Dostarlimab (endometrial cancer)

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

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Dostarlimab (Endometriumkarzinom) – 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.

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

Patient and family involvement

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

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AUC	area under the curve
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
dMMR	mismatch repair deficient
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
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)
MSI-H	microsatellite instability-high
PFS	progression-free survival
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-EN24	Quality of Life Questionnaire-Endometrial Cancer Module 24
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
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 dostarlimab (in combination with carboplatin and paclitaxel). 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 21 December 2023.

Research question

The aim of this report is to assess the added benefit of dostarlimab in combination with carboplatin and paclitaxel (hereinafter referred to as "dostarlimab + carboplatin + paclitaxel") compared with carboplatin and paclitaxel as appropriate comparator therapy (ACT) in patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer and 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 dostarlimab + carboplatin + paclitaxel

Therapeutic indication	**ACT[a]**
Adult patients with dMMR/MSI-H primary advanced or recurrent[b] endometrial cancer and who are candidates for systemic therapy[c]	Carboplatin + paclitaxel[d]

a. Presented is the ACT specified by the G-BA.
b. In the recurrent setting, it is assumed that local therapy options for treating the recurrence (resection, radiotherapy) are not an option.
c. 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.
d. For patients in this therapeutic indication, the evidence-based guideline recommendation and the written statement of the scientific-medical societies recommend treatment with carboplatin in combination with paclitaxel. 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. 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.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficient; G-BA: Federal Joint Committee; MSI-H: microsatellite instability-high

The company followed the G-BA's specification of the ACT.

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 study pool for the present benefit assessment consists of the RUBY study.

The RUBY study is an ongoing 2-part randomized, double-blind study, with Part 1 and Part 2 of the study being conducted independently of each other. Part 1 compares dostarlimab + carboplatin + paclitaxel with placebo + carboplatin + paclitaxel. This part of the study is relevant for the present benefit assessment. The RUBY study included adult patients with primary advanced (International Federation of Gynecology and Obstetrics [FIGO] stage III or stage IV) or recurrent endometrial cancer with a low potential for cure by radiation therapy and/or surgery alone or in combination. For patients at the recurrent stage, this had to be the first recurrence. The patients were not allowed to have received any systemic therapy for the current stage of the disease. At the recurrent stage, patients were allowed to have received one neoadjuvant or adjuvant chemotherapy for the primary disease provided the recurrence occurred at least 6 months after completing this treatment. No restrictions applied to prior hormonal therapies. Enrolment was limited to patients in good general health corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1.

In the RUBY study, a total of 494 patients were randomly assigned in a 1:1 ratio to treatment with dostarlimab + carboplatin + paclitaxel (N = 245) or placebo + carboplatin + paclitaxel (N = 249). Stratification factors were mismatch-repair/microsatellite stability status (dMMR/MSI-H versus mismatch repair-proficient/microsatellite stable), disease status at baseline (primary FIGO stage III versus primary FIGO stage IV versus recurrent), and prior external pelvic radiotherapy (yes versus no).

Treatment with dostarlimab in the intervention arm was in compliance with the Summary of Product Characteristics (SPC). Carboplatin and paclitaxel are not approved for this therapeutic indication. However, according to the current S3 guideline for endometrial cancer and the guideline by the European Society for Medical Oncology (ESMO), these drugs, in combination, are considered standard treatment in the first-line therapy of primary advanced or recurrent endometrial cancer. In the RUBY study, the paclitaxel dose was 175 mg/m² body surface area every 3 weeks. This is the dosage recommended by the guidelines. In the RUBY study, carboplatin was administered intravenously every 3 weeks according to a time-adjusted area under the curve (AUC) of 5 mg/mL/min. The S3 guideline for endometrial cancer and the ESMO guideline specify the dosage of carboplatin as AUC 5 to 6 mg/mL/min. The restriction to 6 treatment cycles can also be found in the ESMO guideline in this therapeutic indication. This restriction cannot be inferred from the S3 guideline. Overall, the choice of treatment regimen in this therapeutic indication is comprehensible.

The study population was treated until progression of disease, unacceptable toxicity, withdrawal of consent, treatment discontinuation upon investigator’s decision, or death, but

for a maximum of 3 years. After treatment discontinuation, patients could receive a subsequent therapy.

The primary outcomes of the RUBY study were progression-free survival (PFS) in the total population and in the relevant subpopulation with dMMR/MSI-H status, as well as overall survival in the total population. Secondary outcomes were outcomes in the categories of morbidity, health-related quality of life and side effects both in the total population and in the population with dMMR/MSI-H status.

Relevant subpopulation of the RUBY study

According to the approval, dostarlimab + carboplatin + paclitaxel is approved for patients with primary advanced or recurrent endometrial cancer with dMMR/MSI-H. The RUBY study included patients irrespective of this status. For the dossier, the company presented a subpopulation of patients with dMMR/MSI-H endometrial cancer, which corresponds to the therapeutic indication according to the SPC and is used for the benefit assessment. The population of patients with dMMR/MSI-H endometrial cancer comprises a total of 118 patients: 53 in the dostarlimab + carboplatin + paclitaxel arm and 65 in the placebo + carboplatin + paclitaxel arm.

Data cut-offs

The study is ongoing. The present benefit assessment uses the results of the first data cut-off from 28 September 2022, planned after 77 PFS events in the relevant subpopulation with dMMR/MSI-H status. According to the company, the analyses of a further data cut-off, conducted on 22 September 2023, are not yet fully available and are expected in the first quarter of 2024.

Risk of bias

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

The results on the outcome of overall survival have a low risk of bias. For the patient-reported outcomes (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30], EORTC Quality of Life Questionnaire-Endometrial Cancer Module 24 [EORTC QLQ-EN24], EQ-5D visual analogue scale [VAS]), the risk of bias of results is rated as high because the questionnaire return rates decreased markedly over time and differed between treatment arms. Due to incomplete observation for potentially informative reasons with different follow-up observation periods between treatment groups, the outcomes of the side effects category have a high risk of bias. Since no suitable analyses are available for the outcome of infusion-related reactions, the risk of bias for this outcome is not assessed. The certainty of results for the outcome of discontinuation due to adverse events (AEs) is limited despite the study's low risk of bias.

Results

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of dostarlimab + carboplatin + paclitaxel. For this outcome, there is an effect modification by the characteristic of disease status at baseline. In the pooled subgroup of patients with primary advanced FIGO stage IV disease or recurrent disease at baseline, there is an indication of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel. For patients with primary advanced FIGO stage III disease at baseline, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven for these patients.

Morbidity

Symptoms (EORTC QLQ-C30 and EORTC QLQ-EN24)

The symptoms outcomes were recorded with the instruments EORTC QLQ-C30 and EORTC QLQ-EN24. Time to first deterioration by ≥ 10 points (scale range 0 to 100) was considered.

Tingling and numbness (EORTC QLQ-EN24)

No statistically significant difference between treatment groups was found for the outcome of tingling and numbness. However, there is an effect modification by the characteristic of disease status at baseline. For patients with primary advanced FIGO stage IV disease at baseline, there is a hint of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel. For patients with primary advanced FIGO stage III disease or recurrent disease at baseline, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven for these patients.

Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea (EORTC QLQ-C30), lymphoedema, urological symptoms, gastrointestinal symptoms, pain in back and pelvis, muscular pain, hair loss, taste change (EORTC QLQ-EN24)

No statistically significant difference between treatment groups was found for the scales of fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea of the EORTC QLQ-C30, and for the scales of lymphoedema, urological symptoms, gastrointestinal symptoms, pain in back and pelvis, muscular pain, hair loss, and taste change of the EORTC QLQ-EN24. In each case, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven for any of them.

Sexual/vaginal problems (EORTC QLQ-EN24)

No usable data are available for the EORTC QLQ-EN24 scale of sexual/vaginal problems because only 19% of patients were included in the analysis. There is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was shown for the outcome of health status recorded with the EQ-5D VAS. There is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-EN24

The health-related quality of life outcomes were recorded with the instruments EORTC QLQ-C30 and EORTC QLQ-EN24. Time to first deterioration by ≥ 10 points (scale range 0 to 100) was considered.

Social functioning (EORTC QLQ-C30)

For the outcome of social functioning, a statistically significant difference was found in favour of dostarlimab + carboplatin + paclitaxel. There is a hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel.

Global health status, physical functioning, role functioning, emotional functioning, cognitive functioning (EORTC QLQ-C30), sexual interest, sexual activity, poor body image (EORTC QLQ-EN24)

No statistically significant difference between treatment groups was found for the scales of global health status, physical functioning, role functioning, emotional functioning, and cognitive functioning of the EORTC QLQ-C30, and for the scales of sexual interest, sexual activity, and poor body image of the EORTC QLQ-EN24. In each case, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven.

Sexual enjoyment (EORTC QLQ-EN24)

No usable data are available for the EORTC QLQ-EN24 scale of sexual enjoyment because only 18% of patients were included in the analysis. There is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven.

Side effects

Severe AEs

No significant difference between treatment groups was found for the outcome of severe AEs. However, there is an effect modification by the characteristic of disease status at baseline. For patients with primary advanced FIGO stage III disease at baseline, there is a hint of greater harm of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel. In the pooled subgroup of patients with primary advanced FIGO stage IV disease or recurrent disease at baseline, there is no hint of greater or lesser harm of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel; greater or lesser harm is therefore not proven.

Serious AEs (SAEs) and discontinuations due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; greater or lesser harm is therefore not proven for any of them.

Specific AEs

Immune-mediated severe AEs

The company provided no information on the hazard ratio (including 95% confidence interval) and p-value for the outcome of immune-mediated severe AEs. In the present data constellation, with an event rate of 19% (n = 10) in the intervention arm versus 0% (n = 0) in the comparator arm, and with Kaplan-Meier curves clearly separating early in the course of the study, a statistically significant difference to the disadvantage of dostarlimab + carboplatin + paclitaxel can be assumed. There is a hint of greater harm of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel.

Immune-mediated SAEs

No statistically significant difference between treatment groups was shown for the outcome of immune-mediated SAEs. There is no hint of greater or lesser harm from dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; greater or lesser harm is therefore not proven.

Infusion-related reactions

No usable data are available for infusion-related reactions. There is no hint of greater or lesser harm from dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; greater or lesser harm is therefore not proven.

Urinary tract infections (AEs)

For the outcome of urinary tract infections (AEs), a statistically significant difference was found in favour of dostarlimab + carboplatin + paclitaxel. There is a hint of lesser harm of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel.

