IQWiG Reports – Commission No. A19-88

Niraparib (ovarian 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 *Niraparib (Ovarialkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 January 2020). 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.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BRCA	breast cancer associated gene
CA-125	cancer antigen-125
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D	European Quality of Life-5 Dimensions
FACT-O	Functional Assessment of Cancer Therapy-Ovarian
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
gBRCAmut	germline BRCA mutation
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
non-gBRCAmut	without germline BRCA mutation
PARP	poly(adenosine diphosphate-ribose) polymerase
PET	positron emission tomography
PFS	progression-free survival
PT	Preferred Term
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
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 niraparib. 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 15 October 2019.

Research question

The aim of the present report is the assessment of the added benefit of niraparib, in comparison with the appropriate comparator therapy (ACT), as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

Table 2: Research questions of the benefit assessment of niraparib

Therapeutic indication	**ACT[a]**
Adult patients with platinum-sensitive relapsed high-grade[b] serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy and require maintenance treatment	**Olaparib** or watchful waiting
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. Designation taken from the English SPC. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics	

In the present dossier assessment, the term "ovarian cancer" includes ovarian, fallopian tube and peritoneal cancer.

From the options presented, the company chose olaparib as comparator therapy, thus following the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier.

Results

Study pool and study characteristics

No randomized controlled trials (RCTs) of direct comparison were identified for the assessment of the added benefit of niraparib in comparison with the comparator therapy olaparib. The company presented an adjusted indirect comparison using the common comparator placebo with one study on the niraparib side and 2 studies on the olaparib side of the indirect comparison.

NOVA (study with niraparib)

The NOVA study was a double-blind, randomized parallel-group study on the comparison of niraparib versus placebo. The study included adult patients with platinum-sensitive relapse of high-grade serous epithelial ovarian cancer who had achieved complete or partial response to prior platinum-containing chemotherapy. The patients were assigned to one of 2 cohorts based on their germline breast cancer associated gene (BRCA) mutation status (with germline BRCA mutation [gBRCAmut] and without germline BRCA mutation [non-gBRCAmut]).

A total of 553 patients were enrolled in the NOVA study. Of these patients, 203 were assigned to the gBRCAmut cohort and 350 to the non-gBRCAmut cohort. These were randomized in a 2:1 ratio and allocated either to treatment with niraparib (N: 372 [gBRCAmut: 138; non-gBRCAmut: 234]) or to placebo (N: 181 [gBRCAmut: 65; non-gBRCAmut: 116]).

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

Treatment with niraparib was until disease progression, unacceptable persistent toxicity, risk for the patient as assessed by the investigator, withdrawal of consent, severe protocol violations or pregnancy. However, at the physician's discretion, patients could continue treatment with the study medication even after disease progression as long as the physician deemed the treatment to be beneficial for the patients and treatment was acceptable.

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

Study 19 (study with olaparib)

Study 19 was a double-blind, randomized parallel-group study on the comparison of olaparib versus placebo. The study included adult patients with platinum-sensitive relapse of high-grade serous epithelial ovarian cancer who had achieved complete or partial response to prior platinum-containing chemotherapy. The patients were included regardless of their BRCA mutation status, which was determined after the primary data cut-off, however.

The study included a total of 265 patients, randomized in a 1:1 ratio either to treatment with olaparib (N = 136) or to placebo (N = 129).

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

Patients were treated until disease progression according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, toxicity or withdrawal of consent. However, at the physician's discretion, patients could continue treatment with the study medication even after disease progression according to RECIST 1.1 as long as the physician deemed the treatment to be beneficial for the patients and there were no other criteria for discontinuation.

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

SOLO2 (study with olaparib)

The SOLO2 study was also a double-blind, randomized parallel-group study on the comparison of olaparib versus placebo. The study only included patients with known BRCA mutation and additionally those with non-serous (endometrioid) histology. Thus, the study included adult patients with platinum-sensitive relapse of BRCA-mutated high-grade serous epithelial or non-serous ovarian cancer who had responded to prior platinum-containing chemotherapy.

The study included a total of 295 patients, randomized in a 2:1 ratio either to treatment with olaparib (N = 196) or to placebo (N = 99).

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

Patients were treated until disease progression according to RECIST 1.1, toxicity or withdrawal of consent. However, at the investigator's discretion, patients could continue treatment with the study medication even after disease progression according to RECIST 1.1 as long as the physician deemed the treatment to be beneficial for the patients and there were no other criteria for discontinuation.

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

Similarity of the studies for the indirect comparison

The check of the similarity of the studies NOVA, 19 and SOLO2 showed no major differences with regard to the patients included and the conduct of the studies. The similarity of the studies was therefore considered to be sufficient for an adjusted indirect comparison using the common comparator placebo. At outcome level, however, there were differences in follow-up observation between the studies NOVA and SOLO2 for health status recorded with the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D). This outcome is therefore unsuitable for the indirect comparison.

Risk of bias

The risk of bias across outcomes was rated as low for the studies NOVA and SOLO2. For Study 19, the risk of bias was rated as high due to the large proportions of patients in both treatment arms with incorrect classification in the stratified block randomization.

For the NOVA study, there was a high risk of bias for the results on all AEs except for the outcome "discontinuation due to AEs". No usable data of the NOVA study were available for outcomes of morbidity and health-related quality of life.

For the 2 studies 19 and SOLO2, the risk of bias of the results of all outcomes, except for the outcome "discontinuation due to AEs" from the SOLO2 study, was rated as high.

Despite a low risk of bias in the studies NOVA and SOLO2, the certainty of conclusions for the outcome "discontinuation due to AEs" was restricted also in these 2 studies.

Since there is only one study on the niraparib side of the adjusted indirect comparison, and there are one study with a high risk of bias across outcomes and one study with a high risk of bias for all outcomes except discontinuation due to AEs on the olaparib side, the certainty of results of the adjusted indirect comparison is no more than low. Hence, at most hints, e.g. of an added benefit, can be derived.

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between niraparib and olaparib for the outcome "overall survival". This resulted in no hint of an added benefit; an added benefit is therefore not proven.

Morbidity

Health status (EQ-5D VAS)

There were no usable data for the outcome "health status", measured with the EQ-5D VAS, as different follow-up observation strategies for this outcome were used in the studies.

This resulted in no hint of an added benefit of niraparib in comparison with olaparib; an added benefit is therefore not proven.

Health-related quality of life

Total score of the Functional Assessment of Cancer Therapy-Ovarian (FACT-O)

There were no sufficient data for an indirect comparison for the outcome "health-related quality of life" measured using the FACT-O total score, as this outcome was not recorded in the NOVA study.

This resulted in no hint of an added benefit of niraparib in comparison with olaparib; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), discontinuation due to AEs, as well as specific AEs (acute myeloid leukaemia, myelodysplastic syndrome and pneumonitis)

No indirect comparison was calculated due to an insufficient certainty of results in the NOVA study.

This resulted in no hint of greater or lesser harm of niraparib in comparison with olaparib; greater or lesser harm is therefore not proven. Overall, greater harm of niraparib in comparison with olaparib cannot be excluded on the basis of the available data, however.

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 niraparib in comparison with olaparib are assessed as follows:

Overall, based on the adjusted indirect comparison using the common comparator placebo, there are neither positive nor negative effects of niraparib in comparison with olaparib.

There is no hint of an added benefit of niraparib for the outcome "overall survival", as the indirect comparison showed no statistically significant difference. There are no usable data for an indirect comparison for the outcome categories of morbidity and side effects. Health-related quality of life was not recorded in the study on the niraparib side of the indirect comparison.

In summary, an added benefit of niraparib in comparison with olaparib is not proven for adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian cancer who are in response (complete or partial) to platinum-based chemotherapy.

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

Table 3: Niraparib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with platinum-sensitive relapsed high-grade[b] serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy and require maintenance treatment	**Olaparib** or watchful waiting	Added benefit not proven
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. Designation taken from the English SPC. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics		

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

[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].

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the framework of the market access in 2017. In this assessment, the G-BA had determined a non-quantifiable added benefit of niraparib. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

2.2 Research question

The aim of the present report is the assessment of the added benefit of niraparib, in comparison with the ACT, as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

Table 4: Research questions of the benefit assessment of niraparib

Therapeutic indication	**ACT**[a]
Adult patients with platinum-sensitive relapsed high-grade[b] serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy and require maintenance treatment	**Olaparib** or watchful waiting
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. Designation taken from the English SPC. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics	

According to the S3 guideline "Diagnostics, Therapy and Follow-up of Malignant Ovarian Tumours", cancers of the ovaries, fallopian tubes, and peritoneum are jointly classified in case of the same pathogenesis and histomorphology [3]. In the present dossier assessment, the term "ovarian cancer" therefore includes ovarian, fallopian tube and peritoneal cancer.

From the options presented, the company chose olaparib as comparator therapy, thus following the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier.

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 niraparib (status: 29 July 2019)
- bibliographical literature search on niraparib (last search on 29 July 2019)
- search in trial registries for studies on niraparib (last search on 26 August 2019)
- bibliographical literature search on the ACT (last search on 29 July 2019)
- search in trial registries for studies on the ACT (last search on 26 August 2019)

To check the completeness of the study pool:

- search in trial registries for studies on niraparib (last search on 30 October 2019)
- search in trial registries for studies on olaparib (last search on 22 November 2019)

Concurring with the company, no relevant RCT on the direct comparison of niraparib versus olaparib was identified from the check of the completeness of the study pool.

The company identified 3 studies for an adjusted indirect comparison based on RCTs. The check of the study pool did not identify any additional relevant studies for the indirect comparison presented by the company (see Section 2.3.1).

2.3.1 Studies included

For the assessment of the added benefit of niraparib, the company presented an adjusted indirect comparison using the common comparator placebo with one study on the niraparib side and 2 studies on the olaparib side. Since there was only one RCT with niraparib in the relevant therapeutic indication and this RCT used placebo as comparison, in agreement with the company, placebo was the only possible common comparator for an adjusted indirect comparison.

