		
Median [min; max]	18.9 [ND]	15.5 [ND]
Mean (SD)	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND

a: Capecitabine or vinorelbine or eribulin at the physician's discretion.
max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

In the OlympiAD study, the median treatment duration in the olaparib arm was approximately 2.5 times longer than in the chemotherapy arm (251 days versus 105 days).

The median observation period for the outcome "overall survival" in the olaparib arm was approximately 3 months longer than in the chemotherapy arm (18.9 versus 15.5 months). There was no information on the observation period for the outcomes on morbidity, health-related quality of life and side effects; according to the study protocol, however, these were only recorded until progression (morbidity and health related quality of life) or until 30 days after the end of treatment (side effects). For the side effect outcomes, it is assumed that there was a similarly large difference between the treatment arms for the observation period as for the treatment duration, as these outcomes were observed only up to 30 days after the end of treatment (for planned follow-up, see Table 8). Based on the fact that a large proportion of patients discontinued treatment due to progression, it can also be assumed for the outcomes of the category of morbidity and health-related quality of life that there was a relevant difference in observation periods between the treatment arms.

Risk of bias across outcomes (study level)

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

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
OlympiAD	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

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

Limitations resulting from the open-label study design are described in Section 2.4.2 with the outcome-specific risk of bias.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms, recorded with the EORTC QLQ-C30 symptom scales
- Health-related quality of life
  - EORTC QLQ-C30, functional scales
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - myelodysplastic syndrome (PT, severe AEs)
  - acute myeloid leukaemia (PT, severe AEs)
  - pneumonitis (PT, AE)
  - hand-foot syndrome (PT, AE)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.4.3.2 of the full dossier assessment).

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

Table 12: Matrix of outcomes – RCT, direct comparison: olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30 symptom scales)	Health-related quality of life (EORTC QLQ-C30 functional scales)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Myelodysplastic syndrome (PT, severe AEs)	Acute myeloid leukaemia (PT, severe AEs)	Pneumonitis (PT, AE)	Hand-foot syndrome (PT, AE)	Further specific AEs[a]
OlympiAD (second data cut-off: 25 September 2017)	Yes	No[b]	No[b]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: The following events are considered (MedDRA coding): "anaemia (PT, severe AEs CTCAE grade ≥ 3)", "neutropenia (PT, severe AEs CTCAE grade ≥ 3)", "vascular disorders (SOC, severe AEs CTCAE grade ≥ 3)", "nausea (PT, AE)", "alopecia (PT, AE)", "general disorders and administration site conditions (SOC, AE)".

b: No usable data are available; for reasons, see Section 2.7.4.3.2 of the full dossier assessment.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.4.2 Risk of bias

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

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study		Outcomes										
	Study level	Overall survival	Symptoms (EORTC QLQ-C30 symptom scales)	Health-related quality of life (EORTC QLQ-C30 functional scales)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Myelodysplastic syndrome (PT, severe AEs)	Acute myeloid leukaemia (PT, severe AEs)	Pneumonitis (PT, AE)	Hand-foot syndrome (PT, AE)	Further specific AEs[a]
OlympiAD (second data cut-off: 25 Sep 2017)	L	L	–[b]	–[b]	H[c]	H[d]	H[c]	H[c]	H[c]	H[c, d]	H[c, d]	H[c, d]

a: The following events are considered (MedDRA coding): "anaemia (PT, severe AEs CTCAE grade ≥ 3)", "neutropenia (PT, severe AEs CTCAE grade ≥ 3)", "vascular disorders (SOC, severe AEs CTCAE grade ≥ 3)", "nausea (PT, AE)", "alopecia (PT, AE)", "general disorders and administration site conditions (SOC, AE)".
b: No usable data are available; for reasons, see Section 2.7.4.3.2 of the full dossier assessment.
c: Incomplete observations for potentially informative reasons with large difference in the median treatment duration (and hence observation period) between the olaparib arm (251 days) and the chemotherapy arm (105 days).
d: Lack of blinding in subjective recording of outcomes (exception: severe and serious specific AEs) or lack of blinding in subjective decision for discontinuation (discontinuation due to AEs).
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

No usable data were available for the outcomes on symptoms and health-related quality of life, measured with the symptom scales or with the functional scales of the EORTC QLQ-C30 instrument (see Section 2.7.4.3.2 of the full dossier assessment). The risk of bias for the results on these outcomes was therefore not assessed.