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 combination of dostarlimab + carboplatin + paclitaxel in comparison with the ACT are assessed as follows:

Overall, both positive and negative effects of dostarlimab + carboplatin + paclitaxel were found in comparison with the ACT. For overall survival and the outcomes in the categories of morbidity and health-related quality of life, the observed effects relate to the entire observation period. For the side effects, however, they refer exclusively to the shortened period (until the 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 dostarlimab + carboplatin + paclitaxel compared with the ACT are derived separately by disease status at baseline:

Patients with primary advanced FIGO stage III disease

On the side of positive effects, there is a hint of a minor added benefit in social functioning in the category of health-related quality of life for patients with primary advanced FIGO stage III disease at baseline. In addition, there is a hint of lesser harm of considerable extent in the outcome of urinary tract infections (AEs). In view of the therapy regimens investigated, however, it is questionable whether the positive effect regarding this outcome is to be allocated to the outcome category of side effects or whether it rather reflects improved symptoms of the disease. A clear distinction is not possible on the basis of the available information.

In contrast, there are 2 negative effects in the category of serious/severe side effects with major or non-quantifiable, but at least considerable extent both in the overall rate of severe AEs and in immune-mediated severe AEs. It should be noted that the immune-mediated

[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].

severe AEs are also included in the analyses of the severe AEs. In summary, weighing the positive and negative effects, there is a hint of lesser benefit due to the major disadvantage in the overall rate of severe AEs for patients with primary advanced FIGO stage III disease at baseline.

Patients with primary advanced FIGO stage IV disease or recurrent disease

For patients with primary advanced FIGO stage IV disease or recurrent disease at baseline, there is an indication of major added benefit for the outcome of overall survival. In addition, there are further positive effects with minor or considerable extent in the categories of non-serious/non-severe symptoms/late complications (only for patients with FIGO stage IV), social functioning of health-related quality of life, and non-serious/non-severe side effects. In view of the therapy regimens investigated, however, it is questionable whether the positive effect regarding the outcome of urinary tract infections (AEs) is to be allocated to the outcome category of side effects or whether it rather reflects improved symptoms of the disease. A clear distinction is not possible on the basis of the available information. In contrast, in the category of serious/severe side effects, there is a negative effect with non-quantifiable, but at least considerable extent in immune-mediated severe AEs. This does not call into question the positive effects, especially the major added benefit in overall survival. The fact that there are no negative effects in the overall rate of severe AEs for this subgroup is also taken into account.

Overall, an indication of major added benefit is derived for patients with primary advanced FIGO stage IV disease or recurrent disease at baseline.

Summary

In summary, there is a hint of lesser benefit of dostarlimab + carboplatin + paclitaxel in comparison with the ACT carboplatin + paclitaxel for patients with dMMR/MSI-H primary advanced FIGO stage III endometrial cancer and who are candidates for systemic therapy. There is an indication of major added benefit of dostarlimab + carboplatin + paclitaxel in comparison with the ACT carboplatin + paclitaxel for patients with dMMR/MSI-H primary advanced FIGO stage IV or recurrent endometrial cancer and who are candidates for systemic therapy.

Table 3 shows a summary of probability and extent of the added benefit of dostarlimab + carboplatin + paclitaxel.

Table 3: Dostarlimab + carboplatin + paclitaxel – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with dMMR/MSI-H primary advanced or recurrent[b] endometrial cancer and who are candidates for systemic therapy[c]	Carboplatin + paclitaxel[d]	▪ Patients with primary FIGO stage III: hint of lesser benefit[e] ▪ Patients with primary FIGO stage IV or recurrent: indication of major added benefit[e]

a. Presented is the ACT specified by the G-BA.
b. In the recurrent setting, it is assumed that local therapy options for treating the recurrence (resection, radiotherapy) are not an option.
c. 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.
d. For patients in this therapeutic indication, the evidence-based guideline recommendation and the written statement of the scientific-medical societies recommend treatment with carboplatin in combination with paclitaxel. 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. 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.
e. The RUBY 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.

dMMR: mismatch repair deficient; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: International Federation of Gynecology and Obstetrics; G-BA: Federal Joint Committee; MSI-H: microsatellite instability-high

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 this report is to assess the added benefit of dostarlimab in combination with carboplatin and paclitaxel (hereinafter referred to as "dostarlimab + carboplatin + paclitaxel") compared with carboplatin and paclitaxel as ACT in patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer and 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 dostarlimab + carboplatin + paclitaxel

Therapeutic indication	**ACT[a]**
Adult patients with dMMR/MSI-H primary advanced or recurrent[b] endometrial cancer and who are candidates for systemic therapy[c]	Carboplatin + paclitaxel[d]

a. Presented is the ACT specified by the G-BA.
b. In the recurrent setting, it is assumed that local therapy options for treating the recurrence (resection, radiotherapy) are not an option.
c. 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.
d. For patients in this therapeutic indication, the evidence-based guideline recommendation and the written statement of the scientific-medical societies recommend treatment with carboplatin in combination with paclitaxel. 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. 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.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficient; G-BA: Federal Joint Committee; MSI-H: microsatellite instability-high

The company followed the G-BA's specification of the ACT.

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 dostarlimab (status: 18 December 2023)
- bibliographical literature search on dostarlimab (last search on 28 November 2023)
- search in trial registries/trial results databases for studies on dostarlimab (last search on 28 November 2023)
- search on the G-BA website for dostarlimab (last search on 28 November 2023)

To check the completeness of the study pool:

- search in trial registries for studies on dostarlimab (last search on 15 January 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
Study 213361 (RUBY[c])	Yes	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7]

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

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: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
RUBY[b]	RCT, double-blind, parallel	Adult patients (≥ 18 years) with primary advanced (FIGO stage III or IV) or recurrent[c] endometrial cancer ▪ with dMMR/MSI-H status or with pMMR/MSS status ▪ without prior systemic chemotherapy[d] ▪ low potential for cure by surgery and/or radiation ▪ ECOG PS ≤ 1	Dostarlimab + carboplatin + paclitaxel (N = 245) placebo + carboplatin + paclitaxel (N = 249) Of which relevant subpopulation (dMMR/MSI-H status): dostarlimab + carboplatin + paclitaxel (n = 53) placebo + carboplatin + paclitaxel (n = 65)	Screening: ≤ 28 days Treatment: for up to 3 years[e], until progression of disease[f], unacceptable toxicity, withdrawal of consent, investigator's decision, or death Observation[g]: outcome-specific, at most until death, lost to follow-up, withdrawal of consent, or end of study	108 study centres in Belarus, Belgium, Canada, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Israel, Italy, Netherlands, Norway, Poland, Sweden, Turkey, Ukraine, United Kingdom, United States 8/2019–ongoing Data cut-offs: ▪ 28 September 2022[h] ▪ 1 March 2023[i] ▪ 22 September 2023[j]	Primary: overall survival, PFS Secondary: morbidity, health-related quality of life, AEs

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

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

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. The RUBY study is a 2-part RCT, both parts of which are considered and conducted as independent studies. Only Part 1 of the RUBY study is relevant for the present benefit assessment, which is why Part 2 is not presented in this table.
c. Patients with first recurrence.
d. At the recurrent stage, patients were allowed to have received neoadjuvant/adjuvant systemic therapy for the primary disease provided the recurrence occurred ≥ 6 months after completing this treatment. Low-dose cisplatin given as a radiation sensitizer or hormonal therapies were allowed if completed ≥ 3 weeks prior to randomization.
e. Patients were allowed to continue treatment with dostarlimab beyond 3 years; this was at the discretion of the investigator and the sponsor.
f. Continued treatment with the study medication was possible even after disease progression if the investigator deemed that the patient was still deriving clinical benefit and the patient was clinically stable. The company provided no information in the CSR or in Module 4 A on how many patients this may affect.
g. Outcome-specific information is provided in Table 8.
h. Prespecified interim analysis (planned after 77 PFS events in the population with dMMR/MSI-H status)
i. Additional administrative interim analysis for overall survival (planned post hoc after 185 deaths in the total population).
j. Prespecified interim analysis (planned after 221 deaths in the total population). According to the information provided by the company, the results will be available in the first quarter of 2024 (see body of text below).

AE adverse event; CSR: clinical study report; dMMR: mismatch repair deficient; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: International Federation of Gynecology and Obstetrics; MSI-H: microsatellite instability-high; MSS: microsatellite stable; n: relevant subpopulation; 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: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study	Intervention[a]	Comparison[a]
RUBY	<u>6 cycles of 3 weeks</u> dostarlimab 500 mg IV on Day 1 of a cycle + paclitaxel 175 mg/m² BSA IV on Day 1 of a cycle + carboplatin AUC 5 mg/mL/min IV on Day 1 of a cycle <u>Maintenance therapy</u> from Cycle 7 dostarlimab monotherapy 1000 mg IV on Day 1 of a 6-week cycle	<u>6 cycles of 3 weeks</u> placebo IV on Day 1 of a cycle + paclitaxel 175 mg/m² BSA IV on Day 1 of a cycle + carboplatin AUC 5 mg/mL/min IV on Day 1 of a cycle <u>Maintenance therapy</u> from Cycle 7 placebo IV on Day 1 of a 6-week cycle
	Dose adjustment[b] ▪ Dostarlimab and placebo: no dose adjustment permitted; dose interruption[c]/treatment discontinuation due to toxicity (e.g. immune-mediated AEs, infusion-related reactions) permitted ▪ Carboplatin and paclitaxel: dose adjustments and interruptions (for a maximum of 6 weeks) and treatment discontinuation permitted in the event of haematologic toxicity, peripheral neuropathy and hypersensitivity reactions	
	Disallowed pretreatment ▪ systemic anticancer therapy for the primary advanced or recurrent stage[d] ▪ anti-PD-1, anti-PD-L1, or anti-PD-L2 drugs ▪ antitumour therapy (chemotherapy, targeted therapy, hormonal therapy, radiotherapy[e], immunotherapy) within 21 days before first dose of study treatment ▪ other investigational drugs ≤ 4 weeks before first dose of study treatment ▪ live vaccines ≤ 30 days before first dose of study treatment **Allowed concomitant treatment** ▪ medications for the treatment of AEs[f] ▪ premedication with corticosteroids, diphenhydramine, and H2 antagonists when administering paclitaxel **Disallowed concomitant treatment** ▪ other antitumour therapies (chemotherapy, targeted therapy, hormonal therapy, radiotherapy[e], immunotherapy) immunotherapies, biological therapies, investigational products ▪ surgical interventions for the treatment of endometrial carcinoma ▪ blood products or colony-stimulating factors within 21 days prior to the first dose ▪ systemic corticosteroids[g] (except for the treatment of AEs) ▪ live vaccines for up to 180 days after receiving the last dose of study treatment, bacterial vaccines	

