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Niraparib (ovarian cancer; first-line maintenance) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Niraparib (Ovarialkarzinom; Erstlinie Erhaltung) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 February 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-OV28	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Ovarian Cancer Module
EoT	end of treatment
EQ-5D	European Quality of Life – 5 Dimensions
FDA	Food and Drug Administration
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
FSD	fixed starting dose
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
HRD	homologous recombination deficiency
ISD	individualized starting dose
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PFS	progression-free survival
PRO	patient-reported outcomes
PT	Preferred Term
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
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 26 November 2020.

Research question

The aim of this report is to assess any added benefit of niraparib maintenance therapy in comparison with the appropriate comparator therapy (ACT) in adult patients with advanced epithelial (Fédération Internationale de Gynécologie et d'Obstétrique [FIGO] stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal carcinoma who exhibited a (complete or partial) response after platinum-based first-line chemotherapy.

The ACT specified by the G-BA served as the basis for the research question presented in Table 2 for this benefit assessment.

Table 2: Research questions of the benefit assessment of niraparib

Indication	ACT[a]
Adult patients with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal carcinoma who exhibited a (complete or partial) response following platinum-based first-line chemotherapy.	Therapy upon the physician's discretion, in consideration of ▪ watchful waiting (after prior therapy with carboplatin in combination with paclitaxel) ▪ bevacizumab (only after prior therapy with carboplatin in combination with paclitaxel and bevacizumab)
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

The PRIMA study was included for assessing the added benefit of niraparib in comparison with the ACT (watchful waiting).

However, the study results presented in the company's dossier are incomplete and were inadequately compiled. This makes it impossible to adequately assess the study data; consequently, none of the results of the PRIMA study were included in the benefit assessment.

Study design

The PRIMA study is a double-blind, randomized study comparing niraparib with placebo. The study includes adult patients with advanced (FIGO stages III and IV) high-grade serous or endometrioid ovarian carcinoma who exhibited a complete or partial response after platinum-based first-line chemotherapy.

A total of 733 patients were randomized to treatment with niraparib (N = 487) or placebo (N = 246) in a 2:1 ratio. Niraparib treatment was administered as approved, except for the individualized starting dose (ISD) (see below).

Primary outcome of the study was progression-free survival. Patient-relevant secondary outcomes were overall survival as well as outcomes on morbidity, health-related quality of life, and adverse events (AEs).

The study is still ongoing (planned end of the study: expected in 2024). For the benefit assessment, the most recent data cut-off is deemed relevant (Food and Drug Administration [FDA] safety update from 17 November 2019).

Relevant subpopulation

In consideration of the available study results, the subpopulation used for the benefit assessment consists of patients who received the ISD regimen recommended for niraparib in the Summary of Product Characteristics (SPC), which is based on body weight and baseline platelet counts (ISD subpopulation). This was due, in particular, to the better AE profile of niraparib in the ISD subpopulation. In total, the ISD subpopulation treated as approved includes 352 patients (equalling 48% of the total population), of which 228 were in the niraparib arm and 124 in the placebo arm.

Implementation of the ACT

While the included placebo-controlled PRIMA study was not designed for a comparison with watchful waiting, it is, with some restrictions, suitable for such a comparison.

Incomplete submitted results

The results of the PRIMA study as presented by the company in the dossier are incomplete and were inadequately compiled. Therefore, it is impossible to adequately assess the study data; consequently, none of the results of the PRIMA study are usable for the benefit assessment. The rationale is provided below.

Incomplete data on patient-reported outcomes (PROs)

Results on PROs are reported incompletely in the company's dossier. This particularly applies to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), which was used in the PRIMA study and, according to its statistical analysis plan, was to be fully analysed. However, in Module 4 A of the dossier, the company presents results only on the global health status scale. Results are missing for the other scales relevant for the benefit assessment (5 functioning and 8 symptom scales).

The incomplete presentation of results of the core module EORTC QLQ-C30 also makes it impossible to use the results of the ovarian cancer-specific supplementary module EORTC QLQ-OV28. OV28 is a supplementary module which must be used and interpreted together with the core module EORTC QLQ-C30. The company presents results on all OV28 scales surveyed in the PRIMA study (including for the relevant ISD subpopulation); but in accordance with the scoring manual, these results are not used in the present benefit assessment, since the results of the core module EORTC QLQ-C30 are unknown.

In addition, it is impossible to use the additional analyses presented by the company (Annex 4-G of the dossier) to assess the results on the missing scales. This is due to the fact that, in the respective chapters, results were presented without explanatory labelling, thus rendering it impossible to match the results to specific outcomes.

For the dossier assessment, extensive information is therefore missing on PROs, and no analyses at all are available on health-related quality of life, despite the fact that these data were surveyed.