In accordance with the company, the risk of bias of the results on overall survival was rated as low.

The risk of bias of the results on the outcomes of the category of side effects was rated as high. For the results of the non-severe or the non-serious AEs of the OlympiAD study (pneumonitis, hand-foot syndrome, and some of the further specific AEs) and for the results of the outcome "discontinuation due to AEs", this was due to the open-label study design. With the exception of the outcome "discontinuation due to AEs", the risk of bias for the results of all AE outcomes

was (additionally) rated as high due to incomplete observations for potentially informative reasons. This is due to the fact that the observation period for the results on side effects was largely determined by disease progression (see Section 2.7.4.2 of the full dossier assessment).

The company conducted a joint assessment of the risk of bias of the results on the AE outcomes because it considered the recording to be uniform. With this approach, the company also arrived at the assessment of a high risk of bias, which it explained only with the open-label study design, however.

2.4.3 Results

Table 14 summarizes the results on the comparison of olaparib in patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

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

Only the results of the second data cut-off (25 September 2017), which was the preplanned, final data cut-off of the study, were included in the benefit assessment (see also Section 2.3.1 and Section 2.7.4.3.3 of the full dossier assessment).

Table 14: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study Outcome category Outcome	Olaparib		Physician's choice chemotherapy[a]		Olaparib vs. physician's choice chemotherapy[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
OlympiAD (second data cut-off: 25 September 2017)					
Mortality					
Overall survival	205	19.25 [17.15; 21.55] 130 (63.4)	97	17.12 [13.86; 21.85] 62 (63.9)	0.90 [0.66; 1.23]; 0.513[c]
Morbidity					
EORTC QLQ-C30 symptom scales					
			No usable data[d]		
Health-related quality of life					
EORTC QLQ-C30 functional scales					
			No usable data[d]		
Side effects					
AEs (supplementary information)	205	0.2 [ND] 200 (97.6)	91	0.2 [ND] 87 (95.6)	–
SAEs	205	NA [ND] 34 (16.6)	91	NA [ND] 15 (16.5)	0.55 [0.28; 1.11]; 0.098
Severe AEs (CTCAE grade ≥ 3)	205	NA [ND] 78 (38.0)	91	NA [ND] 45 (49.5)	0.45 [0.29; 0.69]; < 0.001
Discontinuation due to AEs	205	NA [ND] 10 (4.9)	91	22.3 [ND] 7 (7.7)	0.29 [0.09; 0.95]; 0.042
Myelodysplastic syndrome (PT, severe AEs)	205	0 (0)	91	0 (0)	NC
Acute myeloid leukaemia (PT, severe AEs)	205	0 (0)	91	0 (0)	NC
Pneumonitis (PT, AE)	205	0 (0)	91	0 (0)	NC
Hand-foot syndrome (PT, AE)	205	NA [ND] 1 (0.5)	91	NA [ND] 19 (20.9)	0.02 [0.01; 0.07]; < 0.001
Anaemia (PT, severe AEs CTCAE grade ≥ 3)	205	NA [ND] 32 (15.6)	91	NA [ND] 4 (4.4)	2.22 [1.05; 4.69]; 0.037
Neutropenia (PT, severe AEs CTCAE grade ≥ 3)	205	NA [ND] 11 (5.4)	91	NA [ND] 12 (13.2)	0.32 [0.13; 0.79]; 0.014
Vascular disorders (SOC, severe AEs CTCAE grade ≥ 3)	205	NA [ND] 2 (1.0)	91	NA [ND] 5 (5.5)	0.03 [0.00; 0.22]; < 0.001

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (continued)

