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Niraparib (ovarian cancer) –

Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Niraparib (Ovarialkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 April 2021). 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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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BRCA	breast cancer associated gene
CONSORT	Consolidated Standards of Reporting Trials
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D	European Quality of Life-5 Dimensions
ESMO	European Society for Medical Oncology
FACT-O	Functional Assessment of Cancer Therapy-Ovarian
FOSI	Functional Assessment of Cancer Therapy-Ovarian Cancer Symptom Index
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)
ITT	intention to treat
non-gBRCAmut	BRCA without germline 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)
SPC	Summary of Product Characteristics
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 is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 2 February 2021.

On 15 December 2017, the company submitted the first dossier for the early benefit assessment of niraparib, the drug to be assessed, as a drug for the treatment of an orphan condition. Following a request by the G-BA, the company submitted a dossier on the added benefit of niraparib compared with the appropriate comparator therapy (ACT) by 15 October 2019 because the turnover of the drug in the statutory health insurance had exceeded 50 million euros in the previous 12 calendar months. In this procedure, the G-BA limited its decision until 1 October 2020, a period extended until 1 February 2021.

The decision was limited because the data on overall survival available from the NOVA study were only preliminary with a small number of events for the outcome "overall survival", and the final results of the NOVA study were still pending. The final study results on overall survival and on all other outcomes relevant for proof of the added benefit were to be submitted in the dossier for the reassessment after expiry of the decision.

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.

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

Table 2: Research questions of the benefit assessment of niraparib

Therapeutic indication	**ACT**[a]
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	**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**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

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 provided by the company in the dossier.

Results

Study pool

No randomized controlled trial (RCT) of direct comparison was 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 for the assessment of niraparib in comparison with olaparib. The company included the studies NOVA and NORA on the niraparib side, and Study 19 and SOLO2 on the olaparib side. The NORA study additionally identified by the company was not included in the indirect comparison, as only limited information on study design and study results from publicly available sources is available for this study not conducted by the company. Although the study seems to be potentially relevant to the research question on the basis of the available information, the similarity of the study to the other studies in the indirect comparison cannot be assessed with sufficient certainty due to the limited information.

For the indirect comparison, the studies NOVA on the niraparib side and Study 19 as well as SOLO2 on the olaparib side were considered relevant for the benefit assessment.

NOVA (study with niraparib)

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

A total of 553 patients were enrolled in the NOVA study. These were randomized in a 2:1 ratio and assigned either to treatment with niraparib (N = 372) or to placebo (N = 181). Treatment with niraparib was conducted in compliance with the German approval status.

Treatment with niraparib was conducted until disease progression, unacceptable toxicity, withdrawal of consent, or death. 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, outcomes on morbidity and adverse events (AEs).

The results of the final data cut-off (1 October 2020) were primarily used for the benefit assessment.

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 relapsed high grade serous ovarian cancer who had achieved complete or partial response to prior platinum-containing chemotherapy.

The study included a total of 265 patients, assigned 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, symptoms, health-related quality of life, and AEs.

The results of the final data cut-off (9 May 2016) were used for the benefit assessment.

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 included adult patients with platinum-sensitive relapsed breast cancer associated gene (BRCA)-mutated high grade serous or non-serous ovarian cancer who had responded to prior platinum-containing chemotherapy.

The study included a total of 295 patients, assigned 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.

For the benefit assessment, the results of the final data cut-off (2 March 2020) were used for the outcome "overall survival" and the results of the primary data cut-off (19 September 2016) were used for the outcomes in the category of side effects, as no usable data were available for the final data cut-off.

Similarity of the studies in the indirect comparison

The check of the similarity of the studies NOVA, Study 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. However, the indirect comparison was not always possible for specific outcomes, e.g. due to different follow-up strategies, different outcome operationalizations in the studies or insufficient certainty of results 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.

The results of all outcomes from the studies NOVA, Study 19 and SOLO2 that can be used for the indirect comparison had a high risk of bias except for the outcome "discontinuation due to AEs" in the studies NOVA and SOLO2. The certainty of results for the outcome "discontinuation due to AEs" was limited despite a low risk of bias, however.

The presented indirect comparison included only one study on the niraparib side. At the final data cut-off of this study (1 October 2020), there was either a high risk of bias or limited certainty of results despite a low risk of bias for all outcomes included in the indirect comparison. In the present benefit assessment, there is therefore no sufficient certainty of results to meet the minimum requirement for the certainty of results for the derivation of a hint in the indirect comparison. In the present data situation, however, there is sufficient certainty of results for deriving a hint from the indirect comparison in those cases where the indirect comparison shows sufficiently large effects that cannot be called into question by potential bias alone.

Results of the indirect comparison

Mortality

Based on the final data cut-off (1 October 2020) of the NOVA study, the requirements for being able to derive conclusions on the added benefit from an adjusted indirect comparison are not met for the outcome "overall survival". Therefore, the results of the primary data cut-off (30 May 2016), which has a low risk of bias, of the NOVA study were additionally used. The adjusted indirect comparison showed no statistically significant difference between niraparib and olaparib for the outcome "overall survival". Overall, this resulted in no hint of an added benefit of niraparib in comparison with olaparib; 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 European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS), as different follow-up 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.

FOSI

No indirect comparison was possible for the outcome "Functional Assessment of Cancer Therapy-Ovarian Cancer Symptom Index (FOSI)" because only data from a study with a high risk of bias (Study 19) were available on the olaparib side. 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

FACT-O total score

There were no sufficient data for an indirect comparison for the outcome "health-related quality of life", measured with the Functional Assessment of Cancer Therapy-Ovarian (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

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

For the outcome "severe AEs", only the result from a study with outcome-specific high risk of bias was available on the niraparib side of the adjusted indirect comparison. The prerequisites for the derivation of conclusions on the added benefit from an adjusted indirect comparison were therefore initially not fulfilled. However, a large effect for this outcome was shown both in the comparison of niraparib with placebo in the NOVA study and in the adjusted indirect comparison with olaparib using the common comparator placebo. It is not assumed in the present data situation that the statistically significant effect in the indirect comparison to the disadvantage of niraparib is completely called into question by potential bias. Hence, despite the high outcome-specific risk of bias, the qualitative certainty of results is sufficiently high in the NOVA study to be able to interpret the present effect and derive a hint of greater or lesser harm from niraparib. Overall, there is therefore a hint of greater harm from niraparib in comparison with olaparib. Due to the uncertainties, the extent of the effect cannot be quantified, however.

Serious AEs (SAEs) and discontinuation due to AEs

No indirect comparison was calculated due to the 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.

Specific AEs

No usable data are available for the specific AEs of special importance for the clinical picture (acute myeloid leukaemia, myelodysplastic syndrome), as the studies used different follow-up strategies for these outcomes. No adjusted indirect comparison was calculated for the specific AE "pneumonitis" due to the very few events (and a high risk of bias), as this could not result in a sufficiently large statistically significant effect in each case. This resulted in no hint of greater or lesser harm of niraparib in comparison with olaparib; greater or lesser harm is therefore not proven.

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 the ACT are assessed as follows:

Overall, usable data for the indirect comparison are available for only 2 outcomes (overall survival and severe AEs). Taking into account the results of the primary data cut-off of the NOVA study (30 May 2016), there was no statistically significant difference between niraparib and olaparib for the outcome "overall survival". Thus, only a negative observed effect remains for the outcome "severe AEs", resulting in a hint of non-quantifiable greater harm of niraparib in comparison with olaparib.

In summary, there is therefore a hint of lesser benefit of niraparib versus olaparib for 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.

The result of the assessment of the added benefit of niraparib in comparison with the ACT olaparib is summarized in Table 3.

[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 {Institute for Quality and Efficiency in Health Care, 2017 #12;Skipka, 2016 #11}.

Table 3: Niraparib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
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	**Olaparib** or watchful waiting	Hint of lesser benefit
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**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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

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.

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

Table 4: Research questions of the benefit assessment of niraparib

Therapeutic indication	**ACT[a]**
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	**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**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

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 [1]. 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 provided 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 lists on niraparib (status: 21 January 2021)
- bibliographical literature search on niraparib (last search on 21 December 2020)
- search in trial registries/trial results databases for studies on niraparib (last search on 21 January 2021)
- search on the G-BA website for niraparib (last search on 21 January 2021)
- bibliographical literature search for the ACT (last search on 15 January 2021)

- search in trial registries/trial results databases for studies on the ACT (last search on 21 January 2021)
- search on the G-BA website for the ACT (last search on 21 January 2021)

To check the completeness of the study pool:

- search in trial registries for studies on niraparib (last search on 10 February 2021)
- search in trial registries for studies on the ACT (last search on 10 February 2021)

Concurring with the company, analogous to the previous benefit assessment of niraparib, A19-88 [2], the check of the completeness of the study pool, did not identify any relevant RCT for the direct comparison of niraparib with olaparib.