Incomplete data on AEs

The information on AEs provided by the company is incomplete as well. The dossier template specifies that, alongside the total rates of AEs, results must be provided on all AEs (operationalized as System Organ Class [SOC] and Preferred Terms [PTs] as per Medical Dictionary for Regulatory Activities [MedDRA]), provided they meet a minimum prevalence threshold. A complete presentation of these common AEs (separately for not further differentiated AEs, serious adverse events [SAEs], and AEs differentiated by severity) is essential for assessing AE profiles as well as for selecting specific AEs. In Module 4 A, the company essentially presents only SOCs and PTs for which a significant treatment difference was established. Hence, the information provided in the company's dossier on common AEs is incomplete. For the benefit assessment, this makes it impossible to present common AEs or to select specific AEs on the basis of the AEs which occurred in the PRIMA study.

Further points of criticism

The company's dossier further lacks information on the duration of treatment and follow-up as well as on the follow-up therapies used in the study. Alongside the incompletely presented results, this issue further complicates the interpretation of study data.

Final evaluation and consequences

Taken altogether, the above-described deficiencies of the dossier are deemed grave. The presented data are incomplete, particularly due to missing or unusable results on the EORTC QLQ questionnaire and the incomplete presentation of AE results.

Overall, no usable data are therefore available for the assessment of added benefit of niraparib in comparison with the ACT in adult patients with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal carcinoma who exhibited a (complete or partial) response after platinum-based first-line chemotherapy. Consequently, there is no hint of an added benefit of niraparib in comparison with the ACT; an added benefit is therefore not proven.

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

On the basis of the presented results, the probability and extent of added benefit of the drug niraparib in comparison with the ACT are assessed as follows:

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

Table 3: Niraparib – probability and extent of added benefit

Indication	ACT[a]	Probability and extent of added benefit
Adult patients with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal carcinoma who exhibited a (complete or partial) response following platinum-based first-line chemotherapy.	Therapy upon the physician's discretion, in consideration of ▪ watchful waiting (after prior therapy with carboplatin in combination with paclitaxel) ▪ bevacizumab (only after prior therapy with carboplatin in combination with paclitaxel and bevacizumab)	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

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

2.2 Research question

The aim of this report is to assess any added benefit of niraparib maintenance therapy in comparison with the ACT in adult patients with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal carcinoma who exhibited a (complete or partial) response after platinum-based first-line chemotherapy.

The ACT specified by the G-BA served as the basis for the research question presented in Table 4 for this benefit assessment.

Table 4: Research questions of the benefit assessment of niraparib

Indication	ACT[a]
Adult patients with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal carcinoma who exhibited a (complete or partial) response following platinum-based first-line chemotherapy.	Therapy upon the physician's discretion, in consideration of ▪ watchful waiting (after prior therapy with carboplatin in combination with paclitaxel) ▪ bevacizumab (only after prior therapy with carboplatin in combination with paclitaxel and bevacizumab)
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; G-BA: Federal Joint Committee	

In the presence of shared aetiology and histomorphology, ovarian, fallopian tube, and peritoneal carcinoma are classified together in accordance with the S3 Guideline on Diagnostics, Therapy, and Follow-up of Malignant Ovarian Tumours [3]. Therefore, the present dossier assessment uses the term ovarian cancer as an umbrella term for ovarian, fallopian tube, and peritoneal carcinoma.

The company followed the G-BA's specification of the ACT. 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 cited by the company in the dossier:

- Study list on niraparib (as of 1 October 2020)
- Bibliographic literature search on niraparib (most recent search on 23 September 2020)
- Search in trial registries / study results databases on niraparib (most recent search on 12 October 2020)
- Search on the G-BA website on niraparib (most recent search on 12 October 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on niraparib (most recent search on 1 December 2020)

The check did not identify any additional relevant studies.

2.3.1 Included studies

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

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

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication (yes/no [reference])
PR-30-5017-C (PRIMA[c])	Yes	Yes[d]	No	No[e]	Yes [4,5]	Yes [6]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this short name.
d. The study's sponsor was taken over by the company in 2019 [7].
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

RCT: randomized controlled trial

The study pool used for the benefit assessment is consistent with that of the company, which presented the PRIMA study for deriving any added benefit of niraparib in comparison with the ACT of watchful waiting.

The PRIMA study is viewed as generally relevant for answering the present research question. Therefore, it is included in the benefit assessment and characterized below. However, the study results presented in the company's dossier are incomplete and inadequately prepared. Therefore, it is impossible to adequately assess the study data, and consequently, none of the results of the PRIMA study were included in the benefit assessment (see Section 2.4.2).

2.3.2 Study characteristics

Table 6 and Table 7 present the study used in the benefit assessment.