Study Outcome category Outcome	Olaparib		Physician's choice chemotherapy[a]		Olaparib vs. physician's choice chemotherapy[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
Side effects					
Nausea (PT, AE)	205	1.6 [ND] 119 (58.0)	91	14.5 [ND] 32 (35.2)	1.69 [1.20; 2.37]; 0.003
Alopecia (PT, AE)	205	NA [ND] 7 (3.4)	91	NA [ND] 12 (13.2)	0.12 [0.04; 0.34]; < 0.001
General disorders and administration site conditions (SOC, AE)	205	7.9 [ND] 106 (51.7)	91	1.5 [ND] 56 (61.5)	0.58 [0.40; 0.83]; 0.003

a: Capecitabine or vinorelbine or eribulin at the physician's discretion.
b: HR and CI from log-rank test statistics; p-value: log-rank test; each without stratification unless stated otherwise.
c: HR and CI from log-rank test statistics; p-value: log-rank test; each stratified by prior chemotherapy for metastatic breast cancer, oestrogen receptor and/or progesterone receptor status and prior platinum-based chemotherapy for breast cancer.
d: For reasons, see Section 2.7.4.3.2 of the full dossier assessment.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be determined for the outcomes "overall survival" and "hand-foot syndrome", and, due to the high risk of bias, at most hints for the other outcomes (see also Section 2.4.2 and Section 2.7.4.2 of the full dossier assessment).

Mortality

Overall survival

There was no statistically significant difference between the treatment groups for the outcome "overall survival".

However, there was an effect modification by the characteristic "prior chemotherapy for metastatic breast cancer". For patients with prior chemotherapy for metastatic breast cancer, there was no hint of an added benefit of olaparib in comparison with the ACT; an added benefit is

therefore not proven. For patients without prior chemotherapy for metastatic breast cancer, there is an indication of an added benefit of olaparib in comparison with the ACT (see Section 2.4.4).

This deviates from the assessment of the company, which considered an added benefit as overall not proven for the outcome "overall survival". Although the company described the effect modification, it rated all effect modifications as not relevant for the conclusion and therefore did not consider them in the derivation of the added benefit (see Section 2.7.4.3.4 of the full dossier assessment).

Morbidity

Symptom scales of the EORTC QLQ-C30

There were no usable data for symptoms, measured with the symptom scales of the cancer-specific instrument EORTC QLQ-C30 (see Section 2.7.4.3.2 of the full dossier assessment). This resulted in no hint of an added benefit of olaparib in comparison with the ACT; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived a hint of an added benefit for symptom outcomes using the symptom scales of the cancer-specific instrument EORTC QLQ-C30 based on the operationalizations across all scales used by the company.

Health-related quality of life

Functional scales of the EORTC QLQ-C30

There were no usable data for health-related quality of life, measured with the functional scales of the cancer-specific instrument EORTC QLQ-C30 (see Section 2.7.4.3.2 of the full dossier assessment). This resulted in no hint of an added benefit of olaparib in comparison with the ACT; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived a hint of an added benefit for outcomes of health-related quality of life using the functional scales of the cancer-specific instrument EORTC QLQ-C30 based on the operationalizations across all scales used by the company.

Side effects

The company did not conduct an outcome-specific derivation of the added benefit for the outcomes of the category of side effects, but derived a hint of an added benefit across all AE outcomes. Hence, the company's outcome-specific assessment is not described below.

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". This resulted in no hint of greater or lesser harm from olaparib in comparison with the ACT for this outcome; greater or lesser harm is therefore not proven.

Severe adverse events (CTCAE grade ≥ 3)

For the outcome "severe AEs (CTCAE grade ≥ 3)", there was a statistically significant difference in favour of olaparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). As a result, there was a hint of lesser harm from olaparib in comparison with the ACT.

Discontinuation due to adverse events

For the outcome "discontinuation due to AEs", there was a statistically significant difference in favour of olaparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). As a result, there was a hint of lesser harm from olaparib in comparison with the ACT.

Myelodysplastic syndrome, acute myeloid leukaemia and pneumonitis

In both arms, no events had occurred in the specific AEs of myelodysplastic syndrome, acute myeloid leukaemia and pneumonitis at the time point of the second data cut-off. This resulted in no hint of greater or lesser harm from olaparib in comparison with the ACT for these outcomes; greater or lesser harm is therefore not proven.

Hand-foot syndrome (PT, adverse event)

For the outcome "hand-foot syndrome (PT, AE)", there was a statistically significant difference in favour of olaparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). Due to the size of the effect, there was a high certainty of conclusions for this outcome despite high risk of bias of the results. As a result, there was an indication of lesser harm from olaparib in comparison with the ACT.