No additional relevant studies were identified for the indirect comparison with olaparib presented by the company. The NORA study identified by the company was not considered for the indirect comparison in the present benefit assessment (for justification, see the following text section on the study pool of the company).

For the direct comparison of niraparib with placebo, the company presented the results of the studies NOVA and NORA both individually and in a meta-analytical summary. These studies did not include a comparison against olaparib, the comparator therapy chosen by the company. The comparison with placebo is therefore not considered further in the following text.

Study pool of the company

Besides the studies NOVA, SOLO2 and Study 19, which the previous benefit assessment [2,3] already regarded relevant in the indirect comparison, the company additionally identified the NORA study on the niraparib side and considered this study in the indirect comparison. However, the study was not included in the indirect comparison for the following reasons:

Only little information on the NORA study available

The NORA study is a study that was started in June 2017 and is currently still ongoing. Because it is not conducted by the company itself, the company relied on publicly available information on the study [4-8]. For the dossier assessment, in addition to the trial registry entry [8], which only contains rudimentary information on the study design without results, the company mainly used a presentation of the study results [5], which were presented at the European Society for Medical Oncology (ESMO) Congress 2020. The company itself described that it had only very limited information on study design and study conduct.

According to the available documentation, the NORA study is a multicentre, randomized, double-blind study comparing niraparib with placebo, which is conducted exclusively in China. The study enrolled adult patients with platinum-sensitive relapsed ovarian cancer (high grade serous or predominantly high grade serous) with a complete or partial response to prior platinum-containing chemotherapy and an Eastern Cooperative Oncology Group Performance

Status (ECOG PS) of 0 or 1. The available information on the study design and the interventions used are presented as supplementary information in Appendix E (Table 29 and Table 30) of the full dossier assessment.

The company itself correctly defined "incomplete study information (no full publication, no clinical study report or detailed result report)" as an exclusion criterion for the benefit assessment. The Consolidated Standards of Reporting Trials (CONSORT) Statement for randomized trials [9,10] was used to assess the usability of a full publication. However, the sources on the NORA study [5,8] considered by the company and relevant for this benefit assessment do not contain the complete information required according to the CONSORT Statement. Overall, the data basis for the NORA study is not sufficient for a conclusive assessment of the relevance of the study, but on the basis of the available information, the study seems to be potentially relevant to the research question.

Suitability of the NORA study for the indirect comparison cannot be assessed due to the limited information on the study

A key requirement for the consideration of studies in the adjusted indirect comparison is the evaluation of similarity [11-13]. According to the similarity assumption, all studies considered are comparable with regard to possible effect modifiers across all interventions. In addition to potential effect modifiers (e.g. patient characteristics, study characteristics, intervention characteristics), methodological factors (e.g. outcome characteristics) must also be taken into account [14]. The company itself did not provide any explicit information on the investigation of similarity regarding the studies it included. It only stated that, based on the assessment of all available information, it considered the studies to be sufficiently similar for an adjusted indirect comparison using the common comparator placebo.

Only very limited information is available for the NORA study (see above). Thus, the prerequisite for a sufficient evaluation of similarity is not met. For example, it is not possible to assess the similarity of the common comparator placebo in the NORA study in comparison with the other studies used in the indirect comparison, NOVA, SOLO2 and Study 19. This would require information on the diagnosis of disease progression used in the patients, on the definition of relapse (e.g. based on tumour markers, radiological evidence or symptomatic evidence) and on permitted background therapy and concomitant medications. In addition, there is a lack of information on permitted and administered subsequent therapies or planned and actual observation periods.

With regard to the niraparib dosage used in the study (in contrast to the niraparib dosage used in the NOVA study), there is also a deviation from the Summary of Product Characteristics (SPC): The general starting dose in the maintenance treatment of relapsed ovarian cancer is 300 mg/day [15]. Only in patients with a body weight of < 58 kg can a starting dose of 200 mg/day be considered. In deviation from this, a large proportion of patients with a body weight < 77 kg and a platelet count < 150 000/µL were treated with a reduced starting dose of 200 mg/day (this corresponds to the dose regimen in the first-line treatment of ovarian cancer).

This individualized, reduced starting dose was primarily intended to reduce the frequency of haematological side effects [16]. Although the deviation of the starting dose from the SPC alone does not call the relevance of the study into question, it must be regarded as problematic at least with regard to the similarity to the NOVA study.

Furthermore, the company did not comment on whether the health care context in China, the country conducting the study, differs from that of the other studies. It only referred to a publication that described the pharmacokinetics of niraparib in Chinese and Caucasian patients as largely comparable [7]. From the company's point of view, the NORA study is therefore suitable for supporting the added benefit of niraparib in the German health care context, despite the different family origins of the patients.

Summary

Even though the NORA study seems to be potentially relevant to the research question of the benefit assessment, its suitability for the indirect comparison with olaparib cannot be evaluated with sufficient certainty due to the limited information. The study was therefore not considered in the benefit assessment. Analogous to the previous benefit assessment [2,3], the study pool for the indirect comparison of niraparib and olaparib therefore consists of the studies NOVA as well as Study 19 and SOLO2 (see Section 2.3.1).

Irrespective of the relevance of the NORA study for the present benefit assessment, it is additionally pointed out that the inclusion of the NORA study in the indirect comparison would not change the result for the outcome "overall survival" (see Module 4 A, Section 4.3.2.1.5.1). For other outcomes, there are no results from the NORA study that can be used for indirect comparison.

2.3.1 Studies included

The company presented an adjusted indirect comparison against olaparib using the common comparator placebo for the assessment of the added benefit of niraparib. Since only one RCT with niraparib in the relevant therapeutic indication was included, 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 Table 5 were included in the benefit assessment.

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

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Niraparib vs. placebo						
PR-30-5011-C (NOVA[d])	Yes	Yes[e]	No	No[f]	Yes [17,18]	Yes [2,3,19-25]
Olaparib vs. placebo						
D0810C00019 (Study 19[d])	No	No	Yes	No	Yes [26-28]	Yes [2,3,24,25,29-33]
D0816C00002 (SOLO2[d])	No	No	Yes	No	Yes [34-36]	Yes [2,3,24,25,29-31,37,38]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to with this abbreviated form.
e. The sponsor of the study was Tesaro, taken over by the company in 2019 [39].
f. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

CSR: clinical study report; G-BA: Federal Joint Committee; vs.: versus

The study pool differs from that of the company, which additionally included the NORA study for the niraparib side of the indirect comparison. However, the inclusion of the NORA study in the indirect comparison is not appropriate (see text section on the study pool of the company), so that the study pool for the indirect comparison corresponds to that in the previous benefit assessment [2,3]. Figure 1 shows a schematic representation of the study pool for the indirect comparison.

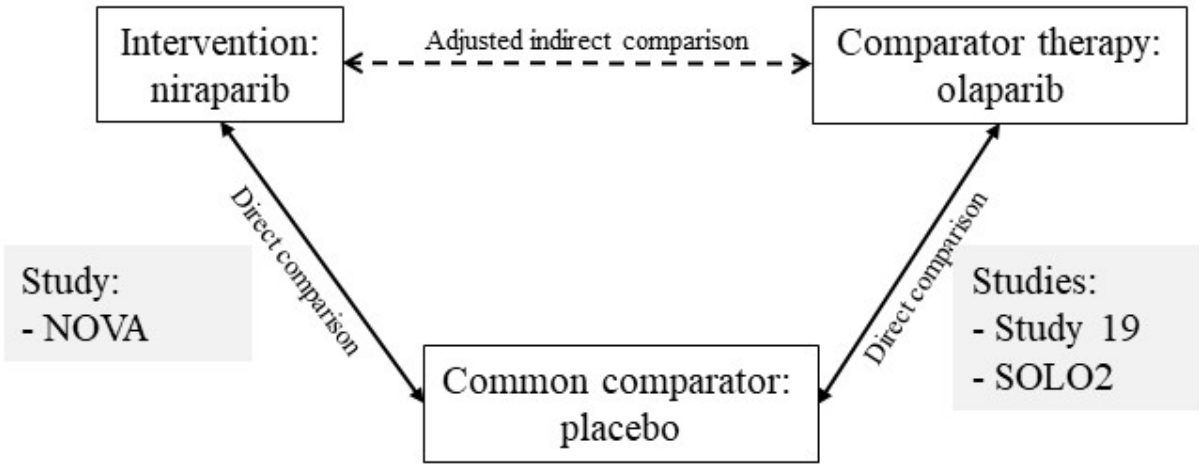

Figure 1: Study pool for the indirect comparison between niraparib and olaparib

In line with the research question, the assessment of the added benefit was conducted regardless of the patients' BRCA mutation status. This concurs with the company's approach. The company also stated that it conducted additional indirect comparisons for the cohorts of patients with and without BRCA mutations. However, it actually only presented results for selected outcomes (e.g. overall survival) exclusively for patients with BRCA mutations. This has no consequence for the present benefit assessment, however, as the subdivision according to BRCA status is not appropriate overall and the additionally submitted analyses were therefore not considered further (for detailed justification see Section 2.4.1 of dossier assessment A19-88 [2]).

