Durvalumab (endometrial cancer, pMMR)

Benefit assessment according to §35a SGB V[1]

EXTRACT

Project: A24-86 Version: 1.0 Status: 28 Nov 2024 DOI: 10.60584/A24-86_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Durvalumab (Endometriumkarzinom, pMMR) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Durvalumab (endometrial cancer, pMMR) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

22 August 2024

Internal Project No.

A24-86

DOI-URL

https://doi.org/10.60584/A24-86_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Volker Heilmann

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.

IQWiG employees involved in the dossier assessment

- Marina Woeste
- Christiane Balg
- Maximilian Kind
- Petra Kohlepp
- Ulrike Lampert
- Ana Liberman
- Anke Schulz
- Volker Vervölgyi

Keywords

Durvalumab, Olaparib, Carboplatin, Paclitaxel, Endometrial Neoplasms, Benefit Assessment, NCT04269200

Part I: Benefit assessment

I Table of contents

Page

I List of tables[2]

Page

[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
AEPI	adverse event of possible interest
AESI	adverse event of special interest
AML	acute myeloid leukaemia
AUC	area under the curve
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
dMMR	mismatch repair deficient
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-EN24	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module 24
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MDS	myelodysplastic syndrome
MMR	mismatch repair
MMRM	mixed-effects model with repeated measures
MRI	magnetic resonance imaging
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
pMMR	mismatch repair proficient
PRO-CTCAE	Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
PT	Preferred Term
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Meaning
RKI	Robert Koch Institute
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	System Organ Class
SPC	Summary of Product Characteristics
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 durvalumab (in combination with carboplatin and paclitaxel), followed by durvalumab in combination with olaparib. 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 22 August 2024.

Research question

The aim of the present report is to assess the added benefit of durvalumab in combination with carboplatin and paclitaxel (hereinafter referred to as "durvalumab + carboplatin + paclitaxel"), followed by maintenance treatment with durvalumab in combination with olaparib (hereinafter referred to as "durvalumab + olaparib"), compared with the appropriate comparator therapy (ACT) for the first-line treatment of adult patients with primary advanced or recurrent mismatch repair proficient (pMMR) endometrial cancer who are candidates for systemic therapy.

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

Table 2: Research question of the benefit assessment of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib

Therapeutic indication	**ACT[a]**
First-line treatment of adult patients with primary advanced or recurrent pMMR endometrial cancer who are candidates for systemic therapy[b], followed by maintenance treatment with durvalumab in combination with olaparib[c]	Carboplatin + paclitaxel[d], followed by watchful waiting

a. Presented is the ACT specified by the G-BA.
b. In this therapeutic indication, the G-BA assumes that the patients have not yet received systemic therapy as postoperative or adjuvant therapy to treat the primary advanced disease and have not yet received chemotherapy to treat the recurrence.
c. According to the SPC, olaparib is used in patients whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel.
d. Treatment with carboplatin in combination with paclitaxel is not approved for this therapeutic indication. Accordingly, the use of carboplatin in combination with paclitaxel represents an off-label use. According to the G-BA, for patients in the present therapeutic indication, the off-label use is generally preferable to the drugs currently approved in the therapeutic indication, according to the generally recognized state of medical knowledge, §6 (2), sentence 3, number 2, AM-NutzenV.

AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; G-BA: Federal Joint Committee; pMMR: mismatch repair proficient; SPC: Summary of Product Characteristics

In this assessment, the initial phase of first-line therapy (durvalumab + carboplatin + paclitaxel or carboplatin + paclitaxel) is referred to as initial treatment. The subsequent therapy phase

with olaparib + durvalumab is referred to as maintenance treatment. This assessment refers to the entire therapeutic strategy.

Deviating from the research question of the G-BA, the company formed 2 subpopulations, specifying an ACT for its subpopulation 2 that deviated from the G-BA:

- Subpopulation 1: patients who have not been pretreated with chemotherapy or for whom – despite pretreatment with chemotherapy – further chemotherapy alone is an option:
  - carboplatin + paclitaxel
- Subpopulation 2: patients who have been pretreated with chemotherapy and for whom re-induction with chemotherapy alone is not an option:
  - pembrolizumab + lenvatinib

For subpopulation 1, the company largely followed the ACT specified by the G-BA. Although the company did not name maintenance treatment with watchful waiting, this deviation has no consequences for the benefit assessment, as it had no effect on the completeness of the study pool. For subpopulation 2, the company departed from the ACT specified by the G-BA. This deviation of the company also remains without consequence, as it did not present any data for this subpopulation.

The present assessment is conducted on the basis of the research question and ACT specified 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. Randomized controlled trials (RCTs) are used to derive added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The DUO-E study was included in the benefit assessment. The DUO-E study is an ongoing 3-arm randomized, double-blind study comparing

- placebo + carboplatin + paclitaxel, followed by placebo (Arm A),
- durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + placebo (Arm B),
- durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + olaparib (Arm C).

The study included adult patients with histologically confirmed diagnosis of epithelial endometrial cancer of all histologies (including carcinosarcomas) and regardless of mismatch

repair (MMR) status. Besides patients with newly diagnosed International Federation of Gynecology and Obstetrics (FIGO) stage III or FIGO stage IV disease, the study also included patients with recurrence where the potential for cure by surgery alone or in combination with radiotherapy or systemic therapy was poor. The patients had to be naive to systemic therapy for the current stage of the disease. For patients with recurrent disease only, prior systemic treatment was allowed only if it was administered in the adjuvant setting (as part of the upfront or adjuvant anti-cancer treatment, which may be concurrent or following chemoradiation) and there was at least 12 months from date of last dose of systemic treatment administered to date of subsequent relapse. The MMR status of the endometrial cancer had to be evaluated before randomization using the Ventana MMR immunohistochemistry panel. Enrolment was limited to patients in good general health corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1.

A total of 718 patients with endometrial cancer were randomly assigned in a 1:1:1 ratio to one of the 3 treatment arms (Arm A, N = 241; Arm B, N = 238; Arm C, N = 239). Stratification was according to MMR status (deficient versus proficient), disease status (newly diagnosed versus recurrent) and geographic region (Asia versus rest of the world).

Treatment with durvalumab and olaparib was in compliance with the recommendations of the Summaries of Product Characteristics (SPCs).

Carboplatin + paclitaxel was administered as chemotherapy in all 3 study arms. The SPC for durvalumab provides no information on the dosage of carboplatin + paclitaxel. The dosages and dose reductions of paclitaxel and carboplatin used in the DUO-E study correspond to the guideline recommendations.

The DUO-E study is divided into 2 phases. In the 1st phase (initial treatment), all patients received carboplatin + paclitaxel in combination with durvalumab or placebo for a minimum of 4 to a maximum of 6 cycles. Patients without signs of radiological disease progression then received maintenance treatment with durvalumab + placebo (Arm B), durvalumab + olaparib (Arm C) or placebo (Arm A), depending on the treatment arm.

Arm B is not relevant for the assessment and is not presented in the following.

Patients received treatment until objective disease progression (per Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1), clinical deterioration as assessed by the investigator, unacceptable toxicity, or withdrawal of consent.

Primary outcome of the DUO-E study was progression-free survival (PFS). Secondary outcomes were overall survival and outcomes of the categories of morbidity, health-related quality of life and side effects.

Implementation of the appropriate comparator therapy

The G-BA specified carboplatin + paclitaxel, followed by watchful waiting, as the ACT. In the DUO-E study, carboplatin + paclitaxel, followed by placebo in the maintenance phase, was used in the control arm (Arm A). In the maintenance phase, the study was thus not designed for a comparison with watchful waiting. The investigations carried out in the DUO-E study during the maintenance phase, in particular imaging investigations, deviate from the recommendations of the S3 guideline. Overall, however, it is assumed that the maintenance phase in the comparator arm is a sufficient approximation to the ACT watchful waiting.

Relevant subpopulation and data cut-off

According to the SPC, durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + olaparib, is only approved for patients with pMMR status. Both patients with pMMR status and patients with mismatch repair deficient (dMMR) status were included in the DUO-E study. In Module 4 A of the dossier, the company presented analyses of the DUO-E subpopulation, which only included patients with pMMR status (intervention arm [Arm C] versus control arm [Arm A]: 191 versus 192 patients). The subpopulation presented by the company is used for the present benefit assessment.

The prespecified data cut-off of 12 April 2023 is used for the benefit assessment.

Risk of bias

The risk of bias across outcomes is rated as low for the DUO-E study. The results on the outcome of overall survival have a high risk of high due to great uncertainties in the subsequent therapies administered. For the patient-reported outcomes on symptoms, health status and health-related quality of life, in addition to the uncertainties in the subsequent therapies administered, there are no baseline values or no values in the course of the study for a relevant proportion of patients. There is therefore a high risk of bias of all effect estimates on patient-reported data.

For all events in the side effects category, with the exception of myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) (serious adverse events [SAEs]), discontinuation of observation was linked to the end of treatment with the study medication. The extensive premature treatment discontinuations, which were due to many potentially informative reasons, lead to a high risk of bias for these results, with the exception of discontinuation due to adverse events (AEs). The risk of bias of the results for the outcome of MDS/AML (SAEs), which was observed until the end of the study, is rated as low.

Although the risk of bias is low for the outcome of discontinuation due to AEs, the certainty of results for this outcome is reduced. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs.

This means that, after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion “discontinuation” can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

Results

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was shown in favour of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with placebo + carboplatin + paclitaxel, followed by placebo. For this outcome, there is an effect modification by the characteristic of disease status. For patients with newly diagnosed disease, there is a hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT. For patients with recurrent disease, there is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit is therefore not proven for patients with recurrent disease.

Morbidity

Symptoms were recorded using the following instruments: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module 24 (EORTC QLQ-EN24), and Patient Global Impression of Severity (PGIS). Health status was recorded using the following instruments: EQ-5D visual analogue scale (VAS) and Patient Global Impression of Change (PGIC). The time to first deterioration was considered in each case.

Symptoms (recorded using EORTC QLQ-C30, EORTC QLQ-EN24)

No statistically significant difference between treatment groups was shown for any of the following outcomes: fatigue, pain, insomnia and diarrhoea (recorded using the EORTC QLQ-C30), as well as lymphoedema, urological symptoms, gastrointestinal symptoms, back and pelvic pain, tingling/numbness, muscular pain and hair loss (recorded using the EORTC QLQ-EN24). In each case, there is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit is therefore not proven for these outcomes.

For the outcome of dyspnoea (recorded using EORTC QLQ-C30), a statistically significant difference was shown to the disadvantage of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with placebo + carboplatin + paclitaxel, followed by placebo. However, the extent of the effect for this outcome in the category of non-severe/non-serious symptoms/late complications was no more than marginal. Overall, there

is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT for the outcome of dyspnoea; an added benefit is therefore not proven for this outcome.

For each of the outcomes of appetite loss and constipation (recorded using EORTC QLQ-C30) and the outcome of taste change (recorded using EORTC QLQ-EN24), a statistically significant difference was shown to the disadvantage of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with placebo + carboplatin + paclitaxel, followed by placebo. In each case, there is a hint of lesser benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT.

For the outcome of nausea and vomiting (recorded using EORTC QLQ-C30), a statistically significant difference was shown to the disadvantage of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with placebo + carboplatin + paclitaxel, followed by placebo. For this outcome, there is an effect modification by the characteristic of disease status. For patients with recurrent disease, there is a hint of lesser benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT. For patients with newly diagnosed disease, there is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit for patients with newly diagnosed disease is therefore not proven for this outcome.

No suitable data are available for the outcome of sexual/vaginal problems (recorded using EORTC QLQ-EN24), as a maximum of 29 versus 25 patients (15% versus 13%) had a baseline value and a further value during the course of the study. There is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit is therefore not proven for this outcome.

Symptoms (recorded using PGIS)

No statistically significant difference between treatment groups was shown for the symptoms recorded using PGIS. There is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit is therefore not proven for the symptoms recorded using PGIS.

Health status (recorded using EQ-5D VAS, PGIC)

No suitable data are available for health status recorded using PGIC. No statistically significant difference between treatment groups was shown for health status recorded using EQ-5D VAS. There is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit is therefore not proven for the outcome of health status.

Health-related quality of life (recorded using EORTC QLQ-C30, EORTC QLQ-EN24)

Health-related quality of life was recorded with the instruments EORTC QLQ-C30 and EORTC QLQ-EN24. The time to first deterioration was considered in each case.

No statistically significant difference between treatment groups was shown for any of the outcomes of global health status, physical functioning, role functioning, emotional functioning, and social functioning (recorded using EORTC QLQ-C30), and for the outcomes of sexual interest, sexual activity, and poor body image (recorded using EORTC QLQ-EN24). In each case, there is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit is therefore not proven for these outcomes.

For the outcome of cognitive functioning (recorded using the EORTC QLQ-C30), no statistically significant difference between treatment groups was found. However, there is an effect modification by the characteristic of age. For patients < 65 years, there is a hint of lesser benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT. For patients ≥ 65 years, there is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit for patients ≥ 65 years is therefore not proven for this outcome.

No suitable data are available for the outcome of sexual enjoyment (recorded using EORTC QLQ-EN24), as a maximum of 29 versus 25 patients (15% versus 13%) had a baseline value and a further value during the course of the study. There is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit is therefore not proven for this outcome.

Side effects

SAEs, severe AEs, and discontinuation due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; greater or lesser harm is therefore not proven for these outcomes.

Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), immune-mediated SAEs, and immune-mediated severe AEs

No suitable data are available for the PRO-CTCAE outcome, immune-mediated SAEs, and immune-mediated severe AEs. In each case, there is no hint of greater or lesser harm of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; greater or lesser harm is therefore not proven for these outcomes.

