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

Benefit assessment according to §35a SGB V[1] (assessment after expiry of the decision)

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	adverse event of special interest
BRCA	breast cancer 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 (International Federation of Gynaecology and Obstetrics)
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HRD	homologous recombination deficiency
IDS	interval debulking surgery
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NED	no evidence of disease
PDS	primary debulking 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
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
tBRCA	tumour breast cancer gene
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug olaparib (in combination with 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 31 October 2022.

For the drug to be assessed, the company had already submitted a dossier for a previous benefit assessment. The dossier was sent to IQWiG on 1 December 2020. In this procedure, a time limit was imposed on the G-BA's decision dated 3 June 2021 until 1 October 2022; the time limit was then extended until 1 December 2022 and subsequently shortened to 1 November 2022.

For the renewed benefit assessment of olaparib (in combination with bevacizumab) after expiration of the time limit, the dossier was to include the results from the final analysis of overall survival as well as all other patient-relevant outcomes from the PAOLA-1 study which were used to demonstrate an added benefit.

Research question

The aim of the present report is to assess the added benefit of olaparib in combination with bevacizumab (hereinafter referred to as olaparib + bevacizumab) in comparison with bevacizumab as the appropriate comparator therapy (ACT) for the 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. Positive HRD status is defined as either a mutation in breast cancer genes 1 or 2 (BRCA 1/2) and/or genomic instability.

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

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

Therapeutic indication	**ACT[a]**
Maintenance treatment 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 bevacizumab treatment started with first-line platinum-based chemotherapy
a. Presented is the ACT specified by the G-BA. b. This term also includes fallopian tube and primary peritoneal cancer. c. Positive HRD status is defined as BRCA 1/2-mutation and/or genomic instability. ACT: appropriate comparator therapy; BRCA: breast cancer 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 germline or somatic cells.

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

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

Study pool and study design

PAOLA-1 is a double-blind, randomized, parallel-group study comparing 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 or taxane-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, with at least the last 3 cycles having been 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. Moreover, side effects from prior chemotherapy had to have subsided to Common Terminology Criteria for Adverse Events (CTCAE) grade ≤ 1.

A total of 806 patients were allocated by stratified randomization in a 2:1 ratio to either up to 2 years of maintenance therapy with olaparib in combination with continued bevacizumab therapy or to continued bevacizumab therapy alone. Stratification characteristics were the mutation status of the tumour's BRCA genes (tBRCA [mutated vs. non-mutated]) and the

result of first-line therapy. For the result of first-line therapy, 4 possible results were distinguished:

- NED (PDS): patients with no evidence of disease (NED) after primary debulking surgery (PDS)
- NED/CR (IDS): patients with NED / with complete response (CR) after interval debulking surgery (IDS)
- NED/CR (chemo): patients with NED / with CR after chemotherapy
- PR: patients with partial response (PR)

During first-line therapy and until randomization, patients had to exhibit no signs of progression of the underlying disease. Treatment with olaparib and bevacizumab was performed according to approval.

The primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival as well as outcomes on morbidity, health-related quality of life, and side effects.

Relevant subpopulation

In accordance with approval, only the subpopulation of patients whose cancer is associated with an HRD-positive status is taken into account in the present benefit assessment. HRD-positive status is defined as BRCA1/2-mutation and/or genomic instability. This subpopulation is relevant for the present benefit assessment and comprises 255 patients in the intervention arm receiving olaparib + bevacizumab and 132 patients in the comparator arm receiving placebo + bevacizumab.

Data cutoffs

Data are available on 4 data cutoffs:

- 1st data cutoff of 22 March 2019: prespecified final PFS analysis after 458 PFS events
- 2nd data cutoff of 30 September 2019: regulatory data cut-off
- 3rd data cutoff of 22 March 2020: prespecified interim analysis for overall survival
- 4th data cutoff of 22 March 2022: prespecified final analysis for overall survival

The company's dossier presents results from the 3rd data cutoff for the patient-relevant outcomes of the categories of morbidity, health-related quality of life, and side effects because at this data cutoff, observation was already complete for all patients. For the outcomes of overall survival and adverse events of special interest (AESIs), the company presents results from the final data cutoff dated 22 March 2022 because these outcomes were

followed up until death or until the final analysis. The data presented by the company from the 22 March 2020 and 22 March 2022 data cutoffs serve as the basis or the benefit assessment.

Risk of bias

For the study, the risk of bias across outcomes was rated as low.

The risk of bias for overall survival, symptoms, health status, health-related quality of life, the AESIs of myelodysplastic syndrome and acute myeloid leukaemia as well as the outcome of discontinuation due to adverse events (AEs) is likewise rated as low. Due to incomplete observations for potentially informative reasons, the risk of bias for the outcomes of serious adverse events (SAEs), severe AEs, and other specific AEs is rated as high. Despite high risk of bias, the results for the specific AEs of nausea (Preferred Term [PT], AEs) and anaemia (PT, severe AEs), can be assumed to have a high certainty of conclusions due to the size of the effect found already at an early time in the study.

The certainty of results for the outcome of discontinuation due to AEs is limited despite a low risk of bias.

Results

Mortality

Overall survival

A statistically significant difference in favour of olaparib + bevacizumab in comparison with placebo + bevacizumab was shown for the outcome of overall survival. However, there is an effect modification by the characteristic of result of first-line therapy (composite subgroups NED [PDS] + NED / CR [chemo] and NED/CR [IDS] + PR). For patients with NED after PDS (NED [PDS]) and patients with NED / with complete response after chemotherapy (NED/CR [chemo]), this results in an indication of added benefit of olaparib + bevacizumab in comparison with bevacizumab. For patients in the NED/CR (IDS) and PR subgroups, this results in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven for these patients.

Morbidity

Symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 [EORTC QLQ-C30])

Nausea and vomiting

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

Insomnia

A statistically significant difference in favour of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcome of insomnia. However, the extent of the effect for this outcome of the category non-serious/non-severe symptoms / late complications was no more than marginal. This results in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven.

Appetite loss

A statistically significant difference to the disadvantage of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcome of appetite loss. However, the extent of the effect for this outcome of the category non-serious/non-severe symptoms / late complications was no more than marginal. This results in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven.

Fatigue, pain, dyspnoea, constipation, and diarrhoea

No statistically significant difference between treatment groups was shown for any of the outcomes of fatigue, pain, dyspnoea, constipation, or diarrhoea. In each case, this results in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven.

Symptoms (EORTC Quality of Life Questionnaire – Ovarian Cancer 28 [EORTC QLQ-OV28])

Hormonal symptoms and side effects of chemotherapy

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

Abdominal/gastrointestinal symptoms, peripheral neuropathy, and individual questions

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

Health status (European Quality of Life Questionnaire – 5 Dimensions [EQ-5D] visual analogue scale [VAS])

There was no statistically significant difference between the treatment groups for the outcome of health status. This results 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

EORTC QLQ-C30

Global health status

No statistically significant difference between treatment arms was shown for the outcome of global health status, but there was an effect modification by the characteristic of age. For patients aged ≥ 65 years, this results in an indication of added benefit of olaparib + bevacizumab in comparison with bevacizumab. For patients aged < 65 years, there is no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven for these patients.

Physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning

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

EORTC QLQ-OV28

Sexual functioning

No usable data are available for the outcome of sexual functioning. This results in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven.

Body image

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

Attitude regarding disease/treatment

No statistically significant difference between treatment groups was shown for the outcome of attitude regarding disease/treatment, but there was an effect modification by the characteristic of result of the first-line therapy. For patients in the NED (PDS), NED/CR

(chemo), and PR subgroups, there was no hint of 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 results in an indication of lesser benefit of olaparib + bevacizumab in comparison with bevacizumab.

Side effects

SAEs and severe AEs

No statistically significant difference between treatment groups was shown for the outcomes of SAEs or severe AEs. In each case, this results in no hint of greater or lesser harm from olaparib + bevacizumab in comparison with bevacizumab; 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 of discontinuation due to AEs. This results in a hint of greater harm from olaparib + bevacizumab in comparison with bevacizumab.

Specific AEs

Myelodysplastic syndrome and acute myeloid leukaemia (SAEs each)

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

Pneumonitis

No usable data were available for the outcome of pneumonitis. This results in no hint of greater or lesser harm from olaparib + bevacizumab in comparison with bevacizumab; greater or lesser harm is therefore not proven.

Nausea (AEs) and anaemia (severe AEs)

A statistically significant difference to the disadvantage of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcomes of nausea (AEs) and anaemia (severe AEs). For each of them, this results in an indication of greater harm from olaparib + bevacizumab in comparison with bevacizumab.

