IQWiG Reports – Commission No. A21-84

Dostarlimab (endometrial cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Dostarlimab (Endometriumkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 September 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Dostarlimab (endometrial cancer) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
16 June 2021

Internal Commission No.
A21-84

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 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.

IQWiG employees involved in the dossier assessment

- Deborah Ingenhag-Reister
- Charlotte Hecker
- Marco Knelangen
- Stefan Kobza
- Matthias Maiworm
- Ulrike Seay
- Beate Wieseler

Keywords: Dostarlimab, Endometrial Neoplasms, Benefit Assessment

Table of contents

Page

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSC	best supportive care
dMMR	mismatch repair deficiency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HDI	Health Data Insight
HTA	Health Technology Assessment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	matching-adjusted indirect comparison
MMR	mismatch repair
MS	microsatellite
MSI-H	microsatellite instability-high
MSS	microsatellite stability
NCRAS	National Cancer Registration and Analysis Service
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dostarlimab. 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 16 June 2021.

Research question

Aim of the present report is the assessment of the added benefit of dostarlimab in comparison with the appropriate comparator therapy (ACT) in adult patients with mismatch repair deficiency (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen.

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

Table 2: Research question of the benefit assessment of dostarlimab

Therapeutic indication	**ACT**[a]
Adult patients with dMMR/MSI-H recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen	Treatment of physician's choice[b]
a. Presentation of the respective ACT specified by the G-BA. b. Overall, the following treatment options are considered suitable comparators within the framework of the treatment of physician's choice: endocrine therapy (medroxyprogesterone acetate, megestrol acetate), systemic chemotherapy, which can also be a platinum-based retreatment (cisplatin [monotherapy or in combination with doxorubicin], doxorubicin [monotherapy or in combination with cisplatin], carboplatin + paclitaxel), and BSC alone. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; dMMR: mismatch repair deficiency; G-BA: Federal Joint Committee; MSI-H: microsatellite instability-high	

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

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Study pool and comparisons presented by the company

For dostarlimab, the company included the ongoing, single-arm GARNET study investigating dostarlimab in patients with recurrent or advanced endometrial cancer with progressive disease during or after platinum-based doublet chemotherapy. Depending on the mismatch repair (MMR)/microsatellite (MS) status, these patients were divided into 2 cohorts (cohort A1: dMMR/MSI-H, cohort A2: MMR competence/microsatellite stability [MSS]).

On the side of the ACT, the company identified a total of 6 studies, including 2 randomized controlled trials (RCTs) (ZoptEC, IXAMPLE2) and 4 retrospective studies (Julius 2013, Makker 2013, Mazgani 2008, Rubinstein 2019). Moreover, the company presented data from the English registry study 216960. This is also a retrospective study conducted by the company using data made available by the National Cancer Registration and Analysis Service (NCRAS).

The company compared the results of cohort A1 (dMMR/MSI-H) from the GARNET study with the results of individual arms from the various studies on the ACT.

Comparisons of individual arms of different studies are not suitable for the benefit assessment

The analyses on the comparison of individual arms of different studies presented by the company are not suitable for the benefit assessment. This is due to the fact that for all studies used by the company for the comparison with the dostarlimab study, the information on the MMR/MS status of the patients is missing and therefore the similarity of the patients with those in the GARNET study cannot be investigated. Furthermore, for all comparisons submitted by the company, either the ACT was not implemented (studies ZoptEC, IXAMPLE2, register study 216960) and/or the analysis method was inadequate (GARNET each vs. IXAMPLE2/Julius 2013/Makker 2013/Mazgani 2008/Rubinstein 2019/register study 216960). Matching-adjusted indirect comparison (MAIC) analyses without a common comparator are generally not an adequate option for confounder adjustment.

Results on added benefit

For the assessment of dostarlimab in adult patients with dMMR/MSI-H recurrent or advanced endometrial cancer that has progressed during or after prior treatment with platinum-based therapy, there are no suitable data to assess the added benefit compared to the ACT. This resulted in no hint of an added benefit of dostarlimab 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 probability and extent of the added benefit of dostarlimab.

[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].