Table 7: Characteristics of the intervention – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study	Intervention[a]	Comparison[a]
a. The following order of study treatment was recommended according to the study protocol: 1) dostarlimab or placebo, 2) paclitaxel, 3) carboplatin. b. Where the investigator clearly determined the specific component causing toxicity, it was possible to interrupt, reduce (except dostarlimab and placebo), or discontinue any drug of the combination therapy independently from the other drugs. Dose reductions for dostarlimab and placebo were not permitted. If one component was discontinued, treatment could be continued with dostarlimab or placebo or chemotherapy alone. c. Dose interruptions due to AEs were permitted for a maximum of 6 weeks. Dose interruptions for no longer than 3 weeks are permitted in the case of medical/surgical events or for logistical reasons not related to study treatment (e.g. elective surgery, unrelated medical events, patient vacation, or holidays). d. At the recurrent stage, patients were allowed to have received neoadjuvant/adjuvant systemic therapy for the primary disease provided the recurrence occurred ≥ 6 months after completing this treatment. Low-dose cisplatin given as a radiation sensitizer or hormonal therapies were allowed if completed ≥ 3 weeks prior to randomization. e. Palliative radiation therapy to a small field ≥ 1 week prior to the start of study treatment was allowed. f. Administration of prophylactic cytokines in the first cycle of the study was not permitted. g. Corticosteroids were allowed to treat immune-mediated AEs or if medically necessary in the opinion of the investigator for a maximum of 24 hours prior to the next dose of study treatment. AE: adverse event; AUC: area under the curve; BSA: body surface area; H2: histamine receptor 2; IV: intravenous; PD-1: programmed cell death 1; PD-L1/2: programmed cell death ligand 1/2; RCT: randomized controlled trial		

Study design

The RUBY study is an ongoing 2-part randomized, double-blind study, with Part 1 and Part 2 of the study being conducted independently of each other. Part 1 compares dostarlimab + carboplatin + paclitaxel with placebo + carboplatin + paclitaxel. This part of the study is relevant for the present benefit assessment. As niraparib is additionally administered in the intervention arm in Part 2 of the study, this part of the study is not relevant for the present benefit assessment and is therefore not presented further.

The RUBY study included adult patients with primary advanced (FIGO stage III or stage IV) or recurrent endometrial cancer with a low potential for cure by radiation therapy and/or surgery alone or in combination. For patients at the recurrent stage, this had to be the first recurrence. The patients were not allowed to have received any systemic therapy for the current stage of the disease. At the recurrent stage, patients were allowed to have received one neoadjuvant or adjuvant chemotherapy for the primary disease provided the recurrence occurred at least 6 months after completing this treatment. No restrictions applied to prior hormonal therapies. Enrolment was limited to patients in good general health corresponding to an ECOG PS ≤ 1.

In the RUBY study, a total of 494 patients were randomly assigned in a 1:1 ratio to treatment with dostarlimab + carboplatin + paclitaxel (N = 245) or placebo + carboplatin + paclitaxel

(N = 249). Stratification factors were mismatch-repair/microsatellite stability status (dMMR/MSI-H versus mismatch repair-proficient/microsatellite stable), disease status at baseline (primary FIGO stage III versus primary FIGO stage IV versus recurrent), and prior external pelvic radiotherapy (yes versus no).

Dostarlimab treatment in the intervention arm was in compliance with the SPC [8].

In both study arms, chemotherapy involved carboplatin in combination paclitaxel. Both drugs are not approved for the present therapeutic indication [9,10]. However, according to the current S3 guideline for endometrial cancer and the ESMO guideline, these drugs, in combination, are considered standard treatment in the first-line therapy of primary advanced or recurrent endometrial cancer [11,12]. In the RUBY study, the paclitaxel dose was 175 mg/m² body surface area. This is the recommended dosage according to the guidelines mentioned [11-13]. In the RUBY study, carboplatin was administered intravenously every 3 weeks according to a time-adjusted AUC of 5 mg/mL/min. In the S3 guideline for endometrial cancer, the recommended dosage of carboplatin in combination with paclitaxel is AUC 6 mg/mL/min and AUC 5 after radiation [11]. According to the ESMO guideline, the dosage of carboplatin is AUC 5 to 6 mg/mL/min [12]. In Module 4 A, the company refers to the fact that in combination treatment with the immune checkpoint inhibitor trastuzumab, the S3 guideline also recommends using carboplatin at AUC 5 mg/mL/min. In addition, the company stated that this dosage corresponds to the actual health care setting in Germany [14]. Besides, treatment with paclitaxel and carboplatin was limited to 6 treatment cycles in the RUBY study. The ESMO guideline also recommends the use of carboplatin and paclitaxel for 6 cycles in this therapeutic indication [12]. This restriction cannot be inferred from the S3 guideline [11]. Overall, the company's reasoning for the choice of the therapeutic regimen is comprehensible, and the carboplatin and paclitaxel dosages seem plausible.

The study population was treated until progression of disease, unacceptable toxicity, withdrawal of consent, treatment discontinuation upon investigator's decision, or death, but for a maximum of 3 years. Treatment could be continued beyond 3 years at the discretion of the investigator and the sponsor. In addition, continued treatment with the study medication was possible even after disease progression if the investigator deemed that the patient was still deriving clinical benefit and the patient was clinically stable. After treatment discontinuation, patients could receive a subsequent therapy. The study protocol did not restrict the choice of subsequent therapies.

The primary outcomes of the RUBY study were PFS in the total population and in the relevant subpopulation with dMMR/MSI-H status, as well as overall survival in the total population. Secondary outcomes were outcomes in the categories of morbidity, health-related quality of life and side effects both in the total population and in the population with dMMR/MSI-H status.

Suitability of systemic therapy for the patients included in the RUBY study

The therapeutic indication of the present assessment is restricted to patients who are candidates for systemic therapy. According to guidelines, no clear criteria are defined as to when patients are eligible for systematic therapy. However, based on the selected inclusion and exclusion criteria of the study and the patient characteristics, it can be assumed that systemic therapy was indicated for the patients in the RUBY study. The study included patients with a low potential for cure by local therapies. According to the guidelines [11,12,15], systemic therapy is indicated for such patients. Also with regard to the good general condition (ECOG PS ≤ 1) and the permitted prior therapies of the patients, it is assumed that systemic therapies were an option for most of the patients included.

Relevant subpopulation of the RUBY study

According to the approval, dostarlimab + carboplatin + paclitaxel is approved for patients with primary advanced or recurrent endometrial cancer with dMMR/MSI-H. The RUBY study included patients irrespective of this status. For the dossier, the company presented a subpopulation of patients with dMMR/MSI-H endometrial cancer, which corresponds to the therapeutic indication according to the SPC and is used for the benefit assessment. The population of patients with dMMR/MSI-H endometrial cancer comprises a total of 118 patients: 53 in the dostarlimab + carboplatin + paclitaxel arm and 65 in the placebo + carboplatin + paclitaxel arm.

Data cut-offs

The RUBY study is still ongoing. Data from the first data cut-off of 28 September 2022 are available for the present benefit assessment. This is a prespecified interim analysis, which was planned after 77 PFS events in the relevant subpopulation with dMMR/MSI-H status and conducted after 66 PFS events.

The company described in Module 4 A that a second data cut-off was conducted on 22 September 2023. This is a further prespecified interim analysis, which was planned after 221 deaths in the total study population. The company further stated that the analyses are not yet fully available and are expected for the first quarter of 2024.

The study protocol version 6.0 dated 31 March 2023, prepared after the first data cut-off, shows that a further data cut-off was carried out on 1 March 2023. This additional data cut-off was not described in the protocol versions prepared before the presented data cut-off of 28 September 2022. The company described the data cut-off of 1 March 2023 as an additional administrative interim analysis for overall survival to support the approval procedure, which was planned post hoc after 185 deaths in the total population. However, it is not clear from the study documents whether the data was requested by regulatory authorities such as the European Medicines Agency as part of the extension of approval. The company did not

present results for this data cut-off in the clinical study report (CSR) or in Module 4 A. The approval documents contain only data for overall survival for this data cut-off [16]. This shows that, in comparison with the presented data cut-off of 28 September 2022, there were 2 additional events each in the intervention and in the control arm in the data cut-off of 1 March 2023. Overall, the result of the analysis for overall survival did not change. Since the data cut-off of 1 March 2023 was not predefined and no information is available to show that it was requested by regulatory authorities, it is not used for the benefit assessment.

The present benefit assessment uses the results from the first data cut-off of 28 September 2022.

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: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel

Study **Outcome category** **Outcome**	**Planned follow-up observation**
RUBY	
Mortality	
Overall survival	Until death or end of data recording[a]
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-EN24)	Until death or end of data recording[a]
Health status (EQ-5D VAS)	Until death or end of data recording[a]
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-EN24)	Until death or end of data recording[a]
Side effects	
AEs, severe AEs[b], specific AEs	Until 30 or 42 days[c] after the last dose of study medication or until initiation of a new antineoplastic treatment (whichever occurred first)
SAEs	Until 90 days after the last dose of study medication or until initiation of a new antineoplastic treatment (whichever occurred first)

a. Up to 4 years after inclusion of the last patient.
b. Operationalized as CTCAE grade ≥ 3.
c. Corresponds to the EOT visit; Cycle 1 to 6: 30 days after the last dose of study medication, from Cycle 7: 42 days after the last dose of study medication.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EOT: end of treatment; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer Module 24; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

In addition to overall survival, the RUBY study also recorded the patient-reported outcomes of morbidity and health-related quality of life beyond progression until the end of the study.

The observation periods for the outcomes of the category of side effects are systematically shortened because they were only recorded for the period of treatment with the study medication (plus 90 days for SAEs and 30 or 42 days for all other AEs in the category of side effects). However, drawing a reliable conclusion on the total study period or the time until patient death would require obtaining data regarding these outcomes throughout the entire period, as was done for the outcomes in the categories of mortality, morbidity and health-related quality of life.

