IQWiG Reports – Commission No. A19-56

Olaparib (ovarian cancer: first-line maintenance) –

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 (Ovarialkarzinom; Erstlinie Erhaltung) – 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
BRCA	breast cancer associated gene
CA-125	Cancer-Antigen 125
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D	European Quality of Life5 Dimensions
FACT-O	Functional Assessment of Cancer Therapy-Ovarian
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
gBRCA	germline BRCA mutation
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MRI	magnetic resonance imaging
PARP	poly(adenosine diphosphate-ribose) polymerase
PET	positron emission tomography
PFS	progression-free survival
PFS	progression-free survival
PR	partial response
PT	Preferred term
RCT	randomized controlled trial
SAE	serious adverse event
sBRCA	somatic BRCA mutation
SGB	Sozialgesetzbuch (Social Code Book)
tBRCA	confirmed BRCA mutation in the tumour independent of the mutation status in the germline
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug olaparib. The assessment 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 in comparison with the ACT "watchful waiting" in adult patients with advanced breast cancer associated gene (BRCA) 1/2-mutated, high-grade epithelial ovarian cancer, fallopian tube or primary peritoneal cancer who showed response (complete or partial) after completed platinum-based first-line chemotherapy.

The research question presented in Table 2 resulted from the appropriate comparator therapy (ACT) specified by the G-BA.

Table 2: Research questions of the benefit assessment of olaparib

Research question	Subindication	ACT[a]
1	Adult patients with advanced[b] BRCA1/2-mutated[c], high-grade epithelial ovarian cancer[d] who showed response (complete or partial) after completed platinum-based first-line chemotherapy	Watchful waiting
a: Presentation of the ACT specified by the G-BA. b: According to the FIGO stage III and IV. c: In the germline and/or somatic. d: This term also includes fallopian tube and primary peritoneal cancer. ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; G-BA: Federal Joint Committee		

In the present dossier assessment, the term "ovarian cancer" includes ovarian, fallopian tube and primary peritoneal cancer. BRCA mutation means pathogenic mutations of the BRCA1 and/or BRCA2 gene in the germline or somatic cells.

The company named "watchful waiting" as ACT and thus followed the G-BA's specification.

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

The study SOLO1 was included in the benefit assessment.

Study design

The SOLO1 study was a double-blind, randomized parallel-group study on the comparison of olaparib with placebo. The study included adult patients with advanced (Fédération Internationale de Gynécologie et d'Obstétrique [FIGO] stage III or IV) high-grade serous or high-grade endometrioid ovarian cancer who had responded (completely or partially) to a prior platinum-containing first-line chemotherapy. Only patients with mutations in the BRCA1 or BRCA2 genes were included. Another inclusion criterion was a good to slightly impaired general condition (Eastern Cooperative Oncology Group Performance Status [ECOG PS] ≤ 1) of the patients.

The study included a total of 391 patients, randomized in a 2:1 ratio either to treatment with olaparib (N = 260) or placebo (N = 131). Treatment with olaparib was conducted in compliance with the German approval status. Patients were treated until disease progression according to RECIST 1.1, unacceptable toxicity or withdrawal of consent. The study medication should be discontinued when none of the criteria for discontinuation described above had occurred and symptoms according to RECIST 1.1 and/or after assessment of the clinical condition of the patient were absent after 2-year treatment. At the time point of the data cut-off, 13 (5.0%) patients in the olaparib arm and 1 (0.8%) patient in the placebo arm still received the study medication.

The primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, health status, health-related quality of life and adverse events (AEs).

Data cut-offs

Two data cut-offs were planned for the SOLO1 study:

- 17 May 2018 (first data cut-off): primary analysis after approx. 196 progression events
- Final analysis: overall survival, depending on the event (60% patients with event)

- To date, only results on the first data cut-off are available. The first data cut-off was planned and the respective data were available for all patient-relevant outcomes for the benefit assessment. The final analysis of the outcome "overall survival" was planned for the time at which 60% of the included patients had had an event.

Implementation of the ACT in the SOLO1 study

The included SOLO1 study was not designed for a comparison with watchful waiting. However, with certain restrictions, the study is suitable for such a comparison.

A main limitation in the implementation of the ACT watchful waiting in the SOLO1 study was the fact that regular examinations with imaging techniques were planned for the diagnosis of disease progression. This may lead to a systematically premature diagnosis of disease progression. However, since patients do not benefit from an earliest possible initiation of subsequent therapy, the S3 guideline recommends a symptom-oriented approach without regular examination intervals.

The fact that the investigator could decide upon treatment discontinuation or further treatment after progression according to RECIST – and thus upon the time point of initiation of subsequent therapy – in the SOLO1 study, must be considered an approximation to watchful waiting. Moreover, a total of 90 (23.0%) patients were unblinded in the course of the study (olaparib: 38 [14.6%] patients; placebo: 52 [39.7%] patients), almost all of them after disease progression (34 [13.1%] in the olaparib arm and 51 [39.0%] in the control arm). It is assumed that this was done also with regard to the subsequent therapy and the patients decided on subsequent therapies together with the investigator. Moreover, there was no indication of a systematic difference between the treatment arms regarding the drugs used as subsequent therapies.

Risk of bias and certainty of conclusions

The risk of bias across outcomes (study level) was rated as low for the SOLO1 study. At the outcome-specific level, the results of all outcomes, except for the outcome "discontinuation due to AEs", were rated as potentially having a high risk of bias. Irrespective of this, the limitations concerning the implementation of the ACT result in a low certainty of conclusions for all outcomes and research questions.

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

Results

Mortality

Overall survival

There was no statistically significant difference between the treatment groups for the outcome "overall survival". At the time point of the data cut-off of 17 May 2018, a total of about 21% (olaparib: 21.2%; placebo 20.6%) of the patients had died. The final analysis of the outcome "overall survival" was planned for the time at which 60% of the included patients had had an event. This resulted in no hint of an added benefit of olaparib in comparison with the ACT "watchful waiting"; an added benefit is therefore not proven.

Morbidity

Health status (visual analogue scale [VAS] of the European Quality of Life5 Dimensions [EQ-5D])

"Health status" was recorded with the EQ-5D VAS. The documentation time also comprised the period after disease progression. There was no statistically significant difference between the

treatment groups over a period of 24 months. This resulted in no hint of an added benefit of olaparib in comparison with the ACT "watchful waiting"; an added benefit is therefore not proven.

Health-related quality of life

Functional Assessment of Cancer Therapy-Ovarian [FACT-O] total score

The health-related quality of life was recorded using the total score of the FACT-O questionnaire. The documentation time also comprised the period after disease progression. There was a statistically significant difference to the disadvantage of olaparib over a period of 24 months. However, the 95% CI of Hedges' g was not fully outside the irrelevance range [−0.2; 0.2]; it can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of olaparib in comparison with the ACT "watchful waiting"; an added benefit is therefore not proven.

Side effects

Serious adverse events [SAEs], severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs

A statistically significant difference to the disadvantage of olaparib in comparison with placebo was shown for the outcomes "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". This resulted in a hint of greater harm from olaparib in comparison with the ACT "watchful waiting" for each of these outcomes. The difference between the treatment arms for the outcome "SAEs" was not statistically significant. Hence, for this outcome, there was no hint of greater or lesser harm from olaparib in comparison with watchful waiting; greater or lesser harm for this outcome is therefore not proven.