Fatigue (severe AEs)

A statistically significant difference to the disadvantage of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcome of fatigue (severe AEs). This results in a hint of greater harm from olaparib + bevacizumab in comparison with bevacizumab.

Hypertension (severe AEs)

A statistically significant difference in favour of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcome of hypertension (severe AEs). This results in a hint 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 presented results, the probability and extent of added benefit of the drug olaparib (in combination with bevacizumab) in comparison with the ACT are assessed as follows:

The overall analysis showed both favourable and unfavourable effects of olaparib + bevacizumab in comparison with bevacizumab. Only for overall survival are the observed effects based on the entire observation period. For morbidity, health-related quality of life, and side effects, in contrast, they are based only on the shortened period (side effects: until treatment end [plus 30 days]; morbidity and health-related quality of life: up to 2 years after study start).

For the outcome of overall survival, an effect modification by the characteristic of result of first-line treatment was shown. For this reason, favourable and unfavourable effects are weighed separately for the subgroups of (a) patients with NED after PDS (NED [PDS]) and patients with NED or with complete response after chemotherapy (NED/CR [chemotherapy]) and (b) patients with NED or with complete response after IDS and patients with PR.

For patients with NED after PDS (NED [PDS]) and patients with NED or with complete response after chemotherapy (NED/CR [chemo]), this results in an indication of major added benefit for the outcome of overall survival. Furthermore, a hint of lesser harm of major extent was found in the category of serious/severe side effects. In contrast, several hints or indications of unfavourable effects with considerable to major or nonquantifiable extents were found in the outcome categories of non-serious/non-severe symptoms and serious/severe side effects as well as non-serious/non-severe side effects. However, the unfavourable effects did not completely call into question the favourable effects. Overall, this results in an indication of considerable added benefit of olaparib + bevacizumab in comparison with the ACT of

[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].

bevacizumab for patients with NED after PDS (NED [PDS]) and patients with NED or with complete response after chemotherapy (NED/CR [chemo]).

For patients with NED or with complete response after IDS and patients with PR, there was a hint of lesser harm with the extent of major for the favourable effects in the category of serious/severe side effects. This is in contrast to several hints or indications of unfavourable effects of considerable to major or nonquantifiable extents in the outcome categories of health-related quality of life (only for patients with NED / with complete response after interval surgery), non-serious/non-severe symptoms and serious/severe side effects as well as non-serious/non-severe side effects. Overall, this results in an indication of lesser benefit of olaparib + bevacizumab in comparison with the ACT of bevacizumab for patients with NED / with complete response after IDS and patients with PR.

Table 3 summarizes the probability and extent of 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 bevacizumab treatment started with first-line platinum-based chemotherapy	▪ Patients with NED after PDS and patients with NED / with CR after chemotherapy: indication of considerable added benefit
		▪ Patients with NED after IDS and patients with PR: indication of lesser benefit

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

ACT: appropriate comparator therapy; BRCA: breast cancer gene; CR: complete response; 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; IDS: interval debulking surgery; NED: no evidence of disease; PR: partial response

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

I 2 Research question

The aim of the present report is to assess the added benefit of olaparib in combination with bevacizumab (hereinafter referred to as olaparib + bevacizumab) in comparison with bevacizumab as the ACT for the 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 homologous recombination deficiency (HRD) positive status. Positive HRD status is defined as either a mutation in breast cancer genes 1 or 2 (BRCA 1/2) and/or genomic instability.

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

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

Therapeutic indication	**ACT**[a]
Maintenance treatment 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 bevacizumab treatment started with first-line platinum-based chemotherapy
a. Presented is the ACT specified by the G-BA. b. This term also includes fallopian tube and primary peritoneal cancer. c. Positive HRD status is defined as BRCA 1/2-mutation and/or genomic instability. ACT: appropriate comparator therapy; BRCA: breast cancer 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 germline or somatic cells.

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

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 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: 10 October 2022)
- bibliographical literature search on olaparib + bevacizumab (last search on 10 August 2022)
- search in trial registries / trial results databases for studies on olaparib + bevacizumab (last search on 11 August 2022)
- search on the G-BA website for olaparib + bevacizumab (last search on 11 August 2022)

To check the completeness of the study pool:

- search in trial registries for studies on olaparib + bevacizumab (last search on 15 November 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following table was disregarded in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: olaparib + bevacizumab versus 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 and other sources[c] yes/no [citation])
GINECO-OV125b (PAOLA-1[d])	Yes	No[e]	Yes	Yes [3-6]	Yes [7-10]	Yes [11-13]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.
e. The sponsor of the study is Arcagy Research. The company is financially involved.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

I 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 versus 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[l] Data cutoffs: 22/03/2019[m] 30/09/2019[n] 22/03/2020[o] 22/03/2022[p]	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: olaparib + bevacizumab versus 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 include only information on relevant available outcomes for this benefit assessment.
b. ECOG-PS ≤ 1 and normal bone marrow and organ function.
c. According to FIGO 1988 staging [13]; corresponds to stages III to IV of the current FIGO classification [14].
d. Or other epithelial, non-mucinous ovarian cancer in the presence of a germline BRCA 1 or BRCA 2 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. Only in case of interval surgery were patients included who received only 2 cycles of bevacizumab in combination with the last 3 cycles of platinum-based chemotherapy.
f. Patients whose tumour is associated with a positive HRD status. HRD-positive status is defined as BRCA1/2-mutation and/or genomic instability. Genomic instability is defined as genomic instability score ≥ 42 according to Myriad [15].
g. Patients were to be randomized within 3 to 9 weeks after the last chemotherapy (last dose is 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 investigator's opinion, drew further benefit from continued therapy were allowed to receive further treatment for 2 years or after progression.
i. Including the doses administered during pretreatment.
j. Outcome-specific data are described in Table 13.
k. Inclusion of the first patient in 07/2015. Inclusion of the last patient in 09/2017.
l. According to the company, the study has not yet been formally completed.
m. Final PFS analysis (planned to occur after 458 PFS events).
n. Regulatory data cut-off.
o. Final PFS2 analysis (planned to occur after 411 PFS2 events or no later than 1 year after the final PFS analysis), interim analysis for overall survival; for the outcomes of the categories of morbidity, health-related quality of life, and side effects (except AESIs), the observation had already been completed at this data cutoff. For these outcomes, the present benefit assessment uses this data cutoff.
p. Final analysis of overall survival (planned to occur from about 60% data maturity or no later than 3 years after the final PFS analysis); in the present benefit assessment, relevant data cutoff for the outcomes of overall survival and specific AEs surveyed in the study as AESIs.

AE: adverse event; AESI: AEs of special interest; BRCA: breast cancer 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 versus 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 i.v. 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 i.v. every 3 weeks for a total of 15 months / 22 cycles[b]
	Dose adjustments, treatment interruptions, and treatment discontinuation due to toxicity were allowed[c]	
	Prior treatment **Required:** ▪ 6–9 cycles of platinum-based/taxane-based chemotherapy[d] ▪ ≥ 3 cycles of bevacizumab together with the last 3 cycles of platinum-based chemotherapy[e] **Disallowed** ▪ Any prior treatment with a PARP inhibitor, including olaparib ▪ Treatment with an investigational medicinal product during first-line chemotherapy	
	Concomitant treatment **Allowed** ▪ Any medication, with the exception of the cited disallowed 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 **Disallowed** ▪ 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 they missed the scheduled dosing time, participants were allowed to take a delayed dose no later than 2 hours after the scheduled time.
b. Including the doses administered during prior treatment.
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 had to 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.

CTCAE: Common Terminology Criteria for Adverse Events; CYP: cytochrome P450; G-CSF: granulocyte colony-stimulating factor; IDS: interval debulking surgery; i.v.: 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 comparing 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 or taxane-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 which 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 prior chemotherapy had to have subsided to CTCAE grade ≤ 1.

A total of 806 patients were allocated by stratified randomization in a 2:1 ratio to either up to 2 years of olaparib maintenance therapy in combination with continuation of the bevacizumab therapy or to continuation of bevacizumab treatment alone. Stratification characteristics were the mutation status of the tumour's BRCA genes (tBRCA [mutated versus non-mutated]) and the result of first-line treatment. For the result of first-line therapy, 4 possible results were distinguished:

- NED (PDS): patients with NED after PDS
- NED/CR (IDS): patients with NED/CR after IDS
- NED/CR (chemo): patients with NED/CR 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 approval, consisted of treatment with carboplatin and paclitaxel in almost all patients. Treatment with olaparib and bevacizumab was performed as per approval [16,17]. 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 first-line treatment). Moreover, patients in the intervention arm received 300 mg olaparib twice daily, while 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 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 investigator's opinion, the patient continued to benefit from the treatment. The study protocol did not specify subsequent therapies to be administered after termination of the study medication; therefore, the investigator in consultation with the patient was free to specify any medical intervention (see Table 11). The study protocol did not provide for unblinding of patients and investigators for this purpose.

The primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival as well as morbidity, health-related quality of life, and side effects outcomes.

Relevant subpopulation

As per approval, only the subpopulation of patients whose cancer is associated with an HRD-positive status is taken into account for the present benefit assessment. HRD-positive status is defined as BRCA1/2-mutation and/or genomic instability. The PAOLA-1 study determined the genomic instability score (GIS) in tissue samples from all patients using the Myriad MyChoice HRD plus assay [15]. 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 intervention arm receiving olaparib + bevacizumab and 132 patients in the comparator arm receiving placebo + bevacizumab.

Data cutoffs

Data are available on 4 data cutoffs:

- 1st data cutoff of 22 March 2019: prespecified final PFS analysis after 458 PFS events
- 2nd data cutoff of 30 September 2019: regulatory data cut-off
- 3rd data cutoff of 22 March 2020: prespecified interim analysis for overall survival
- 4th data cutoff of 22 March 2022: prespecified final analysis for overall survival

The company's dossier presents results from the 3rd data cutoff for the patient-relevant outcomes from the categories of morbidity, health-related quality of life, and side effects (except for the results on adverse events of special interest [AESI]) because at this data cutoff, the observation was already complete for all patients. For the outcomes of overall survival and AESIs, the company presents results for the final data cutoff dated 22 March 2022 because these outcomes were followed up until death or until the final analysis. The data from the 22 March 2020 and 22 March 2022 cutoffs serve as the basis or the benefit assessment.

Table 8 shows the prespecified duration of participant follow-up observation for the individual outcomes.

Table 8: Prespecified duration of follow-up observation – RCT, direct comparison: olaparib + bevacizumab versus placebo + bevacizumab

Study **Outcome category** **Outcome**	**Predefined follow-up observation**
PAOLA-1	
Mortality	
Overall survival	Until death or final analysis
Morbidity	
EORTC QLQ-C30	For 2 years after the start of the study
EORTC QLQ-OV28	For 2 years after the start of the study
EQ-5D VAS	For 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
EORTC QLQ-OV28	For 2 years after the start of the study
Side effects	
AEs/SAEs/severe AEs	For 30 days after the last dose of the study medication
AESIs[a]	Until death or final analysis

a. Specific AEs predefined in the study as AESIs were to be followed up until death or until the final analysis. According to Module 4A, the following AEs were recorded as AESIs: myelodysplastic syndrome, acute myeloid leukaemia, secondary neoplasms and pneumonitis, anaemia, neutropoenia, thrombocytopoenia, nausea, vomiting, fatigue and asthenia, hypertension, proteinuria, GI perforations, abscess and fistulas, complications of wound healing, bleeding, arterial thromboembolism, venous thromboembolism, posterior reversible encephalopathy syndrome, congestive heart failure, non-GI fistulas, and abscesses. According to the study report, however, systematic follow-up until death or final analysis was conducted only for the following AESIs: myelodysplastic syndrome, acute myeloid leukaemia, secondary neoplasms, and pneumonitis. As per study report, the remaining AESIs were systematically followed up only for 30 days after the last dose of the study medication (see Section I 4.1).

AE: adverse event; AESI: adverse event of special interest; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 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 of AEs, SAEs, and severe AEs are systematically shortened because they were recorded only during treatment with the study medication (plus 30 days). While morbidity and health-related quality of life outcomes were recorded for up to 2 years after study start, the observation periods were shortened for them as well. However, drawing a reliable conclusion on the total study period or the time until patient death would require recording these outcomes throughout the total period, as was done for survival.

In addition, the PAOLA-1 study required for predefined AESIs to be followed up until death or final analysis.

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

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: olaparib + bevacizumab versus 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)
Prior surgical therapy[c]		
patients without surgery, n (%)	10 (3.9)	8 (6.1)
prior surgery, n (%)	245 (96.1)	124 (93.9)
with remaining macroscopic tumour tissue	79 (32.2)[d]	44 (35.5)[d]

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: olaparib + bevacizumab versus placebo + bevacizumab (multipage table)

Study **Characteristic** **Category**	**Olaparib + bevacizumab** **N[a] = 255**	**Placebo + bevacizumab** **N[a] = 132**
without remaining macroscopic tumour tissue	166 (67.8)[d]	80 (64.5)[d]
Prior primary debulking surgery (PDS), n (%)	146 (57.3)	79 (59.8)
with remaining macroscopic tumour tissue	55 (37.7)[d]	31 (39.2)[d]
without remaining macroscopic tumour tissue	91 (62.3)[d]	48 (60.8)[d]
Prior interval surgery (IDS), n (%)	99 (38.8)	45 (34.1)
with remaining macroscopic tumour tissue	24 (24.2)[d]	13 (28.9)[d]
without remaining macroscopic tumour tissue	75 (75.8)[d]	32 (71.1)[d]
Cycles of platinum-containing first-line chemotherapy, n (%)		
≤ 6 cycles	177 (69.4)[e]	92 (69.7)[e]
7–8 cycles	60 (23.5)[e]	30 (22.7)[e]
≥ 9 cycles	18 (7.1)[e]	10 (7.6)[e]
Cycles with bevacizumab in first-line chemotherapy, n (%)		
≤ 3 cycles[f]	44 (17.3)[e]	21 (15.9)[e]
4–5 cycles	103 (40.4)[e]	43 (32.6)[e]
≥ 6 cycles[g]	108 (42.4)	68 (51.5)
Result of the first-line therapy before randomization, n (%)		
NED (PDS)[h]	92 (36.1)	48 (36.4)
NED/CR (IDS)[i]	74 (29.0)	38 (28.8)
NED/CR (chemo)[j]	40 (15.7)	20 (15.2)
PR[k]	49 (19.2)	26 (19.7)
Treatment discontinuation, n (%)	120 (47.1)[l]	94 (71.8)[l]
Study discontinuation, n (%)	104 (40.8)[e,m]	71 (53.8)[e,m]

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: olaparib + bevacizumab versus placebo + bevacizumab (multipage table)

Study Characteristic Category	Olaparib + bevacizumab N[a] = 255	Placebo + bevacizumab N[a] = 132

a. Number of randomized patients. Values which are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. According to FIGO classification of 1988 [13]
c. Module 4A and the numbers presented by the company for benefit assessment A20-111 show discrepant information on prior surgical therapy. According to Module 4A, 1 intervention arm patient was counted under prior PDS despite being previously counted under prior IDS. In the control arm, 1 patient was counted under PDS with remaining macroscopic tumour tissue who was previously in the category of PDS without remaining macroscopic tumour tissue.
d. The presented percentages are based on the total number of patients with prior surgery or prior PDS or prior IDS.
e. Institute's calculation.
f. According to the study protocol, patients had to have received at least 3 cycles of bevacizumab together with the last 3 cycles of platinum-based chemotherapy. Patients with IDS were to have received at least 2 cycles of bevacizumab in combination with the last 3 cycles of platinum-based chemotherapy. Module 5 shows that 6 patients (2%) in the intervention arm and 6 patients (5%) in the control arm received ≤ 1 cycle of the combination therapy.
g. The bevacizumab SPC states that, in this therapeutic indication, the drug may be administered for up to 6 cycles in addition to carboplatin and paclitaxel [17]. Module 5 shows that 3 patients (1%) in the intervention arm and 3 patients (2%) in the control arm received more than 6 cycles in combination with carboplatin and paclitaxel.
h. Patients with no evidence of disease after primary debulking surgery.
i. Patients with no evidence of disease / with complete response after interval surgery.
j. Patients with no evidence of disease / with complete response after chemotherapy.
k. Patients with partial response.
l. Common reasons for treatment discontinuation in the intervention arm versus the control arm were disease progression (23% vs. 60%) and AEs (19% vs. 5%).
m. Common reasons for study discontinuation in the intervention arm vs. the control arm were: patient death (37% vs. 52%), withdrawal of consent (2% vs. 2%) and loss to follow-up (2% vs. 0%).