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, indirect comparison: niraparib vs. olaparib

Study	**Study category**		
	Study for approval of the drug to be assessed (yes/no)	**Sponsored study[a] (yes/no)**	**Third-party study (yes/no)**
Niraparib vs. common comparator			
PR-30-5011-C (NOVA[b])	Yes	Yes	No
Olaparib vs. common comparator			
D0810C00019 (Study 19[b])	No	No	Yes
D0816C00002 (ENGOT-Ov21, [SOLO2[b]])	No	No	Yes

a. Study for which the company was sponsor.
b. In the following tables, the study is referred to with this abbreviated form.
RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment concurred with that of the company. Figure 1 shows a schematic representation of the indirect comparison.

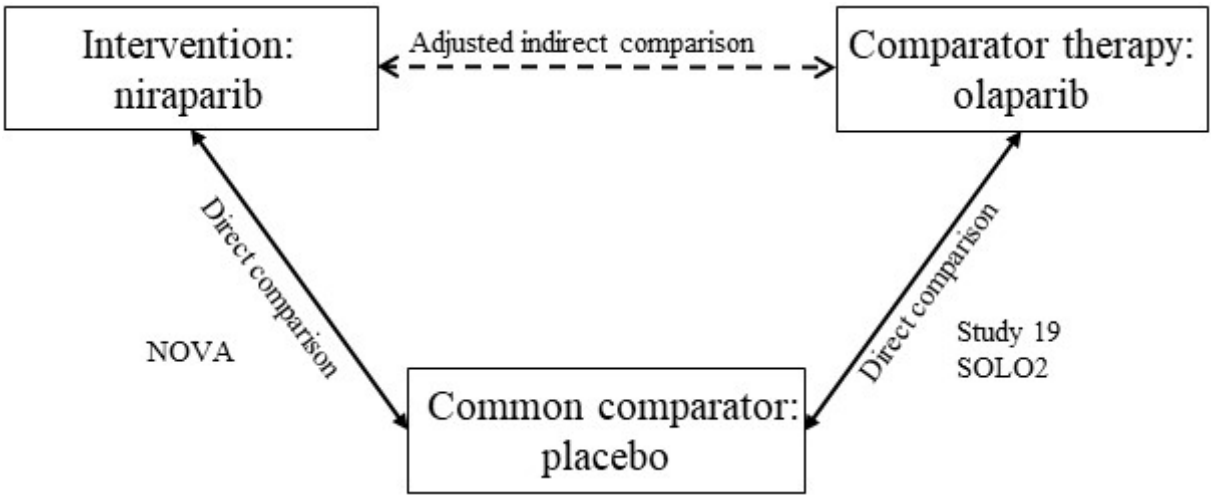

Figure 1: Study pool for the indirect comparison between niraparib and the ACT olaparib

In line with the research question, the assessment of the added benefit was conducted regardless of the patients' BRCA mutation status. This deviates from the approach of the company, which separated the patient populations according to the BRCA mutation status (see Section 2.4.1).

The studies 19 and SOLO2 included on the olaparib side were already subject of the benefit assessment of olaparib in the present therapeutic indication (most recently A18-36 [4]). The company based its description of the studies and the results to a major extent on Module 4 of the dossier of the marketing authorization holder of olaparib [5], without citing this source in the list of the studies included. Furthermore, the company did not consider IQWiG's assessment report on olaparib and the data presented in that report. Deviating from the company's approach, this source was taken into account in the present assessment.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the studies included by the company – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Intervention vs. common comparator						
NOVA	RCT, double-blind, parallel	Adult patients (≥ 18 years) with platinum-sensitive, recurrent[b] ovarian cancer[c] who had a response to prior platinum-based chemotherapy[d], with ECOG PS ≤ 1	**Total population** niraparib: N = 372 placebo: N = 181 **Cohort 1[e] (gBRCAmut)** niraparib (n = 138) placebo (n = 65) **Cohort 2[e] (non-gBRCAmut)** niraparib (n = 234) placebo (n = 116)	Screening: ≤ 28 days Treatment: until disease progression[f], unacceptable toxicity, withdrawal of consent, loss to follow-up, or death Observation[g]: outcome-specific, at most until death, withdrawal of consent or final survival time analysis	128 centres in Austria, Belgium, Canada, Denmark, France, Germany, Hungary, Israel, Italy, Norway, Poland, Spain, Sweden, United Kingdom, USA 8/2013–ongoing Data cut-off: 30 May 2016	Primary: PFS Secondary: overall survival, health status, AEs

Table 6: Characteristics of the studies included by the company – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ACT vs. common comparator						
Study 19	RCT, double-blind, parallel	Adult patients with platinum-sensitive, recurrent[b] high-grade serous epithelial ovarian cancer who had a response to prior platinum-based chemotherapy[h], with ECOG PS ≤ 2	**Total population** olaparib (N = 136) placebo (N = 129)	Screening: ≤ 28 days Treatment: until disease progression according to RECIST[i], toxicity or withdrawal of consent Observation[g]: outcome-specific, at most until death, withdrawal of consent or final survival time analysis	82 centres in Australia, Belgium, Canada, Czech Republic, Estonia, France, Germany, Israel, Netherlands, Poland, Romania, Russia, Spain, Ukraine, United Kingdom and USA 8/2008–5/2016 **Data cut-offs[j]:** ▪ 30 June 2010 (primary analysis) ▪ December 2011 ▪ 26 November 2012 ▪ 31 January 2014 ▪ 3 September 2015 ▪ 9 May 2016 (last data cut-off)	Primary: PFS Secondary: overall survival, health-related quality of life, AEs
SOLO2	RCT, double-blind, parallel	Adult patients with platinum-sensitive, recurrent[b] BRCA-mutated high-grade serous epithelial or endometrioid ovarian cancer who had a response to prior platinum-based chemotherapy[k], with ECOG PS ≤ 1	**Main cohort[l]** olaparib (N = 196) placebo (N = 99)	Screening: ≤ 28 days Treatment: until disease progression according to RECIST[i], toxicity, withdrawal of consent Observation[g]: outcome-specific, at most until death, withdrawal of consent or final survival time analysis	**Main cohort** 119 centres in Australia, Belgium, Brazil, Canada, France, Germany, Israel, Italy, Japan, Korea, Netherlands, Poland, Russia, Spain, United Kingdom and USA 8/2013–ongoing **Data cut-off:** 19 September 2016 (primary analysis[m])	Primary: PFS Secondary: overall survival, health status, health-related quality of life, AEs

Table 6: Characteristics of the studies included by the company – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
b. Defined as disease progression later than 6 months after last dose of the penultimate platinum-containing chemotherapy.
c. High-grade (or grade 3) serous or high-grade mostly serous histology or known germline BRCA mutation.
d. Complete or partial response and either a CA-125 level within the normal range or at least 90 percent reduction in CA-125 level, stable for at least 7 days.
e. Cohorts initially planned for the study. Not relevant for the indirect comparison.
f. Determined by CT/MRI according to RECIST 1.1 and/or by additional diagnostic tests (e.g. histological/cytological, ultrasound, endoscopy, PET) and/or by clear clinical signs and symptoms independent of non-malignant or iatrogenic causes.
g. Outcome-specific information is provided in Table 8.
h. Complete or partial response according to RECIST 1.1 and/or at least 50 percent reduction in CA-125 level in comparison with the last measurement before start of treatment, confirmed after 28 days.
i. 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 discontinuation.
j. Thereof data cut-offs relevant for the benefit assessment: 30 June 2010: primary analysis after 153 progression events; 9 May 2016: last data cut-off after death of 79% of the patients.
k. Complete or partial response according to RECIST 1.1 or no evidence of disease if optimal cytoreductive surgery was conducted prior to chemotherapy and no evidence of a rising CA-125 level.
l. In addition to the main cohort, there is a Chinese cohort of 32 patients, which is not taken into account, as no relevant additional information is expected from this (see benefit assessment A18-36 [4]).
m. Primary analysis after 187 progression events.

ACT: appropriate comparator therapy; AE: adverse event; BRCA: breast cancer associated gene; CA-125: cancer antigen-125; CT: computed tomography; ECOG PS: Eastern Cooperative Oncology Group Performance Status; gBRCAmut: germline BRCA mutation; MRI: magnetic resonance imaging; n: subpopulation; N: number of randomized (included) patients; PET: positron emission tomography; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; vs.: versus

Table 7: Characteristics of the intervention – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study	Intervention	Comparison
Intervention vs. common comparator		
NOVA	Niraparib 300 mg (3 x 100 mg), orally, once daily at the same time of the day, preferably in the morning	Placebo, orally, once daily at the same time of the day, preferably in the morning
	The study medication was administered continuously. The study was divided into cycles of 28 days.	
	Dose adjustments/treatment interruptions In case of toxicity, up to 2 dose reductions (minimum dose per day = 100 mg) and treatment interruptions of up to 28 days were allowed.	
	Pretreatment ***Required:*** ▪ ≥ 2 previous courses of platinum-based therapy (not necessarily sequential) ▫ penultimate platinum-based chemotherapy (decisive for the definition as platinum-sensitive): - response of the patient to the therapy with complete or partial response - disease progression > 6 months after the last dose of platinum-based therapy ▫ most recent platinum-based chemotherapy with ≥ 4 cycles: - response of the patient to the therapy with complete or partial response - after the last treatment, CA-125 within the normal range or CA-125 reduction of more than 90% during therapy, which remained stable for 7 days - no measurable lesion > 2 cm at the time point of inclusion in the study ***Not allowed:*** ▪ drainage of ascites during 2 cycles of the last chemotherapy regimen ▪ ≤ 1 week before start of the study: palliative radiotherapy comprising > 20% of bone marrow within one week ▪ PARP inhibitors **Concomitant treatment** ***Allowed:*** ▪ corticosteroids in stable dosing if treatment was initiated ≥ 4 weeks before the start of the study ▪ palliative radiotherapy for small existing metastases that do not response to local or systemic analgesics ▪ prophylactic cytokines[a] ***Not allowed:*** ▪ other chemotherapy, hormonal therapy (hormone replacement therapy acceptable) ▪ vaccines ▪ drugs that prolong the corrected QT interval	