Table 3: Dostarlimab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with dMMR/MSI-H recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen	Treatment of physician's choice[b]	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Overall, the following treatment options are considered suitable comparators within the framework of the treatment of physician's choice: endocrine therapy (medroxyprogesterone acetate, megestrol acetate), systemic chemotherapy, which can also be a platinum-based retreatment (cisplatin [monotherapy or in combination with doxorubicin], doxorubicin [monotherapy or in combination with cisplatin], carboplatin + paclitaxel), and BSC alone. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; dMMR: mismatch repair deficiency; G-BA: Federal Joint Committee; MSI-H: microsatellite instability-high

The G-BA decides on the added benefit.

2.2 Research question

Aim of the present report is the assessment of the added benefit of dostarlimab in comparison with the ACT in adult patients with dMMR/MSI-H recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen.

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

Table 4: Research question of the benefit assessment of dostarlimab

Therapeutic indication	**ACT[a]**
Adult patients with dMMR/MSI-H recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen	Treatment of physician's choice[b]

a. Presentation of the respective ACT specified by the G-BA.
b. Overall, the following treatment options are considered suitable comparators within the framework of the treatment of physician's choice: endocrine therapy (medroxyprogesterone acetate, megestrol acetate), systemic chemotherapy, which can also be a platinum-based retreatment (cisplatin [monotherapy or in combination with doxorubicin], doxorubicin [monotherapy or in combination with cisplatin], carboplatin + paclitaxel), and BSC alone. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; dMMR: mismatch repair deficiency; G-BA: Federal Joint Committee; MSI-H: microsatellite instability-high

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

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on dostarlimab (status: 17 March 2021)
- bibliographical literature search on dostarlimab (last search on 16 March 2021)
- search in trial registries/trial results databases for studies on dostarlimab (last search on 16 March 2021)
- search on the G-BA website for dostarlimab (last search on 16 March 2021)
- bibliographical literature search on the ACT (last search on 17 March 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 17 March 2021)
- search on the G-BA website for the ACT (last search on 17 March 2021)

To check the completeness of the study pool:

- search in trial registries for studies on dostarlimab (last search on 7 July 2021); for search strategies, see Appendix A of the full dossier assessment

Concurring with the company, no RCT on the direct comparison of dostarlimab versus the ACT specified by the G-BA was identified from the check of the completeness of the study pool.

As the company identified no RCT for a direct comparison, it conducted an information retrieval for further studies. With regard to the patient population, the company stated that the dMMR/MSI-H status was not taken into account in the selection of studies for the ACT.

On the intervention side, the company only identified the single-arm study GARNET, making an adjusted indirect comparison via a common comparator of dostarlimab versus the ACT impossible. The company therefore presented comparisons of individual arms from different studies.

However, the company's information retrieval on the ACT is not suitable for ensuring the completeness of the search results. This has the following reason in particular: The company does not consider all therapy options of the ACT. For example, it does not consider best supportive care (BSC) in the bibliographical literature search as well as in the search in trial registries; furthermore, cisplatin is not included in the search in the trial registries ClinicalTrials.gov and EU Clinical Trials Register.

No additional potentially relevant study on dostarlimab was identified from the check of the completeness of the study pool. A check of the completeness of the study pool on the side of the ACT was not performed, as the data presented by the company were overall unsuitable to

draw conclusions on the added benefit of dostarlimab for patients in the present therapeutic indication. This is explained below.

Study pool of the company

Table 5 shows the studies included by the company.

Table 5: Studies included by the company (multipage table)