AE: adverse event; BRCA: breast cancer gene; chemo: chemotherapy; CR: complete response; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; IDS: interval debulking surgery; n: number of patients in the category; N: number of randomized patients; NED: no evidence of disease; PDS: primary debulking surgery; PR: partial response; RCT: randomized controlled trial; SD: standard deviation; tBRCA: tumour BRCA

The patient characteristics are largely comparable between the 2 treatment arms. The mean participant age was 58 years, and at 96%, the majority of participants were from Europe. A total of 75% of participants were in good general health, corresponding to an ECOG-PS of 0. The majority of participants were diagnosed with a primary tumour localization in the ovary (87%) and serous tumour histology (95%). Just over 60% of participants were classified as FIGO stage IIIC at diagnosis, but it should be noted that the study protocol specified the 1988 FIGO classification [13]. 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 [14]. All carcinomas of the participants in the present relevant subpopulation were associated with a positive HRD status, with about half of participants exhibiting pathogenic BRCA mutation in the tumour. Prior to platinum-containing first-line chemotherapy, about 58% of participants underwent PDS and 37% had IDS. A total of 41% of participants in the intervention arm and 54% of those in the control arm discontinued the study. In both study arms, the most common reason for study discontinuation was patient death (37% in the intervention arm and 52% in the comparator arm).

Since the study included no patients with ECOG-PS ≥ 2 and only few patients with non-serous tumour histology, 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 patients' median treatment duration and the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: olaparib + bevacizumab versus 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; 22 March 2022 data cutoff		
median [min; max]	58.7 [1.4; 77.8]	55.4 [0.3; 76.9]
Morbidity (EORTC QLQ-C30, -OV28, EQ-5D VAS), 22 March 2020 data cutoff		
median [min; max]	24.2 [0; 52.5]	24.1 [0; 41.2]
Health-related quality of life (EORTC QLQ-C30, -OV28), 22 March 2020 data cutoff		
median [min; max]	24.2 [0; 52.5]	24.1 [0; 41.2]
Side effects[a] (AEs/SAEs/severe AEs), 22 March 2020 data cutoff		
median [min; max]	24.8 [1.2; 36.8]	17.8 [1.1; 26.3]
Side effects[a] (AESIs[c]), 22 March 2022 data cutoff		
median [min; max]	58.7 [1.2; 77.8][d]	55.2 [0.7; 76.9][d]

a. Number of analysed patients, olaparib + bevacizumab vs. placebo + bevacizumab: N = 255, N = 131
b. No information is available on how the observation period was calculated.
c. Specific AEs specified in the study as AESIs were to be followed up until death or final analysis. According to Module 4A, the following AEs were recorded as AESIs: myelodysplastic syndrome, acute myeloid leukaemia, secondary neoplasms and pneumonitis, anaemia, neutropoenia, thrombocytopoenia, nausea, vomiting, fatigue and asthenia, hypertension, proteinuria, GI perforations, abscess and fistulas, complications of wound healing, bleeding, arterial thromboembolism, venous thromboembolism, posterior reversible encephalopathy syndrome, congestive heart failure, non-GI fistulas, and abscesses. According to the study report, however, systematic follow-up until death or final analysis was conducted only for the following AESIs: myelodysplastic syndrome, acute myeloid leukaemia, secondary neoplasms, and pneumonitis. As per study report, the remaining AESIs were systematically followed up only for 30 days after the last dose of the study medication (see Section I 4.1).
d. For the 22 March 2020 data cutoff, the minimum observation duration was reported as 8.9 months in the intervention arm and 5.3 months in the control arm. The basis of change by the final data cutoff (22 March 2022) remains unclear because at the time of the 22 March 2020 data cutoff, all patients had already completed therapy.

AE: adverse event; AESI: adverse event of special interest; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; GI: gastrointestinal; 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

The median treatment duration was 7 months longer in the intervention arm than in the comparator arm (23.8 months versus 16.8 months).

The observation periods are comparable for overall survival, the outcomes of the morbidity and health-related quality of life categories, and for the AESIs with observation until death or final analysis. According to Module 4A, the information provided on the observation duration for AESIs includes all AEs specified as AESIs. The study report, in contrast, shows that only some of AESIs were systematically followed up until death or final analysis. The remaining AESIs were systematically followed up for only 30 days after the last dose of the study medication (see Section I 4.1).

Due to the treatment arms having different treatment durations, the respective observation periods for the outcomes of AEs, SAEs, and severe AEs likewise differ because these outcomes are only observed until 30 days after the last dose of the study medication.

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

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: olaparib + bevacizumab versus placebo + bevacizumab; 22 March 2022 data cutoff

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Olaparib + bevacizumab **N = 255**	**Placebo + bevacizumab** **N = 132**
PAOLA-1		
Patients with a 1st subsequent therapy[a]	132 (51.8)	104 (78.8)
Platinum-based chemotherapy	116 (87.9)	89 (85.6)
carboplatin	115 (87.1)	88 (84.6)
other platinum-based chemotherapy	2 (1.5)	1 (1.0)
Non-platinum-based cytotoxic therapy	117 (88.6)	97 (93.3)
gemcitabine	16 (12.1)	14 (13.5)
paclitaxel	13 (9.8)	10 (9.6)
pegylated liposomal doxurubicin (PLD, Caelyx)	88 (66.7)	73 (70.2)
Targeted therapy	54 (40.9)	66 (63.5)
bevacizumab	15 (11.4)	16 (15.4)
PARP inhibitor	34 (25.8)	48 (46.2)
other drugs	17 (12.9)	14 (13.5)
Other	16 (12.1)	11 (10.6)
Patients with a 2nd subsequent therapy[a]	89 (34.9)	79 (59.8)
Platinum-based chemotherapy	28 (31.5)	44 (55.7)
carboplatin	24 (27.0)	39 (49.4)
other platinum-based chemotherapy	4 (4.5)	6 (7.6)
Non-platinum-based cytotoxic therapy	63 (70.8)	50 (63.3)
gemcitabine	21 (23.6)	22 (27.8)
paclitaxel	24 (27.0)	15 (19.0)
pegylated liposomal doxurubicin (PLD-Caelyx)	18 (20.2)	14 (17.7)
Targeted therapy	20 (22.5)	32 (40.5)
bevacizumab	5 (5.6)	13 (16.5)
PARP inhibitor	9 (10.1)	20 (25.3)
other drugs	10 (11.2)	10 (12.7)
Other	15 (16.9)	14 (17.7)

a. Percentages shown for the specific subsequent therapies listed below were calculated based on the total number of patients with 1st or 2nd 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 1st subsequent therapy were largely equally distributed between the arms. In both arms, about 87% of participants received platinum-based chemotherapy as the 1st subsequent therapy. Notably, however, the percentage of patients who received a polyadenosine diphosphate ribose polymerase (PARP) inhibitor in the 1st subsequent therapy was significantly higher in the control arm. According to the study protocol, the choice of subsequent medication was not restricted; unblinding was intended only for medical emergencies in which the attending physician needed to know the administered study medication.

Moreover, the 2nd subsequent therapy differs between the arms: More patients in the control arm received another platinum-based chemotherapy, bevacizumab, and/or a PARP inhibitor in the 2nd 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 versus placebo + bevacizumab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of additional aspects	Risk of bias at study level
			Patients	Treatment providers			
PAOLA-1	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the study.

Transferability of the study results to the German health care context

The company stated that PAOLA-1 was deemed representative for the German health care context with regard to demographic and disease-specific factors. It concluded that the results were transferable to the German health care context without restrictions. The company justified this position by arguing that more than 30% of participants were treated at German study centres and that equivalent care was presumably received at the other European centres as well. The company deemed the German and European guidelines for the treatment of ovarian cancer to be largely consistent. The company described the prior treatment of study participants as consistent with the treatment recommendations issued in the S3 guideline [14]

and with the German Summary of Product Characteristics (SPC) for bevacizumab [17]. 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 PAOLA-1 target population with those of a quality assurance survey on ovarian cancer (QS-OVAR) in German hospitals, identifying no relevant differences with regard to tumour entities and histology, age, and ECOG-PS. However, the company described differences in the timing of debulking surgery (PDS versus IDS) and in the proportion of patients without remaining macroscopic tumour tissue after PDS/IDS.

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms measured using the EORTC QLQ-C30
  - symptoms measured using the EORTC QLQ-OV28
  - health status measured using the EQ-5D VAS
- Health-related quality of life
  - health-related quality of life measured with the EORTC QLQ-C30 and the EORTC QLQ-OV28
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - myelodysplastic syndrome (PT, SAEs)
  - acute myeloid leukaemia (PT, SAEs)
  - pneumonitis
  - further specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: olaparib + bevacizumab versus placebo + bevacizumab

Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30 and EORTC QLQ-OV28)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-OV28)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Myelodysplastic syndrome (PT, SAEs)[b]	Acute myeloid leukaemia (PT, SAEs)[b]	Pneumonitis[b]	Further specific AEs[c]
PAOLA-1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[d]	Yes

a. Operationalized as CTCAE grade ≥ 3.
b. Prespecified in the study as AESIs; follow-up until death or final analysis.
c. The following events were taken into account (MedDRA coding): nausea (PT, AEs), anaemia (PT, severe AEs), fatigue (PT, severe AEs), hypertension (PT, severe AEs).
d. No usable data available; for justification see body of text below.