Characteristics of the study population

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

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study **Characteristic** **Category**	**Dostarlimab + carboplatin + paclitaxel** **N[a] = 53**	**Placebo + carboplatin + paclitaxel** **N[a] = 65**
RUBY		
Age [years], mean (SD)	64 (10)	63 (11)
Family origin, n (%)		
Asian	2 (4)	0
Hawaiian or Pacific Islander	1 (2)	0
American Indian or Alaska Native	0	1 (2)
Caucasian	44 (83)	56 (86)
Black or African American	4 (8)	6 (9)
Unknown	1 (2)	1 (2)
Missing	1 (2)	1 (2)
Region, n (%)		
Europe	17 (32)	15 (23)
North America	36 (68)	50 (77)
ECOG PS, n (%)		
0	28 (54)	39 (60)
1	24 (46)	26 (40)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study Characteristic Category	**Dostarlimab + carboplatin + paclitaxel N[a] = 53**	**Placebo + carboplatin + paclitaxel N[a] = 65**
Histology from most recent examination, n (%)		
Carcinosarcoma	4 (8)	2 (3)
Endometrioid carcinoma (adenocarcinoma or variants)	45 (85)	54 (83)
Mixed carcinoma with ≥ 10% carcinosarcoma, clear cell or serous histology	1 (2)	4 (6)
Other	3 (6)	3 (5)
Serous adenocarcinoma	0	1 (2)
Undifferentiated carcinosarcoma	0	1 (2)
FIGO stage at baseline, n (%)		
Stage III	10 (19)	14 (22)
Stage IV	16 (30)	19 (29)
Recurrent	27 (51)	32 (49)
Prior pelvic radiotherapy, n (%)	19 (36)	22 (34)
Prior surgery of endometrial cancer, n (%)	49 (92)	60 (92)
Prior systemic therapy, n (%)[b]	7 (13)	10 (15)
Treatment discontinuation, n (%)[c]	29 (56)	56 (86)
Study discontinuation, n (%)[d]	13 (25)	32 (49)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. At the recurrent stage, patients were allowed to have received neoadjuvant/adjuvant systemic therapy for the primary disease provided the recurrence occurred ≥ 6 months after completing this treatment. Low-dose cisplatin given as a radiation sensitizer or hormonal therapies were allowed if completed ≥ 3 weeks prior to randomization.
c. Data refer to the discontinuation of all components. Treatment with carboplatin was not completed as planned by 19% of patients in the intervention arm and 14% in the control arm. Treatment with paclitaxel was not completed as planned by 17% of patients in the intervention arm and 23% in the control arm. Common reasons for treatment discontinuation of dostarlimab or placebo were disease progression as per RECIST 1.1 (25% vs. 62%) and adverse event (17% vs. 11%).
d. Common reasons for study discontinuation in the intervention arm vs. the control arm were death (13% vs. 37%), withdrawal of consent (6% vs. 6%), and lost to follow-up (4% vs. 5%).

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 patients; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; 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 Caucasian family origin. The majority of patients had a good general health (ECOG PS of 0). Approximately 50% of patients had recurrent disease, 30% were diagnosed with FIGO stage III and 20% with FIGO stage IV. Before the start of the study, approximately 92% of patients had undergone surgery for endometrial cancer and approximately 35% had undergone radiotherapy. Approximately 14% of patients had already received systemic therapy. 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 proportion of patients with treatment discontinuation was lower in the intervention arm at 56% than in the comparator arm at 86%. These differences can also be seen in study discontinuations, with 25% of patients in the intervention arm and 49% of patients in the comparator arm discontinuing the study.

Information on the course of the study

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

Table 10: Information on the course of the study – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel

Study **Duration of the study phase** **Outcome category**	**Dostarlimab + carboplatin + paclitaxel** **N = 53**	**Placebo + carboplatin + paclitaxel** **N = 65**
RUBY		
Treatment duration [months]		
For dostarlimab/placebo		
Median [Q1; Q3]	17.6 [5.7; 24.6][a]	7.3 [4.8; 11.5][a]
Mean (SD)	16.4 (10.6)[a]	10.4 (8.3)[a]
For carboplatin		
Median [Q1; Q3]	4.1 [4.1; 4.4][a]	4.1 [4.1; 4.4][a]
Mean (SD)	4.0 (0.9)[a]	4.1 (0.9)[a]
For paclitaxel		
Median [Q1; Q3]	4.1 [4.1; 4.4][a]	4.1 [4.1; 4.3][a]
Mean (SD)	3.9 (1.0)[a]	3.9 (1.0)[a]
Observation period [months]		
Overall survival[b]		
Median [Q1; Q3]	22.9 [20.0; 27.4]	19.6 [11.8; 23.8]
Mean (SD)	21.1 (9.3)	18.5 (8.4)
Morbidity		
Symptoms (EORTC QLQ-C30, EORTC QLQ-EN24)		
Median [Q1; Q3]	22.9 [20.0; 27.4]	19.6 [11.8; 23.8]
Mean (SD)	21.1 (9.3)	18.5 (8.4)
Health status (EQ-5D VAS)		
Median [Q1; Q3]	22.9 [20.0; 27.4]	19.6 [11.8; 23.8]
Mean (SD)	21.1 (9.3)	18.5 (8.4)
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-EN24)		
Median [Q1; Q3]	22.9 [20.0; 27.4]	19.6 [11.8; 23.8]
Mean (SD)	21.1 (9.3)	18.5 (8.4)
Side effects		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND

a. Institute's calculation.
b. The observation period was calculated based on the observed time to event/censoring/end of study of all patients (deceased and non-deceased).

EORTC: European Organisation for Research and Treatment of Cancer; max.: maximum; min: minimum; N: number of patients; ND: no data; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer Module 24; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

The median treatment duration in the intervention arm was 17.6 months, about 2.5 times as long as in the comparator arm (7.3 months). The treatment duration for carboplatin and paclitaxel, which was to be administered for a maximum of 6 cycles at 21 days each, is comparable in the 2 treatment arms. The median observation periods for overall survival and

for the outcomes in the category of morbidity and health-related quality of life were about 23 months in the intervention arm and 20 months in the comparator arm.

For the outcomes in the side effects category, no data on the observation periods are available either in Module 4 or in the CSR. For these outcomes, the observation periods were linked to the end of treatment (see Table 8). Hence, the different median treatment durations (17.6 months in the intervention arm and 7.3 months in the control arm) also resulted in differences in median observation periods. Overall, the observation period for these outcomes was shortened in comparison with those observed until death.

Information on subsequent therapy

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

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel

Study **Drug class** **Drug**	**Patients with subsequent therapy[a] n (%)**	
	Dostarlimab + carboplatin + paclitaxel **N = 53**	**Placebo + carboplatin + paclitaxel** **N = 65**
RUBY		
Total	15 (28)	38 (58)
Immunotherapy	8 (53[b])	25 (66[b])
Pembrolizumab	4 (27[b])	20 (53[b])
Pembrolizumab/lenvatinib	3 (20[b])	2 (5[b])
Dostarlimab	0	3 (8[b])
Pembrolizumab/tamoxifen	1 (7[b])	0
Retifanlimab/epacadostat	1 (7[b])	0
Chemotherapy	7 (47[b])	10 (26[b])
Doxorubicin	3 (20[b])	3 (8[b])
Paclitaxel/carboplatin	3 (20[b])	2 (5[b])
Doxorubicin, PEG liposomal	1 (7[b])	1 (3[b])
Carboplatin	1 (7[b])	0
Carboplatin/vinorelbine	0	1 (3[b])
Cisplatin	0	1 (3[b])
Epirubicin	1 (7[b])	0
Gemcitabine	0	1 (3[b])
Paclitaxel	1 (7[b])	0
Topotecan	0	1 (3[b])
Hormonal therapy	3 (20[b])	9 (24[b])
Letrozole	1 (7[b])	6 (16[b])
Megestrol acetate	1 (7[b])	2 (5[b])
Megestrol acetate/tamoxifen	1 (7[b])	1 (3[b])
Everolimus	1 (7[b])	0
Everolimus/letrozole	1 (7[b])	0
Radiotherapy	2 (13[b])	8 (21[b])
Radiation treatment	1 (7[b])	8 (21[b])
Stereotactic radiosurgery	1 (7[b])	0
Other	1 (7[b])	0
Pemigatinib	1 (7[b])	0

a. Patients may be counted in more than one subsequent therapy.
b. Institute's calculation; based on the proportion of patients with subsequent antineoplastic therapy.

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

In Module 4 A, the company did not provide any information on administered subsequent therapies and referred to the CSR. The study documents do not describe any limitations regarding the types of subsequent therapies. The study protocol did not provide for any planned switching of patients from the comparator arm into the intervention arm due to disease progression. A total of 28% of patients in the intervention arm and 58% of patients in the comparator arm received subsequent therapy. This means that the majority of patients with disease progression (n = 19 and n = 47 according to the investigator's assessment) received subsequent therapy. The proportions of the drugs or drug classes used differ between the treatment arms. After discontinuation of study medication, 53% and 66% of patients received immunotherapy, with pembrolizumab (27% versus 53%) and the combination of pembrolizumab + lenvatinib (20% versus 5%) being the most frequently used. At 47%, more patients in the intervention arm received chemotherapy as subsequent therapy than in the comparator arm (26%). Doxorubicin (20% versus 8%) and the combination of paclitaxel + carboplatin (20% versus 5%) were administered. In both study arms, hormonal therapy was used in comparable proportions after discontinuation of the study medication (20% versus 24%). Radiotherapy was administered to 13% and 21% of the patients. Overall, the subsequent therapies used appear plausible and the drugs used largely reflect the recommendations of the guidelines for the treatment of endometrial cancer [12,15,16].

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: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel

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			
RUBY	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

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

Transferability of the study results to the German health care context

According to the company, due to the selected inclusion criteria of the RUBY study, the study population covers the target population according to the therapeutic indication. It further described that demographic and disease-specific characteristics were met and balanced

between the study arms. The company cited the proportion of patients from Europe (about 27%) and the high proportion of included patients of Caucasian origin (about 85%). The company therefore assumed the available study results to be transferable to the German health care context.

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

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 and the EORTC QLQ-EN24
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - EORTC QLQ-C30 and EORTC QLQ-EN24
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - immune-mediated SAEs and severe AEs
  - infusion-related reactions
  - further specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel

Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-EN24)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-EN24)	SAEs	Severe AEs[a]	Discontinuation due to AEs[b]	Immune-mediated SAEs[c]	Immune-mediated severe AEs[a, c]	Infusion-related reactions	Urinary tract infections (PT, AEs)
RUBY	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[d]	Yes

a. Severe AEs are operationalized as CTCAE ≥ 3.
b. Discontinuation of at least one drug component.
c. The operationalization was based on an a priori defined list of PTs; only immune-mediated AEs with CTCAE grade ≥ 2 could be considered immune-mediated, however.
d. No suitable data available (see body of text below for reasons).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer Module 24; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Analyses on outcomes of morbidity and health-related quality of life presented by the company

In the dossier, the company presented different analyses for the outcomes of morbidity and health-related quality of life measured using the EORTC QLQ-C30 and the additional module EORTC QLQ-EN24 as well as for the EQ-5D VAS.