Study	Study design	Population	Information on the MMR/MS status	Interventions	Patient data used by the company	Methods of the comparison conducted by the company
Study with dostarlimab						
GARNET	Single-arm	Patients with recurrent or advanced endometrial cancer with progressive disease during or after platinum-based doublet chemotherapy	Yes	Dostarlimab	IPD	
Studies with the ACT						
ZoptEC	RCT	Patients with advanced, recurrent or metastatic endometrial cancer whose disease is progressive during or after chemotherapy with a platinum and a taxane	ND	Zoptarelin doxorubicin vs. doxorubicin[a]	IPD	Inverse Probability of Treatment Weighting (IPTW)
IXAMPLE2	RCT	Patients with advanced, recurrent or metastatic endometrial cancer whose disease is progressive after platinum-based chemotherapy	ND	Ixabepilon vs. paclitaxel or doxorubicin[a]	Aggregate data	MAIC
Julius 2013	Retrospective analysis of patient data	Patients with recurrent endometrial cancer after pretreatment with chemotherapy	ND	Pegylated liposomal doxorubicinb[b]	Aggregate data	MAIC
Makker 2013	Retrospective analysis of patient data	Patients with advanced recurrent endometrial cancer after pretreatment with carboplatin + paclitaxel	ND	Doxorubicin[b]	Aggregate data	MAIC
Mazgani 2008	Retrospective analysis of patient data	Patients with recurrent endometrial cancer after pretreatment with carboplatin + paclitaxel	ND	Carboplatin + paclitaxel[b]	Aggregate data	MAIC
Rubinstein 2019	Retrospective analysis of patient data	Patients with recurrent endometrial cancer after pretreatment with carboplatin + paclitaxel	ND	Carboplatin + paclitaxel[b]	Aggregate data	MAIC
English registry study 216960[c] (NCRAS)	Retrospective analysis of patient data[d]	Patients with advanced or recurrent endometrial cancer after pretreatment with platinum-based doublet chemotherapy	ND	Several[e]	Aggregate data	MAIC

Table 5: Studies included by the company (multipage table)

Study	Study design	Population	Information on the MMR/MS status	Interventions	Patient data used by the company	Methods of the comparison conducted by the company
a. The company considered the doxorubicin arm (ZoptEC) or the paclitaxel/doxorubicin arm (IXAMPLE2) for the comparison with doxorubicin. b. Place/period of treatment: UTMDACC (USA)/1996 to 2006 (Julius 2013), MSKCC (USA)/1995 to 2009 (Makker 2013), British Columbia Cancer Agency Centres (Canada)/1995 to 2007 (Mazgani 2008), MSKCC (USA)/2000 to 2014 (Rubinstein 2019). c. In Module 4 A of the dossier, the company lists the following study number: 217216. However, this refers to the study protocol for the comparison conducted and not to the underlying registry study. d. Study of the company in collaboration with Health Data Insight (HDI) using data made available by NCRAS. Aim of the study was to evaluate patient characteristics, treatment pathways and results of patients with recurrent or advanced endometrial cancer in England between 2013 and 2018 and to generate a historical control arm for cohort A1 of the GARNET study. e. In Table 3-1 of Module 3 A, the company provides information on 884 of 999 patients considered. According to this information, 168 (16.8%) patients received doxorubicin, 279 (27.9%) received carboplatin + paclitaxel, 153 (15.3%) received carboplatin + doxorubicin, 116 (11.6%) received paclitaxel, 93 (9.3%) received carboplatin, 49 (4.9%) received cisplatin + doxorubicin, 24 (2.4%) received cisplatin and 2 (0.2%) received endocrine therapy (medroxyprogesterone acetate, megestrol acetate). For 115 (11.5%) patients, there was no information on the received therapies. ACT: appropriate comparator therapy; IPD: individual patient data; IPTW: inverse probability of treatment weighting; ND: no data; MAIC: matching-adjusted indirect comparison; MMR: mismatch repair; MS: microsatellites; MSKCC: Memorial Sloan Kettering Cancer Center; NCRAS: National Cancer Registration and Analysis Service; RCT: randomized controlled trial; UTMDACC: University of Texas MD Anderson Cancer Center.						

Study with dostarlimab: GARNET

The GARNET study is an ongoing, single-arm study investigating dostarlimab in patients with recurrent or advanced endometrial cancer with progressive disease during or after platinum-based doublet chemotherapy [3]. Depending on the MMR/MS status, these patients were divided into 2 cohorts (cohort A1: dMMR/MSI-H, cohort A2: MMR competence/MSS).

Studies with the ACT

On the ACT side, the company identified a total of 6 studies, including 2 RCTs (ZoptEC [4], IXAMPLE2 [5]) and 4 retrospective studies (Julius 2013 [6], Makker 2013 [7], Mazgani 2008 [8], Rubinstein 2019 [9]) (for details see Table 5).