MDS/AML (SAEs)

No events occurred in either treatment arm for the outcome of MDS/AML (SAEs), and no statistically significant difference between treatment groups was found. There is no hint of greater or lesser harm of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; greater or lesser harm is therefore not proven for this outcome.

Pneumonitis (severe AEs)

No statistically significant difference between treatment groups was found for the outcome of pneumonitis (severe AEs). There is no hint of greater or lesser harm of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; greater or lesser harm is therefore not proven for this outcome.

Anaemia (severe AEs)

For the outcome of anaemia (severe AEs), a statistically significant difference was shown to the disadvantage of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with placebo + carboplatin + paclitaxel, followed by placebo. There is a hint of greater harm of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT.

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

On the basis of the results presented, the probability and extent of added benefit of the drug durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT is assessed as follows:

Overall, both positive and negative effects of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, were found in comparison with the ACT. For overall survival, the observed effect is based on the entire observation period. For the outcomes in the categories of morbidity, health-related quality of life and side effects, however, they refer exclusively to the shortened period (depending on the outcome, until 2nd disease progression, until start of the 1st subsequent therapy, or until end of treatment [plus a maximum of 90 days]).

[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].

The characteristic of disease status at baseline is an effect modifier for various outcomes. Due to the effect modifications, the results on the added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, compared with the ACT are derived separately by disease status at baseline. The characteristic of age is an effect modifier for the outcome of cognitive functioning (recorded using the EORTC QLQ-C30). However, the results of these subgroup analyses are not taken into account when deriving the added benefit separately according to disease status at baseline, as it is unknown how patients in the subgroups of < 65 years versus ≥ 65 years were distributed in the subgroups of newly diagnosed versus recurrent.

Patients with newly diagnosed disease

For patients with newly diagnosed disease at baseline, there is a hint of major added benefit on the side of positive effects in the category of mortality. On the negative side, however, there are hints of lesser benefit with the extent “considerable” or “minor” in non-serious/ non-severe symptoms/late complications in the outcomes of appetite loss, constipation, and taste change. In addition, there is a hint of greater harm with the extent “considerable” for anaemia (severe AEs). In summary, there is a hint of considerable added benefit for patients with newly diagnosed disease at baseline.

Patients with recurrent disease

No difference between treatment groups for patients with recurrent disease at baseline was found for the outcome of overall survival. On the negative side, there is a hint of lesser benefit with the extent “considerable” for these patients in non-serious/non-severe symptoms/late complications in the outcome of nausea and vomiting. Furthermore, hints of lesser benefit with the extent “considerable” or “minor” were also found for the outcomes of appetite loss, constipation, and taste change. In addition, there is a hint of greater harm with the extent “considerable” for anaemia (severe AEs). In summary, there is a hint of a lesser benefit for patients with recurrent disease at baseline due to the existing negative effects.

Table 3 shows a summary of the probability and extent of added benefit of durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + olaparib.

Table 3: Durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
First-line treatment of adult patients with primary advanced or recurrent pMMR endometrial cancer who are candidates for systemic therapy[b], followed by maintenance treatment with durvalumab in combination with olaparib[c]	Carboplatin + paclitaxel[d], followed by watchful waiting	▪ Patients with newly diagnosed disease: hint of considerable added benefit[e] ▪ Patients with recurrent disease: hint of lesser benefit[e]

a. Presented is the ACT specified by the G-BA.
b. In this therapeutic indication, the G-BA assumes that the patients have not yet received systemic therapy as postoperative or adjuvant therapy to treat the primary advanced disease and have not yet received chemotherapy to treat the recurrence.
c. According to the SPC, olaparib is used in patients whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel.
d. Treatment with carboplatin in combination with paclitaxel is not approved for this therapeutic indication. Accordingly, the use of carboplatin in combination with paclitaxel represents an off-label use. According to the G-BA, for patients in the present therapeutic indication, the off-label use is generally preferable to the drugs currently approved in the therapeutic indication, according to the generally recognized state of medical knowledge, §6 (2), sentence 3, number 2, AM-NutzenV.
e. The DUO-E study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; pMMR: mismatch repair proficient

The approach for the derivation of an overall conclusion on added benefit is 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 durvalumab in combination with carboplatin and paclitaxel (hereinafter referred to as "durvalumab + carboplatin + paclitaxel"), followed by maintenance treatment with durvalumab in combination with olaparib (hereinafter referred to as "durvalumab + olaparib"), compared with the ACT for the first-line treatment of adult patients with primary advanced or recurrent pMMR endometrial cancer who are candidates for systemic therapy.

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

Table 4: Research question of the benefit assessment of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib

Therapeutic indication	**ACT[a]**
First-line treatment of adult patients with primary advanced or recurrent pMMR endometrial cancer who are candidates for systemic therapy[b], followed by maintenance treatment with durvalumab in combination with olaparib[c]	Carboplatin + paclitaxel[d], followed by watchful waiting

a. Presented is the ACT specified by the G-BA.
b. In this therapeutic indication, the G-BA assumes that the patients have not yet received systemic therapy as postoperative or adjuvant therapy to treat the primary advanced disease and have not yet received chemotherapy to treat the recurrence.
c. According to the SPC [3], olaparib is used in patients whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel.
d. Treatment with carboplatin in combination with paclitaxel is not approved for this therapeutic indication. Accordingly, the use of carboplatin in combination with paclitaxel represents an off-label use. According to the G-BA, for patients in the present therapeutic indication, the off-label use is generally preferable to the drugs currently approved in the therapeutic indication, according to the generally recognized state of medical knowledge, §6 (2), sentence 3, number 2, AM-NutzenV.

AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; G-BA: Federal Joint Committee; pMMR: mismatch repair proficient; SPC: Summary of Product Characteristics

In this assessment, the initial phase of first-line therapy (durvalumab + carboplatin + paclitaxel or carboplatin + paclitaxel) is referred to as initial treatment. The subsequent therapy phase with durvalumab and olaparib is referred to as maintenance treatment. This assessment refers to the entire therapeutic strategy.

Deviating from the research question of the G-BA, the company formed 2 subpopulations, specifying an ACT for its subpopulation 2 that deviated from the G-BA:

- Subpopulation 1: patients who have not been pretreated with chemotherapy or for whom – despite pretreatment with chemotherapy – further chemotherapy alone is an option:
  - carboplatin + paclitaxel

- Subpopulation 2: patients who have been pretreated with chemotherapy and for whom re-induction with chemotherapy alone is not an option:
  - pembrolizumab + lenvatinib

For subpopulation 1, the company largely followed the ACT specified by the G-BA. Although the company did not name maintenance treatment with watchful waiting, this deviation has no consequences for the benefit assessment, as it had no effect on the completeness of the study pool. For subpopulation 2, the company departed from the ACT specified by the G-BA. This deviation of the company also remains without consequence, as it did not present any data for this subpopulation.

The present assessment is conducted on the basis of the research question and ACT specified 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 to derive 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 durvalumab + olaparib (status: 2 July 2024)
- bibliographical literature search on durvalumab + olaparib (last search on 2 July 2024)
- search in trial registries/trial results databases for studies on durvalumab + olaparib (last search on 1 July 2024)
- search on the G-BA website for durvalumab + olaparib (last search on 2 July 2024)

To check the completeness of the study pool:

- search in trial registries for studies on durvalumab (last search on 3 September 2024); for search strategies, see Appendix I A of the full dossier assessment

No additional relevant study was identified from the check of the completeness of the company's study pool.

Based on its information retrieval, the company identified the RCT DUO-E and used this study to assess the added benefit for its subpopulation 1. The company did not identify any relevant study for its subpopulation 2 and did not present any data in Module 4 A of the dossier (for the subpopulations formed by the company, see Chapter I 2).

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib vs. carboplatin + paclitaxel, followed by watchful waiting

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
D9311C00001 (DUO-E[c])	Yes	Yes	No	Yes [4-7]	Yes [8-10]	Yes [11]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; RCT: randomized controlled trial

The study pool for the present benefit assessment consists of the RCT DUO-E. The study pool corresponds to that of the company, which used the DUO-E study for its subpopulation 1 (see Chapter I 2).

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: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[c]
DUO-E	RCT, double-blind, parallel	Adult patients (≥ 18 years) with primary advanced (FIGO stage III or IV) or recurrent[d] endometrial cancer ▪ with dMMR or pMMR status ▪ without prior systemic chemotherapy[e] ▪ ECOG PS ≤ 1	▪ Arm A: placebo + carboplatin + paclitaxel, followed by placebo[f] (N = 241)[g] ▪ Arm B: durvalumab + carboplatin + paclitaxel, followed by durvalumab + placebo[f] (N = 238)[g, h] ▪ Arm C: durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib[f] (N = 239)[g] Relevant subpopulation thereof (pMMR status[i]): ▪ Arm A: placebo + carboplatin + paclitaxel, followed by placebo (n = 192) ▪ Arm C: durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib (n = 191)	Screening: 28 days Treatment: until disease progression, clinical deterioration as assessed by the investigator, unacceptable toxicity, withdrawal of consent Observation[j]: outcome-specific, at most until death, lost to follow-up, withdrawal of consent, or end of study	202 centres in Australia, Belgium, Brazil, Canada, China, Colombia, Estonia, Germany, Greece, Hong Kong, Hungary, India, Israel, Japan, Lithuania, Mexico, Poland, Republic of Korea, Russia, Singapore, Spain, United States 5/2020–ongoing Data cut-offs: ▪ 30 June 2022[k] ▪ 12 April 2023[l] ▪ 18 October 2023[m]	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

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

a. Followed by maintenance treatment with durvalumab + olaparib.
b. Followed by maintenance treatment with placebo.
c. 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.
d. Where the potential for cure by surgery alone or in combination with radiotherapy or systemic therapy is poor.
e. For patients with recurrent disease, prior systemic anti-cancer treatment is allowed if it was administered in the adjuvant setting (as part of the upfront/adjuvant anti-cancer treatment, which may be concurrent or following chemoradiation) and there was ≥ 12 months from date of last dose administered to date of relapse.
f. Patients without progression (i.e. complete response [CR], partial response [PR], or stable disease [SD]) during the chemotherapy phase transitioned to the maintenance phase and received placebo (IV) (Arm A), durvalumab + placebo (Arm B) or durvalumab + olaparib (Arm C).
g. Recruitment into the global population took place until 718 patients were included in the study (randomization of the last patient on 20 April 2022). Recruitment was then continued in China and Hong Kong until another 87 patients were included . According to the company, a CSR is not yet available for the China cohort. For an explanation, see the following text section.
h. Arm B is not relevant for the assessment and is not presented in the following.
i. According to the randomization stratification factor.
j. Outcome-specific data are described in Table 8.
k. Futility analysis of PFS for the global population, prespecified after occurrence of 150 PFS events for the comparison of Arm B vs. Arm A, and 141 PFS events for the comparison of Arm C vs. Arm A (expected approx. 2 months after randomization of the first patient).
l. Primary analysis of PFS for the global population, prespecified after occurrence of about 299 PFS events for the comparison of Arm B vs. Arm A, and about 281 PFS events for the comparison of Arm C vs. Arm A (expected approx. 43 months after randomization of the first patient). The first interim analysis of overall survival was also to be carried out at this time point.
m. Data cut-off submitted to the FDA as part of the 120-day safety update.

AE adverse event; CSR: clinical study report; dMMR: mismatch repair deficient; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FDA: Food and Drug Administration; FIGO: International Federation of Gynecology and Obstetrics; N: number of analysed patients; PFS: progression-free survival; pMMR: mismatch repair proficient; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

Study	Intervention	Comparison
DUO-E	6 cycles of 3 weeks each[c, d] durvalumab 1120 mg IV on Day 1 of a cycle + paclitaxel 175 mg/m² IV on Day 1 of a cycle + carboplatin AUC 6 IV on Day 1 of a cycle Maintenance treatment (from Cycle 7[c]) durvalumab 1500 mg IV every 4 weeks[e] + olaparib 600 mg/day orally (300 mg twice daily)[e, f]	6 cycles of 3 weeks each[c, d] placebo IV on day 1 of a cycle + paclitaxel 175 mg/m² IV on Day 1 of a cycle + carboplatin AUC 6 IV on Day 1 of a cycle Maintenance treatment (from Cycle 7[c]) placebo IV every 4 weeks[e] + placebo, orally (twice daily)[e, f]
	Dose adjustment ▪ Carboplatin: Dose reduction to AUC 5 may be considered for patients who have previously received pelvic radiotherapy ▪ Carboplatin and paclitaxel: dose adjustment permitted according to local clinical guidelines; it was possible to substitute carboplatin with cisplatin, or paclitaxel with nab-paclitaxel or docetaxel ▪ Durvalumab: no dose reductions permitted[g] ▪ Olaparib: ▫ in case of toxicity: 2 dose reductions in 50 mg steps allowed (250 mg twice daily and then 200 mg twice daily) ▫ in moderate renal function disorder: dose reduction to 200 mg twice daily ▫ with concomitant use of strong or moderate CYP3A inhibitors (only permitted if no other alternative medication is possible): dose reduction to 100 mg or 150 mg twice daily	

Table 7: Characteristics of the intervention – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

Study	Intervention	Comparison
	Disallowed prior and concomitant treatment ▪ major surgery within 2 weeks before baseline[h] ▪ allogeneic organ transplantation previous allogenic bone marrow transplant or double umbilical cord blood transplantation ▪ ▪ radiotherapy to > 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug, radiotherapy (except palliative) during the study ▪ prior treatment with PARP inhibitors ▪ prior (within 2 weeks before the first dose of durvalumab) or concomitant use of immunosuppressants (e.g. systemic corticosteroids > 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, tumour necrosis factor blocker) ▪ monoclonal antibodies directed against CTLA-4, PD-1, PD-L1 or PD-L2 immunosuppressive therapies ▪ any other concurrent chemotherapy, immunotherapy, or biologic or hormonal therapy for oncological treatment other than the investigational therapy ▪ live vaccines within 30 days before and up to 30 days after the first dose of the study medication ▪ concomitant use of strong or moderate CYP3A inhibitors and inducers (concomitant use only permitted if no other alternative medication is possible; alternatively washout period of 2 to 5 weeks [depending on the drug] prior to starting the study medication) ▪ EGFR tyrosine kinase inhibitors **Allowed concomitant treatment** ▪ intranasal, inhaled, topical steroids, or local steroid injections (e.g. intra-articular injection) ▪ systemic corticosteroids ≤ 10 mg/day of prednisone or its equivalent ▪ steroids as premedication for hypersensitivity reactions	

a. Followed by maintenance treatment with durvalumab + olaparib.
b. Followed by maintenance treatment with placebo.
c. If required due to toxicity, 4 cycles of platinum-based chemotherapy may be given as a minimum. Patients must have a minimum of 4 cycles of platinum-based chemotherapy to continue into the maintenance phase.
d. The following order of study treatment was recommended according to the study protocol: 1) durvalumab/placebo, 2) paclitaxel, 3) carboplatin.
e. If one component of the study medication was discontinued due to toxicity, the other study medication could be continued.
f. Start of treatment at least 3 weeks and at most 9 weeks from the last day of chemotherapy infusion; if a patient could not start olaparib/placebo maintenance treatment within 9 weeks, treatment with durvalumab (1500 mg)/placebo alone every 4 weeks was to be continued in the maintenance phase.
g. Patients with a body weight of ≤ 30 kg or less were to receive a weight-based dosing of 20 mg/kg of durvalumab every 4 weeks until the body weight increased to > 30 kg.
h. Local surgery of isolated lesions for palliative intent or diagnostic staging was allowed.