Specific AEs

- Myelodysplastic syndrome and myeloproliferative neoplasms, acute myeloid leukaemia as well as pneumonitis

Since there were no events regarding the specific AEs "myelodysplastic syndrome" and "myeloproliferative neoplasms", "acute myeloid leukaemia" and "pneumonitis" in the placebo arm, the hazard ratio (HR) for these outcomes cannot be estimated. However, events also occurred in only few patients in the olaparib arm (myelodysplastic syndrome and myeloproliferative neoplasms: 1 patient; acute myeloid leukaemia: 2 patients; pneumonitis: 5 patients). This resulted in no hint of greater or lesser harm from olaparib in comparison with the ACT "watchful waiting" for either of these outcomes; greater or lesser harm is therefore not proven for these outcomes.

- Anaemia, dysgeusia, dyspnoea, nausea, stomatitis, vomiting, muscle spasms, asthenia and mucosal inflammation

A statistically significant disadvantage of olaparib was shown for each of the specific AEs "anaemia", "dysgeusia", "dyspnoea", "nausea", "stomatitis", "vomiting", "muscle spasms",

"asthenia" and "mucosal inflammation". This resulted in a hint of greater harm from olaparib in comparison with the ACT "watchful waiting" for each of these outcomes.

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

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:

In the overall consideration, there were only negative effects of different extents for olaparib in comparison with "watchful waiting", each with the probability "hint". These only concerned outcomes on side effects of different severity grades.

Due to the relatively short observation period and the overall few events (olaparib: 21.2%; placebo: 20.6%), there are no informative results for the outcome "overall survival". Therefore, the present data situation does not permit a meaningful weighing of positive and negative effects; an added benefit is therefore not proven.

In summary, there is no hint of an added benefit of olaparib in comparison with the ACT "watchful waiting" for adult patients with advanced BRCA1/2-mutated, high-grade epithelial ovarian cancer who show response (complete or partial) after platinum-based first-line chemotherapy; an added benefit is therefore not proven.

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

Table 3: Olaparib – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with advanced[b] BRCA1/2-mutated[c], high-grade epithelial ovarian cancer[d] who showed response (complete or partial) after completed platinum-based first-line chemotherapy	Watchful waiting	Added benefit not proven[e]
a: Presentation of the ACT specified by the G-BA. b: According to the FIGO stage III and IV. c: In the germline and/or somatic. d: This term also includes fallopian tube and primary peritoneal cancer. e: The SOLO1 study included only patients with ECOG PS of 0 or 1 as well as only few patients with non-serous histology (olaparib: 15 [5.8%]; placebo: 1 [0.8%]). It remains unclear whether the observed results can be transferred to patients with ECOG PS ≥ 2 or patients with non-serous histology of the ovarian cancer. ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; G-BA: Federal Joint Committee.		

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 in comparison with the ACT "watchful waiting" in adult patients with advanced BRCA 1/2-mutated, high-grade epithelial ovarian cancer, fallopian tube and primary peritoneal cancer who showed response (complete or partial) after completed platinum-based first-line chemotherapy.

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

Table 4: Research questions of the benefit assessment of olaparib

Research question	**Subindication**	**ACT[a]**
1	Adult patients with advanced[b] BRCA1/2-mutated[c], high-grade epithelial ovarian cancer[d] who showed response (complete or partial) after completed platinum-based first-line chemotherapy	Watchful waiting
a: Presentation of the ACT specified by the G-BA. b: According to the FIGO stage III and IV. c: In the germline and/or somatic. d: This term also includes fallopian tube and primary peritoneal cancer. ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; G-BA: Federal Joint Committee.		

In the present dossier assessment, the term "ovarian cancer" includes ovarian, fallopian tube and primary peritoneal cancer. BRCA mutation means pathogenic mutations of the BRCA1 and/or BRCA2 gene in the germline or somatic cells.

The company named "watchful waiting" as ACT and thus followed the G-BA's specification.

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: 3 May 2019)
- bibliographical literature search on olaparib (last search on 3 May 2019)
- search in trial registries for studies on olaparib (last search on 3 May 2019)

To check the completeness of the study pool:

- search in trial registries for studies on olaparib (last search on 22 July 2019)

The check identified no additional relevant study.

2.3.1 Studies included

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

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

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
D0818C00001 (SOLO1[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

The study pool concurred with that of the company.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

2.3.2.1 Description of the study design of the SOLO1 study

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. watchful waiting

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SOLO1	RCT, double-blind, parallel	Adult patients with advanced (FIGO stage III or IV[b]) BRCA1/2-mutated, high-grade serous or high-grade endometrioid ovarian cancer and an ECOG PS ≤ 1who had responded to a prior platinum-containing first-line chemotherapy[c]	**Main cohort** Olaparib (N = 260) placebo (N = 131) **Cohort in China** Olaparib (N = 44) placebo (N = 20)	Screening: ≤ 28 days Treatment: Until treatment progression according to RECIST[d], toxicity, withdrawal of consent or end of treatment after 2 years, when symptoms are absent[e] Observation[f]: Outcome-specific, at most until death, withdrawal of consent or final analysis	**Main cohort** 118 centres in: Australia, Brazil, Canada, China[g], France, Israel, Italy, Japan, Netherlands, Poland, Russia, Spain, South Korea, United Kingdom and USA 08/2013–ongoing **Data cut-offs:** ▪ Primary analysis[h]: 17 May 2018 ▪ Final analysis of overall survival: depending on the event (60% patients with event) **Cohort in China** 12/2014–ongoing **Data cut-offs:** ▪ Primary analysis[h]: 17 May 2018	Primary: PFS Secondary: overall survival, health status, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the study included – RCT, direct comparison: olaparib vs. watchful waiting (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: According to [3].
c: Complete or partial response at the time point of follow-up examination; complete response is defined as no signs of measurable or non-measurable disease according to RECIST 1.1 and a normal cancer antigen-125 (CA-125) level; partial response is defined as reduction of the tumour volume by ≥ 30% from the start to the end of the chemotherapy or no indication of measurable disease according to RECIST 1.1 without normal CA-125 level.
d: At the investigator's discretion, the patients could undergo further treatment with the study medication as long as they benefited from the treatment and there were no other reasons for treatment discontinuation.
e: According to RECIST version 1.1 and/or after assessment of the patient's clinical condition.
f: Outcome-specific information is provided in Table 8.
g: Five patients from China were included in both the main cohort and the cohort in China.
h: The primary analysis should be conducted either after the occurrence of 196 progression events or 36 months after inclusion of the last patients (main cohort), or after the occurrence of at least 29 progression events (cohort in China).

AE: adverse event; BRCA: breast cancer associated gene; CA-125: cancer antigen-125; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; N: number of randomized (included) patients; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: olaparib vs. watchful waiting

Study	Intervention	Comparison
SOLO1	Olaparib 300 mg, orally, twice daily as film-coated tablet (total daily dose: 600 mg), at the same time of the day, at 12-hour intervals	Placebo, orally, twice daily as film-coated tablet, at the same time of the day, at 12-hour intervals
	Dose adjustments, treatment interruption and treatment discontinuation due to toxicity are possible[a]	
	Pretreatment **Required:** ▪ platinum-based first-line chemotherapy (intravenous or intraperitoneal) consisting of 6 to 9 cycles or of at least 4 cycles at treatment discontinuation due to treatment-associated side effects; last dose within 8 weeks before randomization **Not allowed:** ▪ PARP inhibitors ▪ bevacizumab as concomitant treatment for the platinum-based first-line chemotherapy before study inclusion ▪ any test medication during the treatment with platinum-containing first-line chemotherapy	
	Concomitant treatment **Allowed:** ▪ corticosteroids for symptom control in brain metastases as well as bisphosphonates or denosumab for bone disorders, each in a stable dose at the start of the administration at least 4 weeks before start of the study ▪ palliative radiotherapy for pain treatment of bone metastases already existing before the start of the study as long as there are no indications of disease progression ▪ antiemetics, antidiarrhoeal drugs ▪ G-CSF in grade ≥ 3 febrile neutropenia ▪ warfarin, subcutaneous heparin **Not allowed:** ▪ other chemotherapy, other anticancer treatments, immunotherapy, hormonal therapy (hormone replacement therapy acceptable), radiotherapy, biologic therapy or other new and investigational drugs ▪ live vaccines ▪ potent CYP3A4 inhibitors or inducers as well as drugs, herbal products or foods with known CYP3A4 enzyme activity	

a: Toxicity-related dose adjustments up to treatment discontinuation were performed without relevant deviation from the requirements of the SPC.

