IQWiG Reports – Commission No. A20-111

Olaparib (ovarian cancer, first-line maintenance treatment in combination with bevacizumab) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Olaparib (Ovarialkarzinom; Erstlinie Erhaltung in Kombination mit Bevacizumab) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 10 March 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BRCA	breast cancer associated gene
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life Questionnaire-5 Dimensions
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GCP	good clinical practice
GIS	genomic instability score
HRD	homologous recombination deficiency
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDS	interval debulking surgery/interval surgery
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NED	no evidence of disease/no detectable tumour
PARP	polyadenosine diphosphate ribose polymerase
PDS	primary debulking surgery/primary surgery
PFS	progression-free survival
PR	partial response
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-OV28	Quality of Life Questionnaire-Ovarian Cancer 28
QS-OVAR	quality assurance survey on ovarian cancer
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
tBRCA	tumour BRCA
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 combination olaparib + bevacizumab. 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 December 2021.

Research question

The aim of the present report is the assessment of the added benefit of olaparib + bevacizumab in comparison with bevacizumab as appropriate comparator therapy (ACT) as maintenance treatment of adult patients with advanced (Fédération Internationale de Gynécologie et d'Obstétrique [FIGO] stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status. A positive HRD status is defined by either a mutation in breast cancer associated genes 1 or 2 (BRCA1/2) and/or genomic instability.

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

Table 2: Research questions of the benefit assessment of olaparib + bevacizumab

Therapeutic indication	**ACT[a]**
Maintenance therapy of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian cancer[b] who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with HRD positive status[c]	Continuation of the treatment with bevacizumab started with first-line platinum-based chemotherapy
a. Presentation of the respective ACT specified by the G-BA. b. This term also includes fallopian tube and primary peritoneal cancer. c. A positive HRD status is defined by either BRCA1/2-mutation and/or genomic instability. ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; G-BA: Federal Joint Committee; HRD homologous recombination deficiency	

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

The company named "continuation of the treatment with bevacizumab started with first-line platinum-based chemotherapy" as ACT and thus followed the specification of the G-BA.

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

Results

Study pool

The PAOLA-1 study was included for the assessment of the added benefit.

Study characteristics

PAOLA-1 is a double-blind, randomized parallel-group study on the comparison of olaparib + bevacizumab versus placebo + bevacizumab for the maintenance treatment of adult patients with advanced high-grade serous or endometrioid ovarian, fallopian tube and/or primary peritoneal cancer who are in response (complete or partial) following first-line platinum-based chemotherapy in combination with bevacizumab. The study included patients who had received at least 6 cycles of platinum-based/taxane-based chemotherapy during first-line chemotherapy, of whom at least the last 3 cycles were administered in combination with bevacizumab. Patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 and normal bone marrow and organ function.

A total of 806 patients were randomly stratified in a 2:1 ratio to either up to 2 years of maintenance therapy with olaparib in combination with continuation of the bevacizumab therapy or to continuation of treatment with bevacizumab alone. Stratification characteristics were the mutation status of the tumour's BRCA genes (tBRCA [mutated vs. non-mutated]) and the result of the first-line treatment. Regarding the result of the first-line therapy, distinction was made between 4 expressions:

- NED (PDS): Patients without detectable disease/tumour (no evidence of disease [NED]) after primary surgery (primary debulking surgery [PDS])
- NED/CR (IDS): Patients without detectable tumour/with complete response (CR) after interval surgery (interval debulking surgery [IDS])
- NED/CR (chemotherapy): patients without detectable tumour/with complete response after chemotherapy
- PR: Patients with partial response (PR)

During first-line therapy and until randomization, patients were not to have any sign of progression of the underlying disease. Treatment with olaparib and bevacizumab was performed according to the approval.

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

Relevant subpopulation

According to the approval, only the subpopulation of patients whose cancer is associated with an HRD positive status is considered for the present benefit assessment. The status "HRD positive" is defined by either BRCA1/2-mutation and/or genomic instability. This subpopulation is relevant for the present benefit assessment and comprises 255 patients in the olaparib + bevacizumab arm and 132 patients in the comparator arm with placebo + bevacizumab.

Risk of bias

The risk of bias across outcomes was rated as low for the results of the study. The risk of bias is rated as low for the results on "overall survival", "symptoms (symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30] and the EORTC Quality of Life Questionnaire-Ovarian Cancer 28 [QLQ-OV28])", "health status (European Quality of Life Questionnaire-5 Dimensions - visual analogue scale [EQ-5D VAS])", "health-related quality of life (functional scales of the EORTC QLQ-C30 and scales of the EORTC QLQ-OV28)", on the AEs selected as "specific AEs" with observation until death of the patient or end of the study as well as on the outcome "discontinuation due to AEs". Thereby, the certainty of results for the outcome "discontinuation due to AEs" was restricted despite a low risk of bias. Due to incomplete observations for potentially informative reasons, the risk of bias for the results on the outcomes "serious adverse events (SAEs)" and "severe AEs" was rated as high.

Results

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival".

However, there was an effect modification by the characteristic "result of the first-line therapy". For patients in the NED/CR (IDS) and PR subgroups, there was no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven. For patients without detectable tumour after primary surgery (NED [PDS]) and patients without detectable tumour/with complete response after chemotherapy (NED/CR [chemotherapy]), this resulted in an indication of an added benefit of olaparib + bevacizumab in comparison with bevacizumab.

Morbidity

Symptoms (EORTC QLQ-C30 symptom scales)

A statistically significant difference to the disadvantage of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcome "nausea and vomiting". This resulted in an indication of lesser benefit of olaparib + bevacizumab in comparison with bevacizumab.

A statistically significant difference in favour of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcome "insomnia". A statistically significant difference to the disadvantage of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcome "appetite loss". However, the extent of the effects for these outcomes of the category "non-serious/non-severe symptoms/late complications" was no more than marginal. In each case, this resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven for these outcomes.

No statistically significant difference between the treatment arms was shown for each of the outcomes "fatigue", "pain", "dyspnoea", "constipation" and "diarrhoea". This resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab for each of these outcomes; an added benefit is therefore not proven for these outcomes.

Symptoms (EORTC QLQ-OV28 symptom scales)

A statistically significant difference in favour of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcomes "hormonal symptoms" and "side effects of chemotherapy". However, the extent of the effects for these outcomes of the category "non-serious/non-severe symptoms/late complications" was no more than marginal. In each case, this resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven for these outcomes.

For the outcomes "abdominal/gastrointestinal symptoms", "peripheral neuropathy" as well as for the scale of individual questions, there is no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab for each of these outcomes; an added benefit is therefore not proven for these outcomes.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment arms for the outcome "health status" measured using the EQ-5D VAS. This resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven.

Health-related quality of life

Functional scales of the EORTC QLQ-C30

There was no statistically significant difference between the treatment groups for the outcome "global health status". However, there was an effect modification by the characteristic "age". For younger patients (< 65 years), there was no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven. For older patients (≥ 65 years), this resulted in an indication of an added benefit of olaparib + bevacizumab in comparison with bevacizumab.

No statistically significant difference between the treatment groups was shown for each of the outcomes "physical functioning", "role functioning", "cognitive functioning", "emotional functioning", and "social functioning". In each case, this resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven.

EORTC QLQ-OV28

No statistically significant difference between the treatment groups was shown for the outcome "attitude regarding disease/treatment". However, there was an effect modification by the characteristic "result of the first-line therapy". For patients in the NED (PDS), NED/ CR (chemotherapy) and PR subgroups, there was no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven. For patients without detectable tumour/with complete response after interval surgery (NED/CR [IDS]), there is an indication of lesser benefit of olaparib + bevacizumab in comparison with bevacizumab.

No statistically significant difference between the treatment arms was shown for the outcome "body image". This resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab for this outcome; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs" and "severe AEs (CTCAE grade ≥ 3)". In each case, this resulted in no hint of greater or lesser harm from olaparib + bevacizumab in comparison with bevacizumab for these outcomes; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcome "discontinuation due to AEs". This resulted in a hint of greater harm from olaparib + bevacizumab in comparison with bevacizumab.

Myelodysplastic syndrome and acute myeloid leukaemia and pneumonitis (Preferred Terms [PTs], AEs)

No statistically significant difference between the treatment groups was shown for each of the outcomes "myelodysplastic syndrome" and "acute myeloid leukaemia" as well as "pneumonitis". In each case, this resulted in no hint of greater or lesser harm from olaparib + bevacizumab in comparison with bevacizumab for these outcomes; greater or lesser harm is therefore not proven.

Nausea (PTs, AEs), anaemia (PTs, severe AEs [CTCAE grade ≥ 3]) as well as fatigue and asthenia (PTs, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of olaparib + bevacizumab in comparison with placebo + bevacizumab was shown for each of the outcomes "nausea (PT, AEs)", "anaemia (PT, severe AEs [CTCAE grade ≥ 3])" as well as "fatigue" and "asthenia (PTs, severe AEs [CTCAE grade ≥ 3])". This resulted in an indication of greater harm from olaparib + bevacizumab in comparison with bevacizumab in each case.

Hypertension (PT, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference in favour of olaparib + bevacizumab in comparison with placebo + bevacizumab was shown for the outcome "hypertension (PT, severe AEs [CTCAE grade ≥ 3])". This resulted in an indication of lesser harm from olaparib + bevacizumab in comparison with bevacizumab.

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

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

The overall consideration showed both positive and negative effects of olaparib + bevacizumab in comparison with bevacizumab. An additional effect modification by the characteristic "result of the first-line treatment" was shown for the outcome "overall survival". For this reason, the positive and negative effects are assessed below separately for patients without detectable tumour after primary surgery (NED [PDS]) and patients without detectable tumour/with complete response after chemotherapy (NED/CR [chemotherapy]) as well as for patients without detectable tumour/with complete response after interval surgery (IDS) and patients with partial response (PR).