2.3.2 Study characteristics

2.3.2.1 Study design

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

Table 6: Characteristics of the studies included – 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]
Niraparib vs. placebo						
NOVA	RCT, double-blind, parallel	Adult patients (≥ 18 years) with platinum-sensitive relapsed[b] ovarian cancer[c] who had a response to prior platinum-containing chemotherapy[d], with ECOG PS ≤ 1	**Total population[e]** niraparib: N = 372 placebo: N = 181	Screening: ≤ 28 days Treatment: until disease progression[f, g], unacceptable toxicity, withdrawal of consent, loss to follow-up, or death Observation[h]: 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 8/2013–10/2020 Data cut-offs[i]: ▪ Primary analysis: 30 May 2016 ▪ Final analysis: 1 October 2020	Primary: PFS Secondary: overall survival, morbidity, health status, AEs
Olaparib vs. placebo						
Study 19	RCT, double-blind, parallel	Adult patients with platinum-sensitive relapsed[b] high grade serous ovarian cancer who had a response to prior platinum-containing chemotherapy[j], with ECOG PS ≤ 2	Olaparib (N = 136) placebo (N = 129)	Screening: ≤ 28 days Treatment: until disease progression according to RECIST[g], toxicity, or withdrawal of consent Observation[h]: 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[i]: ▪ Primary analysis: 30 June 2010 ▪ Final analysis: 9 May 2016	Primary: PFS Secondary: overall survival, health-related quality of life, AEs

Table 6: Characteristics of the studies included – 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]
SOLO2	RCT, double-blind, parallel	Adult patients with platinum-sensitive relapsed[b] BRCA-mutated high grade serous or endometrioid ovarian cancer who had a response to prior platinum-containing 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[g], toxicity, withdrawal of consent Observation[h]: 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 8/2013–2/2020 Data cut-offs[i]: ▪ Primary analysis: 19 September 2016 ▪ Final analysis: 3 February 2020	Primary: PFS Secondary: overall survival, health status, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. 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. 203 patients were included in the gBRCAmut cohort, and 350 patients in the non-gBRCAmut cohort. The division into these cohorts is 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. 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.
h. Outcome-specific information is provided in Table 8.
i. Further information on the data cut-offs and their relevance for the present benefit assessment can be found in Table 9.
j. 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.
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 dossier assessment A18-36 [31]).

Table 6: Characteristics of the studies included – 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]
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; non-gBRCAmut: BRCA without germline mutation; 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 interventions – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study	Intervention/comparator therapy	Common comparator
Niraparib vs. placebo		
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
	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 respond 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 interventions – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study	Intervention/comparator therapy	Common comparator
Olaparib vs. placebo		
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 interventions – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study	Intervention/comparator therapy	Common comparator
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.

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

NOVA (study with niraparib)

The NOVA study was a double-blind, randomized parallel-group study on the comparison of niraparib versus placebo. The study enrolled adult patients with platinum-sensitive relapsed high grade serous 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 (with germline BRCA mutations [gBRCAmut, N = 203]

and without germline BRCA mutations [non-gBRCAmut, N = 350]). The division into these cohorts is not relevant for the present benefit assessment (see Section 2.3.1). To be eligible for study inclusion, the patients had to be in good general condition (ECOG PS between 0 and 1).

A total of 553 patients were enrolled in the NOVA study. These were randomized in a 2:1 ratio and assigned either to treatment with niraparib (N = 372) or to placebo (N = 181). 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 most recent platinum-containing chemotherapy (complete or partial) and the use of bevacizumab in relation with the penultimate or the most recent platinum-containing treatment regimen (yes/no).

Treatment with niraparib was conducted in compliance with the German approval status [15]. Dose reductions due to toxicity were allowed in the study. At the primary data cut-off (30 May 2016), these took place in 73% of the patients. Corresponding information on the final data cut-off (1 October 2020) is not available.

Treatment with niraparib was conducted until disease progression, unacceptable toxicity, withdrawal of consent, or death. 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 for an adequate reaction to AEs, or if they wanted to participate in a further study on poly(adenosine diphosphate-ribose) polymerase [PARP] inhibitors. Unblinding for other reasons, including determination of subsequent therapy in the case of progression, was only possible with subsequent study exclusion according to the information provided by the company in the protocol (until Amendment 8 in 2019). The decision on follow-up therapies after treatment discontinuation was at the discretion of the physician. There were no further specifications regarding the type of subsequent therapy. Switching to treatment with niraparib was not intended for patients under placebo.

The primary outcome of the study was PFS. Patient-relevant secondary outcomes were overall survival, outcomes on morbidity 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 relapsed high grade serous ovarian cancer who had achieved complete or partial response to prior platinum-containing chemotherapy. Patients were included regardless of their BRCA mutation status. 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, assigned 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 [40].

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. To decide on subsequent therapies or in case of safety concerns, patients could be unblinded individually after disease progression according to RECIST 1.1, upon request to the sponsor. 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, symptoms, 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 relapsed BRCA-mutated high grade serous 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, assigned 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 [N = 32]) 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 [31]).

Treatment with olaparib was conducted in compliance with the German approval status [40].

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.

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.

2.3.2.2 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 (multipage table)

Study **Outcome category** **Outcome**	**Planned follow-up observation**
Niraparib vs. placebo	
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)	8 weeks (± 2 weeks) after the last dose of the study medication
Symptoms (FOSI)	8 weeks (± 2 weeks) after the last dose of the study medication
Health-related quality of life	No patient-relevant outcomes recorded
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
Olaparib vs. placebo	
Study 19	
Mortality	
Overall survival	Until death, withdrawal of consent, or final survival time analysis
Morbidity	
Symptoms (FOSI)	Until disease progression[a]
Health-related quality of life (FACT-O)	Until disease progression[a]
Outcomes in the category of 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
Outcomes in the category of side effects	Until 30 days after the last dose of the study medication[b]

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.
b. Only specific AEs (myelodysplastic syndrome/acute myeloid leukaemia/other neoplasms) were observed indefinitely beyond the end of treatment.

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

The observation periods in the studies NOVA, Study 19 and SOLO2 for the outcomes of the categories 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 study period, as was the case for survival.

However, 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.

According to the information provided by the company, the following additional situation arose in the NOVA study for the outcome "overall survival": According to the study protocol, until Amendment 8 in 2019, unblinding after disease progression to clarify the subsequent therapy was only possible if the patient withdrew her consent. This resulted in a high proportion of patients who dropped out of the study without further observation, so that the follow-up observation for the outcome "overall survival" was also incomplete (affects 14% of the study population). This was considered in the assessment of the risk of bias (see Section 2.4.2).

2.3.2.3 Data cut-offs

Table 9 shows the data cut-offs of the studies used in the present benefit assessment in comparison with the previous benefit assessment for the outcomes that can be used in the indirect comparison [2,3].

Table 9: Included data cut-offs in the previous and current benefit assessments – RCT, indirect comparison: niraparib vs. olaparib

Comparison Study	Included data cut-offs in the previous benefit assessment [2,3]		Included data cut-offs in the present benefit assessment[a]	
	Overall survival	**AEs**	**Overall survival**	**AEs**
Niraparib vs. placebo				
NOVA	30 May 2016[b]	30 May 2016[b]	**1 October 2020[c, d]**	**1 October 2020[c]**
Olaparib vs. placebo				
Study 19	9 May 2016[e]	9 May 2016[e]	9 May 2016[e]	9 May 2016[e]
SOLO2	19 September 2016[f]	19 September 2016[f]	**3 February 2020[g]**	19 September 2016[h]

a. In cases where a new data cut-off was used in comparison with the previous benefit assessment, the date is printed in **bold**.
b. Primary analysis of the NOVA study; conducted after 17% of patients had died.
c. Final analysis of the NOVA study; conducted after ≥ 66% of patients had died.
d. As the results for the outcome "overall survival" at the final data cut-off have a high risk of bias (see Section 2.4.2), the requirement for the certainty of results for conducting an adjusted indirect comparison is not met overall. Therefore, the results of the outcome "overall survival" based on the primary data cut-off (30 May 2016), which have a low risk of bias, are also used in addition.
e. Final data cut-off of Study 19; conducted after 79% of patients had died.
f. Primary analysis of the SOLO2 study; conducted after 24% of patients had died.
g. Final analysis of the SOLO2 study; conducted after 61% of patients had died.
h. Primary analysis of the SOLO2 study; there are no publicly available and usable results on AEs for the final analysis of the SOLO2 study.