Table 6: Characterization of the included study – RCT, direct comparison: niraparib vs. placebo[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[b]
PRIMA	RCT, double-blind, parallel-group	Adult patients[c] with advanced (FIGO stages III and IV) high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal carcinoma who showed a (complete or partial)[e] response following platinum-based first-line chemotherapy[d].	▪ Niraparib (N = 487)[f] ▪ Placebo (N = 246)[f] Relevant subpopulation thereof[g]: ▪ Niraparib (n = 228) ▪ Placebo (n = 124)	▪ Screening: ≤ 28 days ▪ Treatment: until disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, death, or end of treatment after about 3 years[h] ▪ Follow-up observation[i]: ▪ Outcome-specific, at the longest until death, withdrawal of consent, or study end[j]	220 centres in: Belgium, Canada, Czech Republic, Denmark, Germany, Finland, France, Hungary, Ireland, Israel, Italy, Norway, Poland, Russia, Spain, Sweden, Switzerland, Ukraine, United States, United Kingdom 08/2016–ongoing[j] Data cut-off dates: ▪ 17/05/2019 (primary analysis) ▪ 17/11/2019 (FDA 90-day safety update)	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Sufficient approximation of the ACT of watchful waiting, with some limitations (see Section 2.3.2 on Implementation of the ACT).
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
c. Patients in stage III with complete cytoreduction (i.e. no visible residual disease) following primary debulking surgery as well as patients with more than 2 debulking surgeries were excluded. Patients who received neoadjuvant chemotherapy were eligible for study inclusion if the tumour grade could not be determined after chemotherapy.
d. Randomization within 12 weeks from the first day of the most recent chemotherapy cycle.
e. Assessed after ≥ 3 treatment cycles.
f. Among the randomized patients, 3 in the niraparib arm and 2 in the placebo arm received no study drug.
g. Population of all patients who were treated with the ISD recommended in the SPC (Section 4.2) [8]; see Section 2.3.2 on the relevant subpopulation, in the report referred to as ISD population.
h. At the investigator's discretion, it was possible to continue treating patients with the study drug as long as they benefited from the treatment.
i. Outcome-specific information is provided in Table 8.
j. The study runs until the final analysis of overall survival (planned after approx. 440 deaths), which is estimated to occur in 2024.

Table 6: Characterization of the included study – RCT, direct comparison: niraparib vs. placebo[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[b]
ACT: appropriate comparator therapy; AE: adverse event; ECOG: Eastern Cooperative Oncology Group; FDA: Food and Drug Administration; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; HRD: homologous recombination deficiency; ISD: individualized starting dose; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; SPC: Summary of Product Characteristics						

Table 7: Characterization of the intervention – RCT, direct comparison: niraparib vs. placebo[a]

Study	Intervention	Comparison
PRIMA	Niraparib, orally, once daily: ▪ 300 mg (3 x 100 mg)[b] or ▪ 200 mg (2 x 100 mg)[b]	Placebo, orally, once daily: ▪ 3 capsules[b] or ▪ 2 capsules[b]
	The study medication was administered continuously over 28-day cycles.	
	Dose adjustment, treatment interruption (up to 28 days) and treatment discontinuation due to toxicity possible[c]	
	Prior treatment ▪ Patients had to have been treated with ≥ 6 and ≤ 9 cycles of platinum-based therapy[d] (at least 2 cycles after interval debulking surgery) Disallowed: ▪ PARP inhibitors ▪ Bevacizumab administered together with the most recent platinum-based chemotherapy before study inclusion[e] **Concomitant treatment** ▪ Allowed: ▪ Palliative radiotherapy for the treatment of painful metastases which were already present before study start and could not be treated with local or systemic analgesics (so long as there was no suspicion of disease progression) ▪ Prophylactic cytokines (disallowed only during the 1st cycle; thereafter, their use in accordance with local guidelines was allowed). ▪ Disallowed: ▪ Live viruses or bacterial vaccines ▪ Other cancer treatment	

a. Sufficient approximation of the ACT of watchful waiting, with some limitations (see Section 2.3.2 on the Implementation of the ACT).
b. According to the original protocol from 26 October 2015, all patients were treated with a fixed starting dose of 300 mg niraparib. As of Protocol Amendment 2 (16 November 2017), the starting dose of the study drug was determined based on body weight and platelet count at baseline. Patients with
- a body weight ≥ 77 kg and platelet count ≥ 150 000/µL received 300 mg (3 capsules) of niraparib or 3 capsules of placebo
- a body weight < 77 kg or platelet count < 150 000/µL received 200 mg (2 capsules) of niraparib or 2 capsules of placebo

In patients whose initial dose was 2 capsules once daily, an escalation to 3 capsules once daily was permissible, provided that no treatment interruption or discontinuation was necessary during the first two treatment cycles. This escalation is not specified in the SPC [8]; be that as it may, according to the EPAR [9], the escalation was performed in only 13 patients (among the total population).

c. Toxicity-related dose modifications or even treatment discontinuation were possible without relevant deviations from the specifications of the SPC [8].
d. In the total population, 96% received carboplatin and 8% cisplatin as part of prior treatment [9].
e. Patients who received bevacizumab as first-line therapy on a platinum basis but were unable to receive bevacizumab maintenance therapy due to AEs or for other reasons were not excluded from the study, provided that they received the last dose of bevacizumab ≥ 28 days before signing the main consent form.