As primary analysis, it used the results of the responder analyses for the time to first improvement or deterioration, including the respective subgroup analyses. As supplementary information, the company presented analyses for the time to definitive improvement or deterioration as well as analyses based on the mixed-effects model with repeated measures and analyses based on the time-adjusted AUC, in each case for the entire relevant subpopulation.

Responder analyses on outcomes of morbidity and health-related quality of life presented by the company

In the dossier, the company presented responder analyses for the outcomes on morbidity and health-related quality of life measured with the EORTC QLQ-C30 and the additional module EORTC QLQ-EN24, each with an improvement or deterioration by ≥ 10 points (respective scale

range 0 to 100) and for the EQ-5D VAS by ≥ 15 points (scale range 0 to 100). The response criteria of 10 and 15 points, which were used in the analyses presented by the company, fulfil the requirements for response criteria of reflecting with sufficient certainty a change that is perceivable for patients, as described in the *General Methods* of the Institute [1]. Due to the expected progressive course of the disease in this therapeutic indication, deterioration is considered a suitable operationalization in the present benefit assessment.

First deterioration relevant

In Module 4 A, the company presented analyses of the time to first deterioration as well as to definitive deterioration. Both operationalizations were not prespecified a priori. In Module 4 A, the company defined definitive deterioration as decrease of the corresponding score by at least the response criterion without subsequent improvement above the response criterion in at least 3 recordings. Both operationalizations presented by the company are patient relevant in principle. The analyses of the time to first deterioration are used in the present benefit assessment. This is justified below.

It should be emphasized that the recording of patient-reported outcomes in the RUBY study was to be conducted until the end of the study (death or end of observation) and was not terminated prematurely, e.g. in the event of disease progression or treatment switch (see Table 8). This makes it possible to show symptoms and health-related quality of life over the entire course of the study. However, treatment durations differed between the study arms – partly due to the therapy used (see Table 10). This is particularly relevant because the planned intervals between the recordings were longer after treatment discontinuation or termination (3 or 6 weeks during treatment versus 90 days after treatment discontinuation), resulting in a different number of recordings between the study arms. For example, a patient with median treatment and observation duration would have had approximately 18 recordings in the intervention arm and 14 recordings in the comparator arm. Furthermore, there are differences in the median observation periods for these outcomes (23 and 20 months). Although these also have a potential influence on the number of recordings, they alone do not mean that definitive deterioration is not suitable. In addition, there is a differential decrease in the proportion of completed questionnaires between the treatment arms. Furthermore, the presented operationalizations for the responder analyses and in particular the number of necessary confirmations for definitive deterioration were not predefined, and it is also not clear from the company's dossier why it had chosen this operationalization. Overall, these aspects mean that the analyses of definitive deterioration are not usable.

The time to first deterioration is not affected to a relevant extent by the differences in the intervals or number of recordings, as the first deterioration for most outcomes occurred early in the course of treatment (see Kaplan-Meier curves in I Appendix B of the full dossier assessment). As supplementary information, it should be noted that the analyses additionally

presented by the company based on a mixed-effects model with repeated measures also take into account the entire observation period, and that the different recording intervals and recording numbers play a lesser role in these analyses. These analyses show no relevant effects (see I Appendix E of the full dossier assessment).

Side effects

Recording of the progression of the underlying disease

The study protocol describes that progression of the underlying disease should not be documented as an AE. The company did not specify in the dossier which events it classified as progression. The available information on the documented AEs provides no evidence that AEs attributable to the progression of the underlying disease have a relevant impact on the overall rates of SAEs and severe AEs (see I Appendix C of the full dossier assessment). Individual AEs occurring in the study, e.g. urinary tract infections and vaginal bleeding, are difficult to differentiate from events of the underlying disease. When interpreting the results, it must be noted that these may be due to a mixture of side effects and symptoms or late complications of the disease.

Immune-mediated AEs, immune-mediated severe AEs and immune-mediated SAEs

In Module 4 A, the company presented analyses on immune-mediated AEs, immune-mediated SAEs and immune-mediated severe AEs (operationalized as CTCAE grade ≥ 3). The operationalization was based on an a priori defined list of PTs; only immune-mediated AEs with CTCAE grade ≥ 2 could be considered immune-mediated, however. This list of predefined PTs is very extensive and includes all potentially relevant categories with the exception of renal AEs. The company did not justify the exclusion of renal events from its list. However, as only very few renal events occurred overall, the present operationalization is used for this assessment. Both SAEs and severe AEs (CTCAE grade ≥ 3) are used for the benefit assessment. A list of immune-mediated AEs, immune-mediated SAEs, and immune-mediated severe AEs (CTCAE grade ≥ 3) that occurred in the RUBY study is provided in I Appendix D of the full benefit assessment.

In Module 4 A of the dossier, the company provided neither information on the effect estimate nor on statistical significance for immune-mediated severe AEs (CTCAE grade ≥ 3). Even in the data situation with zero events in the control arm, the statistical significance of the time-to-event analyses can be evaluated using the log-rank test. The Firth correction for the Cox model [17-20] in combination with profile likelihood methods for the 95% confidence intervals offers one way of obtaining point and interval estimates in this data situation.

Infusion-related reactions

All drugs used in the RUBY study were administered as infusion. Infusion-related reactions are therefore a relevant side effect. These were defined as any AEs related to drug administration

which occurred within 1 day after the infusion. The company only considered the following prespecified PTs to be relevant: anaphylactic reaction, drug hypersensitivity, hypersensitivity, type I allergy, and infusion-related reactions. This list therefore does not include the symptoms underlying the infusion-related reaction (e.g. chills, headache, nausea, or fever), but the diagnosis made by the investigator (e.g. infusion-related reaction). Based on the available information, it can therefore be assumed that there were no specific criteria for the investigator' assessment of whether a symptom (e.g. fever) was considered to be an infusion-related reaction. Only in certain data constellations, e.g. in the presence of marked effects (see dossier assessment A21-60 [21]), it is conceivable to derive greater or lesser harm based on such an operationalization. Such a data constellation is not present here. The analyses presented by the company for the outcome of infusion-related reactions are therefore not suitable for the 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: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel

Study		Outcomes										
	Study level	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-EN24)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-EN24)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-mediated SAEs[c]	Immune-mediated severe AEs[a, c]	Infusion-related reactions	Urinary tract infections (PT, AEs)
RUBY	L	L	H[d]	H[d]	H[d]	H[e]	H[e]	L[f]	H[e]	H[e]	-[g]	H[e]

a. Severe AEs are operationalized as CTCAE ≥ 3.
b. Discontinuation of at least one drug component.
c. The operationalization was based on an a priori defined list of PTs; only immune-mediated AEs with CTCAE grade ≥ 2 could be considered immune-mediated, however.
d. Marked decrease in questionnaire return rates in the course of the study, which differed between treatment arms.
e. Incomplete observations for potentially informative reasons.
f. Despite the low risk of bias, the certainty of results is presumably limited for the outcome of discontinuation due to AE.
g. No suitable data available (see Section I 4.1 for reasons).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer Module 24; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The results on the outcome of overall survival have a low risk of bias.

The risk of bias of the results for the patient-reported outcomes (EORTC QLQ-C30, EORTC QLQ-EN24, EQ-5D VAS) is to be rated as high due to the marked decrease in the response rates of the questionnaires, which differed between treatment arms.

Due to incomplete observation for potentially informative reasons with different follow-up observation periods between treatment groups, the outcomes of the side effects category have a high risk of bias. Since no suitable analyses are available for the outcome of infusion-related reactions (see Section I 4.1), the risk of bias for this outcome is not assessed.

The risk of bias for the results of the outcome of discontinuation due to AEs is rated as low. Nevertheless, the certainty of conclusions for the outcome is limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs. Consequently, after treatment discontinuation for other reasons, AEs which would have led to discontinuation may have occurred, but the criterion of 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 comparing dostarlimab + carboplatin + paclitaxel with placebo + carboplatin + paclitaxel in adult patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer and 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 on the time-to-event analyses are presented in I Appendix B of the full dossier assessment, and the tables on common AEs, SAEs, severe AEs, and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment. I Appendix D of the full dossier assessment presents the results on the occurred immune-mediated AEs, SAEs and severe AEs summarized in categories defined by the company.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study Outcome category Outcome	Dostarlimab + carboplatin + paclitaxel		Placebo + carboplatin + paclitaxel		Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
RUBY					
Mortality					
Overall survival	53	NA 7 (13.2)	65	NA 24 (36.9)	0.30 [0.13; 0.70]; 0.003
Morbidity					
Symptoms (EORTC QLQ-C30 – time to first deterioration[b])					
Fatigue	53	2.3 [1.6; 4.0] 40 (75.5)	65	1.4 [1.0; 2.8] 49 (75.4)	0.89 [0.58; 1.36]; 0.577
Nausea and vomiting	53	5.8 [2.8; 14.9] 35 (66.0)	65	4.5 [2.6; 11.3] 40 (61.5)	0.89 [0.55; 1.43]; 0.618
Pain	53	11.5 [2.8; 27.1] 30 (56.6)	65	3.3 [2.2; 4.9] 46 (70.8)	0.63 [0.39; 1.02]; 0.053
Dyspnoea	53	4.4 [2.6; 17.7] 35 (66.0)	65	3.7 [2.1; 10.6] 41 (63.1)	0.93 [0.57; 1.50]; 0.739
Insomnia	53	7.5 [2.1; NC] 29 (54.7)	65	4.2 [2.8; NC] 36 (55.4)	0.95 [0.58; 1.56]; 0.837
Appetite loss	53	19.8 [5.6; NC] 24 (45.3)	65	8.5 [2.8; NC] 35 (53.8)	0.76 [0.45; 1.29]; 0.318
Constipation	53	2.8 [1.0; NC] 30 (56.6)	65	3.9 [2.1; 5.8] 42 (64.6)	0.89 [0.54; 1.45]; 0.573
Diarrhoea	53	4.6 [2.4; 14.9] 36 (67.9)	65	5.7 [3.7; 28.5] 35 (53.8)	1.23 [0.76; 2.01]; 0.394
Symptoms (EORTC QLQ-EN24 – time to first deterioration[b])					
Lymphoedema	53	2.8 [2.1; 4.4] 37 (69.8)	65	2.8 [1.7; 3.5] 49 (75.4)	0.86 [0.56; 1.33]; 0.501
Urological symptoms	53	NA [7.2; NC] 21 (39.6)	65	3.8 [2.1; 21.9] 36 (55.4)	0.58 [0.33; 1.01]; 0.053
Gastrointestinal symptoms	53	21.6 [4.4; NC] 24 (45.3)	65	11.7 [6.5; NC] 32 (49.2)	0.92 [0.54; 1.59]; 0.774
Sexual/vaginal problems	No usable data available[c]				

