Cemiplimab (cervical 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 *Cemiplimab (Zervixkarzinom) – 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

I Table of contents

I List of tables[2]

Page

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
BSG	Bundessozialgericht (Federal Social Court)
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

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 cemiplimab. 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 24 April 2023.

Research question

The aim of this report is to assess the added benefit of cemiplimab compared with best supportive care (BSC) as appropriate comparator therapy (ACT) in adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.

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 cemiplimab

Therapeutic indication	**ACT[a]**
Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy	BSC[b, c]

a. Presented is the ACT specified by the G-BA.
b. Best supportive care 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.
c. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list unapproved drug therapies for the treatment of cervical cancer with disease progression on or after first-line treatment. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; G-BA: Federal Joint Committee.; SGB: Social Code Book

The G-BA specified BSC as ACT. It noted that present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a, (para. 7, sentence 4) SGB V list unapproved drug therapies for the treatment of cervical cancer with disease progression on or after first-line treatment. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the Federal Social

Court (BSG) comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

The company departs from the ACT specified by the G-BA. It considered treatment of physician's choice using monotherapy with nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan, or pembrolizumab (for patients with programmed cell death ligand 1 [PD-L1]-positive metastatic cervical cancer) to be an adequate ACT. The approach of the company is not followed; the present assessment is conducted in comparison with the ACT specified by the G-BA (see Table 2).

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

Study pool and study design

No RCT for the direct comparison of cemiplimab with the ACT BSC was identified from the check of the completeness of the study pool. Based on the comparator therapy selected by the company, the company's study pool included the RCT EMPOWER-Cervical 1 comparing cemiplimab with treatment of physician's choice, selecting from monotherapy with pemetrexed, topotecan, irinotecan, gemcitabine or vinorelbine. In Module 4 D of the dossier, the company presented a subpopulation of this study, which it used for its assessment.

The RCT EMPOWER-Cervical 1 is not used for the benefit assessment of cemiplimab, as it did not investigate a comparison with the G-BA's ACT. This is explained below.

Irrespective of the research question described above (see Table 2), the G-BA commissioned IQWiG to conduct an analysis (methodological review and presentation of results) of the data on the EMPOWER-Cervical 1 study presented in Module 4 D. The results of this analysis are summarized below.

Results

Evidence presented by the company – EMPOWER-Cervical 1 study

The EMPOWER-Cervical 1 study is an open-label, multicentre RCT comparing cemiplimab with treatment of physician's choice selecting from monotherapy with pemetrexed, topotecan, irinotecan, gemcitabine or vinorelbine in adult patients with recurrent or metastatic cervical cancer with disease progression on or after platinum-based chemotherapy.

EMPOWER-Cervical 1 study did not investigate the comparison with the appropriate comparator therapy

With reference to the BSG judgement of 22 February 2023, the G-BA defined BSC as the ACT for the present research question (see Table 2). 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. The treatment of physician's choice carried out in the EMPOWER-Cervical 1 study using monotherapy with pemetrexed, topotecan, irinotecan, gemcitabine or vinorelbine does not represent a treatment in the sense of BSC and does not correspond to the implementation of the ACT specified by the G-BA. Thus, the G-BA's ACT was not implemented in the EMPOWER-Cervical 1 study, and the study cannot be used for the benefit assessment.

Results on added benefit

As no data are available for the present research question for comparison with the ACT, there is no hint of an added benefit of cemiplimab; 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 cemiplimab.

Table 3: Cemiplimab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy	BSC[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Best supportive care 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.
c. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list unapproved drug therapies for the treatment of cervical cancer with disease progression on or after first-line treatment. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; G-BA: Federal Joint Committee.; SGB: Social Code Book

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

The G-BA decides on the added benefit.

Supplementary note on the results of the EMPOWER-Cervical 1 study

The assessment of the EMPOWER-Cervical 1 study conducted in accordance with the commission produced the following results:

- Advantages of cemiplimab in comparison with chemotherapy for the outcome of overall survival
- Advantages of cemiplimab in comparison with chemotherapy in morbidity, for the outcomes of pain, nausea and vomiting, and loss of appetite
- Advantages of cemiplimab in comparison with chemotherapy in health-related quality of life, for the outcomes of physical functioning, role functioning, and social functioning
- Advantages of cemiplimab in comparison with chemotherapy in side effects, for the outcomes of severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), nausea (AEs), and blood and lymphatic system disorders (serious AEs [SAEs])
- Disadvantages of cemiplimab in comparison with chemotherapy in side effects, for the outcome of hepatobiliary disorders (severe AEs [CTCAE grade ≥ 3])

Overall, the positive effects of cemiplimab prevail in comparison with chemotherapy using pemetrexed, topotecan, irinotecan or vinorelbine in adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.

I 2 Research question

The aim of this report is to assess the added benefit of cemiplimab compared with BSC as ACT in adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.