For patients without detectable tumour after primary surgery (NED [PDS]) and patients without detectable tumour/with complete response after chemotherapy (NED/CR [chemotherapy]), this resulted in an indication of major added benefit of olaparib + bevacizumab in comparison with bevacizumab for the outcome "overall survival". Moreover, there is a further indication of a positive effect with the extent "considerable" in the category of serious/severe side effects. In contrast, there are several indications of negative effects with considerable or major extents in the outcome categories "non-serious/non-severe symptoms" and "serious/severe side effects"

[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].

as well as "non-serious/non-severe side effects". However, the negative effects did not completely call into question the positive effects. Overall, this resulted in an indication of considerable added benefit of olaparib + bevacizumab in comparison with the ACT bevacizumab for patients without detectable tumour after primary surgery (NED [PDS]) and patients without detectable tumour/with complete response after chemotherapy (NED/CR [chemotherapy]).

For patients without detectable tumour/with complete response after IDS and patients with PR, there was an indication of lesser harm with the extent "considerable" on the side of the positive effects in the category "serious/severe side effects". In contrast, there are several indications of negative effects with considerable or major extents in the outcome categories "non-serious/non-severe symptoms" and "serious/severe side effects" as well as "non-serious/non-severe side effects". For patients without detectable tumour/with complete response after IDS, there is also a negative effect with the extent "considerable" in the outcome category "health-related quality of life". Overall, this resulted in an indication of lesser benefit of olaparib + bevacizumab in comparison with the ACT bevacizumab for patients without detectable tumour/with complete response after IDS and patients with PR.

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

Table 3: Olaparib + bevacizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit[b]**
Maintenance therapy of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian cancer[c] who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with HRD positive status[d]	Continuation of the treatment with bevacizumab started with first-line platinum-based chemotherapy	▪ Patients without detectable tumour after primary surgery and patients without detectable tumour/with complete response following chemotherapy: indication of considerable added benefit
		▪ Patients without detectable tumour after interval surgery and patients with partial response: indication of lesser benefit

a. Presentation of the respective ACT specified by the G-BA.
b. The PAOLA-1 study included only patients with ECOG PS of 0 or 1 as well as only few patients with non-serous tumour histology (5.6% in the relevant subpopulation). It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or patients with non-serous tumour histology.
c. This term also includes fallopian tube and primary peritoneal cancer.
d. A positive HRD status is defined by either BRCA 1/2-mutation and/or genomic instability.

ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; G-BA: Federal Joint Committee.; HRD: homologous recombination deficiency

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 olaparib + bevacizumab in comparison with bevacizumab as ACT as maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with HRD positive status. A positive HRD status is defined by either a mutation in BRCA1/2 and/or genomic instability.

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

Table 4: Research questions of the benefit assessment of olaparib + bevacizumab

Therapeutic indication	**ACT[a]**
Maintenance therapy of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian cancer[b] who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with HRD positive status[c].	Continuation of the treatment with bevacizumab started with first-line platinum-based chemotherapy
a. Presentation of the respective ACT specified by the G-BA. b. This term also includes fallopian tube and primary peritoneal cancer. c. A positive HRD status is defined by either BRCA1/2-mutation and/or genomic instability. ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; G-BA: Federal Joint Committee; HRD homologous recombination deficiency	

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

The company named "continuation of the treatment with bevacizumab started with first-line platinum-based chemotherapy" as ACT and thus followed the specification of the G-BA.

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on olaparib + bevacizumab (status: 2 October 2020)

- bibliographical literature search on olaparib + bevacizumab (last search on 25 September 2020)
- search in trial registries/trial results databases for studies on olaparib + bevacizumab (last search on 2 October 2020)
- search on the G-BA website for olaparib + bevacizumab (last search on 1 October 2020)

To check the completeness of the study pool:

- search in trial registries for studies on olaparib + bevacizumab(last search on 9 December 2020)

The check did not identify any additional relevant studies.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab

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 yes/no [citation])
Study GINECO-OV125b (PAOLA-1[c])	Yes	No[d]	Yes	No[e]	Yes [3-6]	Yes [7]

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. In the following tables, the study is referred to with this abbreviated form.
d. The sponsor of the study is Arcagy Research. The company is financially involved.
e. 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; RCT: randomized controlled trial; vs.: versus

The study pool concurs with that of the company.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PAOLA-1	RCT, double-blind, parallel	Adult patients[b] with newly diagnosed, advanced (FIGO stages IIIB-IV[c]) high-grade serous or endometrioid[d] ovarian, fallopian tube and/or primary peritoneal cancer who are in response (complete or partial) following first-line platinum-based/taxane-based chemotherapy in combination with bevacizumab[e]	Olaparib + bevacizumab (N = 537) placebo + bevacizumab (N = 269) relevant subpopulation thereof[f]: olaparib + bevacizumab (n = 255) placebo + bevacizumab (N = 132)	Screening: ≤ 28 days before randomization[g] treatment: ▪ with olaparib or placebo for up to 2 years or until disease progression according to RECIST[h] ▪ with bevacizumab for up to 15 months[i] observation[j]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	137 centres in Austria, Belgium, Denmark, Finland, France, Germany, Italy, Japan, Monaco, Spain, Sweden 07/2015[k]–ongoing data cut-offs: 22 March 2019[l] 30 September 2019[m] 22 March 2020[n,o]	Primary: PFS secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab (multipage table)

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

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. ECOG PS ≤ 1 and normal bone marrow and organ function.
c. According to the FIGO classification of 1988 [7], corresponding to stages III-IV of the current FIGO classification [8].
d. Or other epithelial, non-mucinous ovarian cancer in the presence of a germline BRCA1 or BRCA2 mutation.
e. Prior to randomization, patients had to have received ≥ 3 cycles of bevacizumab in combination with the last 3 cycles of platinum-based chemotherapy. Receipt of only 2 cycles of bevacizumab in combination with the last 3 cycles of platinum-based chemotherapy was exclusively allowed in the case of interval surgery.
f. Patients whose tumour is associated with a positive HRD status. The status "HRD positive" is defined by either BRCA1/2-mutation and/or genomic instability. Genomic instability is defined as genomic instability score ≥ 42 according to Myriad [9].
g. Patients were to be randomized within 3-9 weeks after the last chemotherapy (last dose was the day of the last infusion) and all major toxicities from the prior chemotherapy had to have subsided to CTCAE grade 1 or better (except alopecia and peripheral neuropathy).
h. Patients who, in the opinion of the investigator, drew further benefit from continued therapy could receive further treatment for 2 years or after progression.
i. Including the doses administered during pretreatment.
j. Outcome-specific data are described in Table 8.
k. Inclusion of the first patient 07/2015. Inclusion of the last patient 09/2017.
l. Final PFS analysis (planned after 458 events for PFS).
m. Regulatory data cut-off.
n. Planned final PFS2 analysis (planned after 411 events for PFS2 or at the latest 1 year after final PFS analysis), planned interim analysis for overall survival. The results of this data cut off were used for the present benefit assessment.
o. The final analysis of overall survival was planned from a data maturity of approx. 60% (the exact number of events should be determined after the interim analysis) or at the latest 3 years after final PFS analysis.

AE: adverse event; BRCA: breast cancer associated gene; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HRD: homologous recombination deficiency; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours

Table 7: Characteristics of the interventions – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab

Study	Intervention	Comparison
PAOLA-1	▪ Olaparib 600 mg/day (2 film-coated tablets of 150 mg twice daily), orally, at the same time of the day[a], at 12-hour intervals ▪ bevacizumab 15 mg/kg IV every 3 weeks for a total of 15 months/22 cycles[b]	▪ Placebo (twice daily), orally, at the same time of the day[a] at 12-hour intervals ▪ bevacizumab 15 mg/kg IV every 3 weeks for a total of 15 months/22 cycles[b]
	Dose adjustments, treatment interruptions and treatment discontinuation due to toxicity were possible[c] **pretreatment** **required:** ▪ 6-9 cycles of platinum-based/taxane-based chemotherapie[d] ▪ ≥ 3 cycles of bevacizumab together with the last 3 cycles of platinum-based chemotherapy[e] **not allowed** ▪ any prior treatment with a PARP inhibitor including olaparib ▪ Treatment with a test medication during first-line chemotherapy **concomitant treatment** **allowed:** ▪ any medication, with the exception of the cited non-permitted concomitant treatments, which, in the investigator's opinion, was necessary for the patient's well-being and did not impair the treatment with the study medication **not allowed:** ▪ other anticancer therapies, i.e. chemotherapy, immunotherapy, hormonal therapy, radiotherapy, therapy with antineoplastic drugs, biological therapies or novel drugs ▪ live vaccines ▪ CYP3A4 inhibitors	

a. If the intake time was missed, the respective medication could only be taken within 2 hours.
b. Including the doses administered during pretreatment.
c. Repeated interruptions of the drug intake for the same reason were allowed for ≤ 4 weeks. Toxicity-related dose adjustments were made without relevant deviations from the requirements of the SPC.
d. If platinum-based/taxane-based treatment was discontinued due to toxicity to platinum therapy, patients must have received at least 4 cycles of platinum-based treatment.
e. In patients with IDS, at least 2 cycles of bevacizumab together with the last 3 cycles of platinum-based chemotherapy.

CYP: cytochrome P450; IDS: interval debulking surgery; IV: intravenous; PARP: poly(adenosine diphosphate-ribose) polymerase; RCT: randomized controlled trial; SPC: Summary of Product Characteristics

PAOLA-1 is a double-blind, randomized parallel-group study on the comparison of olaparib + bevacizumab versus placebo + bevacizumab for the maintenance treatment of adult patients with advanced high-grade serous or endometrioid ovarian, fallopian tube and/or primary peritoneal cancer who are in response (complete or partial) following first-line platinum-based chemotherapy in combination with bevacizumab. The study included patients who had received at least 6 cycles of platinum-based/taxane-based chemotherapy during first-line chemotherapy, of whom at least the last 3 cycles were administered in combination with bevacizumab. Patients had to have an ECOG PS of 0 or 1 and normal bone marrow and organ function. Moreover, side effects from the prior chemotherapy had to have subsided to CTCAE grade ≤ 1.