Anaemia (PT, severe adverse events CTCAE grade ≥ 3)

For the outcome "anaemia (PT, severe AEs CTCAE grade ≥ 3)", there was a statistically significant difference to the disadvantage of olaparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). As a result, there was a hint of greater harm from olaparib in comparison with the ACT.

Neutropenia (PT, severe adverse events CTCAE grade ≥ 3)

For the outcome "neutropenia (PT, severe AEs CTCAE grade ≥ 3)", there was a statistically significant difference in favour of olaparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). As a result, there was a hint of lesser harm from olaparib in comparison with the ACT.

Vascular disorders (SOC, severe adverse events CTCAE grade ≥ 3)

For the outcome "vascular disorders (SOC, severe AEs CTCAE grade ≥ 3)", there was a statistically significant difference in favour of olaparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). As a result, there was a hint of lesser harm from olaparib in comparison with the ACT.

Nausea (PT, adverse event)

For the outcome "nausea (PT, AE)", there was a statistically significant difference to the disadvantage of olaparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). As a result, there was a hint of greater harm from olaparib in comparison with the ACT.

Alopecia (PT, adverse event)

For the outcome "alopecia (PT, AE)", there was a statistically significant difference in favour of olaparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). As a result, there was a hint of lesser harm from olaparib in comparison with the ACT.

General disorders and administration site conditions (SOC, adverse event)

For the outcome "general disorders and administration site conditions (SOC, AE)", there was a statistically significant difference in favour of olaparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). As a result, there was a hint of lesser harm from olaparib in comparison with the ACT.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present assessment:

- prior chemotherapy for metastatic breast cancer (yes/no)
- hormone receptor status (ER- and/or PR-positive/ER- and PR-negative)
- BRCA mutation type (1/2/1 and 2)
- age at randomization (< 65 years/≥ 65 years)
- sex (men/women)
- region (Asia/Europe/other)
- family origin (Caucasian family origin/other)

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

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

Complete subgroup analyses for the outcomes of the categories of mortality and side effects were available for the benefit assessment. Since no usable data were available for the EORTC questionnaire, the subgroup analyses for the outcomes concerned were also not considered.

Table 15 presents the subgroup results of olaparib in comparison with physician's choice chemotherapy (capecitabine or vinorelbine or eribulin).

Table 15: Subgroups (mortality, time to event) – RCT, direct comparison: olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study Outcome	Olaparib		Physician's choice chemotherapy[a]		Olaparib vs. physician's choice chemotherapya	
Characteristic Subgroup	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][b, c]	p-value[d]
OlympiAD (second data cut-off: 25 September 2017)						
Overall survival						
Prior chemotherapy for metastatic breast cancer						
Yes	146	18.8 [16.3; 20.4] 100 (68.5)	69	17.2 [13.5; 27.2] 41 (59.4)	1.13 [0.79; 1.64]	0.519
No	59	22.6 [17.8; NC] 30 (50.8)	28	14.7 [11.0; 21.3] 21 (75.0)	0.51 [0.29; 0.90]	0.013
Total					Interaction[e]:	0.0215

a: Capecitabine or vinorelbine or eribulin.
b: HR and CI: Cox proportional hazards model without stratification factors.
c: In Module 4 A of the dossier, the company used a different methodology for the effect estimation than in the CSR, the data from the prespecified subgroup analysis of the CSR are presented (see also Section 2.7.4.3.4 of the full dossier assessment).
d: p-value: log-rank test without stratification.
e: Likelihood ratio test.
CI: confidence interval; CSR: clinical study report; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Mortality

The available subgroup analyses resulted in an effect modification for the outcome "overall survival" by the characteristic "prior chemotherapy for metastatic breast cancer".

For patients with prior chemotherapy for metastatic breast cancer, there was no statistically significant difference between the treatment groups for the outcome "overall survival". For this subgroup, this resulted in no hint of an added benefit of olaparib in comparison with the ACT; an added benefit is therefore not proven.

For patients without prior chemotherapy for metastatic breast cancer, there was a statistically significant difference in favour of olaparib in comparison with physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). As a result, there was an indication of an added benefit of olaparib in comparison with the ACT for this subgroup.