ACT: appropriate comparator therapy; AE: adverse event; EPAR: European Public Assessment Report; PARP: poly(adenosine diphosphate ribose) polymerase; RCT: randomized controlled trial; SPC: Summary of Product Characteristics

The PRIMA study is a double-blind, randomized study comparing niraparib with placebo. The study includes adult patients with advanced (FIGO stages III and IV) high-grade serous or endometrioid ovarian carcinoma who exhibited a complete or partial response after platinum-based first-line chemotherapy. The required length of this platinum-based therapy was between ≥ 6 and ≤ 9 cycles in all patients (at least 2 cycles had to have been administered following interval debulking surgery). At study inclusion, the first day of the most recent chemotherapy cycle had to be no more than 12 weeks ago. Patients had to be in good general condition (Eastern Cooperative Oncology Group Performance Status [ECOG-PS] of 0 or 1). Patients in stage III with complete cytoreduction (i.e. no visible residual disease) following primary debulking surgery or patients with more than 2 debulking surgeries were ineligible for study participation.

A total of 733 patients were randomized to treatment with niraparib (N = 487) or placebo (N = 246) in a 2:1 ratio. The stratification factors taken into account in randomization were treatment with neoadjuvant therapy (yes/no), best response to prior chemotherapy (full/partial), and homologous recombination deficiency (HRD) status (HRD positive / HRD negative or not determined)[4].

Niraparib treatment was administered as approved, except for the individualized starting dose (see text segment on the subpopulation) [8]. Patients received oral niraparib or placebo once daily continuously. A treatment switch from the placebo arm to the niraparib arm was not allowed in the study. Treatment was continued until disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, death, or end of treatment after about 3 years.

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

Relevant subpopulation

The subpopulation of patients who received the ISD regimen of niraparib, as recommended in the SPC, was used for the benefit assessment [8]. The following dosing is recommended as per approval:

- The recommended starting dose of niraparib is 200 mg (two 100 mg capsules), once daily.
- For patients with a body weight ≥ 77 kg and baseline platelet count ≥ 150 000/μL, the recommended starting dose of niraparib is 300 mg (three 100 mg capsules) once daily.

However, at the start of the study (study protocol from 26 October 2015), all patients were treated with a fixed starting dose (FSD) of 300 mg niraparib or placebo (3 capsules each, once daily). Amendment 2 (study protocol from 16 November 2017) replaced the FSD by an ISD in

[4] At the start of the study, only HRD-positive patients were included. With Amendment 1 from 22 November 2016, HRD-negative patients became eligible for inclusion, and HRD status, to be determined before randomization, was introduced as a stratification variable.

accordance with the SPC. This change was made due to new insights from the NOVA study [10] showing that certain AEs which predominantly occur at the start of niraparib treatment can be reduced by using a lower starting dose. In the NOVA study, body weight and the baseline platelet count were found to be predictive markers for severe thrombocytopenia [11]. Therefore, starting with Amendment 2, the ISD was determined using baseline body weight and platelet count.

A total of 475 patients were included in the study before Amendment 2, and 258 patients were included thereafter. Five of the randomized patients did not receive any study drug (2 before and 3 after the amendment).

In its dossier, the company presents the results for the total population as well as the results of a subpopulation which was defined post hoc and treated as approved (hereinafter referred to as ISD subpopulation). The company includes in this group not only patients who were included after Protocol Amendment 2, but also those who were treated as approved before the change, i.e. patients who met the criteria for a starting dose of 300 mg niraparib (body weight ≥ 77 kg and baseline platelet count ≥ 150 000/µL). In total, this ISD population treated as approved therefore includes 352 patients (48% of the total population), of which 228 were in the niraparib arm and 124 in the placebo arm.

After an analysis of the study results for the total population and the subpopulation [9,12], the ISD subpopulation treated as approved is deemed relevant for the benefit assessment. This decision is supported by the available data on AEs because use of the ISD markedly reduced the incidence of AEs in the intervention arm, in line with the results of the NOVA study (see above). Therefore, the results for the total population would overestimate the harm from niraparib.

All things considered, the ISD subpopulation treated in accordance with approval is therefore deemed relevant for the benefit assessment in this situation.

ACT

Implementation of the ACT of (watchful waiting) in the PRIMA study

While the included PRIMA study was not designed for a comparison with watchful waiting, it is, with some restrictions, suitable for such a comparison.

The key limitation regarding the implementation of the ACT of watchful waiting in the PRIMA study is that it specified regular imaging for diagnosing disease progression (every 12 weeks as per study protocol), which might lead to a systematically earlier diagnosis of disease progression. Presumably, the patient might still be asymptomatic at a time where disease progression is already detectable with imaging. However, current evidence shows that an earlier start of follow-up therapy is not associated with longer overall survival, but instead leads to earlier deterioration of the health-related quality of life [13]. Therefore, guidelines recommend

a symptom-based approach for follow-up care [3,14]. Routine instrument-based diagnostics and tumour marker tests are not recommended for symptom-free patients [14].