A total of 806 patients were randomly stratified in a 2:1 ratio to either up to 2 years of maintenance therapy with olaparib in combination with continuation of the bevacizumab therapy or to continuation of treatment with bevacizumab alone. Stratification characteristics were the mutation status of the tumour's BRCA genes (tBRCA [mutated vs. non-mutated]) and the result of the first-line treatment. Regarding the result of the first-line therapy, distinction was made between 4 expressions:

- NED (PDS): Patients without detectable disease/tumour (NED) after PDS)
- NED/CR (IDS): Patients without detectable tumour/with complete response (CR) after IDS
- NED/CR (chemotherapy): patients without detectable tumour/with complete response after chemotherapy
- PR: Patients with partial response

During first-line therapy and until randomization, patients were not to have any sign of progression of the underlying disease. Randomization took place within 3 to 9 weeks after completion of chemotherapy, which, according to the approval, consisted of treatment with carboplatin and paclitaxel in almost all patients. Treatment with olaparib and bevacizumab was performed according to the approval [10,11]. Patients in both study arms were to continue their therapy with 15 mg/kg bevacizumab for a total of 22 cycles (including the cycles in the first-line treatment). Moreover, patients in the intervention arm received 300 mg olaparib twice daily, while the patients in the control arm received a corresponding placebo.

Patients were to receive the study medication for 2 years or until disease progression according to modified Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 or until another discontinuation criterion was met (patient's decision, AEs, serious protocol violations). However, treatment could also be continued beyond the planned 2 years or disease progression if, in the physician's opinion, the patient continued to benefit from the treatment. Subsequent therapies after termination of the study medication were not specified in the study protocol, so that any medical intervention was freely determined at the physician's discretion together with the patient. According to the study protocol, unblinding of patients and investigators was not planned for this purpose.

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

Relevant subpopulation

According to the approval, only the subpopulation of patients whose cancer is associated with an HRD positive status is considered for the present benefit assessment. The status "HRD positive" is defined by either BRCA1/2-mutation and/or genomic instability. In the PAOLA-1 study, the genomic instability score (GIS) was determined in tissue samples from all patients using the Myriad MyChoice HRD plus assay [9]. The company presented analyses of a

subpopulation with a positive HRD status, defined as genomic instability with a GIS ≥ 42 and/or a pathogenic BRCA mutation in the tumour. This subpopulation is relevant for the present benefit assessment and comprises 255 patients in the olaparib + bevacizumab arm and 132 patients in the comparator arm with placebo + bevacizumab.

Data cut-offs

Data are available on 3 data cut-offs:

- First data cut-off of 22 March 2019: preplanned final PFS analysis after 458 events for PFS
- Second data cut-off of 30 September 2019: regulatory data cut-off
- Third data cut-off of 22 March 2020: preplanned interim analysis for overall survival

The final analysis for "overall survival" is still pending. According to the study protocol, it was to be conducted after the death of 60% of the patients or at the latest 3 years after the final PFS analysis, i.e. in March 2022.

In its dossier, the company presented results on all patient-relevant outcomes for the third data cut-off. These data serve as the basis for the benefit assessment.

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab

Study **outcome category** **outcome**	**Planned follow-up observation**
PAOLA-1	
Mortality	
Overall survival	Until death or final analysis
Morbidity	
EORTC QLQ-C30	Up to 2 years after the start of the study
EORTC QLQ-OV28	Up to 2 years after the start of the study
EQ-5D VAS	Up to 2 years after the start of the study
Health-related quality of life	
EORTC QLQ-C30	Up to 2 years after the start of the study
Side effects	
AEs/SAEs/severe AEs	Until 30 days after the last dose of the study medication
Selected specific AEs[a]	Until death or final analysis

a. Specific AEs prespecified in the study as AESIs or expected AEs should be monitored until death or end of the study. The analyses on these AEs are available as AESI analyses in Module 4 A of the company. Extended follow-up concerned the following AEs: anaemia, neutropenia, thrombocytopenia, nausea, vomiting, fatigue and asthenia, hypertension, proteinuria, GI perforations, abscess and fistulas, wound healing complications, haemorrhages, arterial thromboembolism, venous thromboembolism, posterior reversible encephalopathy syndrome, congestive heart failure, non-GI fistulas or abscesses, myelodysplastic syndrome, acute myeloid leukaemia, secondary neoplasms, pneumonitis.

AE: adverse event; AESI: adverse event of special interest; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; GI: gastrointestinal; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OV28: Quality of Life Questionnaire-Ovarian Cancer 28; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for the outcomes “AEs”, “severe AEs” and “SAEs” were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days). The outcomes on morbidity and health-related quality of life were recorded for up to 2 years after the start of the study, however, the observation times were shortened here as well. To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Moreover, in PAOLA-1 specific AEs prespecified as AEs of special interest or as expected AEs, were to be monitored until death or end of the study.

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

Table 9: Characteristics of the study population – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab (multipage table)

Study characteristic category	**Olaparib + bevacizumab N[a] = 255**	**Placebo + bevacizumab N[a] = 132**
PAOLA-1		
Age [years], mean (SD)	59 (9)	57 (10)
Region, n (%)		
Europe	245 (96.1)	126 (95.5)
Japan	10 (3.9)	6 (4.5)
ECOG PS, n (%)		
0	190 (74.5)	100 (75.8)
1	61 (23.9)	31 (23.5)
Missing	4 (1.6)	1 (0.8)
Primary tumour location, n (%)		
Ovary	217 (85.1)	118 (89.4)
Fallopian tubes	24 (9.4)	5 (3.8)
Peritoneal	14 (5.5)	9 (6.8)
Histology, n (%)		
Serous	242 (94.9)	124 (93.9)
Endometrioid	9 (3.5)	4 (3.0)
Clear-cell	1 (0.4)	0 (0)
Undifferentiated	1 (0.4)	3 (2.3)
Other	2 (0.8)	1 (0.8)
FIGO stage[b], n (%)		
IIIB	25 (9.8)	9 (6.8)
IIIC	157 (61.6)	81 (61.4)
IV	73 (28.6)	42 (31.8)
tBRCA mutation status before randomization, n (%)		
tBRCA-mutated	150 (58.8)	65 (49.2)
Not tBRCA-mutated	105 (41.2)	67 (50.8)
Surgical pretreatment		
Patients without surgery, n (%)	10 (3.9)	8 (6.1)
Prior surgery, n (%)	245 (96.1)	124 (93.9)
Of which with macroscopic tumour remnant	79 (32.2[c])	43 (34.7[c])
Of which without macroscopic tumour remnant	166 (67.8[c])	81 (65.3[c])
Prior primary surgery (PDS), n (%)	145 (56.9)	79 (59.8)
Of which with macroscopic tumour remnant	55 (37.9[c])	30 (38.0[c])
Of which without macroscopic tumour remnant	90 (62.1[c])	49 (62.0[c])

Table 9: Characteristics of the study population – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab (multipage table)

Study characteristic category	**Olaparib + bevacizumab N[a] = 255**	**Placebo + bevacizumab N[a] = 132**
Prior interval surgery (IDS), n (%)	100 (39.2)	45 (34.1)
Of which with macroscopic tumour remnant	24 (24.0[c])	13 (28.9[c])
Of which without macroscopic tumour remnant	76 (76.0[c])	32 (71.1[c])
Cycles of platinum-containing first-line chemotherapy, n (%)		
≤ 6 cycles	177 (69.4)[c]	92 (69.7)[c]
7-8 cycles	60 (23.5)[c]	30 (22.7)[c]
≥ 9 cycles	18 (7.1)[c]	10 (7.6)[c]
Cycles with bevacizumab in first-line chemotherapy, n (%)		
≤ 3 cycles	44 (17.3)[c]	21 (15.9)[c]
4-5 cycles	103 (40.4)[c]	43 (32.6)[c]
≥ 6 cycles[h]	108 (42.4)	68 (51.5)
Result of the first-line therapy before randomization, n (%)		
NED (PDS)[d]	92 (36.1)	48 (36.4)
NED/CR (IDS)[e]	74 (29.0)	38 (28.8)
NED/CR (chemotherapy)[f]	40 (15.7)	20 (15.2)
PR[g]	49 (19.2)	26 (19.7)
Treatment discontinuation, n (%)	120 (47.1)[i, j]	94 (71.8)[i, j]
Study discontinuation, n (%)	ND[k]	ND[k]

a. Number of randomized patients.
b. According to FIGO classification of 1988 [7]
c. Institute's calculation.
d. Patients without detectable tumour after primary surgery.
e. Patients without detectable tumour/with complete response after interval surgery.
f. Patients without detectable tumour/with complete response after chemotherapy.
g. Patients with partial response.
h. According to the SPC for bevacizumab, the drug may be administered for up to 6 cycles in addition to carboplatin and paclitaxel in the therapeutic indication [11]. The data in Module 4 A provide no information on how many patients received more than 6 cycles in combination with carboplatin and paclitaxel.
i. Institute's calculation; the percentage refers to the number of treated patients.
j. In the relevant subpopulation, 21.6% of patients in the intervention arm and 55.7% of patients in the comparator arm discontinued the study medication due to disease progression according to RECIST.
k. No data for the relevant subpopulation. In the total population, 29% of the randomized patients in both the intervention and the control arm discontinued the study (of which due to death: 89% vs. 91%).

BRCA: breast cancer associated gene; CR: complete response; ECOG PS: Eastern Cooperative Oncology Group Performance Status ;FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; ND: no data; IDS: interval surgery; n: Number of patients in the category; N: number of randomized patients; NED: no detectable tumour; PDS: primary surgery; PR: partial response; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours; SD: standard deviation; tBRCA: tumour BRCA

The patient characteristics are largely comparable between the two treatment arms. The mean age of the patients was 58 years, and the majority (approx. 95%) of the patients were from Europe. 75% of the patients had a good general condition, corresponding to an ECOG PS of 0. Corresponding to the higher incidence [12,13], the majority of patients were diagnosed with a primary tumour location in the ovary (87%) and a serous tumour histology (95%). Moreover, just over 60% of patients were classified as FIGO stage IIIC at diagnosis, although it should be noted that the 1988 FIGO classification [7] was used in the study protocol. Patients who were assigned to this stage at diagnosis solely due to metastases in retroperitoneal lymph nodes would be assigned to stage IIIA according to the current FIGO classification [8]. All carcinomas of the patients in the present relevant subpopulation were associated with a positive HRD status, of which about half of the patients had a pathogenic BRCA mutation in the tumour. Prior to first-line platinum-containing chemotherapy 58% of the patients underwent PDS and 37% underwent IDS.