CYP: cytochrome P450; G-CSF: granulocyte colony-stimulating factor; PARP: poly(adenosine diphosphate-ribose) polymerase; RCT: randomized controlled trial; vs.: versus

The SOLO1 study was a double-blind, randomized parallel-group study on the comparison of olaparib with placebo. The study included adult patients with advanced (FIGO stage III or IV) high-grade serous or high-grade endometrioid ovarian cancer who had responded (completely or partially) to a prior platinum-containing first-line chemotherapy. Only patients with mutations in the BRCA1 or BRCA2 genes were included. Another inclusion criterion was a good to slightly impaired general condition (ECOG PS ≤ 1) of the patients.

Within the framework of the study, all patients were examined with regard to a possible BRCA mutation in the germline. These examinations were performed using either the Myriad Integrated BRACAnalysis or the Myriad BRACAnalysis CDx test and, for patients in China, the BGI test. Moreover, as far as available, retrospective analyses were performed with archived tumour samples by means of the Foundation-Medicine-FoundationOne-CDx Clinical Trial Assay to evaluate the BRCA mutation status in the tumour tissue. An archived tumour sample was only missing for a total of 23 patients. The results on the germline BRCA mutation (gBRCA) and confirmed BRCA mutation in the tumour independent of the mutation status in the germline [tBRCA] mutation status are presented in Table 9.

The main cohort included a total of 391 patients, randomized in a 2:1 ratio either to treatment with olaparib (N = 260) or placebo (N = 131). Randomization was stratified by response to the platinum-containing first-line chemotherapy at the time point of the follow-up examination (complete/partial). Complete response (CR) was defined as no signs of measurable or non-measurable disease according to modified RECIST 1.1 and a normal cancer antigen-125 (CA-125) level. Partial response (PR) was defined as a reduction of the tumour volume by ≥ 30% from the start to the end of the chemotherapy or as no indication of measurable disease according to RECIST 1.1, but a CA-125 level above the normal range.

In Appendix 4-G6 of Module 4 A, the company presented the data of a cohort in China belonging to the SOLO1 study as supplementary information. The cohort in China comprised 64 patients, 59 of which were included after completed randomization of the main cohort. Until the present data cut-off (17 May 2018), the study duration of the cohort in China was approx. 3.4 years; it was thus only 1.4 years shorter than the duration of the main cohort with a current duration of approx. 4.8 years. The company stated that the data of the cohort in China were not expected to provide relevant additional information particularly with regard to long-term effects. Therefore, it did not use them for the derivation of an added benefit. The company's approach was not adequate (see Section 2.7.3.2 of the full dossier assessment). In the present evaluation situation, however, this remains without consequence, since the results of the cohort in China show the same direction of effect as those of the main cohort (see Appendix E of the full dossier assessment) and their consideration would not change the overall conclusion on the added benefit.

Treatment with olaparib was conducted in compliance with the German approval status.

Patients were treated until disease progression according to RECIST 1.1, unacceptable toxicity or withdrawal of consent. At the investigator's discretion, however, the patients still could receive further treatment with the study medication after disease progression according to RECIST 1.1, as long as they benefited from the treatment and there were no other criteria for discontinuation. The study medication should be discontinued when none of the criteria for discontinuation described above had occurred and symptoms according to RECIST 1.1 and/or after assessment of the clinical condition of the patient were absent after 2-year treatment. The CA 125 level was regularly recorded; however, an increased CA-125 level presented no

criterion for discontinuation. At the time point of the data cut-off, 13 (5.0%) patients in the olaparib arm and 1 (0.8%) patient in the placebo arm still received the study medication (see also Section 2.3.2.4).

The decision on the kind of the subsequent therapy was made on the investigator's discretion. According to the protocol, unblinding of patients and investigators was not planned for this purpose. However, a total of 90 (23.0%) patients were unblinded during the course of the study (olaparib: 38 [14.6%] patients; placebo: 52 [39.7%] patients). Moreover, the protocol allowed no switch from the placebo arm to treatment with olaparib after progression of the disease. A total of 22.9% (n = 30) of the patients in the placebo arm, however, received olaparib as first subsequent therapy deviating from the study design. There was no other limitation regarding subsequent therapy.

At the time point of the data cut-off, the proportion of patients with subsequent anticancer therapy was 35.0% (n = 91) in the olaparib arm and 71.8% (N = 94) in the comparator arm (see Table 26 of the full dossier assessment). It could be inferred from the study documents that at the time point of the data cut-off, patients in the olaparib arm had received up to 7 lines of further treatments, while it were 5 lines for patients in the placebo arm.

The primary outcome of the study was PFS. Patient-relevant secondary outcomes were overall survival, health status, health-related quality of life and AEs.

Data cut-offs

Two data cut-offs were planned for the SOLO1 study:

- 17 May 2018 (first data cut-off): primary analysis after approx. 196 progression events
- Final analysis: overall survival, depending on the event (60% patients with event)

Only results on the first data cut-off are available. The first data cut-off was planned and the respective data were available for all patient-relevant outcomes for the benefit assessment. The final analysis of the outcome "overall survival" was planned for the time at which 60% of the included patients had had an event.

2.3.2.2 Implementation of the ACT in the SOLO1 study

Operationalization of watchful waiting

For the present benefit assessment, watchful waiting was operationalized as a follow-up strategy until the death of the patients, which comprises both diagnosis of relapse according to the S3 guideline [4] and, if required, its treatment. In essence, the S3 guideline recommends a symptom-oriented approach without regular examination intervals. It advises against the routine use of device-based diagnostics and marker determination in symptom-free patients. Physical and gynaecological examinations are recommended instead. If an elevated level of CA-125 has been measured in asymptomatic patients nonetheless, this should not be decisive for the diagnosis of a relapse, but further diagnostics should be decided upon in consultation

with the patient. Consultation with the patient is generally regarded as one of the most important elements in the care of patients with ovarian cancer, also when deciding on subsequent therapies. According to the guideline, computed tomography (CT), positron emission tomography (PET), PET/CT and magnetic resonance imaging (MRI) have been established as imaging procedures, for example if relapse is suspected due to symptoms.

Implementation of watchful waiting in the SOLO1 study

The included SOLO1 study was not designed for a comparison with watchful waiting. However, with certain restrictions, the study is suitable for such a comparison.

A main limitation in the implementation of the ACT watchful waiting in the SOLO1 study was the fact that regular examinations with imaging techniques were planned for the diagnosis of disease progression. This may lead to a systematically premature diagnosis of disease progression. It can be assumed that already a progress of the disease can be detected by means of device-based diagnostics, but that the patient is still symptom-free at the time of the imaging test. However, according to current data, an earlier start of subsequent therapy is not associated with a prolongation of overall survival, but rather leads to an earlier deterioration in quality of life [5]. Hence, the S3 guideline recommends a symptom-oriented approach without regular examination intervals [4]. The study documents do not describe to what extent regular clinical examinations also include gynaecological examinations.