If an elevated cancer antigen 125 (CA 125) level is nevertheless measured in asymptomatic patients, it should not be determinative for the diagnosis of recurrence or the initiation of follow-up therapy; instead, the further procedure is to be decided in consultation with the patient [14]. In this context, the fact that after treatment discontinuation, the investigator was informed upon request about the type of study medication used (niraparib or placebo) in order to facilitate the optimal planning of follow-up therapies is viewed as an approximation to watchful waiting. After this unblinding, it is assumed that a decision on follow-up therapies was made jointly by the patient and the investigator. Module 4 A of the dossier does not report on the types of follow-up therapies used.

As another approximation to watchful waiting, disease progression (operationalized using the outcome of PFS) had been diagnosed a considerably long time before follow-up therapy was initiated (operationalized using the outcome of time to first follow-up therapy). In the placebo arm, for instance, approximately 3 months passed between reaching of the primary outcome of PFS and the initiation of the first follow-up therapy (data for to the relevant ISD subpopulation [12]). These results demonstrate that the decision about the continued patient treatment with follow-up therapies was not solely based on the diagnosis of disease progression by means of imaging. However, the study documents provide no information as to the extent to which the initiation of follow-up therapy was linked to the presence of symptoms of disease.

Suitability of the population in the PRIMA study for the ACT of watchful waiting

As specified by the G-BA, only patients previously treated with carboplatin in combination with paclitaxel are eligible for watchful waiting as therapy upon the physician's discretion. As far as patients with prior treatment with carboplatin in combination with paclitaxel and bevacizumab are concerned, bevacizumab was specified as the ACT (see Table 4).

The PRIMA study excluded patients who were to receive bevacizumab as maintenance therapy. Only patients who received bevacizumab in platinum-based first-line therapy, but were ineligible for bevacizumab maintenance therapy due to AEs or for other reasons were eligible for study inclusion, provided the last dose of bevacizumab was taken at least 28 days before consent to study participation. In the study, however, this was the case for only 7 patients (6 in the niraparib arm and 1 in the placebo arm), making the total population included in the study suitable for a comparison with watchful waiting.

Summary assessment of the ACT

In summary, the approach used in the PRIMA study is rated as an adequate implementation of the ACT, and the study was used for the assessment of added benefit in comparison with watchful waiting. However, the described aspects concerning the implementation of the ACT limit the certainty of results of the study. On the basis of the available data for all outcomes, at most hints, e.g. of an added benefit, can therefore be derived.

Data cut-off dates

PRIMA is an ongoing study. At the time the benefit was assessed, 2 data cut-offs were available:

- 17 May 2019: a priori planned, primary data cut-off after approximately 270 events,
- 17 November 2019: according to the company, safety update generated upon FDA request

In the dossier, the company uses the data cut-off 17 November 2019 (FDA safety update) and presents results for this time point for all outcomes it took into account. The company argues that this data cut-off offers more mature data than the primary data cut-off and therefore provides better information for the benefit assessment. While the company does not provide a source confirming that an FDA safety update was necessary, the arguments presented by the company are reasonable and are accepted for the purposes of the benefit assessment.

The study will continue until the final analysis of overall survival (planned after approx. 440 deaths, estimated to occur in 2024). No further interim analyses are planned.

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

Table 8: Planned follow-up observation – RCT, direct comparison: Niraparib vs. placebo[a]

Study **Outcome category** **Outcome**	**Planned follow-up observation**
PRIMA	
Mortality	
Overall survival	▪ Until death or final survival analysis
Morbidity	
EQ-5D VAS; EORTC QLQ-C30 (symptom scales) as well as EORTC QLQ-OV28 (symptom scales), FOSI-8	▪ Up to 24 weeks after treatment end (regardless of the start of follow-up therapy)
Health-related quality of life	
EORTC QLQ-C30 (functioning scales) as well as EORTC QLQ-OV28 (functioning scales)	▪ Up to 24 weeks after treatment end (regardless of the start of follow-up therapy)
AEs	
All outcomes of the AE category	▪ Up to 30 days after the last dose of the study drug or until the start of a new clinical study or start of a new chemotherapy regimen[b]

a. Sufficient approximation of the ACT of watchful waiting, with some limitations (see Section 2.3.2 on the Implementation of the ACT)
b. Selected AEs (e.g. SAEs with an at least suspected causal relationship to the intervention or AEs of special interest [e.g. myelodysplastic syndrome]) were surveyed beyond both the end of follow-up and the end of the study and reported to the competent pharmacovigilance department.