Since no patients with ECOG PS ≥ 2 and only few patients with non-serous tumour histology were included in the study, it remains unclear whether the study results can be transferred to these patients, who are also comprised by the therapeutic indication to be assessed.

Table 10 shows the median treatment duration of the patients and the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab

Study **duration of the study phase** **outcome category**	**Olaparib + bevacizumab** **N = 255**	**Placebo + bevacizumab** **N = 132**
PAOLA-1		
Treatment duration[a] [months]		
Median [min; max]	23.8 [0; 36]	16.8 [0; 25]
Observation period[b] [months]		
Overall survival		
Median [min; max]	36.6 [1.4; 55.5]	36.1 [0.3; 53.7]
Morbidity (EORTC QLQ-C30, QLQ-OV28, EQ-5D VAS)		
Median [min; max]	24.2 [0.0; 52.5]	24.1 [0.0; 41.2]
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	24.2 [0.0; 52.5]	24.1 [0.0; 41.2]
Side effects[a] (AEs/SAEs/severe AEs)		
Median [min; max]	24.8 [1.2; 36.8]	17.8 [1.1; 26.3]
Side effects[a] (selected specific AEs[c])		
Median [min; max]	38.5 [8.9; 55.6]	36.8 [5.3; 53.8]

a. Number of analysed patients olaparib + bevacizumab vs. placebo + bevacizumab: N = 255, N = 131
b. The company did not provide any information on the determination of observation periods.
c. Specific AEs prespecified in the study as AESIs or expected AEs should be monitored until death or end of the study. The analyses on these AEs are available as AESI analyses in Module 4 A of the company.

AE: adverse event; AESI: adverse event of special interest; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; max: maximum; min: minimum; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OV28: Quality of Life Questionnaire-Ovarian Cancer 28; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Median treatment duration in the intervention arm was 7 months longer than in the comparator arm (23.8 months vs. 16.8 months).

The observation periods for overall survival, the outcomes of the categories “morbidity” and “health-related quality of life” and for the specific AEs with observation until death or end of the study were comparable. The differences in the observation periods between the treatment arms entail a difference in the respective observation periods for the outcomes “AEs”, “SAEs” and “severe AEs”, because these outcomes are only observed until 30 days after the last dose of the study medication.

Table 11 shows which subsequent antineoplastic therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab

Study drug class drug	Patients with subsequent therapy n (%)	
	Olaparib + bevacizumab N = 255	Placebo + bevacizumab N = 132
PAOLA-1		
Patients with a first subsequent therapy[a]	113 (44.3)	98 (74.2)
Platinum-based chemotherapy	98 (86.7)	84 (85.7)
Carboplatin	98 (86.7)	84 (85.7)
Other platinum-based chemotherapy	2 (1.8)	1 (1.0)
Non-platinum-based cytoreductive therapy	99 (87.6)	91 (92.9)
Gemcitabine	15 (13.3)	14 (14.3)
Paclitaxel	11 (9.7)	8 (8.2)
Pegylated liposomal doxurubicin (PLD, Caelyx)	73 (64.6)	69 (70.4)
Targeted therapy	36 (31.9)	57 (58.2)
Bevacizumab	14 (12.4)	16 (16.3)
PARP inhibitor	16 (14.2)	40 (40.8)
Other drugs	16 (14.2)	14 (14.3)
Other	15 (13.3)	10 (10.2)
Patients with a second subsequent therapy[a]	66 (25.9)	62 (47.0)
Platinum-based chemotherapy	18 (27.3)	29 (46.8)
Carboplatin	18 (27.3)	29 (46.8)
Other platinum-based chemotherapy	4 (6.1)	5 (8.1)
Non-platinum-based cytoreductive therapy	49 (74.2)	39 (62.9)
Gemcitabine	16 (24.2)	16 (25.8)
Paclitaxel	20 (30.3)	13 (21.0)
Pegylated liposomal doxurubicin (PLD, Caelyx)	13 (19.7)	10 (16.1)
Targeted therapy	13 (19.7)	19 (30.6)
Bevacizumab	4 (6.1)	11 (17.7)
PARP inhibitor	4 (6.1)	11 (17.7)
Other drugs	8 (12.1)	7 (11.3)
Other	10 (15.2)	15 (24.2)

a. Percentages shown for the specific subsequent therapies listed below were calculated in relation to the total number of patients with first or second subsequent therapy.

n: number of patients with subsequent therapy; N: number of analysed patients; PARP: poly-adenosine diphosphate ribose polymerase; RCT: randomized controlled trial

The drugs chosen for the first subsequent therapy were largely equally distributed between the arms. Patients in both arms received platinum-based chemotherapy as first-line therapy in 86%

of the cases. However, it was notable that the percentage of patients who received a polyadenosine diphosphate ribose polymerase (PARP) inhibitor in the first subsequent therapy was significantly higher in the comparator arm. According to the study protocol, the choice of subsequent medication was not restricted; unblinding was only intended for medical emergencies in which knowledge of the administered study medication was necessary for the attending physician.

Moreover, the second subsequent therapy differs between the arms: more patients in the comparator arm received further platinum-based chemotherapy, bevacizumab and/or a PARP inhibitor in the second subsequent therapy.

The reasons for these differences are unclear.

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, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab

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			
PAOLA-1	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

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

Transferability of the study results to the German health care context

The company stated that PAOLA-1 was considered representative for the German health care context with regard to demographic and disease-specific factors. Therefore, the results could be transferred to the German health care context without restrictions. It justified this with the fact that more than 30% of the patients were treated in German study centres and that it could also be assumed that the patients received equivalent treatment within the other European centres. The company considered the German and the European guideline for the treatment of ovarian cancer to be largely compliant. The company described that the pretreatment of the patients included in the study complied with the treatment recommendations of the S3 guideline [8] and with the German SPC on bevacizumab [11]. It stated that the study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/good clinical practice (GCP) guidelines.

The company also compared the patient characteristics of the target population of the PAOLA-1 study with those of a quality assurance survey on ovarian cancer (QS-OVAR) in German hospitals. In doing so, the company identified no relevant differences with regard to tumour entities and histology, age and ECOG PS. However, it described differences in the time point of the debulking surgery (PDS vs. IDS) and the proportion of patients without macroscopic tumour remnants after PDS/IDS.

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
  - Symptoms measured with the EORTC QLQ-C30 symptom scales
  - Symptoms measured using the EORTC QLQ-OV28 symptom scales
  - Health status measured with the EQ-5D VAS
- Health-related quality of life
  - health-related quality of life measured with the functional scales of the EORTC QLQ-C30 and scales of the EORTC QLQ-OV28
- Side effects
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Myelodysplastic syndrome (PT, AEs)
  - Acute myeloid leukaemia (PT, AEs)
  - Pneumonitis (PT, AEs)
  - Further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4). The specific AEs “myelodysplastic syndrome” and “acute myeloid leukaemia” were jointly analysed in the company’s dossier.

Table 13 shows for which outcomes data were available in the study included.

Table 13: Matrix of the outcomes – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab

Study	Outcomes									
	Overall survival	Symptoms (EORTC QLQ-C30 symptom scales; EORTC QLQ-OV28 symptom scales)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 functional scales and EORTC QLQ-OV28)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Myelodysplastic syndrome and acute myeloid leukaemia (PTs, AEs)	Pneumonitis (PT, AEs)[b]	Further specific AEs[c]
PAOLA-1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Operationalized as CTCAE grade ≥ 3.
b. Prespecified in the study as AESIs, follow-up until death or end of study.
c. The following events were considered (MedDRA coding): nausea (PT, AEs), anaemia (PT, severe AEs [CTCAE grade ≥ 3]), fatigue and asthenia (PTs, severe AEs [CTCAE grade ≥ 3]), hypertension (PT, severe AEs [CTCAE grade ≥ 3]). All AEs specified as specific AEs were monitored until death or end of study.

AE: adverse event; AESI: adverse event of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OV28: Quality of Life Questionnaire-Ovarian Cancer 28; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Symptoms and health-related quality of life

The company presented responder analyses up to a deterioration by 10 points for the outcomes recorded with the symptom and functional scales of the EORTC QLQ-C30 and the EORTC QLQ-OV28. As explained in the General Methods of the Institute [1,14], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). This is not the case with the response criteria presented. The responder analyses submitted by the company were nevertheless used for the benefit assessment, as with a response threshold of 10 points the analysis represents a sufficient approximation to an analysis with a 15 % threshold (15 points). An explanation can be found in benefit assessment A20-97 [15].

EORTC QLQ-OV28

The EORTC QLQ-OV28 is an additional disease-specific module to the EORTC QLQ-C30 for patients with ovarian cancer and comprises 28 items.

In its dossier, the company used the validated version of the questionnaire and analysed the scales in accordance with the general EORTC QLQ-C30 Scoring Manual of 2001 [16], which is available on the EORTC website. There, the following allocation of the items to scales can be found for the EORTC QLQ-OV28: "abdominal/gastrointestinal symptoms" (6 items), "peripheral neuropathy" (2 items), "side effects of chemotherapy" (5 items), "hormonal symptoms" (2 items), "body image" (2 items), "attitude regarding disease/treatment" (3 items), "other individual items" (4) and "sexuality" (4 items; not presented by the company in Module 4 A, as the 2001 manual provides no analysis algorithm).

Upon request to the EORTC, the current EORTC-QLQ-OV28 Scoring Manual [17] was made available. According to this scoring manual, the items are assigned to the scales as follows: "abdominal/gastrointestinal symptoms" (7 items), "peripheral neuropathy" (3 items), "side effects of chemotherapy" (7 items), "hormonal symptoms" (2 items), "body image" (2 items), "attitude regarding disease/treatment" (3 items) and sexuality (2 + 2 conditional items). This assignment results from the field test of the EORTC-QLQ-OV28 [18].

The analyses submitted by the company were used, as the partly deviating assignment of the items to the scales was not assumed to result in a relevant loss of information.

