Durvalumab (endometrial cancer, dMMR)

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

EXTRACT

Project: A24-87 Version: 1.0 Status: 18 Nov 2024 DOI: 10.60584/A24-87_en

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

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

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

Commissioning agency

Federal Joint Committee

Commission awarded on

22 August 2024

Internal Project No.

A24-87

DOI-URL

https://doi.org/10.60584/A24-87_en

Address of publisher

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

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

Medical and scientific advice

- Volker Heilmann

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

Patient and family involvement

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

IQWiG employees involved in the dossier assessment

- Jana Göbel
- Christiane Balg
- Maximilian Kind
- Ulrike Lampert
- Ana Liberman
- Prateek Mishra
- Volker Vervölgyi
- Frank Weber

Keywords

Durvalumab, Carboplatin, Paclitaxel, Endometrial Neoplasms, Benefit Assessment

Part I: Benefit assessment

I Table of contents

Page

I List of tables[2]

Page

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
dMMR	mismatch repair deficient
ECOG PS	Eastern Cooperative Oncology Group Performance Status
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)
MMR	mismatch repair
PFS	progression-free survival
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug durvalumab (in combination with carboplatin and paclitaxel), followed by durvalumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 22 August 2024.

Research question

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

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

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

Therapeutic indication	**ACT[a]**
First-line treatment of adult patients with primary advanced or recurrent dMMR endometrial cancer who are candidates for systemic therapy[b], followed by maintenance treatment with durvalumab	Dostarlimab in combination with carboplatin + paclitaxel, followed by dostarlimab as monotherapy
a. Presented is the ACT specified by the G-BA. b. In this therapeutic indication, the G-BA assumes that the patients have not yet received systemic therapy as postoperative or adjuvant therapy to treat the primary advanced disease and have not yet received chemotherapy to treat the recurrence. ACT: appropriate comparator therapy; dMMR: mismatch repair deficient; G-BA: Federal Joint Committee	

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

Deviating from the research question of the G-BA, the company formed 2 subpopulations, for each of which it specified an ACT that deviated from the G-BA:

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

- carboplatin + paclitaxel

  or

- dostarlimab in combination with carboplatin + paclitaxel, followed by dostarlimab

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

    or

  - pembrolizumab

    or

  - dostarlimab in combination with carboplatin + paclitaxel, followed by dostarlimab

For subpopulation 1, the company justified the choice of carboplatin + paclitaxel as part of the ACT with the original consultation request of 12 October 2023, where the G-BA specified carboplatin + paclitaxel as ACT. The company's justification of its deviation from the G-BA's ACT is not appropriate, however. In its justification, the company referred to a consultation that is no longer current. Carboplatin + paclitaxel are not approved in the present therapeutic indication, whereas dostarlimab (in combination with carboplatin + paclitaxel, followed by dostarlimab) is an approved treatment regimen in this therapeutic indication. Accordingly, carboplatin + paclitaxel is not an appropriate ACT option.

The company's deviation from the G-BA's ACT had no consequences for subpopulation 2, as it did not present any data for this subpopulation.

However, the company's approach had no effect on the completeness of the study pool, as its information retrieval was based on the target population according to the approval and the research question of the G-BA, and included the ACT specified by the G-BA. The effect of the deviation from the G-BA's ACT on its study pool is described below.

The present assessment is conducted on the basis of the research question and ACT specified by the G-BA.

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

Results

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab, in comparison with the ACT.

The DUO-E study included by the company is not suitable for the assessment of the added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab, in comparison with the ACT because the ACT was not implemented. This is justified below.

Evidence presented by the company – description of the DUO-E study

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

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

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

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

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

was in line with the recommendations of the S3 guideline on endometrial cancer and the European Society for Medical Oncology (ESMO) guideline.

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

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

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

ACT specified by the G-BA not implemented

The G-BA specified dostarlimab in combination with carboplatin + paclitaxel, followed by dostarlimab as monotherapy, as the ACT. None of the study arms in the DUO-E study investigated the corresponding treatment regimen. Thus, the DUO-E study did not implement the ACT. The DUO-E study is therefore unsuitable for the assessment of the added benefit of durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab as monotherapy, compared with the G-BA's ACT.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab as monotherapy, in comparison with the ACT; an added benefit is therefore not proven.

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

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

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
First-line treatment of adult patients with primary advanced or recurrent dMMR endometrial cancer who are candidates for systemic therapy[b], followed by maintenance treatment with durvalumab	Dostarlimab in combination with carboplatin + paclitaxel, followed by dostarlimab as monotherapy	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In this therapeutic indication, the G-BA assumes that the patients have not yet received systemic therapy as postoperative or adjuvant therapy to treat the primary advanced disease and have not yet received chemotherapy to treat the recurrence.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficient; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

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

I 2 Research question

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

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

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

Therapeutic indication	**ACT**[a]
First-line treatment of adult patients with primary advanced or recurrent dMMR endometrial cancer who are candidates for systemic therapy[b], followed by maintenance treatment with durvalumab	Dostarlimab in combination with carboplatin + paclitaxel, followed by dostarlimab as monotherapy
a. Presented is the ACT specified by the G-BA. b. In this therapeutic indication, the G-BA assumes that the patients have not yet received systemic therapy as postoperative or adjuvant therapy to treat the primary advanced disease and have not yet received chemotherapy to treat the recurrence. ACT: appropriate comparator therapy; dMMR: mismatch repair deficient; G-BA: Federal Joint Committee	