AUC: area under the curve; CTLA-4: cytotoxic T-lymphocyte-associated antigen; EGFR: epidermal growth factor receptor; CYP3A: cytochrome P450 3A; IV: intravenous; PARP: poly(adenosine diphosphate-ribose) polymerase; PD-1: programmed cell death 1; PD-L1/2: programmed death ligand 1/2; RCT: randomized controlled trial

Study design

The DUO-E study is an ongoing 3-arm randomized, double-blind study comparing

- placebo + carboplatin + paclitaxel, followed by placebo (Arm A),
- durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + placebo (Arm B),
- durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + olaparib (Arm C).

The study included adult patients with histologically confirmed diagnosis of epithelial endometrial cancer of all histologies (including carcinosarcomas) and regardless of MMR status. Besides patients with newly diagnosed FIGO stage III or FIGO stage IV disease, the study also included patients with recurrence where the potential for cure by surgery alone or in combination with radiotherapy or systemic therapy was poor. The patients had to be naive to systemic therapy for the current stage of the disease. For patients with recurrent disease only, prior systemic treatment was allowed only if it was administered in the adjuvant setting (as part of the upfront or adjuvant anti-cancer treatment, which may be concurrent or following chemoradiation) and there was at least 12 months from date of last dose of systemic treatment administered to date of subsequent relapse. The MMR status of the endometrial cancer had to be evaluated before randomization using the Ventana MMR immunohistochemistry panel. Enrolment was limited to patients in good general health corresponding to an ECOG PS ≤ 1.

A total of 718 patients with endometrial cancer were randomly assigned in a 1:1:1 ratio to one of the 3 treatment arms (Arm A, N = 241; Arm B, N = 238; Arm C, N = 239). Stratification was according to MMR status (deficient versus proficient), disease status (newly diagnosed versus recurrent) and geographic region (Asia versus rest of the world).

Treatment with durvalumab and olaparib was in compliance with the recommendations of the SPCs [3,12].

Carboplatin + paclitaxel was administered as chemotherapy in all 3 study arms. The SPC for durvalumab provides no information on the dosage of carboplatin + paclitaxel. The dosages and dose reductions of paclitaxel and carboplatin used in the DUO-E study correspond to the guideline recommendations [13,14]. In compliance with the SPC [12], treatment with carboplatin and paclitaxel in the DUO-E study was restricted to a maximum of 6 treatment cycles. The number of cycles could be reduced to 4 cycles in case of toxicity. However, at least 4 cycles of chemotherapy were required for patients to continue into the maintenance phase. Overall, treatment regimen and dosage are comprehensible.

The DUO-E study is divided into 2 phases. In the 1st phase (initial treatment), all patients received carboplatin + paclitaxel in combination with durvalumab or placebo for a minimum of 4 to a maximum of 6 cycles. Patients without signs of radiological disease progression then received maintenance treatment with durvalumab + placebo (Arm B), durvalumab + olaparib (Arm C) or placebo (Arm A), depending on the treatment arm.

Arm B is not relevant for the assessment and is not presented in the following.

Patients received treatment until objective disease progression (per RECIST version 1.1), clinical deterioration as assessed by the investigator, unacceptable toxicity, or withdrawal of consent.

Primary outcome of the DUO-E study was PFS. Secondary outcomes were overall survival and outcomes of the categories of morbidity, health-related quality of life and side effects.

Implementation of the appropriate comparator therapy in the maintenance phase

The G-BA specified carboplatin + paclitaxel, followed by watchful waiting, as the ACT.

In the DUO-E study, carboplatin + paclitaxel, followed by placebo in the maintenance phase, was used in the control arm (Arm A). In the maintenance phase, the study was thus not designed for a comparison with watchful waiting. The implementation of the ACT in the maintenance phase is described below.

The following examinations were performed for the assessment of the disease status or the detection of disease progression in the maintenance phase of the DUO-E study:

- computed tomography (CT) or magnetic resonance imaging (MRI) scans of chest, abdomen and pelvis (and any area where disease was identified at baseline and any other sites at which new lesions were suspected) every 12 weeks (± 1 week) until disease progression
- vital signs (blood pressure, heart rate, temperature) and ECOG PS every 4 weeks until disease progression
- physical examination every 4 weeks until disease progression (extent of examination based on clinical signs or symptoms)

The S3 guideline on endometrial cancer [13] recommends clinical gynaecological examination with speculum and rectovaginal palpation examination at 3 to 6-month intervals for the first 3 years after completion of primary therapy and every 6 months in years 4 and 5. Physical examinations were performed more frequently in the DUO-E study than recommended by the guidelines (every 4 weeks). The extent to which gynaecological examinations were part of the physical examinations in the DUO-E study is not explicitly stated in the study documents.

However, it is assumed that gynaecological examinations were included. According to the S3 guideline [13], imaging studies should not be performed in asymptomatic patients. In the DUO-E study, in contrast, imaging examinations were performed at short intervals (every 3 months) regardless of symptoms. Overall, however, it is assumed that the maintenance phase in the comparator arm is a sufficient approximation to the ACT watchful waiting.

Relevant subpopulation of the DUO-E study

According to the SPC [12], durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + olaparib, is only approved for patients with pMMR status. Both patients with pMMR status and patients with dMMR status were included in the DUO-E study. In Module 4 A of the dossier, the company presented analyses of the DUO-E subpopulation, which only included patients with pMMR status (intervention arm [Arm C] versus control arm [Arm A]: 191 versus 192 patients). The subpopulation presented by the company is used for the present benefit assessment.

Cohorts

According to the study protocol, patients were to be recruited globally (including China) into the DUO-E study until approximately 699 patients were randomized (global population). On reaching these patient numbers, global recruitment was to be closed. The study protocol stipulated that, if necessary, enrolment in China and Hong Kong was to be continued until a total of approximately 129 patients were included (China cohort).

The clinical study report (CSR) presented the global population (n = 718; randomization of the last patient on 20 April 2022), which comprises a total of 42 patients from China and Hong Kong. The data on the relevant subpopulation presented in Module 4 A of the dossier were also based on the global population. After the global recruitment closure, 87 additional patients in China and Hong Kong were included in the study (11% in relation to the total study population of 805 patients). It can be assumed that this group also included patients with pMMR, who are relevant to the present research question. The company did not present any data for these patients in Module 4; according to the company, a CSR does not yet exist for the China cohort. For the present benefit assessment, it is therefore assumed that no results are yet available for the patients from the China cohort. The data based on the global population presented by the company are used for the benefit assessment.

Data cut-offs

To date, 3 data cut-offs have been performed for the ongoing DUO-E study:

- Data cut-off of 30 June 2022: futility analysis on PFS for the global population, prespecified after occurrence of at least 50% of the planned number of PFS events (i.e.

150 of 299 or 141 of 281 PFS events) for the comparison of Arm B versus Arm A or Arm C versus Arm A (approx. 2 months after randomization of the first patient)

- Data cut-off of 12 April 2023: primary analysis of PFS for the global population, prespecified after occurrence of about 299 PFS events for the comparison of Arm B versus Arm A, and about 281 PFS events for the comparison of Arm C versus Arm A (approx. 43 months after randomization of the first patient); the first interim analysis of overall survival was also to be carried out at this time point
- Data cut-off of 18 October 2023: data cut-off submitted to the Food and Drug Administration (FDA) as part of the 120-day safety update

The company presented the prespecified data cut-off of 12 April 2023 for the outcomes of the outcome categories of mortality, morbidity, health-related quality of life, and side effects. This means that the data cut-off is complete in accordance with the requirements of the dossier templates (see G-BA rules of procedure [15]). For the data cut-off of 18 October 2023, the company presented analyses for the outcomes of the categories of mortality and side effects. To derive the added benefit, the company used the data cut-off of 12 April 2023 for all outcome categories except side effects. For the outcome category of side effects, it used the data cut-off of 18 October 2023.

It is not clear from the available information that the FDA explicitly requested the data cut-off of 18 October 2023 submitted by the company. The prespecified data cut-off of 12 April 2023 is therefore used for the benefit assessment.

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b]

Study **Outcome category** **Outcome**	**Planned follow-up observation**
DUO-E	
Mortality	
Overall survival	▪ Until death, withdrawal of consent, loss to follow-up or final analysis of overall survival[c]
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-EN24, PGIS)	▪ Until 2nd disease progression[d] or death (PFS2)
Health status (EQ-5D VAS, PGIC)	▪ Until 2nd disease progression[d] or death (PFS2)
Health-related quality of life	
EORTC QLQ-C30, EORTC QLQ-EN24	▪ Until 2nd disease progression[d] or death (PFS2)
Side effects	
All outcomes of the side effects category (except PRO-CTCAE, MDS/AML)	▪ Until the earlier of the following 2 time points: ▫ Start of first subsequent therapy ▫ End of the follow-up observation period (30 days after the last dose of olaparib/placebo or 90 days after the last dose of durvalumab/placebo [whichever occurs last])
PRO-CTCAE	▪ UP to 30 days after the last dose of the study medication
MDS/AML (SAEs[e])	▪ Until end of study

a. Followed by maintenance treatment with durvalumab + olaparib.
b. Followed by maintenance treatment with placebo.
c. For the global population, prespecified after occurrence of about 280 events for the comparison of Arm B vs. Arm A, and for the comparison of Arm C vs. Arm A (approx. 63 months after randomization of the first patient).
d. Defined as the earliest progression event after the first subsequent therapy.
e. All MDS/AML events were recorded as SAEs, according to the study protocol.

AE: adverse event; AML: acute myeloid leukaemia; EORTC: European Organisation for Research and Treatment of Cancer; MDS: myelodysplastic syndrome; PFS: progression-free survival; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Follow-up observation until death, withdrawal of consent, lost to follow-up or final analysis of overall survival was planned for the outcome of overall survival.

A positive aspect to be noted for the outcomes on morbidity and health-related quality of life is that these continued to be observed beyond the first disease progression until the 2nd disease progression or death (PFS2). In the case of 2nd disease progression, observation was still shortened compared with overall survival, however.

The observation periods for all outcomes in the side effects category (except MDS/AML) are systematically shortened, as they were only recorded up to the start of the first subsequent therapy or for the period of treatment with the study medication (plus 30 days or 90 days), whichever occurred first. The observation period is also systematically shortened for the symptomatic AEs recorded using the PRO-CTCAE, as the observation only covered the period of treatment with the study medication plus 30 days. For MDS/AML, however, follow-up observation was planned until the end of the study.

However, drawing a reliable conclusion on the total study period or the time until patient death would require recording the outcomes with shortened observation period described above throughout the entire period, as was done for survival and MDS/AML.

Characteristics of the relevant subpopulation

Table 9 shows the patient characteristics in the pMMR subpopulation of the DUO-E study relevant for the benefit assessment.