Specific AEs

In the PAOLA-1 study, follow-up observation was planned until 30 days after the end of treatment for most AEs. Moreover, specific AEs prespecified as AEs of special interest or as expected AEs were to be monitored until death or end of the study. The specific AEs considered in the present benefit assessment were those with extended follow-up. The observation periods for these outcomes were comparable between the treatment groups (see Table 10), so that a consideration of the proportions of patients with event using the relative risk would also be adequate. However, in the present situation, event time analyses corresponding to the superordinate AE outcomes were used for these outcomes. When considering the relative risk, the same results are also shown with regard to statistical significance.

2.4.2 Risk of bias

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

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab:

Study		Outcomes									
	Study level	Overall survival	Symptoms (EORTC QLQ-C30 symptom scales; EORTC QLQ-OV28 symptom scales)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 functional scales and EORTC QLQ-OV28)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Myelodysplastic syndrome and acute myeloid leukaemia (PTs, AEs)	Pneumonitis (PT, AEs)[b]	Further specific AEs[c]
PAOLA-1	L	L	L	L	L	H[d]	H[d]	L[e]	L	L	L

a. Operationalized as CTCAE grade ≥ 3.
b. Prespecified in the study as AESIs, follow-up until death or end of study.
c. The following events were considered (MedDRA coding): nausea (PT, AEs), anaemia (PT, severe AEs [CTCAE grade ≥ 3]), fatigue and asthenia (PTs, severe AEs [CTCAE grade ≥ 3]), hypertension (PT, severe AEs [CTCAE grade ≥ 3]). All AEs specified as specific AEs were monitored until death or end of study.
d. Incomplete observations for potentially informative reasons.
e. Despite the low risk of bias, limited certainty of results is assumed for the outcome "discontinuation due to AEs".

AE: adverse event; AESI: adverse event of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OV28: Quality of Life Questionnaire-Ovarian Cancer 28; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Concurring with the company, the risk of bias was rated as low for the results on "overall survival", "symptoms (symptom scales of the EORTC QLQ-C30 and the EORTC QLQ-OV28)", "health status (EQ-5D VAS)", "health-related quality of life (functional scales of the EORTC QLQ-C30 and scales of the EORTC QLQ-OV28)", for the AEs selected as "specific AEs" with observation periods until death or end of study, as well as for the outcome "discontinuation due to AEs".

Thereby, the certainty of results for the outcome "discontinuation due to AEs" was restricted despite a low risk of bias. 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 discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It cannot be estimated how many AEs are concerned.

Deviating from the company's assessment, the risk of bias was rated as high for the outcomes "SAEs" and "severe AEs" due to incomplete observations for potentially informative reasons. In the relevant subpopulation, 21.6% of patients in the intervention arm and 55.7% in the comparator arm discontinued their study medication due to disease progression according to RECIST; the median observation time differed significantly between the study arms (24.8 months in the intervention arm vs. 17.8 months in the comparator arm).

2.4.3 Results

Table 15 and Table 16 summarize the results on the comparison of olaparib + bevacizumab with placebo + bevacizumab in patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with HRD positive status. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Kaplan-Meier curves for the results of the included outcomes can be found in Appendix A of the full dossier assessment. Kaplan-Meier curves on relevant subgroup results can be found in Appendix B of the full dossier assessment. Forest plots of own meta-analyses are presented in Appendix C, and results on the outcome "health status" are presented as supplementary information in Appendix D. Results on common AEs can be found in Appendix E of the full dossier assessment.

All results refer exclusively to the relevant subpopulation and the data cut-off of 22 March 2020.

Table 15: Results (overall survival, morbidity, health-related quality of life, time to event) – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab (multipage table)

Study outcome category outcome	Olaparib + bevacizumab N	Olaparib + bevacizumab median time to event in months [95% CI] patients with event n (%)	Placebo + bevacizumab N	Placebo + bevacizumab median time to event in months [95% CI] patients with event n (%)	Olaparib + bevacizumab vs. placebo + bevacizumab HR [95 % CI]; p-value[a]
PAOLA-1					
Mortality					
Overall survival	255	NA 61 (23.9)	132	NA 42 (31.8)	0.70 [0.47; 1.05]; 0.078
Morbidity					
EORTC QLQ-C30 – symptom scales[b]					
Fatigue	255	5.6 [3.1; 6.0] 199 (78.0)	132	5.7 [5.5; 11.1] 98 (74.2)	1.10 [0.86; 1.41]; 0.482
Nausea and vomiting	255	5.8 [5.6; 8.7] 178 (69.8)	132	19.2 [12.7; 23.5] 70 (53.0)	1.81 [1.37; 2.42]; < 0.001
Pain	255	5.8 [5.6; 8.3] 183 (71.8)	132	5.6 [3.0; 8.1] 95 (72.0)	0.92 [0.72; 1.19]; 0.551
Dyspnoea	255	20.7 [16.0; 52.5] 125 (49.0)	132	18.7 [12.3; 24.9] 67 (50.8)	0.92 [0.68; 1.25]; 0.580
Insomnia	255	11.3 [8.4; 14.0] 159 (62.4)	132	8.3 [5.6; 11.1] 91 (68.9)	0.73 [0.56; 0.95]; 0.019
Appetite loss	255	13.6 [11.1; 22.1] 146 (57.3)	132	22.3 [16.6; 28.7] 65 (49.2)	1.42 [1.06; 1.92]; 0.023
Constipation	255	19.9 [16.6; 23.4] 133 (52.2)	132	19.7 [14.0; 22.3] 69 (52.3)	1.03 [0.77; 1.39]; 0.831
Diarrhoea	255	24.0 [16.6; 25.9] 124 (48.6)	132	23.5 [19.9; 35.0] 58 (43.9)	1.15 [0.84; 1.58]; 0.409
EORTC QLQ-OV28 – symptom scales[b]					
Abdominal/ gastrointestinal symptoms	255	11.1 [8.3; 14.0] 169 (66.3)	132	8.3 [5.7; 11.3] 89 (67.4)	0.88 [0.68; 1.15]; 0.351
Peripheral neuropathy	255	25.3 [18.6; NC 114 (44.7)]	132	23 [12.7; NC] 58 (43.9)	0.93 [0.68; 1.29]; 0.654
Hormonal symptoms	255	19.1 [14.3; 24.2] 135 (52.9)	132	11.3 [5.6; 19.1] 76 (57.6)	0.75 [0.56; 0.996]; 0.046
Side effects of chemotherapy	255	17.9 [12.0; 24.6] 135 (52.9)	132	11.1 [8.3; 16.6] 82 (62.1)	0.75 [0.57; 0.997]; 0.045
Individual questions[c]	255	21.9 [16.6; 25.7] 127 (49.8)	132	19.4 [16.4; NC] 64 (48.5)	1.01 [0.75; 1.38]; 0.954

Table 15: Results (overall survival, morbidity, health-related quality of life, time to event) – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab (multipage table)

Study outcome category outcome	Olaparib + bevacizumab N	 median time to event in months [95% CI] patients with event n (%)	Placebo + bevacizumab N	 median time to event in months [95% CI] patients with event n (%)	Olaparib + bevacizumab vs. placebo + bevacizumab HR [95 % CI]; p-value[a]
Sexual functioning				No usable data[d]	
Health-related quality of life					
EORTC QLQ-C30 functional scales[e]					
Global health status	255	16.6 [11.5; 21.8] 146 (57.3)	132	13.8 [9.3; 17.2] 81 (61.4)	0.85 [0.65; 1.12]; 0.234
Physical functioning	255	20 [13.9; 52.5] 125 (49.0)	132	16.4 [11.5; 22.4] 74 (56.1)	0.85 [0.64; 1.14]; 0.279
Role functioning	255	8.4 [5.8; 11.2] 167 (65.5)	132	9.3 [6.1; 16.2] 82 (62.1)	1.11 [0.85; 1.46]; 0.450
Cognitive functioning	255	11.1 [8.5; 14.0] 174 (68.2)	132	8.5 [5.9; 13.6] 85 (64.4)	0.91 [0.70; 1.19]; 0.484
Emotional functioning	255	13.8 [9.0; 19.3] 158 (62.0)	132	11.1 [8.3; 13.8] 85 (64.4)	0.93 [0.71; 1.22]; 0.571
Social functioning	255	13.5 [8.6; 19.6] 148 (58.0)	132	11.3 [8.5; 16.4] 81 (61.4)	0.91 [0.69; 1.20]; 0.471
EORTC QLQ-OV28[b]					
Body image	255	21.9 [12.7; NC] 126 (49.4)	132	18.7 [11.5; 25.1] 71 (53.8)	0.93 [0.70; 1.26]; 0.638
Attitude regarding disease/treatment	255	12.2 [8.3; 24.1] 134 (52.5)	132	17.5 [11.2; NC] 65 (49.2)	1.15 [0.86; 1.57]; 0.362
Side effects					
AEs (supplementary information)	255	0.2 [0.2; 0.3] 255 (100)	131	0.3 [0.2; 0.7] 127 (96.9)	-
SAEs	255	NA 73 (28.6)	131	NA 45 (34.4)	0.75 [0.52; 1.10]; 0.133
Severe AEs[f]	255	8.6 [5.6; 15.3] 147 (57.6)	131	16.7 [6.6; NC] 65 (49.6)	1.20 [0.90; 1.63]; 0.221
Discontinuation due to AEs	255	NA 50 (19.6)	131	NA 8 (6.1)	3.14 [1.57; 7.18]; 0.002

Table 15: Results (overall survival, morbidity, health-related quality of life, time to event) – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab (multipage table)

Study outcome category outcome	Olaparib + bevacizumab		Placebo + bevacizumab		Olaparib + bevacizumab vs. placebo + bevacizumab
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95 % CI]; p-value[a]
Myelodysplastic syndrome and acute myeloid leukaemia (PTs, AEs)[g, h]	255	NA 2 (0.8)	131	NA 2 (1.5)	0.54 [0.06; 4.51]; 0.531
Pneumonitis (PT, AEs)[g]	255	NA 3 (1.2)	131	NA 0 (0)	NC; 0.195
Nausea (PT, AEs)[g]	255	2.9 [0.8; 16.0] 144 (56.5)	131	NA 33 (25.2)	3.10 [2.14; 4.63]; < 0.001
Anaemia (PT severe UEs)[f, g]	255	NA 47 (18.4)	131	NA 1 (0.8)	27.79 [6.08; 492.43]; < 0.001
Fatigue and asthenia (PTs, severe AEs)[f, g]	255	NA 17 (6.7)	131	NA 2 (1.5)	4.54 [1.29; 28.70]; 0.027
Hypertension (PT, severe AEs)[f, g]	255	NA 50 (19.6)	131	NA 42 (32.1)	0.52 [0.34; 0.79]; 0.002

a. HR and CI: Cox proportional hazards model, p-value: log-rank test, each stratified by the result of first-line therapy and tBRCA mutation status.
b. Time to deterioration; defined as increase of the score by ≥ 10 points compared with baseline.
c. The individual questions included in this scale refer to the presence of indigestion or heartburn, hair loss and altered sense of taste. According to the current scoring manual, this scale is no longer analysed, but the individual questions are included in the analysis of the other scales (see Section 2.4.1).
d. The company presented no analyses for the "sexuality" scale, as the scoring manual used by it provides no analysis algorithm [16].
e. Time to deterioration; defined as decrease of the score by ≥ 10 points compared with baseline.
f. Operationalized as CTCAE grade ≥ 3.
g. Follow-up observation until death or end of study.
h. Discrepant data within Module 4 A of the dossier; data on the outcome "MDS/AML intervention vs. control n (%)"; HR [95% CI]; p: 2 (0.8) vs. 1 (0.8); 1.07 [0.10; 23.20]; 0.955.