This deviates from the assessment of the company, which did not consider the result of the subgroup analysis in the derivation of the added benefit. Although the company described the effect modification as "remarkable in this therapeutic situation, since no comparable results

have been shown so far", it classified the subgroup analyses as overall not relevant for the conclusion (see Section 2.7.4.3.4 of the full dossier assessment).

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. 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.

2.5.1 Assessment of the added benefit at outcome level

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

Determination of the outcome category for outcomes on side effects

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were serious/severe or non-serious/non-severe. In case of a statistically significant effect, these outcomes are allocated to an outcome category and the explanation for this allocation is provided.

Discontinuation due to adverse events

It can be inferred from the study documents that the majority of the AEs that resulted in treatment discontinuation were severe (CTCAE grade ≥ 3). Hence, the outcome "discontinuation due to AEs" was allocated to the category of serious/severe side effects.

Nausea (PT, adverse event)

It can be inferred from the study documents that the majority of the events in this outcome were non-severe (CTCAE grade < 3). The outcome "nausea" was therefore allocated to the category of non-serious/non-severe side effects.

Hand-foot syndrome (PT, adverse event)

It can be inferred from the study documents that the majority of the events in this outcome were non-severe (CTCAE grade < 3). Only 2 of the 19 patients in the chemotherapy arm had a CTCAE grade 3 event. The outcome "hand-foot syndrome" was therefore allocated to the category of non-serious/non-severe side effects.

General disorders and administration site conditions (SOC, adverse event)

It can be inferred from the study documents that the majority of the AEs in this outcome were non-severe (CTCAE grade < 3). The outcome "general disorders and administration site conditions" was therefore allocated to the category of non-serious/non-severe side effects.

Table 16: Extent of added benefit at outcome level: olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Olaparib vs. physician's choice chemotherapy[a]** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival		
Prior chemotherapy for metastatic breast cancer		
Yes	18.8 vs. 17.2 months HR: 1.13 [0.79; 1.64]; 0.519	Lesser benefit/added benefit not proven
No	22.6 vs. 14.7 months HR: 0.51 [0.29; 0.90]; 0.013 probability: "indication"	Outcome category: "mortality" $0.85 \leq CI_u < 0.95$ Added benefit, extent: "considerable"
Morbidity		
EORTC QLQ-C30 symptom scales		
	No usable data[d]	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 functional scales		
	No usable data[d]	Lesser benefit/added benefit not proven
Side effects		
SAEs	NA vs. NA HR: 0.55 [0.28; 1.11]; 0.098	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	NA vs. NA HR: 0.45 [0.29; 0.69]; < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% lesser harm, extent: "major"
Discontinuation due to AEs	NA vs. 22.3 months HR: 0.29 [0.09; 0.95]; 0.042 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Myelodysplastic syndrome (PT, severe AEs)	Proportions of events: 0% vs. 0% HR: NC[e]	Greater/lesser harm not proven
Acute myeloid leukaemia (PT, severe AEs)	Proportions of events: 0% vs. 0% HR: NC[e]	Greater/lesser harm not proven
Pneumonitis (PT, AE)	Proportions of events: 0% vs. 0% HR: NC[e]	Greater/lesser harm not proven
Hand-foot syndrome (PT, AE)	NA vs. NA HR: 0.02 [0.01; 0.07]; < 0.001 probability: "indication"[f]	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"

(continued)

Table 16: Extent of added benefit at outcome level: olaparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (continued)

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Olaparib vs. physician's choice chemotherapy[a]** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Anaemia (PT, severe AEs CTCAE grade ≥ 3)	NA vs. NA HR: 2.22 [1.05; 4.69]; 0.037 HR: 0.45 [0.21; 0.95][g] probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Neutropenia (PT, severe AEs CTCAE grade ≥ 3)	NA vs. NA HR: 0.32 [0.13; 0.79]; 0.014 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Vascular disorders (SOC, severe AEs CTCAE grade ≥ 3)	NA vs. NA HR: 0.03 [0.00; 0.22]; < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% lesser harm, extent: "major"
Nausea (PT, AE)	1.6 vs. 14.5 months HR: 1.69 [1.20; 2.37]; 0.003 HR: 0.59 [0.42; 0.83][g] probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"
Alopecia (PT, AE)	NA vs. NA HR: 0.12 [0.04; 0.34]; < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
General disorders and administration site conditions (SOC, AE)	7.9 vs. 1.5 months HR: 0.58 [0.40; 0.83]; 0.003 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.90$ lesser harm, extent: "minor"