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study Outcome category Outcome	Dostarlimab + carboplatin + paclitaxel		Placebo + carboplatin + paclitaxel		Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Pain in back and pelvis	53	21.6 [8.8; NC] 23 (43.4)	65	18.2 [4.6; NC] 30 (46.2)	0.87 [0.50; 1.51]; 0.628
Tingling/numbness	53	1.5 [1.0; 2.1] 45 (84.9)	65	1.4 [0.9; 2.1] 56 (86.2)	0.88 [0.58; 1.32]; 0.509
Muscular pain	53	1.4 [0.9; 3.5] 42 (79.2)	65	2.1 [1.4; 2.9] 50 (76.9)	1.15 [0.76; 1.75]; 0.556
Hair loss	53	0.8 [0.7; 0.8] 47 (88.7)	65	0.8 [0.7; 0.8] 61 (93.8)	1.15 [0.77; 1.71]; 0.574
Taste change	53	2.2 [0.9; 3.5] 35 (66.0)	65	2.2 [1.4; 3.0] 48 (73.8)	0.88 [0.57; 1.38]; 0.559
Health status (EQ-5D VAS – time to first deterioration[d])	53	NA 14 (26.4)	65	16.3 [4.2; NC] 28 (43.1)	0.56 [0.29; 1.08]; 0.080
Health-related quality of life					
EORTC QLQ-C30 – time to first deterioration[e]					
Global health status	53	12.9 [4.0; NC] 27 (50.9)	65	4.2 [2.0; 9.0] 46 (70.8)	0.63 [0.39; 1.04]; 0.067
Physical functioning	53	4.0 [2.1; 23.5] 31 (58.5)	65	3.7 [2.1; 10.8] 41 (63.1)	0.95 [0.59; 1.52]; 0.818
Role functioning	53	4.4 [2.3; NC] 30 (56.6)	65	2.5 [1.4; 4.4] 47 (72.3)	0.62 [0.39; 1.00]; 0.052
Emotional functioning	53	20.5 [3.5; NC] 27 (50.9)	65	13.9 [4.2; NC] 33 (50.8)	0.86 [0.51; 1.47]; 0.574
Cognitive functioning	53	4.0 [2.3; 8.8] 32 (60.4)	65	2.9 [2.1; 4.1] 48 (73.8)	0.70 [0.44; 1.11]; 0.119
Social functioning	53	4.2 [2.5; NC] 27 (50.9)	65	2.8 [1.5; 8.8] 47 (72.3)	0.58 [0.36; 0.94]; 0.024
EORTC QLQ-EN24 – time to first deterioration[e]					
Sexual interest	53	NA 10 (18.9)	65	NA 17 (26.2)	0.64 [0.29; 1.41]; 0.262
Sexual activity	53	NA 6 (11.3)	65	NA 5 (7.7)	1.22 [0.37; 4.01]; 0.738

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study **Outcome category** **Outcome**	**Dostarlimab + carboplatin + paclitaxel**		**Placebo + carboplatin + paclitaxel**		**Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
Sexual enjoyment	No usable data available[f]				
Poor body image[g]	53	1.4 [0.8; 4.0] 32 (60.4)	65	1.4 [0.9; 1.4] 52 (80.0)	0.71 [0.45; 1.11]; 0.126
Side effects[h]					
AEs (supplementary information)	52	0.1 [0.0; 0.1] 52 (100)	65	0.1 [0.0; 0.1] 65 (100)	–
SAEs	52	NA 14 (26.9)	65	NA [13.5; NC] 20 (30.8)	0.79 [0.40; 1.58]; 0.493
Severe AEs[i]	52	3.2 [1.4; 5.2] 37 (71.2)	65	3.4 [1.9; 9.9] 42 (64.6)	1.18 [0.75; 1.85]; 0.493
Discontinuation due to AEs[j]	52	NA 9 (17.3)	65	NA 11 (16.9)	0.88 [0.35; 2.23]; 0.795
Immune-mediated AEs (supplementary information)[k]	52	2.8 [0.7; 4.6] 38 (73.1)	65	NA [3.9; NC] 24 (36.9)	–
Immune-mediated SAEs[k]	52	NA 2 (3.8)	65	NA 1 (1.5)	1.67 [0.13; 20.95]; 0.687
Immune-mediated severe AEs[i, k]	52	NA 10 (19.2)	65	NA 0	ND[l]
Infusion-related reactions	No usable data available[m]				
Urinary tract infections (PT, AEs)	52	NA 4 (7.7)	65	NA [13.3; NC] 16 (24.6)	0.25 [0.08; 0.78]; 0.010

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

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

a. Effect and CI: Cox proportional hazards model; p-value: log-rank test. In each case stratified according to prior pelvic radiotherapy (yes vs. no) and disease status at baseline (primary FIGO stage III vs. primary FIGO stage IV vs. recurrent).
b. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
c. 81% of the patients had no value at baseline and were therefore not included in the analysis.
d. A score decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
e. A score decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
f. 82% of the patients had no value at baseline and were therefore not included in the analysis.
g. In departure from the company's approach, this scale was assigned to health-related quality of life, rather than to symptoms.
h. According to the study protocol, events which were attributable to progression of the underlying disease were not to be reported as AEs. However, 2 (3.1%) patients with event for the PT "cancer pain" from the SOC "neoplasms benign, malignant and unspecified (incl cysts and polyps)" were documented under AEs in the control arm.
i. Operationalized as CTCAE grade ≥ 3.
j. Discontinuation of one or more drug components.
k. The operationalization was based on an a priori defined list of PTs; only immune-mediated AEs with CTCAE grade ≥ 2 could be considered immune-mediated, however.
l. The company did not present any information on HR (including 95% CI) and p-value. In the present data constellation, with an event rate of 19% (n = 10) in the intervention arm versus 0% (n = 0) in the comparator arm, and with Kaplan-Meier curves clearly separating early in the course of the study (see Figure 32 of the full dossier assessment), a statistically significant difference to the disadvantage of dostarlimab + carboplatin + paclitaxel can be assumed.
m. See Section I 4.1 for reasons.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FIGO: International Federation of Gynecology and Obstetrics; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer Module 24; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

On the basis of the available information, at most an indication, e.g. of added benefit, can be derived for the outcome of overall survival, and due to the high risk of bias or limited certainty of results (discontinuation due to AEs), at most hints can be derived for the outcomes in the categories of morbidity, health-related quality of life, and side effects.

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of dostarlimab + carboplatin + paclitaxel. There is an effect modification by the characteristic of disease status at baseline for this outcome (see Section I 4.4). In the pooled subgroup of patients with primary advanced FIGO stage IV disease or recurrent disease at baseline, there is an indication of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel. For patients with primary advanced FIGO stage III disease at baseline, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven for these patients.

Morbidity

Symptoms (EORTC QLQ-C30 and EORTC QLQ-EN24)

The symptoms outcomes were recorded with the instruments EORTC QLQ-C30 and EORTC QLQ-EN24. Time to first deterioration by ≥ 10 points (scale range 0 to 100) was considered.

Tingling and numbness (EORTC QLQ-EN24)

No statistically significant difference between treatment groups was found for the outcome of tingling and numbness. There is an effect modification by the characteristic of disease status at baseline, however (see Section I 4.4). For patients with primary advanced FIGO stage IV disease at baseline, there is a hint of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel. For patients with primary advanced FIGO stage III disease or recurrent disease at baseline, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven for these patients.

Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea (EORTC QLQ-C30), lymphoedema, urological symptoms, gastrointestinal symptoms, pain in back and pelvis, muscular pain, hair loss, taste change (EORTC QLQ-EN24)

No statistically significant difference between treatment groups was found for the scales of fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea of the EORTC QLQ-C30, and for the scales of lymphoedema, urological symptoms, gastrointestinal symptoms, pain in back and pelvis, muscular pain, hair loss, and taste change of the EORTC QLQ-EN24. In each case, there is no hint of an added benefit of dostarlimab +

carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven for any of them.

Sexual/vaginal problems (EORTC QLQ-EN24)

No usable data are available for the EORTC QLQ-EN24 scale of sexual/vaginal problems because only 19% of patients were included in the analysis. There is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was shown for the outcome of health status recorded with the EQ-5D VAS. There is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-EN24

The health-related quality of life outcomes were recorded with the instruments EORTC QLQ-C30 and EORTC QLQ-EN24. Time to first deterioration by ≥ 10 points (scale range 0 to 100) was considered.

Social functioning (EORTC QLQ-C30)

For the outcome of social functioning, a statistically significant difference was found in favour of dostarlimab + carboplatin + paclitaxel. There is a hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel.

Global health status, physical functioning, role functioning, emotional functioning, cognitive functioning (EORTC QLQ-C30), sexual interest, sexual activity, poor body image (EORTC QLQ-EN24)

No statistically significant difference between treatment groups was found for the scales of global health status, physical functioning, role functioning, emotional functioning, and cognitive functioning of the EORTC QLQ-C30, and for the scales of sexual interest, sexual activity, and poor body image of the EORTC QLQ-EN24. In each case, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven for any of them.

Sexual enjoyment (EORTC QLQ-EN24)

No usable data are available for the EORTC QLQ-EN24 scale of sexual enjoyment because only 18% of patients were included in the analysis. There is no hint of an added benefit of

dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven.

Side effects

Severe AEs

No significant difference between treatment groups was found for the outcome of severe AEs. There is an effect modification by the characteristic of disease status at baseline, however (see Section I 4.4). For patients with primary advanced FIGO stage III disease at baseline, there is a hint of greater harm of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel. In the pooled subgroup of patients with primary advanced FIGO stage IV disease or recurrent disease at baseline, there is no hint of greater or lesser harm of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel; greater or lesser harm is therefore not proven.

SAEs and discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; greater or lesser harm is therefore not proven for any of them.