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 Questionnaire – 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, health status, and health-related quality of life

EORTC QLQ-OV28

Comprising 28 items, the EORTC QLQ-OV28 is a disease-specific supplementary module of the EORTC QLQ-C30 for patients with ovarian cancer.

The company's dossier used the validated version of the questionnaire and analysed the scales in accordance with the general EORTC QLQ-C30 Scoring Manual of 2001 [18], which is available on the EORTC website. For the EORTC QLQ-OV28, it shows the following item-to-scale allocation: 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 items), and sexual functioning (4 items; not presented in the company's Module 4 A because the 2001 manual provides no analysis algorithm).

Upon request to the EORTC, the current EORTC QLQ-OV28 Scoring Manual [19] was made available in the initial assessment A20-111. According to this scoring manual, the item-to-scale allocation is 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 sexual functioning (2 + 2 conditional items). This allocation results from the field test of the EORTC QLQ-OV28 [20].

The analyses presented by the company were used, as was the case in the initial assessment A20-111.

Response criteria

The company's dossier presents both responder analyses for time to deterioration by ≥ 10 points and those for time to deterioration by ≥ 15 points for the EORTC QLQ-C30 and EORTC QLQ-OV28 (scale ranges of 0 to 100). For all scales of both instruments, 15 points corresponds to 15% of the scale range. According to the "Answers to frequently asked questions about the benefit assessment procedure" [21] provided by the G-BA, only analyses of the currently accepted minimal important difference (MID) of ≥ 10 points are to be presented in the dossier for analyses of the EORTC QLQ-C30 questionnaire and the corresponding validated supplementary disease-specific modules. These were disregarded in the present benefit assessment.

The company used 7 or 10 or 15 points as thresholds for the analyses of the EQ-5D VAS. In this context, 15 points correspond to 15% of the instrument's scale range. According to the IQWiG General Methods [1,22], the analysis of deterioration by ≥ 15 points is used for the benefit assessment.

Operationalizations of the responder analyses

For the EORTC QLQ-C30, EORTC QLQ-OV28, and EQ-5D VAS outcomes, the company presented responder analyses with the following operationalizations:

- Time to the first clinically relevant deterioration (corresponds to the analyses presented by the company for benefit assessment A20-111).
- Time to the company-defined "definitive clinically relevant deterioration" without subsequent survey showing a score below the respective response threshold compared to baseline

The survey of patient-reported outcomes was conducted for 2 years after study start, irrespective of disease progression. In both treatment arms, the median observation duration is 24 months (Table 10), but it is unclear how it was calculated. Compared to the observation duration for the outcome of overall survival, however, the observation duration is shortened.

Given the available evidence, this results in the problem of the observation period for patient-reported outcomes not covering the entire observation period for the operationalization of “definitive clinically relevant deterioration”. In this situation, it is therefore inappropriate to call the operationalization "definitive deterioration". Rather, it is a deterioration confirmed across the shortened observation period.

Both operationalizations presented by the company are patient relevant. In the present benefit assessment, as in the initial assessment A20-111, the operationalization of time to first clinically relevant deterioration is used for the patient-reported outcomes on morbidity and health-related quality of life. While the 2 treatment arms were reported to have the same median observation periods (see Table 10), the percentage of completed questionnaires was found to continuously decrease over the course of the study. This decrease cannot be explained solely by the patients who died during the observation period (see Kaplan-Meier curves in I Appendix B.1 of the full dossier assessment). After only 12 months, the percentage of completed questionnaires had already dropped to about 67% in the intervention arm and 63% in the control arm. In the 2nd year, the decrease was even more pronounced, with major differences between the percentages (≥ 10%) being observed. Overall, the observation periods cannot be assumed with sufficient certainty to be adequately similar across the course of the study; given the available data, therefore, time to first clinically relevant deterioration was used.

AEs of special interest

The company’s Module 4A lists a number of AESIs (myelodysplastic syndrome, acute myeloid leukaemia, secondary neoplasms, pneumonitis, anaemia, neutropoenia, thrombocytopoenia, nausea, vomiting, fatigue and asthenia, hypertension, proteinuria, gastrointestinal perforations, abscess and fistulas, complications of wound healing, bleeding, arterial thromboembolism, venous thromboembolism, posterior reversible encephalopathy syndrome, congestive heart failure, nongastrointestinal fistulas or abscesses), which according to Module 4A were followed up until death or final analysis. For these AESIs, the company presents results on the final data cutoff of 22 March 2022. The results on the AESIs are disregarded for the following reasons:

- As per study report, said AESIs are based on PTs or PT collections selected by the company. But these were not clearly prespecified. As per statistical analysis plan, they were to be available before data lock and reported in the study report. However, the latter lists the PT collections only for some of the AESIs (AEs to be expected on bevacizumab). For the remaining AESIs, it is therefore unclear which PTs were taken into account in the analyses.
- According to the study report, systematic follow-up until death or final analysis was conducted only for the 4 AESIs of myelodysplastic syndrome, acute myeloid leukaemia,

secondary neoplasms, and pneumonitis. According to the study report, all other AESIs were followed up only until 30 days after the last dose of the study medication.

For the present benefit assessment, results from the 22 March 2020 data cut-off were used on the PT level for specific AEs. For the AESIs of myelodysplastic syndrome and acute myeloid leukaemia, the assessment used the results presented by the company as supplementary information from the 22 March 2022 final data cutoff. For the AESI pneumonitis, no usable data are available because the company presents no results on the PT level.

I 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 versus placebo + bevacizumab

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

a. Operationalized as CTCAE grade ≥ 3.
b. Prespecified in the study as AESIs; follow-up until death or final analysis.
c. The following events were taken into account (MedDRA coding): nausea (PT, AEs), anaemia (PT, severe AEs), fatigue (PT, severe AEs), hypertension (PT, severe AEs).
d. Incomplete observations for potentially informative reasons.
e. Despite the low risk of bias, the certainty of results is presumably limited for the outcome of discontinuation due to AEs.
f. No usable data available; see Section I 4.1 for the reasoning.

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 Questionnaire – 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

The risk of bias is rated as low for the results on overall survival, symptoms, health status, health-related quality of life, the AESIs of myelodysplastic syndrome and acute myeloid leukaemia as well as the outcome of discontinuation due to AEs.

The risk of bias of results for the outcomes of SAEs, severe AEs, and other specific AEs is rated as high due to incomplete observations for potentially informative reasons. In the relevant subpopulation, 23% of patients in the intervention arm and 60% in the comparator arm discontinued the study medication due to disease progression; the median observation period differed significantly between study arms (24.8 months in the intervention arm versus 17.8 months in the comparator arm). For the results of the specific AEs of nausea (PTs, AEs) and anaemia (PT, severe AEs), the certainty of conclusions is presumably high despite high risk of bias due to the effect size found already at an early time in the study. The observation periods being shortened for potentially informative reasons does not call into question the observed effect.

The certainty of results for the outcome of discontinuation due to AEs is limited despite a low risk of bias. Premature treatment discontinuation for reasons other than AEs represents a competing event for the outcome to be recorded, discontinuation due to AEs. Consequently, after discontinuation for other reasons, AEs that would have led to discontinuation may have occurred, but the criterion of discontinuation could no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

No usable data are available for the outcome of pneumonitis (see Section I 4.1). Therefore, the risk of bias was not assessed for the results pertaining to this outcome.