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

Study **Characteristic** **Category**	**Durvalumab + carboplatin + paclitaxel[a]** **N[c] = 191**	**Placebo + carboplatin + paclitaxel[b]** **N[c] = 192**
DUO-E		
Age [years], mean (SD)	63 (10)	62 (10)
Family origin, n (%)		
White	104 (55)	113 (59)
Asian	57 (30)	58 (30)
Black or African American	13 (7)	8 (4)
Other	9 (5)	10 (5)
Native American or Alaska Native	6 (3)	0 (0)
Native Hawaiian or other Pacific Islander	1 (< 1)	2 (1)
Not reported	1 (< 1)	1 (< 1)
Region, n (%)		
Asia[d]	54 (28)	54 (28)
Rest of the world	137 (72)	138 (72)
ECOG PS, n (%)		
0	135 (71)	127 (66)
1	56 (29)	65 (34)
2	0 (0)	0 (0)

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

Study Characteristic Category	**Durvalumab + carboplatin + paclitaxel[a] N[c] = 191**	**Placebo + carboplatin + paclitaxel[b] N[c] = 192**
Histology type, n (%)		
Endometrioid	107 (56)	98 (51)
Serous	42 (22)	52 (27)
Carcinosarcoma	18 (9)	19 (10)
Mixed, epithelial	8 (4)	8 (4)
Other	5 (3)	5 (3)
Clear-cell	8 (4)	7 (4)
Undifferentiated	3 (2)	3 (2)
Mucinous	0 (0)	0 (0)
Disease status at baseline[e], n (%)		
Recurrent	99 (52)	101 (53)
Newly diagnosed	92 (48)	91 (47)
FIGO stage at the time of primary diagnosis, n (%)		
IA	22 (12)	28 (15)
IB	26 (14)	22 (11)
II	6 (3)	11 (6)
IIIA	13 (7)	8 (4)
IIIB	6 (3)	4 (2)
IIIC	19 (10)	22 (11)
IIIC1	12 (6)	15 (8)
IIIC2	7 (4)	7 (4)
Not specified	0 (0)	0 (0)
IVA	0 (0)	0 (0)
IVB	98 (51)	96 (50)
Missing	1 (< 1)	1 (< 1)
Disease classification at baseline, n (%)		
Metastatic	156 (82)	163 (85)
Locally advanced	21 (11)	20 (10)
Missing	14 (7)	9 (5)
Duration of disease: time from last progression to randomization – recurrent patients [weeks], mean (SD)	N = 101 8.1 (6.3)	N = 102 8.6 (10.8)
Debulking surgery history, n (%)	167 (87)	164 (85)
Prior chemotherapy, n (%)	50 (26)	46 (24)

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

Study Characteristic Category	**Durvalumab + carboplatin + paclitaxel[a] N[c] = 191**	**Placebo + carboplatin + paclitaxel[b] N[c] = 192**
Prior cancer therapy by drug class[f], n (%)		
Cytotoxic chemotherapy	50 (26)	46 (24)
Hormonal therapy	0 (0)	2 (1)
Targeted therapy	1 (< 1)	0 (0)
Radiotherapy	67 (35)	53 (28)
Treatment discontinuation total[g], n (%)[h]	N = 191 117 (61)	N = 190 159 (84)
Treatment discontinuation durvalumab/placebo, n (%)[i]	N = 191 121 (63)	N = 190 160 (84)
Treatment discontinuation olaparib/placebo, n (%)[j]	N = 151 87 (58)	N = 144 115 (80)
Study discontinuation, n (%)[k]	56 (29)	70 (36)

a. Followed by maintenance treatment with durvalumab + olaparib.
b. Followed by maintenance treatment with placebo.
c. Number of randomized patients; values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. Treatment discontinuation refers to the number of patients who received at least one dose of the respective treatment.
d. Of which from China: 10 vs. 10 patients, or 5% vs. 5% of the intervention vs. control arm.
e. According to the randomization stratification factor; in the intervention vs. control arm, 11 vs. 10 of the patients with newly diagnosed disease had FIGO stage III at initial diagnosis, 78 vs. 77 patients had FIGO stage IV.
f. Patients who received more than one drug from a drug class were only counted once for this drug class.
g. Number of patients who were no longer receiving any of the following drugs at the time of the data cut-off: carboplatin (or cisplatin as substitute), paclitaxel (or nab-paclitaxel as substitute), durvalumab/placebo, olaparib/placebo; 2 patients in the control arm did not receive any treatment.
h. No reasons were provided for discontinuation of the last discontinued drug/placebo.
i. Common reasons for treatment discontinuation of durvalumab or placebo in the intervention vs. control arm were: objective disease progression in 47% vs. 63%, AEs in 10% vs. 7% of randomized patients.
j. Common reasons for treatment discontinuation of olaparib or placebo in the intervention vs. control arm were: objective disease progression in 32% vs. 52%, AEs in 8% vs. 2% of randomized patients
k. Common reasons for study discontinuation in the intervention vs. control arm were: withdrawal of consent in 6% vs. 7% of randomized patients; the data also include patients who died during the study (intervention arm: 23% vs. control arm: 29%).

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: International Federation of Gynecology and Obstetrics; n: number of patients in the category; N: number of randomized (or analysed) patients; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics are largely balanced between the 2 treatment arms.

The mean patient age was about 63 years, and most patients were of White (57%) or Asian (30%) family origin. The majority of patients had a good general health (ECOG PS of 0). Around 52% of patients had recurrent disease; around 11% patients with newly diagnosed disease had FIGO stage III, and 85% had FIGO stage IV at initial diagnosis. Before the start of the study, 86% of patients had undergone surgery for endometrial cancer; 35% of patients in the intervention arm and 28% of patients in the control arm had undergone radiotherapy. 25% of patients had already received cytotoxic chemotherapy. As the inclusion criteria did not allow the patients to have received systemic therapy for the current stage, it can be assumed that this was the neoadjuvant or adjuvant treatment of the primary disease of the patients with recurrence.

The maintenance phase was started by 79% of patients in the intervention arm and 75% of patients in the control arm. The proportion of patients with treatment discontinuation regardless of treatment phase was lower in the intervention arm at 61% than in the control arm at 84%. 29% of patients in the intervention arm and 36% of those in the control arm discontinued the study.

Information on the course of the study

Table 10 shows patients' mean and median treatment durations and the mean and median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

Study **Duration of the study phase** **Outcome category/outcome**	**Durvalumab + carboplatin + paclitaxel[a]** **N = 191**	**Placebo + carboplatin + paclitaxel[b]** **N = 192**
DUO-E		
Treatment duration for carboplatin[c]		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Treatment duration for paclitaxel[d]		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Treatment duration for durvalumab/placebo [months[e]]	N = 191	N = 190
Median [min; max]	10.6 [0.2; 32.3]	8.7 [0.2; 32.5]
Mean (SD)	11.7 (7.0)	9.5 (5.7)
Treatment duration for olaparib/placebo [months[e]]	N = 151	N = 144
Median [min; max]	8.5 [0.1; 28.2]	5.5 [-0.1; 28.6]
Mean (SD)	9.3 (6.2)	7.1 (5.2)

Table 10: Information on the course of the study – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

Study **Duration of the study phase** **Outcome category/outcome**	**Durvalumab + carboplatin + paclitaxel[a]** **N = 191**	**Placebo + carboplatin + paclitaxel[b]** **N = 192**
Observation period [months]		
Overall survival[f]	N = 191	N = 192
Median [min; max]	17.3 [0.2; 33.4]	16.5 [0.2; 32.9]
Mean (SD)	ND	ND
Morbidity (symptoms)[g]	N = 191	N = 192
EORTC QLQ-C30		
Median [min; max]	12.4 [0.0; 32.8]	9.6 [0.0; 32.6]
Mean (SD)	ND	ND
EORTC QLQ-EN24		
Median [min; max]	11.7 [0.0; 32.8]	9.6 [0.0; 32.6]
Mean (SD)	ND	ND
PGIS		
Median [min; max]	11.7 [0.0; 32.8]	9.6 [0.0; 32.6]
Mean (SD)	ND	ND
Morbidity (health status)[g]	N = 191	N = 192
EQ-5D VAS		
Median [min; max]	11.7 [0.0; 32.8]	9.6 [0.0; 32.6]
Mean (SD)	ND	ND
PGIC		
Median [min; max]	13.3 [0.0; 32.8]	10.3 [0.0; 32.6]
Mean (SD)	ND	ND
Health-related quality of life[g]	N = 191	N = 192
EORTC QLQ-C30		
Median [min; max]	12.4 [0.0; 32.8]	9.6 [0.0; 32.6]
Mean (SD)	ND	ND
EORTC QLQ-EN24		
Median [min; max]	11.7 [0.0; 32.8]	9.6 [0.0; 32.6]
Mean (SD)	ND	ND

Table 10: Information on the course of the study – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

Study **Duration of the study phase** **Outcome category/outcome**	**Durvalumab + carboplatin + paclitaxel[a]** **N = 191**	**Placebo + carboplatin + paclitaxel[b]** **N = 192**
Side effects	N = 191	N = 190
All outcomes of the side effects category (except PRO-CTCAE, MDS/AML)[h]		
Median [min; max]	12.5 [0.2; 33.2]	10.1 [0.2; 32.9]
Mean (SD)	ND	ND
PRO-CTCAE	ND	ND
MDS/AML (SAEs)[i]	N = 191	N = 190
Median [min; max]	17.1 [0.2; 33.3]	16.5 [0.2; 32.9]
Mean (SD)	ND	ND

a. Followed by maintenance treatment with durvalumab + olaparib.
b. Followed by maintenance treatment with placebo.
c. Number of carboplatin infusions (or cisplatin as substitute) or placebo infusions received in the intervention vs. control arm, mean (SD): 5.5 (1.1) vs. 5.5 (1.2); median [min; max]: 6.0 [1; 6] vs. 6.0 [1; 6]; administration of at least 4 to a maximum of 6 cycles was planned (see Table 7).
d. Number of paclitaxel infusions (or nab-paclitaxel as substitute) or placebo infusions received in the intervention vs. control arm, mean (SD): 5.5 (1.1) vs. 5.5 (1.3); median [min; max]: 6.0 [1; 7] vs. 6.0 [1; 7]; administration of at least 4 to a maximum of 6 cycles was planned (see Table 7).
e. Institute's calculation from information provided by the company in weeks; the company provided a negative value as the minimum treatment duration for placebo for olaparib in the control arm, which is implausible.
f. All patients are included in the calculation with the time observed for them until event or censoring.
g. All patients with at least one dose of study treatment are included in the calculation with the time observed for them until the earliest of the following points in time: last questionnaire recording, death, data cut-off. For patients without any usable recording in the course of the study, the observation period is set to 1 day. Except for the PGIC, the observation period is also set to 1 day for patients who do not have a baseline value.
h. All patients with at least one dose of study treatment are included in the calculation with the time observed for them until censoring. Censoring takes place at the initiation of the first subsequent antineoplastic therapy or at the end of follow-up observation, whichever was first. Follow-up observation ended 30 days after discontinuation of olaparib/placebo or 90 days after discontinuation of durvalumab/placebo, whichever was last.
i. All patients are included in the calculation with the time observed for them until withdrawal of consent, loss to follow-up, end of study, or death.

AE: adverse event; AML: acute myeloid leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; MDS: myelodysplastic syndrome; min: minimum; N: number of analysed patients; ND: no data; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; pMMR: mismatch repair proficient; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale

The median treatment duration for durvalumab and placebo was longer in the intervention arm (approx. 11 months) than in the control arm (approx. 9 months). The median treatment duration for olaparib and placebo was also longer in the intervention arm (approx. 9 months) than in the control arm (approx. 6 months).

The median observation periods for overall survival and MDS/AML were around 17 months in the intervention and control arm. The median observation periods for the outcomes in the category of morbidity (except PGIC) and health-related quality of life were about 12 months in the intervention arm and about 9 months in the control arm. The median observation periods for the outcomes in the side effects category (except PRO-CTCAE, MDS/AML) and PGIC were about 13 months in the intervention arm and about 10 months in the control arm. No information on the observation period is available for the symptomatic AEs recorded using PRO-CTCAE. Since the recording for the PRO-CTCAE was linked to the end of treatment (up to 30 days after the last dose of study medication; see Table 8), it is assumed that the observation period also differed between the treatment arms. Overall, the observation periods for all outcomes in the categories of morbidity, health-related quality of life and side effects (except MDS/AML) differed between the treatment arms.

Overall, the observation period for the outcomes in the category of morbidity, health-related quality of life and side effects (except MDS/AML) is shortened compared with the outcomes on mortality and MDS/AML, which were recorded over the entire period.

Information on subsequent therapies

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

Table 11: Information on subsequent antineoplastic therapies – direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b]

Study (data cut-off) Drug class[c] Drug[c]	Patients with subsequent therapy, n (%)	
	Durvalumab + carboplatin + paclitaxel[a] N = 191	Placebo + carboplatin + paclitaxel[b] N = 192
DUO-E (data cut-off 18 October 2023)		
Total (all subsequent treatment lines)[d, e]	94 (49.2)	114 (59.4)
Immunotherapy	29 (30.9)	53 (46.5)
Pembrolizumab	28 (29.8)	47 (41.2)
Hormonal therapy	8 (8.5)	14 (12.3)
Letrozole	3 (3.2)	7 (6.1)
Cytotoxic chemotherapy	55 (58.5)	48 (42.1)
Carboplatin	24 (25.5)	13 (11.4)
Cisplatin	9 (9.6)	8 (7.0)
Doxorubicin	10 (10.6)	13 (11.4)
Doxorubicin hydrochloride	13 (13.8)	6 (5.3)
Doxorubicin, liposomal	6 (6.4)	5 (4.4)
Paclitaxel	17 (18.1)	12 (10.5)
Targeted therapy	34 (36.2)	57 (50.0)
Bevacizumab	5 (5.3)	9 (7.9)
Lenvatinib	15 (16.0)	32 (28.1)
Lenvatinib mesilate	8 (8.5)	8 (7.0)
Radiopharmaceuticals	0 (0)	0 (0)
Radiotherapy	25 (26.6)	28 (24.6)
Other	1 (1.1)	4 (3.5)

a. Followed by maintenance treatment with durvalumab + olaparib.
b. Followed by maintenance treatment with placebo.
c. Institute's calculation at drug class/drug level in relation to all patients with (at least one) subsequent therapy after discontinuation of the study medication.
d. At drug level, ≥ 3% of patients in ≥ 1 treatment arm.
e. Patients who received more than one drug from a drug class were only counted once for this drug class.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

The study protocol did not provide for any planned switching of patients from the control arm into the intervention arm due to disease progression. For the data cut-off of 12 April 2023, the dossier does not contain any detailed information on subsequent therapies that also include individual drugs, but only information on the total number of patients who received subsequent therapy or on superordinate drug categories. Based on the data cut-off on 18 October 2023, approx. 49% (n = 94) of patients in the intervention arm and approx. 59% (n = 114) of patients in the control arm received subsequent therapy. Until the data cut-off on

12 April 2023, however, approx. 42% (n = 80) of patients in the intervention arm and approx. 56% (n = 107) of patients in the control arm received subsequent therapy. Since the deviations are rated as minor, the information on individual subsequent therapies at drug level based on the data cut-off of 18 October 2023 is considered as an approximation.