Against this background, the fact that the investigator could decide upon treatment discontinuation or further treatment after progression according to RECIST – and thus upon the time point of initiation of subsequent therapy – in the SOLO1 study, must be considered an approximation to watchful waiting. Moreover, a total of 90 (23.0%) patients were unblinded in the course of the study (olaparib: 38 [14.6%] patients; placebo: 52 [39.7%] patients), almost all of them after disease progression (34 [13.1%] in the olaparib arm and 51 [39.0%] in the control arm). It is assumed that this was done also with regard to the subsequent therapy and the patients decided on subsequent therapies together with the investigator. Moreover, there was no indication of a systematic difference between the treatment arms regarding the drugs used as subsequent therapies.

In summary, the approach used in the SOLO1 study was assessed as sufficient implementation of the ACT and the study was used for the benefit assessment. Due to the described aspects, the certainty of conclusions of the study is limited, however. Based on the available data, at most hints, e.g. of an added benefit, can therefore be determined for all outcomes.

2.3.2.3 Planned duration of follow-up observation in the SOLO1 study

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. watchful waiting

Study **Outcome category** **Outcome**	**Planned follow-up observation**
Study SOLO1	
Mortality	
Overall survival	Until death or final analysis
Morbidity	
Health status (EQ-5D VAS)	Until 30 days after the last dose of the study medication or primary analysis
Health-related quality of life (FACT-O)	Until 30 days after the last dose of the study medication or primary analysis
Side effects	
AEs, SAEs	Until 30 days after the last dose of the study medication
Myelodysplastic syndrome/ acute myeloid leukaemia/further neoplasms	Until death or final analysis

a: Originally, recording ended after disease progression. Due to a protocol amendment of 19 December 2014 (inclusion of the first patient: 26 August 2013), recording took place for up to 36 months or until the first data cut-off, irrespective of disease progression. With another protocol amendment of 19 February 2016, recording took place until the first data cut-off, irrespective of the treatment duration.

AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; FACT-O: Functional Analysis of Cancer Therapy – Ovarian; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The observation periods for the outcomes on side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days). The documentation time for the outcomes “morbidity” and “health-related quality of life” comprised the time after disease progression according to RECIST 1.1 or end of treatment until the data cut-off analysed in this benefit assessment (primary analysis). However, recording of these outcomes beyond disease progression had not been planned from the start of the study. This was first introduced with a protocol amendment of 19 December 2014. Recording was initially planned for maximally 36 months or until primary data cut-off, and was extended until the primary data cut-off with protocol amendment of 19 February 2016 (without possible earlier end of recording). The study had been running for about 16 months at the time point of the protocol amendment. It is therefore unclear how many patients already had disease progression before 19 December 2014 and recording of health status and health-related quality of life was thus terminated earlier. The fact that recording was then planned for maximally 36 months had no consequences, since the study had been running for only about 30 months at the time point of the protocol amendment.

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

2.3.2.4 Patient characteristics and course of the study

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

Table 9: Characteristics of the study population – RCT, direct comparison: olaparib vs. watchful waiting

Study Characteristics Category	Olaparib	Placebo[a]
SOLO1	N[b] = 260	N[b] = 131
Age [years], mean (SD)	54 (9)	53 (10)
Origin, n (%)		
white	214 (82)	106 (81)
non-white	46 (18)[c]	25 (19)[c]
Region, n (%)		
Europe	101 (38.8[c])	53 (40.5[c])
other	159 (61.2)[c]	78 (59.5)[c]
ECOG PS, n (%)		
0	200 (76.9)	105 (80.2)
1	60 (23.1)	25 (19.1)
missing	0 (0)	1 (0.8)
Type of the BRCA mutation, n (%)		
gBRCA[d]	253 (97.3)	130 (99.2)
tBRCA[e]	214 (82.3)	110 (84.0)
sBRCA	2 (0.8[c])	0 (0)
Gene location of the BRCA mutation, n (%)[f]		
BRCA1	191 (73.5)	91 (69.5)
BRCA2	66 (25.4)	40 (30.5)
both	3 (1.2)	0 (0)
Histology, n (%)		
serous	245 (94.2)	130 (99.2)
non-serous[g]	15 (5.8)[c]	1 (0.8)
Primary tumour location, n (%)		
ovaries	220 (84.6)	113 (86.3)
fallopian tubes	22 (8.5)	11 (8.4)
primary peritoneum	15 (5.8)	7 (5.3)
other	3 (1.2)	0 (0)
Tumour grade, n (%)		
G1 (well differentiated)	0 (0)	0 (0)
G2 (moderately differentiated)	26 (10.0)	12 (9.2)
G3 (poorly differentiated)	215 (82.7)	105 (80.2)
G4 (undifferentiated)	5 (1.9)	4 (3.1)
GX (not assessable)	14 (5.4)	10 (7.6)
Disease duration [months], mean (SD)	ND	ND

(continued)

Table 9: Characteristics of the study population – RCT, direct comparison: olaparib vs. watchful waiting (continued)

Study **Characteristics** **Category**	**Olaparib**	**Placebo[a]**
SOLO1	N[b] = 260	N[b] = 131
FIGO stage at diagnosis, n (%)		
stages I-II	0 (0)	0 (0)
stage III[h]	220 (84.6)[c]	105 (80.2)[c]
stage IV	40 (15.4)	26 (19.8)
Debulking surgery prior to randomization, n (%)		
yes	256 (98.5)	128 (97.7)
no	4 (1.5)	3 (2.3)
Macroscopic residual disease after debulking surgery, n (%)		
yes	55 (21.2)	29 (22.1)
no	200 (76.9)	98 (74.8)
unknown	1 (0.4)	1 (0.8)
Cycles of platinum-containing first-line chemotherapy, n (%)		
< 6 cycles	4 (1.5)[c]	1 (0.8)
6 cycles	198 (76.2)	106 (80.9)
> 6 cycles	58 (22.3)[c]	24 (18.3)[c]
Objective response to most recent platinum-containing chemotherapy, n (%)[i]		
CR	213 (81.9)	107 (81.7)
PR	47 (18.1)	24 (18.3)
Treatment discontinuation, n (%)	247 (95.0)[j]	129 (98.5[c])[j]
Study discontinuation, n (%)	77 (29.6)[k]	40 (30.5)[k, l]

a: Sufficient approximation to the ACT "watchful waiting", but with limitations (see Section 2.3.2.2).
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: According to Myriad; there was one patient with BRCA variant of unknown significance (BRCA VUS) and two patients with BRCA wild type (BRCA-WT), both in the olaparib arm.
e: According to Foundation Medicine; there were a total of 5 patients with BRCA VUS (olaparib: 3 patients; placebo: 2 patients); a total of 12 patients had BRCA-WT (olaparib: 10 patients; placebo: 2 patients).
f: According to Myriad or BGI, and otherwise according to locally reported BRCA gene name at study inclusion.
g: Endometrioid, mixed epithelial, serous papillary
h: Composed of the categories III, IIIA, IIIB and IIIC.
i: According to randomization.
j: 123 (47.3%) patients in the olaparib arm and 35 (26.9%) patients in the placebo arm terminated treatment after 2 years in line with the protocol.
k: From these, 55 (21.2%) patients in the olaparib arm and 26 (19.8%) patients in the placebo arm had died.
l: One patient discontinued the study before the first dose of the study medication.