ACT: appropriate comparator therapy; AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-OV28: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Ovarian Module; EQ-5D: European Quality of Life – 5 Dimensions; FOSI-8: Functional Assessment of Cancer Therapy – Ovarian Symptom Index-8; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The follow-up durations for AEs are systematically shortened since they were surveyed only for the period of treatment with the study drug (plus 30 days). While the PROs in the categories of morbidity and health-related quality of life were surveyed for up to 24 weeks beyond the end of treatment, even these PROs were not surveyed until the end of the study.

Yet to allow drawing reliable conclusions over the entire study duration or until patient death, these outcomes, like survival, would have to be measured and analysed for the entire duration of the study.

Table 9 shows the patient characteristics of the relevant ISD subpopulation of the included PRIMA study.

Table 9: Characterization of the relevant ISD subpopulation[a] – RCT, direct comparison: Niraparib vs. placebo[b] (multipage table)

Study Characteristic Category	Niraparib N = 228	Placebo N = 124
PRIMA		
Age [years], mean (SD)	60 (10)	60 (10)
Body weight [kg], mean [SD]	75.1 (16.8)[c]	76.4 (18.7)[c]
Region, n (%)		
Europe	124 (54.4)	62 (50.0)
North America	104 (45.6)	62 (50.0)
Family origin, n (%)		
White	205 (89.9)	110 (88.7)
Non-white[d]	23 (10.1)	14 (11.3)
HRD status, n (%)		
HRD positive	120 (52.6)	56 (45.2)
HRD negative	77 (33.8)	45 (36.3)
HRD not determined	31 (13.6)	23 (18.5)
ECOG-PS, n (%)		
0	154 (67.5)	83 (66.9)
1	74 (32.5)	41 (33.1)
BRCA status, n (%)		
BRCAmut	76 (33.3)	31 (25.0)
BRCAwt	143 (62.7)	86 (69.4)
BRCAnd	9 (3.9)	7 (5.6)
Best response during the first platinum-based therapy, n (%)		
Complete response	149 (65.4)	84 (67.7)
Partial response	79 (34.6)	42 (32.3)
Time from first diagnosis to first dose (months), mean (SD)	7.8 (1.7)	7.8 (1.8)
Histological subtype, n (%)		
Serous	218 (95.6)	118 (95.2)
Other[e]	10 (4.4)	6 (4.8)
Residual tumour		
R0 (macroscopically tumour-free)	105 (46.1)	54 (43.5)
R1/R2 (residual tumour < 1 cm / ≥ 1 cm)	106 (46.5)	67 (54.0)
Unknown[f]	17 (7.5)	3 (2.4)
FIGO stage, n (%)		
III[g]	155 (68.0)	80 (64.5)
IV	73 (32.0)	44 (35.5)

Table 9: Characterization of the relevant ISD subpopulation[a] – RCT, direct comparison: Niraparib vs. placebo[b] (multipage table)

Study Characteristic Category	Niraparib N = 228	Placebo N = 124
Primary tumour site, n (%)		
Ovaries	187 (82.0)	99 (79.8)
Primary peritoneum	18 (7.9)	8 (6.5)
Fallopian tube	23 (10.1)	17 (13.7)
Type of surgery, n (%)		
Primary surgery	77 (33.8)	48 (38.7)
Interval surgery	143 (62.7)	74 (59.7)
No surgery	8 (3.5)	2 (1.6)
Treatment discontinuation, n (%)	ND[h]	ND[h]
Study discontinuation, n (%)	ND[i]	ND[i]

a. Patients with dosing in accordance with approval (see relevant subpopulation in Section 2.3.1).
b. Sufficient approximation of the ACT of watchful waiting, albeit with limitations (see Implementation of the ACT in Section 2.3.1).
c. In comparison with the total population, the patients of the relevant subpopulation are approx. 6.6 kg heavier on average across treatment arms (see M4 A, Section 4.3.1.2.1).
d. IQWiG calculations: Black, Asian, Native American/Alaska Native, Hawaiian/Pacific Islander, other, unknown.
e. IQWiG calculation: endometrioid, mucinous, other.
f. IQWiG calculation; no data available on this category in the company's dossier.
g. IQWiG calculation: stage IIIA, IIIB, and IIIC, unspecified stage III.
h. In the total population, 63% of treated patients in the intervention arm and 71% of treated patients in the control arm discontinued treatment. In both study arms, the main reason for discontinuation was progression of disease.
i. In the total population, 19% of treated patients in the intervention arm and 23% of treated patients in the control arm discontinued the study.

ACT: appropriate comparator therapy; BRCA: breast cancer susceptibility gene; BRCAmut: BRCA mutated; BRCAwt: BRCA wild type; BRCAnd: BRCA gene not determined; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; HRD: homologous recombination deficiency; ISD: individualized starting dose; N: number of included patients; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SD: standard deviation

In the relevant subpopulation, the two treatment arms are comparable in terms of demographic and disease-specific patient characteristics. Patients are 60 years on average, largely white, and about one-half each are from Europe and from North America. Two-thirds of patients had an ECOG-PS of 0 and hence were able to pursue their routine daily activities without limitations. In both study arms, half of the included patients were HRD positive, about one-third was HRD negative, and in about 15% of patients, the HRD status had not been determined. About two-thirds of patients exhibited a complete response during the first platinum-based therapy; the remainder had a partial response. In the majority (approx. 80%) of patients, ovaries were the primary tumour site. Almost all patients had undergone surgery before the study, with interval surgery (approx. 62%) being more common than primary surgery (approx. 36%).