The overall proportion of patients who received subsequent therapy in relation to those who are eligible for subsequent therapy can only be estimated on the basis of the data cut-off of 12 April 2023. Assuming that the subsequent therapies were administered to patients with disease progression (n = 108 and n = 148 as assessed by the investigator; including death without prior progression), 74% of patients with progression in the intervention arm and 72% of patients with progression in the control arm received subsequent therapy. In contrast, a relevant proportion of 26% of patients with progression in the intervention arm and 28% of patients with progression in the control arm did not receive any subsequent therapy under this assumption.

The proportions of drugs or drug classes used based on the data cut-off of 18 October 2023 differ between the treatment arms. 31% and 47% of patients with subsequent therapy received immunotherapy, with pembrolizumab (30% versus 41%) being the most common. At 59%, more patients in the intervention arm received chemotherapy as subsequent therapy than in the control arm (42%). Carboplatin (26% versus 11%) and doxorubicin (11% versus 11%) were the most common. Of the patients with subsequent therapies, comparable proportions in the 2 study arms received hormonal therapy (9% versus 12%). Radiotherapy was administered to 27% and 25% of the patients with subsequent therapy.

The guideline recommendations for primary advanced or recurrent endometrial cancer with microsatellite-stable/mismatch-repair functional tumour tissue (pMMR status) are decisive for the assessment of subsequent therapies administered after disease progression. The S3 guideline on endometrial cancer [13] recommends combined immune and multikinase inhibitor therapy with pembrolizumab and lenvatinib after at least one line of chemotherapy. In addition, the G-BA has determined considerable added benefit for this therapy [16]. Based on these guideline recommendations, it can be assumed that immunotherapies such as pembrolizumab in combination with lenvatinib are used much more frequently in the German health care context than in the DUO-E study. Based on the available data, it is therefore assumed that the subsequent therapies administered in the DUO-E study do not adequately reflect the current standard of care. The deficiencies with regard to the subsequent therapies used are taken into account in the assessment of the outcome-specific risk of bias for overall survival, symptoms (recorded using EORTC QLQ-C30, EORTC QLQ-EN24 and PGIS), health status (recorded using EQ-5D VAS) and health-related quality of life (recorded using EORTC QLQ-C30 and EORTC QLQ-EN24) (see I 4.2).

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: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b]

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
DUO-E	Yes	Yes	Yes	Yes	Yes	Yes	Low

a. Followed by maintenance treatment with durvalumab + olaparib.
b. Followed by maintenance treatment with placebo.

RCT: randomized controlled trial

The risk of bias across outcomes is rated as low for the DUO-E study.

Transferability of the study results to the German health care context

The company described that in the DUO-E study, carboplatin was used at a dose of an area under the curve (AUC) 5 to AUC 6 and paclitaxel at a dose of 175 mg/m^2, which adequately reflects the standard of care [13,17].

Furthermore, the company explained that the median age of disease onset of the subpopulation with pMMR status in the DUO-E study (64 years) was comparable to the median age of disease onset of 67 years provided by the Robert Koch Institute (RKI) [18]. It added that the DUO-E study predominantly included patients of Caucasian family origin (> 54% of the patients with pMMR status). According to the company, the study population is therefore an adequate representation of the German health care context. Overall, the company assumed that the results of the DUO-E study are transferable to the German health care context and can be used for the assessment of added benefit.

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
    - recorded using the EORTC QLQ-C30
    - recorded using the EORTC QLQ-EN24
    - recorded using the PGIS
  - Health status
    - recorded using the EQ-5D VAS
    - recorded using the PGIC
- Health-related quality of life
  - recorded using the EORTC QLQ-C30
  - recorded using the EORTC QLQ-EN24
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - PRO-CTCAE
  - immune-mediated SAEs and immune-mediated severe AEs
  - MDS and AML (SAEs)
  - pneumonitis (severe AEs)
  - other specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b]

Study	Outcomes													
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-EN24, PGIS)	Health status (EQ-5D VAS)	Health status (PGIC)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-EN24)	SAEs	Severe AEs[c]	Discontinuation due to AEs	PRO-CTCAE	Immune-mediated SAEs	Immune-mediated severe AEs[c]	MDS/AML[d] (SAEs)	Pneumonitis[d] (severe AEs[c])	Anaemia (PT, severe AEs[c])
DUO-E	Yes	Yes	Yes	No[e]	Yes	Yes	Yes	Yes	No[e]	No[e]	No[e]	Yes	Yes	Yes

a. Followed by maintenance treatment with durvalumab + olaparib.
b. Followed by maintenance treatment with placebo.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. Considered is the operationalization in accordance with the AEs of special interest recorded in the study is considered; for explanations, see following text section.
e. No suitable data available; see the following text section for reasons.

AE: adverse event; AML: acute myeloid leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MDS: myelodysplastic syndrome; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Patient-reported outcomes on symptoms, health status and health-related quality of life

Relevant operationalization

In Module 4 A, the company presented time-to-event analyses for the first deterioration, as well as supplementary analyses using a mixed-effects model with repeated measures (MMRM) for each of the patient-reported outcomes on symptoms (recorded using EORTC QLQ-C30, EORTC QLQ-EN24 and PGIS), for health status (recorded using EQ-5D VAS and PGIC), and for health-related quality of life (recorded using EORTC QLQ-C30 and EORTC QLQ-EN24). The present benefit assessment uses the time-to-event analyses for the first deterioration for all outcomes for which suitable data are available.

Time-to-event analyses for the first deterioration with the response criterion of ≥ 10 points were prespecified in the DUO-E study only for physical functioning and role functioning (recorded using the EORTC QLQ-C30), as well as urological symptoms, gastrointestinal symptoms and back and pelvic pain (recorded using the EORTC QLQ-EN24). The time to the first deterioration by ≥ 10 points for all outcomes recorded using the EORTC QLQ-C30 and

EORTC QLQ-EN24 is considered for the present benefit assessment. For the other outcomes, the response criteria defined post hoc are discussed below.

Symptoms recorded using the PGIS

The PGIS consists of a single question asking the patient to rate her cancer symptoms over the past 7 days. There are 6 possible responses (“no symptoms”, “very mild”, “mild”, “moderate”, “severe”, “very severe”). The company converted the PGIS scale into numerical values from 1 to 6, where 1 means that the patient has no symptoms and 6 means that the patient has very severe symptoms. The recording of symptoms by means of a PGIS is regarded as patient relevant. In Module 4 A, the company presented post hoc time-to-event analyses on the first deterioration, defining a deterioration as an increase by ≥ 1 point from baseline. A ≥ 1 point increase from baseline is considered a deterioration that is sufficiently certain to reflect a noticeable change for the patients. The time-to-event analyses on the first deterioration presented by the company are used for the present benefit assessment.

Health status recorded using the PGIC

The PGIC consists of a single question asking the patient to rate the change in her health status compared with the time before starting the study medication. There are 7 possible responses (“much better”, “moderately better”, “a little better”, “about the same”, “a little worse”, “moderately worse”, “much worse”). The recording of health status by means of a PGIC is regarded as patient relevant. In Module 4 A, the company presented post hoc time-to-event analyses on the first deterioration, defining only the responses “moderately worse” or “much worse” as event. Patients who rated their health status as “a little worse” compared with the start of study medication were therefore not included in the company’s analysis. This is not adequate because even a slight deterioration represents a patient-noticeable and thus patient-relevant change. The time-to-event analyses on the first deterioration presented by the company are therefore unsuitable for the present benefit assessment.

Side effects

Recording of the progression of the underlying disease

According to the DUO-E study protocol, the investigator was not to record progression of the underlying disease as an AE. The available information on the documented AEs provides no evidence that these contain AEs attributable to the progression of the underlying disease to a relevant extent (see I Appendix C of the full dossier assessment). Individual AEs occurring in the study, e.g. vaginal bleeding, cannot be clearly differentiated from events of the underlying disease. When interpreting the results, it must be noted that these may be due to a combination of side effects and symptoms or late complications of the disease. The overall rates of SAEs and severe AEs (CTCAE grade ≥ 3) are used for the benefit assessment.

PRO-CTCAE

As per study protocol, the DUO-E study also recorded side effects using the PRO-CTCAE instrument. The PRO-CTCAE was only recorded in countries where a translation of the questionnaire into the national language was available. Overall, the PRO-CTCAE system is a valuable addition to the usual survey and analysis of AEs. The system comprises a total of 78 symptomatic AEs of the CTCAE system, which are compiled into a questionnaire adapted to the respective study situation. The selection process is to be planned a priori and carried out transparently. The individual symptomatic AEs must be transparently selected, e.g. all important potential AEs of the drug in the intervention and the control arm must be recorded. For a detailed description of the PRO-CTCAE system, see the corresponding explanations in benefit assessment A20-87 [19]. According to the study protocol, 2 symptomatic AEs from the PRO-CTCAE system were to be recorded in the DUO-E study:

- itching
- chills

For both symptomatic AEs, the worst severity (“none” to “very severe”) within the last 7 days was assessed. For the AE of chills, the number of times this AE occurred within the last 7 days was also recorded.

The company presented no information on the PRO-CTCAE in Module 4. In the study protocol, the selection of the PRO-CTCAE items is justified by the fact that the selected AEs were not already captured by other patient-reported questionnaires. The company does not provide more detailed information on its approach, e.g. on the search or the type of documents reviewed. Based on the information provided by the company, however, it presumably did not implement the approaches described in A20-87 [19] for selecting the items according to Tolstrup [20] or Taarnhøj [21]. It is not possible to determine whether side effects of durvalumab, carboplatin, paclitaxel and olaparib are adequately depicted.

Overall, the outcome of PRO-CTCAE is disregarded in the benefit assessment due to the nontransparent selection process and the inexplicable selection of items for depicting the symptomatic AEs of durvalumab, carboplatin, paclitaxel and olaparib.

Immune-mediated AEs

Immune-mediated AEs are a relevant aspect of the side effect profile of PD-L1 inhibitors such as durvalumab. In the DUO-E study, AEs of special interest (AESIs) assumed to be potentially caused by an inflammatory or immune-mediated reaction and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy were recorded for durvalumab. In principle, these AESIs for durvalumab, minus infusion-related reactions and hypersensitivity/anaphylactic reactions,

could be used to represent immune-mediated AEs, as the underlying categories or Preferred Terms (PTs) included in them are considered to be a sufficient approximation. However, the company did not present any results on immune-mediated AEs based on this operationalization for the relevant subpopulation. Instead, the data presented by the company in Module 4 A are based on a combination of the AESIs for durvalumab and the AESIs recorded in the study for olaparib (including new primary malignancy, MDS/AML) and AEs of possible interest (AEPIs) for durvalumab which are less likely to be potentially caused by an inflammatory or immune-mediated reaction and/or which are mostly or usually due to other causes. Overall, the analyses presented by the company are not suitable for the representation of immune-mediated AEs.

Myelodysplastic syndrome and acute myeloid leukaemia (SAEs)

All MDS/AML events were to be recorded as SAEs, according to the study protocol. In the DUO-E study, the composite outcome of MDS/AML was recorded as AESI and defined using 2 PT lists (MDS and malignant or unspecified tumours), which are described in the CSR. When compared with the Standardized Medical Dictionary for Regulatory Activities Query (SMQ) [narrow] MDS, the company's PT list on MDS can be used as a suitable operationalization for the present benefit assessment. The company's PT list on malignant or unspecified tumours is considered to be a sufficient representation of events that are typically attributable to AML and is used for the present benefit assessment.

The company did not state in Module 4 A to what extent the AESI of MDS/AML occurred in the relevant subpopulation. However, the CSR shows that no MDS or AML event occurred in the overall population, and thus also in the relevant subpopulation.

Pneumonitis (severe AEs)

For the specific AE of pneumonitis, the SMQ interstitial lung disease [narrow] is considered a sufficient approximation to represent this specific AE of olaparib. When compared with this SMQ, the PT list of the AESI of pneumonitis defined in the study for olaparib (consisting of the subcategory of interstitial lung disease) can be used as a suitable operationalization for the present benefit assessment. In Module 4, the company presented results on pneumonitis (AEs, SAEs, severe AEs). However, it did not specify on which operationalization these results were based (in the study, pneumonitis was not only recorded as AESI for olaparib, but also as AESI for durvalumab; its operationalization is not suitable for fully reflecting the inflammatory pneumonitis caused by olaparib, however). The CSR shows that the PTs occurring in the overall population were mostly those included in the SMQ of interstitial lung disease relevant for this specific AE, and that the event numbers were almost identical for the 2 operationalizations for olaparib and durvalumab. The data on pneumonitis (severe AEs) presented by the company in Module 4 A of the dossier are therefore used for the present benefit assessment.