BRCA: breast cancer associated gene; BRCAm: BRCA-mutated; BRCA-WT: BRCA wild type; BRCA-VUS: BRCA mutation of unknown significance; CR: complete response; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; gBRCA: germline BRCA mutation; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; PR: partial response; RCT: randomized controlled trial; SD: standard deviation; sBRCA: somatic BRCA mutation; tBRCA: confirmed BRCA mutation in the tumour independent of the mutation status in the germline; vs.: versus

The characteristics of the study population were sufficiently comparable between the olaparib and the placebo arm. The mean age of the patients was approx. 54 years and most of them were white; almost half of them were in Europe. Upon diagnosis, most of the patients had a FIGO stage III tumour as well as an unimpaired general condition (ECOG PS of 0). Almost all patients had undergone debulking surgery prior to randomization; thereafter, approx. 76% of them had no macroscopic residual disease. About 82% of the patients showed complete response (CR) to the subsequent platinum-containing first-line chemotherapy.

Almost all patients had a gBRCA, and a total of 83% also had tBRCA. Only two patients in the olaparib arm had a purely somatic mutation (sBRCA), i.e., a BRCA mutation only in the tumour, but not in the germline. Moreover, the SOLO1 study included very few patients with non-serous histology.

Treatment duration and observation period

Table 10 shows the mean and median treatment duration of the patients.

Table 10: Information on the course of the study – RCT, direct comparison: olaparib vs. watchful waiting

Study **Duration of the study phase** **Outcome category**	**Olaparib**	**Placebo[a]**
SOLO1	N = 260	N = 131
Treatment duration [months]		
median [min; max]	24.6 [0; 52.0][b]	13.9 [0.2; 45.5][b]
mean (SD)	20.0 (10.8)[b]	15.0 (8.9)[b]
Observation period		
overall survival	ND[c]	ND[c]
morbidity	ND	ND
health-related quality of life	ND	ND
AEs / SAEs / myelodysplastic syndrome/ acute myeloid leukaemia/further neoplasms	ND	ND

a: Sufficient approximation to the ACT "watchful waiting", but with limitations (see Section 2.3.2.2).
b: Institute's calculation from data in weeks.
c: Only data on the time from randomization to censoring are available as approximation for the observation period of overall survival with a median interquartile range [IQR] of 43.5 [40.3; 47.9] months in the olaparib arm and 42.5 [40.7; 46.5] months in the placebo arm.
AE: adverse event; IQR: interquartile range; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; vs.: versus

Median treatment duration in the SOLO1 study was almost twice as long in the olaparib arm (24.6 months) as in the placebo arm (13.9 months). The difference in the treatment duration is chiefly due to a difference in the time to treatment discontinuation. 123 (47.3%) patients in the olaparib arm and 35 (26.7%) patients in the placebo arm terminated their treatment after 2 years,

since they had no symptoms. At the time point of the data cut-off, 13 (5.0%) patients in the olaparib arm and 1 (0.8%) patient in the placebo arm still received the study medication.

Information on the observation periods of the outcomes included was not available. There is only one information on the time from randomization to censoring, which presents an approximation for the observation period of the outcome "overall survival". The median time from randomization to censoring was 43.5 months in the olaparib arm and 42.5 months in the placebo arm; it was thus balanced in both treatment arms. For the remaining outcomes, it was assumed that the difference in the observation period between the arms was similar to the difference in treatment duration if these outcomes were not observed indefinitely (see Table 8 for the planned duration of follow-up observation).

2.3.2.5 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) – olaparib vs. watchful waiting

Study	Adequate randomization sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
SOLO1	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the included SOLO1 study. This concurs with the company's assessment.

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
  - Health status measured with the EQ-5D VAS
- Health-related quality of life

- Measured using the Functional Analysis of Cancer Therapy – Ovarian (FACT-O) total score

- Side effects
  - SAEs
- severe AEs (Common-Terminology-Criteria-for-Adverse-Events [CTCAE] grade ≥ 3)
- Discontinuation due to AEs
- Myelodysplastic syndrome (preferred term [PT], AEs) and myeloproliferative neoplasm (PT, AEs)
- acute myeloid leukaemia (PT, AEs)
- Pneumonitis (PT, AE)
- 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). The specific AEs "myelodysplastic syndrome" and "acute myeloid leukaemia" were jointly analysed in the company's dossier. A comparison with the study documents showed that one event of myeloproliferative regeneration was included in this analysis.

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

Table 12: Matrix of outcomes – RCT, direct comparison: olaparib vs. watchful waiting

Study	Outcomes									
	Overall survival	**Health status (EQ-5D VAS)**	**Health-related quality of life (FACT-O total score)**	**SAEs**	**Discontinuation due to AEs**	**Severe AEs (CTCAE grade ≥ 3)**	**Myelodysplastic syndrome (PT, AEs) and myeloproliferative neoplasm (PT, AEs)**	**Acute myeloid leukaemia (PT, AEs)**	**Pneumonitis (PT, AE)**	**Further specific AEs[a]**
SOLO1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: The following events were considered (MedDRA coding): anaemia (PT, severe AEs [CTCAE grade ≥ 3]), dysgeusia (PT, AEs), hypertension (PT, AEs), dyspnoea (PT, AEs), nausea (PT, AEs), stomatitis (PT, AEs), vomiting (PT, AEs), muscle spasms (PT, AEs), asthenia (PT, AEs) and mucosal inflammation (PT, AEs)

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-O: Functional Assessment of Cancer Therapy – Ovarian; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial: SAE: serious adverse event; VAS: visual analogue scale; 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 – olaparib vs. watchful waiting

Study	Study level	Outcomes									
		Overall survival	Health status (EQ-5D VAS)	Health-related quality of life (FACT-O total score)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Myelodysplastic syndrome (PT, AEs) and myeloproliferative neoplasm (PT, AEs)	Acute myeloid leukaemia (PT, AEs)	Pneumonitis (PT, AE)	Further specific AEs[a]
SOLO1	L	H[b]	H[b, c, d]	H[b, c, d]	H[d]	L[e]	H[d]	H[b]	H[b]	H[d]	H[d]

a: The following events were considered (MedDRA coding): anaemia (PT, severe AEs [CTCAE grade ≥ 3]), dysgeusia (PT, AEs), hypertension (PT, AEs), dyspnoea (PT, AEs), nausea (PT, AEs), stomatitis (PT, AEs), vomiting (PT, AEs), muscle spasms (PT, AEs), asthenia (PT, AEs) and mucosal inflammation (PT, AEs)
b: After progression, patients in the intervention arm could receive olaparib outside the approval status at the investigator's discretion. The number of patients and the duration of this continued treatment are not known; high proportion of patients who received a PARP inhibitor as first subsequent therapy (33 [25.2%] patients) in the placebo arm.
c: High number of unblinded patients in the course of the study (38 [14.6%] in the olaparib arm and 52 [39.7%] in the control arm) at subjective recording of outcomes; it is not known how many unblinded recordings were considered in the analyses.
d: Incomplete observations for potentially informative reasons.
e: Despite low risk of bias, a restricted certainty of results was assumed for the outcome "discontinuation due to AEs" (see Section 2.7.4.2 of the full dossier assessment).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-O: Functional Assessment of Cancer Therapy – Ovarian; MedDRA: Medical Dictionary for Regulatory Activities; PARP: poly(adenosine diphosphate-ribose) polymerase; PT: Preferred Term; RCT: randomized controlled trial: SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The results of the outcomes "overall survival", myelodysplastic syndrome (PT, AEs) and myeloproliferative neoplasms (PT, AEs) as well as acute myeloid leukaemia (PT, AEs), which were recorded in addition to "progression", were rated as high, since patients in the intervention arm of the SOLO1 study still could receive olaparib outside the approval status at the investigator's discretion after progression of the disease. The number of patients and the duration of this continued treatment are not known. Moreover, there was a large proportion of patients in the placebo arm who received a poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor as first subsequent therapy. This subsequent therapy was not approved for patients in the treatment line after first platinum-containing chemotherapy following progression; initiation of another therapy is not indicated for patients who have no symptoms two years after termination of the platinum-containing first-line chemotherapy [4].