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 cemiplimab

Therapeutic indication	**ACT**[a]
Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy	BSC[b, c]

a. Presented is the ACT specified by the G-BA.
b. Best supportive care 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.
c. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list unapproved drug therapies for the treatment of cervical cancer with disease progression on or after first-line treatment. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; G-BA: Federal Joint Committee.; SGB: Social Code Book

The G-BA specified BSC as ACT. It noted that present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a, (para. 7, sentence 4) SGB V list unapproved drug therapies for the treatment of cervical cancer with disease progression on or after first-line treatment. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

The company departs from the ACT specified by the G-BA. It considered treatment of physician's choice using monotherapy with nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan, or pembrolizumab (for patients with PD-L1-positive metastatic cervical cancer) to be an adequate ACT. The approach of the company is not followed; the present assessment is conducted in comparison with the ACT specified by the G-BA (see Table 4).

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

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on cemiplimab (status: 28 February 2023)
- bibliographical literature search on cemiplimab (last search on 28 February 2023)
- search in trial registries/trial results databases for studies on cemiplimab (last search on 28 February 2023)
- search on the G-BA website for cemiplimab (last search on 28 February 2023)

To check the completeness of the study pool:

- search in trial registries for studies on cemiplimab (last search on 11 May 2023); for search strategies, see I Appendix A of the full dossier assessment

No RCT for the direct comparison of cemiplimab with the ACT BSC was identified from the check of the completeness of the study pool. Based on the comparator therapy selected by the company, the company's study pool included the RCT EMPOWER-Cervical 1 (see Section I Appendix B.1 of the full dossier assessment) comparing cemiplimab with treatment of physician's choice, selecting from monotherapy with pemetrexed, topotecan, irinotecan, gemcitabine or vinorelbine. In Module 4 D of the dossier, the company presented a subpopulation of this study, which it used for its assessment (see Section I Appendix B.2 of the full dossier assessment).

The RCT EMPOWER-Cervical 1 is not used for the benefit assessment of cemiplimab, as it did not investigate a comparison with the G-BA's ACT. This is explained below.

Irrespective of the research question described in Chapter I 2, the G-BA commissioned IQWiG to conduct an analysis (methodological review and presentation of results) of the data on the EMPOWER-Cervical 1 study presented in Module 4 D. This analysis is shown in Section I Appendix B of the full dossier assessment, and a summary of the results is provided in Chapter I 5.

Evidence presented by the company – EMPOWER-Cervical 1 study

The EMPOWER-Cervical 1 study is an open-label, multicentre RCT comparing cemiplimab with treatment of physician's choice selecting from monotherapy with pemetrexed, topotecan, irinotecan, gemcitabine or vinorelbine in adult patients with recurrent or metastatic cervical cancer with disease progression on or after platinum-based chemotherapy (for details, see Section I Appendix B of the full dossier assessment). With reference to the BSG judgement of

22 February 2023, the G-BA defined BSC as the ACT for the present research question (see Table 4). 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. The treatment of physician's choice carried out in the EMPOWER-Cervical 1 study using monotherapy with pemetrexed, topotecan, irinotecan, gemcitabine or vinorelbine does not represent a treatment in the sense of BSC and does not correspond to the implementation of the ACT specified by the G-BA. Thus, the G-BA's ACT was not implemented in the EMPOWER-Cervical 1 study, and the study is not used for the benefit assessment.

I 4 Results on added benefit

No data on the comparison with the ACT are available for the assessment of the added benefit of cemiplimab in adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy. There is no hint of an added benefit of cemiplimab 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 cemiplimab in comparison with the ACT is summarized in Table 5.

Table 5: Cemiplimab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy	BSC[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Best supportive care 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.
c. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list unapproved drug therapies for the treatment of cervical cancer with disease progression on or after first-line treatment. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; G-BA: Federal Joint Committee.; SGB: Social Code Book

The assessment described above departs from that by the company, which derived an indication of major added benefit based on the results of the EMPOWER-Cervical 1 study.

The G-BA decides on the added benefit.

Supplementary note on the results of the EMPOWER-Cervical 1 study

The assessment of the EMPOWER-Cervical 1 study (see I Appendix B of the full dossier assessment) conducted in accordance with the commission produced the following results:

- Advantages of cemiplimab in comparison with chemotherapy for the outcome of overall survival
- Advantages of cemiplimab in comparison with chemotherapy in morbidity, for the outcomes of pain, nausea and vomiting, and loss of appetite
- Advantages of cemiplimab in comparison with chemotherapy in health-related quality of life, for the outcomes of physical functioning, role functioning, and social functioning
- Advantages of cemiplimab in comparison with chemotherapy in side effects, for the outcomes of severe AEs (CTCAE grade ≥ 3), nausea (AEs), and blood and lymphatic system disorders (SAEs)

- Disadvantages of cemiplimab in comparison with chemotherapy in side effects, for the outcome of hepatobiliary disorders (severe AEs [CTCAE grade ≥ 3])

Overall, the positive effects of cemiplimab prevail in comparison with chemotherapy using pemetrexed, topotecan, irinotecan or vinorelbine in adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.

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 6.1 [online]. 2022 [Accessed: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.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.

The full report (German version) is published under https://www.iqwig.de/en/projects/a23-36.html.