I 4.3 Results

Table 15 and Table 16 summarize the results on the comparison of olaparib + bevacizumab versus 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 on the results of the outcomes included are presented in I Appendix B of the full dossier assessment. Results on common AEs can be found in I Appendix C of the full dossier assessment. Forest plots on the Institute’s metaanalyses are shown in I Appendix D of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: olaparib + bevacizumab versus 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]
PAOLA-1					
Mortality					
Overall survival (22 March 2022 data cutoff)	255	75.2 [73.3; NC] 93 (36.5)	132	57.3 [51.6; NC] 69 (52.3)	0.68 [0.50; 0.94]; 0.017
Morbidity (22 March 2020 data cutoff)					
Symptoms (EORTC QLQ-C30)[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
Symptoms (EORTC QLQ-OV28)[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 (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: olaparib + bevacizumab versus 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]
Health status (EQ-5D VAS)[d]	255	25.3 [17.5; NC] 116 (45.5)	132	26.7 [19.9; NC] 58 (43.9)	1.05 [0.77; 1.46]; 0.749
Health-related quality of life (22 March 2020 data cutoff)					
EORTC QLQ-C30[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
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
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
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]					
Sexual functioning	No usable data[f]				
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 (22 March 2020 data cutoff)					
AEs (supplementary information)	255	0.2 [0.2; 0.3] 255 (100)	131	0.3 [0.2; 0.7] 127 (96.9)	–
SAEs	255	NR 73 (28.6)	131	NR 45 (34.4)	0.75 [0.52; 1.10]; 0.133
Severe AEs[g]	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	NR 50 (19.6)	131	NR 8 (6.1)	3.14 [1.57; 7.18]; 0.002
Nausea (PT, AEs)	255	2.9 [0.8; 14.5] 144 (56.5)	131	NR 30 (22.9)	3.38 [2.30; 5.13]; < 0.001

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: olaparib + bevacizumab versus 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]
Anaemia (PT, severe AEs[g])	255	NR 47 (18.4)	131	NR 1 (0.8)	27.85 [6.08; 493.74]; < 0.001
Fatigue (PT, severe AEs[g])	255	NR 14 (5.5)	131	NR 0 (0)	NC; 0.007
Hypertension (PT, severe AEs[g])	255	NR 45 (17.6)	131	NR 42 (32.1)	0.47 [0.30; 0.72]; < 0.001

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 first clinically relevant deterioration; a score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
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 instead, the individual questions are included in the analysis of the other scales (see Section I 4.1).
d. Time to first clinically relevant deterioration; a score decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
e. Time to first clinically relevant deterioration; a score decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
f. The company presented no analyses for the sexual functioning scale because the scoring manual used by it provides no analysis algorithm [18].
g. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; BRCA: breast cancer gene; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; 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; tBRCA: tumour BRCA; VAS: visual analogue scale

Table 16: Results (side effects, dichotomous) – RCT, direct comparison: olaparib + bevacizumab versus placebo + bevacizumab

Study Outcome category Outcome	Olaparib + bevacizumab		Placebo + bevacizumab		Olaparib + bevacizumab vs. placebo + bevacizumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
PAOLA-1					
Side effects (22 March 2022 data cutoff)					
Myelodysplastic syndrome (PT, SAEs)[b,c]	255	1 (0.4)	131	3 (2.3)	0.17 [0.02; 1.63]; 0.085
Acute myeloid leukaemia (PT, SAEs)[b,c]	255	4 (1.6)[d]	131	1 (0.8)	2.05 [0.23; 18.20]; 0.616
Pneumonitis	Data not usable[e]				

a. Institute's calculation; unconditional exact test (CSZ method according to [23]).
b. Follow-up observation until death or final analysis.
c. In Module 4A, the company describes these events as AEs. As per study report, all events which occurred in the study's overall population were SAEs (except 1 event, which was recorded as an AE).
d. According to Module 5, in 1 intervention-arm participant from among the study's total population, acute myeloid leukaemia was recorded as an AE. The patient died from this event. It is unclear whether this patient belongs to the subpopulation.
e. No usable data available; see Section I 4.1 for the reasoning.

AE: adverse event; CI: confidence interval; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

On the basis of the available data, at most indications, e.g. of added benefit, can be derived for the outcomes of overall survival, symptoms, health status, health-related quality of life, and specific AEs of myelodysplastic syndrome (PT, SAEs), acute myeloid leukaemia (PT, SAEs), nausea (PT, AEs), and anaemia (PT, severe AEs). For the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3), the specific AEs of fatigue and hypertension (PTs, severe AEs), and discontinuation due to AEs, at most hints, e.g. of added benefit, can be derived due to high risk of bias or limited certainty of results.

Mortality

Overall survival

A statistically significant difference in favour of olaparib + bevacizumab in comparison with placebo + bevacizumab was shown for the outcome of overall survival.

However, there is an effect modification by the characteristic of result of first-line therapy (composite subgroups NED [PDS] + NED/CR [chemo] or NED/CR [IDS] + PR) (see Section I 4.4). For patients with NED after PDS (NED [PDS]) and patients with NED / with complete response after chemotherapy (NED/CR [chemo]), this results in an indication of added benefit of

olaparib + bevacizumab in comparison with bevacizumab. For patients in the NED/CR (IDS) and PR subgroups, this results in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven for these patients.

Morbidity

Symptoms

The symptoms outcomes were surveyed using the EORTC QLQ-C30 and the disease-specific module EORTC QLQ-OV28. Time to first clinically relevant deterioration by ≥ 10 points (scale range 0 to 100) was analysed in each case.

EORTC QLQ-C30

Nausea and vomiting

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

Insomnia

A statistically significant difference in favour of olaparib + bevacizumab compared with placebo+ bevacizumab was shown for the outcome of insomnia. For this outcome of the non-serious/non-severe symptoms / late complications category, however, the extent of the effect was no more than marginal (see Section I 5.1). This results in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven.

Appetite loss

A statistically significant difference to the disadvantage of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcome of appetite loss. For this outcome of the non-serious/non-severe symptoms / late complications category, however, the extent of the effect was no more than marginal (see Section I 5.1). This results in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven.

Fatigue, pain, dyspnoea, constipation, and diarrhoea

No statistically significant difference between treatment groups was shown for any of the outcomes of fatigue, pain, dyspnoea, constipation, or diarrhoea. In each case, this results in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven.

EORTC QLQ-OV28

Hormonal symptoms and side effects of chemotherapy

A statistically significant difference in favour of olaparib + bevacizumab compared with placebo + bevacizumab was shown for each of the outcomes of hormonal symptoms and side effects of chemotherapy. However, the extent of the effects is no more than marginal for these outcomes of the non-serious/non-severe symptoms / late complications category (see Section I 5.1). In each case, this results in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven.

Abdominal/gastrointestinal symptoms, peripheral neuropathy, and individual questions

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

Health status

The outcome of health status was surveyed by EQ-5D VAS. Time to first clinically relevant deterioration by ≥ 15 points (scale range 0 to 100) was analysed.

There was no statistically significant difference between treatment groups for the outcome of health status. This results 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 health-related quality of life outcomes were surveyed using the EORTC QLQ-C30 and the disease-specific module EORTC QLQ-OV28. Time to first clinically relevant deterioration by ≥ 10 points (scale range 0 to 100) was analysed in each case.

EORTC QLQ-C30

Global health status

No statistically significant difference between treatment arms was shown for the outcome of global health status, but there was an effect modification by the characteristic of age (see Section I 4.4). For patients aged ≥ 65 years, this results in an indication of added benefit of olaparib + bevacizumab in comparison with bevacizumab. For patients aged < 65 years, there is no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven for these patients.

Physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning

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

EORTC QLQ-OV28

Sexual functioning

No usable data are available for the outcome of sexual functioning. This results in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven.

Body image

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

Attitude regarding disease/treatment

No statistically significant difference between treatment groups was shown for the outcome of attitude regarding disease/treatment, but there was an effect modification by the characteristic of result of the first-line therapy (see Section I 4.4). For patients in the NED (PDS), NED/ CR (chemo), and PR subgroups, there was no hint of 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 results in an indication of lesser benefit of olaparib + bevacizumab in comparison with bevacizumab.

Side effects

SAEs and severe AEs

No statistically significant difference between treatment groups was shown for the outcomes of SAEs or severe AEs. In each case, this results in no hint of greater or lesser harm from olaparib + bevacizumab in comparison with bevacizumab; 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 of discontinuation due to AEs. This results in a hint of greater harm from olaparib + bevacizumab in comparison with bevacizumab.

Specific AEs

Myelodysplastic syndrome and acute myeloid leukaemia (SAEs each)

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

Pneumonitis

No usable data were available for the outcome of pneumonitis. This results in no hint of greater or lesser harm from olaparib + bevacizumab in comparison with bevacizumab; greater or lesser harm is therefore not proven.

Nausea (AEs) and anaemia (severe AEs)

A statistically significant difference to the disadvantage of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcomes of nausea (AEs) and anaemia (severe AEs). For each of them, this results in an indication of greater harm from olaparib + bevacizumab in comparison with bevacizumab.

Fatigue (severe AEs)

A statistically significant difference to the disadvantage of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcome of fatigue (severe AEs). This results in a hint of greater harm from olaparib + bevacizumab in comparison with bevacizumab.