Mean/median treatment duration

Information on patients' mean/median treatment duration and mean/median follow-up duration for individual outcomes is not available for the relevant ISD subpopulation (see Table 10). In Module 4 A, the company merely mentions that due to "different treatment and follow-up times for niraparib and placebo", it submits event-time analyses for AE outcomes. In this regard, the European Public Assessment Report provides data only on the median treatment duration for the total population at the earlier data cut-off (11.1 months or 8.3 months, data cut-off: 17 May 2019 [9]).

Table 10: Information on the course of the study for the relevant ISD subpopulation[a] – RCT, direct comparison: Niraparib vs. placebo[b]

Study **Duration of the study phase** **Outcome category**	**Niraparib** **N = 228**	**Placebo** **N = 124**
PRIMA		
Treatment duration [months]		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Follow-up duration [months]		
Outcomes of the categories of mortality, morbidity, health-related quality of life, AEs		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

a. Patients with dosing in accordance with approval (see relevant subpopulation in Section 2.3.1).
b. Sufficient approximation of the ACT of watchful waiting, albeit with limitations (see Implementation of the ACT in Section 2.3.1).

ACT: appropriate comparator therapy; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - All-cause mortality
- Morbidity
  - Symptoms surveyed using the symptom scales of the EORTC QLQ-C30 and the EORTC QLQ-OV28
  - Health status as measured by the European Quality of Life – 5 Dimensions visual analogue scale (EQ-5D VAS)

- Functional Assessment of Cancer Therapy-Ovarian Symptom Index-8 (FOSI-8)

- Health-related quality of life
  - as surveyed with global health status and the EORTC QLQ-C30 and EORTC QLQ-OV28 functioning scales

- AEs
  - SAEs
  - Severe AEs (Common-Terminology-Criteria-for-Adverse-Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Further specific AEs, if any

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

Since the results presented by the company are not used in the benefit assessment (see Section 2.4.2), an assessment of the risk of bias at study and outcome levels for the PRIMA study was foregone.

2.4.2 Usability of the study results for the benefit assessment

The results of the PRIMA study as presented by the company in the dossier are incomplete and insufficiently prepared. Therefore, it is impossible to adequately assess the study data, and consequently, none of the results of the PRIMA study are usable for the benefit assessment. The rationale is provided below.

Incomplete data on PROs

In the company's dossier, the results on PROs are reported incompletely. This primarily applies to the EORTC QLQ-C30 questionnaire.

The EORTC QLQ-C30 measures both the health-related quality of life and the general symptoms of cancer patients [15,16]. The instrument consists of a scale on global health status, 5 functioning scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning) as well as 8 symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea). Furthermore, the questionnaire contains 1 item on financial difficulties. With the exception of the financial difficulties item, the questionnaire is relevant for the benefit assessment.

The PRIMA study used the questionnaire, which according to its statistical analysis plan was to be analysed in full, i.e. including all scales. However, in Module 4 A of the dossier, the company presents only results on the global health status (referred to by the company as "general health status / quality of life"). Results are missing for the other scales relevant for the benefit assessment (5 functioning and 8 symptom scales). The dossier provides no rationale for

this selective reporting. In addition, it is impossible to use the additional analyses presented by the company (Annex 4-G of the dossier) to assess the results on the missing scales. This is due to the fact that the results are not labelled in the relevant chapters, making it impossible to discern which table pertains to what outcome (concerns Sections 3 to 9 of Appendix 4-G [pp. 88 to 1134], see, e.g. Figure 1 in Appendix A of the full dossier assessment).

The incomplete presentation of results from the core module EORTC QLQ-C30 also precludes the use of the results from the ovarian cancer-specific supplementary module EORTC QLQ-OV28. The latter is a supplementary module which must be used and interpreted in conjunction with the core module EORTC QLQ-C30 [15]. While some EORTC modules can be used without the core module (see [17]), the ovarian carcinoma module is not among them. Although the company presents results on all OV28 scales surveyed in the PRIMA study (including for the relevant ISD subpopulation), as per scoring manual, these results are not used in the present benefit assessment in ignorance of the results of the core module EORTC QLQ-C30.

Hence, comprehensive information on PROs is missing for the dossier assessment, and no analyses at all are available on health-related quality of life, despite the fact that these data were surveyed.