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

Deviating from the research question of the G-BA, the company formed 2 subpopulations, for each of which it specified an ACT that deviated from the G-BA:

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

    or
  - dostarlimab in combination with carboplatin + paclitaxel, followed by dostarlimab
- Subpopulation 2: patients who have been pretreated with chemotherapy and for whom re-induction with chemotherapy alone is not an option:
  - dostarlimab

    or

- pembrolizumab

  or

- dostarlimab in combination with carboplatin + paclitaxel, followed by dostarlimab

For subpopulation 1, the company justified the choice of carboplatin + paclitaxel as part of the ACT with the original consultation request of 12 October 2023, where the G-BA specified carboplatin + paclitaxel as ACT [3]. The company's justification of its deviation from the G-BA's ACT is not appropriate, however. In its justification, the company referred to a consultation that is no longer current. Carboplatin + paclitaxel are not approved in the present therapeutic indication, whereas dostarlimab (in combination with carboplatin + paclitaxel, followed by dostarlimab) is an approved treatment regimen in this therapeutic indication. Accordingly, carboplatin + paclitaxel is not an appropriate ACT option.

The company's deviation from the G-BA's ACT had no consequences for subpopulation 2, as it did not present any data for this subpopulation.

However, the company's approach had no effect on the completeness of the study pool, as its information retrieval was based on the target population according to the approval and the research question of the G-BA, and included the ACT specified by the G-BA. The effect of the deviation from the G-BA's ACT on its study pool is described in Chapter I 3.

The present assessment is conducted on the basis of the research question and ACT specified by the G-BA.

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

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on durvalumab (status: 2 July 2024)
- bibliographical literature search on durvalumab (last search on 2 July 2024)
- search in trial registries/trial results databases for studies on durvalumab (last search on 1 July 2024)
- search on the G-BA website for durvalumab (last search on 2 July 2024)

To check the completeness of the study pool:

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

The check of completeness of the study pool – based on the research question and the ACT according to the G-BA – did not reveal any relevant study for assessing the added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab, in comparison with the ACT.

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

The DUO-E study included by the company is not suitable for the assessment of the added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab, in comparison with the ACT specified by the G-BA because the ACT was not implemented. This is justified below.

Evidence presented by the company – description of the DUO-E study

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

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

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

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

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

Treatment with durvalumab and olaparib was in compliance with the recommendations of the SPCs [5,6].

Carboplatin + paclitaxel was administered as chemotherapy in all 3 study arms. The SPC for durvalumab provides no information on the dosage of carboplatin + paclitaxel. The dosages and dose reductions of paclitaxel and carboplatin used in the DUO-E study correspond to the guideline recommendations [7,8]. In compliance with the SPC [6], treatment with carboplatin and paclitaxel in the DUO-E study was restricted to a maximum of 6 treatment cycles. The number of cycles could be reduced to 4 cycles in case of toxicity. However, at least 4 cycles of chemotherapy were required for patients to continue into the maintenance phase. Overall, treatment regimen and dosage are comprehensible.

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

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

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

ACT specified by the G-BA not implemented

The G-BA specified dostarlimab in combination with carboplatin + paclitaxel, followed by dostarlimab as monotherapy, as the ACT. None of the study arms in the DUO-E study investigated the corresponding treatment regimen. Thus, the DUO-E study did not implement the ACT. The DUO-E study is therefore unsuitable for the assessment of the added benefit of durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab as monotherapy, compared with the G-BA's ACT.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab as monotherapy, compared with the ACT for the first-line treatment of adult patients with primary advanced or recurrent dMMR endometrial cancer who are candidates for systemic therapy. There is no hint of an added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab, in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of durvalumab + carboplatin + paclitaxel, followed by durvalumab, in comparison with the ACT is summarized in Table 5.

Table 5: Durvalumab + carboplatin + paclitaxel, followed by durvalumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
First-line treatment of adult patients with primary advanced or recurrent dMMR endometrial cancer who are candidates for systemic therapy[b], followed by maintenance treatment with durvalumab	Dostarlimab in combination with carboplatin + paclitaxel, followed by dostarlimab as monotherapy	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In this therapeutic indication, the G-BA assumes that the patients have not yet received systemic therapy as postoperative or adjuvant therapy to treat the primary advanced disease and have not yet received chemotherapy to treat the recurrence.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficient; G-BA: Federal Joint Committee

The assessment described above differs from that of the company, which derived an indication of considerable added benefit for patients who have not been pretreated with chemotherapy or for whom, despite pretreatment, further chemotherapy alone is an option (subpopulation 1). The company derived no added benefit for patients who have been pretreated with chemotherapy and for whom re-induction with chemotherapy alone is not an option (subpopulation 2).

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

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

3. Gemeinsamer Bundesausschuss. Niederschrift (finale Fassung) zum Beratungsgespräch gemäß § 8 AM-NutzenV, Beratungsanforderung 2023-B-214, Durvalumab zur Behandlung des fortgeschrittenen oder rezidivierenden Endometriumkarzinoms [unpublished]. 2023.

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

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

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

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

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

The full report (German version) is published under https://www.iqwig.de/en/projects/a24-87.html.