AE: adverse event; RCT: randomized controlled trial; vs.: versus

NOVA

In accordance with the G-BA's condition of the limitation, the company presented results for the final data cut-off for the NOVA study (1 October 2020). This final analysis was conducted after approximately 66% of the patients included in the study had died. The results of this data cut-off were used primarily for the benefit assessment. As the results for the outcome "overall survival" at the final data cut-off have a high risk of bias, however (see Section 2.4.2), the minimum requirement for the certainty of results for the derivation of a hint based on an adjusted indirect comparison is not met (see Section 2.3.4). Therefore, the results based on the primary data cut-off (30 May 2016), which have a low risk of bias, were also used for the outcome "overall survival" in the present benefit assessment. This differs from the approach of the company in that it primarily used the results of the primary data cut-off from 30 May 2016 for the outcome "overall survival". From the company's point of view, these represent the best available evidence. Although the company conducted an additional indirect comparison based on the final data cut-off of the NOVA study, it considered the results on overall survival (ITT analysis) for the final data cut-off of the NOVA study to be generally uninformative "due to massive confounding" caused by the use of PARP inhibitors in the placebo arm and, even after adjustment, only interpretable to a limited extent.

Study 19

As in the previous benefit assessment, the final data cut-off (9 May 2016) was used for Study 19. This concurs with the company's approach.

SOLO2

For the SOLO2 study, in addition to results from the primary data cut-off (19 September 2016), which was used in the previous benefit assessment, results for the outcome "overall survival" are also available for the final data cut-off (3 February 2020) [38]. For the present benefit assessment, the results of the final data cut-off were therefore used for the outcome "overall survival". The results of the primary data cut-off were used for the outcomes of the category of side effects, as no usable data were available for the final data cut-off. This concurs with the company's approach.

2.3.2.4 Patient characteristics

Table 10 shows the characteristics of the patients in the studies included.

Table 10: Characteristics of the study populations – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study Characteristic Category	Study with niraparib		Studies with olaparib			
	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
Age [years]						
Mean (SD)	60 (10)	60 (10)	59 (11)	59 (10)	57 (9)	57 (9)
Family origin, n (%)						
White	324 (87)	156 (86)	130 (96)	126 (98)	173 (88)	91 (92)
Non-white	48 (13)	25 (14)	6 (4)	3 (2)	23 (12)	8 (8)
Region, n (%)						
Europe	ND[b]	ND[b]	95 (70)	89 (69)	114 (58)	62 (63)
Other	ND[b]	ND[b]	41 (30)	40 (31)	82 (42)	37 (37)
gBRCA mutation, n (%)						
Yes	138 (37.1)	65 (35.9)	53 (39.0)c	43 (33.3)c	193 (98.5)[d]	99 (100)[d]
No	234 (62.9)	116 (64.1)	78 (57.4)	80 (62.0)	2 (1.0)	0 (0)
Missing/unknown	0 (0)	0 (0)	5 (3.7)	6 (4.7)	1 (0.5)	0 (0)
Histology, n (%)						
Serous	332 (89.2)	169 (93.4)	136 (100)	129 (100)	183 (93.4)	86 (86.9)
Non-serous	23 (6.2)	7 (3.9)	0 (0)	0 (0)	12 (6.1)	13 (13.1)
Missing/unknown	17 (4.6)	5 (2.8)	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)
Missing/unknown	0 (0)	1 (0.6)	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 10: Characteristics of the study populations – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study Characteristic Category	Study with niraparib		Studies with olaparib			
	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
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)	73 (40.3)	76 (55.9)	66 (51.2)	87 (44.4)	39 (39.4)
Missing/unknown	0 (0)	1 (0.6)	0 (0)	0 (0)	1 (0.5)	0 (0)
Number of previous platinum-containing chemotherapies, n (%)						
1	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2	253 (68.0)	124 (68.5)	76 (55.9)	84 (65.1)	110 (56.1)	62 (62.6)
≥ 3	118 (31.7)	56 (30.9)	60 (44.1)	45 (34.9)	85 (43.4)	37 (37.4)
Missing/unknown	0 (0)	1 (0.6)	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)
Missing/unknown	0 (0)	0 (0)	2 (1.5)	2 (1.6)	2 (1.0)	0 (0)
FIGO stage at diagnosis, n (%)						
Stage 0	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Stage I[e]	14 (3.8)	11 (6.1)	3 (2.2)	4 (3.1)	6 (3.1)	2 (2.0)
Stage II[f]	31 (8.3)	4 (2.2)	11 (8.1)	8 (6.2)	17 (8.7)	6 (6.1)
Stage III[g]	268 (72.0)	132 (72.9)	103 (75.7)	98 (76.0)	142 (72.4)	79 (79.8)
Stage IV	58 (15.6)	33 (18.2)	17 (12.5)	17 (13.2)	29 (14.8)	12 (12.1)
Missing/unknown	0 (0)	1 (0.65)	2 (1.5)	2 (1.6)	2 (1.0)	0 (0)

Table 10: Characteristics of the study populations – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study Characteristic Category	Study with niraparib		Studies with olaparib			
	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
Tumour grade[h], n (%)						
G1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
G2	16 (4.3)	10 (5.5)	36 (26.5)	34 (26.4)	16 (8.2)	6 (6.1)
G3	121 (32.5)	67 (37.0)	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)	1 (0.6)	ND	ND	ND	ND
High grade	200 (53.8)	90 (49.7)	ND	ND	ND	ND
Not assessable	15 (4.0)	8 (4.4)	1 (0.7)	2 (1.6)	7 (3.6)	5 (5.1)
Missing/unknown	17 (4.6)	5 (2.8)	0 (0)	0 (0)	1 (0.5)	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 cytoreductive surgery, n (%)						
Yes	ND	ND	44 (32.4)	40 (31.0)	18 (9.2)[i]	10 (10.1)[i]
No	ND	ND	92 (67.6)	89 (69.0)	178 (90.8)	89 (89.9)
Treatment discontinuation, n (%)	341 (92.9[j])	173 (96.6[j])	117 (86.0)	127 (98.4)	152 (78)[k]	91 (92)[k]
Study discontinuation[l], n (%)	308 (83.9[j])	153 (85.5[j])	97 (71.3)	103 (79.8)	127 (64.8[m])[n]	73 (73.7[m])[n]

Table 10: Characteristics of the study populations – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study Characteristic Category	Study with niraparib		Studies with olaparib			
	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

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Niraparib: USA and Canada: 149 (40.1%); Western Europe, Australasia and Israel: 211 (56.7%); Eastern Europe, Latin America and Asia: 12 (3.2%); placebo: USA and Canada: 72 (39.8%); Western Europe, Australasia and Israel: 103 (56.9%); Eastern Europe, Latin America and Asia: 6 (3.3%).
c. 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 start of the study.
d. Confirmed with local measurement or with test of the company Myriad.
e. Composed of stages I, IA, IB and IC (only stages IB and IC were present in Study 19).
f. Composed of stages II, IIA, IIB, IIC.
g. Composed of stages III, IIIA, IIIB, IIIC.
h. Different systems were used for tumour grading. The study documents do not provide any specific information on the grading systems used.
i. For study SOLO2, "previous" means that the cytoreductive surgery was conducted after the last progression and before randomization.
j. Institute's calculation, based on the number of patients treated (367 in the niraparib arm and 179 in the placebo arm); data for the final data cut-off from 1 October 2020.
k. Data for the final data cut-off (3 February 2020 [38]).
l. Including study discontinuation due to death.
m. Institute's calculation.
n. Data for the final data cut-off (3 February 2020 [35]), these are mainly deaths (110 patients in the olaparib arm and 60 patients in the placebo arm); at the primary data cut-off (19 September 2016), 55 (28.1%) patients in the olaparib arm and 37 (37.4%) in the placebo arm had discontinued the study.

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 mean age of the patients in all 3 studies was about 59 years; most of them were of white family origin 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 Study 19 had no germline BRCA mutation. Since the approval of niraparib and olaparib is independent from the BRCA mutation status, this had no consequences for the present benefit assessment, however. There was a noticeable difference also regarding tumour grades. These differences were discussed in detail in the examination of similarity of dossier assessment A19-88 [2] (see Section 2.3.3 there). However, they do not call into question the suitability of the studies for inclusion in the indirect comparison.