Hypertension (severe AEs)

A statistically significant difference in favour of olaparib + bevacizumab compared with placebo + bevacizumab was shown for the outcome of hypertension (severe AEs). This results in a hint of lesser harm from olaparib + bevacizumab in comparison with bevacizumab.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- result of first-line therapy (NED [PDS] versus NED/CR [IDS] versus NED/CR [chemotherapy] versus PR)

All mentioned subgroup characteristics and cutoff values had been prespecified for the primary outcome of PFS.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

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

In the initial assessment A20-111, an effect modification for the result of the first-line therapy was found on the basis of the 22 March 2020 data cutoff. At that time, it was examined whether it was possible to meaningfully summarize subgroups. The Institute's calculations show that overall analyses of the subgroups NED (PDS) + NED/CR (chemo) and NED/CR (IDS) + PR each reveal homogeneous data for the outcome of overall survival. For the outcome of overall survival, the respective results from a corresponding meta-analysis (Institute's calculation; fixed-effect model; method with inverse variance) were therefore taken into account for these composite subgroups NED (PDS) + NED/CR (chemo) or NED/CR (IDS) + PR [24].

For the 22 March 2022 data cutoff, an effect modification for the attribute of result of first-line therapy was likewise shown on the basis of the Institute’s calculations of the composite subgroups NED (PDS) + NED/CR (chemo) and NED/CR (IDS) + PR. The composite subgroups each showed homogeneous data for the outcome of overall survival (see I Appendix D of the full dossier assessment). The effect modification is taken into account in the present benefit assessment as well.

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]	Olaparib + bevacizumab vs. placebo + bevacizumab p-value[a]
PAOLA-1						
Mortality						
Overall survival (22 March 2022 data cutoff)						
Result of the first-line therapy						
NED (PDS)[b]	92	NR 15 (16.3)	48	NR 21 (43.8)	0.29 [0.15; 0.57]	< 0.001
NED/CR (IDS)[c]	74	73.3 [45.0; NC] 34 (45.9)	38	57.3 [45.2; NC] 20 (52.6)	0.88 [0.51; 1.55]	0.641
NED/CR (chemo)[d]	40	NR 15 (37.5)	20	56.9 [31.8; 66.4] 12 (60.0)	0.56 [0.26; 1.23]	0.146
PR[e]	49	50.4 [32.3; NC] 29 (59.2)	26	43.0 [25.2; NC] 16 (61.5)	0.88 [0.48; 1.66]	0.679
Total					Interaction:	0.050[f]
NED (PDS)[b] + NED/CR (chemo)[d]					0.38 [0.23; 0.64][g]	< 0.001[g]
NED/CR (IDS)[c] + PR[e]					0.88 [0.58; 1.33][g]	0.545[g]
Total					Interaction:	0.013[h]
Health-related quality of life						
EORTC QLQ-C30 (22 March 2020 data cutoff)						
Global health status						
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]

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]	Olaparib + bevacizumab vs. placebo + bevacizumab p-value[a]
EORTC QLQ-OV28 (22 March 2020 data cutoff)						
Attitude regarding disease/treatment						
Result of the first-line therapy						
NED (PDS)[b]	92	NR 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	NR 15 (39.5)	2.34 [1.34; 4.33]	0.002
NED/CR (chemo)[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]

a. HR, CI, and p-value: Cox proportional hazards model, unstratified.
b. Patients with no evidence of disease after primary debulking surgery.
c. Patients with no evidence of disease / with complete response after interval surgery.
d. Patients with no evidence of disease / 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.

CI: confidence interval; CR: complete response; EORTC: European Organization for Research and Treatment of Cancer; HR: hazard ratio; IDS: interval debulking surgery; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NED: no evidence of disease; NR: not reached; 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

For the outcome of overall survival, however, there is an effect modification by the characteristic of result of first-line therapy (composite subgroups NED [PDS] + NED / CR [chemo] and NED / CR [IDS]+ PR).

For patients with NED after PDS (NED [PDS]) and patients with NED / 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 of

overall survival. This result concurs with the results for PFS. Both for PFS (either first progression recorded using imaging techniques as per RECIST or death) and for PFS2 (either second progression [assessed by the investigator by means of radiological methods, CA-125, or symptoms] or death), a statistically significant advantage was found for these patients (see I Appendix E of the full dossier assessment). This results in an indication of added benefit of olaparib + bevacizumab in comparison with bevacizumab.

For patients with NED / with complete response after interval surgery (NED/CR [IDS]) and for patients with PR, there is no statistically significant difference between treatment groups regarding the outcome of overall survival. In this situation, the PFS results are unsuitable for supporting the results on overall survival. Regarding PFS, a statistically significant advantage of olaparib + bevacizumab in comparison with placebo + bevacizumab was initially shown for these 2 subgroups, but like for overall survival, the result for PFS2 shows no statistically significant difference between treatment groups (see I Appendix E of the full dossier assessment). This results in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven for these patients.

Health-related quality of life

EORTC QLQ-C30

Global health status

The available subgroup analyses show an effect modification for the outcome of global health status by the characteristic of age.

For patients aged ≥ 65 years, a statistically significant difference was found in favour of olaparib + bevacizumab in comparison with placebo + bevacizumab. This results in an indication of added benefit of olaparib + bevacizumab in comparison with bevacizumab.

For patients aged < 65 years, there was no statistically significant difference between treatment arms. Regarding this outcome, this results in no hint of an added benefit of olaparib + bevacizumab in comparison with placebo + bevacizumab; an added benefit is therefore not proven for these patients.

EORTC QLQ-OV28

Attitude regarding disease/treatment

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

For patients with NED / with complete response after interval surgery (NED/CR [IDS]), there is a statistically significant difference to the disadvantage of olaparib + bevacizumab in

comparison with placebo + bevacizumab. This results in an indication of lesser benefit of olaparib + bevacizumab in comparison with bevacizumab for this subgroup.

There was no statistically significant difference between treatment arms for patients in the 3 subgroups of NED/CR (PDS), NED/CR (chemo), and PR. For each of these subgroups, this results in no hint of an added benefit of olaparib + bevacizumab in comparison with placebo + bevacizumab; an added benefit is therefore not proven for these patients.

I 5 Probability and extent of added benefit

The probability and extent of 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 IQWiG General Methods [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.

I 5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4 (see Table 18).

Determination of the outcome category for outcomes on symptoms and side effects

It cannot be inferred from the dossier whether the following outcomes were serious/severe or non-serious/non-severe. The classification of these outcomes is justified as follows.

Symptoms

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

For the outcomes of insomnia, appetite loss as well as nausea and vomiting, the available information is insufficient for a classification as serious/severe. The outcomes of insomnia, appetite loss as well as nausea and vomiting were therefore allocated to the outcome category non-serious/non-severe symptoms / late complications.

Hormonal symptoms and side effects of chemotherapy (EORTC QLQ-OV28)

For the outcomes of hormonal symptoms and side effects of chemotherapy, the available severity data are insufficient for a classification as serious/severe. The outcomes of hormonal symptoms and side effects of chemotherapy are therefore allocated to the outcome category of non-serious/non-severe symptoms / late complications.

Side effects

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, the available severity data are insufficient for a classification as serious/severe. The outcome of discontinuation due to AEs was therefore assigned to the outcome category of non-serious/non-severe side effects.

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

Outcome category **Outcome** **Effect modifier**	**Olaparib + bevacizumab vs. bevacizumab** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Total observation period		
Mortality		
Overall survival Result of the first-line therapy NED (PDS)[c] + NED/CR (chemo)[d]	ND HR: 0.38 [0.23; 0.64]; p < 0.001 Probability: indication	Outcome category: mortality CI_u < 0.85 Added benefit; extent: major
NED/CR (IDS)[d] + PR[f]	ND HR: 0.88 [0.58; 1.33]; p = 0.545	Lesser/added benefit not proven
Side effects		
Myelodysplastic syndrome (SAEs)	0.4% vs. 2.3% RR: 0.17 [0.02; 1.63]; p = 0.085	Lesser/added benefit not proven
Acute myeloid leukaemia (SAEs)	1.6% vs. 0.8% RR: 2.05 [0.23; 18.20]; p = 0.616	Lesser/added benefit not proven
Pneumonitis	No usable data	Lesser/added benefit not proven
Shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30, first deterioration ≥ 10 points)		
Fatigue	5.6 vs. 5.7 HR: 1.10 [0.86; 1.41]; p = 0.482	Lesser/added benefit not proven
Nausea and vomiting	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