AE: adverse event; AML: acute myeloid leukaemia; BRCA: breast cancer associated gene; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; MDS: myelodysplastic syndrome; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OV28: Quality of Life Questionnaire-Ovarian Cancer 28; RCT: randomized controlled trial; SAE: serious adverse events; tBRCA: tumour BRCA

Table 16: Results (morbidity, continuous) – RCT, direct comparison: olaparib + bevacizumab vs. placebo + olaparib

Study outcome category outcome	Olaparib + bevacizumab			Placebo + bevacizumab			Olaparib + bevacizumab vs. placebo + bevacizumab
	N	values at baseline mean (SD)	mean change in the course of the study mean[a] (SE)	N	values at baseline mean (SD)	mean change in the course of the study mean[a] (SE)	MD [95% CI]; p-value[a]
PAOLA-1							
Morbidity							
Health status (EQ-5D VAS)[b]	217	72.6 (16.5)	1.5 (0.8)	121	72.3 (14.7)	1.4 (1.1)	0.07 [-2.60; 2.74]; 0.959

a. Mean value and SE (change per treatment group) as well as MD, CI and p-value (group comparison): MMRM; adjusted for baseline value.
b. Higher values indicate a better health status; positive effects (intervention vs. control) mean an advantage for intervention. The EQ-5D VAS values can range from 0 to 100.

CI: confidence interval; EQ-5D: European Quality of Life Questionnaire-Core 5 Dimensions; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed Patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be determined for the outcomes “overall survival”, “symptoms”, “health status”, “health-related quality of life” and “specific AEs”, and at most hints, e.g. of an added benefit, can be determined for the outcomes “SAEs”, “severe AEs (CTCAE grade ≥ 3)” and “discontinuation due to AEs” because of the high risk of bias or a limited certainty of results.

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome “overall survival”.

However, there was an effect modification by the characteristic “result of the first-line therapy”. For patients in the NED/CR (IDS) and PR subgroups, there was no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven. For patients without detectable tumour after primary surgery (NED [PDS]) and patients without detectable tumour/with complete response after chemotherapy (NED/CR [chemotherapy]), this resulted in an indication of an added benefit of olaparib + bevacizumab in comparison with bevacizumab (see Section 2.4.4).

This deviates from the company’s assessment, which only derived an indication of an added benefit for the subgroup of patients without detectable tumour after primary surgery (NED).

Morbidity

The company did not perform an outcome-specific derivation of the added benefit for the outcomes of the category "morbidity", but derived the added benefit across all outcomes. Hence, the company's outcome-specific assessment is not described below.

Symptoms (EORTC QLQ-C30 symptom scales)

Symptom outcomes were recorded using the EORTC QLQ-C30 symptom scales.

A statistically significant difference to the disadvantage of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcome "nausea and vomiting". This resulted in an indication of lesser benefit of olaparib + bevacizumab in comparison with bevacizumab.

A statistically significant difference in favour of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcome "insomnia". A statistically significant difference to the disadvantage of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcome "appetite loss". However, the extent of the effects for these outcomes of the category "non-serious/non-severe symptoms/late complications" was no more than marginal. In each case, this resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven for these outcomes.

No statistically significant difference between the treatment arms was shown for each of the outcomes "fatigue", "pain", "dyspnoea", "constipation" and "diarrhoea". This resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab for each of these outcomes; an added benefit is therefore not proven for these outcomes.

Symptoms (EORTC QLQ-OV28 symptom scales)

Symptom outcomes were recorded using the EORTC QLQ-OV28 symptom scales.

A statistically significant difference in favour of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcomes "hormonal symptoms" and "side effects of chemotherapy". However, the extent of the effects for these outcomes of the category "non-serious/non-severe symptoms/late complications" was no more than marginal. In each case, this resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven for these outcomes.

For the outcomes "abdominal/gastrointestinal symptoms", "peripheral neuropathy" as well as for the scale of individual questions, there is no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab for each of these outcomes; an added benefit is therefore not proven for these outcomes.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment arms for the outcome "health status measured using the EQ-5D VAS". This resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven.

Health-related quality of life

The company did not perform an outcome-specific derivation of the added benefit for the outcomes of the category of "health-related quality of life", but derived the added benefit across all outcomes. Hence, the company's outcome-specific assessment is not described below.

EORTC QLQ-C30

Outcomes on health-related quality of life were recorded with the EORTC QLQ-C30 functional scales.

There was no statistically significant difference between the treatment groups for the outcome "global health status". However, there was an effect modification by the characteristic "age". For younger patients (< 65 years), there was no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven. For older patients (≥ 65 years), this resulted in an indication of an added benefit of olaparib + bevacizumab in comparison with bevacizumab (see Section 2.4.4).

No statistically significant difference between the treatment groups was shown for the outcomes "physical functioning", "role functioning", "cognitive functioning", "emotional functioning", and "social functioning". This resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven.

EORTC QLQ-OV28

Outcomes on health-related quality of life were recorded with the scales of the EORTC QLQ-OV28.

No statistically significant difference between the treatment groups was shown for the outcome "attitude regarding disease/treatment". However, there was an effect modification by the characteristic "result of the first-line therapy". For patients in the NED (PDS), NED/ CR (chemotherapy) and PR subgroups, there was no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven. For patients in the NED/CR (IDS) subgroup, this resulted in an indication of lesser benefit of olaparib + bevacizumab in comparison with bevacizumab (see Section 2.4.4).

No statistically significant difference between the treatment arms was shown for the outcome "body image". This resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven.

Side effects

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

According to the study protocol, AEs that are doubtlessly due to a progression of the underlying disease should not be reported as AE.

SAEs and severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs" and "severe AEs (CTCAE grade ≥ 3)". In each case, this resulted in no hint of greater or lesser harm from olaparib + bevacizumab in comparison with bevacizumab for these outcomes; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcome "discontinuation due to AEs". This resulted in a hint of greater harm from olaparib + bevacizumab in comparison with bevacizumab.

Specific AEs

All specific AEs considered in the benefit assessment were observed until the end of the study.

Myelodysplastic syndrome and acute myeloid leukaemia and pneumonitis (PTs, AEs)

No statistically significant difference between the treatment groups was shown for each of the outcomes "myelodysplastic syndrome" and "acute myeloid leukaemia" as well as "pneumonitis". In each case, this resulted in no hint of greater or lesser harm from olaparib + bevacizumab in comparison with bevacizumab for these outcomes; greater or lesser harm is therefore not proven.

Nausea (PTs, AEs), anaemia (PTs, severe AEs [CTCAE grade ≥ 3]) as well as fatigue and asthenia (PTs, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of olaparib + bevacizumab in comparison with placebo + bevacizumab was shown for each of the outcomes "nausea (PT, AEs)", "anaemia (PT, severe AEs [CTCAE grade ≥ 3])" as well as "fatigue" and "asthenia (PTs, severe AEs [CTCAE grade ≥ 3])". This resulted in an indication of greater harm from olaparib + bevacizumab in comparison with bevacizumab in each case.

Hypertension (PT, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference in favour of olaparib + bevacizumab in comparison with placebo + bevacizumab was shown for the outcome "hypertension (PT, severe AEs [CTCAE

grade ≥ 3])". This resulted in an indication of lesser harm from olaparib + bevacizumab in comparison with bevacizumab.

The assessment on side effects deviates from the company's assessment, which, in summary, regards an added benefit as not being proven.

2.4.4 Subgroups and other effect modifiers

The following predefined potential effect modifiers were considered for the present assessment:

- Age at randomization (< 65 vs. ≥ 65 years)
- Result of first-line therapy (NED [PDS] vs. NED/CR [IDS] vs. NED/CR [chemotherapy] vs. PR)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be 10 events in at least one subgroup.

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

Table 17 presents the subgroup results of olaparib + bevacizumab in comparison with placebo + bevacizumab.