2.3.2.5 Treatment duration and observation period

Table 11 shows the mean/median treatment duration of the patients and the mean/median observation period for individual outcomes.

Table 11: Information on the course of the study – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study **Duration of the study phase** **Outcome category**	**Intervention**	**Common comparator**
Studies with niraparib	Niraparib	Placebo
NOVA	N = 372	N = 181
Data cut-off 30 May 2016		
Treatment duration [months]		
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	No data suitable for the indirect comparison are available[a]	
Health-related quality of life	No patient-relevant outcomes recorded	
Side effects	ND	
Data cut-off 1 October 2020		
Treatment duration [months]	ND	
Observation period [months]		
Overall survival		
Median [min; max]	32.3 [ND; ND]	33.4 [ND; ND]
Mean (SD)	ND	
Morbidity	No data suitable for the indirect comparison are available[a]	
Health-related quality of life	No patient-relevant outcomes recorded	
Side effects	ND	
Studies with olaparib		
Study 19	N = 136	N = 129
Treatment duration [months]		
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	No data suitable for the indirect comparison are available[a]	
Side effects	ND	

Table 11: Information on the course of the study – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Study **Duration of the study phase** **Outcome category**	**Intervention**	**Common comparator**
SOLO2	N = 196	N = 99
Data cut-off 19 September 2016		
Treatment duration [months]		
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	
Morbidity	No data suitable for the indirect comparison are available[a]	
Health-related quality of life	No data suitable for the indirect comparison are available[a]	
Side effects	ND	
Data cut-off 3 February 2020		
Treatment duration [months]	ND	
Observation period [months]		
Overall survival; median [min; max]	66.0 [ND; ND]	64.8 [ND; ND]
Morbidity	No data suitable for the indirect comparison are available[a]	
Health-related quality of life	No data suitable for the indirect comparison are available[a]	
Side effects	ND	

a. See explanation in Sections 2.4.1 and 2.4.2.

max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

In the previous benefit assessment, there were already differences in the treatment and observation durations between the treatment arms of the studies NOVA, Study 19 and SOLO2 (see dossier assessment A19-88 [2]). In all studies, differences between the treatment arms were due to differences in the treatment discontinuation rates mainly due to disease progression. For the now relevant final data cut-offs of the studies NOVA (1 October 2020) and SOLO2 (3 February 2020), no data on median and mean treatment duration are available. However, it can be assumed that the differences between the study arms became larger at the later data cut-offs, as only very few patients in the placebo arms (in comparison with the intervention arms) were still under treatment already at the time of the respective earlier data cut-off in both studies (see [24]).

For the outcomes whose follow-up was linked to treatment duration (see Table 8), it is assumed that there is a similar difference in observation period as in treatment duration between the arms.

2.3.2.6 Subsequent therapies

For the subsequent therapies at the time points of the primary data cut-offs of the studies NOVA (30 May 2016) and SOLO2 (19 September 2016) and at the final data cut-off of Study 19 (9 May 2016), please refer to Appendix B of dossier assessment A19-88 [2]. In all studies included, chemotherapy was by far the most common subsequent therapy after treatment discontinuation. For the data cut-offs of the studies NOVA (1 October 2020) and SOLO2 (3 February 2020) that are new in comparison with the previous benefit assessment, only data on the administration of PARP inhibitors (for the study NOVA also only for the placebo arm) as subsequent therapy are available (see Appendix D of the full dossier assessment), so that a comprehensive assessment of the subsequent therapies is not possible. This is particularly problematic as the similarity of the studies cannot be assessed with regard to the subsequent therapies used (see Section 2.3.3). The consequences of administering PARP inhibitors as subsequent therapy in the placebo arm are taken into account in the assessment of the risk of bias (see Section 2.4.2).

2.3.3 Investigation of the central assumptions for the indirect comparison

All adjusted indirect comparisons and network meta-analyses are based on 3 central assumptions, which must be checked [41]: the similarity assumption, the homogeneity assumption and the consistency assumption.

Since the study pool in the present benefit assessment has not changed compared with the assessment in the previous benefit assessment [2,3], reference is made to benefit assessment A19-88 for the explanations on the investigation of the central assumptions [2] and only the summary assessment is reproduced here.

Investigation of the similarity of the studies

The check of the similarity of the studies NOVA, Study 19 and SOLO2 showed no major differences with regard to the patients included and the conduct of the studies (treatment and observation duration, similarity of the common comparator placebo) (see Section 2.3.3 of dossier assessment A19-88 [2] for a detailed rationale). With regard to the subsequent therapies used, an assessment of the similarity of the studies is not possible for the newly available data cut-offs of the studies NOVA and SOLO2, as only rudimentary information is available on this (see Section 2.3.2.6). The similarity of the studies was still considered to be sufficient for an adjusted indirect comparison using the common comparator placebo.

At outcome level, there were differences in follow-up observation between the studies NOVA and SOLO2 for health status recorded with the EQ-5D VAS, as well as for the specific AEs “acute myeloid leukaemia (AML)” and “myelodysplastic syndrome (MDS)” (see Table 8). Hence, no usable data for these outcomes are available for the indirect comparison between niraparib and olaparib. For other outcomes, problems arise with regard to the availability of the outcomes or the certainty of results that is sufficient for the indirect comparison (possibly also in addition to the differences in follow-up observation; see Sections 2.4.1 and 2.4.2).

For the outcomes that can be used for the indirect comparison, it was checked whether different observation periods play a role for the adjusted indirect comparison. 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.

The company did not explicitly comment on the investigation of the similarity of the studies it included (see Section 2.3, study pool of the company).

Investigation of the homogeneity assumption

For both olaparib studies included, heterogeneity was checked in the framework of the meta-analytical summary for dossier assessment A18-36 [31]. No important heterogeneity was determined for the results of the outcomes assessed. For the niraparib side, an investigation of homogeneity was not necessary as only one study was available.

Investigation of the consistency assumption

The company stated that it was not possible to investigate the consistency between direct and indirect comparisons because no studies of direct comparison were available. This view was shared. The absence of the investigation of consistency was taken into account when assessing the certainty of results.

2.3.4 Risk of bias across outcomes (study level)

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

Table 12: Risk of bias across outcomes (study level) – RCT, 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. This concurs with the company's assessment for all 3 studies included.

General comment on the certainty of results in the indirect comparison

Results from indirect comparisons have per se a low certainty of results [11]. Only results from adjusted indirect comparisons of particularly high methodological quality and a sufficient number of studies with sufficient certainty of results can be considered as having a moderate certainty of results. However, the aspect of the consistency check necessary for upgrading is not possible here. The adjusted indirect comparisons therefore have a low certainty of results, and at most hints can be derived.

However, no hint of an added benefit or of greater/lesser harm is generally derived if only one study with insufficient qualitative certainty of results is available on one or both sides of the comparison, for example due to high risk of bias, in the adjusted indirect comparison between the intervention or the control treatment with the same comparator treatment (common comparator). In the present data situation, however, there is sufficient certainty of results for deriving a hint from the indirect comparison in those cases where the indirect comparison shows sufficiently large effects so that these cannot be called into question by potential bias alone. This is checked for the outcomes available for the indirect comparison.

Transferability of the study results to the German health care context

For the NOVA study, the company stated that the study population covers the target population and meets its demographic and disease-specific characteristics. According to the company, 85% of the patients were of Caucasian family origin and recruited in the USA, Canada, Europe and Israel, and 13 of the study centres were located in Germany. The company was unable to identify any additional influencing factors that would argue against the transferability of the results of the NOVA study to the German health care context.

For the studies with olaparib (Study 19 and SOLO2), the company only stated that they were transferable to the German health care context.

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - overall survival

- Morbidity
  - health status (EQ-5D VAS)
  - FOSI
- Health-related quality of life
  - health-related quality of life measured by 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)
  - further specific AEs, if any

The choice of patient-relevant outcomes differs from the choice of the company, which used additional outcomes in the dossier (Module 4 A) (see Section 2.7.5.3.2 of dossier assessment A19-88 [2] for reasons).

Table 13 shows whether the outcomes were recorded in the included studies (yes/no) and whether an indirect comparison is possible based on the available data (yes/no).