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: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b]

Study		Outcomes													
	Study level	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-EN24, PGIS)	Health status (EQ-5D VAS)	Health status (PGIC)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-EN24)	SAEs	Severe AEs[c]	Discontinuation due to AEs	PRO-CTCAE	Immune-mediated SAEs	Immune-mediated severe AEs[c]	MDS/AML[d] (SAEs)	Pneumonitis[d] (severe AEs[c])	Anaemia (PT, severe AEs[c])
DUO-E	L	H[e]	H[e, f]	H[e, f]	–[g]	H[e, f]	H[f]	H[f]	L[h]	–[g]	–[g]	–[g]	L	H[f]	H[f]

a. Followed by maintenance treatment with durvalumab + olaparib.
b. Followed by maintenance treatment with placebo.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. Considered is the operationalization of the AEs of special interest recorded in the study is considered; for explanations, see Section I 4.1 of this dossier assessment.
e. Due to uncertainties in the use of subsequent therapies.
f. Shortened observation periods due to potentially informative censoring.
g. No suitable data available; for reasoning, see Section I 4.1 of this dossier assessment.
h. Despite a low risk of bias, the certainty of results is assumed to be limited for the outcome of discontinuation due to AEs (see text section below).

AE: adverse event; AML: acute myeloid leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MDS: myelodysplastic syndrome; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

No suitable data are available for the outcomes recorded using PGIC and PRO-CTCAE or for immune-mediated SAEs and immune-mediated severe AEs. Therefore, the risk of bias for the corresponding results is not assessed.

For the results on the outcome of overall survival, the risk of bias is rated as high. This is due to uncertainties regarding the subsequent therapies administered (see Section I 3.2, *Information on subsequent therapies*).

For the patient-reported outcomes on symptoms, health status and health-related quality of life, there are no baseline values or no values in the course of the study for a relevant

proportion of patients. In the time-to-event analyses for the EORTC QLQ-C30, 15% of patients in the intervention arm and 22% in the control arm were therefore censored on Day 1 and do not contribute any information to the analyses. The respective rates are 18% and 23% for the EORTC QLQ-EN24 and the EQ-5D VAS, and 18% and 24% for the PGIS. The questionnaire return rates also continue to decrease sharply over the course of the study. In addition, the results for these outcomes are also subject to uncertainties with regard to the subsequent therapies administered (see Section I 3.2, *Information on subsequent therapies*). There is therefore a high risk of bias of all effect estimates on patient-reported data. It should also be noted that in the analyses of the time to first deterioration, the company conducted censorings at the time of death if there was no previous deterioration. Censoring at the time of the last usable recording would be more suitable, but this aspect alone would not lead to a high risk of bias in the present assessment.

For all events in the side effects category, with the exception of MDS/AML (SAEs), discontinuation of observation was linked to the end of treatment with the study medication. The extensive premature treatment discontinuations, which were due to many potentially informative reasons (see Table 9), lead to a high risk of bias for these results, with the exception of discontinuation due to AEs. The risk of bias of the results for the outcome of MDS/AML (SAEs), which was observed until the end of the study, is rated as low.

Although the risk of bias is low for the outcome of discontinuation due to AEs, the certainty of results for this outcome is reduced. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion “discontinuation” can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

I 4.3 Results

Table 15 summarizes the results of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with carboplatin + paclitaxel, followed by placebo, for the first-line treatment of adult patients with primary advanced or recurrent pMMR endometrial cancer who are candidates for systemic therapy. Where necessary, IQWiG calculations are provided to supplement the data from the company’s dossier.

The Kaplan-Meier curves for the time-to-event analyses are presented in I Appendix B of the full dossier assessment, and the results on common AEs, SAEs, severe AEs, and discontinuations due to AEs at System Organ Class (SOC) level can be found in I Appendix C of the full dossier assessment. No Kaplan-Meier curves are available for the outcome of MDS/AML (SAEs), but no MDS or AML events occurred in either treatment arm.

Table 15: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

Study Outcome category Outcome	Durvalumab + carboplatin + paclitaxel[a]		Placebo + carboplatin + paclitaxel[b]		Durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b]
	N[c]	Median time to event in months [95% CI] Patients with event n (%)	N[c]	Median time to event in months [95% CI] Patients with event n (%)	MD [95% CI]; p-value[d]
DUO-E					
Mortality					
Overall survival	191	NA 46 (24.1)	192	25.9 [25.1; NC] 64 (33.3)	0.68 [0.46; 0.99]; 0.044
Morbidity					
Symptoms (time to first deterioration)					
EORTC QLQ-C30[e]					
Fatigue	163	1.3 [0.8; 1.4] 127 (66.5)	149	1.4 [1.3; 2.0] 122 (63.5)	0.98 [0.76; 1.26]; 0.859
Nausea and vomiting	163	2.8 [2.2; 3.5] 110 (57.6)	149	6.0 [3.6; 9.6] 81 (42.2)	1.60 [1.20; 2.15]; 0.002
Pain	163	3.5 [2.1; 6.0] 98 (51.3)	149	2.8 [2.1; 4.1] 100 (52.1)	0.81 [0.61; 1.08]; 0.153
Dyspnoea	163	2.9 [2.1; 4.2] 103 (53.9)	149	4.2 [3.4; 8.7] 81 (42.2)	1.37 [1.02; 1.84]; 0.037
Insomnia	163	5.1 [3.4; 17.0] 78 (40.8)	149	9.0 [3.5; 15.1] 71 (37.0)	1.05 [0.76; 1.46]; 0.744
Appetite loss	163	3.4 [2.7; 4.2] 110 (57.6)	149	7.7 [4.1; 14.4] 73 (38.0)	1.74 [1.29; 2.35]; < 0.001
Constipation	163	3.5 [2.1; 6.0] 97 (50.8)	149	9.7 [3.5; NC] 68 (35.4)	1.52 [1.12; 2.09]; 0.008
Diarrhoea	163	6.1 [4.1; 12.5] 80 (41.9)	149	5.1 [3.5; 8.8] 79 (41.1)	0.93 [0.68; 1.28]; 0.657
EORTC QLQ-EN24[e]					
Lymphoedema	156	2.0 [1.4; 2.2] 115 (60.2)	148	2.1 [1.5; 2.9] 101 (52.6)	1.33 [1.01; 1.74]; 0.051
Urological symptoms	156	7.0 [4.1; 14.2] 73 (38.2)	148	9.6 [6.0; NC] 66 (34.4)	1.13 [0.81; 1.58]; 0.482
Gastrointestinal symptoms	156	4.2 [2.8; 13.3] 78 (40.8)	148	9.6 [6.8; 18.2] 66 (34.4)	1.33 [0.95; 1.85]; 0.094

Table 15: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

Study **Outcome category** **Outcome**	**Durvalumab + carboplatin + paclitaxel[a]**		**Placebo + carboplatin + paclitaxel[b]**		**Durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b]**
	N[c]	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N[c]**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**MD [95% CI]; p-value[d]**
Sexual/vaginal problems	No suitable data[f]				
Back and pelvic pain	156	15.1 [7.8; NC] 63 (33.0)	148	10.5 [6.9; 17.9] 63 (32.8)	1.02 [0.71; 1.45]; 0.929
Tingling/numbness	156	1.4 [0.8; 1.4] 120 (62.8)	148	1.4 [0.9; 1.4] 117 (60.9)	0.94 [0.72; 1.22]; 0.605
Muscular pain	156	2.1 [1.4; 2.8] 110 (57.6)	148	1.9 [1.4; 2.2] 109 (56.8)	0.86 [0.66; 1.13]; 0.272
Hair loss	156	0.7 [NC] 148 (77.5)	148	0.7 [NC] 141 (73.4)	1.03 [0.81; 1.30]; 0.827
Taste change	156	1.4 [1.4; 2.2] 118 (61.8)	148	2.1 [1.4; 4.2] 87 (45.3)	1.55 [1.17; 2.06]; 0.003
PGIS[g]	156	2.0 [1.4; 2.7] 101 (52.9)	145	2.8 [1.6; 4.2] 89 (46.4)	1.14 [0.86; 1.52]; 0.398
Health status (time to first deterioration)					
EQ-5D VAS[i]	156	4.1 [3.4; 9.7] 80 (41.9)	147	8.7 [4.2; 16.1] 69 (35.9)	1.19 [0.86; 1.65]; 0.282
PGIC	No suitable data[h]				
Health-related quality of life (time to first deterioration)					
EORTC QLQ-C30[j]					
Global health status	163	3.5 [2.7; 5.1] 96 (50.3)	149	3.4 [2.1; 4.2] 97 (50.5)	0.94 [0.71; 1.25]; 0.707
Physical functioning	163	2.8 [2.2; 3.5] 103 (53.9)	149	2.9 [2.1; 3.6] 98 (51.0)	0.96 [0.73; 1.27]; 0.812
Role functioning	163	2.1 [1.4; 2.7] 116 (60.7)	149	1.6 [1.4; 2.1] 115 (59.9)	0.92 [0.71; 1.20]; 0.557
Emotional functioning	163	6.0 [3.5; 13.4] 77 (40.3)	149	15.2 [7.1; NC] 61 (31.8)	1.24 [0.89; 1.74]; 0.209
Cognitive functioning	163	2.7 [2.1; 2.9] 111 (58.1)	149	3.4 [2.2; 4.3] 94 (49.0)	1.23 [0.93; 1.62]; 0.153
Social functioning	163	2.2 [1.6; 2.9] 107 (56.0)	149	2.8 [2.1; 3.6] 92 (47.9)	1.17 [0.88; 1.55]; 0.288

Table 15: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

Study Outcome category Outcome	Durvalumab + carboplatin + paclitaxel[a]		Placebo + carboplatin + paclitaxel[b]		Durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b]
	N[c]	Median time to event in months [95% CI] Patients with event n (%)	N[c]	Median time to event in months [95% CI] Patients with event n (%)	MD [95% CI]; p-value[d]
EORTC QLQ-EN24					
Sexual interest[j]	156	NA 36 (18.8)	148	NA 34 (17.7)	1.01 [0.63; 1.62]; 0.983
Sexual activity[j]	156	NA 25 (13.1)	148	NA 33 (17.2)	0.68 [0.40; 1.14]; 0.147
Sexual enjoyment[j]	No suitable data[f]				
Poor body image[e, k]	156	1.4 [1.0; 1.5] 117 (61.3)	148	1.4 [1.4; 2.1] 100 (52.1)	1.27 [0.97; 1.67]; 0.080
Side effects[l]					
AEs (supplementary information)	191	0.1 [0.1; 0.1] 190 (99.5)	190	0.1 [0.1; 0.1] 190 (100)	–
SAEs	191	24.7 [24.7; NC] 69 (36.1)	190	NA 58 (30.5)	1.14 [0.80; 1.62]; 0.470
Severe AEs[m]	191	3.4 [2.3; 6.2] 129 (67.5)	190	5.3 [3.1; 12.2] 104 (54.7)	1.28 [0.99; 1.66]; 0.063
Discontinuation due to AEs	191	NA 47 (24.6)	190	NA 37 (19.5)	1.19 [0.78; 1.85]; 0.418
PRO-CTCAE	No suitable data[h]				
Immune-mediated AEs (supplementary information)	No suitable data[h]				
Immune-mediated SAEs	No suitable data[h]				
Immune-mediated severe AEs[m]	No suitable data[h]				
MDS/AML (SAEs)[n]	191	NA 0 (0)	190	NA 0 (0)	–
Pneumonitis (severe AEs[m])[n]	191	NA 3 (1.6)	190	NA 0 (0)	NC; 0.112
Anaemia (PT, severe AEs[m])	191	NA 46 (24.1)	190	NA 24 (12.6)	1.96 [1.21; 3.26]; 0.007

Table 15: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

Study Outcome category Outcome	Durvalumab + carboplatin + paclitaxel[a]		Placebo + carboplatin + paclitaxel[b]		Durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b]
	N[c]	Median time to event in months [95% CI] Patients with event n (%)	N[c]	Median time to event in months [95% CI] Patients with event n (%)	MD [95% CI]; p-value[d]

a. Followed by maintenance treatment with durvalumab + olaparib.
b. Followed by maintenance treatment with placebo.
c. For the outcomes on morbidity and health-related quality of life: The information provided by the company on the patients included in the time-to-event analyses is not plausible when compared with the MMRM analyses. Provided was the number of patients included in the MMRM analyses for the change from baseline at at least one point in time. Only these patients can contribute data to the time-to-event analysis.
d. HR and CI: Cox model with proportional hazards; p-value: log-rank test; except for the operationalizations on side effects, the calculations for all analyses were stratified according to disease status (newly diagnosed vs. recurrent) and region (Asia vs. rest of the world).
e. An increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
f. No suitable data available because a maximum of 29 vs. 25 patients (15% vs. 13%) had a baseline value and a further value during the course of the study.
g. An increase by ≥ 1 point from baseline is considered a clinically relevant deterioration (scale range from "no symptoms" to "very severe"; the company converted the scale into numerical values from 1 ["no symptoms"] to 6 ["very severe"] for the analyses).
h. No suitable data available; for justification see Section I 4.1 of this dossier assessment.
i. A decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
j. A decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
k. In departure from the company's approach, this scale is assigned to health-related quality of life, rather than symptoms.
l. Events attributable to progression of the underlying disease were not recorded as AEs, in accordance with the study protocol.
m. Operationalized as CTCAE grade ≥ 3.
n. The operationalization of the AEs of special interest recorded in the study is considered; for explanations, see Section I 4.1 of this dossier assessment.

AE: adverse event; AML: acute myeloid leukaemia; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; MDS: myelodysplastic syndrome; MMRM: mixed-effects model with repeated measures; n: number of patients with (at least one) event; N: number of patients who contribute data to the analysis; NA: not achieved; NC: not calculable; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; pMMR: mismatch repair proficient; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

On the basis of the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes, except for the outcome of MDS/AML. For the outcome of MDS/AML, at most an indication, e.g. of an added benefit, can be determined (see Section I 4.2).