Table 17: Subgroups (mortality health-related quality of life) – RCT, direct comparison: olaparib + bevacizumab versus placebo + bevacizumab (multipage table)

Study outcome characteristic subgroup	Olaparib + bevacizumab N	Olaparib + bevacizumab median time to event in months [95 % CI] patients with event n (%)	Placebo + bevacizumab N	Placebo + bevacizumab median time to event in months [95 % CI] patients with event n (%)	Olaparib + bevacizumab vs. placebo + bevacizumab HR [95% CI][a]	 p-value[a]
PAOLA-1						
Overall survival						
Result of the first-line therapy						
NED (PDS)[b]	92	NA 8 (8.7)	48	NA 14 (29.2)	0.26 [0.11; 0.61]	0.002
NED/CR (IDS)[c]	74	NA 23 (31.1)	38	NA 11 (28.9)	1.04 [0.52; 2.23]	0.904
NED/CR (chemotherapy)[d]	40	NA 9 (22.5)	20	NA 8 (40.0)	0.54 [0.21; 1.45]	0.216
PR[e]	49	44.0 [32.3; NC] 21 (42.9)	26	NA 9 (34.6)	1.13 [0.53; 2.60]	0.758
Total					Interaction:	0.043[f]
NED (PDS)[b] + NED/CR (chemotherapy)[d]					0.36 [0.19; 0.68][g]	0.002[g]
NED/CR (IDS)[c] + PR[e]					1.08 [0.63; 1.85][g]	0,778[g]
Total					Interaction	0.010[h]
Global Health Status (EORTC QLQ-C30 functional scale)[i]						
Age						
< 65 years	185	15.2 [11.0; 19.7] 109 (58.9)	98	16.2 [9.3; 20.8] 56 (57.1)	0.97 [0.70; 1.34]	0.843
≥ 65 years	70	22.1 [11.3; NC] 37 (52.9)	34	9.9 [5.5; 15.4] 25 (73.5)	0.51 [0.31; 0.86]	0.013
Total					Interaction:	0.041[f]
Attitude regarding disease/treatment (EORTC QLQ-OV28)[j]						
Result of the first-line therapy						
NED (PDS)[b]	92	NA 35 (38.0)	48	11.3 [5.6; NC] 25 (52.1)	0.60 [0.36; 1.01]	0.053
NED/CR (IDS)[c]	74	5.7 [3.0; 8.7] 47 (63.5)	38	NA 15 (39.5)	2.34 [1.34; 4.33]	0.002
NED/CR (chemotherapy)[d]	40	8.3 [3.1; NC] 22 (55.0)	20	12.6 [5.7; NC] 12 (60.0)	1.18 [0.59; 2.46]	0.646
PR[e]	49	12.1 [6.2; 22.1] 30 (61.2)	26	17.0 [3.0; NC] 13 (50.0)	1.03 [0.55; 2.04]	0.931
Total					Interaction:	0.006[f]

Table 17: Subgroups (mortality health-related quality of life) – RCT, direct comparison: olaparib + bevacizumab versus placebo + bevacizumab (multipage table)

Study outcome	Olaparib + bevacizumab		Placebo + bevacizumab		Olaparib + bevacizumab vs. placebo + bevacizumab	
characteristic subgroup	N	median time to event in months [95 % CI] patients with event n (%)	N	median time to event in months [95 % CI] patients with event n (%)	HR [95% CI][a]	p-value[a]

a. HR, CI and p-value: Cox proportional hazards model, unstratified.
b. Patients without detectable tumour after primary surgery.
c. Patients without detectable tumour/with complete response after interval surgery.
d. Patients without detectable tumour/with complete response after chemotherapy.
e. Patients with partial response.
f. Cox proportional hazards model with corresponding interaction term; unstratified.
g. Institute's calculation; meta-analysis with fixed effect (method with inverse variance).
h. Institute's calculation, Q test.
i. Time to deterioration; defined as decrease of the score by ≥ 10 points compared with baseline.
j. Time to deterioration; defined as increase of the score by ≥ 10 points compared with baseline.

CI: confidence interval; CR: complete response; EORTC: European Organization for Research and Treatment of Cancer; HR: hazard ratio; IDS: interval surgery; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; NED: no detectable tumour; PDS: primary debulking surgery; PR: partial response; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OV28: Quality of Life Questionnaire-Ovarian Cancer 28; RCT: randomized controlled trial

Mortality

Overall survival

The available subgroup analyses resulted in an effect modification for the outcome "overall survival" by the characteristic "result of the first-line therapy". First, it was examined whether subgroups could be meaningfully summarized. Institute's calculations show that a summarizing consideration of the subgroups "NED (PDS) + NED/CR (chemotherapy)" and "NED/CR (IDS) + PR" results in a homogeneous data situation for the outcome "overall survival" in each case (see results in Appendix C). The results for each of these summarized subgroups are also homogeneous for the outcome PFS. For the outcome "overall survival", the respective results from a corresponding meta-analysis (Institute's calculation; fixed-effect model; method with inverse variance) were therefore considered for these summarized subgroups NED (PDS) + NED/CR (chemotherapy) or NED/CR (IDS) + PR.

For patients without detectable tumour after primary surgery (NED [PDS]) and patients without detectable tumour/with complete response after chemotherapy (NED/CR [chemotherapy]), a statistically significant difference in favour of olaparib + bevacizumab in comparison with bevacizumab was shown for the outcome "overall survival". This result fits with the results for PFS. Both for PFS (first progression recorded using imaging techniques according to RECIST or death) and for PFS2 (second progression [assessed by the investigator by means of radiological methods, CA-125 or symptoms] or death), there is a statistically significant

advantage for these patients. Overall, there is an indication of an added benefit of olaparib + bevacizumab compared to bevacizumab for the patients in the subgroups NED (PDS) and NED/CR (chemotherapy).

For patients without detectable tumour/with complete response after interval surgery (NED/CR [IDS]) and for patients with partial response (PR), there is no statistically significant difference between the treatment groups for the outcome "overall survival". In this situation, the results on PFS are not suitable to support the results on overall survival. For PFS, a statistically significant advantage of olaparib + bevacizumab in comparison with placebo + bevacizumab was initially shown for these two subgroups, but as with overall survival, the result for PFS2 shows no statistically significant difference between the treatment groups. Overall, this resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab for these subgroups; an added benefit is therefore not proven.

This deviates from the company's assessment, which only derived an indication of an added benefit for the subgroup of patients without detectable tumour after primary NED (PDS).

Health-related quality of life

Global Health Status (EORTC QLQ-C30 functional scale)

The available subgroup analyses resulted in an effect modification for the outcome "global health status" by the characteristic "age".

For younger patients (< 65 years) no statistically significant difference between the treatment groups was shown for the outcome "global health status". This resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab for this subgroup; an added benefit is therefore not proven.

A statistically significant difference in favour of olaparib + bevacizumab compared with placebo + bevacizumab was shown for older patients (≥ 65 years). This resulted in an indication of an added benefit of olaparib + bevacizumab in comparison with bevacizumab for this subgroup.

Attitude regarding disease/treatment (EORTC QLQ-OV28)

The available subgroup analyses resulted in an effect modification for the outcome "attitude regarding disease/treatment" by the characteristic "result of the first-line therapy".

For the outcome "attitude regarding disease/treatment", there was no statistically significant difference between the treatment groups for patients in the 3 subgroups NED/CR (PDS), NED/CR (chemotherapy) and PR. This resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab for these subgroups; an added benefit is therefore not proven.

For patients without detectable tumour/with complete response after interval surgery (NED/CR [IDS]), there is a statistically significant difference to the disadvantage of olaparib + bevacizumab in comparison with bevacizumab. This resulted in an indication of lesser benefit of olaparib + bevacizumab in comparison with bevacizumab for this subgroup.

This deviates from the assessment of the company, which did not consider the result of the subgroup analysis in the derivation of the added benefit.

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 [1].

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

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 18).

Determination of the outcome category for outcomes on symptoms, health-related quality of life and side effects

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

Insomnia, appetite loss as well as nausea and vomiting (EORTC QLQ-C30 symptom scales)

- It cannot be inferred from the information in Module 4 A whether the events that led to a worsening of insomnia, loss of appetite or nausea and vomiting were predominantly severe or serious. Therefore, the outcomes were assigned to the category of non-serious/non-severe symptoms or late complications.

Hormonal symptoms, side effects of chemotherapy and attitude regarding disease/treatment (EORTC QLQ-OV28)

- It cannot be inferred from the information in Module 4 A whether the events that led to a worsening of hormonal symptoms, side effects of chemotherapy and with regard to the attitude to the disease/treatment were predominantly severe or serious. Therefore, the outcome was assigned to the category of non-serious/non-severe symptoms or late complications.

Discontinuation due to AEs

It cannot be inferred from the information in Module 4 A whether the majority of AEs that resulted in treatment discontinuation were serious or severe (CTCAE - grade ≥ 3). Therefore, the outcome "discontinuation due to AEs" was assigned to the category of non-serious/non-severe side effects.

Table 18: Extent of added benefit at outcome level: olaparib + bevacizumab vs. bevacizumab (multipage table)

Outcome category **outcome** **effect modifier** **Subgroup**	**Olaparib + bevacizumab vs. bevacizumab** **median time to event (months) or mean value of the mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival		
Result of the first-line therapy		
NED (PDS)[c] + NED/CR (chemotherapy)[e]	Median: ND HR: 0.36 [0.19; 0.68] p = 0.002 probability: "indication"	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
NED/CR (IDS)[d] + PR[f]	Median: ND HR: 1.08 [0.63; 1.85] p = 0.778	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30 symptom scales)		
Fatigue	Median: 5.6 vs. 5.7 HR: 1.10 [0.86; 1.41] p = 0.482	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: 5.8 vs. 19.2 HR: 1.81 [1.37; 2.42] HR: 0.55 [0.41; 0.73][g] p = < 0.001 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ lesser benefit, extent: "considerable"
Pain	Median: 5.8 vs. 5.6 HR: 0.92 [0.72; 1.19] p = 0.551	Lesser benefit/added benefit not proven
Dyspnoea	Median: 20.7 vs. 18.7 HR: 0.92 [0.68; 1.25] p = 0.580	Lesser benefit/added benefit not proven
Insomnia	Median: 11.3 vs. 8.3 HR: 0.73 [0.56; 0.95] p = 0.019	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[h]
Appetite loss	Median: 13.6 vs. 22.3 HR: 1.42 [1.06; 1.92] HR: 0.70 [0.52; 0.94][g] p = 0.023	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[h]

Table 18: Extent of added benefit at outcome level: olaparib + bevacizumab vs. bevacizumab (multipage table)