Table 7: Characteristics of the intervention – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study	Intervention	Comparison
ACT vs. common comparator		
Study 19	Olaparib 400 mg, orally, twice daily as hard capsules (total daily dose: 800 mg), at least 1 hour after and 2 hours before a meal	Placebo 400 mg, orally, twice daily as hard capsules (total daily dose: 800 mg), at least 1 hour after and 2 hours before a meal
	Dose adjustments, treatment interruptions and treatment discontinuation due to toxicity are possible[b]. Dose increases after prior reductions were not allowed.	
	Pretreatment ***Required:*** ▪ ≥ 2 platinum-based chemotherapy regimens (not necessarily sequential) ▫ penultimate platinum-containing chemotherapy decisive for definition as platinum-sensitive with disease progression ≥ 6 months after the last dose of platinum-containing chemotherapy ▫ most recent platinum-containing chemotherapy with ≥ 4 cycles and partial or complete response; last dose within 8 weeks before study inclusion ***Not allowed:*** ▪ PARP inhibitors **Concomitant treatment** ***Allowed:*** ▪ corticosteroids as well as bisphosphonates 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 existing small areas of painful bone metastases that cannot be treated with local or systemic analgesics, as long as there is no evidence of disease progression ▪ antiemetics, antidiarrhoeal drugs (not as routine prophylaxis) ▪ warfarin, subcutaneous heparin ***Not allowed:*** ▪ other chemotherapies, immunotherapy, hormonal therapy (hormone replacement therapy is acceptable) or other novel agents ▪ G-CSF/GM-CSF and erythropoietin prophylaxis in the first treatment cycle ▪ potent CYP3A4 inhibitors or inducers as well as drugs, herbal products or foods (e.g. grapefruit juice, star fruit) with known CYP3A4 enzyme activity	

Table 7: Characteristics of the intervention – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study	Intervention	Comparison
SOLO2	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 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
	Dose adjustments, treatment interruptions and treatment discontinuation due to toxicity are possible[b]	
	Pretreatment ***Required:*** ▪ ≥ 2 platinum-based chemotherapy regimens (not necessarily sequential) ▫ penultimate platinum-containing chemotherapy decisive for definition as platinum-sensitive with disease progression ≥ 6 months after the last dose of platinum-containing chemotherapy ▫ most recent platinum-containing chemotherapy with ≥ 4 cycles and partial or complete response; last dose within 8 weeks before randomization ***Not allowed:*** ▪ PARP inhibitors ▪ Bevacizumab as concomitant treatment to the last platinum-containing chemotherapy before study inclusion **Concomitant treatment** ***Allowed:*** ▪ corticosteroids for symptom control in brain metastases as well as bisphosphonates or denosumab in 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 at the start of the study as long as there is no evidence of disease progression ▪ antiemetics, antidiarrhoeal drugs ▪ G-CSF in febrile neutropenia ▪ Warfarin, subcutaneous heparin ***Not allowed:*** ▪ other chemotherapy, other anticancer treatments, immunotherapy, hormonal therapy (hormone replacement therapy acceptable), radiotherapy, biologic therapy or other novel and investigational drugs ▪ potent CYP3A4 inhibitors or inducers as well as drugs, herbal products or foods with known CYP3A4 enzyme activity	

a. These were only disallowed during the first cycle, then allowed according to local guidelines.
b. Toxicity-related dose adjustments up to treatment discontinuation were performed without relevant deviations from the requirements of the SPC.

ACT: appropriate comparator therapy; CA: cancer antigen, CYP: cytochrome P450; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; PARP: poly(adenosine diphosphate-ribose) polymerase; RCT: randomized controlled trial; vs.: versus

Study design

NOVA (study with niraparib)

The NOVA study was a double-blind, randomized parallel-group study on the comparison of niraparib versus placebo. The study included adult patients with platinum-sensitive relapse of high-grade serous epithelial ovarian cancer who had achieved complete or partial response to

prior platinum-containing chemotherapy. The patients were assigned to one of 2 cohorts based on their germline BRCA mutation status (gBRCAmut and non-gBRCAmut). To be eligible for study inclusion, the patients had to be in good general condition (Eastern Cooperative Oncology Group Performance Status [ECOG PS] between 0 and 1).

A total of 553 patients were enrolled in the NOVA study. Of these patients, 203 were assigned to the gBRCAmut cohort and 350 to the non-gBRCAmut cohort. These were randomized in a 2:1 ratio and allocated either to treatment with niraparib (N: 372 [gBRCAmut: 138; non-gBRCAmut: 234]) or to placebo (N: 181 [gBRCAmut: 65; non-gBRCAmut: 116]). Randomization was stratified according to the time to disease progression after the last dose of the penultimate platinum-containing chemotherapy before inclusion in the study (> 6 to 12 months/> 12 months), response during the last platinum-containing chemotherapy (complete or partial) and the use of bevacizumab in relation with the penultimate or the last platinum-containing treatment regimen (yes/no).

Treatment with niraparib was conducted in compliance with the German approval status [6]. Dose reductions due to toxicity were allowed in the study and were performed in 73% of the patients in the course of the study.

Treatment with niraparib was until disease progression, unacceptable persistent toxicity, risk for the patient as assessed by the investigator, withdrawal of consent, severe protocol violations or pregnancy. Three criteria could be used in the NOVA study to determine disease progression: RECIST 1.1, other diagnostic tests (e.g. histological/cytological, ultrasound, endoscopy, positron emission tomography [PET]) or clear clinical signs and symptoms. However, at the physician's discretion, patients could continue treatment with the study medication even after disease progression as long as the physician deemed the treatment to be beneficial for the patients and treatment was acceptable.

Patients could only be unblinded in case of emergency or if they wanted to participate in a further study on poly(adenosine diphosphate-ribose) polymerase [PARP] inhibitors. Unblinding to make a decision on subsequent therapies after disease progression was not intended. Switching to treatment with niraparib was also not intended for patients under placebo.

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

Study 19 (study with olaparib)

Study 19 was a double-blind, randomized parallel-group study on the comparison of olaparib versus placebo. The study included adult patients with platinum-sensitive relapse of high-grade serous epithelial ovarian cancer who had achieved complete or partial response to prior platinum-containing chemotherapy. The patients were included regardless of their BRCA

mutation status, which was determined after the primary data cut-off, however. The patient's general condition at baseline had to be good to restricted (ECOG PS of 0 to 2).

The study included a total of 265 patients, randomized in a 1:1 ratio either to treatment with olaparib (N = 136) or to placebo (N = 129). Randomization was stratified according to the time to disease progression after the last dose of the penultimate platinum-containing chemotherapy before inclusion in the study (> 6 to 12 months/> 12 months), objective response to the last platinum-containing chemotherapy before inclusion in the study (complete or partial) and Jewish family origin (yes/no; due to an increased BRCA mutation prevalence in this population).

Treatment with olaparib was conducted in compliance with the German approval status [7].

Patients were treated until disease progression according to RECIST 1.1, toxicity or withdrawal of consent. However, at the physician's discretion, patients could continue treatment with the study medication even after disease progression according to RECIST 1.1 as long as the physician deemed the treatment to be beneficial for the patients and there were no other criteria for discontinuation.

The decision on follow-up therapies after treatment discontinuation was at the discretion of the physician. For the decision on follow-up therapies after disease progression according to RECIST 1.1, patient and physician could be unblinded individually upon request to the sponsor, if essential for the protection of the patients. It was not allowed to switch from the placebo arm to treatment with olaparib after disease progression. However, olaparib was already available in some study centres when the study was conducted, so that some patients from the placebo arm received olaparib as follow-up therapy nonetheless.

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

SOLO2 (study with olaparib)

The SOLO2 study was also a double-blind, randomized parallel-group study on the comparison of olaparib versus placebo. The study only included patients with known BRCA mutation and additionally those with non-serous (endometrioid) histology. Thus, the study included adult patients with platinum-sensitive relapse of BRCA-mutated high-grade serous epithelial or non-serous ovarian cancer who had responded to prior platinum-containing chemotherapy. Regarding the general condition of the patients, an ECOG PS between 0 and 1 was an inclusion criterion of the SOLO2 study.

The study included a total of 295 patients, randomized in a 2:1 ratio either to treatment with olaparib (N = 196) or to placebo (N = 99). Randomization was stratified according to the response to the most recent platinum-containing chemotherapy (complete or partial) and the

time to disease progression after the penultimate platinum-containing chemotherapy before inclusion in the study (> 6 to 12 months/> 12 months).

In China, there was a cohort (Chinese cohort) with the same study protocol, which was started later and thus investigated separately. This cohort was not taken into account, as no relevant additional information was expected from this (see benefit assessment A18-36 [4]).

Treatment with olaparib was conducted in compliance with the German approval status [7].

Patients were treated until disease progression according to RECIST 1.1, toxicity or withdrawal of consent. However, at the investigator's discretion, patients could continue treatment with the study medication even after disease progression according to RECIST 1.1 as long as the physician deemed the treatment to be beneficial for the patients and there were no other criteria for discontinuation. The cancer antigen-125 (CA-125) level was regularly recorded; however, an increased CA-125 level presented no criterion for discontinuation.

As in Study 19, the decision on follow-up therapies after treatment discontinuation was at the discretion of the physician. To decide on follow-up therapies after disease progression according to RECIST 1.1 with commercially available olaparib or with a PARP inhibitor in the framework of another study, patient and physician could be unblinded. It was not allowed to switch from the placebo arm to treatment with olaparib after disease progression. However, as during Study 19, olaparib was available in some study centres, so that some patients from the placebo arm received olaparib as follow-up therapy nonetheless.