Moreover, the company presented data from the English registry study 216960. This is also a retrospective study conducted by the company in collaboration with Health Data Insight (HDI) using data made available by NCRAS. Aim of the company's study was to evaluate patient characteristics, treatment pathways and courses of disease of patients with recurrent or advanced endometrial cancer in England between 2013 and 2018 and to generate a historical control arm for cohort A1 of the GARNET study.

Comparisons presented by the company

The company compared the results of cohort A1 (dMMR/MSI-H) from the GARNET study with the results of individual arms from the various studies on the ACT. Each of the comparisons is based on 3 separate study protocols (GARNET vs. ZoptEC, GARNET each vs. IXAMPLE2/Julius 2013/Makker 2013/Mazgani 2008/Rubinstein 2019 and GARNET vs. registry study 216960). For the comparison of the data from the GARNET study versus registry study 216960, the company states in Module 4 A, Appendix 4 E, that the protocol was originally set up for the UK Health Technology Assessment (HTA) application for dostarlimab. In total, the company thus presented 7 comparisons of individual arms of different studies. Depending on the data availability (IPD vs. aggregate data), the comparisons presented by the company are based on an IPTW analysis or on a MAIC analysis (see Table 5).

Comparisons of individual arms of different studies are not suitable for the benefit assessment

No information on the MMR/MS status in the studies on the ACT

Dostarlimab is approved for patients with recurrent or advanced endometrial cancer after platinum-containing pretreatment, whose tumours have dMMR or MSI-H. Accordingly, in its analyses from the GARNET study, the company only considered cohort A1 that included patients with dMMR/MSI-H. However, the company stated that it did not take into account the MMR/MS status of the patients when selecting studies on the ACT, as it was rarely determined in studies and has not yet been routinely recorded in health care. Moreover, reviews and studies would show a heterogeneous picture regarding the prognostic value of the dMMR/MSI-H status [10-12].

The approach of the company was not appropriate. The MMR/MS status is a relevant criterion for the assessment of the similarity of the study populations. This is shown, for example, by a comparison of the patient populations included in the GARNET study. The study included both patients with dMMR/MSI-H endometrial cancer (cohort A1) and patients with MMR competence/MSS endometrial cancer (cohort A2). There are clear differences in the disease characteristics of the patients between the two populations. Thus, in cohort A1 (dMMR/MSI-H), endometrioid type I carcinomas predominate with a proportion of 66%, and in cohort A2 (MMR competence/MSS), on the other hand, non-endometrioid type II carcinomas predominate with a proportion of 77%. Different pathogenesis mechanisms and prognoses are assumed for type I and type II carcinomas [13].

A survey of oncologists conducted by the company also showed that MMR/MS status, in addition to other characteristics such as histology, is a relevant prognostic factor in endometrial cancer. This can also be learned from the current European consensus guideline on endometrial cancer, which accordingly recommends a molecular classification for all endometrial carcinomas [14].

As no information on the MMR/MS status of the patients is available for any of the studies submitted by the company on the side of the ACT, the similarity of the study populations cannot be investigated for any of the comparisons submitted by the company.

Implementation of the ACT

The G-BA specified treatment of physician's choice as ACT, among which the following treatment options were considered suitable comparators:

- Endocrine therapy:
  - medroxyprogesterone acetate
  - megestrol acetate
- Systemic chemotherapy that can also be platinum-based retreatment:
  - cisplatin (monotherapy or in combination with doxorubicin)
  - doxorubicin (monotherapy or in combination with cisplatin)
  - carboplatin + paclitaxel
- BSC

In the two interventional studies ZoptEC and IXAMPLE2, the choice of therapy in the comparator arm was limited to doxorubicin (ZoptEC) or to doxorubicin or paclitaxel (IXAMPLE2, see also Table 5). As no therapy according to the physician's choice choosing from the therapy options named by the G-BA was offered in the two studies, the ACT was not implemented in either case.

The retrospective studies identified by the company included patients who had received doxorubicin (Julius 2013, Makker 2013) or carboplatin + paclitaxel (Mazgani 2008, Rubinstein 2019) for the treatment of their recurrent endometrial cancer. For these studies, it can be assumed that the analysed patient data originate from a daily treatment routine that is based on a free choice of therapy at the physician's discretion and on the availability of the ACT therapy options. For these studies, the ACT was considered adequately implemented.