The outcomes “health status (EQ-5D VAS)” and “health-related quality of life” (FACT-O total score) were only partially recorded after progression (see Section 2.3.2.3). Therefore, the aspects described for “overall survival” and the specific AEs “myelodysplastic syndrome (PT, AEs)” and “myeloproliferative neoplasms (PT, AEs)” as well as “acute myeloid leukaemia (PT, AEs)” only apply to the results of the outcomes “health status (EQ-5D VAS)” and “health-related quality of life (FACT-O total score)”, when recordings were considered beyond progression. Moreover, in case of recording beyond progression, a high proportion of patients (38 [14.6%] in the olaparib arm and 52 [39.7%] in the control arm) were unblinded in the course of the study, which has to be considered for the subjectively recorded outcomes “health status (EQ-5D VAS)” and “health-related quality of life (FACT-O total score)”. However, it is not known how many unblinded recordings were included in the analyses. For the results of the outcomes “health status (EQ-5D VAS)” and “health-related quality of life (FACT-O total score)”, for which no recordings on disease progressions were considered, there is the problem of the number of incomplete observations due to potentially informative reasons.

The risk of bias for the results of the outcomes “SAEs”, “severe AEs (CTCAE grade ≥ 3)”, “pneumonitis” and the further specific AEs (which had all been subject to follow-up observation for only 30 days in line with the plan) was also rated as potentially high, because there are incomplete observations for potentially informative reasons.

The certainty of conclusions for the outcome “discontinuation due to AEs” was restricted despite low risk of bias (see Section 2.7.4.2 of the full dossier assessment).

This deviates from the assessment of the company, which assessed the risk of bias for the results of all outcomes on side effects as low.

Overall assessment of the certainty of conclusions

In summary, the certainty of conclusions of the results of all outcomes is low according to the results on the risk of bias, except for the outcome “discontinuation due to AEs”. However, the limitations concerning the implementation of the ACT (see Section 2.3.2.2) result in a low certainty of conclusions for all outcomes.

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

2.4.3 Results

Table 14 summarizes the results on the comparison of olaparib with “watchful waiting” in adult patients with advanced BRCA1/2-mutated, high-grade epithelial ovarian cancer who are in response after completed platinum-based first-line chemotherapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier. Results on common AEs are presented in Appendix B of the full dossier assessment. Kaplan-Meier curves can be found in Appendix A of the full dossier assessment. Since the company jointly analysed the specific AEs “myelodysplastic syndrome” and “myeloproliferative neoplasms” as well as “acute myeloid leukaemia”, a corresponding Kaplan-Meier curve can be found there.

The results of the cohort in China presented as supplementary information are presented in Appendix E.1, and the Kaplan-Meier curves are shown in Appendix E.2 of the full dossier assessment. For the cohort in China, the company did not present Kaplan-Meier curves on the specific AEs "myelodysplastic syndrome" and "myeloproliferative neoplasms" as well as "acute myeloid leukaemia" and "pneumonitis".

Table 14: Results (mortality, side effects, time to event) – RCT, direct comparison: olaparib vs. watchful waiting

Study	Olaparib		Placebo[a]		Olaparib vs. placebo[a]
Outcome category Outcome	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]; p-value[c]
SOLO1					
Mortality					
Overall survival	260	NA 55 (21.2)	131	NA 27 (20.6)	0.95 [0.60; 1.53]; 0.890
AEs[d]					
AEs (supplementary information)	260	0.1 [ND] 256 (98.5)	130	0.3 [ND] 120 (92.3)	–
SAEs	260	NA [ND] 54 (20.8)	130	NA [ND] 16 (12.3)	1.58 [0.93 2.87]; 0.099
Severe AEs (CTCAE grade ≥ 3)	260	42.1 [ND] 102 (39.2)	130	NA [ND] 24 (18.5)	2.30 [1.50; 3.68]; 0.002
Discontinuation due to AEs	260	NA [ND] 30 (11.5)	130	NA [ND] 3 (2.3)	4.86 [1.73; 20.30]; 0.004
Myelodysplastic syndrome (PT, AEs) and myeloproliferative neoplasm (PT, AEs)	260	NA [ND] 1 (0.4[e])	130	NA [ND] 0 (0)	NC
Acute myeloid leukaemia (PT, AEs)	260	NA [ND] 2 (0.8[e])	130	NA [ND] 0 (0)	NC
Pneumonitis (PT, AE)	260	NA [ND] 5[f] (1.9)	130	NA [ND] 0 (0)	NC
Further specific AEs					
Anaemia (PT, severe AEs with CTCAE grade ≥ 3)	260	NA [ND] 55 (21.2)	130	NA [ND] 2 (1.5)	15.42 [4.80; 94.13]; < 0.001
Dysgeusia (PT, AE)	260	NA [ND] 68 (26.2)	130	NA [ND] 5 (3.8)	7.45 [3.32; 21.27]; < 0.001
Dyspnoea (PT, AE)	260	NA [ND] 39 (15.0)	130	NA [ND] 7 (5.4)	2.49 [1.18; 6.10]; 0.029
Nausea (PT, AEs)	260	0.3 [ND] 201 (77.3)	130	NA [ND] 49 (37.7)	3.31 [2.44; 4.58]; < 0.001

(continued)

Table 14: Results (mortality, side effects, time to event) – RCT, direct comparison: olaparib vs. watchful waiting (continued)

Study Outcome category Outcome	Olaparib N	Olaparib Median time to event in months [95% CI] Patients with event n (%)	Placebo[a] N	Placebo[a] Median time to event in months [95% CI] Patients with event n (%)	Olaparib vs. placebo[a] HR [95% CI][b]; p-value[c]
SOLO1					
Stomatitis (PT, AEs)	260	NA [ND] 23 (8.8)	130	NA [ND] 3 (2.3)	3.62 [1.26; 15.30]; 0.025
Vomiting (PT, AEs)	260	NA [ND] 104 (40.0)	130	NA [ND] 19 (14.6)	3.08 [1.94; 5.18]; < 0.001
Muscle spasms (PT, AEs)	260	NA [ND] 17 (6.5)	130	NA [ND] 1 (0.8)	7.61 [1.55; 137.23]; 0.021
Asthenia (PT, AEs)	260	NA [ND] 63 (24.2)	130	NA [ND] 16 (12.3)	2.06 [1.22; 3.68]; 0.008
Mucosal inflammation (PT, AEs)	260	NA [ND] 17 (6.5)	130	NA [ND] 1 (0.8)	7.69 [1.57; 138.62]; 0.022

a: Sufficient approximation to the ACT "watchful waiting", but with limitations (see Section 2.3.2.2).
b: HR and 95% CI calculated using the Cox proportional hazards model, adjusted by response to the prior platinum-containing first-line chemotherapy (CR/PR).
c: p-value calculated using log-rank test stratified by the factor "response to the prior platinum-containing first-line chemotherapy (CR/PR)".
d: AEs until 30 days after the end of treatment (except for "myelodysplastic syndrome", "myeloproliferative neoplasms" and "acute myeloid leukaemia"); as planned without recording of the events associated with the underlying disease.
e: Institute's calculation.
f: Including one patient with interstitial lung disease (PT).