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

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, indirect comparison: niraparib vs. olaparib

Study **Outcome category** **Outcome**	**Planned follow-up observation**
NOVA	
Mortality	
Overall survival	Until death, withdrawal of consent, lost to follow-up, unblinding or final survival time analysis
Morbidity	
Health status (EQ-5D VAS, FOSI-8)	8 weeks (± 2 weeks) after the last dose of the study medication
Side effects	
AEs/severe AEs (CTCAE grade ≥ 3)	No follow-up after the last administration of the study medication
SAEs	30 days after the last administration of the study medication
Study 19	
Mortality	
Overall survival	Until death, withdrawal of consent or final survival time analysis
Morbidity	No patient-relevant outcomes recorded
Health-related quality of life (FACT-O)	Until disease progression[a]
Side effects	
All outcomes in the category "side effects"	Until 30 days after the last dose of the study medication
SOLO2	
Mortality	
Overall survival	Until death, withdrawal of consent or final survival time analysis
Morbidity	
Health status (EQ-5D VAS)	Over a total period of 24 months or until the data cut-off of the primary analysis
Health-related quality of life (FACT-O)	Over a total period of 24 months or until the data cut-off of the primary analysis
Side effects	
AEs/SAEs	Until 30 days after the last dose of the study medication
Specific AEs (myelodysplastic syndrome/acute myeloid leukaemia/further neoplasms)	Unlimited observation beyond the end of treatment

a. With Amendment 4 to the protocol (2 November 2010), the recording of health-related quality of life was no longer considered necessary based on the results of the primary data cut-off.

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; FOSI-8: FACT Ovarian Symptom Index-8; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The observation periods in the studies NOVA, 19 and SOLO2 for the outcomes of morbidity, health-related quality of life and side effects were systematically shortened. 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.

Deviating from this, the SOLO2 study had unlimited observation periods at least for the specific AEs “myelodysplastic syndrome”, “acute myeloid leukaemia” and “new primary malignant neoplasms”, besides overall survival. In addition, the patient-reported outcomes in this study were observed beyond treatment discontinuation up to 24 months.

Data cut-offs

- For the NOVA study, one preplanned data cut-off (30 May 2016) for the primary analysis is available so far. This was planned after 98 progression events in the gBRCAmut cohort and 98 progression events in the subgroup of patients in the gBRCA cohort with homologous recombination deficiency. Data for all patient-relevant outcomes are available for this data cut-off. This data cut-off was used for the benefit assessment.
- For Study 19, an analysis of overall survival after death of about 85% of the patients was planned as the final data cut-off; the present 6th data cut-off (9 May 2016) took place after the death of 79% of the patients. For the benefit assessment, data on the 6th data cut-off are available for all patient-relevant outcomes except health-related quality of life. Only data on the first data cut-off (30 June 2010) are available for health-related quality of life, as this outcome was analysed only once and its recording was then discontinued based on the results of the analysis.
- For the SOLO2 study, one preplanned data cut-off (19 September 2016) for the primary analysis after 187 progression events is available so far. Data for all patient-relevant outcomes are available for this data cut-off. This data cut-off was used for the benefit assessment.

Study population

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

Table 9: Characteristics of the study populations – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study	NOVA		Study 19		SOLO2	
Characteristics	Niraparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
Category	N[a] = 372	N[a] = 181	N[a] = 136	N[a] = 129	N[a] = 196	N[a] = 99
Age [years], mean (SD)	60 (10)	60 (10)	59 (11)	59 (10)	57 (9)	57 (9)
Family origin, n (%)						
White	324 (87.1)	156 (86.2)	130 (96)	126 (98)	173 (88)	91 (92)
Non-white	48 (12.9)[b]	25 (13.8)[b]	6 (4)[b]	3 (2)[b]	23 (12)[b]	8 (8)[b]
Region, n (%)						
Europe	–[c]	–[d]	95 (70)[b, e]	89 (69)[b, e]	114 (58[b])	62 (63[b])
Other	–[c]	–[d]	41 (30)[b]	40 (31)[b]	82 (42[b])	37 (37[b])
gBRCA mutation, n (%)						
Yes	138 (37.1[b])	65 (35.9[b])	53 (39.0)[b, f, g]	43 (33.3)[b, f, g]	193 (98.5)[b, h]	99 (100)[b, h]
No[i]	234 (62.9[b])	116 (64.1[b])	78 (57.4)[b]	80 (62.0)[b]	2 (1.0)[b]	0 (0)[b]
Missing	0 (0)	0 (0)	5 (3.7[b])	6 (4.7[b])	1 (0.5)	0 (0)
Histology, n (%)						
Serous	332 (89.2[b])	169 (93.4[b])	136 (100)	129 (100)	183 (93.4)	86 (86.9)
Non-serous	23 (6.2)[b]	7 (3.9)[b]	0 (0)	0 (0)	12 (6.1)[j]	13 (13.1)[j]
Missing	17 (4.6)[b]	5 (2.8)[b]	0 (0)	0 (0)	1 (0.5)	0 (0)
Primary tumour location, n (%)						
Ovaries	314 (84.4)	149 (82.3)	119 (87.5)	109 (84.5)	162 (82.7)	86 (86.9)
Fallopian tubes	27 (7.3)	17 (9.4)	3 (2.2)	3 (2.3)	13 (6.6)	4 (4.0)
Primary peritoneum	31 (8.3)	14 (7.7)	14 (10.3)	16 (12.4)	18 (9.2)	9 (9.1)
Other	0 (0)	0 (0)	0 (0)	1 (0.8)	2 (1.0)	0 (0)
Unknown	0 (0)	1 (0.6)[b]	0 (0)	0 (0)	1 (0.5)	0 (0)
Duration of disease [years], mean (SD)	3.7 (2.4)	3.8 (2.4)	ND	ND	ND	ND

Table 9: Characteristics of the study populations – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study	NOVA		Study 19		SOLO2	
Characteristics	Niraparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
Category	N[a] = 372	N[a] = 181	N[a] = 136	N[a] = 129	N[a] = 196	N[a] = 99
Number of previous chemotherapies, n (%)						
1	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2	225 (60.5)	107 (59.1)	60 (44.1)	63 (48.8)	108 (55.1)	60 (60.6)
≥ 3	146 (39.2)[b]	73 (40.3)[b]	76 (55.9)	66 (51.2)	87 (44.4)	39 (39.4)
Unknown	0 (0)	1 (0.6)	0 (0)	0 (0)	1 (0.5)	0 (0)
Number of previous platinum-containing chemotherapies, n (%)						
< 2	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2	253 (68.0)	124 (68.5)	76 (55.9)	84[k] (65.1)	110 (56.1)	62 (62.6)
≥ 3	118 (31.7)	56 (30.9)	60 (44.1)[b]	45 (34.9)[b]	85 (43.4)[b]	37 (37.4)[b]
Unknown	0 (0)	1 (0.6)	0 (0)	0 (0)	1 (0.5)	0 (0)
FIGO stage at diagnosis, n (%)						
Stage 0	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Stage I[l]	14 (3.8)[b]	11 (6.1)[b]	3 (2.2)[b]	4 (3.1)[b]	6 (3.1)[b]	2 (2.0)[b]
Stage II[m]	31 (8.3)[b]	4 (2.2)[b]	11 (8.1)[b]	8 (6.2)[b]	17 (8.7)[b]	6 (6.1)[b]
Stage III[n]	268 (72.0)[b]	132 (72.9)[b]	103 (75.7)[b]	98 (76.0)[b]	142 (72.4)[b]	79 (79.8)[b]
Stage IV	58 (15.6)	33 (18.2)	17 (12.5)	17 (13.2)	29 (14.8)	12 (12.1)
Unknown	0 (0)	1 (0.65)[b]	2 (1.5)	2 (1.6)	2 (1.0)	0 (0)

Table 9: Characteristics of the study populations – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study	NOVA		Study 19		SOLO2	
Characteristics	Niraparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
Category	N[a] = 372	N[a] = 181	N[a] = 136	N[a] = 129	N[a] = 196	N[a] = 99
Tumour grade[o], n (%)						
G1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
G2	16 (4.3[b])	10 (5.5[b])	36 (26.5)	34 (26.4)	16 (8.2)	6 (6.1)
G3	121 (32.5[b])	67 (37.0[b])	97 (71.3)	89 (69.0)	167 (85.2)	85 (85.9)
G4	ND	ND	2 (1.5)	4 (3.1)	5 (2.6)	3 (3.0)
Low grade	3 (0.8[b])	1 (0.6[b])	ND	ND	ND	ND
High grade	200 (53.8[b])	90 (49.7[b])	ND	ND	ND	ND
Not assessable	15 (4.0[b])	8 (4.4[b])	1 (0.7)	2 (1.6)	7 (3.6)	5 (5.1)
Unknown	17 (4.6)[b]	5 (2.8)[b]	0 (0)	0 (0)	1 (0.5)	0 (0)
ECOG PS, n (%)						
0	251 (67.5)	126 (69.6)	110 (80.9)	95 (73.6)	162 (82.7)	77 (77.8)
1	121 (32.5)	55 (30.4)	23 (16.9)	30 (23.3)	32 (16.3)	22 (22.2)
2	0 (0)	0 (0)	1 (0.7)	2 (1.6)	0 (0)	0 (0)
Unknown	0 (0)[b]	0 (0)[b]	2 (1.5)	2 (1.6)	2 (1.0)	0 (0)
Time to progression after penultimate platinum-containing chemotherapy, n (%)						
6–12 months	144 (38.7)	70 (38.7)	53 (39.0)	54 (41.9)	79 (40.3)	40 (40.4)
≥ 12 months	228 (61.3)	111 (61.3)	83 (61.0)	75 (58.1)	117 (59.7)	59 (59.6)
Objective response to most recent platinum-containing chemotherapy, n (%)						
Complete	188 (50.5)	93 (51.4)	57 (41.9)	63 (48.8)	91 (46.4)	47 (47.5)
Partial	184 (49.5)	88 (48.6)	79 (58.1)	66 (51.2)	105 (53.6)	52 (52.5)
Previous[p] cytoreductive surgery, n (%)						
Yes	ND	ND	44 (32.4)	40 (31.0)	18 (9.2)	10 (10.1)
No	ND	ND	92 (67.6)[b]	89 (69.0)[b]	178 (90.8)	89 (89.9)