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was shown in favour of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with placebo + carboplatin + paclitaxel, followed by placebo. There is an effect modification by the characteristic of disease status for this outcome (see Section I 4.4). For patients with newly diagnosed disease, there is a hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT. For patients with recurrent disease, there is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit is therefore not proven for patients with recurrent disease.

Morbidity

Symptoms were recorded using the instruments of EORTC QLQ-C30, EORTC QLQ-EN24, and PGIS. Health status was recorded using the instruments of EQ-5D VAS and PGIC. The time to first deterioration was considered in each case.

Symptoms (recorded using EORTC QLQ-C30, EORTC QLQ-EN24)

No statistically significant difference between treatment groups was shown for any of the following outcomes: fatigue, pain, insomnia and diarrhoea (recorded using the EORTC QLQ-C30), as well as lymphoedema, urological symptoms, gastrointestinal symptoms, back and pelvic pain, tingling/numbness, muscular pain and hair loss (recorded using the EORTC QLQ-EN24). In each case, there is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit is therefore not proven for these outcomes.

For the outcome of dyspnoea (recorded using EORTC QLQ-C30), a statistically significant difference was shown to the disadvantage of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with placebo + carboplatin + paclitaxel, followed by placebo. However, the extent of the effect for this outcome in the category of non-severe/non-serious symptoms/late complications was no more than marginal. Overall, there is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT for the outcome of dyspnoea; an added benefit is therefore not proven for this outcome.

For each of the outcomes of appetite loss and constipation (recorded using EORTC QLQ-C30) and the outcome of taste change (recorded using EORTC QLQ-EN24), a statistically significant difference was shown to the disadvantage of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with placebo + carboplatin + paclitaxel, followed by placebo. In each case, there is a hint of lesser benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT.

For the outcome of nausea and vomiting (recorded using EORTC QLQ-C30), a statistically significant difference was shown to the disadvantage of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with placebo + carboplatin + paclitaxel, followed by placebo. There is an effect modification by the characteristic of disease status for this outcome (see Section I 4.4). For patients with recurrent disease, there is a hint of lesser benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT. For patients with newly diagnosed disease, there is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit for patients with newly diagnosed disease is therefore not proven for this outcome.

No suitable data are available for the outcome of sexual/vaginal problems (recorded using EORTC QLQ-EN24), as a maximum of 29 versus 25 patients (15% versus 13%) had a baseline value and a further value during the course of the study. There is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit is therefore not proven for this outcome.

Symptoms (recorded using PGIS)

No statistically significant difference between treatment groups was shown for the symptoms recorded using PGIS. There is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit is therefore not proven for the symptoms recorded using PGIS.

Health status (recorded using EQ-5D VAS, PGIC)

No suitable data are available for health status recorded using PGIC (see Section I 4.1 for reasons). No statistically significant difference between treatment groups was shown for health status recorded using EQ-5D VAS. There is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit is therefore not proven for the outcome of health status.

Health-related quality of life (recorded using EORTC QLQ-C30, EORTC QLQ-EN24)

Health-related quality of life was recorded with the instruments EORTC QLQ-C30 and EORTC QLQ-EN24. The time to first deterioration was considered in each case.

No statistically significant difference between treatment groups was shown for any of the outcomes of global health status, physical functioning, role functioning, emotional functioning, and social functioning (recorded using EORTC QLQ-C30), and for the outcomes of sexual interest, sexual activity, and poor body image (recorded using EORTC QLQ-EN24). In each case, there is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit is therefore not proven for these outcomes.

For the outcome of cognitive functioning (recorded using the EORTC QLQ-C30), no statistically significant difference between treatment groups was found. There is an effect modification by the characteristic of age, however (see Section I 4.4). For patients < 65 years, there is a hint of lesser benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT. For patients ≥ 65 years, there is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit for patients ≥ 65 years is therefore not proven for this outcome.

No suitable data are available for the outcome of sexual enjoyment (recorded using EORTC QLQ-EN24), as a maximum of 29 versus 25 patients (15% versus 13%) had a baseline value and a further value during the course of the study. There is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit is therefore not proven for this outcome.

Side effects

SAEs, severe AEs, and discontinuation due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; greater or lesser harm is therefore not proven for these outcomes.

PRO-CTCAE, immune-mediated SAEs, and immune-mediated severe AEs

No suitable data are available for the PRO-CTCAE outcome, immune-mediated SAEs, and immune-mediated severe AEs (see Section I 4.1 for reasons). In each case, there is no hint of greater or lesser harm of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; greater or lesser harm is therefore not proven for these outcomes.

MDS/AML (SAEs)

No events occurred in either treatment arm for the outcome of MDS/AML (SAEs), and no statistically significant difference between treatment groups was found. There is no hint of

greater or lesser harm of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; greater or lesser harm is therefore not proven for this outcome.

Pneumonitis (severe AEs)

No statistically significant difference between treatment groups was found for the outcome of pneumonitis (severe AEs). There is no hint of greater or lesser harm of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; greater or lesser harm is therefore not proven for this outcome.

Anaemia (severe AEs)

For the outcome of anaemia (severe AEs), a statistically significant difference was shown to the disadvantage of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with placebo + carboplatin + paclitaxel, followed by placebo. There is a hint of greater harm of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT.

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)
- disease status (recurrent versus newly diagnosed)

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 one subgroup.

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

The results are presented in Table 16. The Kaplan-Meier curves on the subgroup results are presented in I Appendix B.5 of the full dossier assessment.

Table 16: Subgroups (mortality, morbidity, health-related quality of life, time to event) – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

Study Outcome category Outcome Characteristic Subgroup	Durvalumab + carboplatin + paclitaxel[a] N	Median time to event in months [95% CI] Patients with event n (%)	Placebo + carboplatin + paclitaxel[b] N	Median time to event in months [95% CI] Patients with event n (%)	Durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] HR [95% CI][c]	p-value[c]
DUO-E						
Mortality						
Overall survival						
Disease status at baseline						
Recurrent	99	NA 25 (25.3)	101	NA 26 (25.7)	1.04 [0.60; 1.81]	0.883
Newly diagnosed	92	NA 21 (22.8)	91	25.1 [17.4; NC] 38 (41.8)	0.45 [0.26; 0.77]	0.003
Total					Interaction:	0.033
Morbidity (symptoms)						
Nausea and vomiting (EORTC QLQ-C30 – time to first deterioration[d])						
Disease status at baseline						
Recurrent	99	2.8 [1.4; 4.1] 63 (63.6)	101	7.0 [3.6; NC] 39 (38.6)	2.16 [1.45; 3.25]	< 0.001
Newly diagnosed	92	3.4 [2.7; 5.1] 47 (51.1)	91	5.2 [2.1; 9.6] 42 (46.2)	1.17 [0.77; 1.78]	0.473
Total					Interaction:	0.036
Health-related quality of life						
Cognitive functioning (EORTC QLQ-C30 – time to first deterioration[e])						
Age						
< 65 years	101	2.3 [1.5; 2.8] 64 (63.4)	99	5.9 [3.4; 11.6] 43 (43.4)	1.82 [1.24; 2.70]	0.002
≥ 65 years	90	2.9 [2.1; 7.8] 47 (52.2)	93	2.1 [1.4; 3.4] 51 (54.8)	0.78 [0.52; 1.16]	0.212
Total					Interaction:	0.003

Table 16: Subgroups (mortality, morbidity, health-related quality of life, time to event) – RCT, direct comparison: durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b] (multipage table)

Study Outcome category Outcome Characteristic Subgroup	Durvalumab + carboplatin + paclitaxel[a]		Placebo + carboplatin + paclitaxel[b]		Durvalumab + carboplatin + paclitaxel[a] vs. placebo + carboplatin + paclitaxel[b]	
	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][c]	p-value[c]
a. Followed by maintenance treatment with durvalumab + olaparib. b. Followed by maintenance treatment with placebo. c. HR, CI and p-value: Cox regression with treatment, subgroup characteristic and interaction term between treatment and subgroup characteristic. d. An increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). e. A decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial						

Mortality

Overall survival

There is a statistically significant effect modification by the characteristic of disease status for the outcome of overall survival. For patients with newly diagnosed disease, a statistically significant difference was shown in favour of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with placebo + carboplatin + paclitaxel, followed by placebo. For patients with newly diagnosed disease, there is a hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT. However, there was no statistically significant difference between the treatment groups for patients with recurrent disease. For this subgroup, there is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit for patients with recurrent disease is therefore not proven for this outcome.

Morbidity (symptoms)

Nausea and vomiting (recorded using EORTC QLQ-C30)

For the outcome of nausea and vomiting (recorded with the EORTC QLQ-C30), there was a statistically significant effect modification by the characteristic of disease status. For patients with recurrent disease, a statistically significant difference was shown to the disadvantage of

durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with placebo + carboplatin + paclitaxel, followed by placebo. For patients with recurrent disease, there is a hint of lesser benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT. However, there was no statistically significant difference between the treatment groups for patients with newly diagnosed disease. For this subgroup, there is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit for patients with newly diagnosed disease is therefore not proven for this outcome.

Health-related quality of life

Cognitive functioning (EORTC QLQ-C30)

For the outcome of cognitive functioning (recorded with the EORTC QLQ-C30), there was a statistically significant effect modification by the characteristic of age. For patients < 65 years, a statistically significant difference was shown to the disadvantage of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with placebo + carboplatin + paclitaxel, followed by placebo. For patients < 65 years, there is a hint of lesser benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT. In contrast, no statistically significant difference between treatment groups was found for patients ≥ 65 years of age. For this subgroup, there is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT; an added benefit for patients ≥ 65 years is therefore not proven for this outcome.

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 added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 17).

Determination of the outcome category for symptom outcomes

For the symptom outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Nausea and vomiting, dyspnoea, appetite loss and constipation (recorded using EORTC QLQ-C30)

For the outcomes of nausea and vomiting, dyspnoea, appetite loss and constipation (recorded using the EORTC QLQ-C30), there is insufficient information available to assign the severity category. The outcomes of nausea and vomiting, dyspnoea, appetite loss and constipation are therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Taste change (recorded using EORTC QLQ-EN24)

For the outcome of taste change (recorded using the EORTC QLQ-EN24), there is insufficient information available to assign the severity category. The outcome of taste change is therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 17: Extent of added benefit at outcome level: durvalumab + carboplatin + paclitaxel[a] vs. carboplatin + paclitaxel[b] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Durvalumab[a] vs. placebo[b]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[c]**	**Derivation of extent[d]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival Disease status		
Recurrent	NA vs. NA HR: 1.04 [0.60; 1.81]; p = 0.883	Lesser/added benefit not proven
Newly diagnosed	NA vs. 25.1 HR: 0.45 [0.26; 0.77]; p = 0.003 Probability: "hint"	Outcome category: mortality CI_u < 0.85 Added benefit; extent: "major"
Side effects		
MDS/AML (SAEs)	NA vs. NA HR: –; p: –	Greater/lesser harm not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (time to first deterioration)		
EORTC QLQ-C30		
Fatigue	1.3 vs. 1.4 HR: 0.98 [0.76; 1.26]; p = 0.859	Lesser/added benefit not proven
Nausea and vomiting Disease status		
Recurrent	2.8 vs. 7.0 HR: 2.16 [1.45; 3.25] HR: 0.46 [0.31; 0.69][e]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Lesser benefit, extent: "considerable"
Newly diagnosed	3.4 vs. 5.2 HR: 1.17 [0.77; 1.78]; p = 0.473	Lesser/added benefit not proven
Pain	3.5 vs. 2.8 HR: 0.81 [0.61; 1.08]; p = 0.153	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: durvalumab + carboplatin + paclitaxel[a] vs. carboplatin + paclitaxel[b] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Durvalumab[a] vs. placebo[b]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[c]**	**Derivation of extent[d]**
Dyspnoea	2.9 vs. 4.2 HR: 1.37 [1.02; 1.84] HR: 0.73 [0.54; 0.98][e]; p = 0.037	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[f]
Insomnia	5.1 vs. 9.0 HR: 1.05 [0.76; 1.46]; p = 0.744	Lesser/added benefit not proven
Appetite loss	3.4 vs. 7.7 HR: 1.74 [1.29; 2.35] HR: 0.57 [0.43; 0.78][e]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Lesser benefit, extent: "considerable"
Constipation	3.5 vs. 9.7 HR: 1.52 [1.12; 2.09] HR: 0.66 [0.48; 0.89][e]; p = 0.008 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Lesser benefit, extent: "minor"
Diarrhoea	6.1 vs. 5.1 HR: 0.93 [0.68; 1.28]; p = 0.657	Lesser/added benefit not proven
EORTC QLQ-EN24		
Lymphoedema	2.0 vs. 2.1 HR: 1.33 [1.01; 1.74]; p = 0.051	Lesser/added benefit not proven
Urological symptoms	7.0 vs. 9.6 HR: 1.13 [0.81; 1.58]; p = 0.482	Lesser/added benefit not proven
Gastrointestinal symptoms	4.2 vs. 9.6 HR: 1.33 [0.95; 1.85]; p = 0.094	Lesser/added benefit not proven
Sexual/vaginal problems	No suitable data	Lesser/added benefit not proven
Back and pelvic pain	15.1 vs. 10.5 HR: 1.02 [0.71; 1.45]; p = 0.929	Lesser/added benefit not proven
Tingling/numbness	1.4 vs. 1.4 HR: 0.94 [0.72; 1.22]; p = 0.605	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: durvalumab + carboplatin + paclitaxel[a] vs. carboplatin + paclitaxel[b] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Durvalumab[a] vs. placebo[b]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[c]**	**Derivation of extent[d]**
Muscular pain	2.1 vs. 1.9 HR: 0.86 [0.66; 1.13]; p = 0.272	Lesser/added benefit not proven
Hair loss	0.7 vs. 0.7 HR: 1.03 [0.81; 1.30]; p = 0.827	Lesser/added benefit not proven
Taste change	1.4 vs. 2.1 HR: 1.55 [1.17; 2.06] HR: 0.65 [0.49; 0.85][e]; p = 0.003 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Lesser benefit, extent: "minor"
PGIS	2.0 vs. 2.8 HR: 1.14 [0.86; 1.52]; p = 0.398	Lesser/added benefit not proven
Health status (time to first deterioration)		
EQ-5D VAS	4.1 vs. 8.7 HR: 1.19 [0.86; 1.65]; p = 0.282	Lesser/added benefit not proven
PGIC	No suitable data	Lesser/added benefit not proven
Health-related quality of life (time to first deterioration)		
EORTC QLQ-C30		
Global health status	3.5 vs. 3.4 HR: 0.94 [0.71; 1.25]; p = 0.707	Lesser/added benefit not proven
Physical functioning	2.8 vs. 2.9 HR: 0.96 [0.73; 1.27]; p = 0.812	Lesser/added benefit not proven
Role functioning	2.1 vs. 1.6 HR: 0.92 [0.71; 1.20]; p = 0.557	Lesser/added benefit not proven
Emotional functioning	6.0 vs. 15.2 HR: 1.24 [0.89; 1.74]; p = 0.209	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: durvalumab + carboplatin + paclitaxel[a] vs. carboplatin + paclitaxel[b] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Durvalumab[a] vs. placebo[b]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[c]**	**Derivation of extent[d]**
Cognitive functioning Age < 65 years	2.3 vs. 5.9 HR: 1.82 [1.24; 2.70] HR: 0.55 [0.37; 0.81][e]; p = 0.002 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Lesser benefit, extent: "minor"
≥ 65 years	2.9 vs. 2.1 HR: 0.78 [0.52; 1.16]; p = 0.212	Lesser/added benefit not proven
Social functioning	2.2 vs. 2.8 HR: 1.17 [0.88; 1.55]; p = 0.288	Lesser/added benefit not proven
EORTC QLQ-EN24		
Sexual interest	NA vs. NA HR: 1.01 [0.63; 1.62]; p = 0.983	Lesser/added benefit not proven
Sexual activity	NA vs. NA HR: 0.68 [0.40; 1.14]; p = 0.147	Lesser/added benefit not proven
Sexual enjoyment	No suitable data	Lesser/added benefit not proven
Poor body image	1.4 vs. 1.4 HR: 1.27 [0.97; 1.67]; p = 0.080	Lesser/added benefit not proven
Side effects		
SAEs	24.7 vs. NA HR: 1.14 [0.80; 1.62]; p = 0.470	Greater/lesser harm not proven
Severe AEs	3.4 vs. 5.3 HR: 1.28 [0.99; 1.66]; p = 0.063	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. NA HR: 1.19 [0.78; 1.85]; p = 0.418	Greater/lesser harm not proven
PRO-CTCAE	No suitable data	Greater/lesser harm not proven
Immune-mediated SAEs	No suitable data	Greater/lesser harm not proven