Table 13: Matrix of outcomes – RCT, indirect comparison: niraparib vs. olaparib

Study	Outcomes							
	Overall survival	Health status (EQ-5D VAS)	Symptoms (FOSI)	Health-related quality of life (FACT-O total score)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Specific AEs
Niraparib vs. placebo								
NOVA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Olaparib vs. placebo								
Study 19	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
SOLO2	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Indirect comparison possible	No[b]	No[c]	No[b]	No[c]	No[b]	Yes[d]	No[b]	No[c]

a. Operationalized as CTCAE grade ≥ 3.
b. Requirement for the certainty of results to perform an adjusted indirect comparison is not met (see Section 2.4.2 and Table 14).
c. There are no results suitable for the indirect comparison, see running text for reasons.
d. Due to the size of the observed effect in the indirect comparison, it can be assumed that it is not completely called into question by potential biases alone (see Section 2.4.3).

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

No data usable for the indirect comparison are available for the following outcomes:

- EQ-5D VAS: Due to the different follow-up observation strategies (see Table 8), the analyses between the studies NOVA and SOLO2 are not comparable and cannot be used for the indirect comparison.
- FACT-O (total score): The subscales of the FACT-O were not completely recorded in the NOVA study, but only the 8 items for the calculation of the FOSI symptom score. Therefore, an indirect comparison for the outcome "FACT-O" is not possible overall.
- For the selected AEs of special interest for the clinical picture (AML and MDS), different follow-up observation strategies were available (see Table 8), which is why the analyses between the studies NOVA and SOLO2 are not comparable and cannot be used for the indirect comparison. No adjusted indirect comparison was calculated for the specific AE "pneumonitis" due to high risk of bias and the very few events, as this could not result in a sufficiently large statistically significant effect in each case.

- In addition, a selection of specific AEs based on the frequency and differences between the treatment arms for the indirect comparison was not possible because the company did not have all the information necessary for a comprehensive selection (event time analyses on frequent AEs) for the olaparib studies. This would have allowed him to make only selective indirect comparisons based on the study results.
- No indirect comparison can be calculated for the outcomes "overall survival", "FOSI", "SAEs" and "discontinuation due to AEs", as the requirement for the certainty of results for carrying out an adjusted indirect comparison was not met, taking into account the final data cut-off (1 October 2020) of the NOVA study (see Sections 2.3.4 and 2.4.2).

Assessment of the analyses presented by the company to correct for "bias due to crossover" for the outcome "overall survival" in the NOVA study

In addition to the intention to treat (ITT) analyses, which are generally relevant for the benefit assessment, the company presented additional analyses for the outcome "overall survival" for the NOVA study. The company used these analyses in an attempt to adjust for a potential bias that, in its opinion, existed due to the treatment switch from placebo to a PARP inhibitor (e.g. analyses with the "inverse probability of censoring weighting" [IPCW] method or analyses with imputations of missing values on subsequent therapies). These were not considered in the benefit assessment for the following reasons:

- These analyses do not eliminate the potentially biasing effect arising in the final data cut-off (1 October 2020) of the NOVA study, mainly due to the high proportion of study participants with unknown survival status (see Section 2.4.2).
- As the company did not provide any information on which PARP inhibitors were actually given in the NOVA study, it is unclear whether a crossover (or treatment switching in the sense of [42]) is present at all, or whether the PARP inhibitors used are an adequate subsequent therapy according to current guidelines [1,43] (see Section 2.4.2).
- Analytical methods for adjusting effect estimates for treatment switching are themselves prone to bias and there is no validated statistical method that allows with sufficient certainty the analysis of the outcome "overall survival" in studies with treatment switching [42].

2.4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes in the individual studies.

Table 14: 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)	Symptoms (FOSI)	Health-related quality of life (FACT-O total score)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Specific AEs
Niraparib vs. placebo									
NOVA	L	H[b, c, d, e]	–[f]	–[g]	–[f]	H[b]	H[b]	L[h]	–[f]
Olaparib vs. placebo									
Study 19	H[i]	H[d, j]	–[f]	–[g]	–[f]	H[j, k]	H[j, k]	H[j]	–[f]
SOLO2	L	H[d, e]	–[f]	–[g]	–[f]	H[b]	H[b]	L[h]	–[f]

a. Operationalized as CTCAE grade ≥ 3.
b. Incomplete observations with potentially biasing influence.
c. Since the requirement for the certainty of results for conducting an adjusted indirect comparison is not met overall due to the high risk of bias for the outcome "overall survival" in the final data cut-off (1 October 2020), the results of the outcome "overall survival" with potentially low risk of bias, based on the primary data cut-off (30 May 2016) are additionally used (see Table 15).
d. After progression, patients in the intervention arm could still receive niraparib (NOVA) or olaparib (Study 19 and SOLO2) outside the approval status at the physician's discretion. The number of patients and the duration of this continued treatment are not known.
e. Unclear proportion of patients in the placebo arms who received niraparib (NOVA) or olaparib (SOLO2) after progression.
f. No indirect comparison is carried out (see Section 2.4.1 for reasons).
g. No indirect comparison possible because on the olaparib side, only data from one study with a high risk of bias (Study 19) are available (the outcome was not analysed in the SOLO2 study).
h. Despite the low risk of bias, the certainty of results for the outcome "discontinuation due to AEs" was assumed to be limited (see running text).
i. Large proportion of patients with incorrect classification in the stratified block randomization in the total study population (olaparib: 35.3%, placebo: 24.0%).
j. Due to the high risk of bias across outcomes.
k. 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).

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: FACT Ovarian Symptom Index; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The results of all outcomes from the studies NOVA, Study 19 and SOLO2 that can be used for the indirect comparison had a high risk of bias except for the outcome "discontinuation due to AEs" in the studies NOVA and SOLO2. The certainty of results for the outcome "discontinuation due to AEs" was limited despite a low risk of bias, however. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome

"discontinuation due to AEs" to be recorded. This means that, after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It cannot be estimated how many AEs this concerns.

Below, the classification of the risk of bias is justified separately for the 3 studies.

NOVA

The high risk of bias for the results of the outcome "overall survival" in the final data cut-off (1 October 2020) of the NOVA study resulted in particular from the high proportion of study participants who were no longer available for recording data on the outcome "overall survival". A total of 76 study participants (14% of the study population) ended the study prematurely without any subsequent information on survival status being included in the analysis for these patients[4]. This incomplete observation led to missing data, which increased the risk of bias, as it is unclear how the missing information was distributed between the 2 study arms and whether the losses occurred randomly (missing completely at random). The direction and extent of the potential bias is therefore unclear.

Furthermore, the high risk of bias in the NOVA study for the results of the outcome "overall survival" resulted from the fact that a high proportion of patients in the placebo arm was receiving a PARP inhibitor at the time of the final data cut-off. According to the company, this concerns at least 45 patients (24.9%). For another 28% of the patients, no information at all is available on subsequent therapies. The company did not provide any information on which PARP inhibitors the study participants actually received. It is thus unclear whether the PARP inhibitors used were the study intervention niraparib and thus treatment switching in the sense of [42], which can lead to a potential bias of the treatment effect, or another PARP inhibitor approved in the therapeutic indication (e.g. olaparib), which would be assessed as an adequate subsequent therapy according to current guideline recommendations [1,43,44]. Since the present dossier assessments do not consider the pure treatment effect of the experimental intervention, but the effect of the therapeutic strategy that starts with an experimental intervention (in comparison with a therapeutic strategy without the drug), the results under a subsequent treatment after discontinuation of the study medication must be taken into account in the derivation of the added benefit. Adequate subsequent therapy does not affect the risk of bias.

Based on the results of the final data cut-off of the NOVA study for this outcome, which have a high risk of bias, no indirect comparison was performed for the outcome "overall survival" as the requirement for the certainty of results for performing an adjusted indirect comparison was not met (see Section 2.3.4). Therefore, the results of the primary data cut-off (30 May 2016),

[4] A total of 155 patients had completed the study without being followed up for the outcome "overall survival". However, through research into the survival status after the end of the study, the company was able to identify 59 deaths among these patients.

where the risk of bias was rated as low, were additionally used for overall survival, (see dossier assessment A19-88 [2]). The analyses at this earlier point in time did not yet have a high risk of bias from the incomplete observation of the outcome "overall survival". This concurs with the company's assessment.

No data of the NOVA study usable for the indirect comparison were available for outcomes of morbidity and health-related quality of life (see Section 2.4.1). This concurs with the company's assessment.

For the results of all outcomes in the category of side effects except the outcome "discontinuation due to AEs", the assessment of a high risk of bias resulted from incomplete observations for potentially informative reasons (see also Section 2.7.5.2 in dossier assessment A19-88 [2]). This deviates from the assessment of the company, which rated the risk of bias of the results for the outcomes of the category of side effects as low.