a: Capecitabine or vinorelbine or eribulin at the physician's discretion.
b: Probability provided if there is a statistically significant and relevant effect.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: No usable data are available; for reasons, see Section 2.7.4.3.2 of the full dossier assessment.
e: Since no events occurred in either study arm, the HR cannot be estimated.
f: The certainty of conclusions is not downgraded despite the high risk of bias (see Section 2.7.4.2 of the full dossier assessment).
g: Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; NA: not achieved; NC: not calculable; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.5.2 Overall conclusion on added benefit

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

Table 17: Positive and negative effects from the assessment of olaparib in comparison with the ACT

Positive effects	**Negative effects**
Mortality ▪ overall survival ▫ for patients without prior chemotherapy for metastatic breast cancer: indication of an added benefit – extent: “considerable”	
Serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3): hint of lesser harm – extent: “major” ▪ discontinuation due to AEs: hint of lesser harm – extent “minor” ▪ neutropenia (CTCAE grade ≥ 3): hint of lesser harm – extent “considerable” ▪ vascular disorders (CTCAE grade ≥ 3): hint of lesser harm – extent: “major”	Serious/severe side effects ▪ anaemia (CTCAE grade ≥ 3): hint of greater harm – extent: “minor”
Non-serious/non-severe side effects ▪ hand-foot syndrome: indication of lesser harm – extent: “considerable” ▪ alopecia: hint of lesser harm – extent: “considerable” ▪ general disorders and administration site conditions: hint of lesser harm – extent: “minor”	Non-serious/non-severe side effects ▪ nausea: hint of greater harm – extent: “minor”
There are no usable data for morbidity and health-related quality of life (see Section 2.7.4.3.2 of the full dossier assessment).	
ACT: appropriate comparator therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

Overall, there are both positive and negative effects of olaparib. In the outcome “overall survival”, there is additionally an effect modification by the characteristic “prior chemotherapy for metastatic breast cancer”. For this reason, there are separate assessments of the positive and negative effects for patients with and for patients without prior chemotherapy for metastatic breast cancer:

For patients without prior chemotherapy for metastatic breast cancer, there is an indication of considerable added benefit of olaparib in comparison with physician’s choice chemotherapy (capecitabine or vinorelbine or eribulin) for overall survival. For these patients, there are additional positive effects, some of which of major extent, in the category of side effects, which were shown both in the superordinate AE outcomes and in the specific AEs. This is accompanied by 2 hints of negative effects in the outcome category of non-serious/non-severe side effects, each with minor extent. The positive effects are not weakened to an important

degree by the negative effects. Overall, there is therefore an indication of considerable added benefit for patients without prior chemotherapy for metastatic breast cancer.

For patients with prior chemotherapy for metastatic breast cancer, the positive effect for the outcome "overall survival" is not present in an otherwise identical situation to the one described for patients without prior chemotherapy for metastatic breast cancer. Overall, mostly positive effects were shown under treatment with olaparib in comparison with physician's choice chemotherapy (capecitabine or vinorelbine or eribulin); these only concern the outcome category of side effects, however. The consideration of the results in other outcome categories is therefore of particular importance for the overall conclusion on the added benefit. For this patient group, there was no statistically significant difference between the treatment groups for overall survival; the point estimation for this outcome was numerically on the side of a disadvantage of olaparib. In addition, there were no usable data for the outcome categories of morbidity and health-related quality of life. Hence, the certainty of conclusions was downgraded for patients with prior chemotherapy and a hint of considerable added benefit was derived overall.