Adequate analyses needed for PROs

For the assessment of PROs which were operationalized using (complex) scales, such as the PROs in the PRIMA study, it is particularly important to not only evaluate the statistical significance of effects, but also to assess the relevance of the observed effects of the interventions under investigation [1]. This relevance assessment can be done on the basis of responder analyses (e.g. using the hazard ratio [HR]) or analyses of continuous data (by means of mean value differences), with preference given to responder analyses:

- As discussed in IQWiG General Methods [1,18], a response criterion should be predefined to cover at least 15% of the range of an instrument's scale (for post hoc analyses, exactly 15% of the range of the scale) in order to reflect with sufficient certainty a change that is perceivable for patients [19].
- Further, between-group comparisons can also be made on the basis of continuous data. An analysis of the mean change from baseline over the entire course of the study is appropriate.

In addition to suffering from incompleteness as discussed above, the company's analyses provided in the dossier invite criticism in the following respects: The company presents responder analyses (using HR) only for the treatment duration. It is puzzling why available surveys done after the end of treatment are not included in the analysis. For the analysis of continuous data, the company assigns values which were surveyed at different times from randomization to a constructed time point (end of treatment [EoT], follow-up weeks 4, 8, 12, 24 after EoT). This approach can result in serious bias, particularly in progressive courses of

disease with different individual follow-up periods – as found in the PRIMA study. Therefore, the surveyed values should be presented with the time from randomization.

Incomplete data on common AEs

The information on AEs provided by the company is incomplete as well. According to the dossier template, alongside the total rates of AEs, results on all AEs (operationalized as SOC and PT as per MedDRA) must be presented, provided they exceed a minimum prevalence [20]. A complete presentation of these common AEs (separately by AEs without further differentiation, SAEs, AEs differentiated by severity) is essential for assessing the AE profile as well as for selecting specific AEs [1].

However, in Module 4 A of its dossier, the company presents only a subset of these AEs. The company does refer to the minimum prevalences specified in the dossier template. In Module 4 A, however, the company presents exclusively those SOCs and PTs for which a significant treatment difference was found (hazard ratio [HR] or relative risk [RR]) as well as the AEs which occurred in at least 10 patients on niraparib treatment, but in none on placebo, and for which it was not possible to calculate HR or RR. For further AEs required as per dossier template, the company refers to Appendix 4-G, which, however, provides only Kaplan-Meier curves without data on absolute frequencies or treatment effects. Hence, the information provided in the company's dossier on common AEs is incomplete. For the benefit assessment, this makes it impossible to present common AEs (independently of the treatment effect) or to select specific AEs based on the AEs which occurred in the PRIMA study.

Further points of criticism

As already described in Section 2.3.2, the company's dossier also lacks information on the duration of treatment and follow-up as well as on the follow-up therapies used in the study. Alongside the incompletely presented results, this issue further complicates the interpretation of study data.

Final evaluation and consequences

Taken altogether, the above-described deficiencies of the dossier are deemed grave. Due in particular to the missing or unusable results on the EORTC QLQ questionnaire and the incomplete presentation of AE results, the presented data are incomplete.

This is true despite the fact that the company itself describes the maintenance of health status and quality of life as important treatment goals in the present treatment situation. In addition, for the PRIMA study's available data cut-off for overall survival, there is no statistically significant difference between treatment arms, although the total rates of severe AEs (CTCAE ≥ 3) and serious AEs, for instance, each show an effect to the disadvantage of niraparib [6,12]. Further, it can be inferred from the assessment report of the European Medicines Agency (EMA) that the missing PRO results might reveal a disadvantage of the intervention [9]: With regard to PRO results in the total population, the EMA notes that particularly gastrointestinal symptoms (e.g. constipation, appetite loss) were more common in

the niraparib arm than in the placebo arm of the PRIMA study. In consideration of the available results on AEs and the typical AE profile for niraparib (e.g. 56.1% of patients in the niraparib arm suffered from nausea, versus only 23.4% of patients in the placebo arm [data relative to the ISD subpopulation]), this result is to be expected as well.

Due to the incomplete data, it is therefore impossible to adequately weigh benefit and harm and hence to assess the added benefit of niraparib in comparison with the ACT. A presentation of usable study results presented in the dossier is foregone as well.

No usable data are available for the assessment of added benefit of niraparib in comparison with the ACT in adult patients with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal carcinoma who showed (complete or partial) response after platinum-based first-line chemotherapy. Consequently, there is no hint of an added benefit of niraparib in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 11 presents a summary of the results of the benefit assessment of niraparib in comparison with the ACT.

Table 11: Niraparib – probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal carcinoma who exhibited a (complete or partial) response following platinum-based first-line chemotherapy.	Therapy upon the physician's discretion, in consideration of ▪ watchful waiting (after prior therapy with carboplatin in combination with paclitaxel) ▪ bevacizumab (only after prior therapy with carboplatin in combination with paclitaxel and bevacizumab)	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived a hint of minor benefit based on the results of the PRIMA study. The G-BA decides on the added benefit.

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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