Study 19

For Study 19, there was a high risk of bias for all outcomes already from the high risk of bias across outcomes alone, which was due to the high proportion of patients with misclassification in the stratified block randomization in the total study population (olaparib: 35.3%, placebo: 24.0% [see Section 2.3.4]). In addition, there are other outcome-specific reasons (see Table 14 as well as Section 2.7.5.2 of dossier assessment A19-88 [2]). This deviates from the assessment of the company, which, despite the high risk of bias across outcomes, rated the risk of bias of the results for the outcome "overall survival" and the outcomes of the category of side effects as low with reference to the benefit dossier of olaparib from 4 June 2018 [29].

SOLO2

The high risk of bias for the results of the outcome "overall survival" in the final data cut-off of the SOLO2 study (3 February 2020) resulted – analogous to the NOVA study – from the high proportion of patients in the placebo arm who switched to a PARP inhibitor after progression (38% [38], see also Table 28 of the full dossier assessment). As described in Section 2.3.2.1, patients could be unblinded after progression to decide on subsequent therapies with commercially available olaparib or with a PARP inhibitor in the framework of another study. As in the NOVA study, it is unclear exactly which PARP inhibitors were used and whether this was treatment switching or adequate subsequent therapy (see above). Since the studies NOVA and SOLO2 were conducted in parallel (study start in 2013, study end in 2020), a comparable health care context can be assumed, so that, in accordance with guideline recommendations regarding the administration of PARP inhibitors, there was an increased use of PARP inhibitors as subsequent therapy in both studies. The company did not assess the risk of bias for the results on overall survival for the final data cut-off (3 February 2020).

No data of the SOLO2 study usable in the indirect comparison were available for outcomes of morbidity and health-related quality of life (see Section 2.4.1 of the full dossier assessment). This concurs with the company's assessment.

For the results of all outcomes of the category of side effects, 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. This deviates from the assessment of the company, which rated the risk of bias of all results for the outcomes of the category of side effects as low with reference to the benefit dossier of olaparib from 4 June 2018 [29].

2.4.3 Results

Table 15 summarizes the results of the comparison of niraparib with olaparib in patients with platinum-sensitive relapsed high-grade serous 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. Kaplan-Meier curves on the outcomes "overall survival" and "severe AEs" can be found in Appendix A of the full dossier assessment. Forest plots of the meta-analyses calculated by the Institute can be found in Appendix B of the full dossier assessment. The results on common AEs, SAEs, severe AEs, and discontinuations due to AEs for the NOVA study (final data cut-off [1 October 2020]) are presented in Appendix C of the full dossier assessment. The meta-analytical summary of both olaparib studies was taken from benefit assessment A19-88 [2]. The corresponding forest plots as well as the results on common AEs, SAEs, severe AEs, and discontinuations due to AEs for Study 19 (final data cut-off [9 May 2016]) and the SOLO2 study (primary data cut-off [19 September 2016]) can be found in dossier assessment A18-36 [31] (Appendix A.2 as well as Appendix A.3). No usable information on common side effects was available for the final data cut-off (3 February 2020) of the SOLO2 study, so that no tables on common side effects for the final data cut-off of the SOLO2 study can be presented in the appendix.

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Outcome category Outcome Comparison Study (data cut-off)	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
Mortality					
All-cause mortality					
Niraparib vs. placebo					
NOVA (1 October 2020)	372	35.6 [32.2; 40.6] 245 (65.9)	181	37.1 [29.9; 41.8] 120 (66.3)	1.01 [0.81; 1.27]; 0.903[a]
NOVA (30 May 2016)[b]	*372*	*NA* *60 (16.1)*	*181*	*NA* *35 (19.3)*	*0.73 [0.48; 1.13]; 0.155[a]*
Olaparib vs. placebo					
Study 19 (9 May 2016)	136	29.8 [ND] 98 (72.1)	129	27.8 [ND] 112 (86.8)	0.73 [0.55; 0.95]; 0.021[c]
SOLO2 (3 February 2020)	196	51.7 [41.5; 59.1] 116 (59.2)	99	38.8 [31.4; 48.6] 65 (65.7)	0.74 [0.54; 1.0] 0.054[d]
Total[e]					0.73 [0.60; 0.90]; 0.003
Indirect comparison using common comparators[f]: **Niraparib vs. olaparib (with NOVA 1 October 2020)**					–[g]
Niraparib vs. olaparib (with NOVA 30 May 2016)					*1.00 [0.62; 1.61]; > 0.999*
Morbidity					
Health status (EQ-5D VAS)	No usable data[h]				
FOSI	No usable data[i]				
Health-related quality of life					
FACT-O total score	No usable data[j]				
Side effects					
AEs (supplementary information)					
Niraparib vs. placebo					
NOVA (1 October 2020)	367	0.1 [NC] 367 (100.0)	179	0.3 [0.2; 0.3] 172 (96.1)	–
Olaparib vs. placebo					
Study 19 (9 May 2016)	136	0.1 [ND] 132 (97.1)	128	0.3 [ND] 119 (93.0)	–
SOLO2 (19 September 2016)	195	0.1 [ND] 192 (98.5)	99	0.2 [ND] 94 (94.9)	–

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Outcome category **Outcome** **Comparison** **Study (data cut-off)**	**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**
SAEs					
Niraparib vs. placebo					
NOVA (1 October 2020)	367	43.2 [29.6; 70.9] 126 (34.3)[k]	179	NA 27 (15.1)[k]	2.14 [1.41; 3.25]; < 0.001[l]
Olaparib vs. placebo					
Study 19 (9 May 2016)	136	67.9 [ND] 31 (22.8)	128	42.0 [ND] 11 (8.6)	1.61 [0.79; 3.46]; 0.218[c]
SOLO2 (19 September 2016)	195	NA 35 (17.9)	99	NA 8 (8.1)	1.64 [0.79; 3.84]; 0.234[d]
Total[m]					1.62 [0.94; 2.81]; 0.083
Indirect comparison using common comparators[f]:					
Niraparib vs. olaparib					–[g]
Severe AEs[n]					
Niraparib vs. placebo					
NOVA (1 October 2020)	367	1.6 [1.0; 2.1] 280 (76.3)	179	72.4 [20.1; NC] 43 (24.0)	5.24 [3.79; 7.27]; < 0.001[l]
Olaparib vs. placebo					
Study 19 (9 May 2016)	136	22.9 [ND] 59 (43.4)	128	NA 28 (21.9)	1.88 [1.20; 3.01]; 0.013[c]
SOLO2 (19 September 2016)	195	NA 72 (36.9)	99	NA 18 (18.2)	1.92 [1.17; 3.33]; 0.012[d]
Total[m]					1.90 [1.34; 2.68]; < 0.001
Indirect comparison using common comparators[f]:					
Niraparib vs. olaparib					2.76 [1.71; 4.44]; < 0.001[o]

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Outcome category **Outcome** **Comparison** **Study (data cut-off)**	**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**
Discontinuation due to AEs					
Niraparib vs. placebo					
NOVA (1 October 2020)	367	NA [58.4; NC] 67 (18.3)	179	NA 4 (2.2)	6.61 [2.40; 18.20]; < 0.001[l]
Olaparib vs. placebo					
Study 19 (9 May 2016)	136	NA 8 (5.9)	128	NA 2 (1.6)	1.96 [0.44; 13.68]; 0.528[c]
SOLO2 (19 September 2016)	195	NA 21 (10.8)	99	NA 2 (2.0)	3.71; [1.07; 23.40]; 0.063[d]
Total[m]					2.79 [0.89; 8.80]; 0.080
Indirect comparison using common comparators[f]:					
Niraparib vs. olaparib					–[g]

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, indirect comparison: niraparib vs. olaparib (multipage table)

Outcome category Outcome Comparison Study (data cut-off)	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
a. HR and associated CI: Cox proportional hazards model stratified by time to disease progression after penultimate platinum-based therapy prior to study inclusion, use of bevacizumab on penultimate or most recent platinum-based therapy, and best response during most recent platinum-based therapy; p-value from log-rank test. b. Additional consideration of the primary data cut-off (30 May 2016) due to the certainty of results insufficient for conducting an indirect comparison for the outcome "overall survival" in the final data cut-off (1 October 2020; see Section 2.4.2). c. 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). d. 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). e. Institute's calculation from meta-analysis with fixed effect. f. Indirect comparison according to Bucher [45]. g. No indirect comparison is calculated due to an insufficient certainty of results in the NOVA study (see Sections 2.3.4 and 2.4.2). h. No indirect comparison possible because of different follow-up observation strategies for this outcome in the studies NOVA and SOLO2 (see Table 8 and Section 2.4.1) i. No indirect comparison possible because only data from a study with a high risk of bias (Study 19) are available on the olaparib side. j. No indirect comparison possible because the subscales of the FACT-O were not completely recorded in the NOVA study, but only the 8 items for the calculation of the FOSI symptom score. k. Nonfatal SAEs; in the study, there were an additional 3 (0.8%) fatal SAEs in the niraparib arm and none in the placebo arm. l. Unstratified Cox proportional hazards model; p-value from log-rank test. m. Meta-analysis with fixed effect (results were taken from dossier assessment A19-88). n. Operationalized as CTCAE ≥ 3. o. Institute's calculation; due to the size of the observed effect in the indirect comparison, it can be assumed that it is not completely called into question by potential biases alone. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-O: Functional Assessment of Cancer Therapy-Ovarian; FOSI: FACT-Ovarian Symptom Index; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus					