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

Table 18: Olaparib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Olaparib as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer[b, c]	**Capecitabine** or **vinorelbine** or **eribulin** or, if applicable, anthracycline- or taxane-containing therapy	▪ Patients without prior chemotherapy for metastatic breast cancer: indication of considerable added benefit[d] ▪ Patients with prior chemotherapy for metastatic breast cancer: hint of considerable added[d]
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. c: Patients with hormone receptor-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy. d: The OlympiAD study included only patients with an ECOG PS of 0 or 1 and patients in the metastatic stage. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or to patients in the locally advanced stage. ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2		

The assessment described above deviates from that of the company insofar as the company did not consider the effect modification by the characteristic "prior chemotherapy for metastatic

breast cancer" in the derivation of the added benefit and derived an indication of a considerable added benefit for all patients.

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

2.6 List of included studies

OlympiAD

AstraZeneca. Assessment of the efficacy and safety of olaparib monotherapy versus physicians choice chemotherapy in the treatment of metastatic breast cancer patients with germline BRCA1/2 mutations (OlympiAD): study results [online]. In: ClinicalTrials.gov. 07.06.2019 [Accessed: 31.07.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02000622?show_locs=Y.

AstraZeneca. A phase 3, open label, randomised, controlled, multi-centre study to assess the efficacy and safety of olaparib monotherapy versus physicians choice chemotherapy in the treatment of metastatic breast cancer patients with germline BRCA1/2 mutations [online]. In: JAPIC Clinical Trials Information. 17.12.2018 [Accessed: 31.07.2019]. URL: https://www.clinicaltrials.jp/cti-user/trial/ShowDirect.jsp?japicId=JapicCTI-142527.

AstraZeneca. A phase III, open label, randomised, controlled, multi-centre study to assess the efficacy and safety of olaparib monotherapy versus physician's choice chemotherapy in the treatment of metastatic breast cancer patients with germline BRCA1/2 mutations [online]. In: Clinical Trials Peruvian Registry. 26.02.2019 [Accessed: 31.07.2019]. URL: https://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=033-14.

AstraZeneca. A phase III, open label, randomised, controlled, multi-centre study to assess the efficacy and safety of olaparib monotherapy versus physician's choice chemotherapy in the treatment of metastatic breast cancer patients with germline BRCA1/2 mutations [online]. In: EU Clinical Trials Register. [Accessed: 31.07.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-005137-20.

AstraZeneca. Assessment of the efficacy and safety of olaparib monotherapy versus physicians choice chemotherapy in the treatment of metastatic breast cancer patients with germline BRCA1/2 mutations (OlympiAD): study details [online]. In: ClinicalTrials.gov. 07.06.2019 [Accessed: 31.07.2019]. URL: https://ClinicalTrials.gov/show/NCT02000622.

AstraZeneca. A phase III, open label, randomised, controlled, multi-centre study to assess the efficacy and safety of olaparib monotherapy versus physician's choice chemotherapy in the treatment of metastatic breast cancer patients with germline BRCA1/2 mutations: study D0819C00003; clinical study report [unpublished]. 2017.

AstraZeneca. A phase III, open label, randomised, controlled, multi-centre study to assess the efficacy and safety of olaparib monotherapy versus physician's choice chemotherapy in the treatment of metastatic breast cancer patients with germline BRCA1/2 mutations: final analysis of overall survival and safety update; study D0819C00003; clinical study report addendum [unpublished]. 2018.

AstraZeneca. A phase III, open label, randomised, controlled, multi-centre study to assess the efficacy and safety of olaparib monotherapy versus physician's choice chemotherapy in the treatment of metastatic breast cancer patients with germline BRCA1/2 mutations; study D0819C00003; Zusatzanalysen [unpublished]. 2019.

AstraZeneca. A phase III, open label, randomised, controlled, multi-centre study to assess the efficacy and safety of olaparib monotherapy versus physician's choice chemotherapy in the treatment of metastatic breast cancer patients with germline BRCA1/2 mutations; study D0819C00003; outputs: tables and figures (1st and 2nd extended OS) [unpublished]. 2019.

Robson ME, Im SA, Senkus E, Xu B, Domchek SM, Masuda N et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med 2017; 377(6): 523-533.

Robson ME, Tung N, Conte P, Im SA, Senkus E, Xu B et al. OlympiAD final overall survival and tolerability results: olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol 2019; 30(4): 558-566.

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Please see full dossier assessment for full reference list.

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

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