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

Outcome category **Outcome** **Effect modifier**	**Olaparib + bevacizumab vs. bevacizumab** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Pain	5.8 vs. 5.6 HR: 0.92 [0.72; 1.19]; p = 0.551	Lesser/added benefit not proven
Dyspnoea	20.7 vs. 18.7 HR: 0.92 [0.68; 1.25]; p = 0.580	Lesser/added benefit not proven
Insomnia	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/added benefit not proven[h]
Appetite loss	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/added benefit not proven[h]
Constipation	19.9 vs. 19.7 HR: 1.03 [0.77; 1.39]; p = 0.831	Lesser/added benefit not proven
Diarrhoea	24.0 vs. 23.5 HR: 1.15 [0.84; 1.58]; p = 0.409	Lesser/added benefit not proven
Symptoms (EORTC QLQ-OV28, first deterioration ≥ 10 points)		
Abdominal/gastrointestinal symptoms	11.1 vs. 8.3 HR: 0.88 [0.68; 1.15]; p = 0.351	Lesser/added benefit not proven
Peripheral neuropathy	25.3 vs. 23 HR: 0.93 [0.68; 1.29]; p = 0.654	Lesser/added benefit not proven
Hormonal symptoms	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/added benefit not proven[h]
Side effects of chemotherapy	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/added benefit not proven[h]

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

Outcome category **Outcome** **Effect modifier**	**Olaparib + bevacizumab vs. bevacizumab** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Individual questions	21.9 vs. 19.4 HR: 1.01 [0.75; 1.38]; p = 0.954	Lesser/added benefit not proven
Health status (EQ-5D VAS, first deterioration by ≥ 15 points)		
EQ-5D VAS	25.3 vs. 26.7 HR: 1.05 [0.77; 1.46]; p = 0.749	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (first deterioration ≥ 10 points)		
Global health status		
Age		
< 65 years	15.2 vs. 16.2 HR: 0.97 [0.70; 1.34]; p = 0.843	Lesser/added benefit not proven
≥ 65 years	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	20 vs.16.4 HR: 0.85 [0.64; 1.14]; p = 0.279	Lesser/added benefit not proven
Role functioning	8.4 vs. 9.3 HR: 1.11 [0.85; 1.46]; p = 0.450	Lesser/added benefit not proven
Emotional functioning	13.8 vs. 11.1 HR: 0.93 [0.71; 1.22]; p = 0.571	Lesser/added benefit not proven
Cognitive functioning	11.1 vs. 8.5 HR: 0.91 [0.70; 1.19]; p = 0.484	Lesser/added benefit not proven
Social functioning	13.5 vs. 11.3 HR: 0.91 [0.69; 1.20]; p = 0.471	Lesser/added benefit not proven
EORTC QLQ-OV28 (first deterioration ≥ 10 points)		
Sexual functioning	No usable data	Lesser/added benefit not proven

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

Outcome category **Outcome** **Effect modifier**	**Olaparib + bevacizumab vs. bevacizumab** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Body image	21.9 vs. 18.7 HR: 0.93 [0.70; 1.26]; p = 0.638	Lesser/added benefit not proven
Attitude regarding disease/treatment		
Result of first-line therapy		
NED (PDS)[c]	NR vs. 11.3 HR: 0.60 [0.36; 1.01]; p = 0.053	Lesser/added benefit not proven
NED/CR (IDS)[d]	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 CI_u < 0.75, risk ≥ 5% Lesser benefit; extent: major
NED/CR (chemotherapy)[e]	8.3 vs. 12.6 HR: 1.18 [0.59; 2.46]; p = 0.646	Lesser/added benefit not proven
PR[f]	12.1 vs. 17.0 HR: 1.03 [0.55; 2.04]; p = 0.931	Lesser/added benefit not proven
Side effects		
SAEs	NR vs. NR HR: 0.75 [0.52; 1.10]; p = 0.133	Lesser/added benefit not proven
Severe AEs	8.6 vs. 16.7 HR: 1.20 [0.90; 1.63]; p = 0.221	Lesser/added benefit not proven
Discontinuation due to AEs	NR vs. NR 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
Nausea (AEs)	2.9 vs. NR HR: 3.38 [2.30; 5.13]; HR: 0.30 [0.19; 0.43][g]; p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm; extent: considerable

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

Outcome category **Outcome** **Effect modifier**	**Olaparib + bevacizumab vs. bevacizumab** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Anaemia (severe AEs)	NR vs. NR HR: 27.85 [6.08; 493.74]; 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 (severe AEs)	NR vs. NR Proportions of events: 14 (5.5) vs. 0 (0) HR: NC p = 0.007 Probability: hint	Outcome category: serious/severe side effects Greater harm; extent: non-quantifiable
Hypertension (severe AEs)	NR vs. NR HR: 0.47 [0.30; 0.72]; p < 0.001 Probability: hint	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Lesser harm; extent: major

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 with no evidence of disease after primary debulking surgery.
d. Patients with no evidence of disease / with complete response after chemotherapy.
e. Patients with no evidence of disease / with complete response after interval surgery.
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; chemo: chemotherapy; 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 Questionnaire – 5 Dimensions; HR: hazard ratio; IDS: interval debulking surgery; MD: mean difference; NC: not calculable; ND: no data; NED: no evidence of disease; NR: not reached; PDS: primary debulking surgery; PR: partial response; 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

I 5.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 19: Favourable and unfavourable effects found in the assessment of olaparib + bevacizumab in comparison with bevacizumab

Favourable effects	**Unfavourable effects**
Total observation period	
Mortality ▪ Overall survival: ▫ Patients with NED after primary debulking surgery and patients with NED / with complete response following chemotherapy: indication of added benefit – extent: major	–
Shortened observation period	
–	Non-serious/non-severe symptoms / late complications Symptoms (EORTC QLQ-C30) ▪ Nausea and vomiting: indication of lesser benefit – extent: considerable
Health-related quality of life (EORTC QLQ-C30) ▪ Global health status ▫ Age (≥ 65 years): indication of an added benefit – extent: considerable	Health-related quality of life (EORTC QLQ-OV28) ▪ Attitude regarding disease/treatment ▫ Patients with NED / with complete response after interval surgery: indication of lesser benefit – extent: major
Serious/severe side effects ▪ Hypertension (severe AEs): hint of lesser harm – extent: major	Serious/severe side effects ▪ Anaemia (severe AEs): indication of greater harm – extent: major ▪ Fatigue (severe AEs): hint of greater harm – extent: non-quantifiable
–	Non-serious/non-severe side effects ▪ Nausea (AEs): indication of greater harm – extent: considerable ▪ Discontinuation due to AEs: hint of greater harm – extent: considerable
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire–Core 30; QLQ-OV28: Quality of Life Questionnaire–Ovarian Cancer 28	

The overall analysis showed both favourable and unfavourable effects of olaparib + bevacizumab in comparison with bevacizumab. Only for overall survival are the observed effects based on the entire observation period. For morbidity, health-related quality of life, and side effects, in contrast, they are based only on the shortened period (side effects: until treatment end [plus 30 days]; morbidity and health-related quality of life: up to 2 years after study start).

For the outcome of overall survival, an effect modification by the characteristic of result of first-line treatment was shown. For this reason, favourable and unfavourable effects are weighed separately for the subgroups of (a) patients with NED after PDS (NED [PDS]) and

patients with NED or CR after chemotherapy (NED/CR [chemo]) and (b) patients with NED or CR after IDS and patients with PR.

For patients with NED after PDS (NED [PDS]) and patients with NED or CR after chemotherapy (NED/CR [chemo]), this results in an indication of major added benefit for the outcome of overall survival. Furthermore, a hint of lesser harm of major extent was found in the category of serious/severe side effects. In contrast, several hints or indications of unfavourable effects with considerable to major or nonquantifiable extents were found in the outcome categories of non-serious/non-severe symptoms and serious/severe side effects as well as non-serious/non-severe side effects. However, the unfavourable effects did not completely call into question the favourable effects. Overall, this results in an indication of considerable added benefit of olaparib + bevacizumab in comparison with the ACT of bevacizumab for patients with NED after PDS (NED [PDS]) and patients with NED or CR after chemotherapy (NED/CR [chemo]).

For patients with NED or with complete response after IDS and patients with PR, there was a hint of lesser harm with the extent of major for the favourable effects in the category of serious/severe side effects. This is in contrast to several hints or indications of unfavourable effects of considerable to major or nonquantifiable extents in the outcome categories of health-related quality of life (only for patients with NED / with complete response after interval surgery), non-serious/non-severe symptoms and serious/severe side effects as well as non-serious/non-severe side effects. Overall, this results in an indication of lesser benefit of olaparib + bevacizumab in comparison with the ACT of bevacizumab for patients with NED / with complete response after IDS and patients with PR.

Table 20 summarizes the result of the assessment of 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 bevacizumab treatment started with first-line platinum-based chemotherapy	▪ Patients with NED after PDS and patients with NED or CR after chemotherapy: indication of considerable added benefit
		▪ Patients with NED after IDS and patients with PR: indication of lesser benefit

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

ACT: appropriate comparator therapy; BRCA: breast cancer gene; CR: complete response; 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; IDS: interval debulking surgery; NED: no evidence of disease; PDS: primary debulking surgery; PR: partial response

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

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

I 6 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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