ACT: appropriate comparator therapy; AE: adverse event; CI: confidence interval; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PR: partial response; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: olaparib vs. watchful waiting

Study Outcome category Outcome	Olaparib			Placebo[a]			Olaparib vs. placebo[a]
	N[b]	Values at start of study mean (SD)	Change after 24 months mean[c] (SE)	N[b]	Values at start of study mean (SD)	Change after 24 months mean[c] (SE)	MD [95% CI]; p-value[c]
SOLO1							
Morbidity							
Health status EQ-5D VAS[d]	237	77.1 (15.40)	1.85 (0.66)	127	80.4 (13.09)	2.06 (0.95)	−0.21 [−2.49; 2.07]; 0.854
Health-related quality of life							
FACT-O total score[d]	238	113.46 (18.23)	−0.56 (0.73)	124	115.83 (18.57)	2.11 (1.06)	−2.67 [−5.20; −0.14]; 0.038 Hedges' g: −0.23 [−0.45; −0.02]
FACT-O subscales (additional information) Physical wellbeing Social well-being Emotional well-being Functional well-being Additional issues					ND		

a: Sufficient approximation to the ACT "watchful waiting", but with limitations (see Section 2.3.2.2).
b: Number of patients considered in the analysis for the calculation of the effect estimation; baseline values may be based on other patient numbers.
c: MMRM analysis adjusted for treatment, visit and value at baseline as well as interaction terms for treatment and visit, baseline value and visit.
d: A positive change from the start until the end of the study indicates improvement; a positive effect estimation indicates an advantage for the intervention.

ACT: appropriate comparator therapy; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FACT-O: Functional Assessment of Cancer Therapy-Ovarian; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

As shown in Sections 2.4.2 and 2.3.2.2, based on the available data, at most hints, e.g. of an added benefit, can be determined for all outcomes due to the high risk of bias and the limited implementation of the ACT.

Mortality

Overall survival

There was no statistically significant difference between the treatment groups for the outcome "overall survival". At the time point of the data cut-off of 17 May 2018, a total of about 21% (olaparib: 21.2%; placebo 20.6%) of the patients had died. The final analysis of the outcome

"overall survival" was planned for the time at which 60% of the included patients had had an event. This resulted in no hint of an added benefit of olaparib in comparison with the ACT "watchful waiting"; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Health status (VAS of the EQ-5D)

"Health status" was recorded with the EQ-5D VAS. The documentation time also comprised the period after disease progression. There was no statistically significant difference between the treatment groups over a period of 24 months. This resulted in no hint of an added benefit of olaparib in comparison with the ACT "watchful waiting"; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived proof of an added benefit on the basis of several operationalizations.

Health-related quality of life

FACT-O total score

The health-related quality of life was recorded using the total score of the FACT-O questionnaire. The documentation time also comprised the period after disease progression. There was a statistically significant difference to the disadvantage of olaparib over a period of 24 months. However, the 95% CI of Hedges' g was not fully outside the irrelevance range [−0.2; 0.2]; it can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of olaparib in comparison with the ACT "watchful waiting"; an added benefit is therefore not proven.

The result of this assessment concurs with that of the company.

Side effects

SAEs

There was no statistically significant difference between the treatment groups for the outcome "SAEs". Hence, there was no hint of greater or lesser harm from olaparib in comparison with "watchful waiting"; greater or lesser harm is therefore not proven for these outcomes.

The result of this assessment concurs with that of the company, which, however, conducted a summarizing analysis of the outcomes on side effects.

Severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs

A statistically significant difference between the treatment arms to the disadvantage of olaparib in comparison with placebo was shown for the outcomes severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs. This resulted in a hint of greater harm from olaparib in comparison with the ACT "watchful waiting" for each of these outcomes.

This deviates from the assessment of the company, which conducted a summarizing analysis of the side effect outcomes and overall derived no added benefit for treatment with olaparib in comparison with watchful waiting.

Specific AEs

Myelodysplastic syndrome and myeloproliferative neoplasms, acute myeloid leukaemia as well as pneumonitis

Since there were no events regarding the specific AEs "myelodysplastic syndrome" and "myeloproliferative neoplasms", "acute myeloid leukaemia" and "pneumonitis" in the placebo arm, the HR for these outcomes cannot be estimated. However, events also occurred in only few patients in the olaparib arm (myelodysplastic syndrome and myeloproliferative neoplasms: 1 patient; acute myeloid leukaemia: 2 patients; pneumonitis: 5 patients). This resulted in no hint of greater or lesser harm from olaparib in comparison with the ACT "watchful waiting" for either of these outcomes; greater or lesser harm is therefore not proven for these outcomes.

This deviates from the assessment of the company, which did not consider specific AEs in the derivation of the added benefit.

Anaemia, dysgeusia, dyspnoea, nausea, stomatitis, vomiting, muscle spasms, asthenia and mucosal inflammation

A statistically significant disadvantage of olaparib was shown for each of the specific AEs "anaemia", "dysgeusia", "dyspnoea", "nausea", "stomatitis", "vomiting", "muscle spasms", "asthenia" and "mucosal inflammation". This resulted in a hint of greater harm from olaparib in comparison with the ACT "watchful waiting" for each of these outcomes.

This deviates from the assessment of the company, which did not consider specific AEs in the derivation of the added benefit.

2.4.4 Subgroups and other effect modifiers

The present analysis assesses the following potential effect modifiers, which had been defined a priori, except for the characteristic "region" (Europe, Asia, rest of the world):

- age (< 65, ≥ 65)
- region (Europe, Asia, rest of the world)
- Disease stage at initial diagnosis (FIGO stage III, FIGO stage IV)
- Type of the BRCA mutation (gBRCA + tBRCA, sBRCA)
- Response to prior platinum-containing first-line chemotherapy according to randomization (CR, PR)
- Macroscopic residual disease after debulking surgery before study inclusion (yes, no)

The company presented subgroup analyses for all relevant outcomes apart from the specific AEs "hypertension", "stomatitis", "muscle spasms" and "mucosal inflammation". Since only two patients with BRCA mutation only in the tumour (sBRCA) were included, subgroup analyses by the prespecified characteristic "type of the BRCA mutation" (gBRCA + tBRCA, sBRCA) could not be performed.

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

No relevant effect modification was identified according to this methodology. This concurs with the company's assessment.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived 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

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

The outcome "discontinuation due to AEs" was assigned to the category "serious/severe side effects", because the majority of the events included in this outcome were "severe AEs (CTCAE grade ≥ 3)".