Table 9: Characteristics of the study populations – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study Characteristics Category	NOVA		Study 19		SOLO2	
	Niraparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
	N[a] = 372	N[a] = 181	N[a] = 136	N[a] = 129	N[a] = 196	N[a] = 99
Treatment discontinuation, n (%)	274 (73.7)	163 (90.1)	117 (86.0[b])	127 (98.4[b])	112 (57.1[b])	86 (86.9[b])
Study discontinuation[q], n (%)	106 (28.5)	65 (35.9)	97 (71.3[b])	103 (79.8[b])	55 (28.1[b])	37 (37.4[b])

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant (> 10 percent).
b. Institute's calculation.
c. USA and Canada: 149 (40.1%); Western Europe, Australasia and Israel: 211 (56.7%); Eastern Europe, Latin America and Asia: 12 (3.2%).
d. USA and Canada: 72 (39.8%); Western Europe, Australasia and Israel: 103 (56.9%); Eastern Europe, Latin America and Asia: 6 (3.3%).
e. Including Russia and Israel.
f. Either based on measurements with tests of the companies Myriad or Foundation Medicine or based on the information provided in the case report form at the beginning of the study.
g. Values based on the number of randomized patients with BRCA mutation (olaparib: 74 patients vs. placebo: 62 patients).
h. Confirmed with local measurement or with test of the company Myriad.
i. Patients may have somatic BRCA mutations.
j. Mainly endometrioid (olaparib: 4.6%; placebo: 8.1%), otherwise mixed epithelial (olaparib: 1.5%; placebo: 4.0%) and one patient in the placebo arm with simultaneous declaration of serous, papilliferum and endometrioid.
k. Discrepancy between tables in the study documents, as erroneously no initial entry was made for one patient.
l. Composed of stages I, IA, IB and IC (only stages IB and IC were present in Study 19).
m. Composed of stages II, IIA, IIB, IIC.
n. Composed of stages III, IIIA, IIIB, IIIC.
o. Different systems were used for tumour grading. The study documents do not provide any specific information on the grading systems used.
p. For study SOLO2, "previous" means that the cytoreductive surgery was conducted after the last progression and before randomization.
q. Including study discontinuation due to death.

BRCA: breast cancer associated gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; gBRCA: germline BRCA mutation; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The characteristics of the patients between the arms of the individual studies were sufficiently balanced. The average age of the patients in all 3 studies was about 59 years; most of them were white and they were in good general condition (ECOG PS of 0 or 1). The patients' primary tumours were mostly ovarian and, at diagnosis, in Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage III.

Differences in the characteristics resulted from the inclusion criteria regarding the BRCA mutation status. Only patients with germline BRCA mutation were included in the SOLO2 study, whereas most patients in the studies NOVA and 19 had no germline BRCA mutation. There was a noticeable difference also regarding tumour grades. These aspects are discussed in detail in the examination of similarity in Section 2.3.3.

Treatment duration and observation period

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

Table 10: Information on the course of the study – RCT, indirect comparison: niraparib vs. olaparib

Study **Duration of the study phase** **Outcome category**		
Niraparib vs. common comparator	**Niraparib**	**Placebo**
NOVA	N = 372	N = 181
Treatment duration [months[a]]		
Median [Q1; Q3]	8.2 [3.7; 15.2]	5.4 [3.5; 8.7]
Mean (SD)	9.9 (6.9)	7.0 (5.4)
Observation period [months]		
Overall survival		
Median [Q1; Q3]	15.9 [13.0; 20.7]	15.0 [12.5; 19.2]
Mean (SD)	16.3 (6.1)	15.3 (6.1)
Morbidity	ND	
Health-related quality of life	No patient-relevant outcomes recorded	
Side effects	ND	
Olaparib vs. common comparator	**Olaparib**	**Placebo**
Study 19[b]	N = 136	N = 129
Treatment duration [months[a]]		
Median [min; max]	8.7 [0.1; 85.7]	4.6 [1.1; 83.9]
Mean (SD)	20.0 (24.7)	7.1 (9.6)
Observation period [months]		
Overall survival	ND	
Morbidity	No patient-relevant outcomes recorded	
Health-related quality of life	ND	
Side effects	ND	
SOLO2	N = 196	N = 99
Treatment duration [months[c]]		
Median [min; max]	19.3 [0.23; 34.7]	5.6 [0.9; 31.5]
Mean (SD)	17.4 (9.8)	9.0 (8.1)
Observation period [months]		
Overall survival		
Median [min; max]	25.3 [ND; ND]	25.1 [ND; ND]
Mean (SD)	ND	ND
Morbidity	ND	
Health-related quality of life	ND	
Side effects	ND	

a. Institute's calculation from data in days.
b. Data cut-off 9 May 2016.
c. Institute's calculation from data in weeks.

max: maximum; min: minimum; N: number of randomized patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

There were differences in treatment duration and observation periods of the total population between the treatment arms of the studies NOVA, 19 and SOLO2. In all studies, differences between the treatment arms were due to differences in the treatment discontinuation rates mainly due to disease progression.

Observation periods and treatment duration also differed between the studies. The studies NOVA and 19 showed similar treatment durations and observation periods. The 2 olaparib studies 19 and SOLO2, in contrast, showed clear differences in treatment duration and observation period. This was mainly due to the fact that the median onset of disease progression was about 11 months earlier in the olaparib arm of Study 19, which entailed the planned termination of treatment and observation of most outcomes.

2.3.3 Similarity of the studies for the indirect comparison

From the study characteristics described in the previous Section 2.3.2, several aspects concerning the similarity of studies arise. These are discussed in more detail below.

Similarity of study conduct

Treatment duration and observation period

The median treatment duration in the common comparator arm (placebo) is comparable with 5.4 months in the NOVA study, 4.6 months in Study 19 and 5.6 months in the SOLO2 study. The median observation period for overall survival was 15 months in the NOVA study and 25.1 months in the SOLO2 study. No information on the observation period was available for Study 19. This means for the adjusted indirect comparison that outcome- and analysis-specific checks must be made as to whether the different observation periods play a role. Provided that time-adjusted analyses (effect measure hazard ratio) are available and no heterogeneity was observed between the olaparib studies, it is assumed that these differences are acceptable.

Furthermore, with few exceptions, outcomes on morbidity, health-related quality of life and side effects were not observed far beyond the end of treatment in all studies. In the NOVA study, AEs were recorded during treatment, and only SAEs were recorded for 30 days beyond the end of treatment. For the studies 19 and SOLO2, AE outcomes were observed until 30 days after the last study medication. The differences in follow-up observation for AE outcomes between the NOVA study on the one side and the studies 19 and SOLO2 on the other were so marginal that the assumption of similarity was not rejected because of this.

Similarity of the common comparator

Treatment and observation of the patients in the placebo arms were similar in the 3 studies NOVA, 19 and SOLO2. In all 3 studies, the patients underwent regular radiological diagnostics for disease progression. In the NOVA study, the patients had radiological examinations every 8 weeks for the first 14 treatment cycles (about 14 months), and every 12 weeks after cycle 14. In the studies 19 and SOLO2, radiological examinations were conducted every 12 weeks in the

first phase, and every 24 weeks after 60 weeks (Study 19) or after 72 weeks (SOLO2). The similarity of the examination intervals of the studies was considered sufficient.

Unblinding and subsequent therapies

There were differences regarding unblinding between the NOVA study on the niraparib side and the studies 19 and SOLO2 on the olaparib side, however. In the studies 19 and SOLO2, unblinding was possible to make an informed decision regarding subsequent therapies. In the NOVA study, in contrast, unblinding for the decision regarding subsequent therapies was not intended. This had no major influence on the choice of subsequent therapies, however. In all studies included, chemotherapy was by far the most common subsequent therapy after treatment discontinuation (see Appendix B of the full dossier assessment).

Similarity of the patient population

The demographic and clinical characteristics of the patients included were mostly comparable between the placebo arms of the studies. The SOLO2 study only included patients with germline BRCA mutations, whereas the studies NOVA and 19 included patients both with and without BRCA mutations. Since the approval of niraparib and olaparib is independent from the BRCA mutation status, this had no consequences for the present benefit assessment. However, the influence of the BRCA mutation status should be investigated in a subgroup analysis, since it is discussed whether the BRCA mutation status has an influence on tumour sensitivity to PARP inhibitors [8]. Benefit assessment A18-36 on olaparib [4] did not identify an effect modification by the characteristic of BRCA mutation status in a comparable therapeutic indication, however (based on data of the studies 19 and SOLO2).

The studies also showed differences in the tumour grades of the patients included. Thus, 26% of the patients in the placebo arm of Study 19 had tumour grade G2, whereas this proportion was only 6% in the other 2 studies. Furthermore, the tumour grade G4 was not recorded at all in the NOVA study. Instead, patients in this study could also be recorded using a 2-stage grading system (high grade/low grade). It is known that several grading systems exist for serous epithelial ovarian cancers [9]. The documents on the NOVA study show that no tumour grading in the patients was conducted on enrolment, and that information on 2 different grading systems was obtained instead.

Summary of the similarity

The check of the similarity of the studies NOVA, 19 and SOLO2 showed no major differences with regard to the patients included and the conduct of the studies. The similarity of the studies was therefore considered to be sufficient for an adjusted indirect comparison using the common comparator placebo. At outcome level, however, there were differences in follow-up observation between the studies NOVA and SOLO2 for health status recorded with the EQ-5D VAS (see Section 2.7.5.3.2 of the full dossier assessment). Hence, no usable data for this outcome are available for the indirect comparison between niraparib and olaparib.

2.3.4 Check of the homogeneity assumption

The assumption of homogeneity is one of the central assumptions in adjusted indirect comparisons (see Section 2.7.5.3.1 of the full dossier assessment). For both olaparib studies included, heterogeneity was checked in the framework of the meta-analytical summary for the A18-36 report. No important heterogeneity was determined for the results of the outcomes assessed.