Specific AEs

Immune-mediated severe AEs

The company provided no information on the hazard ratio (including 95% confidence interval) and p-value for the outcome of immune-mediated severe AEs. In the present data constellation, with an event rate of 19% (n = 10) in the intervention arm versus 0% (n = 0) in the comparator arm, and with Kaplan-Meier curves clearly separating early in the course of the study (see Figure 32 of the full dossier assessment), a statistically significant difference to the disadvantage of dostarlimab + carboplatin + paclitaxel can be assumed. There is a hint of greater harm of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel.

Immune-mediated SAEs

No statistically significant difference between treatment groups was shown for the outcome of immune-mediated SAEs. There is no hint of greater or lesser harm from dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; greater or lesser harm is therefore not proven.

Infusion-related reactions

No usable data are available for infusion-related reactions. There is no hint of greater or lesser harm from dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; greater or lesser harm is therefore not proven.

Urinary tract infections (AEs)

For the outcome of urinary tract infections (AEs), a statistically significant difference was found in favour of dostarlimab + carboplatin + paclitaxel. There is a hint of lesser harm of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics are taken into account in the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- disease status at baseline (primary FIGO stage III versus primary FIGO stage IV versus recurrent)

All mentioned subgroup characteristics and cut-off values had been prespecified for the primary outcomes of overall survival and PFS.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 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, side effects) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study Outcome Characteristic Subgroup	Dostarlimab + carboplatin + paclitaxel N	Median time to event in months [95% CI] Patients with event n (%)	Placebo + carboplatin + paclitaxel N	Median time to event in months [95% CI] Patients with event n (%)	Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel HR [95% CI][a]	p-value[b]
RUBY						
Mortality						
Overall survival						
Disease status at baseline						
Primary FIGO stage III	10	NA [2.4; NC] 3 (30.0)	14	NA 1 (7.1)	4.89 [0.51; 47.12]	0.128
Primary FIGO stage IV	16	NA 2 (12.5)	19	18.2 [11.6; NC] 10 (52.6)	0.22 [0.05; 1.01]	0.033
Recurrent	27	NA 2 (7.4)	32	24.0 [20.3; NC] 13 (40.6)	0.14 [0.03; 0.62]	0.003
					Interaction[c]:	0.029
Primary FIGO stage III	10	NA [2.4; NC] 3 (30.0)	14	NA 1 (7.1)	4.89 [0.51; 47.12]	0.128
Primary FIGO stage IV and recurrent[d]	43[e]	ND 4 (9.3)[e]	51[e]	ND 23 (45.1)[e]	0.17 [0.06; 0.51][f]	0.001[f]
					Interaction[g]:	0.009
Morbidity						
Symptoms (EORTC QLQ-EN24 – time to first deterioration[h])						
Tingling/numbness						
Disease status at baseline						
Primary FIGO stage III	10	1.4 [0.7; 2.1] 9 (90.0)	14	1.2 [0.8; 2.1] 12 (85.7)	0.84 [0.35; 2.01]	0.699
Primary FIGO stage IV	16	3.5 [2.1; 6.1] 11 (68.8)	19	0.8 [0.7; 2.1] 18 (94.7)	0.38 [0.18; 0.84]	0.012
Recurrent	27	1.0 [0.8; 2.1] 25 (92.6)	32	1.8 [1.4; 2.3] 26 (81.3)	1.35 [0.77; 2.36]	0.317
					Interaction[c]:	0.037

Table 16: Subgroups (mortality, morbidity, side effects) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study Outcome Characteristic Subgroup	Dostarlimab + carboplatin + paclitaxel N	Dostarlimab + carboplatin + paclitaxel Median time to event in months [95% CI] Patients with event n (%)	Placebo + carboplatin + paclitaxel N	Placebo + carboplatin + paclitaxel Median time to event in months [95% CI] Patients with event n (%)	Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel HR [95% CI][a]	 p-value[b]
Severe AEs[i]						
Disease status at baseline						
Primary FIGO stage III	10	3.2 [0.0; 4.6] 9 (90.0)	14	16.5 [2.6; NC] 6 (42.9)	5.83 [1.74; 19.59]	0.001
Primary FIGO stage IV	15	4.1 [0.3; 11.3] 10 (66.7)	19	2.4 [0.7; 4.5] 15 (78.9)	0.75 [0.34; 1.70]	0.486
Recurrent	27	2.7 [1.0; 25.6] 18 (66.7)	32	2.3 [1.4; 9.9] 21 (65.6)	0.91 [0.48; 1.74]	0.763
					Interaction[c]:	0.013
Primary FIGO stage III	10	3.2 [0.0; 4.6] 9 (90.0)	14	16.5 [2.6; NC] 6 (42.9)	5.83 [1.74; 19.59]	0.001
Primary FIGO stage IV and recurrent[d]	42[e]	ND 28 (66.7)[e]	51[e]	ND 36 (70.6)[e]	0.84 [0.51; 1.40][f]	0.511[f]
					Interaction[g]:	0.004

a. Effect and CI: Cox proportional hazards model stratified according to prior pelvic radiotherapy (yes vs. no) and disease status at baseline (primary FIGO stage III vs. primary FIGO stage IV vs. recurrent).
b. p-value: log-rank test stratified according to prior pelvic radiotherapy (yes vs. no) and disease status at baseline (primary FIGO stage III vs. primary FIGO stage IV vs. recurrent).
c. p-value of the interaction term of the stratified Cox proportional hazards model.
d. Summary of the subgroups of primary FIGO stage IV and recurrent.
e. Institute's calculation.
f: Institute's calculation: meta-analytical summary of the subgroup results for primary FIGO stage IV and recurrent (fixed-effect model).
g. Institute's calculation: p-value from Q test for heterogeneity, related to the 2 subgroups of primary FIGO stage III vs. primary FIGO stage IV and recurrent.
h. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
i. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FIGO: International Federation of Gynecology and Obstetrics; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer Module 24; RCT: randomized controlled trial

Mortality

Overall survival

There is an effect modification for the characteristic of disease status at baseline for the outcome of overall survival. First, it was examined whether subgroups could be meaningfully summarized. Calculations conducted by the Institute show that a pooled consideration of the subgroups of primary FIGO stage IV and recurrent result in a homogeneous data situation for the outcome of overall survival (see I Appendix F of the full dossier assessment). Below, the derivation of added benefit for the outcome of overall survival is based on the results of calculations conducted by the Institute.

In patients with primary advanced FIGO stage III disease at baseline, there was no statistically significant difference between treatment groups. For patients with primary advanced FIGO stage III disease at baseline, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven for these patients.

For patients with primary advanced FIGO stage IV disease or recurrent disease at baseline, there was a statistically significant difference in favour of dostarlimab + carboplatin + paclitaxel. For patients with primary advanced FIGO stage IV disease or recurrent disease at baseline, there is an indication of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel.

Morbidity

Symptoms (EORTC QLQ-EN24)

Tingling and numbness (EORTC QLQ-EN24)

There is an effect modification for the characteristic of disease status at baseline for the outcome of tingling and numbness. First, it was examined whether subgroups could be meaningfully summarized. In the present data constellation, this was not meaningfully possible for this outcome.

In patients with primary advanced FIGO stage III disease or recurrent disease at baseline, there was no statistically significant difference between treatment groups. For patients with primary advanced FIGO stage III disease or recurrent disease at baseline, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel; an added benefit is not proven for these patients.

For patients with primary advanced FIGO stage IV disease at baseline, there was a statistically significant difference in favour of dostarlimab + carboplatin + paclitaxel. For patients with primary advanced FIGO stage IV disease at baseline, there is a hint of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel.

Side effects

Severe AEs

There is an effect modification for the characteristic of disease status at baseline for the outcome of severe AEs. First, it was examined whether subgroups could be meaningfully summarized. Calculations conducted by the Institute show that a pooled consideration of the subgroups of primary FIGO stage IV and recurrent result in a homogeneous data situation for the outcome of severe AEs (see I Appendix F of the full dossier assessment). Below, the derivation of added benefit for the outcome of severe AEs is based on the results of calculations conducted by the Institute.

In patients with primary advanced FIGO stage III disease at baseline, there was a statistically significant difference to the disadvantage of dostarlimab + carboplatin + paclitaxel. For patients with primary advanced FIGO stage III disease at baseline, there is a hint of greater harm of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel.

For patients with primary advanced FIGO stage IV disease or recurrent disease at baseline, there was no statistically significant difference between treatment groups. For patients with primary advanced FIGO stage IV disease or recurrent disease at baseline, there is no hint of greater or lesser harm of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel; greater or lesser harm is therefore not proven for these patients.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

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

I 5.1 Assessment of 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 the outcomes on side effects

It cannot be inferred from the dossier whether the following outcomes were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms

Tingling/numbness (EORTC QLQ-EN24)

For the outcome of tingling/numbness, insufficient severity data are available which would allow classifying them as serious/severe. The outcome of tingling/numbness was therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Urinary tract infections (AEs)

The CSR contains information on the CTCAE severity grade of the specific side effect of urinary tract infections (PT, AEs), which show that the majority of events were non-serious or non-severe (CTCAE grade < 3). Therefore, the specific AE was assigned to the outcome category of non-serious/non-severe side effects.