Table 16: Extent of added benefit at outcome level: olaparib vs. watchful waiting

Outcome category **Outcome**	**Olaparib vs. placebo**[a] **Quantile of time to event (months) or mean** **Effect estimation [95% CI]; p-value** **Probability**[b]	**Derivation of extent**[c]
Mortality		
Overall survival	Median: NA vs. NA HR: 0.95 [0.60; 1.53] p = 0.890	Lesser benefit/added benefit not proven
Morbidity		
Health status (EQ-5D VAS)	Mean: 1.85 vs. 2.06 MD: −0.21 [−2.49; 2.07] p = 0.854	Lesser benefit/added benefit not proven
Health-related quality of life		
FACT-O total score	Mean: −0.56 vs. 2.11 MD: −2.67 [−5.20; −0.14] p = 0.038 Hedges' g: −0.23 [−0.45; −0.02][d]	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: NA vs. NA HR: 1.58 [0.93; 2.87] p = 0.099	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: 42.1 vs. NA HR: 2.30 [1.50; 3.68] HR: 0.43 [0.27; 0.67][e] p = 0.002 Probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"
discontinuation due to AEs	Median: NA vs. NA HR: 4.86 [1.73; 20.30] HR: 0.21 [0.05; 0.58][e] p = 0.004 Probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"
Myelodysplastic syndrome (PT, AEs) and myeloproliferative neoplasm (PT, AEs)	Median: NA vs. NA HR: NC	Greater/lesser harm not proven
Acute myeloid leukaemia (PT, AEs)	Median: NA vs. NA HR: NC	Greater/lesser harm not proven
Pneumonitis (PT, AE)	Median: NA vs. NA HR: NC	Greater/lesser harm not proven

(continued)

Table 16: Extent of added benefit at outcome level: olaparib vs. watchful waiting (continued)

Outcome category **Outcome**	**Olaparib vs. placebo[a]** **Quantile of time to event (months) or mean** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Further specific AEs		
Anaemia (PT, severe AEs with CTCAE grade ≥ 3)	Median: NA vs. NA HR: 15.42 [4.80; 94.13] HR: 0.06 [0.01; 0.21][e] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Dysgeusia (PT, AE)	Median: NA vs. NA HR: 7.45 [3.32; 21.27] HR: 0.13 [0.05; 0.30][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Dyspnoea (PT, AE)	Median: NA vs. NA HR: 2.49 [1.18; 6.10] HR: 0.40 [0.16; 0.85][e] p = 0.029 probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"
Nausea (PT, AEs)	Median: 0.3 vs. NA HR: 3.31 [2.44; 4.58] HR: 0.30 [0.22; 0.41][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Stomatitis (PT, AEs)	Median: NA vs. NA HR: 3.62 [1.26; 15.30] HR: 0.28 [0.07; 0.79][e] p = 0.025 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Vomiting (PT, AEs)	Median: NA vs. NA HR: 3.08 [1.94; 5.18] HR: 0.32 [0.19; 0.52][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Muscle spasms (PT, AEs)	Median: NA vs. NA HR: 7.61 [1.55; 137.23] HR: 0.13 [0.01; 0.65][e] p = 0.021 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

(continued)

Table 16: Extent of added benefit at outcome level: olaparib vs. watchful waiting (continued)

Outcome category **Outcome**	**Olaparib vs. placebo[a]** **Quantile of time to event (months) or mean** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Asthenia (PT, AEs)	Median: NA vs. NA HR: 2.06 [1.22; 3.68] HR: 0.49 [0.27; 0.82][e] p = 0.008 probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"
Mucosal inflammation (PT, AEs)	Median: NA vs. NA HR: 7.69 [1.57; 138.62] HR: 0.13 [0.01; 0.64][e] p = 0.022 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

a: Sufficient approximation to the ACT "watchful waiting", but with limitations (see Section 2.3.2.2).
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 upper limit of the confidence interval (CI_u).
d: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.

ACT: appropriate comparator therapy; AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life5 Dimensions; FACT-O: Functional Assessment of Cancer Therapy-Ovarian; HR: hazard ratio; MD: mean difference; NA: not achieved; NC: not calculable; PT: Preferred Term; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

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

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

Positive effects	**Negative effects**
–	Serious/severe side effects ▪ discontinuation due to AEs: hint of greater harm – extent "major" ▪ severe AEs (CTCAE grade ≥ 3): hint of greater harm – extent: "major" ▪ specific AEs: ▫ anaemia (PT, severe AE [CTCAE grade ≥ 3]): hint of greater harm – extent: "major"
–	Non-serious/non-severe side effects ▪ specific AEs: ▫ dysgeusia, nausea, stomatitis, vomiting, muscle spasms, mucosal inflammation: in each case hint of greater harm – extent: "considerable" ▫ dyspnoea, asthenia: in each case hint of greater harm – extent: "minor"
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

In the overall consideration, there were only negative effects of different extents for olaparib in comparison with "watchful waiting", each with the probability "hint". These only concerned outcomes on side effects of different severity grades.

Due to the relatively short observation period and the overall few events (olaparib: 21.2%; placebo: 20.6%), there are no informative results for the outcome "overall survival". Therefore, the present data situation does not permit a meaningful weighing of positive and negative effects; an added benefit is therefore not proven.

In summary, there is no hint of an added benefit of olaparib in comparison with the ACT "watchful waiting" for adult patients with advanced BRCA1/2-mutated, high-grade epithelial ovarian cancer who show response (complete or partial) after platinum-based first-line chemotherapy; an added benefit is therefore not proven.

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

Table 18: Olaparib – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Adult patients with advanced[b] BRCA1/2-mutated[c], high-grade epithelial ovarian cancer[d] who showed response (complete or partial) after completed platinum-based first-line chemotherapy	Watchful waiting	Added benefit not proven[e]
a: Presentation of the ACT specified by the G-BA. b: According to FIGO stage III and IV. c: In the germline and/or somatic. d: This term also includes fallopian tube and primary peritoneal cancer. e: The SOLO1 study included only patients with ECOG PS of 0 or 1 as well as only few patients with non-serous histology (olaparib: 15 [5.8%]; placebo: 1 [0.8%]). It remains unclear whether the observed results can be transferred to patients with ECOG PS ≥ 2 or patients with non-serous histology of the ovarian cancer. ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; G-BA: Federal Joint Committee.		

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

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

AstraZeneca. Olaparib maintenance monotherapy in patients with BRCA mutated ovarian cancer following first line platinum based chemotherapy (SOLO-1): study results [online]. In: ClinicalTrials.gov. 09.07.2019 [Accessed: 24.07.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01844986.

AstraZeneca. A phase 3, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO stage 3-4) ovarian cancer following first line platinum based chemotherapy [online]. In: JAPIC Clinical Trials Information. 12.04.2019 [Accessed: 24.07.2019]. URL: https://www.clinicaltrials.jp/cti-user/trial/ShowDirect.jsp?japicId=JapicCTI-132360.

AstraZeneca. A phase III, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO stage III-IV) ovarian cancer following first line platinum based chemotherapy [online]. In: EU Clinical Trials Register. [Accessed: 24.07.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-001551-13.

AstraZeneca. Olaparib maintenance monotherapy in patients with BRCA mutated ovarian cancer following first line platinum based chemotherapy (SOLO-1): study details [online]. In: ClinicalTrials.gov. 09.07.2019 [Accessed: 24.07.2019]. URL: https://ClinicalTrials.gov/show/NCT01844986.

AstraZeneca. A phase III, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO stage III-IV) ovarian cancer following first line platinum based chemotherapy: study D0818C00001; clinical study report [unpublished]. 2018.

AstraZeneca. A phase III, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO stage III-IV) ovarian cancer following first line platinum based chemotherapy: China cohort; study D0818C00001; clinical study report [unpublished]. 2018.

AstraZeneca. A phase III, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO stage III-IV) ovarian cancer following first line platinum based chemotherapy: study D0818C00001; additional analyses [unpublished]. 2019.

AstraZeneca. A phase III, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO stage III-IV) ovarian cancer following first line platinum based chemotherapy: China cohort; study D0818C00001; additional analyses [unpublished]. 2019.

Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2018; 379(26): 2495-2505.

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Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/2019/a19-56-olaparib-ovarialkarzinom-nutzenbewertung-gemaess-35a-sgb-v.12478.html.