The presented indirect comparison included only one study on the niraparib side. At the final data cut-off of this study (1 October 2020), all outcomes included in the indirect comparison either had a high risk of bias or limited certainty of results despite a low risk of bias (see Section 2.4.2). In the present benefit assessment, there is therefore no sufficient certainty of results to meet the minimum requirement for the certainty of results for the derivation of a hint on the basis of an indirect comparison. In the present data situation, however, there is sufficient

certainty of results for deriving a hint from the indirect comparison in those cases where the indirect comparison shows sufficiently large effects so that these cannot be called into question by potential bias alone (see Section 2.3.4). This was checked for the outcomes available in the indirect comparison.

Mortality

For the outcome "overall survival", the risk of bias for the result for the final data cut-off (1 October 2020) of the NOVA study was rated as high. Therefore, the prerequisites for being able to derive conclusions on the added benefit from an adjusted indirect comparison were not fulfilled based on the final data cut-off of the NOVA study, and no indirect comparison was calculated.

In order to be able to still draw conclusions on the outcome "overall survival", the results of the primary data cut-off (30 May 2016) of the NOVA study, which had a low risk of bias, were therefore additionally used (see Section 2.4.2) and compared with the results of the final data cut-offs of Study 19 and SOLO2. Taking into account the results of the primary data cut-off of the NOVA study, which had a low risk of bias, the adjusted indirect comparison showed no statistically significant difference between niraparib and olaparib for the outcome "overall survival".

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

The result of the assessment corresponds to that of the company, which, however, interpreted the results for the outcome "overall survival" in the indirect comparison with additional consideration of the NORA study and further analyses to correct for "bias due to crossover", which were not considered in the present benefit assessment, however (for justification, see Sections 2.3 and 2.4.1).

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 2.4.1 and Table 8).

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.

FOSI

No indirect comparison was possible for the outcome "FOSI" because only data from a study with a high risk of bias across outcomes (Study 19) were available on the olaparib side (see Table 14).

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.

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 with the FACT-O total score, as this outcome was not recorded in the NOVA study (see Section 2.4.1).

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

Severe AEs

For the outcome "severe AEs", only the result from a study with outcome-specific high risk of bias was available on the niraparib side of the adjusted indirect comparison. The prerequisites for the derivation of conclusions on the added benefit from an adjusted indirect comparison were therefore initially not fulfilled. However, a large effect for this outcome was shown both in the comparison of niraparib with placebo in the NOVA study and in the adjusted indirect comparison with olaparib using the common comparator placebo. It is not assumed in the present data situation that the statistically significant effect in the indirect comparison to the disadvantage of niraparib is completely called into question by potential bias. Hence, despite the high outcome-specific risk of bias, the qualitative certainty of results is sufficiently high in the NOVA study to be able to interpret the present effect and derive a hint of greater or lesser harm from niraparib.

Overall, there is therefore a hint of greater harm from niraparib in comparison with olaparib. Due to the uncertainties, the extent of the effect cannot be quantified, however.

This deviates from the assessment of the company, which described the statistically significant difference to the disadvantage of niraparib, but did not derive greater harm from niraparib compared with olaparib.

SAEs and discontinuation due to AEs

For the outcomes "SAEs" and "discontinuation due to AEs", there were also only results with a high risk of bias (SAEs) or results with limited certainty of results (discontinuation due to AEs) available on the niraparib side of the indirect comparison. The prerequisites for drawing conclusions on the added benefit from an adjusted indirect comparison were therefore not fulfilled also for these outcomes. However, irrespective of the usability of the data of the adjusted indirect comparison, there was (in contrast to the severe AEs) no statistically significant difference between niraparib and olaparib, neither for the outcome "SAEs" nor for the outcome "discontinuation due to AEs". The results are not interpretable due to an insufficient certainty of results for this data constellation.

This resulted in no hint of greater or lesser harm of niraparib in comparison with olaparib; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Specific AEs

There were no usable data for the specific AEs of special importance for the clinical picture (AML, MDS), as different follow-up observation strategies for these outcomes were used in the studies (see Section 2.4.1 and Table 8). No adjusted indirect comparison was calculated for the specific AE "pneumonitis" due to the very few events (and a high risk of bias), as this could not result in a sufficiently large statistically significant effect in each case (see Section 2.4.1).

This resulted in no hint of greater or lesser harm of niraparib in comparison with olaparib; greater or lesser harm is therefore not proven.

For the specific AEs "AML" and "MDS", this corresponds to the assessment of the company. The company did not comment on the specific AE "pneumonitis" in the dossier section on the indirect comparison.

2.4.4 Subgroups and other effect modifiers

No subgroup analyses for the indirect comparison are available for the present benefit assessment of niraparib. Thus, no conclusions on potential effect modifications are possible for the comparison of niraparib and olaparib.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [11].

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

2.5.1 Assessment of the added benefit at outcome level

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

Table 16: 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	Indirect comparison under consideration of the final data cut-off of the NOVA study (1 October 2020): No usable data[c]	Lesser benefit/added benefit not proven
	Indirect comparison under consideration of the primary data cut-off of the NOVA study (30 May 2016): *HR: 1.00 [0.62; 1.61];* *p > 0.999*	
Morbidity		
Health status (EQ-5D VAS)	No usable data[d]	Lesser benefit/added benefit not proven
FOSI	No usable data[c]	Lesser benefit/added benefit not proven
Health-related quality of life		
FACT-O total score	No sufficient data available[e]	Lesser benefit/added benefit not proven
Side effects		
SAEs	No usable data[c]	Greater/lesser harm not proven
Severe AEs	HR: 2.76 [1.71; 4.44] p < 0.001 probability: "hint"[f]	Outcome category: serious/severe side effects greater harm, extent: "non-quantifiable"
Discontinuation due to AEs	No usable data[c]	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
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 indirect comparison is calculated due to the insufficient certainty of results (see Section 2.4.2).
d. No usable data available, as different strategies for follow-up observation of this outcome were used in the studies (see Section 2.4.1).
e. This outcome was not recorded in the NOVA study.
f. Due to the size of the observed effect in the indirect comparison, it can be assumed that it is not completely called into question by potential biases alone.

AE: adverse event; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FACT-O: Functional Assessment of Cancer Therapy-Ovarian; FOSI: FACT Ovarian Symptom Index; HR: hazard ratio; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

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

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

Positive effects	**Negative effects**
–	Serious/severe side effects: ▪ Overall rate of severe AEs: hint of greater harm – extent: "non-quantifiable"
For the outcomes of the categories of morbidity and health-related quality of life as well as specific AEs, there are no data usable for the indirect comparison.	
AE: adverse event	

Overall, usable data for the indirect comparison are available for only 2 outcomes (overall survival and severe AEs). Taking into account the results of the primary data cut-off of the NOVA study (30 May 2016), there was no statistically significant difference between niraparib and olaparib for the outcome "overall survival". Thus, only a negative observed effect of niraparib remains for the outcome "severe AEs", resulting in a hint of non-quantifiable greater harm of niraparib in comparison with olaparib.

In summary, there is therefore a hint of lesser benefit of niraparib versus olaparib for 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.

The result of the assessment of the added benefit of niraparib in comparison with the ACT olaparib is summarized in Table 18.

Table 18: Niraparib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
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	**Olaparib** or watchful waiting	Hint of lesser benefit
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**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above differs from that of the company, which concluded "no added benefit and no added harm in comparison with olaparib".

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

Supplementary information on the implementation of the conditions of the limitation

In its justification on the first decision on niraparib, the G-BA explained the following:

> *"For the renewed benefit assessment after the deadline, the dossier should include the results expected in second quarter of 2020 from the final analysis on overall survival as well as all other patient-relevant outcomes from the NOVA study used to demonstrate an additional benefit. In particular for the specific adverse events, the data for the total population of the study should also be provided [25]."*

The company met these requirements in the present dossier.

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.

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