2.3.5 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) – RCT, indirect comparison: niraparib vs. olaparib

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			
Niraparib vs. placebo							
NOVA	Yes	Yes	Yes	Yes	Yes	Yes	Low
Olaparib vs. placebo							
Study 19	No[a]	Yes	Yes	Yes	Yes	Yes	High
SOLO2	Yes	Yes	Yes	Yes	Yes	Yes	Low

a. Large proportion of patients with incorrect classification in the stratified block randomization in the total study population (olaparib: 35.3%, placebo: 24.0%).

RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for the studies NOVA and SOLO2. For Study 19, the risk of bias was rated as high due to the large proportions of patients in both treatment arms with incorrect classification in the stratified block randomization. For the studies NOVA and SOLO2, this concurs with the assessment of the company, which rated the risk of bias across outcomes for Study 19 as low, however.

2.4 Results on added benefit

2.4.1 Analyses of the company unsuitable for adjusted indirect comparison

The company conducted the indirect comparison separately for 3 subpopulations. For this purpose, it distinguished between patients with germline BRCA mutations, patients with BRCA mutations of any kind, and patients without BRCA mutations. This approach is inadequate for the following reasons:

- The research question of the G-BA (and the approval) is independent from the BRCA mutation status, and benefit assessment A18-36 on olaparib in the identical therapeutic indication was also conducted independent from the mutation [4]. It would be meaningful to conduct subgroup analyses according to BRCA mutation status, however.
- In addition, due to the high risk of bias of the 2 olaparib studies 19 and SOLO2 for all relevant outcomes, only a meta-analysis of both studies offers sufficient certainty of results for an indirect comparison (see Section 2.7.5.3.1 of the full dossier assessment).
- Besides, in the division made by the company, patients with germline BRCA mutations from the NOVA study are included both in the subpopulation of patients with germline BRCA mutations and in the subpopulation of patients with BRCA mutations of any kind and are therefore represented twice in the analysis. Thus, the approach is also methodologically inadequate.

Against this background, in the present assessment, the adjusted indirect comparison was calculated by the Institute for the respective total populations, provided that data with sufficient certainty of results were available for this comparison. The meta-analytical summary of both olaparib studies was taken from benefit assessment A18-36 [4].

2.4.2 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.5.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - health status (EQ-5D VAS)
- Health-related quality of life
  - health-related quality of life measured using the FACT-O total score
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - acute myeloid leukaemia (Preferred Term [PT])
  - myelodysplastic syndrome (PT)
  - pneumonitis (PT)
  - 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 2.7.5.3.2 of the full dossier assessment).

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

Table 12: Matrix of outcomes – RCT, indirect comparison: olaparib vs. niraparib

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)	Specific AEs[a]
Niraparib vs. placebo							
NOVA	Yes	No[b]	No[c]	Yes	Yes	Yes	Yes
Olaparib vs. placebo							
Study 19	Yes	No	Yes	Yes	Yes	Yes	Yes
SOLO2	Yes	No[b]	Yes	Yes	Yes	Yes	Yes

a. Consideration of the following events: acute myeloid leukaemia, myelodysplastic syndrome, pneumonitis (for further specific AEs, see Section 2.7.5.3.2 of the full dossier assessment).
b. No usable data available, as different strategies for follow-up observation of this outcome were used in the studies; for reasons, see Section 2.7.5.3.2 of the full dossier assessment).
c. The FACT-O was not completely recorded in the NOVA study, but only the 8 items for the calculation of the FOSI-8 symptom score.

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; FOSI-8: FACT Ovarian Symptom Index-8; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.3 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, indirect comparison: niraparib vs. olaparib

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)	Further specific AEs[a]
Niraparib vs. placebo								
NOVA	L	L	-[b]	-[c]	H[d]	L	H[d]	H[d]
Olaparib vs. placebo								
Study 19	H[e]	H[f, g]	-[b]	H[f, h]	H[f, i]	H[f]	H[f, i]	H[f, i]
SOLO2	L	H[g, j]	-[b]	H[k]	H[l]	L	H[l]	H[l]

a. Consideration of the following events: acute myeloid leukaemia, myelodysplastic syndrome, pneumonitis (for further specific AEs, see Section 2.7.5.3.2 of the full dossier assessment).
b. No usable data available, as different strategies for follow-up observation of this outcome were used in the studies NOVA and SOLO2; for reasons, see Section 2.7.5.3.2 of the full dossier assessment. This outcome was not recorded for Study 19.
c. The FACT-O was not completely recorded in the NOVA study, but only the 8 items for the calculation of the FOSI-8 symptom score.
d. Incomplete observations for potentially informative reasons; large difference in the median treatment duration (and hence observation period) between the intervention arm (8.2 months) and the control arm (5.4 months).
e. Large proportion of patients with incorrect classification in the stratified block randomization in the total study population (olaparib: 35.3%, placebo: 24.0%).
f. Due to the high risk of bias across outcomes.
g. After progression, patients in the intervention arm could still receive olaparib outside the approval status at the physician's discretion. The number of patients and the duration of this continued treatment are not known.
h. 10% missing and thus unconsidered patients at baseline in the total study population; large differences in response rates in the course of the study; event-driven discontinuation of outcome recording.
i. Incomplete observations for potentially informative reasons; large difference in the median time to treatment discontinuation or death between the intervention arm (8.6 months) and the control arm (4.6 months).
j. Large proportion of patients in the placebo arm who switched to a PARP inhibitor after progression (22.2% as first subsequent therapy).
k. Different proportions of usable data at the documentation times with differences of up to about 35%.
l. Incomplete observations for potentially informative reasons; large difference in the median time to treatment discontinuation or death between the intervention arm (19.4 months) and the control arm (5.6 months).

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; FOSI-8: FACT Ovarian Symptom Index-8; H: high; L: low; PARP: poly(adenosine diphosphate-ribose) polymerase; RCT: randomized controlled trial: SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Except for the outcomes “overall survival” from the NOVA study and “discontinuation due to AEs” from the studies NOVA and SOLO2, the results of all outcomes from the studies NOVA, 19 and SOLO2 had a high risk of bias. This is justified below.

NOVA

For the NOVA study, there was a high risk of bias for the results on all AEs except for the outcome “discontinuation due to AEs”. Due to the notable differences in the median times to treatment discontinuation or death between the treatment arms (niraparib: 8.2 months versus placebo: 5.4 months), it can also be assumed that there were notable differences in the observation periods between the treatment arms and associated potentially informative censorings.

No usable data of the NOVA study were available for outcomes of morbidity and health-related quality of life (see Section 2.7.5.3.2 of the full dossier assessment).

Study 19

For Study 19, there was a high risk for all outcomes already due to the high risk of bias across outcomes. There are also other outcome-specific reasons (see Section 2.7.5.2 of the full dossier assessment).

SOLO2

On the one hand, as in Study 19, there was a high risk of bias of the result for the outcome “overall survival”, as patients in the intervention arm could continue treatment with olaparib outside the approval status after progression at the physician’s discretion. The number of patients and the duration of this continued treatment are also not known. On the other hand, there was a large proportion of patients in the placebo arm in the SOLO2 study who switched to a PARP inhibitor after progression (22.2% as first subsequent therapy [see Table 23 in Appendix B of the full dossier assessment]. There was a high risk of bias of the results for the outcomes “health status” and “health-related quality of life” due to different proportions of usable data at the documentation times with differences of up to about 35%. For the results of all AEs, except for the outcome “discontinuation due to AEs”, the assessment of a high risk of bias was due to incomplete observations for potentially informative reasons. There were notable differences in the median time to treatment discontinuation or death between the treatment arms (olaparib: 19.4 versus placebo: 5.6 months).

For all 3 studies, the certainty of results for the outcome “discontinuation due to AEs” was restricted despite low risk of bias (see Section 2.7.5.2 of the full dossier assessment).

2.4.4 Results

Table 14 summarizes the results of the comparison of niraparib with olaparib in patients with platinum-sensitive relapsed high-grade serous epithelial ovarian cancer who are in response (complete or partial) to platinum-based chemotherapy. Where necessary, calculations conducted

by the Institute are provided in addition to the data from the company's dossier. This concerns in particular the pooled patient group with different mutation status (see Section 2.4.1). The meta-analytical summary of both olaparib studies was taken from benefit assessment A18-36 [4]. The corresponding forest plots can also be found there. Kaplan-Meier curves on the outcome "overall survival" can be found in Appendix A of the full dossier assessment.

Table 14: Results (mortality, morbidity, side effects) – RCT, indirect comparison using common comparators: niraparib vs. olaparib (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Niraparib or olaparib** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Placebo** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Group difference** **HR [95% CI]; p-value**
Mortality					
Overall survival					
Niraparib vs. placebo					
NOVA[a]	372	NA 60 (16.1)	181	NA 35 (19.3)	0.73 [0.48; 1.13]; 0.155[b]
Olaparib vs. placebo					
Study 19[c]	136	29.8 [ND] 98 (72.1)	129	27.8 [ND] 112 (86.8)	0.73 [0.55; 0.95]; 0.021[d]
SOLO2[e]	196	NA 45 (23.0)	99	NA 27 (27.3)	0.80 [0.50; 1.31]; 0.427[f]
Total					0.74 [0.59; 0.94][g]; 0.011[h]
Indirect comparison with common comparator[i]:					
Niraparib vs. olaparib					0.99 [0.61; 1.60]; 0.956
Morbidity					
Health status (EQ-5D VAS)				No usable data[j]	
Health-related quality of life					
FACT-O total score				No usable data[k]	
Side effects					
AEs (supplementary information)					
Niraparib vs. placebo					
NOVA[a]	367	ND 367 (100.0)	179	ND 171 (95.5)	–
Olaparib vs. placebo					
Study 19[c]	136	0.1 [ND] 132 (97.1)	128	0.3 [ND] 119 (93.0)	–
SOLO2[e]	195	0.1 [ND] 192 (98.5)	99	0.2 [ND] 94 (94.9)	–

Table 14: Results (mortality, morbidity, side effects) – RCT, indirect comparison using common comparators: niraparib vs. olaparib (multipage table)