For registry study 216960, the information in Module 3 A of the company's dossier shows that 36% of the patients received a therapy that was not included in the ACT specified by the G-BA (carboplatin + doxorubicin or paclitaxel monotherapy or carboplatin monotherapy). Moreover, the information provided by the company only includes 884 of the 999 patients considered in the registry study, so that for 115 (11.5%) patients no information is available on the therapies administered and it is therefore unclear whether these patients received a therapy that was included in the ACT. In addition, the company provided discrepant information in Module 3 A and Module 5. In Module 5, there is only information on the two most frequent forms of treatment. Deviating from the data in Module 3 A, 321 (32%) instead of 279 (28%) patients received carboplatin + paclitaxel and 220 (22%) instead of 116 (12%) patients received paclitaxel monotherapy. The dossier provides no information on why the figures differ. Therefore, an adequate implementation of the ACT cannot be assumed for the registry study 216960.

Method of the comparison of individual arms of different studies

With the exception of the ZoptEC study, the company has only aggregate data on the side of the ACT studies. The comparisons with the dostarlimab study GARNET presented by the company for these studies are each based on MAIC analyses without a common comparator.

The MAIC analyses without a common comparator are generally not an adequate option for confounder adjustment [1]. In the case of non-randomized comparisons without a common comparator, as a rule only those approaches that, in contrast to the MAIC analysis, use IPD are meaningful for the confounder adjustment [15]. The MAIC analysis, in contrast, considers confounding on the basis of aggregate data. Irrespective of the lack of consideration of the MMR/MS status and the assessment of the implementation of the ACT in the studies submitted by the company, all comparisons conducted by the company on the basis of MAIC analyses without a bridge comparator are therefore not suitable for the assessment of the added benefit of dostarlimab.

For the comparison of the GARNET study with data of the 216960 registry study, the company presented results without adjustment as a sensitivity analysis in addition to the MAIC analysis. Regardless of the lack of consideration of the MMR/MS status as well as the inadequate implementation of the ACT, the observed effects (see Module 4 A, Appendix 4-G) were not large enough that they could not be caused by systematic bias alone [1].

The IPDs for the ZoptEC study were available to the company. For the comparison with the GARNET study, the company presented an IPTW analysis in which the confounder adjustment was performed using the IPD. However, the ZoptEC study is irrelevant for the assessment, since no data are available on the MMR/MS status of the patients and the ACT was not implemented in the study (see above). Regardless of this, it should be noted with regard to the IPTW analysis that the company did not address essential components of the methodical implementation such as positivity, overlap and balance [15] in Module 4 A of the dossier.

Summary

The analyses on the comparison of individual arms of different studies presented by the company are not suitable for the benefit assessment. This is due to the fact that for all studies used by the company for the comparison with the dostarlimab study, the information on the MMR/MS status of the patients is missing and therefore the similarity of the patients with those in the GARNET study cannot be investigated. Furthermore, for all comparisons submitted by the company, either the ACT was not implemented and/or the analysis method was inadequate.

2.4 Results on added benefit

For the assessment of dostarlimab in adult patients with dMMR/MSI-H recurrent or advanced endometrial cancer that has progressed during or after prior treatment with platinum-based therapy, there are no suitable data to assess the added benefit compared to the ACT. This resulted in no hint of an added benefit of dostarlimab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

As for the assessment of the added benefit dostarlimab in adult patients with dMMR/MSI-H recurrent or advanced endometrial cancer that has progressed during or after prior treatment with platinum-based therapy, there are no suitable data to assess the added benefit compared to the ACT.

The result of the assessment of the added benefit of dostarlimab in comparison with the ACT is summarized in Table 6.