Table 17: Extent of added benefit at outcome level: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival		
Disease status at baseline		
Primary FIGO stage III	NA vs. NA HR: 4.89 [0.51; 47.12] p = 0.128	Lesser/added benefit not proven
Primary FIGO stage IV and recurrent	ND HR: 0.17 [0.06; 0.51] p = 0.001 Probability: “indication”	Outcome category: mortality Added benefit, extent: “major”
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration by ≥ 10 points)		
Fatigue	2.3 vs. 1.4 HR: 0.89 [0.58; 1.36] p = 0.577	Lesser/added benefit not proven
Nausea and vomiting	5.8 vs. 4.5 HR: 0.89 [0.55; 1.43] p = 0.618	Lesser/added benefit not proven
Pain	11.5 vs. 3.3 HR: 0.63 [0.39; 1.02] p = 0.053	Lesser/added benefit not proven
Dyspnoea	4.4 vs. 3.7 HR: 0.93 [0.57; 1.50] p = 0.739	Lesser/added benefit not proven
Insomnia	7.5 vs. 4.2 HR: 0.95 [0.58; 1.56] p = 0.837	Lesser/added benefit not proven
Appetite loss	19.8 vs. 8.5 HR: 0.76 [0.45; 1.29] p = 0.318	Lesser/added benefit not proven
Constipation	2.8 vs. 3.9 HR: 0.89 [0.54; 1.45] p = 0.573	Lesser/added benefit not proven
Diarrhoea	4.6 vs. 5.7 HR: 1.23 [0.76; 2.01] p = 0.394	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Symptoms (EORTC QLQ-EN24 – time to first deterioration by ≥ 10 points)		
Lymphoedema	2.8 vs. 2.8 HR: 0.86 [0.56; 1.33] p = 0.501	Lesser/added benefit not proven
Urological symptoms	NA vs. 3.8 HR: 0.58 [0.33; 1.01] p = 0.053	Lesser/added benefit not proven
Gastrointestinal symptoms	21.6 vs. 11.7 HR: 0.92 [0.54; 1.59] p = 0.774	Lesser/added benefit not proven
Sexual/vaginal problems	No usable data available	Lesser/added benefit not proven
Pain in back and pelvis	21.6 vs. 18.2 HR: 0.87 [0.50; 1.51] p = 0.628	Lesser/added benefit not proven
Tingling/numbness		
Disease status at baseline		
Primary FIGO stage III	1.4 vs. 1.2 HR: 0.84 [0.35; 2.01] p = 0.699	Lesser/added benefit not proven
Primary FIGO stage IV	3.5 vs. 0.8 HR: 0.38 [0.18; 0.84] p = 0.012 Probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: “minor”
Recurrent	1.0 vs. 1.8 HR: 1.35 [0.77; 2.36] p = 0.317	Lesser/added benefit not proven
Muscular pain	1.4 vs. 2.1 HR: 1.15 [0.76; 1.75] p = 0.556	Lesser/added benefit not proven
Hair loss	0.8 vs. 0.8 HR: 1.15 [0.77; 1.71] p = 0.574	Lesser/added benefit not proven
Taste change	2.2 vs. 2.2 HR: 0.88 [0.57; 1.38] p = 0.559	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Health status		
EQ-5D VAS – time to first deterioration by ≥ 15 points	NA vs. 16.3 HR: 0.56 [0.29; 1.08] p = 0.080	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (time to first deterioration by ≥ 10 points)		
Global health status	12.9 vs. 4.2 HR: 0.63 [0.39; 1.04] p = 0.067	Lesser/added benefit not proven
Physical functioning	4.0 vs. 3.7 HR: 0.95 [0.59; 1.52] p = 0.818	Lesser/added benefit not proven
Role functioning	4.4 vs. 2.5 HR: 0.62 [0.39; 1.00] p = 0.052	Lesser/added benefit not proven
Emotional functioning	20.5 vs. 13.9 HR: 0.86 [0.51; 1.47] p = 0.574	Lesser/added benefit not proven
Cognitive functioning	4.0 vs. 2.9 HR: 0.70 [0.44; 1.11] p = 0.119	Lesser/added benefit not proven
Social functioning	4.2 vs. 2.8 HR: 0.58 [0.36; 0.94] p = 0.024 Probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: “minor”
EORTC QLQ-EN24 (time to first deterioration by ≥ 10 points)		
Sexual interest	NA vs. NA HR: 0.64 [0.29; 1.41] p = 0.262	Lesser/added benefit not proven
Sexual activity	NA vs. NA HR: 1.22 [0.37; 4.01] p = 0.738	Lesser/added benefit not proven
Sexual enjoyment	No usable data available	Lesser/added benefit not proven
Poor body image	1.4 vs. 1.4 HR: 0.71 [0.45; 1.11] p = 0.126	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Outcomes with shortened observation period		
Side effects		
SAEs	NA vs. NA HR: 0.79 [0.40; 1.58] p = 0.493	Greater/lesser harm not proven
Severe AEs Disease status at baseline		
Primary FIGO stage III	3.2 vs. 16.5 HR: 5.83 [1.74; 19.59] HR: 0.17 [0.05; 0.58][c] p = 0.001 Probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Greater harm, extent: "major"
Primary FIGO stage IV and recurrent	ND HR: 0.84 [0.51; 1.40] p = 0.511	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. NA HR: 0.88 [0.35; 2.23] p = 0.795	Greater/lesser harm not proven
Immune-mediated SAEs	NA vs. NA HR: 1.67 [0.13; 20.95] p = 0.687	Greater/lesser harm not proven
Immune-mediated severe AEs	NA vs. NA (patients with event: 19% vs. 0%) HR: ND p = ND Probability: "hint"	Outcome category: serious/severe side effects Greater harm, extent: "non-quantifiable", at least "considerable"[c]
Infusion-related reactions	No usable data available	Greater/lesser harm not proven
Urinary tract infections (PT, AEs)	NA vs. NA HR: 0.25 [0.08; 0.78] p = 0.010 Probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: "considerable"

Table 17: Extent of added benefit at outcome level: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u). c. The company did not present any information on HR (including 95% CI) and p-value. In the present data constellation, with an event rate of 19% (n = 10) in the intervention arm versus 0% (n = 0) in the comparator arm, and with Kaplan-Meier curves clearly separating early in the course of the study (see Figure 32 of the full dossier assessment), a statistically significant difference to the disadvantage of dostarlimab + carboplatin + paclitaxel can be assumed. The extent is estimated to be “non-quantifiable”, but be at least “considerable”. AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; FIGO: International Federation of Gynecology and Obstetrics; HR: hazard ratio; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer Module 24; 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 dostarlimab + carboplatin + paclitaxel in comparison with carboplatin + paclitaxel

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival ▫ Disease status at baseline (primary FIGO stage IV or recurrent): indication of an added benefit – extent: “major”	–
Non-serious/non-severe symptoms/late complications Symptoms (EORTC QLQ-EN24): ▪ Tingling/numbness ▫ Disease status at baseline (primary FIGO stage IV): hint of an added benefit – extent: “minor”	–
Health-related quality of life EORTC QLQ-C30: ▪ Social functioning: hint of an added benefit – extent: “minor”	–
Outcomes with shortened observation period	
–	Serious/severe side effects ▪ Severe AEs: ▫ Disease status at baseline (primary FIGO stage III): hint of greater harm – extent: “major” ▪ Immune-mediated severe AEs: hint of greater harm – extent: “non-quantifiable”, at least “considerable”
Non-serious/non-severe side effects ▪ Urinary tract infection (AE): hint of lesser harm – extent: “considerable”	–
No usable data are available for the outcome of infusion-related reactions from the side effects category.	
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; FIGO: International Federation of Gynecology and Obstetrics; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer Module 24	

Overall, both positive and negative effects of dostarlimab + carboplatin + paclitaxel were found in comparison with the ACT. For overall survival and the outcomes in the categories of morbidity and health-related quality of life, the observed effects relate to the entire observation period. For the side effects, however, they refer exclusively to the shortened period (until the 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 dostarlimab + carboplatin + paclitaxel compared with the ACT are derived separately by disease status at baseline:

Patients with primary advanced FIGO stage III disease

On the side of positive effects, there is a hint of a minor added benefit in social functioning in the category of health-related quality of life for patients with primary advanced FIGO stage III disease at baseline. In addition, there is a hint of lesser harm of considerable extent in the outcome of urinary tract infections (AEs). In view of the therapy regimens investigated, however, it is questionable whether the positive effect regarding this outcome is to be allocated to the outcome category of side effects or whether it rather reflects improved symptoms of the disease. A clear distinction is not possible on the basis of the available information.

In contrast, there are 2 negative effects in the category of serious/severe side effects with major or non-quantifiable, but at least considerable extent both in the overall rate of severe AEs and in immune-mediated severe AEs. It should be noted that the immune-mediated severe AEs are also included in the analyses of the severe AEs. In summary, weighing the positive and negative effects, there is a hint of lesser benefit due to the major disadvantage in the overall rate of severe AEs for patients with primary advanced FIGO stage III disease at baseline.

Patients with primary advanced FIGO stage IV disease or recurrent disease

For patients with primary advanced FIGO stage IV disease or recurrent disease at baseline, there is an indication of major added benefit for the outcome of overall survival. In addition, there are further positive effects with minor or considerable extent in the categories of non-serious/non-severe symptoms/late complications (only for patients with FIGO stage IV), social functioning of health-related quality of life, and non-serious/non-severe side effects. In view of the therapy regimens investigated, however, it is questionable whether the positive effect regarding the outcome of urinary tract infections (AEs) is to be allocated to the outcome category of side effects or whether it rather reflects improved symptoms of the disease. A clear distinction is not possible on the basis of the available information. In contrast, in the category of serious/severe side effects, there is a negative effect with non-quantifiable, but at least considerable extent in immune-mediated severe AEs. This does not call into question the positive effects, especially the major added benefit in overall survival. The fact that there are no negative effects in the overall rate of severe AEs for this subgroup is also taken into account.

Overall, an indication of major added benefit is derived for patients with primary advanced FIGO stage IV disease or recurrent disease at baseline.

Summary

In summary, there is a hint of lesser benefit of dostarlimab + carboplatin + paclitaxel in comparison with the ACT carboplatin + paclitaxel for patients with dMMR/MSI-H primary

advanced FIGO stage III endometrial cancer and who are candidates for systemic therapy. There is an indication of major added benefit of dostarlimab + carboplatin + paclitaxel in comparison with the ACT carboplatin + paclitaxel for patients with dMMR/MSI-H primary advanced FIGO stage IV or recurrent endometrial cancer and who are candidates for systemic therapy.

The result of the assessment of the added benefit of dostarlimab + carboplatin + paclitaxel in comparison with the ACT is summarized in Table 19.

Table 19: Dostarlimab + carboplatin + paclitaxel – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with dMMR/MSI-H primary advanced or recurrent[b] endometrial cancer and who are candidates for systemic therapy[c]	Carboplatin + paclitaxel[d]	▪ Patients with primary FIGO stage III: hint of lesser benefit[e] ▪ Patients with primary FIGO stage IV or recurrent: indication of major added benefit[e]

a. Presented is the ACT specified by the G-BA.
b. In the recurrent setting, it is assumed that local therapy options for treating the recurrence (resection, radiotherapy) are not an option.
c. 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.
d. For patients in this therapeutic indication, the evidence-based guideline recommendation and the written statement of the scientific-medical societies recommend treatment with carboplatin in combination with paclitaxel. 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. 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.
e. The RUBY 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.

dMMR: mismatch repair deficient; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: International Federation of Gynecology and Obstetrics; G-BA: Federal Joint Committee; MSI-H: microsatellite instability-high

The assessment described above differs from that of the company, which, based on the RUBY study, derived an indication of major added benefit of dostarlimab + carboplatin + paclitaxel over the ACT for all patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy.

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.

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