Outcome category Outcome Comparison Study	Niraparib or olaparib N	Niraparib or olaparib Median time to event in months [95% CI] Patients with event n (%)	Placebo N	Placebo Median time to event in months [95% CI] Patients with event n (%)	Group difference HR [95% CI]; p-value
SAEs					
Niraparib vs. placebo					
NOVA[a]	367	ND 110 (30.0)	179	ND 27 (15.1)	ND
Olaparib vs. placebo					
Study 19[c]	136	67.9 [ND] 31 (22.8)	128	42.0 [ND] 11 (8.6)	1.61 [0.79; 3.46]; 0.218[d]
SOLO2[e]	195	NA 35 (17.9)	99	NA 8 (8.1)	1.64 [0.79; 3.84]; 0.234[f]
Total					1.62 [0.94; 2.81]; 0.083[l]
Indirect comparison with common comparator[i]:					
Niraparib vs. olaparib					–[m]
Severe AEs (CTCAE grade ≥ 3)					
Niraparib vs. placebo					
NOVA[a]	367	ND 272 (74.1)	179	ND 41 (22.9)	ND
Olaparib vs. placebo					
Study 19[c]	136	22.9 [ND] 59 (43.4)	128	NA 28 (21.9)	1.88 [1.20; 3.01]; 0.013[d]
SOLO2[e]	195	NA 72 (36.9)	99	NA 18 (18.2)	1.92 [1.17; 3.33]; 0.012[f]
Total					1.90 [1.34; 2.68]; < 0.001[l]
Indirect comparison with common comparator[i]:					
Niraparib vs. olaparib					–[m]
Discontinuation due to AEs					
Niraparib vs. placebo					
NOVA[a]	367	ND 54 (14.7)	179	ND 4 (2.2)	ND
Olaparib vs. placebo					
Study 19[c]	136	NA 8 (5.9)	128	NA 2 (1.6)	1.96 [0.44; 13.68]; 0.528[d]
SOLO2[e]	195	NA 21 (10.8)	99	NA 2 (2.0)	3.71 [1.07; 23.40]; 0.063[f]
Total					2.79 [0.89; 8.80]; 0.080[l]
Indirect comparison with common comparator[i]:					
Niraparib vs. olaparib					–[m]

Table 14: Results (mortality, morbidity, side effects) – RCT, indirect comparison using common comparators: niraparib vs. olaparib (multipage table)

Outcome category Outcome Comparison Study	Niraparib or olaparib N	Median time to event in months [95% CI] Patients with event n (%)	Placebo N	Median time to event in months [95% CI] Patients with event n (%)	Group difference HR [95% CI]; p-value
Acute myeloid leukaemia					
Niraparib vs. placebo					
NOVA[a, n]	367	ND 0 (0)	179	ND 0 (0)	ND
Olaparib vs. placebo					
Study 19[c, o]	136	NA 0 (0)	128	NA 0 (0)	NC
SOLO2[e, o]	195	NA 1 (0.5)[p]	99	NA 0 (0)[p]	NC
Indirect comparison with common comparator[i]:					
Niraparib vs. olaparib					_[m]
Myelodysplastic syndrome					
Niraparib vs. placebo					
NOVA[a, n]	367	ND 3 (0.8)	179	ND 0 (0)	ND
Olaparib vs. placebo					
Study 19[c, o]	136	NA 0 (0)	128	NA 1 (0.8)	NC
SOLO2[e, o]	195	NA 1 (0.5)[p]	99	NA 0 (0)[p]	NC
Indirect comparison with common comparator[i]:					
Niraparib vs. olaparib					_[m]
Pneumonitis					
Niraparib vs. placebo					
NOVA[a, n]	367	ND 2 (0.5)[q]	179	ND 1 (0.6)[q]	ND
Olaparib vs. placebo					
Study 19[c, o]	136	NA 1 (0.7)	128	NA 1 (0.8)	0.91 [0.04; 23.06]; 0.919[d]
SOLO2[e, o]	195	NA 3 (1.5)[r]	99	NA 0 (0)	NC
Indirect comparison with common comparator[i]:					
Niraparib vs. olaparib					_[m]

Table 14: Results (mortality, morbidity, side effects) – RCT, indirect comparison using common comparators: niraparib vs. olaparib (multipage table)

Outcome category	Niraparib or olaparib		Placebo		Group difference
Outcome Comparison Study	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value

a. Results of the first data cut-off on 30 May 2016 (primary analysis).
b. No information on the estimation method used.
c. Results of the last data cut-off on 9 May 2016 (final analysis).
d. Cox proportional hazards model with profile likelihood method for estimation of the 95% CI; p-value: log-rank test; both analyses by the company adjusted for Jewish family origin (yes/no), time to progression after the penultimate platinum-containing chemotherapy (> 6–12 months vs. > 12 months), and objective response to the last platinum-containing chemotherapy before inclusion in the study (complete vs. partial).
e. Results of the first data cut-off on 19 September 2016 (primary analysis).
f. Cox proportional hazards model with profile likelihood method for estimation of the 95% CI; p-value: log-rank test; both analyses adjusted for objective response to the last platinum-containing chemotherapy before inclusion in the study (complete vs. partial) and time to progression after the penultimate platinum-containing chemotherapy (> 6–12 months vs. > 12 months).
g. Cox proportional hazards model with profile likelihood method for estimation of the 95% CI, adjusted for objective response to the last platinum-containing chemotherapy before inclusion in the study (CR vs. PR) and time to progression after the penultimate platinum-containing chemotherapy (> 6–12 months vs. > 12 months), stratified by study.
h. p-value: Institute's calculation, asymptotic.
i. Effect, CI and p-value: Institute's calculation (indirect comparison according to Bucher [10]).
j. No usable data available, as different strategies for follow-up observation of this outcome were used in the studies; for reasons, see Section 2.7.5.3.2 of the full dossier assessment.
k. No usable data available, as this outcome was not recorded in the NOVA study.
l. Institute's calculation from meta-analysis with fixed effect (inverse variance method).
m. No indirect comparison was calculated due to an insufficient certainty of results in the NOVA study (see Section 2.7.5.2 of the full dossier assessment).
n. Data contain all AE severity grades.
o. No information on AE severity grade available.
p. > 30 days after the end of treatment, 0 patients (olaparib) vs. 3 further patients (placebo) had myelodysplastic syndrome, and 1 patient (olaparib) vs. 1 patient (placebo) had acute myeloid leukaemia.
q. In the NOVA study, pneumonitis was operationalized using the PTs "pneumonitis" and "acute interstitial pneumonitis".
r. Including 1 patient with radiation-related pneumonitis.

AE: adverse event; CI: confidence interval; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-O: Functional Assessment of Cancer Therapy-Ovarian; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculated; ND: no data; PT: Preferred Term; PR: partial response; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Since there is only one study on the niraparib side of the adjusted indirect comparison, and there are one study with a high risk of bias across outcomes and one study with a high risk of bias for all outcomes except discontinuation due to AEs on the olaparib side, the certainty of results of the adjusted indirect comparison is no more than low. Hence, at most hints, e.g. of an added benefit, can be derived (see Section 2.7.5.3.1 of the full dossier assessment).

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between niraparib and olaparib for the outcome "overall survival". This resulted in no hint of an added benefit; an added benefit is therefore not proven.

This is not in line with the assessment of the company, which derived a positive prognosis for overall survival on the basis of PFS as surrogate for overall survival. Besides, it used deviating analyses for 3 different subpopulations according to BRCA mutation status for this purpose.

Morbidity

Health status (EQ-5D VAS)

There were no usable data for the outcome "health status", measured with the EQ-5D VAS, as different follow-up observation strategies for this outcome were used in the studies (see Section 2.7.5.3.2 of the full dossier assessment).

This resulted in no hint of an added benefit of niraparib in comparison with olaparib; an added benefit is therefore not proven.

In the result, this concurs with the assessment of the company, which considered the time to deterioration by 7 points and the time to improvement by 7 points for the subpopulation of patients with germline BRCA mutations, however.

Health-related quality of life

FACT-O total score

There were no sufficient data for an indirect comparison for the outcome "health-related quality of life" measured using the FACT-O total score, as this outcome was not recorded in the NOVA study.

This resulted in no hint of an added benefit of niraparib in comparison with olaparib; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs, as well as specific AEs (acute myeloid leukaemia, myelodysplastic syndrome and pneumonitis)

No indirect comparison was calculated due to an insufficient certainty of results in the NOVA study (see Section 2.7.5.2 of the full dossier assessment).

This resulted in no hint of greater or lesser harm of niraparib in comparison with olaparib; greater or lesser harm is therefore not proven. Overall, greater harm of niraparib in comparison with olaparib cannot be excluded on the basis of the available data, however.

In the result, this concurs with the assessment of the company, which considered the AE outcomes separately for 3 different subpopulations according to BRCA mutation status, however. Besides, the company identified in all 3 subpopulations a statistically significant difference to the disadvantage of niraparib for the outcome "severe AEs (CTCAE grade ≥ 3)" from its adjusted indirect comparison, but did not derive greater harm of niraparib versus olaparib from this.

2.4.5 Subgroups and other effect modifiers

No subgroup analyses for the indirect comparison are available for the present benefit assessment of niraparib (see Section 2.7.5.3.4 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 15).

Table 15: Extent of added benefit at outcome level: niraparib vs. olaparib

Outcome category **Outcome**	**Niraparib vs. olaparib** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	HR: 0.99 [0.61; 1.60]; p = 0.956	Lesser benefit/added benefit not proven
Morbidity		
Health status (EQ-5D VAS)	No usable data[c]	Lesser benefit/added benefit not proven
Health-related quality of life		
FACT-O total score	No sufficient data available[d]	Lesser benefit/added benefit not proven
Side effects		
SAEs	No usable data[e]	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)		
Discontinuation due to AEs		
Specific AEs[f]		

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. No usable data available, as different strategies for follow-up observation of this outcome were used in the studies; for reasons, see Section 2.7.5.3.1 of the full dossier assessment.
d. This outcome was not recorded in the NOVA study.
e. No indirect comparison was calculated due to an insufficient certainty of results in the NOVA study (see Section 2.7.5.3.2 of the full dossier assessment).
f. Acute myeloid leukaemia, myelodysplastic syndrome and pneumonitis.

AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-O: Functional Assessment of Cancer Therapy-Ovarian; HR: hazard ratio; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 16 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of niraparib in comparison with olaparib

Positive effects	**Negative effects**
—	—
No usable data are available for the outcomes “morbidity”, “health-related quality of life” and “side effects”.	

Overall, based on the adjusted indirect comparison using the common comparator placebo, there are neither positive nor negative effects of niraparib in comparison with olaparib.

There is no hint of an added benefit of niraparib for the outcome "overall survival", as the indirect comparison showed no statistically significant difference. There are no usable data for an indirect comparison for the outcome categories of morbidity and side effects. Health-related quality of life was not recorded in the study on the niraparib side of the indirect comparison.

In summary, an added benefit of niraparib in comparison with olaparib is not proven for adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian cancer who are in response (complete or partial) to platinum-based chemotherapy.

The result of the assessment of the added benefit of niraparib in comparison with the ACT is summarized in Table 17.

Table 17: Niraparib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with platinum-sensitive relapsed high-grade[b] serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy and require maintenance treatment	**Olaparib** or watchful waiting	Added benefit not proven

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. Designation taken from the English SPC.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

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

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the framework of the market access in 2017. In this assessment, the G-BA had determined a non-quantifiable added benefit of niraparib. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

2.6 List of included studies

NOVA

Del Campo JM, Matulonis UA, Malander S, Provencher D, Mahner S, Follana P et al. Niraparib maintenance therapy in patients with recurrent ovarian cancer after a partial response to the last platinum-based chemotherapy in the ENGOT-OV16/NOVA Trial. J Clin Oncol 2019; 37(32): 2968-2973.

Fabbro M, Moore KN, Dørum A, Tinker AV, Mahner S, Bover I et al. Efficacy and safety of niraparib as maintenance treatment in older patients (≥ 70 years) with recurrent ovarian cancer: results from the ENGOT-OV16/NOVA trial. Gynecol Oncol 2019; 152(3): 560-567.

Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 2016; 375(22): 2154-2164.

Oza AM, Matulonis UA, Malander S, Hudgens S, Sehouli J, Del Campo JM et al. Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): results from a double-blind, phase 3, randomised controlled trial. Lancet Oncol 2018; 19(8): 1117-1125.

Tesaro. A maintenance study with niraparib versus placebo in patients with platinum sensitive ovarian cancer: study details [online]. In: ClinicalTrials.gov. 01.05.2019 [Accessed: 18.11.2019]. URL: https://ClinicalTrials.gov/show/NCT01847274.

TESARO. A phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum sensitive ovarian cancer [online]. In: EU Clinical Trials Register. [Accessed: 25.11.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-000685-11.

Tesaro. A maintenance study with niraparib versus placebo in patients with platinum sensitive ovarian cancer: study results [online]. In: ClinicalTrials.gov. 01.05.2019 [Accessed: 18.11.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01847274.

Tesaro. A phase 3, randomized, double-blind trial of maintenance with niraparib versus placebo in patients with platinum-sensitive ovarian cancer: study PR-30-5011-C; clinical study report [unpublished]. 2016.

Tesaro. A phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum sensitive ovarian cancer: study PR-30-5011-C; clinical study protocol [unpublished]. 2016.

Tesaro. Quality of life analysis in platinum-sensitive ovarian cancer: a phase 3 clinical study analysis; study PR-30-5011-C; patient reported outcomes report [unpublished]. 2016.

Tesaro. A phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum sensitive ovarian cancer: study PR-30-5011-C; statistical anaylsis plan [unpublished]. 2016.

Tesaro. A phase 3, randomized, double-blind trial of maintenance with niraparib versus placebo in patients with platinum-sensitive ovarian cancer: study PR-30-5011-C; Zusatzanalysen [unpublished]. 2019.

Study 19

Astra Zeneca. Phase II randomised, double blind, multicentre study to assess the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens [online]. In: Australian New Zealand Clinical Trials Registry. 26.03.2009 [Accessed: 04.12.2019]. URL: http://www.anzctr.org.au/ACTRN12609000159257.aspx.

AstraZeneca. Olaparib (Lynparza): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 04.06.2018 [Accessed: 27.09.2018]. URL: https://www.g-ba.de/informationen/nutzenbewertung/369/#tab/dossier.

AstraZeneca. Assessment of efficacy of AZD2281 in platinum sensitive relapsed serous ovarian cancer: study details [online]. In: ClinicalTrials.gov. 02.09.2019 [Accessed: 04.12.2019]. URL: https://ClinicalTrials.gov/show/NCT00753545.

AstraZeneca. Phase II randomised, double blind, multicentre study to assess the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens [online]. In: EU Clinical Trials Register. [Accessed: 04.12.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-003439-18.

AstraZeneca. Assessment of efficacy of AZD2281 in platinum sensitive relapsed serous ovarian cancer: study results [online]. In: ClinicalTrials.gov. 02.09.2019 [Accessed: 04.12.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00753545.

Friedlander M, Matulonis U, Gourley C, Du Bois A, Vergote I, Rustin G et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. Br J Cancer 2018; 119(9): 1075-1085.

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Olaparib (Ovarialkarzinom): Nutzenbewertung gemäß § 35a SGB V (Zulassungserweiterung / Ablauf Befristung); Dossierbewertung; Auftrag A18-36 [online]. 13.09.2018 [Accessed: 25.09.2018]. (IQWiG-Berichte; Volume 666). URL: https://www.iqwig.de/download/A18-36_Olaparib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

Ledermann J, Harter P, Gourley C. Correction to Lancet Oncol 2014; 15: 856: Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol 2015; 16(4): e158.

Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012; 366(15): 1382-1392.

Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol 2014; 15(8): 852-861.

Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G et al. Quality of life during olaparib maintenance therapy in platinum-sensitive relapsed serous ovarian cancer. Br J Cancer 2016; 115(11): 1313-1320.

Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Oncol 2016; 17(11): 1579-1589.

Matulonis UA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G et al. Olaparib maintenance therapy in patients with platinum-sensitive, relapsed serous ovarian cancer and a BRCA mutation: overall survival adjusted for postprogression poly(adenosine diphosphate ribose) polymerase inhibitor therapy. Cancer 2016; 122(12): 1844-1852.

SOLO2

AstraZeneca. Olaparib (Lynparza): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 04.06.2018 [Accessed: 27.09.2018]. URL: https://www.g-ba.de/informationen/nutzenbewertung/369/#tab/dossier.

AstraZeneca. Olaparib treatment in BRCA mutated ovarian cancer patients after complete or partial response to platinum chemotherapy: study details [online]. In: ClinicalTrials.gov. 28.10.2019 [Accessed: 04.12.2019]. URL: https://ClinicalTrials.gov/show/NCT01874353.

AstraZeneca. A phase III randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in platinum sensitive relapsed BRCA mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy [online]. In: EU Clinical Trials Register. [Accessed: 04.12.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-001211-75.

AstraZeneca. Phase 3 randomised, double blind, placebo controlled study of olaparib maintenance monotherapy in platinum sensitive relapsed brca mutated ovarian cancer patients with a complete or partial response following platinum based chemotherapy [online]. In: JAPIC Clinical Trials Information. 12.04.2019 [Accessed: 04.12.2019]. URL: https://www.clinicaltrials.jp/cti-user/trial/ShowDirect.jsp?japicId=JapicCTI-132359.

AstraZeneca. Olaparib treatment in BRCA mutated ovarian cancer patients after complete or partial response to platinum chemotherapy: study results [online]. In: ClinicalTrials.gov. 28.10.2019 [Accessed: 04.12.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01874353.

Friedlander M, Gebski V, Gibbs E, Davies L, Bloomfield R, Hilpert F et al. Health-related quality of life and patient-centred outcomes with olaparib maintenance after chemotherapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT Ov-21): a placebo-controlled, phase 3 randomised trial. Lancet Oncol 2018; 19(8): 1126-1134.

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Olaparib (Ovarialkarzinom): Nutzenbewertung gemäß § 35a SGB V (Zulassungserweiterung / Ablauf Befristung); Dossierbewertung; Auftrag A18-36 [online]. 13.09.2018 [Accessed: 25.09.2018]. (IQWiG-Berichte; Volume 666). URL: https://www.iqwig.de/download/A18-36_Olaparib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

Oza AM, Cibula D, Benzaquen AO. Correction to olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol 2015; 16(2): e55.

Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017; 18(9): 1274-1284.

References for English extract

Please see full dossier assessment for full reference list.

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

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 01.07.2019]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58.

3. Leitlinienprogramm Onkologie. S3-Leitlinie Diagnostik, Therapie und Nachsorge maligner Ovarialtumoren: Langversion 3.0; Januar 2019.

4. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Olaparib (Ovarialkarzinom): Nutzenbewertung gemäß § 35a SGB V (Zulassungserweiterung / Ablauf Befristung); Dossierbewertung; Auftrag A18-36 [online]. 13.09.2018 [Accessed: 25.09.2018]. (IQWiG-Berichte; Volume 666). URL: https://www.iqwig.de/download/A18-36_Olaparib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

5. AstraZeneca. Olaparib (Lynparza): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4 A; Anwendung als Monotherapie für die Erhaltungstherapie von erwachsenen Patientinnen mit einem Platin-sensitiven Rezidiv eines high-grade epithelialien Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms, die auf eine Platin-basierte Chemotherapie ansprechen (vollständig oder partiell) [online]. 04.06.2018 [Accessed: 10.01.2020]. URL: https://www.g-ba.de/downloads/92-975-2453/2018-06-04_Modul4A_Olaparib.pdf.

6. TESARO. Zejula 100mg Hartkapseln: Fachinformation [online]. 06.2019 [Accessed: 15.11.2019]. URL: https://www.fachinfo.de.

7. AstraZeneca. Fachinformation Lynparza 100 mg/- 150 mg Filmtabletten; Stand: Juni 2019.

8. European Medicines Agency. CHMP assessment report: Zejula. 2017.

9. Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24(Suppl 6): vi24-v32.

10. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997; 50(6): 683-691.

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