Outcome category **outcome** **effect modifier** **Subgroup**	**Olaparib + bevacizumab vs. bevacizumab** **median time to event (months) or mean value of the mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Constipation	Median: 19.9 vs. 19.7 HR: 1.03 [0.77; 1.39] p = 0.831	Lesser benefit/added benefit not proven
Diarrhoea	Median: 24.0 vs. 23.5 HR: 1.15 [0.84; 1.58] p = 0.409	Lesser benefit/added benefit not proven
Symptoms (EORTC QLQ-OV28 symptom scales)		
Abdominal/gastrointestinal symptoms	Median: 11.1 vs. 8.3 HR: 0.88 [0.68; 1.15] p = 0.351	Lesser benefit/added benefit not proven
Peripheral neuropathy	Median: 25.3 vs. 23 HR: 0.93 [0.68; 1.29] p = 0.654	Lesser benefit/added benefit not proven
Hormonal symptoms	Median: 19.1 vs. 11.3 HR: 0.75 [0.56; 0.996] p = 0.046	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[h]
Side effects of chemotherapy	Median: 17.9 vs. 11.1 HR: 0.75 [0.57; 0.997] p = 0.045	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[h]
Individual questions	Median: 21.9 vs. 19.4 HR: 1.01 [0.75; 1.38] p = 0.954	Lesser benefit/added benefit not proven
Sexual functioning	No usable data	Lesser benefit/added benefit not proven
Health status		
EQ-5D VAS	mean: 1.5 vs. 1.4 MD: 0.07 [-2.60; 2.74] p = 0.959	Lesser benefit/added benefit not proven

Table 18: Extent of added benefit at outcome level: olaparib + bevacizumab vs. bevacizumab (multipage table)

Outcome category **outcome** **effect modifier** **Subgroup**	**Olaparib + bevacizumab vs. bevacizumab** **median time to event (months) or mean value of the mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
EORTC QLQ-C30 – functional scales		
Global health status		
Age		
< 65 years	Median: 15.2 vs. 16.2 HR: 0.97 [0.70; 1.34] p = 0.843	Lesser benefit/added benefit not proven
≥ 65 years	Median: 22.1 vs. 9.9 HR: 0.51 [0.31; 0.86] p = 0.013 probability: "indication"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
Physical functioning	Median: 20 vs. 16.4 HR: 0.85 [0.64; 1.14] p = 0.279	Lesser benefit/added benefit not proven
Role functioning	Median: 8.4 vs. 9.3 HR: 1.11 [0.85; 1.46] p = 0.450	Lesser benefit/added benefit not proven
Cognitive functioning	Median: 11.1 vs. 8.5 HR: 0.91 [0.70; 1.19] p = 0.484	Lesser benefit/added benefit not proven
Emotional functioning	Median: 13.8 vs. 11.1 HR: 0.93 [0.71; 1.22] p = 0.571	Lesser benefit/added benefit not proven
Social functioning	Median: 13.5 vs. 11.3 HR: 0.91 [0.69; 1.20] p = 0.471	Lesser benefit/added benefit not proven
EORTC QLQ-OV28		
Body image	Median: 21.9 vs. 18.7 HR: 0.93 [0.70; 1.26] p = 0.638	Lesser benefit/added benefit not proven

Table 18: Extent of added benefit at outcome level: olaparib + bevacizumab vs. bevacizumab (multipage table)

Outcome category **outcome** **effect modifier** **Subgroup**	**Olaparib + bevacizumab vs. bevacizumab** **median time to event (months) or mean value of the mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Attitude regarding disease/treatment		
Result of the first-line therapy		
NED (PDS)[c]	Median: NA vs. 11.3 HR: 0.60 [0.36; 1.01] p = 0.053	Lesser benefit/added benefit not proven
NED/CR (IDS)[d]	Median: 5.7 vs. NA HR: 2.34 [1.34; 4.33] HR: 0.43 [0.23; 0.746]g p = 0.002 probability: “indication”	Outcome category: health-related quality of life CIu < 0.75, risk ≥ 5% lesser benefit, extent: “major”
NED/CR (chemotherapy)[e]	Median: 8.3 vs. 12.6 HR: 1.18 [0.59; 2.46] p = 0.646	Lesser benefit/added benefit not proven
PR[f]	Median: 12.1 vs. 17.0 HR: 1.03 [0.55; 2.04] p = 0.931	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: NA vs. NA HR: 0.75 [0.52; 1.10] p = 0.133	Lesser benefit/added benefit not proven
Severe AEs	Median: 8.6 vs. 16.7 HR: 1.20 [0.90; 1.63] p = 0.221	Lesser benefit/added benefit not proven
Discontinuation due to AEs	Median: NA vs. NA HR: 3.14 [1.57; 7.18] HR: 0.32 [0.14; 0.64]g p = 0.002 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Myelodysplastic syndrome and acute myeloid leukaemia (AEs)	Median: NA vs. NA HR: 0.54 [0.06; 4.51] p = 0.531	Lesser benefit/added benefit not proven
Pneumonitis (AEs)	Median: NA vs. NA HR: NC p = 0.195	Lesser benefit/added benefit not proven

Table 18: Extent of added benefit at outcome level: olaparib + bevacizumab vs. bevacizumab (multipage table)

Outcome category **outcome** **effect modifier** **Subgroup**	**Olaparib + bevacizumab vs. bevacizumab** **median time to event (months) or mean value of the mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Nausea (AEs)	Median: 2.9 vs. NA HR: 3.10 [2.14; 4.63] HR: 0.32 [0.22; 0.47][g] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Anaemia (severe AEs)	Median: NA vs. NA HR: 27.79 [6.08; 492.43] HR: 0.04 [0.00; 0.16][g] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Fatigue and asthenia (severe AEs)	Median: NA vs. NA HR: 4.54 [1.29; 28.70] HR: 0.22 [0.03; 0.78][g] p = 0.027 probability: "indication"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Hypertension (severe AEs)	Median: NA vs. NA HR: 0.52 [0.34; 0.79] p = 0.002 probability: "indication"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"

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. Patients without detectable tumour after primary surgery.
d. Patients without detectable tumour/with complete response after interval surgery.
e. Patients without detectable tumour/with complete response after chemotherapy.
f. Patients with partial response.
g. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
h. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CR: complete response; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; IDS: interval surgery; MD: mean difference; NA: not achieved; NC: not calculable; ND: no data; NED: no detectable tumour; PDS: primary debulking surgery; PR: partial response; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OV28: Quality of Life Questionnaire-Ovarian Cancer 28; SAE: serious adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 19 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of olaparib + bevacizumab in comparison with bevacizumab

Positive effects	**Negative effects**
Mortality ▪ overall survival ▫ for patients without detectable tumour after primary surgery and patients without detectable tumour/with complete response following chemotherapy ▫ indication of an added benefit – extent: “major“	
Serious/severe side effects ▪ severe hypertension ▪ indication of lesser harm – extent “considerable”	Serious/severe side effects ▪ severe anaemia: indication of greater harm – extent: “major” ▪ severe fatigue and asthenia: indication of greater harm – extent: “considerable”
Health-related quality of life ▪ global health status ▫ for patients ≥ 65 years ▫ indication of an added benefit – extent: “considerable”	▪ Health-related quality of life: ▪ attitude regarding disease/treatment ▫ for patients without detectable tumour/with complete response after interval surgery ▫ indication of lesser benefit – extent: “major”
▪	Non-serious/non-severe symptoms ▪ nausea and vomiting: indication of lesser benefit – extent: “considerable”
	Non-serious/non-severe side effects ▪ nausea: indication of greater harm – extent “considerable” ▪ discontinuation due to AEs: hint of greater harm – extent: “considerable”
AE: adverse event	

The overall consideration showed both positive and negative effects of olaparib + bevacizumab in comparison with bevacizumab. An additional effect modification by the characteristic “result of the first-line treatment” was shown for the outcome “overall survival”. For this reason, the positive and negative effects are assessed below separately for patients without detectable tumour after primary surgery (NED [PDS]) and patients without detectable tumour/with complete response after chemotherapy (NED/CR [chemotherapy]) as well as for patients without detectable tumour/with complete response after interval surgery (IDS) and patients with partial response (PR).

For patients without detectable tumour after primary surgery (NED [PDS]) and patients without detectable tumour/with complete response after chemotherapy (NED/CR [chemotherapy]), this

resulted in an indication of major added benefit of olaparib + bevacizumab in comparison with bevacizumab for the outcome "overall survival". Moreover, there is a further indication of a positive effect with the extent "considerable" in the category of serious/severe side effects. In contrast, there are several indications of negative effects with considerable or major extents in the outcome categories "non-serious/non-severe symptoms" and "serious/severe side effects" as well as "non-serious/non-severe side effects". However, the negative effects did not completely call into question the positive effects. Overall, this resulted in an indication of considerable added benefit of olaparib + bevacizumab in comparison with the ACT bevacizumab for patients without detectable tumour after primary surgery (NED [PDS]) and patients without detectable tumour/with complete response after chemotherapy (NED/CR [chemotherapy]).

For patients without detectable tumour/with complete response after IDS and patients with PR, there was an indication of lesser harm with the extent "considerable" on the side of the positive effects in the category "serious/severe side effects". In contrast, there are several indications of negative effects with considerable or major extents in the outcome categories "non-serious/non-severe symptoms" and "serious/severe side effects" as well as "non-serious/non-severe side effects". For patients without detectable tumour/with complete response after IDS, there is also a negative effect with the extent "considerable" in the outcome category "health-related quality of life". Overall, this resulted in an indication of lesser benefit of olaparib + bevacizumab in comparison with the ACT bevacizumab for patients without detectable tumour/with complete response after IDS and patients with PR.

Table 20 summarizes the result of the assessment of the added benefit of olaparib + bevacizumab in comparison with the ACT.

Table 20: Olaparib + bevacizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit[b]**
Maintenance therapy of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian cancer[c] who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with HRD positive status[d].	Continuation of the treatment with bevacizumab started with first-line platinum-based chemotherapy	▪ Patients without detectable tumour after primary surgery and patients without detectable tumour/with complete response following chemotherapy: indication of considerable added benefit
		▪ Patients without detectable tumour after interval surgery and patients with partial response: indication of lesser benefit

a. Presentation of the respective ACT specified by the G-BA.
b. The PAOLA-1 study included only patients with ECOG PS of 0 or 1 as well as only few patients with non-serous tumour histology (5.6% in the relevant subpopulation). It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or patients with non-serous tumour histology.
c. This term also includes fallopian tube and primary peritoneal cancer.
d. A positive HRD status is defined by either BRCA1/2-mutation and/or genomic instability.

ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; G-BA: Federal Joint Committee.; HRD: homologous recombination deficiency

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

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.

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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