Table 17: Extent of added benefit at outcome level: durvalumab + carboplatin + paclitaxel[a] vs. carboplatin + paclitaxel[b] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Durvalumab[a] vs. placebo[b]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[c]**	**Derivation of extent[d]**
Immune-mediated severe AEs	No suitable data	Greater/lesser harm not proven
Pneumonitis (severe AEs)	NA vs. NA HR: NC; p = 0.112	Greater/lesser harm not proven
Anaemia (severe AEs)	NA vs. NA HR: 1.96 [1.21; 3.26] HR: 0.51 [0.31; 0.83][e]; p = 0.007 Probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: “considerable”

a. Followed by maintenance treatment with durvalumab + olaparib.
b. Followed by watchful waiting.
c. Probability provided if there is a statistically significant and relevant effect.
d. Estimates of the effect size are made with different limits depending on the outcome category using the upper limit of the confidence interval (CI_u).
e. Institute’s calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
f. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AE: adverse event; AML: acute myeloid leukaemia; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; MDS: myelodysplastic syndrome; NA: not achieved; NC: not calculable; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of durvalumab + carboplatin + paclitaxel[a] in comparison with carboplatin + paclitaxel[b]

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival ▫ Disease status at baseline (newly diagnosed) hint of added benefit – extent: “major”	–
Outcomes with shortened observation period	
–	Non-serious/non-severe symptoms/late complications ▪ Nausea and vomiting ▫ Disease status at baseline (recurrent) hint of lesser benefit – extent: “considerable” ▪ Appetite loss hint of lesser benefit – extent: “considerable” ▪ Constipation hint of lesser benefit – extent: “minor” ▪ Taste change hint of lesser benefit – extent: “minor”
–	Health-related quality of life ▪ Cognitive functioning ▫ Age (< 65 years): hint of lesser benefit – extent: “minor”
–	Serious/severe side effects ▪ Anaemia (severe AEs): hint of greater harm – extent: “considerable”
No suitable data are available for the outcomes of immune-mediated SAEs and immune-mediated severe AEs.	
a. Followed by maintenance treatment with durvalumab + olaparib. b. Followed by watchful waiting. AE: adverse event; SAE: serious adverse event	

Overall, both positive and negative effects of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, were found in comparison with the ACT. For overall survival, the observed effect is based on the entire observation period. For the outcomes in the categories of morbidity, health-related quality of life and side effects, however, they refer exclusively to the shortened period (depending on the outcome, until 2nd disease progression, until start of the 1st subsequent therapy, or until end of treatment [plus a maximum of 90 days]).

The characteristic of disease status at baseline is an effect modifier for various outcomes. Due to the effect modifications, the results on the added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, compared with the ACT are derived separately by disease status at baseline. The characteristic of age is an effect modifier for the outcome

of cognitive functioning (recorded using the EORTC QLQ-C30). However, the results of these subgroup analyses are not taken into account when deriving the added benefit separately according to disease status at baseline, as it is unknown how patients in the subgroups of < 65 years versus ≥ 65 years were distributed in the subgroups of newly diagnosed versus recurrent.

Patients with newly diagnosed disease

For patients with newly diagnosed disease at baseline, there is a hint of major added benefit on the side of positive effects in the category of mortality. On the negative side, however, there are hints of lesser benefit with the extent "considerable" or "minor" in non-serious/non-severe symptoms/late complications in the outcomes of appetite loss, constipation, and taste change. In addition, there is a hint of greater harm with the extent "considerable" for anaemia (severe AEs). In summary, there is a hint of considerable added benefit for patients with newly diagnosed disease at baseline.

Patients with recurrent disease

No difference between treatment groups for patients with recurrent disease at baseline was found for the outcome of overall survival. On the negative side, there is a hint of lesser benefit with the extent "considerable" for these patients in non-serious/non-severe symptoms/late complications in the outcome of nausea and vomiting. Furthermore, hints of lesser benefit with the extent "considerable" or "minor" were also found for the outcomes of appetite loss, constipation, and taste change. In addition, there is a hint of greater harm with the extent "considerable" for anaemia (severe AEs). In summary, there is a hint of a lesser benefit for patients with recurrent disease at baseline due to the existing negative effects.

Table 19 summarizes the result of the assessment of the added benefit of durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + olaparib, in comparison with carboplatin + paclitaxel, followed by watchful waiting.

Table 19: Durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
First-line treatment of adult patients with primary advanced or recurrent pMMR endometrial cancer who are candidates for systemic therapy[b], followed by maintenance treatment with durvalumab in combination with olaparib[c]	Carboplatin + paclitaxel[d], followed by watchful waiting	▪ Patients with newly diagnosed disease: hint of considerable added benefit[e] ▪ Patients with recurrent disease: hint of lesser benefit[e]

a. Presented is the ACT specified by the G-BA.
b. In this therapeutic indication, the G-BA assumes that the patients have not yet received systemic therapy as postoperative or adjuvant therapy to treat the primary advanced disease and have not yet received chemotherapy to treat the recurrence.
c. According to the SPC [3], olaparib is used in patients whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel.
d. Treatment with carboplatin in combination with paclitaxel is not approved for this therapeutic indication. Accordingly, the use of carboplatin in combination with paclitaxel represents an off-label use. According to the G-BA, for patients in the present therapeutic indication, the off-label use is generally preferable to the drugs currently approved in the therapeutic indication, according to the generally recognized state of medical knowledge, §6 (2), sentence 3, number 2, AM-NutzenV.
e. The DUO-E study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; pMMR: mismatch repair proficient

The assessment described above differs from that of the company, which in its dossier derived an indication of a minor added benefit of durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + olaparib, in comparison with the ACT for all patients with primary advanced or recurrent pMMR endometrial cancer in its subpopulation 1 (not pretreated with chemotherapy or suitable for further chemotherapy alone despite pretreatment). For patients with newly diagnosed disease, the company found an indication of major added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib, in comparison with the ACT.

The company presented no data for its subpopulation 2, which comprises patients who have been pretreated with chemotherapy and for whom re-induction with chemotherapy alone is not an option, and for whom the company considered pembrolizumab + lenvatinib to be the ACT (see Chapter I 2).

The approach for the derivation of an overall conclusion on added benefit is 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.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 09.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. AstraZeneca. Lynparza 100 mg Filmtabletten, Lynparza 150 mg Filmtabletten [online]. 2024 [Accessed: 23.08.2024]. URL: https://www.fachinfo.de.

4. AstraZeneca. A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination with Durvalumab, Followed by Maintenance Durvalumab with or without Olaparib in Patients with Newly Diagnosed Advanced or Recurrent Endometrial Cancer (DUO-E); study DUO-E; Clinical Study Report [unpublished]. 2023.

5. AstraZeneca. A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination with Durvalumab, Followed by Maintenance Durvalumab with or without Olaparib in Patients with Newly Diagnosed Advanced or Recurrent Endometrial Cancer (DUO-E); study DUO-E; Summary of Clinical Safety; 120-Day Safety Update [unpublished]. 2024.

6. AstraZeneca. A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination with Durvalumab, Followed by Maintenance Durvalumab with or without Olaparib in Patients with Newly Diagnosed Advanced or Recurrent Endometrial Cancer (DUO-E); study DUO-E; Post-hoc Overall Survival Descriptive Analysis [unpublished]. 2024.

7. AstraZeneca. A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination with Durvalumab, Followed by Maintenance Durvalumab with or without Olaparib in Patients with Newly Diagnosed Advanced or Recurrent Endometrial Cancer (DUO-E); study DUO-E; Zusatzanalysen [unpublished]. 2024.

8. AstraZeneca. A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination with Durvalumab, Followed by Maintenance Durvalumab with or without Olaparib in Patients with Newly Diagnosed Advanced or Recurrent Endometrial Cancer (DUO-E) [online]. [Accessed: 18.09.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-004112-60.

9. AstraZeneca. A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination with Durvalumab, Followed by Maintenance Durvalumab with or without Olaparib in Patients with Newly Diagnosed Advanced or Recurrent Endometrial Cancer (DUO-E) [online]. 2024 [Accessed: 18.09.2024]. URL: https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2022-502746-27-00.

10. AstraZeneca. Durvalumab With or Without Olaparib as Maintenance Therapy After First-Line Treatment of Advanced and Recurrent Endometrial Cancer (DUO-E) [online]. 2024 [Accessed: 18.09.2024]. URL: https://clinicaltrials.gov/study/NCT04269200.

11. Westin SN, Moore K, Chon HS et al. Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial. J Clin Oncol 2024; 42(3): 283-299. https://doi.org/10.1200/JCO.23.02132.

12. AstraZeneca. IMFINZI 50 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2024 [Accessed: 09.09.2024]. URL: https://www.fachinfo.de.

13. Leitlinienprogramm Onkologie. S3-Leitlinie Endometriumkarzinom; Langversion 3.0; AWMF-Registernummer: 032-034OL [online]. 2024 [Accessed: 19.09.2024]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Endometriumkarzinom/Version_3/LL_Endometriumkarzinom_Langversion_3.0.pdf.

14. Oaknin A, Bosse TJ, Creutzberg CL et al. Endometrial cancer; ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2022; 33(9): 860-877. https://doi.org/10.1016/j.annonc.2022.05.009.

15. Gemeinsamer Bundesausschuss. Verfahrensordnung des Gemeinsamen Bundesausschusses [online]. URL: https://www.g-ba.de/richtlinien/42/.

16. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pembrolizumab (Endometriumkarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022 [Accessed: 04.11.2024]. URL: https://www.iqwig.de/download/a21-164_pembrolizumab_nutzenbewertung-35a-sgb-v_v1-1.pdf.

17. Concin N, Matias-Guiu X, Vergote I et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer 2021; 31(1): 12-39. https://doi.org/10.1136/ijgc-2020-002230.

18. Robert Koch-Institut. Krebs in Deutschland für 2019/2020; 14. Auflage. 2023.

19. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Durvalumab (kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2020 [Accessed: 04.11.2024]. URL: https://www.iqwig.de/download/a20-87_durvalumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

20. Tolstrup LK, Bastholt L, Zwisler AD et al. Selection of patient reported outcomes questions reflecting symptoms for patients with metastatic melanoma receiving immunotherapy. J Patient Rep Outcomes 2019; 3(1): 19. https://doi.org/10.1186/s41687-019-0111-8.

21. Taarnhøj GA, Lindberg H, Johansen C, Pappot H. Patient-reported outcomes item selection for bladder cancer patients in chemo- or immunotherapy. J Patient Rep Outcomes 2019; 3(1): 56. https://doi.org/10.1186/s41687-019-0141-2.

The full report (German version) is published under https://www.iqwig.de/en/projects/a24-86.html.