Table 6: Dostarlimab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with dMMR/MSI-H recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen	Treatment of physician's choice[b]	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Overall, the following treatment options are considered suitable comparators within the framework of the treatment of physician's choice: endocrine therapy (medroxyprogesterone acetate, megestrol acetate), systemic chemotherapy, which can also be a platinum-based retreatment (cisplatin [monotherapy or in combination with doxorubicin], doxorubicin [monotherapy or in combination with cisplatin], carboplatin + paclitaxel), and BSC alone. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; dMMR: mismatch repair deficiency; G-BA: Federal Joint Committee; MSI-H: microsatellite instability-high

The assessment described above deviates from that of the company, which overall derived a hint of a non-quantifiable, probably major, but at least considerable added benefit on the basis of the presented comparisons of individual arms from different studies.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.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://dx.doi.org/10.1002/bimj.201300274.

3. Oaknin A, Tinker AV, Gilbert L et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol 2020; 6(11): 1766-1772. https://dx.doi.org/10.1001/jamaoncol.2020.4515.

4. AEterna Zentaris. Zoptarelin Doxorubicin (AEZS 108) as Second Line Therapy for Endometrial Cancer (ZoptEC) [online]. 2018 [Accessed: 24.06.2021]. URL: https://clinicaltrials.gov/ct2/show/NCT01767155.

5. McMeekin S, Dizon D, Barter J et al. Phase III randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer. Gynecol Oncol 2015; 138(1): 18-23. https://dx.doi.org/10.1016/j.ygyno.2015.04.026.

6. Julius JM, Tanyi JL, Nogueras-Gonzalez GM et al. Evaluation of pegylated liposomal doxorubicin dose on the adverse drug event profile and outcomes in treatment of recurrent endometrial cancer. Int J Gynecol Cancer 2013; 23(2): 348-354. https://dx.doi.org/10.1097/IGC.0b013e31827c18f3.

7. Makker V, Hensley ML, Zhou Q et al. Treatment of advanced or recurrent endometrial carcinoma with doxorubicin in patients progressing after paclitaxel/carboplatin: Memorial Sloan-Kettering Cancer Center experience from 1995 to 2009. Int J Gynecol Cancer 2013; 23(5): 929-934. https://dx.doi.org/10.1097/IGC.0b013e3182915c20.

8. Mazgani M, Le N, Hoskins PJ. Reuse of carboplatin and paclitaxel in patients with relapsed endometrial cancer—the British Columbia Cancer Agency experience. Gynecol Oncol 2008; 111(3): 474-477. https://dx.doi.org/10.1016/j.ygyno.2008.08.029.

9. Rubinstein M, Halpenny D, Makker V et al. Retreatment with carboplatin and paclitaxel for recurrent endometrial cancer: A retrospective study of the Memorial Sloan Kettering Cancer Center experience. Gynecol Oncol Rep 2019; 28: 120-123. https://dx.doi.org/10.1016/j.gore.2019.04.002.

10. Diaz-Padilla I, Romero N, Amir E et al. Mismatch repair status and clinical outcome in endometrial cancer: a systematic review and meta-analysis. Crit Rev Oncol Hematol 2013; 88(1): 154-167.

11. Fiecon. Systematic Literature Review; clinical study evidence for the prognostic or predictive value of mismatch repair and microsatellite biomarkers in the treatment of recurrent or advanced endometrial cancer [unpublished]. 2020.

12. Mathews C, Im E, Alfaya L et al. Review of evidence for predictive value of microsatellite instability/mismatch repair status in response to non-anti-PD-(L) 1 therapies in patients with advanced or recurrent endometrial cancer. Journal for Immunotherapy of Cancer 2019; 7.

13. Leitlinienprogramm Onkologie. S3-Leitlinie; Diagnostik, Therapie und Nachsorge der Patientinnen mit Endometriumkarzinom [online]. 2018 [Accessed: 21.06.2021]. URL: https://www.awmf.org/uploads/tx_szleitlinien/032-034OLl_S3_Endometriumkarzinom-Diagnostik-Therpie-Nachsorge_2018-04.pdf.

14. Concin N, Matias-Guiu X, Vergote I et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. International Journal of Gynecologic Cancer 2021; 31(1).

15. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V; Rapid Report [online]. 2020 [Accessed: 02.06.2020]. URL: https://www.iqwig.de/download/A19-43_Versorgungsnahe-Daten-zum-Zwecke-der-Nutzenbewertung_Rapid-Report_V1-1.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-84.html.